Olefin Metathesis Reactions with Fluorinated Substrates, Catalysts and Solvents

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CONTENTS

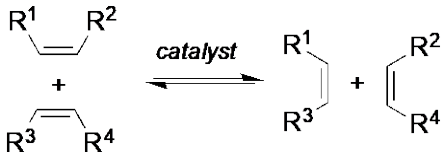
1. INTRODUCTION

Organofluorine compounds[1] have found increasing applications in key industrial fields such as the pharmaceutical[2] and medicinal chemistry[3] or crop[4] and material sciences,[5] owing to the unique physico-chemical features brought about by the introduction of fluorine atoms in organic molecules.[6] Its high electronegativity, small size and polarizability, the strength of the C-F bond (the strongest made by C; 105.4 Kcal/mol) or the C-F bond distance being intermediate between the C-H and the C-O allow isosteric substitution of H or OH by F or C=O by CF_2, while modifying key chemical characteristics such as acidity/basicity of neighbouring groups,[7] H-bond forming ability, electron-density distribution or preferred conformations. In turn, these physico-chemical changes result in more favorable pharmacological profiles such as increased lipophilicty or metabolic stability. 5-Fluorouracil, Fluoxetine (Prozac®), Atorvastatin (Lipitor®), Ciprofloxacin (Ciprobay®) or Efavirenz (Sustiva® and Stocrin®) are representative examples of fluorine containing top-selling drugs that benefit from the aforementioned features.[2] In addition, the excellent NMR properties of ^{19}F (100% natural abundance, high sensitivity) and the long half-life of the radioactive ^{18}F nucleus broaden the applicability of fluorinated molecules, specially in medicinal chemistry.[8,9] Despite its widespread distribution in Nature, fluorine is the most abundant halogen and the thirteenth most abundant element in the Earth's crust,[10] the incorporation of fluorine in natural occurring organic molecules is very scarce mainly due to the lack of fluoroperoxidase enzymes analogous to chloro- and bromoperoxydases that account for the large number of natural products bearing other halogen atoms.[11] For this reason, most of the known organofluorine compounds are manmade. There are two main ways of introducing fluorine in complex organic molecules. One is the direct introduction of fluorine atoms, by using either nucleophilic or electrophilic agents, or small fluorinated groupings (*e.g.* CF_3) into a more

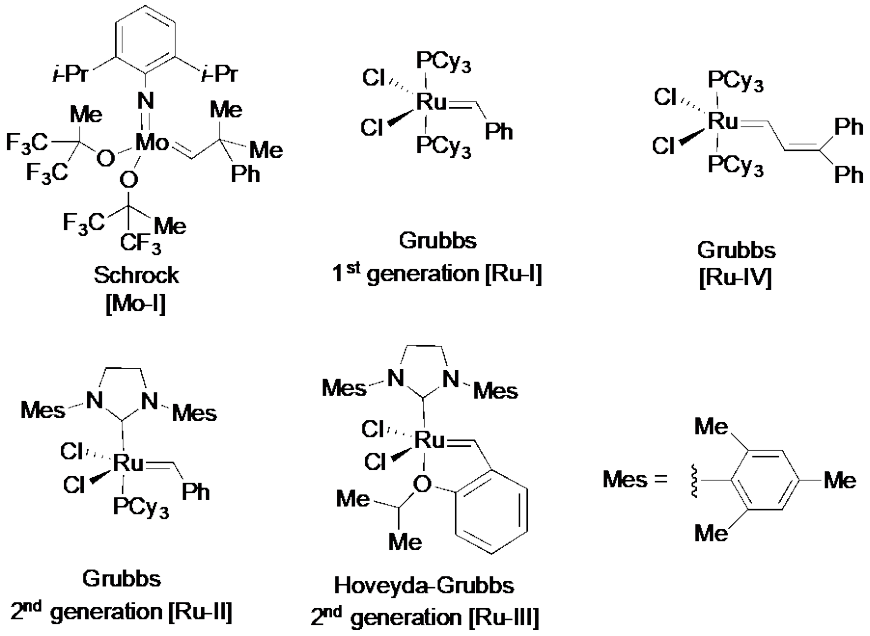
or less complex organic backbone.[12] The second is the use of fluorinated building blocks that are incorporated into a synthetic sequence.[13] The results discussed in this review are found mostly in this second category.

The first olefin metathesis reaction has been described in 1955 and the term "olefin metathesis" was used first by Calderon.[14] This term is taken from the Greek word *μεταθεση* "change of position" and describes the exchange of carbon atoms between a pair of double bonds (Chart 1).

Chart 1. General scheme of metathesis reaction



Though olefin metathesis is a relatively young method for carbon-carbon bond formation, the discovery of second generation catalysts in 1990 consisting of well-defined metal-carbene complexes, mostly based on molybdenum or ruthenium has brought about a huge development of many applications in synthetic organic chemistry (Figure 1).[15] Key-advantages of the latter catalysts are their tolerance to a variety of different substituents in the substrate[16] and their stability to air and moisture.



** Strictly speaking, these metal complexes are precatalysts differing significantly from the active species involved in the catalytic cycle. However, as commonly agreed, we will use the term "catalyst"*

Figure 1. Some representative Mo- and Ru-based olefin catalysts*

Besides the industrial application in ring opening metathesis polymerization (ROMP) and acyclic diene metathesis polymerization (ADMET), olefin metathesis is used for the preparation of low molecular weight organic compounds by cross metathesis (CM) or by ring closing metathesis (RCM). The latter variation is one of the most frequently used methods of C-C-bond formation in synthesis of carbocyclic and heterocyclic compounds bearing numerous endocyclic functions.[16b-d,17] Also, cyclic amino acids[18], peptides and peptidomimetics,[19] polycyclic alkaloids[20] as well as carbohydrates[21] have been synthesized. Particularly medium sized and macrocyclic compounds[22] and other thermodynamically less favored ring systems and those bearing special substituent patterns including tetrasubstituted alkenes[23] can be more easily prepared by RCM than by classical methods, making this type of reaction one of the most frequently applied methods for elegant syntheses of carbo- and heterocyclic natural products.[24]

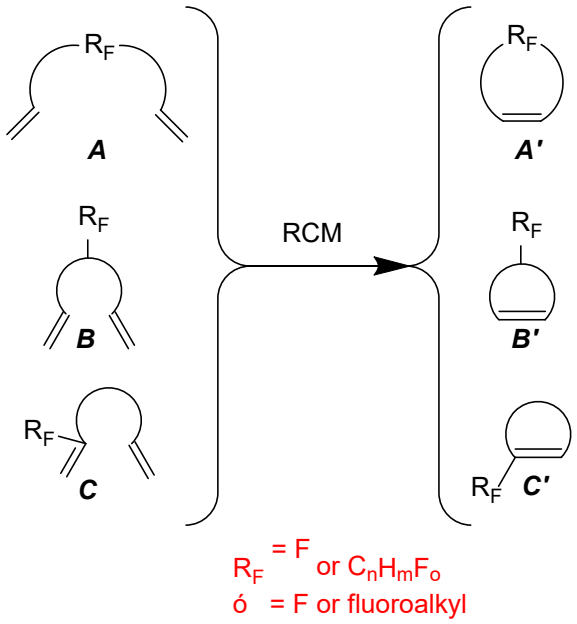
Although many excellent books and reviews have been written in the last 20 years on both fields, organofluorine chemistry[1] and olefin metathesis reactions, they have never before been comprehensively compiled as it is to be in this review. Moreover, some classes of compounds described in this review (*e.g.* cyclic amino acids) have recently also been reviewed from both points of view (cyclic amino acids by RCM and fluorinated cyclic amino acids) but never linking both aspects (fluorinated amino acids by RCM).[25] In addition to metathesis reactions on fluorine containing organic substrates, including polymerization processes and fluorous technologies, we have also reviewed the use of fluorine containing catalysts and fluorinated solvents in metathesis reactions. For these reasons, we believe that the present review may be of as much utility for researchers in the field of metathesis as well as for those in fluorine chemistry. Among the various topics covered in the present manuscript, only ROMP on fluorinated substrates has previously been reviewed in 1999.[26] The lack of reviewing coverage of the topic forces us to review the whole timeframe since Schrock's seminal report in 1990[15a] until 2013, except for ROMP reviewed from 1999 on.

2. RING-CLOSING METATHESIS (RCM) WITH FLUORINATED DERIVATIVES

Arguably, among the several existing categories within metathesis reactions those that proceed intramolecularly giving rise to cyclic molecules, the so-called ring closing metathesis RCM (only a few examples of ring closing enyne metathesis RCEYM on fluorinated substrates have been found and will be discussed within this sections) has been the most frequently used in synthetic organic chemistry.[27] This fact is probably due to two factors: 1) cyclic molecules of many kinds are of central importance in every branch of organic chemistry and related scientific areas (natural products, medicinal chemistry, crop science, material science, etc.); 2) the intramolecular nature of the process benefits from entropic factors and avoids some of the drawbacks encountered in

the intermolecular reaction (cross metathesis CM, see section 3), such as, the use of one of the olefins in excess amounts, homocoupling products, etc.

Three general fluorinated structural motifs which may participate in an RCM can be designed, namely: a diene (or enyne) bearing either a fluorinated tether which will from a part of the cycle upon ring formation (Figure 2, ***A*** to ***A'***), a non-fluorinated tether bearing a fluorinated appendage which will constitute a substituent of the final cyclic structure (Figure 2, ***B*** to ***B'***) or a diene containing a fluorine atom or a fluorinated residue directly attached to one of the double bonds participating in the metathesis (Figure 2, ***C*** to ***C'***).



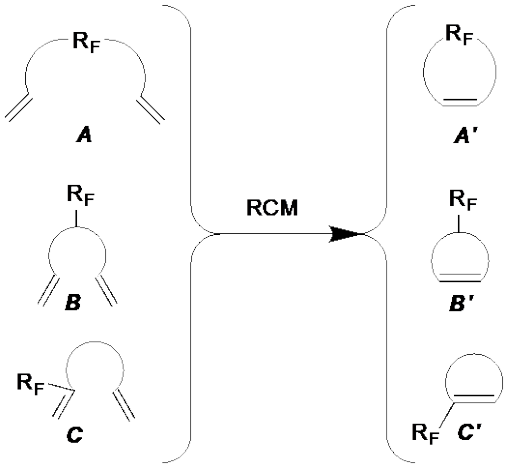


Figure 2. General fluorinated structures arising from RCM

The following three subsections cover examples of the three kinds of substrates.

2.1. Ring-Closing Metathesis giving rise products containing an endocyclic fluorinated moiety

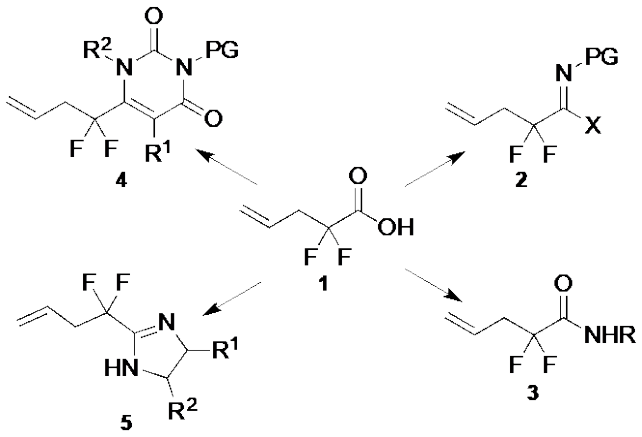
In this section RCM based strategies for the synthesis of important classes of compounds, such as cyclic α- and β-amino acids, lactams, uracils or glycosides, among others, bearing an endocyclic fluorinated domain are described. For all of them, the design and synthesis of a suitable fluorinated building block is crucial. Hence, the section is divided into subsections focusing on the specific key fluorinated building block used.

2.1.1 Building blocks derived from 2,2-difluoro-4-pentenoic acid

In 2001, Fustero and co-workers started a series of reports[28, 29, 30, 31] in which the identification of 2,2-difluoro-4-pentenoic acid[32] (**1**) as a versatile fluorinated building block is of key importance (Scheme 1). Compound **1** is readily available from inexpensive chlorodifluoroacetic acid through a Reformatskii-Claisen rearrangement[33] and can easily be transformed into a

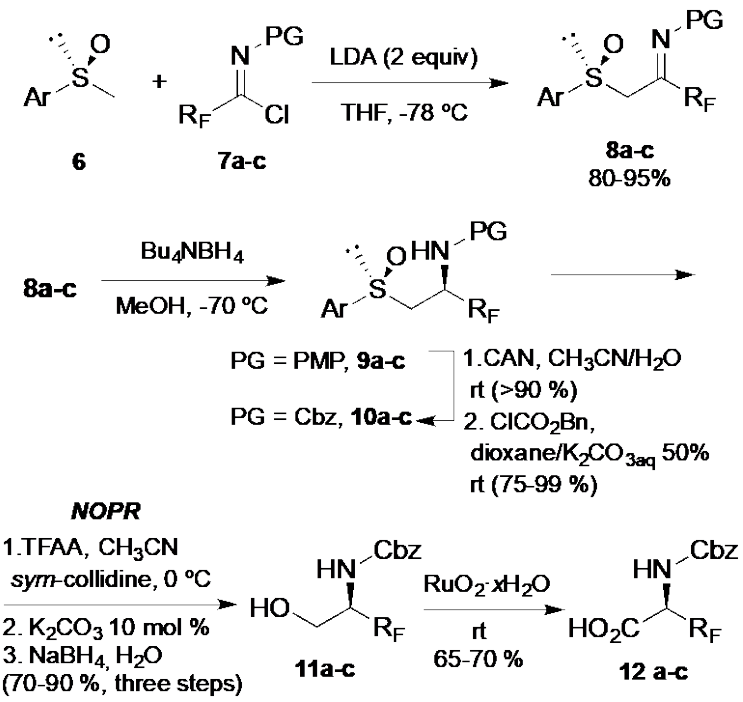
number of nitrogen containing building blocks, mainly imidoyl halides[28] but also amides,[29] uracils[30] and imidazolines,[31] precursors of *N*-heterocycles by RCM (Scheme 1).

Scheme 1. Nitrogen Containing Fluorinated Building Blocks from 2,2-Difluoro-4-pentenoic Acid



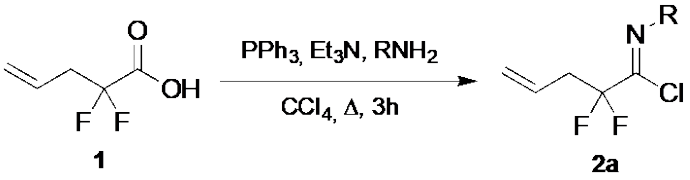
In the first of this series of reports,[28a] the asymmetric synthesis of fluorinated α-amino acids **12** was described (Scheme 2). To this end, the diastereoselective reduction of optically pure fluorinated β-sulfinylimines **8** was used for installing the stereochemistry of the future α-carbon in the targeted amino acid (Scheme 2). The required sulfinylimines **8** were, in turn, synthesized from the corresponding enantiomerically pure arylmethylsulfones **6** and a suitable fluorinated imidoyl chloride **7** (Scheme 2).[32] From the thus obtained fluorinated β-sulfinylamines **9**, after some protecting groups exchange, the synthesis was completed by a "nonoxidative" Pummerer reaction protocol (NOPR)[34] affording the corresponding alalinol **11**, which was in turn oxidized towards the final amino acid **12** by treatment with $RuO_2 \cdot xH_2O/NaIO_4$ (Scheme 2).

Scheme 2. Asymmetric Synthesis of Fluorinated α-Amino Acids 12 using a Chiral Sulfoxide as Auxiliary



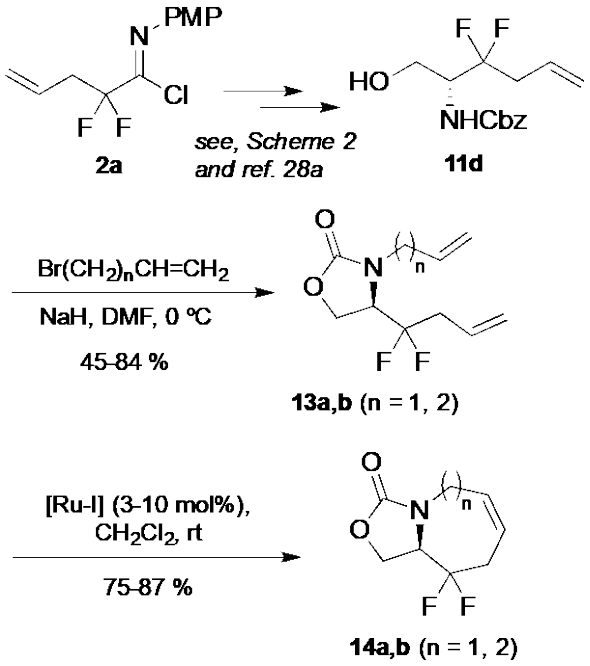
In this context, fluorinated imidoyl chloride **2a** was described for the first time using the methodology developed by Apple[35] using Uneyama's conditions (Scheme 3).[36]

Scheme 3. Synthesis of Fluorinated Imidoyl Chlorides 2



Hence, when substrate **2a** was subjected to the reaction sequence depicted in Scheme 2 followed by imidazolidinone formation and *N*-(homo)allylation, suitable substrates for the RCM **13a,b** were obtained (Scheme 4).[28a] Treatment of **13a,b** with Grubbs first generation catalyst in DCM at room temperature afforded the first RCM process on a substrate of type-***I*** (Figure 2) giving rise to β-amino alcohol derivatives **14a,b** bearing a *gem*-difluoromethylene unit in the cyclic backbone (Scheme 4).

Scheme 4. Synthesis of 7- and 8-Membered Fluorinated Cyclic β-Amino Alcohol Derivatives

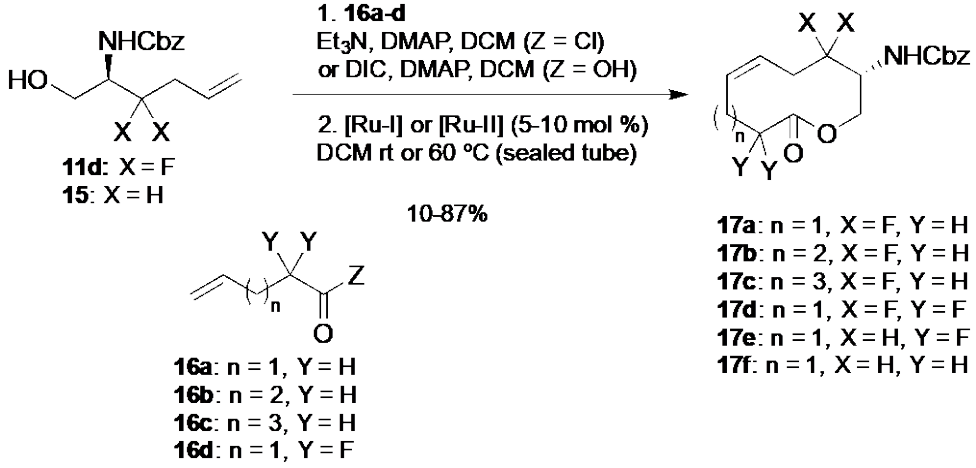


It should be mentioned that the homologated substrate **13c** (n = 3) failed to cyclize to the corresponding 9-membered analog **14c**, giving rise instead to dimerization and oligomerization products. The reluctance of 9-membered rings to be formed under RCM conditions was also documented for non-fluorinated substrates.[29,37]

Compound **11d** was also used in the synthesis of fluorinated amino macrolactones **17a-d** (Scheme 5).[28d] To this end, esterification with a suitable ω-alkenyl carboxylic acid derivative was carried out followed by RCM using either 1st or 2nd generation Grubbs catalyst (Scheme 5). Of the three ring size formations tested, the ten-membered ring formation (n = 1) was by far the most efficient, followed by twelve (n = 3) and eleven (n = 2), which was the most challenging. In this case, mixtures of 11- and 10-membered lactones (the latter arising from a double-bond isomerization/RCM process) were obtained, in favor of the former. In addition, 10-membered

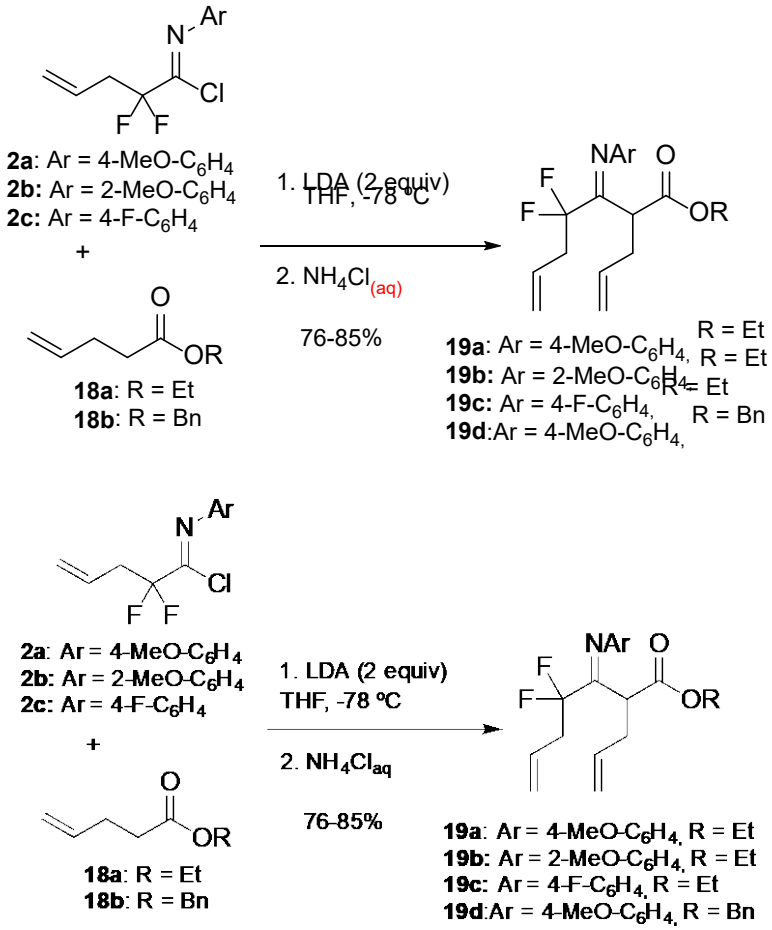
lactones were formed exclusively as *Z*-isomers. In order to investigate the influence of both the presence and the position of the CF_2 moiety in the RCM step, a parent difluorinated 1,11-dodecadiene bearing the difluoromethylene in a different position **17e** and a non-fluorinated one **17f** were synthesized and subjected to RCM reaction conditions (Scheme 5). The low chemical yield obtained in both cases (18% and 12%, respectively) suggested a beneficial effect of the C7-difluoromethylene grouping; the authors attributed this experimental observation to the diminished Lewis basicity of the amino group, owing to the –I effect of the CF_2 unit, as it is well-known that potentially chelating groups hamper metathesis reactions.

Scheme 5. Synthesis of Fluorinated Amino Macrolactones 17



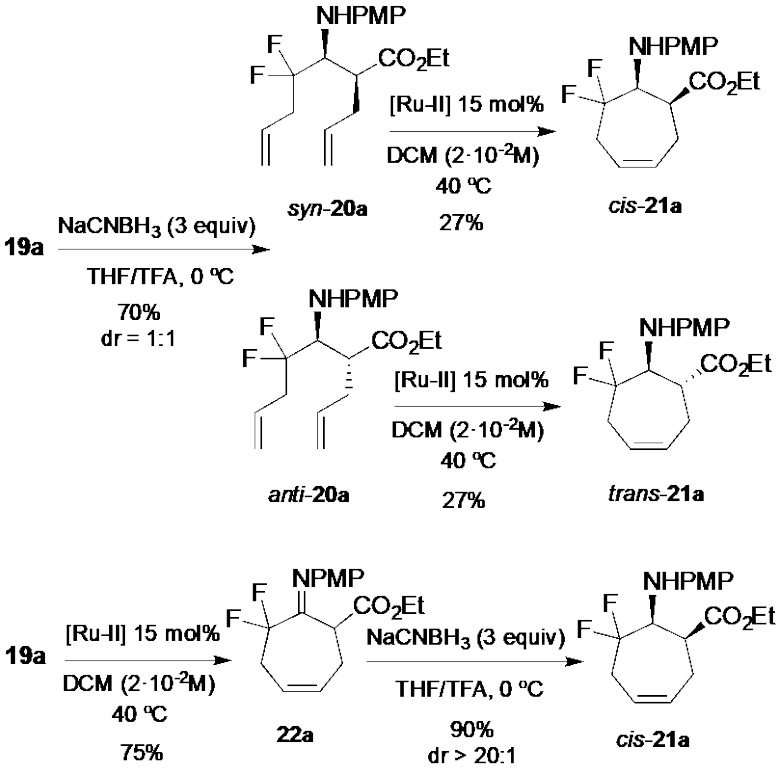
A second application of fluorinated imidoyl halides **2** can be found in the diastereoselective synthesis of fluorinated cyclic β-amino acid derivatives, which were unknown until then.[28b] Treatment of the lithium enolate of esters of 4-pentenoic acid **18a,b** with imidoyl chlorides **2a-c** afforded fluorinated β-imino esters **19a-d** in good yields (Scheme 6).

Scheme 6. Addition of Ester Lithium Enolates of 4-Pentenoic Acid to Imidoyl Chlorides



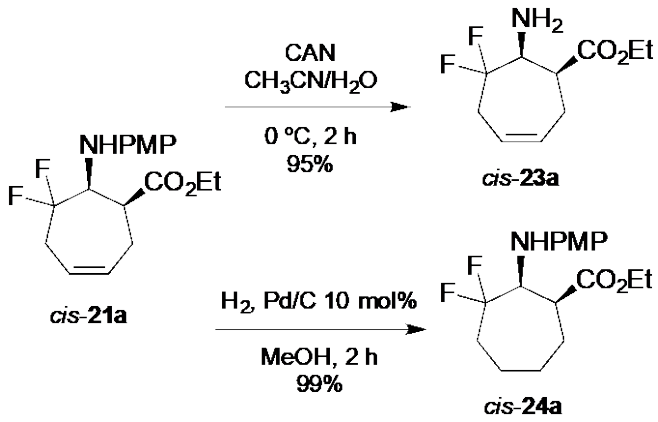
These substrates already bear the two olefinic appendages required for the RCM. However, the next two steps, imine reduction–RCM, may be carried out either in this order or in the reversed one, RCM–imine reduction. The results obtained for each route are summarized in Scheme 7.

Scheme 7. Imine Reduction–RCM *vs* RCM–Imine Metathesis Strategies



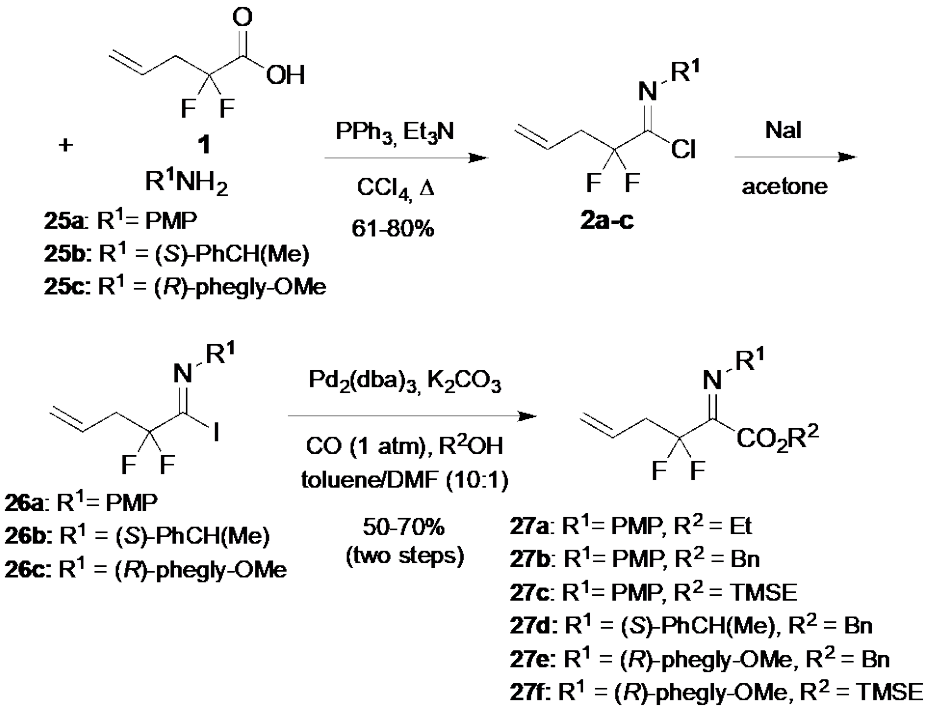
From the above results, it can be concluded that carrying out the RCM prior to the imine reduction leads to much better results both in terms of overall yield and diastereoselectivity. The lower yields obtained in the RCM of reduced compounds *syn*- and *anti*-**20a** may be explained by the deactivation of the catalysts, caused by the higher basicity of the amine nitrogen atom when compared to the imine one.[38] On the other hand, the higher diastereoselectivity reached with the cyclized substrate **22a** is not surprising in view of its higher rigidity compared to the linear one **19a**. Finally, some simple transformations were carried out on substrate *cis*-**21a**, namely the deprotection of the amino group and the hydrogenation of the double bond (Scheme 8).

Scheme 8. Synthetic Transformations on Substrate *cis*-21a



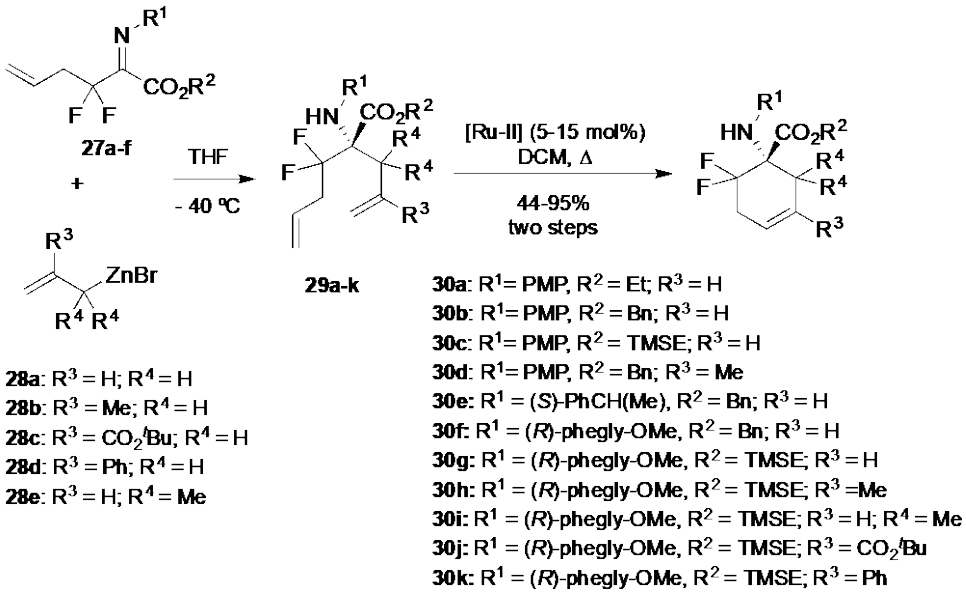
Besides the diastereoselective synthesis of fluorinated cyclic β-amino acid derivatives, the same group also reported the asymmetric synthesis of the corresponding α-derivatives.[28c] In this case, fluorinated imidoyl halides **2** were used as substrates for the synthesis of the corresponding imino esters **27** by palladium-catalyzed alkoxycarbonylation (Scheme 9).[39] For this purpose, imidoyl chlorides **2a-c** must be transformed into the corresponding imidoyl iodides **26** under Filkenstein conditions (Scheme 9). An interesting feature was the use, for the first time in this context, of chiral amines such as (*S*)-1-phenylethylamine **25b** or (*R*)-phenylgycinol methyl ether **25c** during the imidoyl chloride formation, which in turn were used as chirality inductors.

Scheme 9. Synthesis of Fluorinated Iminoesters 27



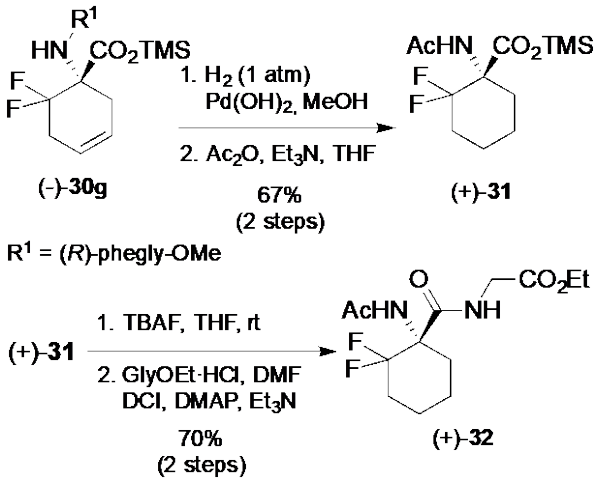
The chemoselective addition of organometallic reagents to the iminic carbon of fluorinated iminoesters has been reported by several authors.[39,40] For substrates **27a-f**, allylzinc derivatives showed the best reactivity both in terms of chemical yield, chemoselectivity and, for chiral substrates **27e,f** derived from the methyl ether of (*R*)-phenylglycinol, also diastereoselectivity (Scheme 10).[41] The addition products **29a-k** were then treated with 2nd generation Grubbs catalyst affording cyclic α-amino esters **30a-k** in good overall yield (Scheme 10).

Scheme 10. Allylzinc Addition–RCM Sequence on Derivatives 27



Finally, in order to show the applicability of this methodology for the incorporation of cyclic fluorinated amino acids into peptide chains by orthogonal removal of the *N*- and *C*-termini, the following reaction sequence was carried out on enantioenriched substrate (-)-**30g** (Scheme 11).[28c]

Scheme 11. Synthesis of Dipeptide (+)-32

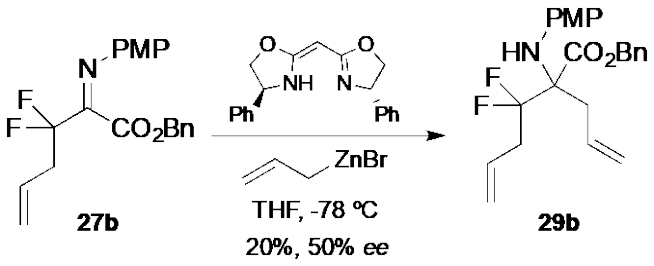


Thus, concomitant hydrogenation of the chiral auxiliary and the cyclohexene double bond followed by acetylation of the free amine afforded (+)-**31**. X-ray analysis of suitable crystals of

this intermediate allowed to assign the stereochemistry of the newly created quaternary stereocenter as *S*. The choice of TMSE as protecting group for the acid allowed its deprotection under very mild conditions (TBAF, THF, rt); coupling of the thus obtained free carboxylic acid with the ethyl ester of glycine showcases the orthogonal protection of derivative (-)-**30g** and its applicability in peptide synthesis.

The enantioselective allylation of imino ester **27b** in the presence of equimolecular amounts of a bis-oxazoline ligand was also attempted.[42] Hence, under the conditions depicted in Scheme 12 the addition product was obtained although in low yield and moderate enantioselectivity (Scheme 12).[28c]

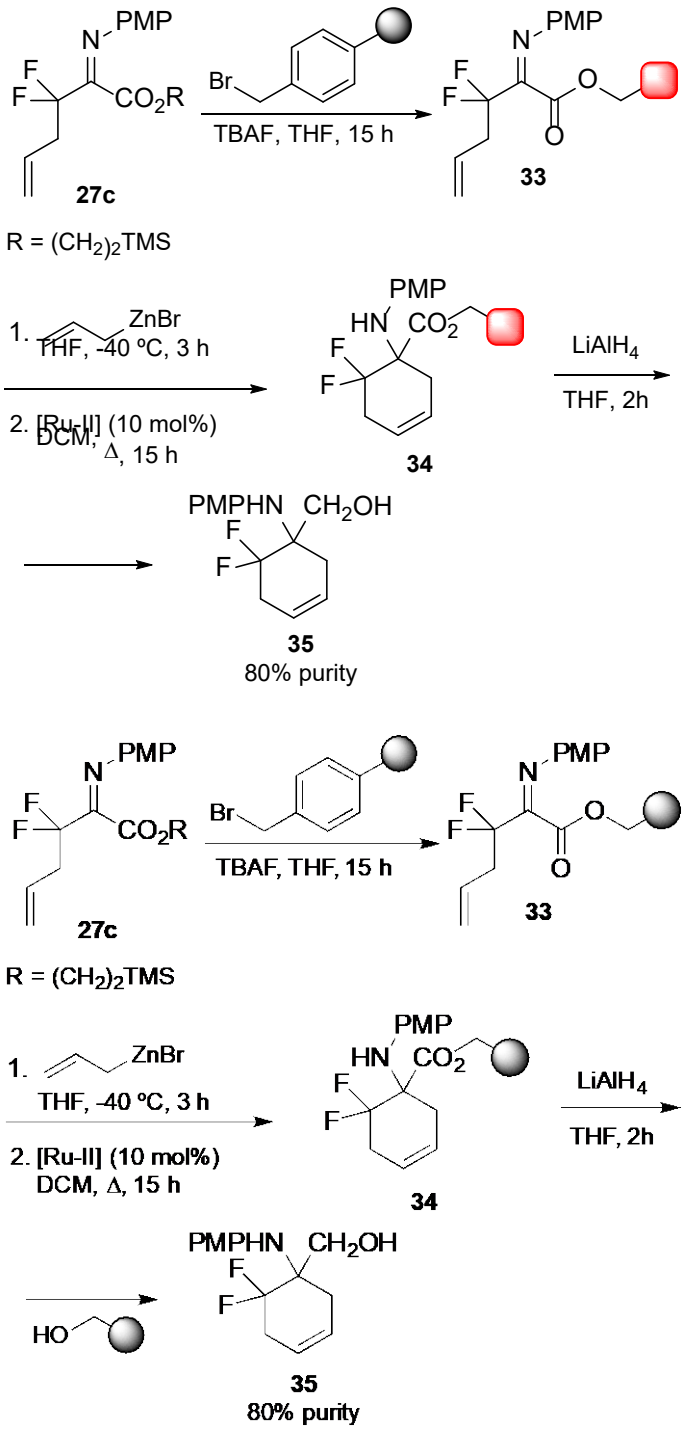
Scheme 12. Enantioselective Allylation Attempt



In addition, Fustero and co-workers have successfully adapted the solution synthesis of these cyclic fluorinated α-amino acids to *solid-phase* and *fluorous-phase* techniques.[28e] Solid-phase technologies facilitate the preparation of libraries of compounds by reducing the separation to a simple filtration and wash. However, these methodologies have scarcely been used for the synthesis of fluorinated compounds.[43] The solid phase variant started loading fluorinated α-imino ester **27c**, bearing a trimethylsilylethyl group, to a modified Wang's resin by TBAF- mediated transesterification (Scheme 13). Resin-bound substrate **33** was obtained in pure form after washing with DCM and MeOH and subjected in turn to the previously reported allylation–RCM

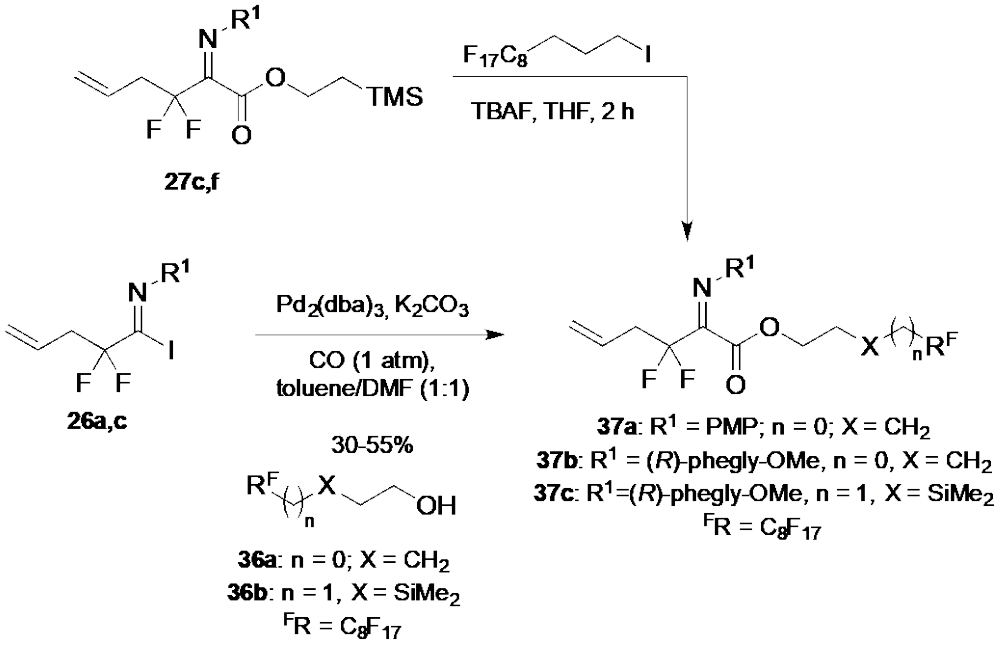
reaction sequence affording the corresponding fluorinated cyclic α-amino ester **34**. Pure cyclic amino alcohol **35** was obtained upon reductive cleavage from the resin (Scheme 13).

Scheme 13. Solid-Phase Synthesis of α-Amino Alcohol 35



Finally, as an extension of their previous work[44] the same authors extended the reaction sequence to fluorous synthesis techniques.[45] This relatively new type of synthesis combines the purification advantages of solid-phase separations (through fluorous solid-phase extraction techniques F-SPE[46]) with solution phase reactions (better kinetics, lower excess of reagents needed, simplicity of analysis of the reaction mixture by TLC, NMR, etc.). In a first approach, a commercially available fluorous tag $C_8F_{17}(CH_2)_3$ was introduced either by palladium-catalyzed alkoxycarbonylation of imidoyl iodide **26a** or by TBAF-mediated alkylation from the corresponding trimethylsilylethanol derivatives **27c,f** (Scheme 14).

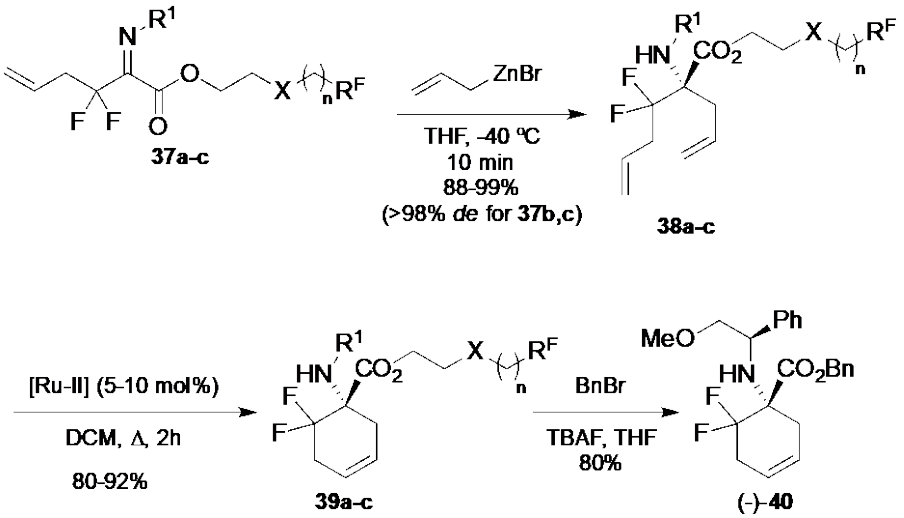
Scheme 14. Synthesis of Fluorinated Iminoesters 37a-c



The reaction sequence worked uneventfully on the fluorous substrates affording derivatives **39a-c** in excellent yields and complete diastereocontrol when the (*R*)-phenylglycinol methyl ether derivative was used (Scheme 15). It is worth noting that every fluorous synthetic intermediate was purified through F-SPE, eliminating any excess of non-fluorinated reagents, thus making the

purification steps faster and simpler. However, the detagging step proved ineffective for substrates **39a,b** under a variety of hydrolysis and transesterification reaction conditions. To overcome this limitation, the reaction sequence was repeated using as fluorous tag the fluorous analog of trimethylsilylethanol,[47] previously developed by the same authors.[44a] Hence, fluorous intermediates **38c**and **39c** were obtained in comparable yields and diastereoselectivities. Final detagging of derivative **39c** was achieved by TBAF-mediated alkylation of the corresponding carboxylate with benzyl bromide in good yield (Scheme 15). From this comparative study the authors concluded that fluorous chemistry is the most convenient methodology for the synthesis of cyclic α-amino acid derivatives by diastereoselective allylation of fluorinated imino ester derivatives followed by RCM, followed by standard solution chemistry and solid-phase synthesis being the least suitable one.

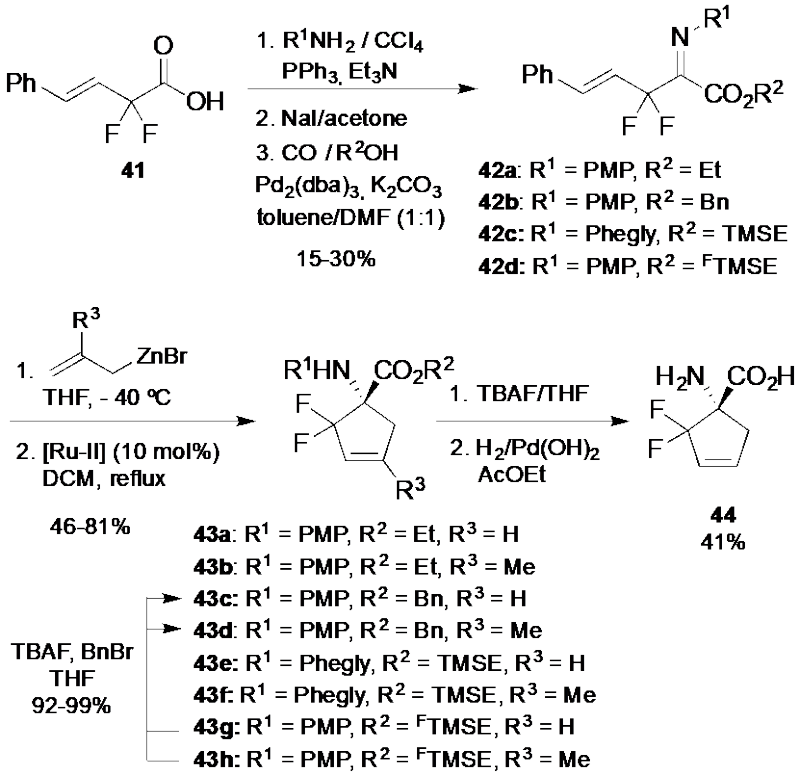
Scheme 15. Fluorous Synthesis of Fluorinated Cyclic Amino Acid Derivatives



An analogous reaction sequence was then applied to the synthesis of the corresponding 5-membered fluorinated cyclic amino acids, starting from **41**.[48] Hence, palladium catalyzed alkoxycarbonylation of the corresponding imidoylchlorides followed by diastereoselective

(meta)allylzinc bromide addition and final RCM afforded target fluorinated 5-membered cyclic amino acid derivatives **43a-f** (Scheme 16). It should be mentioned that the (meta)allylation step on chiral derivative **42c** proceeds with complete diastereoselectivity. Finally, the complete deprotection of the free amino acid was achieved on **43e** by fluoride-mediated deprotection of the trimethylsilylethanol ester and subsequent hydrogenolysis of the phenylglycinol chiral auxiliary (which takes place with concomitant hydrogenation of the double bond) affording 1-amino-2,2-difluoro-cyclopentane carboxylic acid **44** (Scheme 16). The reaction sequence was then adapted to fluorous chemistry techniques as well as for the six-membered analogs (*vide supra*). Both syntheses led to similar results in terms of number of steps and chemical yields. The main advantage of the fluorous variant being the much easier purification of all the intermediates along the synthesis and the high purity of the thus obtained products.

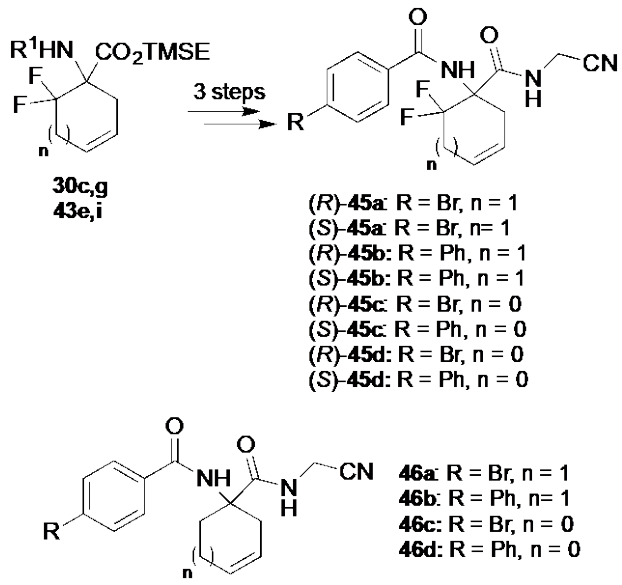
Scheme 16. Synthesis of Fluorinated 5-Membered Cyclic Amino Acid Derivatives



The previous syntheses of fluorinated 5- and 6-membered cyclic amino acids described in schemes 9-16 were applied to the synthesis of dipeptide nitriles **45a-d** (Table 1), a class of peptidomimetics,[19a] having shown activity as cathepsin (Cat) inhibitors.[49] The corresponding non-fluorinated reference compounds **46** were also synthesized in order to evaluate the fluorophilic properties of the S^2 pocket of Cat B. Cysteine cathepsins are involved in several pathophysiological processes and are regarded as promising therapeutic targets in fields such as cancer or osteoporosis.[50] The inhibitory activities of the best four fluorinated dipeptide nitriles synthesized, (*R*)-and (*S*)-**45a,b**, are summarized in Table 1.[49d] The first two entries show the activities of the corresponding non-fluorinated derivatives **46a,b** for comparative purposes. From this table, the authors concluded that: (1) the fluorinated compounds show a higher selectivity for Cat K and B, being much less active towards Cat S and L, compared to their non-fluorinated analogs; (2) the *R* eutomers are *circa* one order of magnitude more active than the *S* distomers

against both Cat K and B; (3) fluorinated *R* eutomers are more potent against Cat B than the corresponding non-fluorinated achiral derivatives. These data together with docking and NMR studies allowed demonstrating the fluorophilic nature of the lipophilic S^2 pocket of Cat B.[49d]

Table 1. Cathepsin Inhibition

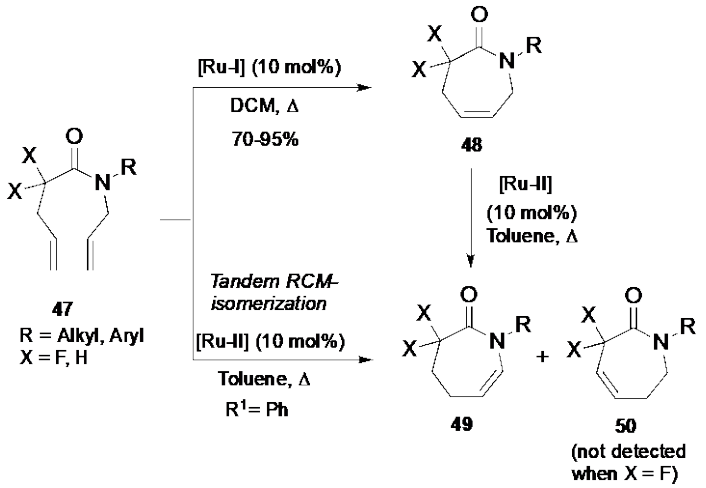


	K_i [μM]			
Compound	*Cat K*	*Cat B*	*Cat S*	*Cat L*
46a	0.010±0.001	1.3±0.1	4.6±0.1	21±4
46b	0.0037±0.0004	0.93±0.02	7.0±0.3	>28
(-)-(*S*)-**45a**	0.36±0.01	7.2±0.2	>85	>28
(+)-(*R*)-**45a**	0.036±0.001	0.25±0.01	>85	16±1
(-)-(*S*)-**45b**	0.01±0.01	3.8±0.2	>85	>28
(+)-(*R*)-**45b**	0.034±0.001	0.29±0.02	>85	>28

A tandem RCM–isomerization reaction that allows preparation of fluorinated and non-fluorinated, unsaturated lactam derivatives of various ring sizes was reported in 2006 (Scheme 17).[29] In this case, the RCM-isomerization sequence did not require the use of any additives to generate ruthenium hydride species, which are believed to be responsible for the regioselective isomerization reaction. Starting from fluorinated acyclic diene **47**, the formation of ε-lactams **48**

(X = F) was carried out in the presence of [Ru-I] in refluxing dichloromethane. By contrast, in refluxing toluene the corresponding seven-membered enamide **49** (X = F) was exclusively formed by *tandem RCM-isomerization* sequence catalyzed by [Ru-II]. This overall process could also be carried out in two steps, since heating lactam **48** in toluene with [Ru-II] results in a smooth isomerization reaction affording lactam **49** in excellent yield. When this protocol was applied to the corresponding non-fluorinated diene **47** and lactam **48** (X = H), the formation of expected lactam **49** (X = H) along with the isomeric lactam **50** was observed in a 2:1 ratio[29] (Scheme 17). It should be noted that the isomerized lactam **50** was never detected in the reaction mixture when X = F (Scheme 17).

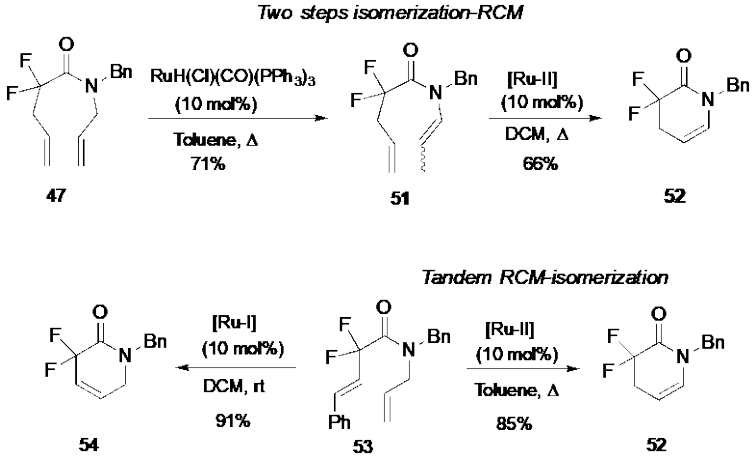
Scheme 17. Tandem RCM–Olefin Isomerization: Regioselective Preparation of Unsaturated Lactams



This study was extended to the preparation and isomerization of lactams with different ring sizes.[29] Thus, the preparation of the six-membered difluorinated analogue **52** was carried out using a different strategy. Treatment of amide **47** with the ruthenium hydride catalyst [$RuHCl(CO)(PPh_3)_3$] regioselectively afforded, the enamidic isomer **51**, which was then cyclized

under standard RCM conditions to yield exclusively the desired δ-lactam **52** (Scheme 18). Another alternative strategy using amide **53** as starting material was carried out. In this case, a tandem RCM-isomerization took place by treatment with [Ru-II] catalyst in the same conditions as before providing **52**. Additionally, the isomeric lactam **54** was also synthesized by using [Ru-I] catalyst in DCM at room temperature (Scheme 18). In contrast with the formation of the six- and seven-membered rings the preparation of the eight- and nine-membered fluorinated lactams was less efficient due to the formation of complex mixtures of lactams.

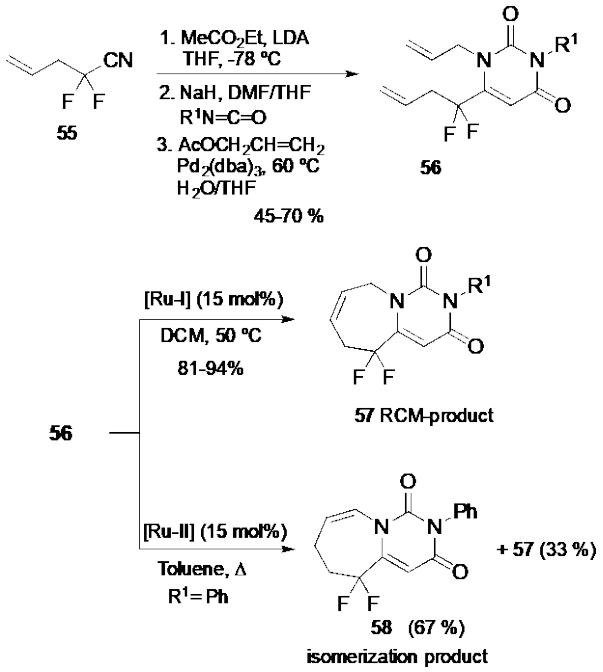
Scheme 18. Preparation of Fluorinated Six-Membered Lactams



Another interesting application of this methodology was the synthesis of two new families of fused bicyclic fluorinated uracils with potential activity as acaricides.[30] For this purpose, α,α-difluoro-4-pentenoic nitrile **55** was used as the starting material. Fustero and co-workers obtained different uracils all containing an allyl CF_2 group as a substituent at C-6. Nitrogen alkylation with allyl acetate under Pd(0) catalysis, followed by treatment of the obtained uracil **56** with catalytic amounts of [Ru-I] catalyst in refluxing dichloromethane afforded a new category of bicyclic fluorinated uracils **57** in good yields and as single isomers. By contrast, the use of [Ru-II] catalyst

in refluxing toluene led to the partial isomerization of the double bond resulting in a mixture of uracils **57** and **58** (33:67 ratio) (Scheme 19).

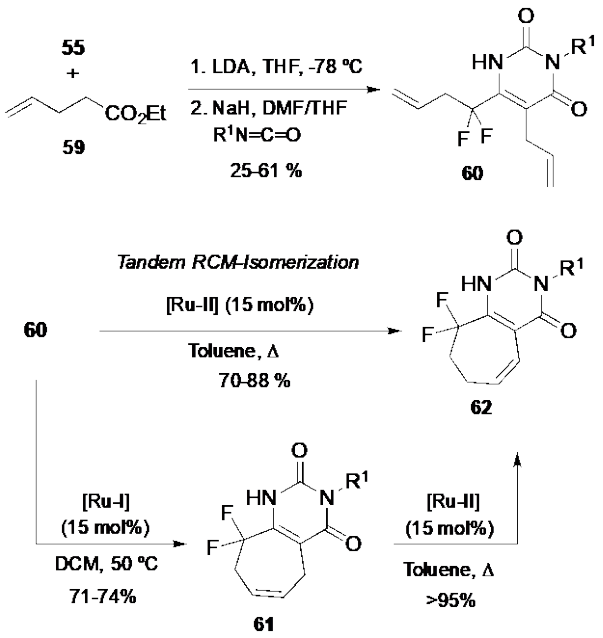
Scheme 19. Synthesis of Fluorinated Uracil Derivatives



In the same fashion, the reaction of enolates of pentenoic esters **59** with **55** provided β-enamino esters, which were then reacted with isocyanates affording C-5, C-6 disubstituted uracils. These latter compounds were finally transformed into new bicyclic fluorinated uracils by treatment with the first or second generation Grubbs catalyst under the same conditions as described before. Thus, the use of [Ru-I] catalyst in refluxing DCM yielded only the isomer **61**, whereas heating either **60** or **61** in the presence of [Ru-II] catalyst in toluene (120 °C in a sealed flask) led to the isomerization of the double bond giving **62** as a single product **(**Scheme 20). It should be noted that the other possible isomers (coming from the migration of the double bond toward the fluorine atoms in **57** and **61**) were not detected, apparently due to a stereoelectronic effect of the contiguous difluoromethylene moiety.[30] In summary, two new families of fused

bicyclic fluorinated uracils using either a RCM or a tandem RCM-isomerization processes were synthesized.

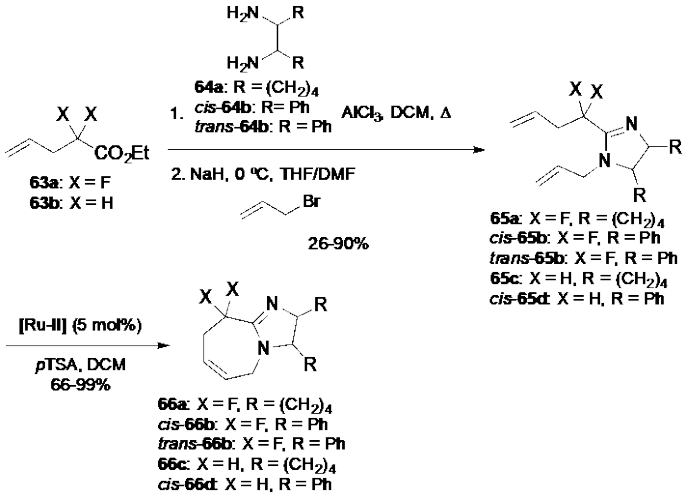
Scheme 20. Tandem RCM–Isomerization in Bicyclic Uracils



The last application in this subsection, dealing with 2,2-difluoro-4-pentenoic acid (**1**) derivatives, describes the synthesis of fluorinated and non-fluorinated bicyclic amidines **66** by RCM.[51] The amidine moiety may be regarded as an arginine mimic in drug design.[52] Besides, it can be found in several natural product scaffolds[53] as well as in compounds with tumor suppressor properties[54] and ligands in coordination chemistry.[55] In this report, the influence of a *gem*-difluoro moiety in this type of heterocycles was studied. The reaction sequence started with imidazoline formation by $AlCl_3$ mediated condensation of the corresponding alkenyl esters **63a,b** with suitable 1,2-diamines **64a-b** (Scheme 21). Subsequent *N*-alkylation of the crude imidazoline with allylbromide afforded the required substrates **65a-d** for the key RCM step. A careful optimization allowed identifying suitable reaction conditions –[Ru-II] (5 mol %), *p*TSA, DCM–

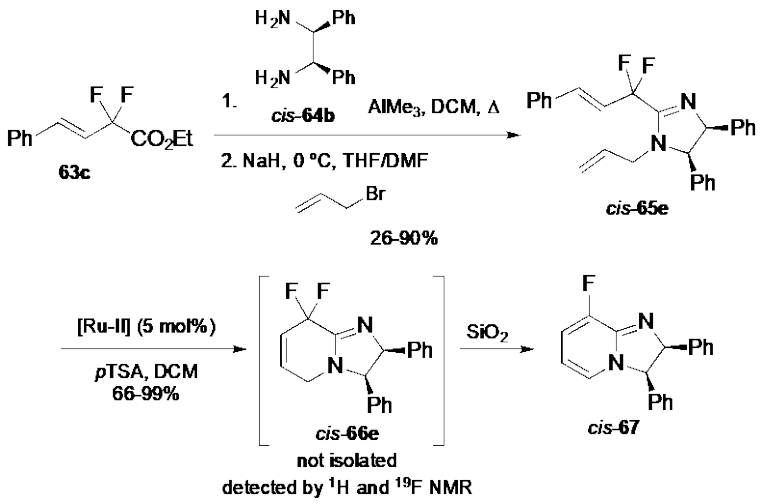
for the synthesis of the targeted compounds **66a-d** (Scheme 21). The use of a Brønsted or a Lewis acid in metathesis processes involving substrates with a basic nitrogen atom is a well-established strategy.[56]

Scheme 21. Synthesis of Seven-Membered Bicyclic Amidines



An analogous synthetic pathway starting from difluorobutenoic acid derived ester **63c** achieved six-membered bicyclic structure precursor *cis*-**65e** (Scheme 22). Upon cyclization under the optimized conditions, formation of the desired bicyclic amidine *cis*-**66e** was observed in the crude reaction mixture as the major product. However, the major isolated species was dihydroimidazopyridine derivative *cis*-**67** arising from HF elimination during the purification step resulting in the greater limitation of the reported methodology.

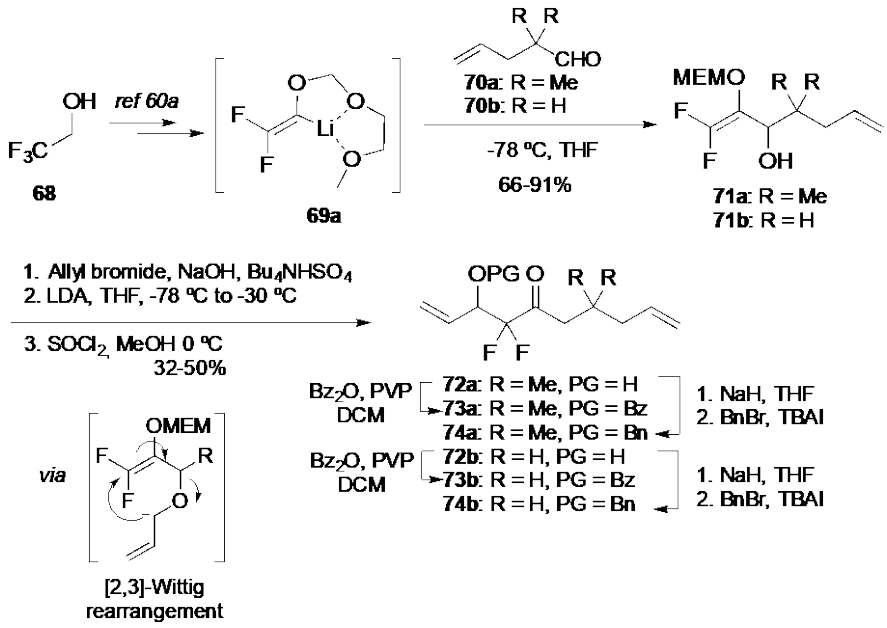
Scheme 22. Extension Attempt to Six-Membered Analogs



2.1.2. Building blocks derived from trifluoroethanol

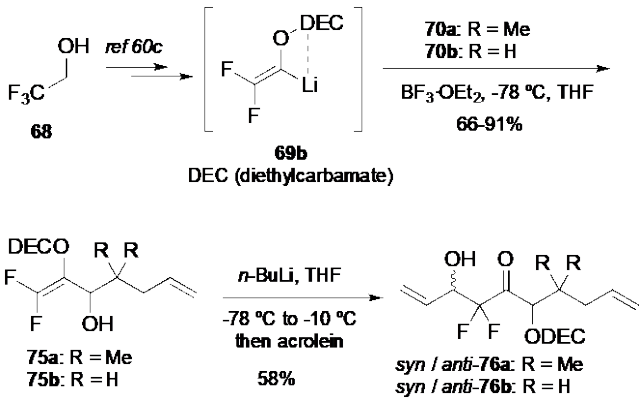
Approximately at the same time as the studies using 2,2-difluoropent-4-enoic acid described in section 2.1.1 were carried out, Percy and co-workers performed a thorough investigation concerning the synthesis of *gem*-difluoro eight-membered cyclooctenones and carbohydrate analogs using trifluoroethanol **68** as the common starting material.[57, 58, 59] Actually, these reports belong to a more general study on the use of trifluoroethanol as starting material for the preparation of fluorinated building blocks in the synthesis of complex molecules containing the *gem*-difluoro moiety.[60] In this context, the authors used their own previously reported methodologies[60b,c] to achieve fluorinated 1,9-enyne precursors of eight-membered carbocycles by RCM (Scheme 23).[57] Hence, on the first route described towards cyclooctenone derivatives, key intermediate **69a** was trapped with the commercial aldehydes **70a,b** affording difluoroallylic alcohols **71a,b** in 66-91% yield. Elongation of the carbon chain to the required 1,9-decadienes **72a,b** was performed in three steps, namely, *O*-allylation under transfer phase conditions, LDA mediated [2,3]-Wittig rearrangement[60b] and MEM protecting group cleavage[60d] (Scheme 23).

Scheme 23. First Generation Synthetic Route towards Fluorinated Cylooctenone Derivatives



A second approach based upon metallated difluoroenolcarbamate **69b**,[60c] allowed the elongation of the corresponding difluoroallylic alcohols **75a,b** by means of an aldol reaction with acrolein in moderate yield and as an equimolecular mixture of diastereoisomers, separable in the case of **75a** (Scheme 24). The reactive lithium difluoroenolate was formed by intramolecular transacylation of the allylic alkoxide resulting from direct deprotonation of intermediates **75a,b**.

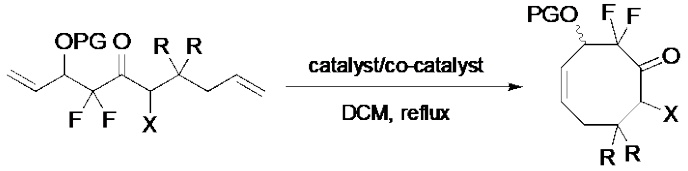
Scheme 24. Second-Generation Synthetic Route towards Fluorinated Cylooctenone Derivatives



Finally, cyclization of dienes **72-74a,b** and **76a,b** were achieved using Fürstner's variation of the original Grubbs conditions (consisting of the addition of $Ti(OEt)_4$ as co-catalyst)[61] and either 1st or 2nd generation Grubbs catalyst in refluxing DCM (Table 2). The preferred conformations and fluxional behavior of the obtained cyclooctenone derivatives are thoroughly discussed based upon NMR data, X-ray structures and theoretical calculations but these results will not be disclosed here. Taking the results described in the three reports summarized in Schemes 23-24 as a whole, a number of conclusions may be drawn with regard to the influence of the co-catalyst, concentration and substitution pattern in the ring closing reaction outcome (Table 2).[57] The use of a Lewis acid co-catalyst, *e.g.* $Ti(OEt)_4$, was mandatory in combination with first generation Grubbs catalyst (Table 2, entries 1,2 and 3,4), while with the second generation catalyst the reaction proceeded in good yield even in the absence of a co-catalyst. However, the reaction was notably accelerated by the use of a substoichiometric amount of $Ti(OEt)_4$ (Table 2, entries 5,6). According to Fürstner, the role of the Lewis acid would be to destabilize any possible intramolecular interaction between the carbonyl group and the ruthenium resulting in an unproductive intermediate.[61] This hypothesis is in agreement with the lower effect of the co-catalyst in combination with the less Lewis acidic second generation Grubbs catalyst. On the other hand, a four-fold slower reaction was observed when derivative **76b** (lacking the *gem*-

dimethyl subunit) was used instead of **76a**, suggesting a modest Thorpe-Ingold effect (Table 2, entries 6, 7).[62] Competition experiments using **74a** and **74b** showed significant differences in their kinetic profiles accounting for an approximate rate difference of less than an order of magnitude, in the typical range for a *gem*-dialkyl effect. This result is in sharp contrast with the dramatic acceleration effect upon introduction of a single methyl substituent reported by Murphy,[63] highlighting the importance of the conformational bias of the substrate in medium-sized ring forming reactions.

Table 2. Dependence of RCM Efficiency Related to their Structural Features



72a: X = H, R = Me, PG = H
73a: X = H, R = Me, PG = Bz
74a: X = H, R = Me, PG = Bn
72b: X = H, R = H, PG = H
73b: X = H, R = H, PG = Bz
74b: X = H, R = H, PG = Bn
syn/anti-**76a** X = ODEC, R = Me, PG = H
syn/anti-**76b**: X = ODEC, R = H, PG = H

77a: X = H, R = Me, PG = H
78a: X = H, R = Me, PG = Bz
79a: X = H, R = Me, PG = Bn
77b: X = H, R = H, PG = H
78b: X = H, R = H, PG = Bz
79b: X = H, R = H, PG = Bn
cis/trans-**80a**: X = ODEC, R = Me, PG = H
cis/trans-**80b**: X = ODEC, R = H, PG = H

Entry	Substrate	Catalyst	Co-catalyst	Time (h)	Yield (%)
1	**72a**	5 mol% [Ru-I]	-	24	0
2	**72a**	5 mol% [Ru-I]	$Ti(OEt)_4$	24	78
3	*anti*-**76a**	5 mol% [Ru-I]	-	144	0
4	*anti*-**76a**	5 mol% [Ru-I]	$Ti(OEt)_4$	144	77
5	*anti*-**76a**	2.5 mol% [Ru-I]	-	72	82
6	*anti*-**76a**	2.5 mol% [Ru-I]	$Ti(OEt)_4$	18	75
7	*syn*/*anti*-**76a**	2.5 mol% [Ru-I]	$Ti(OEt)_4$	72	63
8	**73a**	2.5 mol% [Ru-I]	$Ti(OEt)_4$	16	76
9	**74a**	2.5 mol% [Ru-I]	$Ti(OEt)_4$	16	60
10	**72b**	2.5 mol% [Ru-I]	$Ti(OEt)_4$	2	60
11	**73b**	2.5 mol% [Ru-I]	$Ti(OEt)_4$	n. s.[a]	46
12	**74b**	2.5 mol% [Ru-I]	$Ti(OEt)_4$	n. s.[a]	75

[a] non-specified

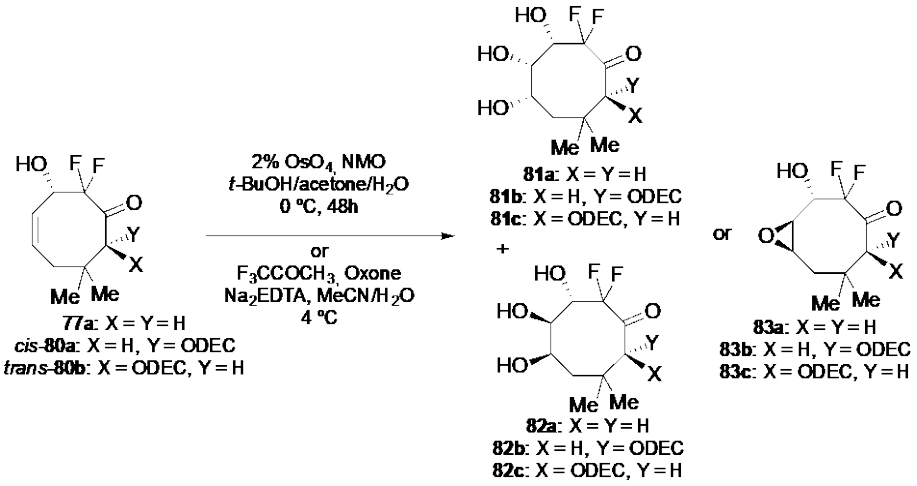
Another interesting observation deals with the substitution at the allylic alcohol. Hence, while the presence of a hydroxyl group at the allylic position has been reported to benefit RCM processes,[64] the authors established an order of reactivity among the free hydroxyl, the benzoate

and the benzyl ether derivatives taking into account kinetics and efficiency. A study of the kinetic profile of the RCM[65] by competition experiments revealed the following order of reactivity **72**>**73**>**74**.[57c] Interestingly, effective molarity (EM, k_{intra}/k_{inter}) measurements, carried out for the first time for an RCM reaction, showed a different order of efficiency, namely, **73**>**74**>**72**. The obtained values, measuring the relative efficiency of the cyclization rate *vs* oligomerization, are in most cases in the typical range for cyclooctannulations (0.001 to 0.1 M).[66] However, the high EM values obtained for benzoate derivatives (**72b** 0.25 M and **73b** 1.09 M) explain that an RCM on these substrates can be carried out at higher concentrations (20 mM for **73b** instead of 1 mM for **72b**) having important practical consequences as reactions carried out at very high dilutions are difficult to scale up with common laboratory ware. From these results, it can be concluded that the free hydroxyl group may accelerate RCM processes but protected ones may cyclize more efficiently.

Besides the inherent interest of the formation of highly functionalized cyclooctenone derivatives, Percy's group used them as intermediates in the synthesis of conformationally locked difluorosugar analogs.[58] In derivatives of this kind, both *aspects* (conformationally locked and difluoro) play an important role in their chemical and, therefore, biological behavior. On the one hand, Kirby showed that the stereoelectronic restrictions imposed by locking the ring conformation into a bicyclic framework results in deactivation of the pseudoglycosidic bond by a factor of 10^{13}. [67] Built upon this seminal contribution, several authors reported conformationally committed analogs of saccharides.[68] On the other hand, Withers demonstrated that pure electronic effects are also important.[69] Thus, the introduction of a *gem*-difluoromethylene vicinal to the anomeric carbon gave rise, upon glycosidation with an aspartate, to an acylal stable towards proteolytic digestion. In view of these antecedents, the authors decided to explore the

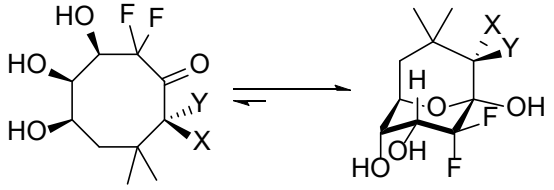
combination of both electronic and stereoelectronic lowering of the glycosidic reactivity, which may find applications as probes for glycosidases and glycosyltransferases. With an array of cyclooctenone derivatives in hand, described in Schemes 23-24, the study started with the selective oxidation of the double bond by means of either dihydroxylation or epoxidation (Scheme 25).

Scheme 25. Dihydroxylation and Epoxydation Reactions on Cyclooctenone Derivatives 77a and *cis*/*trans*-80



Actually, derivatives **81a-c** and **82a-c** are in equilibrium with **84a-c** and **85a-c**, respectively, by transannular hemiacetalization (Scheme 26). Derivative **84b** was in turn protected as the corresponding acetonide and converted to allyl ether **86** under PTC, confirming its stability towards alkali (Scheme 26). Moreover, epoxides **83a-c** underwent a tandem nucleophilic carbonyl addition– transannular epoxide opening with double strain release affording derivatives **87a-c** (NuH = NH_3) and **88a-c** (NuH = H_2O) (Scheme 26).

Scheme 26. Transannular Cyclizations on Cyclooctenone Derivatives



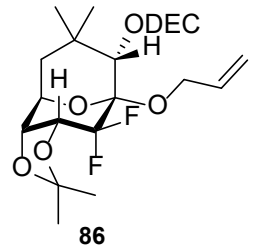
81a-c

84a: X = Y = H
84b: X = ODEC, Y = H
84c: X = H, Y = ODEC

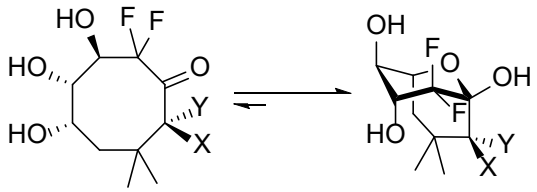
1. acetone, $CuSO_4$
TsOH, rt, 16h

2. 50% NaOH, Bu_4NHSO_4
Bu_4NI, allyl bromide, rt

>99%

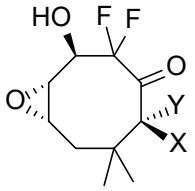


86



82a-c

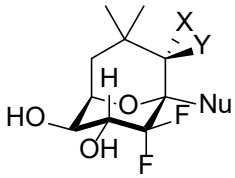
85a: X = Y = H
85b: X = ODEC, Y = H
85c: X = H, Y = ODEC



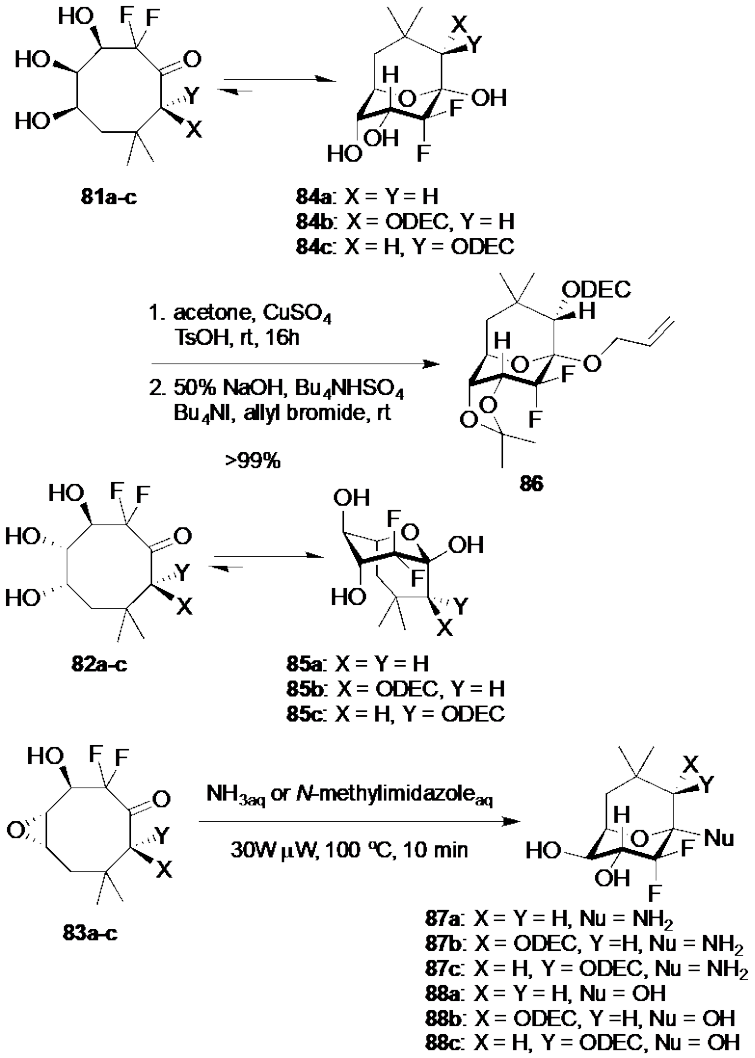
83a-c

$NH_{3(aq)}$ or *N*-methylimidazole$_{aq}$

30W μW, 100 °C, 10 min



87a: X = Y = H, Nu = NH_2
87b: X = ODEC, Y =H, Nu = NH_2
87c: X = H, Y = ODEC, Nu = NH_2
88a: X = Y = H, Nu = OH
88b: X = ODEC, Y =H, Nu = OH
88c: X = H, Y = ODEC, Nu = OH



In the following years, Percy and co-workers applied their experience in this field to the synthesis of difluorinated molecules with interesting properties such as pentopyranose and pentopyranosyl phosphate mimics (Figure 3, **89a,b**),[58c] analog of *fucose* (Figure 3, **90**)[58d] and an analog of a ring-expanded *calysteginde* B_2 (Figure 2, **91**). [58e] Interesting stereochemical issues were discussed throughout these entire series of publications being beyond the scope of this review.

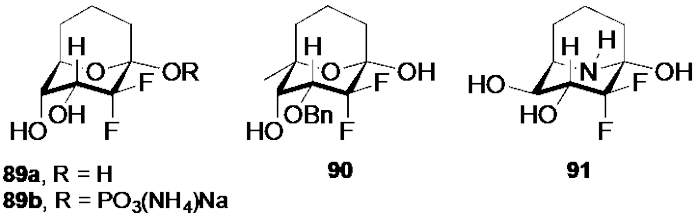
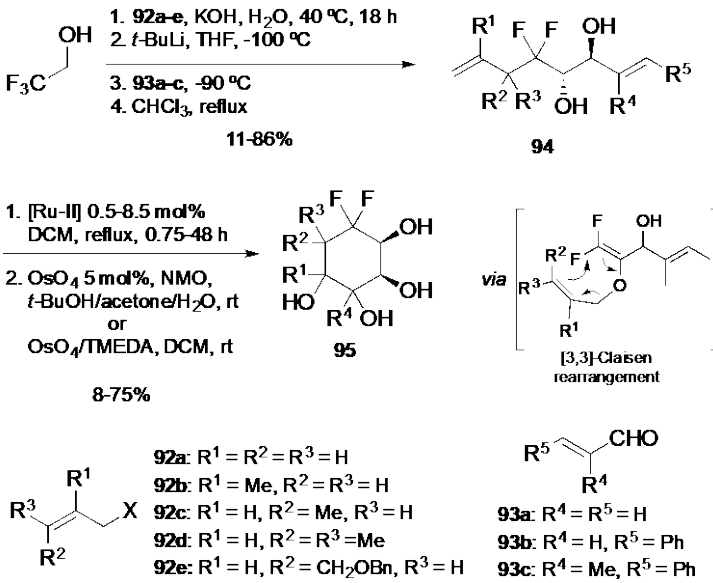


Figure 3. Conformationally locked difluorinated analogs of sugars

In addition to the aforementioned decade-long thorough study of fluorinated cyclooctenone derivatives, Percy's group also investigated the synthesis of difluorinated carbasugar derivatives.[59] Substitution of the endocyclic oxygen atom of a saccharide by a CH_2 results in major changes in its conformation and, more importantly, in its reactivity.[70] The most important one is the conversion of the C1 hydroxy group into a "regular" alcohol instead of part of a hemiacetal and, therefore any linkages made thereof would be ethers instead of acetals. Besides, anomeric pseudorotation[71] is inhibited as well as any "glycosidic" bond cleavage *via* oxacarbenium ion-like transition states, as those catalyzed by glycosidases and glycosyl transferases,[72] resulting in a practically inert C1-O bond. Replacement of the pyranose oxygen with a CF_2 instead of a CH_2 presents a number of advantages, namely, (1) the electron-withdrawing character of the *gem*-difluoro moiety would minimize the perturbation on the pK_a of the vicinal hydroxylic groups and, therefore, their H-bond forming ability with a receptor; (2) ^{19}F NMR spectroscopy would allow getting conformational information from $^3J_{H\text{-}F}$ coupling constants[73] as well as identification and monitoring of fluorinated ligands or probes even in a complex biological matrix,[74] given the extremely low occurrence of natural organofluorine compounds. Nucleophilic difluorination of hydroxyl or carbonyl groups within sugars using DAST and Deoxofluor has been carried out, although this transformation presents a number of stereoelectronic issues and each derivative would require a different starting material for its synthesis.[75] For these reasons, the authors suggested a divergent synthetic route, which would

allow accessing a number of deoxyhexose derivatives in which the pyrane oxygen atom would be replaced by a CF_2 grouping. Hence, they adapted the previously described dehydrofluorination–metallation of trifluoroethanol derivatives, [3,3]-Claisen rearrangement reaction sequence to the synthesis of suitable densely functionalized 1,7-octadienes **94**, precursors of cyclohexene derivatives **95** (Scheme 27). The situation presented increased complexity as poor 1,4-stereoinduction in the [3,3]-Claisen rearrangement and only moderate diastereoselectivity in the reduction of the precursor α-hydroxyketone leading to derivatives **94** (5:1-10:1, except for products derived from **93c** which gave rise to exclusive *anti* reduction). However, at this stage most of these diastereomeric mixtures were separable allowing the preparation of a wider library of sugar analogs. Regarding the final dihydroxylation, the choice of appropriate reaction conditions led to the stereodivergent synthesis of the *trans*- and the *cis*-diastereoisomers. Its scalability (25-70 mmol), minimal use of protecting group chemistry and the *rapid delivery of the target compounds from inexpensive and commercial starting materials* are among the remarkable features of this strategy.

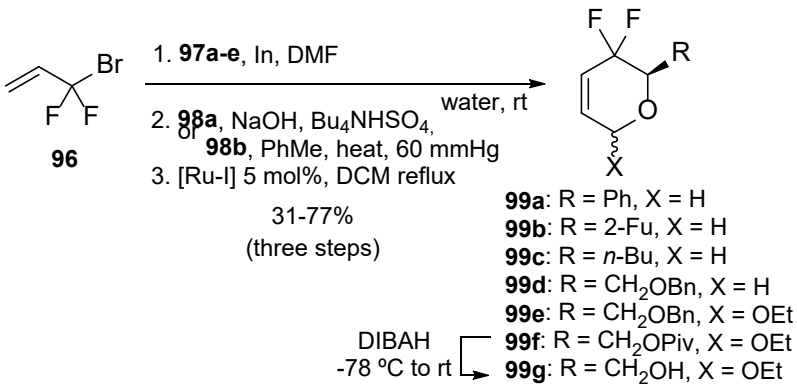
Scheme 27. Synthesis of Carbasugar Analogs

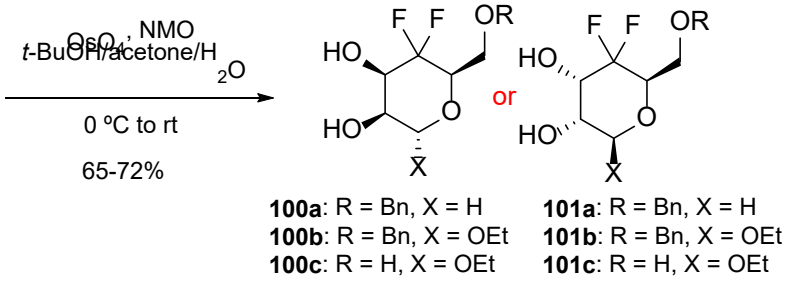


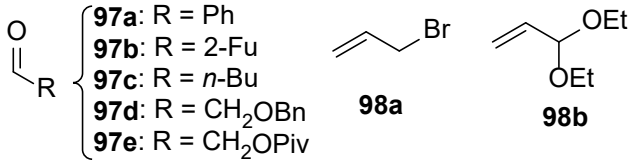
2.1.3 Building blocks derived from 3-bromo-3,3-difluoropropene (difluoroallyl bromide)

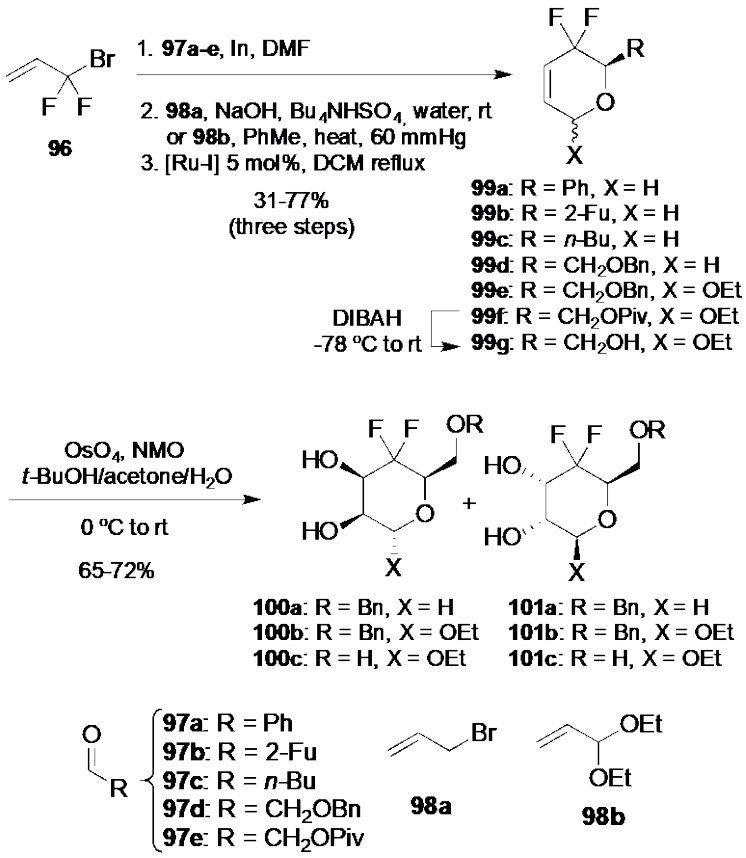
Probably, one of the most obvious starting materials for the synthesis of suitable difluorinated building blocks to participate in a RCM is 3-bromo-3,3-difluoropropene **96**. However, its use for this purpose is rather limited.[76] In 2000, Percy described the *first synthesis of a ring-fluorinated heterocycle by RCM* in a straightforward synthesis of difluoro-dihydropyranes.[76a] The reaction sequence consisted of an indium-mediated allylation using **96**, followed by *O*-allylation under phase-transfer conditions and final RCM (Scheme 28). The use of suitable aldehydes **97d,e** and replacing the *O*-allylation step with a transacetalization with acrolein diethylacetal **98b** allowed the obtention of conveniently substituted dihydropyranes **99e-g** suitable for subsequent OsO_4 mediated *syn* dihydroxylation (Scheme 28).[76b]

Scheme 28. Synthesis of Fully Functionalized Pyranes


Br
F F
96
1. 97a-e, In, DMF
water, rt
2. 98a, NaOH, Bu4NHSO4,
or
98b, PhMe, heat, 60 mmHg
3. [Ru-I] 5 mol%, DCM reflux
31-77%
(three steps)
F F
R
O
X
99a: R = Ph, X = H
99b: R = 2-Fu, X = H
99c: R = n-Bu, X = H
99d: R = CH2OBn, X = H
99e: R = CH2OBn, X = OEt
DIBAH
-78 ºC to rt
99f: R = CH2OPiv, X = OEt
99g: R = CH2OH, X = OEt


OsO4, NMO
t-BuOH/acetone/H2O
0 ºC to rt
65-72%
F F OR
HO
HO
O
X
or
100a: R = Bn, X = H
100b: R = Bn, X = OEt
100c: R = H, X = OEt
101a: R = Bn, X = H
101b: R = Bn, X = OEt
101c: R = H, X = OEt

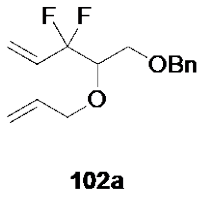

O
R
97a: R = Ph
97b: R = 2-Fu
97c: R = n-Bu
97d: R = CH2OBn
97e: R = CH2OPiv
Br
98a
OEt
OEt
98b



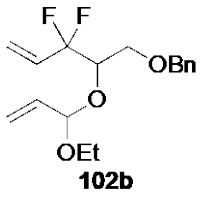
An interesting trend regarding the cyclization rate was observed, the RCM reaction being slower as the oxidation state of C1 increases from ether to acetal and finally ester (Table 3).[76b] Thus, while ether **102a** readily cyclized at rt upon treatment with 5 mol% Grubbs catalyst in 24 h, the corresponding acetal **102b** took 3 days in refluxing DCM to reach completion and the corresponding acryloyl ester **102c** did not react even after 7 days in refluxing DCM and doubled catalyst loading (Table 3, entries 1-3). By comparison with data taken from the literature, the authors concluded that the behavior for fluorinated substrates seemed to be more pronounced and suggested an electronic rather than conformational origin for that observation. Specifically, while the reactivity at the ether oxidation state was comparable, fluorinated acetals ring-closed noticeably more slowly than non-fluorinated ones and cyclization of non-fluorinated acryloyl esters was not hampered (Table 3, compare entries 1 and 4, 2 and 5, 3 and 6). Keeping in mind

the difficulty in comparing reaction rates accurately from bibliographic data, their conclusions suitably adhered to the experimental data; the least convincing being the assumption that *at the ether level, there is no difference in reactivity between the fluorinated and non-fluorinated systems, indicating that the fluorine atoms exert no conformational effect* (Table 3, compare entries 1 and 4).

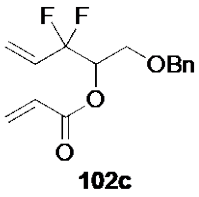
Table 3. Fluorine Effect in C1-Oxidation State



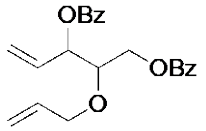
102a



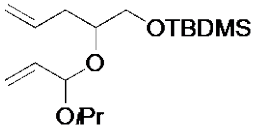
102b



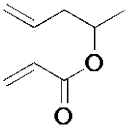
102c



103



104



105

Entry	Substrate	Cat (mol%)	T (ºC)	t (h)	Yield (%)	Ref
1	**102a**	5	rt	24	97	76a
2	**102b**	5	40	72	76	76b
3	**102c**	10	40	168	0	76b
4	**103**	5-7	40	1	90	77
5	**104**	4-6	40	2	88	78
6	**105**	10	40	-[a]	81	79

[a] Not reported

To explain these observations the authors argue that steric factors played a determinant role in the formation of the intermediate metal alkylidene ***I***, reacting through the terminal allyl end (present in **102a** and **103-105**). This reactive new alkylidene ***I*** would, in turn, undergo rapid six-membered ring closure (Figure 4). On the other hand, derivatives **102b,c** did not present any terminal allyl scaffold, which explains their diminished reactivity. For acetal **102b**, the reaction is believed to take place through the intermediacy of ***II*** as the presence of electron-withdrawing groups at the allylic position has been shown to be deleterious for metathesis reactions (Figure

4).[64] The increased electron-withdrawing character of the carbonyl group explains the complete lack of reactivity of **102c**.

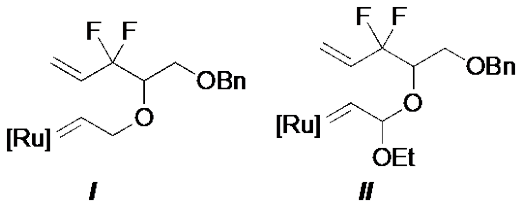
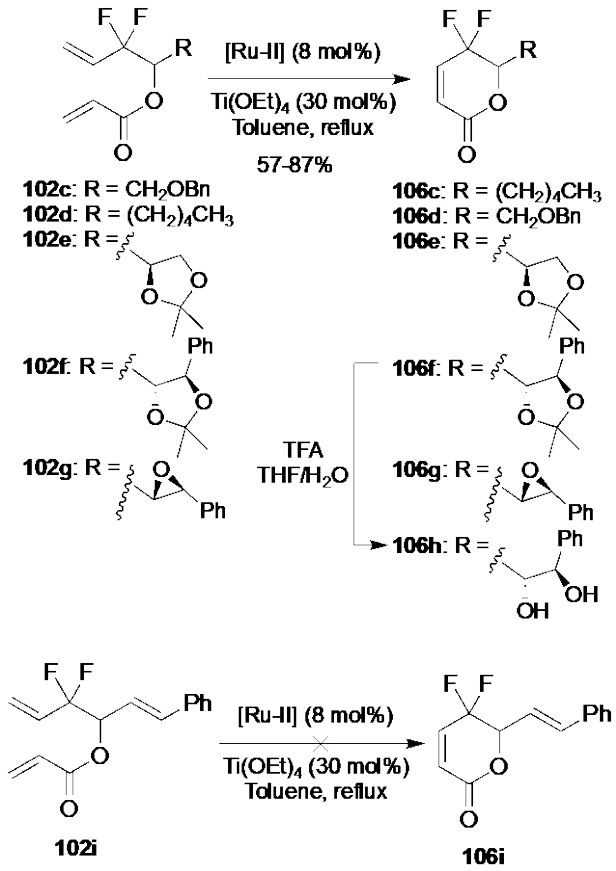


Figure 4. Intermediate metal alkylidenes I and II

Almost at the same time, whilst carrying out the synthesis of a fluorinated analog of the natural product *massoialactone*[77] a similar reluctant reactivity on a closely related substrate **102d** was reported by Qing.[76c] However, the authors were able to overcome this limitation by using $Ti(OEt)_4$ as co-catalyst along with 2nd generation Grubbs catalyst in refluxing toluene (Scheme 29). Then, the authors applied these improved reaction conditions to Percy's system **102c** and a parent substrate **102e** (Scheme 29). The scope of this methodology was then further extended for the synthesis of fluorinated analogs of *goniodiols* **106h** and *goniothalamin* epoxides **106g**.[76d] Surprisingly, the reaction of epoxide derivative **102g** proceeded even in the absence of the Lewis acid co-catalyst in moderate yield (57-66%). Unfortunately, the aforementioned reaction conditions failed on a substrate exhibiting a subtle structural modification **102i**, an intermediate in the enantioselective synthesis of *gem*-difluorinated *goniothalamin* **106i** (Scheme 29)[78] Presumably, the more electron rich styrene unit is more reactive under RCM. This limitation resulted in a dead end, and a whole *de novo* strategy had to be used for the synthesis of **106i**.[78]

Scheme 29. Synthesis of Fluorinated Lactones by RCM



2.1.4. Miscellanea

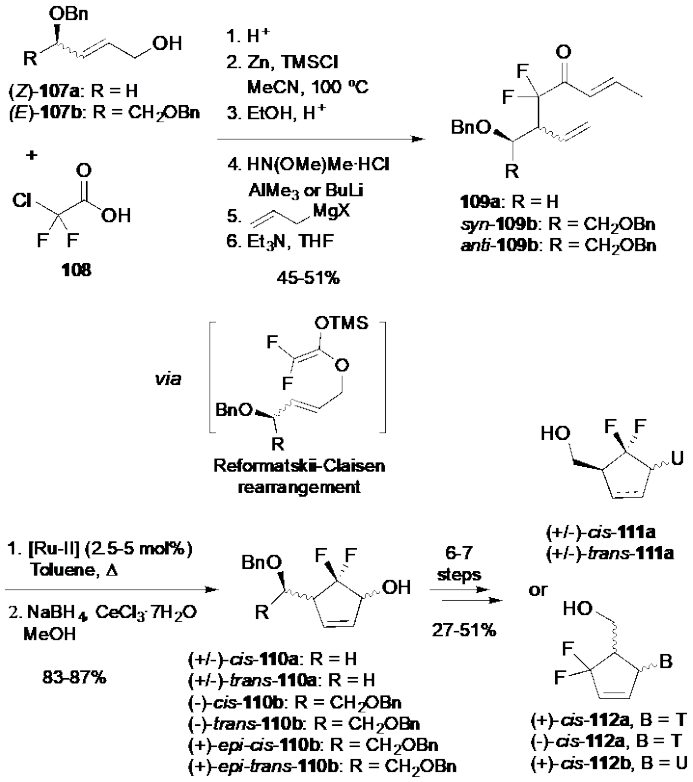
Besides the most commonly used fluorinated building blocks described in the previous sections, a number of authors have prepared carbo- and heterocycles containing an endocyclic fluorinated moiety either starting with a different fluorinated building block or using a late-stage fluorination strategy. These results will be gathered in this section.

In a series of papers, Qing and co-workers reported the synthesis of 6'-fluoro- and 6',6'-difluorocarbocyclic nucleosides[79,80] by a multistep approach including a silicon-induced Reformatskii–Claisen rearrangement and an RCM as the crucial steps. Key for the success of this approach was the identification of 2,2-difluoro-4-pentenoic acid ester derivatives as *gem*-difluoromethyl containing building blocks, which were synthesized using a methodology

analogous to the one reported in the literature for 2,2-difluoro-4-pentenoic acid **1**.[33] First, a racemic synthesis 2',3'-dideoxy-6',6'-difluorocarbocyclic nucleosides was disclosed starting from monobenzylated (*Z*)-2-buten-1,4-diol (*Z*)-**107a** (Scheme 30).[80a] The common reaction sequence started with the condensation with chlorodifluoroacetic acid **108** followed by silicon-mediated Reformatskii-Claisen rearrangement. Allylation of the Weinreb amide intermediate followed by base-promoted double bond isomerization afforded the substrate for the subsequent RCM **109a** (Scheme 30). Cyclization was achieved in excellent yield using second generation Grubbs catalyst in toluene at 80 ºC. The thus obtained difluorocyclopentenone was subjected to a Luche reduction, giving rise to diastereoisomeric alcohols *cis*- and *trans*-**110a** in a 2.9:1 ratio, which were separated by column chromatography (Scheme 30). A seven-step reaction sequence, including an S_N2 with NaN_3 on the corresponding triflate and formation of the uracil ring by reaction with an appropriate isocyanate, was then carried out separately affording racemic compounds *cis*- and *trans*-**111a**, respectively, in moderate overall yields (Scheme 30). Second-generation synthesis started with the condensation of the readily available chiral alcohol (*E*)-**107b** and **108** (Scheme 30).[80b] An identical reaction sequence as the aforementioned one afforded *syn*- and *anti*-**109b** as a 3:1 mixture of separable diastereoisomers. For these substrates, the Luche reduction had to be carried out before RCM in order to reach completion. On the acyclic precursor, the reduction did not show any stereoselection-giving rise to equimolecular separable mixtures of (-)-*cis*-**110b**/(-)-*trans*-**110b** and (+)-epi-*cis*-**110b**/(+)-epi-*trans*-**110b** upon cyclization, respectively. The authors argued that the low conversion obtained on substrates **109b** may be ascribed to the strong electron-withdrawing effect of the *gem*-difluoromethylene unit added to the carbonyl group; however, substrate **109a** exhibited this difluoromethylene enone motif and cyclized in an excellent 98% yield (*vide supra*). Comparing both structures, steric

encumbrance at the homoallylic carbon of the other reactive site seems to be the major structural difference. Regarding the introduction of the pyrimidine base, a shorter reaction sequence involving a palladium-catalyzed allylic substitution on the corresponding carbonate with the appropriate 3-benzyloxypyrimidinone was adopted. Removal of the protecting groups followed by $NaIO_4$ promoted oxidative cleavage of the 1,2-diol subunit and final reduction afforded products **112a,b** in good overall yields (Scheme 30).

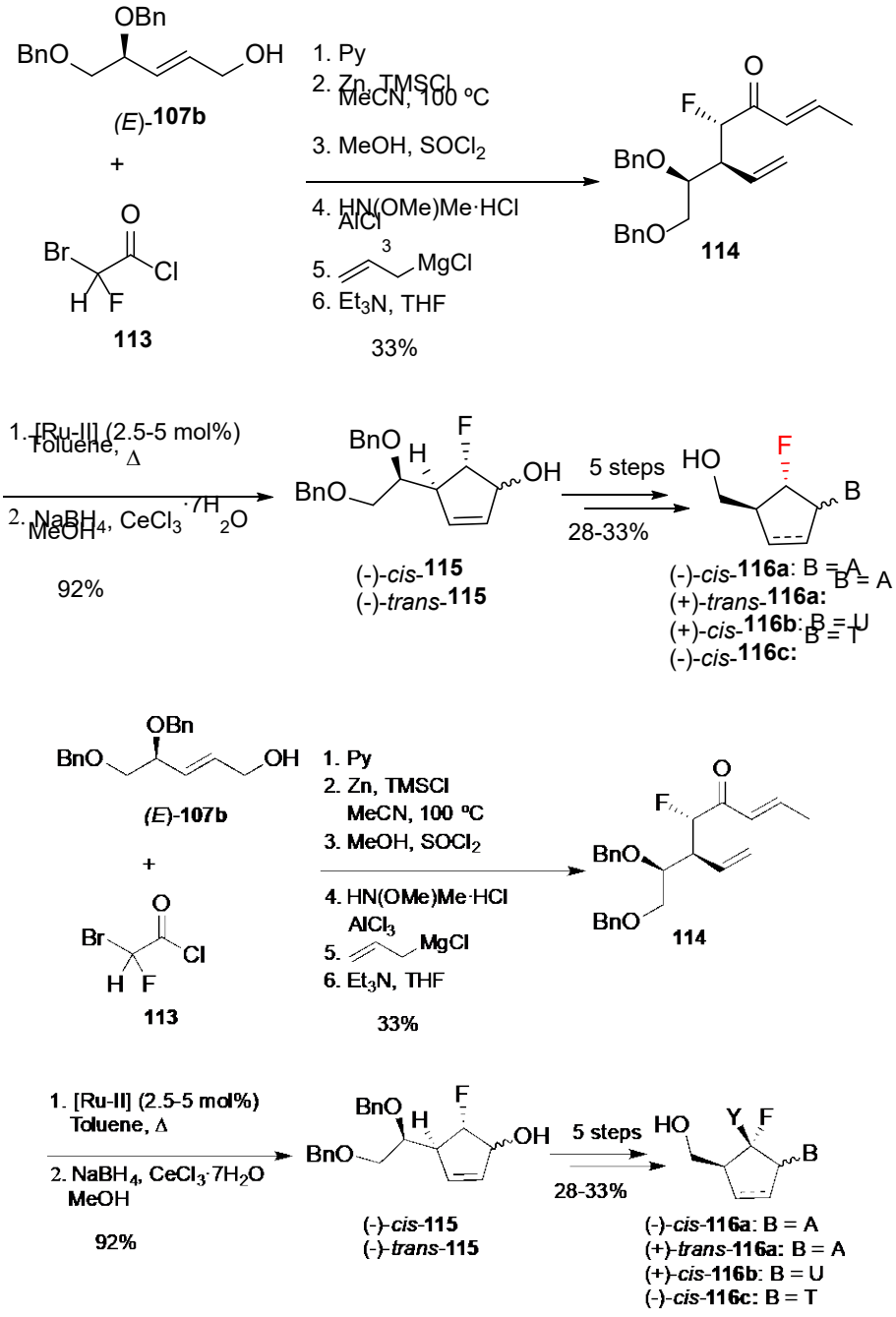
Scheme 30. Synthesis of 3',3'-Difluorocarbocyclic Nucleoside Derivatives



In the last report of this series, the same strategy was used for the synthesis of 6'-fluoro analogs using bromofluorocetyl chloride **113** as fluorine containing starting material.[80c] The introduction of an extra stereocenter resulted in a mixture of all possible four diastereoisomers upon Claisen rearrangement in an 8.7:3.4:1.8:1 ratio. The major isomer could be separated by column

chromatography in 45% yield, and the reaction sequence was continued with the pure *syn*, *anti* diastereoisomer affording **114**, on which RCM proceeded uneventfully. Luche reduction took place in moderate diastereoselectivity (3.2:1) achieving *cis*- and *trans*-**115** in an excellent 92% combined yield (Scheme 31). A third and even shorter five-step sequence was used to introduce the purine or pyrimidine bases, consisting of a Mitsunobu reaction on the free alcohol with either 6-chloropurine or 3-benzoyl thymine followed by deprotection, oxidative 1,2-diol cleavage and reduction to the final products **116a-c** (Scheme 31).

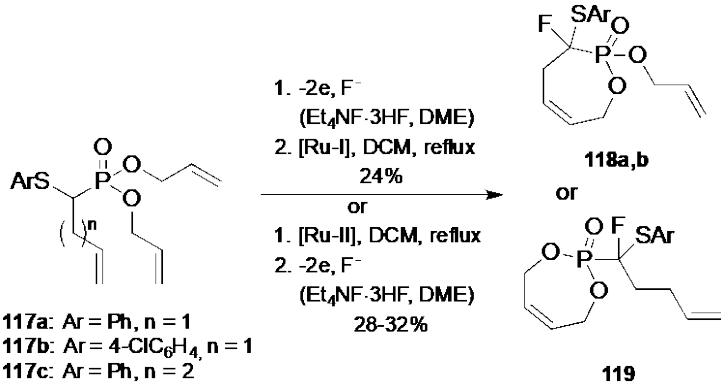
Scheme 31. Synthesis of 6'-Fluoro- and 6',6'-Difluorocarbocyclic Nucleosides



The first example of late-stage introduction of a fluorine atom before RCM deals with the synthesis of cyclic monofluorinated phosphonate esters.[81] Cyclic phosphonate esters play critical roles in several biological processes, such as cellular recognition.[82] Given the drawbacks associated with the use of DAST, the authors envisaged on an anodic fluorination, using an α-

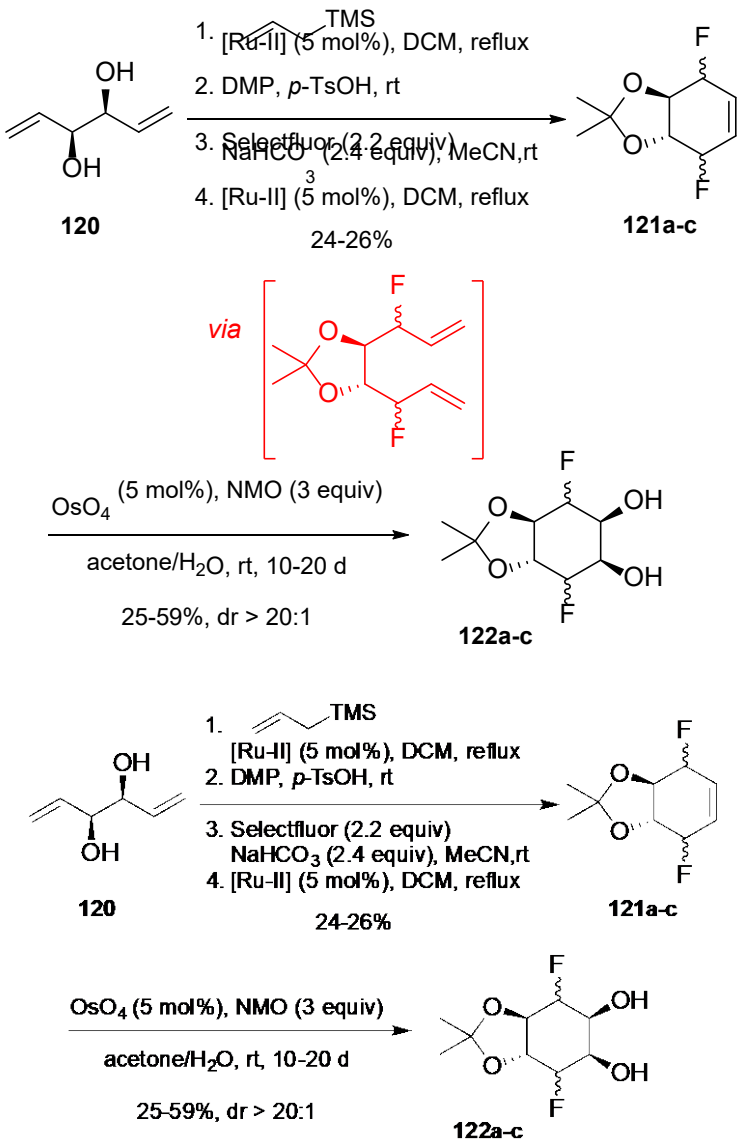
arylthio group as electro-auxiliary; this methodology had never been used in combination with RCM. The authors compared the results obtained by altering the order of the reaction sequence and concluded that better yields were obtained if the cyclization was carried out prior to fluorination, although the differences are almost negligible (Scheme 32). More interesting was the increased reactivity of the α-fluorinated thioether derivatives towards Grubbs 1st generation catalyst. Hence, while no conversion was observed for the corresponding non-fluorinated analogs, the presence of a fluorine atom allowed the reaction to take place in a moderate 45% yield. This result was explained by the decreased σ-donor ability of the sulfur atom, owing to the high electronegativity of the α-fluorine atom, thus suppressing the de-activation of the catalyst. On the other hand, a homologated analog **117c** was subjected to RCM aiming to form the corresponding 8-membered cyclic phosphonate. However, cyclization took place between the two allyloxy substituents affording an exocyclic α-arylthio group, which underwent anodic fluorination in low yield affording **119** (Scheme 32). Finally, the authors also showed the failure of several electrophilic fluorination methodologies on substrate **117a**.

Scheme 32. Synthesis of Fluorinated Cyclic Phosphonates by Anodic Fluorination / RCM



Gouverneur reported the last example of the late-stage fluorination strategy prior to the RCM step in 2008.[83] The authors reported a two-directional approach to enantiopure 1,4-difluorocyclohexenes, which were in turn used as substrates for the synthesis of fluorinated cyclitol analogs. The reaction sequence consisted of a double cross-metathesis reaction of the chiral-pool derived diene **120** with allyltrimethylsilane, followed by electrophilic fluorination of the corresponding acetonide-protected bisallylsilane and final RCM (Scheme 33). The formation of the three possible isomers in the fluorination step could be anticipated since the bis-silylated diene did not contain silylated stereogenic centers. The determination of the relative configuration of the two new stereocenters by NMR spectroscopy was discussed in detail. Finally, dihydroxylation of diastereomeric difluorocyclohexenes **121a-c** under Upjohn conditions (OsO_4 (5 mol%), NMO (3 equiv)) afforded diols **122a-c** in moderate yields and as single diastereoisomers (Scheme 33).

Scheme 33. Synthesis of Difluorocyclitol Analogs



2.2. Ring-Closing Metathesis giving rise to Products Containing an Exocyclic Fluorinated Moiety

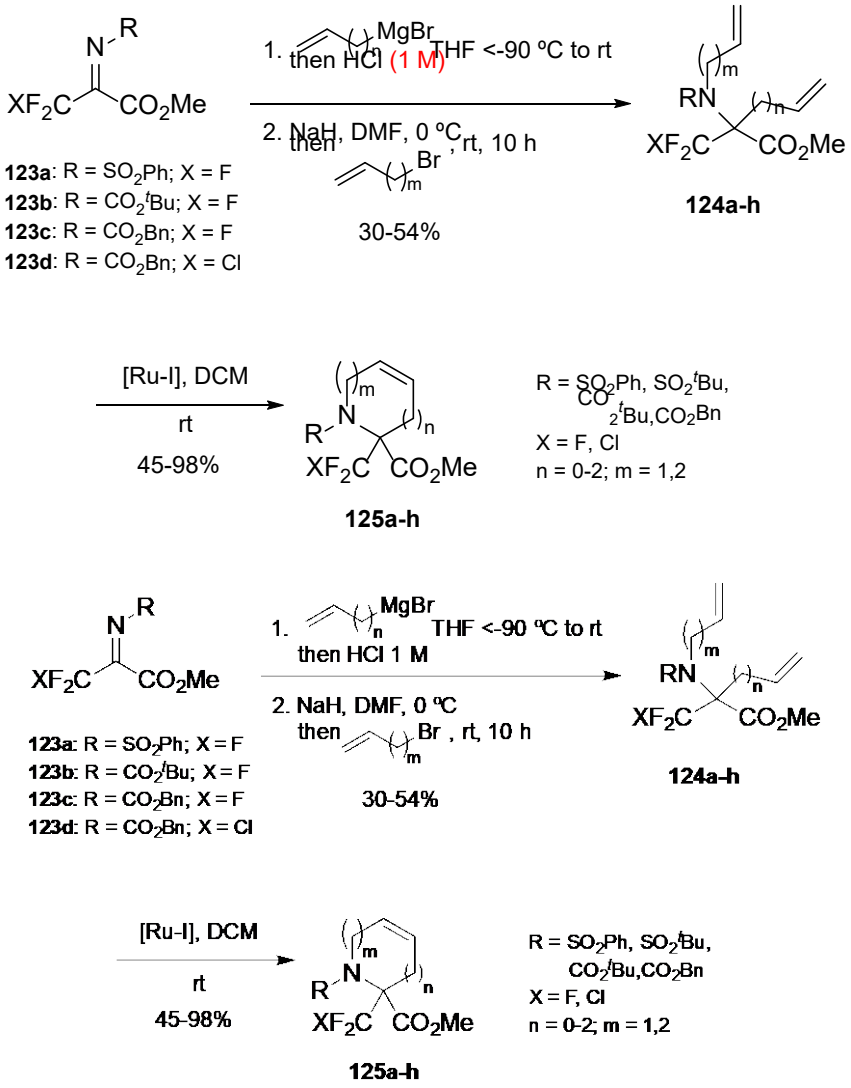
Type-II substrates show fluoroalkyl appendages in the carbon backbone that tether the two reactive olefins, instead of fluorine atoms directly attached to the tether (Figure 2). This difference results in cyclized products bearing an exocyclic fluoroalkyl substituent instead of a fluorine-containing carbo- or heterocycle. In contrast to the previous section, divided according to the

fluorine containing starting material, this section is divided considering the fluoroalkyl substituent (CF_3, CH_2F and others).

2.2.1. $R_F = CF_3$

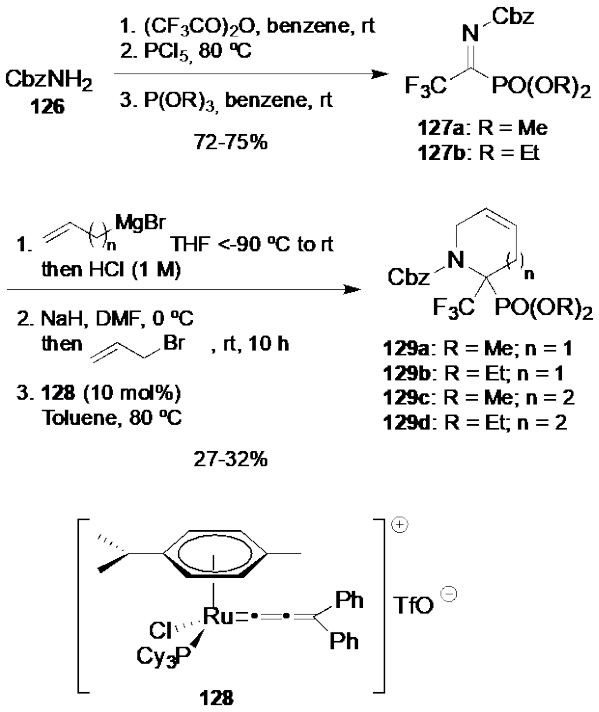
More than fifteen years ago, Osipov and Dixneuf pioneered the use of trifluoropiruvate derived iminoesters for the synthesis of cyclic trifluoro amino acids.[84] Thus, the low temperature addition of vinyl- or allylmagnesium bromide to electrophilic imines **123a-d**, containing protecting groups such as SO_2Ph, Boc or Cbz on the nitrogen, followed by *N*-allylation afforded the ring closing metathesis precursors **124** (Scheme 34).[84a] Finally, cyclization was achieved under standard RCM conditions using first generation Grubbs catalyst in DCM at room temperature (Scheme 34), which was claimed to be the *first RCM based synthesis of α-CF_3 containing heterocycles*. Interestingly, the authors found a great difference in the cyclization rate for the 5- and 6-membered heterocycles. Hence, while the formation of the pipecolinic acid derivatives **125** (n = 1, m = 1) took place in 10 h, affording the desired products in excellent yields, the formation of the corresponding proline derivatives **125** (n = 0, m = 1) proceeded in only moderate conversion and, therefore, moderate yields were obtained (Scheme 34). This strategy was then extended to trifluoromethyl as well as chlorodifluoromethyl 6- and 7-membered cyclic amino acid analogs.[84d]

Scheme 34. Synthesis of Trifluoromethyl Pipecolinic Acid and Proline Derivatives



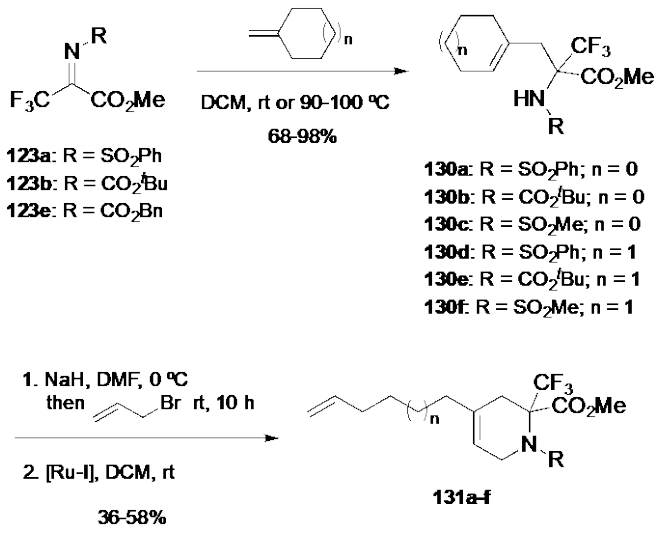
As a further extension of this work, 6- and 7-membered cyclic amino phosphonate analogs **129** were synthesized by a (homo)allylation/*N*-allylation/RCM reaction sequence (Scheme 35).[84b,d] The starting *N*-protected α-trifluoromethyl α-iminophosphonates **127a,b** were prepared from benzylcarbamate **126** in three steps, including an Arbuzov rearrangement on the corresponding trifluoromethylimidoyl chloride (Scheme 35). Interestingly, the authors reported that for this new class of substrates, the cationic allenylidene ruthenium complex **128** is more effective than the previously used first generation Grubbs catalyst (Scheme 35).

Scheme 35. Synthesis of Trifluoromethyl Pipecolinic Acid and Proline Phosphonate Analogs



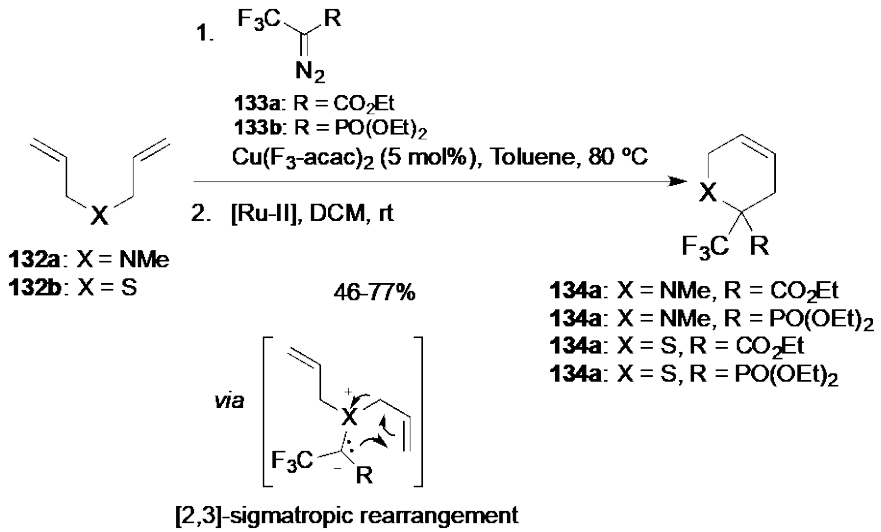
Additionally, the same authors reported an alternative synthesis of trifluoromethyl cyclic amino acids derivatives relying on a ROM / RCM tandem process.[84c] The allylation step was replaced by an ene-reaction between ethyl trifluoropyruvate and several sized methylenecycloalkanes (Scheme 36). *N*-Allylation followed by treatment with first generation Grubbs catalyst afforded the ROM/RCM rearranged products in moderate overall yields (Scheme 36).

Scheme 36. Ene-Reaction/ROM/RCM Reaction Sequence towards Cyclic Trifluoromethyl Amino Acid Derivatives



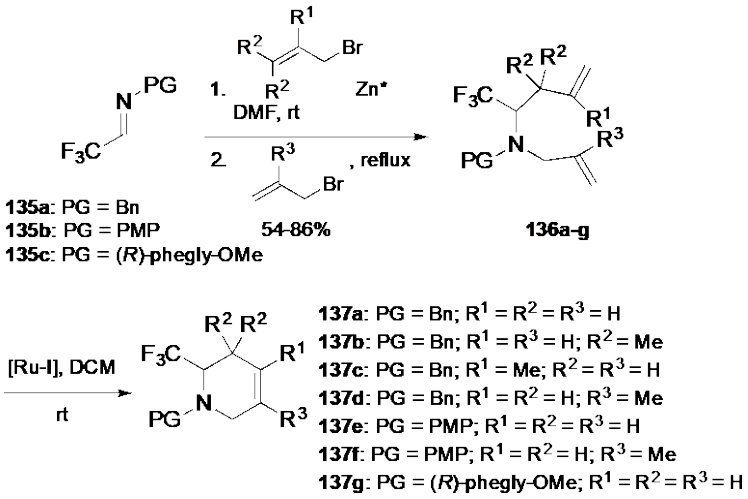
Finally, an elegant copper-catalyzed tandem ylide formation/[2,3]-sigmatropic rearrangement was developed by the same authors accesing heteroatom tethered 1,7-dienes, precursors of 6-membered heterocycles **134a-d**, in one step from X-diallyl substrates **132a,b** and trifluoromethyl diazocompounds **133a,b** (Scheme 37).[84e] After screening a number of rhodium and copper sources, the authors determined that copper trifluoroacetoacetate was the optimum catalyst for the key tandem transformation (Scheme 37).

Scheme 37. Copper-Catalyzed Tandem Ylide Formation/[2,3]-Sigmatropic Rearrangement for the Synthesis of 1,7-Dienes



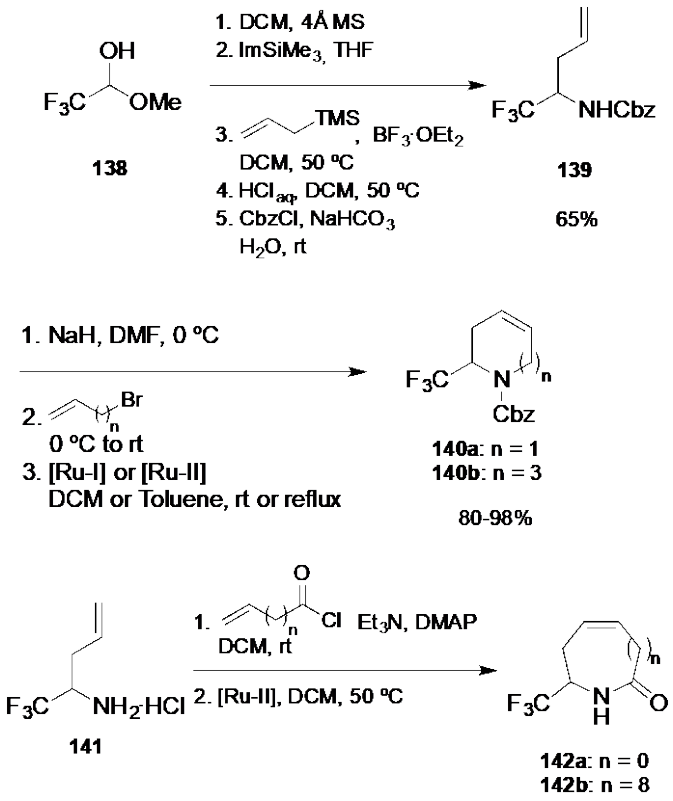
By changing the starting material to simple aldimines **135**, Bonnet-Delpon described the synthesis of trifluoromethyl piperidines using a similar synthetic strategy as the one depicted in Scheme 34 (Scheme 38).[85] The two main differences with the report by Osipov[84a] were the use of a variety of *in situ* formed allylzinc reagents, instead of the corresponding Grignard ones, under Barbier conditions[86] and the one-pot *N*-allylation of the intermediate zinc amide (Scheme 38). The use of a chiral auxiliary on the iminic nitrogen (phenylglycinol methyl ether) afforded product **136g** with complete diastereocontrol. The subsequent RCM was carried out under identical conditions affording piperidine derivatives **137a-g** in excellent yields, in most cases (Scheme 38).

Scheme 38. Synthesis of CF_3-Substituted Piperidines



Using their previously reported methodology,[87] Billard and Langlois developed a synthesis of α-trifluoromethylated nitrogen heterocycles **140** and **142** starting from fluoral methyl hemiketal **138**.[88] The key step was the Sakurai-type allylation of an *in situ* generated iminium cation with allyltrimethylsilane (Scheme 39). The thus obtained Cbz protected trifluoromethyl homoallylamine **139**, or the corresponding hydrochloride **141**, are in turn either alkylated or acylated giving rise to suitable dienes for the subsequent RCM (Scheme 39).

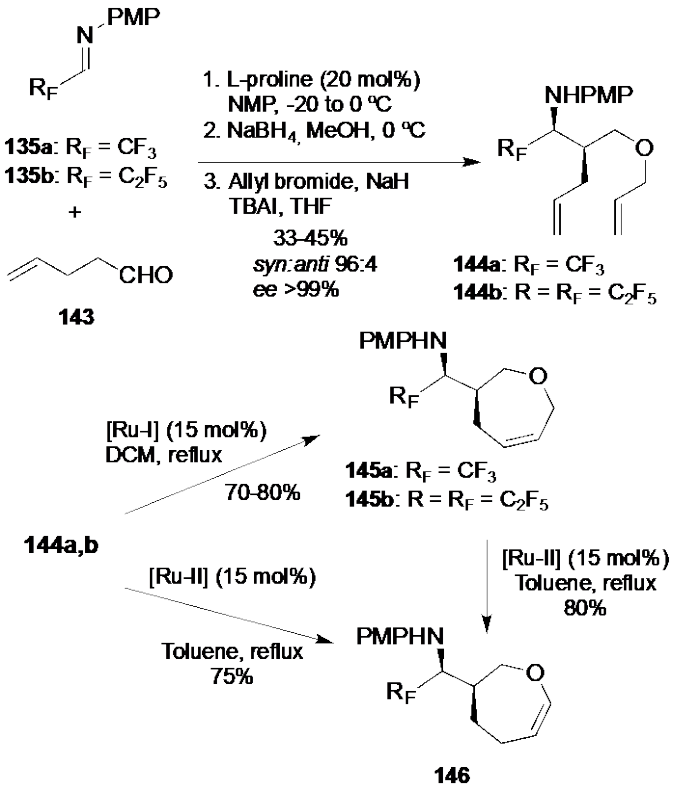
Scheme 39. Synthesis of Trifluoromethylated *N*-Heterocycles from Fluoral Hemiketal



One decade ago, Fustero reported an organocatalytic approach towards fluorinated α-alkyl γ-amino alcohols by means of a highly diastereo- and enantioselective indirect proline-catalyzed Mannich reaction between fluorinated aldimines **135** and aliphatic aldehydes.[89] As an application of this methodology,[90] the same authors reported the synthesis of fluorinated aminoalkyloxepines **145** by RCM using an appropriate ω-alkenyl aldehyde **143** for the Mannich reaction and subsequent *O*-allylation of the intermediate amino alcohol (Scheme 40). In addition to trifluoromethyl, a pentafluoroethyl chain could also be incorporated in the final products. The authors observed that while the reaction performed with first generation Grubbs catalyst in refluxing DCM afforded a simple RCM process, by switching to the second-generation catalyst and a higher boiling point solvent, namely toluene, a tandem RCM/olefin isomerization took place-giving rise to an oxepine product having the double bond conjugated to the oxygen **146**.

The RCM product **145a** obtained with the first generation catalyst in DCM readily isomerized to **146** in the presence of the second-generation catalyst in refluxing toluene (Scheme 40).

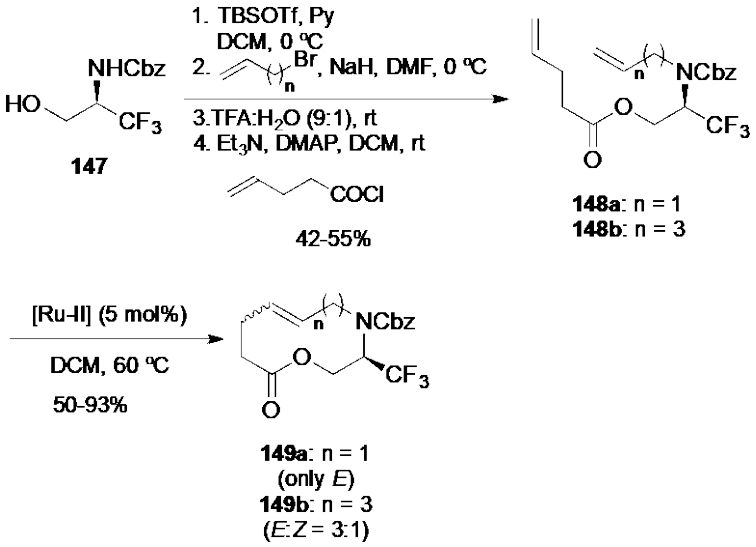
Scheme 40. Synthesis of Fluorinated Aminoalkyl Oxepines



During their study on the synthesis of fluorinated amino lactones (see Scheme 5),[28d] Fustero and co-workers also described the synthesis of 10- and 12-membered trifluoromethyl azalactone derivatives **149a,b** (Scheme 41). Unlike difluoromethylene derivatives, in this case an *N*-alkylation step of **147** was needed prior to *O*-acylation in order to obtain suitable RCM precursors **148a,b** (Scheme 41). Treatment with 2nd generation Grubbs catalyst in DCM at 60 ºC afforded the desired lactones in moderate to excellent yields, the 10- membered analog being formed as a single isomer, while the 12-membered one was formed as a 3:1 (*E*:*Z*) mixture (Scheme 41).

Increasing the catalyst loading (15 mol%) resulted in the formation of complex mixtures arising from double bond isomerization processes both before and after RCM.

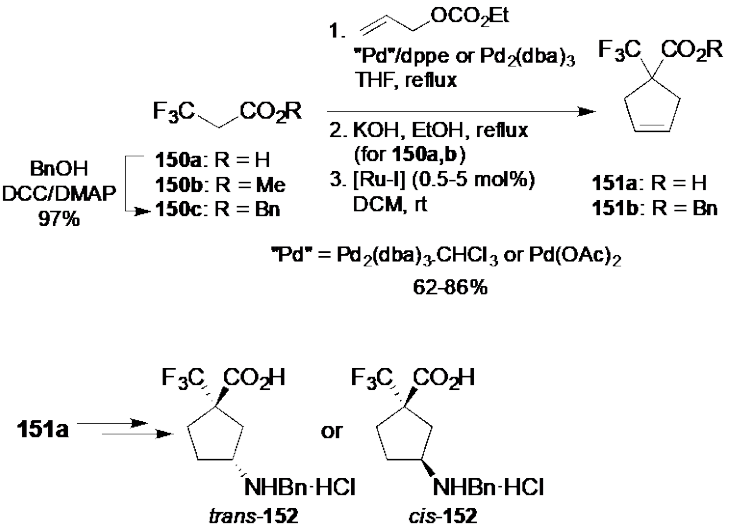
Scheme 41. Synthesis of 10- and 12-Membered Trifluoromethyl Lactones



Finally, Grellepois and Portella reported the synthesis of 1-(trifluoromethyl)cyclopentene carboxylic acid derivatives.[91] Firstly, inspired by their own results leading to trifluoromethyl α,α-diallyl dithioesters,[92] 1-(trifluoromethyl)cyclopent-3-ene carboxylic acid **152** was obtained in three steps. However, the RCM proved somewhat inefficient requiring 10 mol% of 2nd generation Grubbs catalyst. For that reason, together with the commercial availability of 3,3,3-trifluoropropanoic acid **150a** and its methyl ester **150b**, the authors decided to switch to a more straightforward approach (Scheme 42). To this end, the authors adapted a procedure by Kitazume[93] consisting of a palladium-catalyzed Tsuji-Trost allylation with allyl ethyl carbonate **151** as electrophile to the synthesis of α,α-diallyl-trifluoropropanoates. These intermediates were in turn cyclized with 0.5-5 mol% of 1st generation Grubbs catalyst (Scheme 42). The resulting cyclopentene carboxylic acid derivatives were shown to participate in a number of

transformations giving rise to interesting fluorinated building blocks such as epoxides, lactones, alcohols, ketones and amino acids. Amongst them, the synthesis of trifluoromethyl γ-aminocyclopentane carboxylic acid derivatives deserves special mention (Scheme 42).

Scheme 42. Synthesis of 1-(Trifluoromethyl)cyclopent-3-ene Carboxylic Acid Derivatives

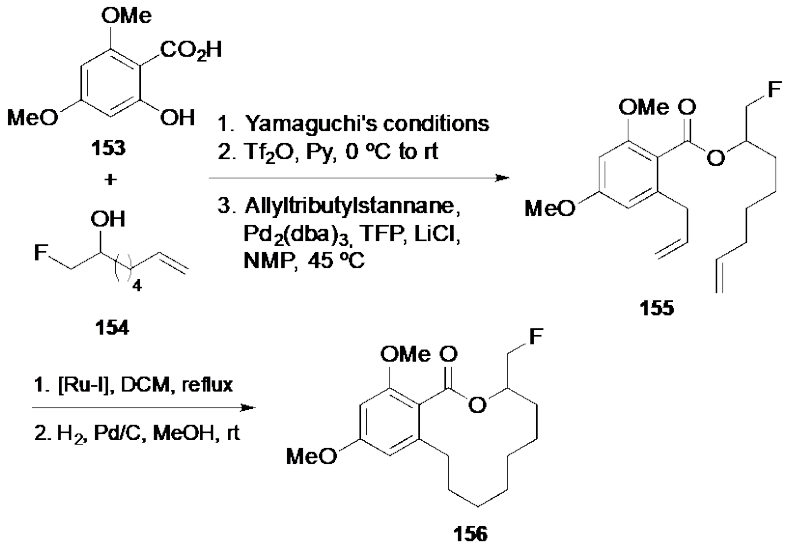


2.2.2. $R_F = CH_2F$

In the context of a long-standing interest in the synthesis of monofluoromacrolides,[94] Haufe reported the synthesis of monofluorinated analogs of both enantiomers of the natural product *lasiodiplodin* **156**, a 12-membered *orsellinic* acid type lactone, using a RCM as the key step (Scheme 43).[95] The synthesis started with the esterification of salicylic acid derivative **153** with fluorohydrine **154**, under Yamaguchi's mixed anhydride conditions. Fluorohydrin **154** was readily available from 1,7-octadiene by epoxydation followed by regioselective epoxide opening, while **153** was obtained in four steps from 3,5-dimethoxyphenol. The second olefin moiety in **155** was introduced by means of a Stille coupling on the corresponding aryl triflate. Finally, the RCM was accomplished using 1st generation Grubbs catalyst in refluxing DCM followed by

catalytic hydrogenation of the double bond affording the targeted fluorinated analog **156** (Scheme 43). The RCM gave rise to a 20:1 (*E*:*Z*) mixture; however, this mixture was inconsequential since the double bond was hydrogenated in the next step. Next, the authors tried to apply their own enantioselective ring opening of epoxides with a fluoride source to prepare **154** in an optically pure manner.[96] However, the ring opening of 7,8-epoxy-1-octene proceeded in low enantioselectivity (50 % e. e.).[95b] For that reason, enantioenriched (+)- (*R*)-**154** was obtained by *Candida Antartica* lipase (CAL, Novozym435) catalyzed acetylation with vinyl acetate. Thus, both enantiomers of the final product were obtained.

Scheme 43. Synthesis of a Fluorinated Analog of *Lasiodiplodin*

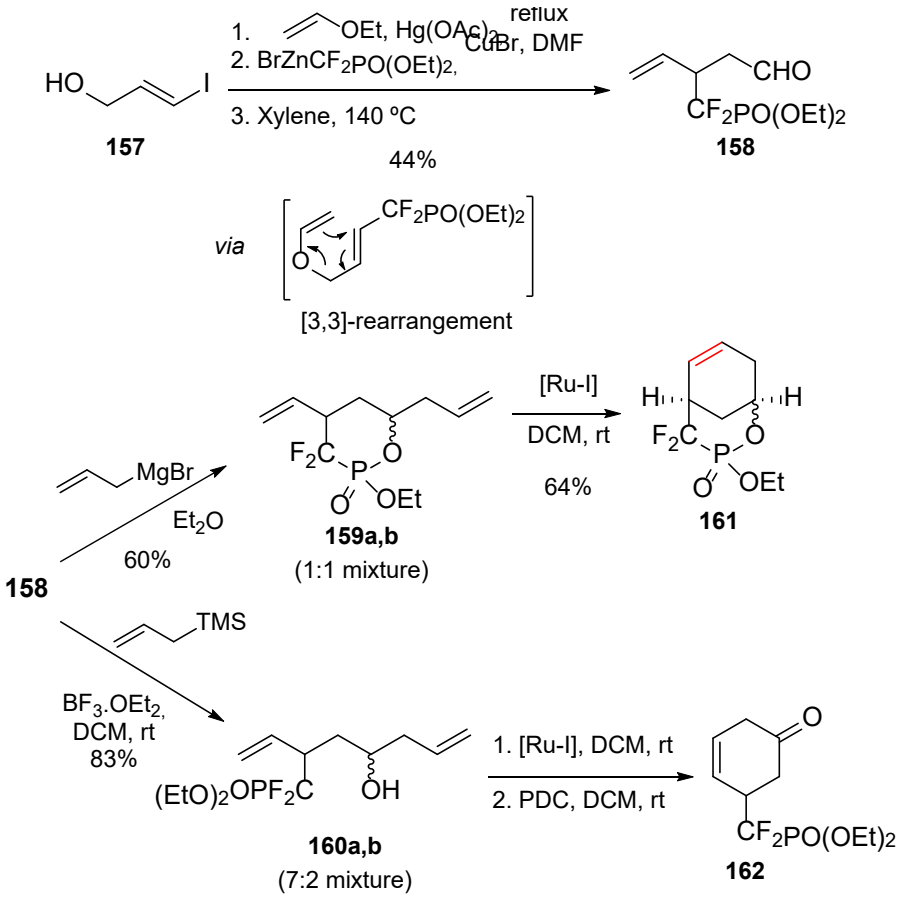


2.2.3. Miscellanea

In section 2.1 several examples of isosteric replacement of an oxygen atom by a CF_2 unit have been discussed. Besides the aforementioned examples, Percy extensively applied this isosteric replacement to the synthesis of difluorophosphates.[97] Specifically, secondary inositol-related secondary difluorophosphate derivatives were obtained using a [3,3] sigmatropic rearrangement

and an RCM as key steps.[98] The reaction sequence started with vinylation of the known alcohol **157** followed by Shibuya-Yokomatsu coupling and a Claisen-type Dauben-Dietsche rearrangement affording enal **158**, formally arising from the selective 1,4-addition of a difluoromethylphosphonate anion to 2,4-pentadienal (Scheme 44). Allylation under either basic (Grignard addition) or acidic conditions (Sakurai's BF_3-catalyzed allyltrimethylsilane addition) gave rise to different outcomes; isomeric cyclic difluorophosphonates **159a,b** were obtained for the former, while isomeric homoallylic alcohols **160a,b** were formed for the latter (Scheme 44). Both isomeric mixtures were in turn subjected to RCM conditions: **159a** afforded **161** leaving **159b** unaltered and the mixture of cyclohexenols achieved from **160a,b** was readily converged to cyclohexenone **162** by PDC oxidation (Scheme 44).

Scheme 44. A Rearrangement-Based Approach to Secondary Difluorophosphonates



1. OEt, Hg(OAc)2, reflux
2. BrZnCF2PO(OEt)2, CuBr, DMF
3. Xylene, 140 ºC
44%
HO
I
157
CHO
CF2PO(OEt)2
158
via
CF2PO(OEt)2
O
[3,3]-rearrangement
MgBr
Et2O
60%
158
F2C
P
O
OEt
159a,b
(1:1 mixture)
[Ru-I]
DCM, rt
64%
H
H
161
TMS
BF3.OEt2,
DCM, rt
83%
(EtO)2OPF2C
OH
160a,b
(7:2 mixture)
1. [Ru-I], DCM, rt
2. PDC, DCM, rt
O
CF2PO(OEt)2
162

2.3. Ring-Closing Metathesis of Substrates Containing a Fluoroolefin or a Trifluoromethyl Substituted Olefin

Vinyl fluorides have proved to be versatile building blocks for the preparation of more complex organic molecules.[99] Moreover, the interest in these compounds originates from their bioisosteric behavior with amides[100] or peptides.[101] Figure 5 visualizes the bioisosterism[99c] and atom charges.[101a] Last but certainly not least, vinyl fluorides are frequently constituents of pharmacologically important compounds.[102]

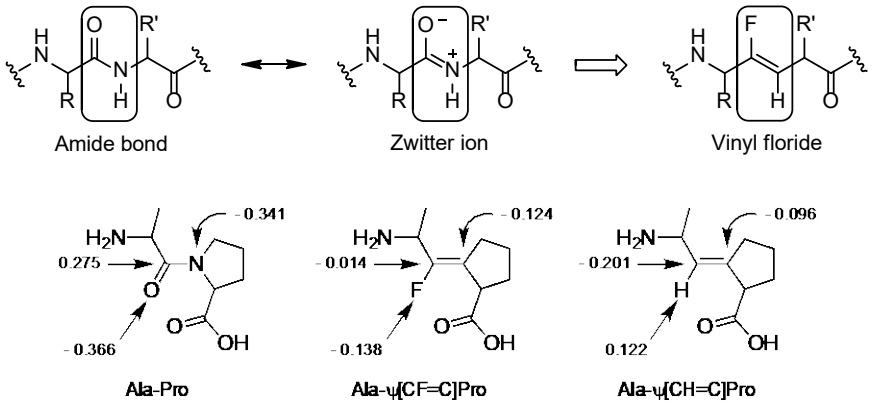
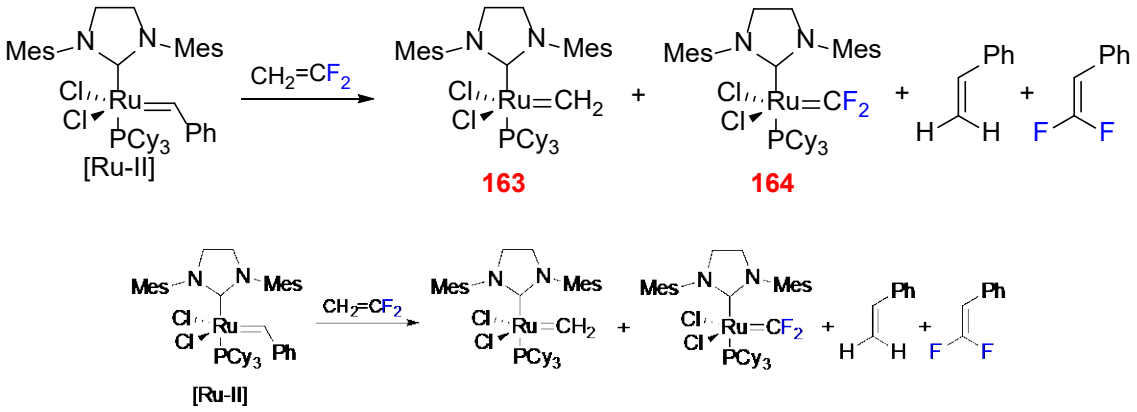


Figure 5. Fluoroalkenes as peptide mimetics

However, it was not until 2003 that any successful olefin metathesis including vinyl fluorides was published, although there had been several futile attempts. In 1983 Beauchamp and coworkers speculated about nickel-catalyzed metathesis of directly fluorinated olefins and concluded that "the nickel ion carbene and difluorocarbene may be only marginally able to catalyze the metathesis of ethylene and tetrafluoroethylene to form 1,1-difluoroethylene".[103] In 1997 and 2000 Grubbs and coworkers reported that ring closing metathesis reactions of vinyl halides failed using both the first generation ruthenium alkylidene complex [Ru-I] and the more reactive molybdenum alkylidene complex [Mo-I].[104] Applying the more reactive second

generation ruthenium alkylidene [Ru-II] pre-catalyst (Figure 1), they observed the metathesis with difluoroethylene and isolated and characterized both the Ru=CH_2 **163** and the Ru=CF_2 **164** complexes by X-ray analysis (Figure 6) as well as styrene and β,β-difluorostyrene (Scheme 45).

Scheme 45. Stoichiometric Metathesis of 1,1-Difluoroethylene



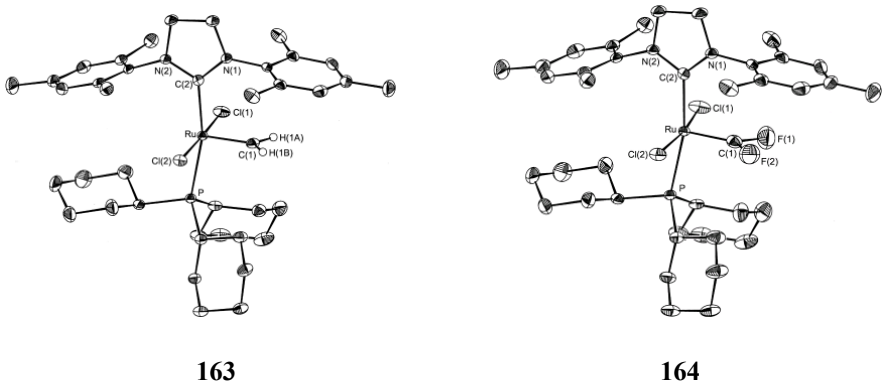
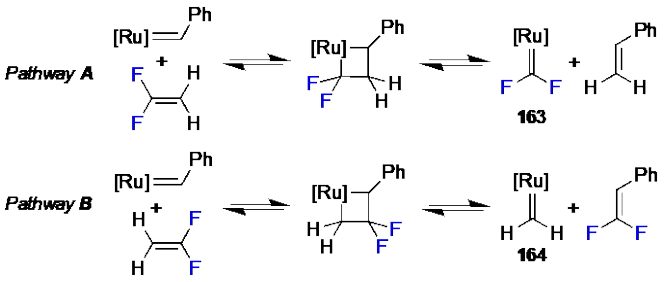


Figure 6. X-ray structure of Ru-complexes

Surprisingly, ethylene and tetrafluoroethylene, the products of a second metathesis step, were not found among the products indicating that the reaction is stoichiometric and not catalytic. Nevertheless, formation of the complexes required the metathesis of 1,1-difluoroethylene double bond and hence, this reaction was the first olefin metathesis example involving a vinylfluoride. At room temperature and under an atmosphere of 1,1-difluoroethylene, the complexes were

formed in a 2:3 ratio, while the amount of the difluorocarbene complex increased to >98% at 60 °C. Thus, reaction pathway **A** is favored over **B** (Scheme 46).[105]

Scheme 46. Possible Pathways for the First Metathesis Step



Comparison of the olefin metathesis activity in ROMP of cycloocta-1,5-diene of the original Grubbs second generation catalyst and the complexes **163** and **164** revealed that methylene complex **164** was less active than [Ru-II] (**IV** in Figure 1), while **163** was even less active and a poor catalyst.[105] A couple of years ago a monofluorocarbene complex analogous to **164** was generated from β-fluorostyrene and [Ru-II]. This complex exhibited some catalytic activity, but was slow and less stable compared to [Ru-II]. Moreover, when using this complex, the fluorinated part is cleaved off and fluorine free homocoupling products are formed. However, reaction of dec-5-ene with excess of fluoroethylene gave maximum 25% of cross coupled *cis/trans*-isomeric 1-fluoro-1-hexenes.[106]

2.3.1. Ring closing metathesis reactions involving 2-fluoroallyl moieties

First attempts to use α,ω-dienes (Figure 7) with one of the double bonds bearing a fluorine in position 2 with either 2 mol% Grubbs catalyst [Ru-II] or Hoveyda's catalyst [Ru-III] (Figure 1) in toluene at 80 °C failed to produce cyclized products. The reactions were very slow and if any, gave only minor amounts of homodimeric[107] products formed by cross-metathesis of the non-fluorinated double bonds.[108]

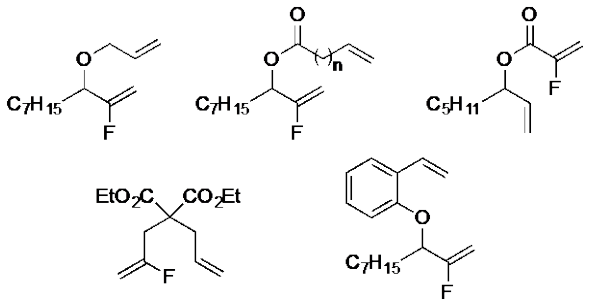


Figure 7. Monofluorinated α,ω-dienes which failed to cyclize

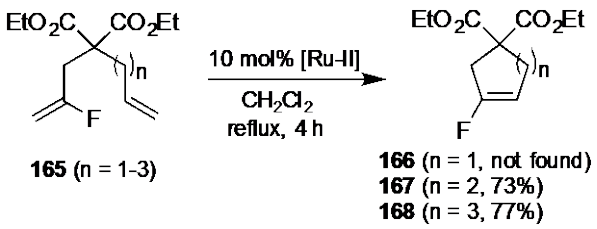
In contrast, similar reactions with non-fluorinated dienes led to cyclized products in moderate to good yields using the same catalysts.[109]

In 2003/2004 the groups of Brown, Haufe, and Rutjes reported the first successful RCM reactions incorporating fluoroalkenes independently and almost simultaneously. [108,110,111]

2.3.1.1. Ring closing metathesis reactions to form carbocycles

In the carbocyclic series, probably facilitated by the Thorpe-Ingold effect of geminal carboxyl groups, the RCM proceeded to form the six- and seven-membered products **167** and **168**,[111] while the corresponding fluorocyclopentene derivative **166** was not observed, neither under the conditions shown in Scheme 47 [111] nor with 2 mol% of catalyst [Ru-III] in toluene at 80 °C for 2 hours.[108] The starting materials **165** (n = 1-3) were prepared from diethyl 2-(2-fluoroallyl)malonate by reaction with the corresponding ω-bromoalkene in the presence of NaHMDS.

Scheme 47. Formation of Fluoroalkenes via RCM

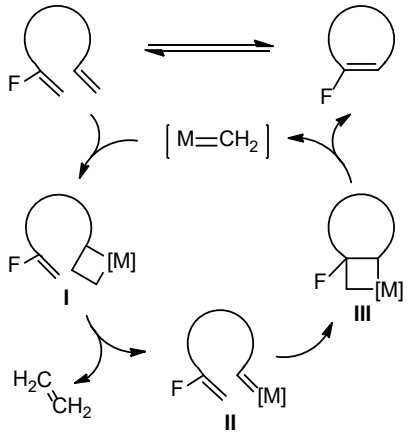


165 (n = 1-3)

166 (n = 1, not found)
167 (n = 2, 73%)
168 (n = 3, 77%)

Brown *et al.* observed that RCM reactions incorporating vinyl fluorides typically proceeded slower than their fluorine-free parent compounds. Consequently, they suggested that the first step of the catalytic cycle should be the reaction of the precatalyst with the non-fluorinated double bond forming the metallacyclobutane **I** (Scheme 48). After splitting off ethylene, the metalla alkylidene complex **II** is formed, which undergoes formal [2+2]-cycloaddition to form the metallabicycle **III**. Cycloreversion regenerates the catalyst and delivers the final RCM product containing a vinylic fluorine. The failure of the RCM to form the five-membered fluoroolefin **166** was attributed to a combination of lower reactivity of the fluorinated double bond and greater ring strain energy developing in the formation of the metallabicycle **III** giving rise to side-reactions.[111]

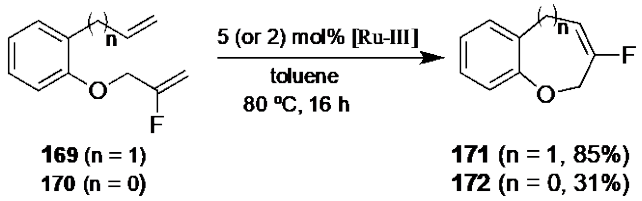
Scheme 48. Catalytic Cycle for RCM of Vinyl Fluorides



2.3.1.2. Ring closing metathesis reactions to form oxygen heterocycles

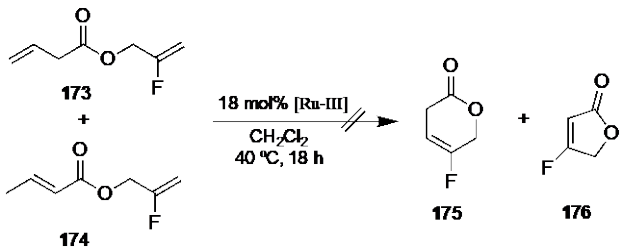
As for carbocyclic systems, there are only few examples for the preparation of fluorinated unsaturated oxygen heterocycles. The reaction of compound **169** with 20 mol% [Ru-II] gave 40% of the partially purified benzooxepin derivative **171**.[111] A significant improvement was achieved with 5 mol% of Hoveyda's catalyst [Ru-III] in toluene at 80 °C. Under these conditions **171** was isolated in 85% yield, while the corresponding 2-fluorochromene **172** was available from styrene **170** in 31% yield under the same conditions with 2 mol% of [Ru-III] (Scheme 49).[112] Compounds **169** and **170** were prepared from the corresponding phenols and 2-fluoroallylchloride [111] or 2-fluoroallyltosylate,[113] respectively. The corresponding reaction with the but-2-en-1-yl derivative failed to give benzooxepin derivative **171**.

Scheme 49. Synthesis of 2-Fluorochromene and its Homologue



Also, all attempts to carry out the RCM of 2-fluoroallylbut-3-enoate (**173**) or 2-fluoroallylcrotonate (**174**) (submitted as a 1.2:1 mixture of both) with either catalyst [Ru-II] or [Ru-III] failed to give the corresponding fluorinated, unsaturated δ- or γ-lactones **175** or **176**, only 17 % of the 'homodimers' were obtained with 18 mol% of catalyst [Ru-III] in refluxing methylene chloride for 18 hours (Scheme 50).[114]

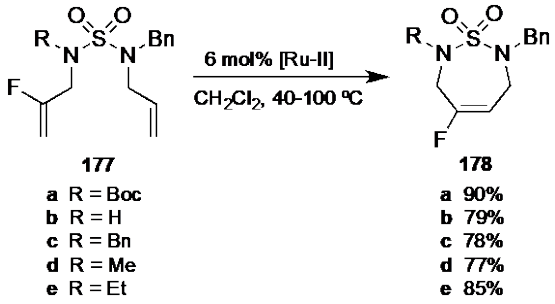
Scheme 50. Cyclization to Unsaturated Fluorinated δ- and γ-Lactones Failed



2.3.1.3. Ring closing metathesis reactions to form nitrogen heterocycles

The reactions with amino compounds to form *N*-heterocycles were more successful. Brown and coworkers published the first examples of this type of olefin metathesis reactions in 2003. The sulfamides **177** prepared in four known steps from chlorosulfonyl isocyanate gave the seven-membered target compounds **178** in good yields in the presence of 6 mol% catalyst [Ru-II] by refluxing in methylene chloride (**177a** and **177b**) or heating at 100 °C in sealed, crimped-cap vials (Scheme 51).[111]

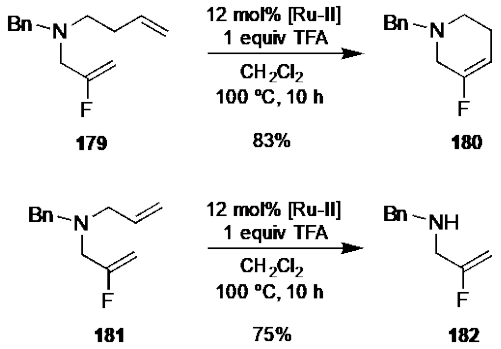
Scheme 51. RCM of Sulfamides



In their quest for other fluorinated azadiene substrates, which might undergo RCM reactions, these authors found that *N*-benzyl-*N*-(2-fluoroallyl)but-3-en-1-amine (**179**) was cyclized to 1-benzyl-5-fluoro-1,2,3,6-tetrahydropyridine (**180**) in the presence of 12 mol% [Ru-II] and 1 equivalent of TFA,[115] while the corresponding prop-2-en-1-amine **181** underwent deallylation to form **182** under the same conditions (Scheme 52). A principally known isomerization in the

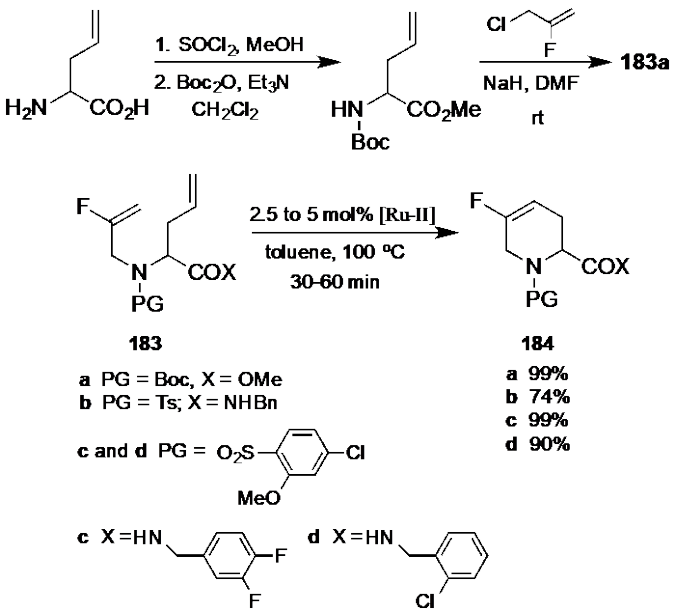
presence of catalyst [Ru-II] [116] of the allylamine moiety towards the corresponding enamine and *in situ* hydrolysis might account for this unexpected result.[112]

Scheme 52. Synthesis of *N*-Benzyl-5-fluoro-1,2,3,6-tetrahydropyridine (180)



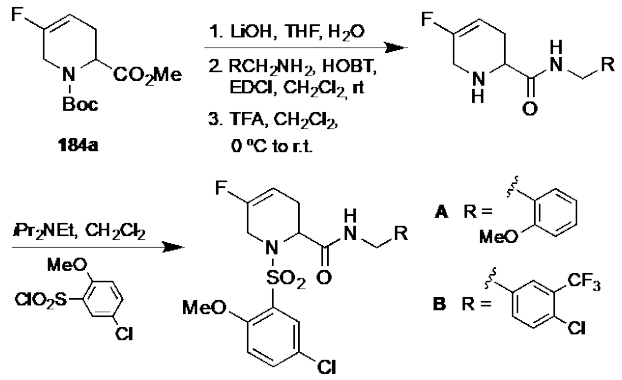
A couple of years later, Rutjes and co-workers adapted this strategy for the preparation of pipecolic acid derivatives. Thus, allylglycine was transformed to the metathesis precursor **183a** in three steps. In order to lower the basicity, the amine was Boc- or Ts-protected or substituted by other arylsulfonyl groups (Scheme 53). By heating in toluene at 100 °C in the presence of 2.5 or 5 mol% of catalyst [Ru-II] for 30-60 min, the substituted pipecolic acid derivatives **184a-d** were formed from **183a-d** in 74-99% yield.[117]

Scheme 53. Synthesis of Fluorinated Pipecolic Acid Derivatives 184



Compound **184a** prepared in four steps from allyl glycine in 71% overall yield was used in some applications as shown in Scheme 54.[117]

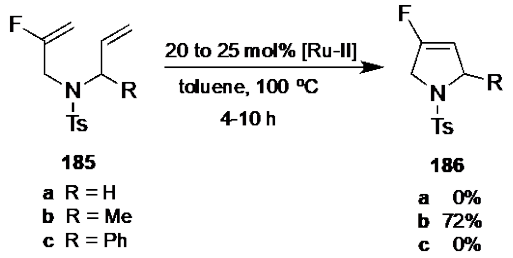
Scheme 54. Synthesis of *N*-Arylsulfonylpipecolic Acid from Amides 184a



Also, the effect of the ring size, of additional substituents in the α- or in γ-position to nitrogen as well as the electron withdrawing third substituent on nitrogen on the RCM outcome, was investigated. Thus, of the *N*-tosyl-4-aza-2-fluorohepta-1,7-dienes **185** when heated with 20 mol% catalyst [Ru-II] in toluene at 100 °C, only methyl derivative **185b** gave the corresponding

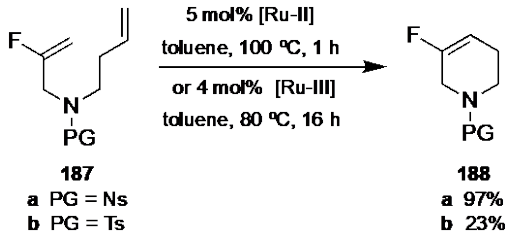
pyrroline **186b** in 72% yield, while the others failed to cyclize.[118] RCM of **185a** also failed with catalyst [Ru-III] (Scheme 55).[112]

Scheme 55. Synthesis of Fluorinated Pyrrolines



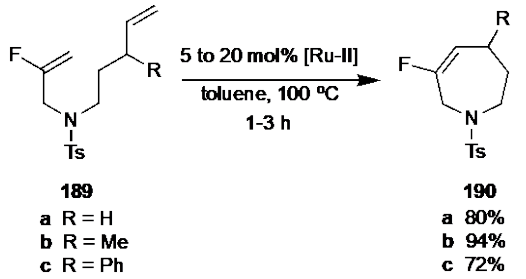
A fluorinated dihydropyridin **188a** was synthesized in 97% yield from **187a** with the nosyl protecting group using 5 mol% of catalyst [Ru-II].[118] The reaction with the corresponding tosylate was less successful providing **188b** in 23% yield, using 4 mol% of the Hoveyda's catalyst [Ru-III] (Scheme 56).[112]

Scheme 56. Synthesis of *N*-Protected Dihydropyridines



RCM reactions to form tetrahydro-1*H*-azepins **190** were successful (72-94% yield) by heating the precursors **189** with 5-20 mol% of catalyst [Ru-II] in toluene at 100 °C for 1-3 hours (Scheme 57).[118]

Scheme 57. Synthesis of Fluorinated Tetrahydro-1*H*-azepines 190

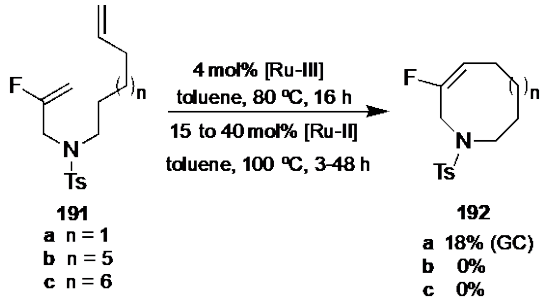


189
a R = H
b R = Me
c R = Ph

190
a 80%
b 94%
c 72%

In case of the reactions of homologs of compound **189a**, only the eight-membered heterocycle **192a** was formed from **191a** to some extent (18% in GC) together with 5% of the 'homodimer' with 4 mol% of catalyst [Ru-III] in toluene (Scheme 58).[112] With catalyst [Ru-II] diene **191a** gave the seven-membered **190a** after isomerization of the non-fluorinated double bond and split off of propylene in RCM, while the twelve- and thirteen-membered rings were not formed at all in the presence of up to 40 mol% of catalyst [Ru-II].[118]

Scheme 58. Preparation of a Fluorinated Hexahydroazocine 192



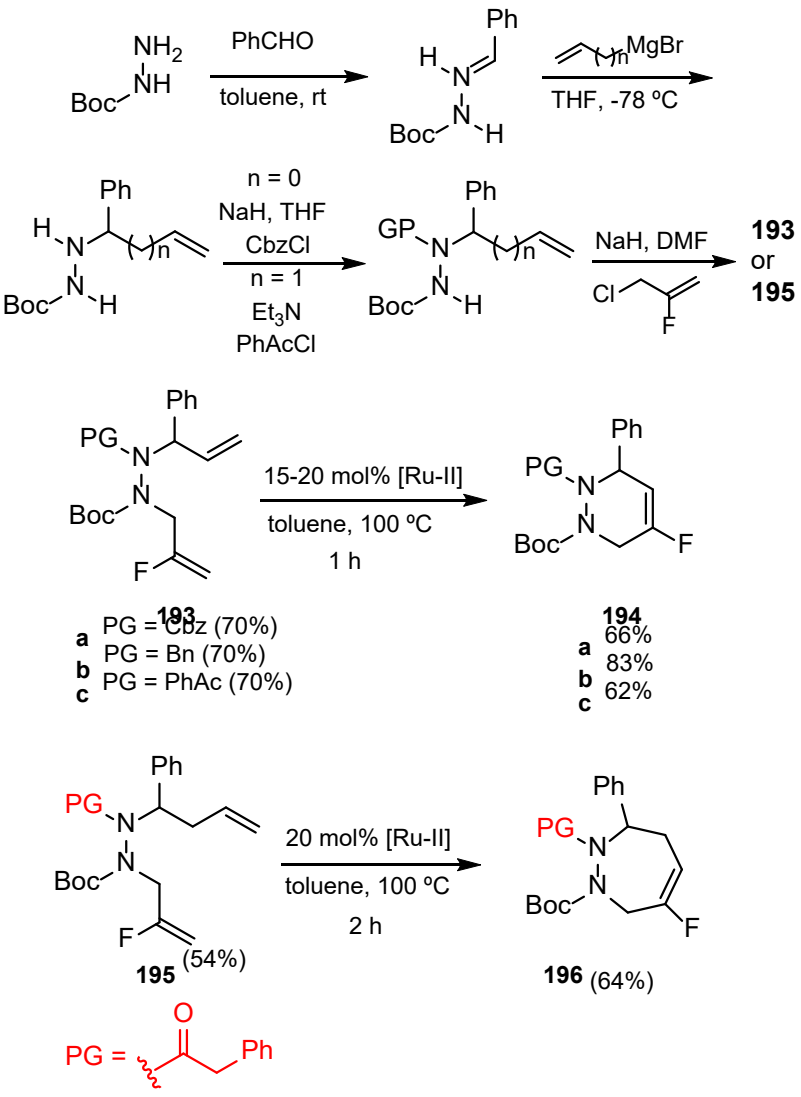
191
a n = 1
b n = 5
c n = 6

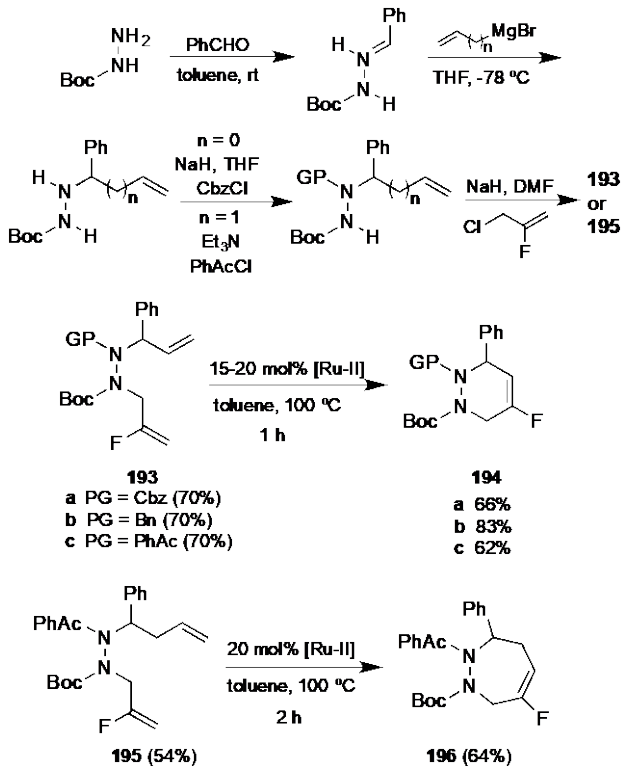
192
a 18% (GC)
b 0%
c 0%

Cyclic hydrazine derivatives belong to a group of biologically relevant compounds, which were developed as antibiotic substances. A couple of fluorine-free representatives[119] as well as fluorinated derivatives[120] were prepared by RCM. The metathesis precursors were synthesized from *tert*-butyl carbazate in four steps, as shown in Scheme 59. Different protecting groups were used in the RCM step in order to reduce the basicity of the nitrogen atoms. In this way, the fluorinated, unsaturated pyridazine derivatives **194** were prepared in moderate to good yields

starting from **193** using 15-20 mol% of Grubbs-II catalyst [Ru-II] in toluene at 100 °C. Also, one seven-membered ring hydrazine derivative **196** was synthesized from **195** in 64% yield (Scheme 59).[120]

Scheme 59. Synthetic Sequence towards a Fluorinated Tetrahydropyridazine and a 2,3,5,6-Tetrahydro-1,2-Diazepine Derivatives

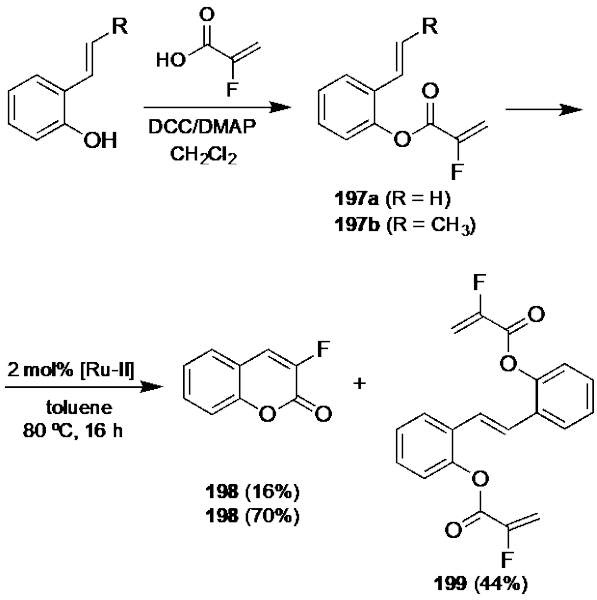

NH2
NH
Boc
PhCHO
toluene, rt
Ph
H
N
N
Boc
H
MgBr
n
THF, -78 ºC
Ph
H
N
n
N
Boc
H
n = 0
NaH, THF
CbzCl
n = 1
Et3N
PhAcCl
Ph
GP
N
n
N
Boc
H
NaH, DMF
Cl
F
193
or
195
Ph
PG
N
N
Boc
F
15-20 mol% [Ru-II]
toluene, 100 ºC
1 h
Ph
PG
N
N
Boc
F
193
a PG = Cbz (70%)
b PG = Bn (70%)
c PG = PhAc (70%)
194
a 66%
b 83%
c 62%
Ph
PG
N
N
Boc
F
195 (54%)
20 mol% [Ru-II]
toluene, 100 ºC
2 h
Ph
PG
N
N
Boc
F
196 (64%)
PG =
O
Ph



2.3.1.4. Ring closing metathesis reactions to form lactones

Similarly to the preparation of cyclic ethers, coumarin derivative **198** was also prepared from the corresponding fluoroacrylate **197a** using 2 mol% of catalyst [Ru-II]. However, **198** was isolated in only 16% yield in addition to 44% of the 'homodimeric' compound **199**.[108] The isolated yield was significantly increased to 70% by replacing the vinyl by a prop-2-en-1-yl substituent **197b** (Scheme 60). The starting materials **197a,b** were prepared from the corresponding phenols and α-fluoroacrylic acid in the presence of DCC/DMAP in dichloromethane.[112]

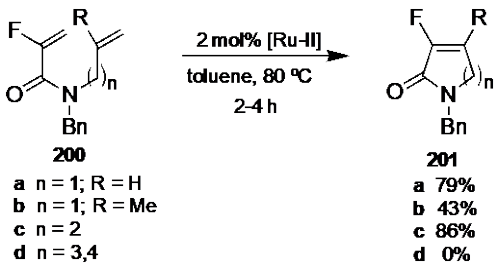
Scheme 60. Synthesis of 3-Fluorocoumarin by RCM



2.3.1.5. Ring closing metathesis reactions to form lactams

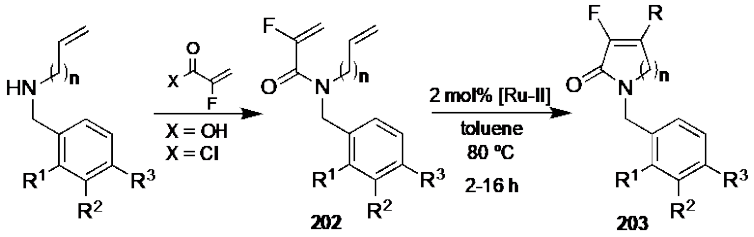
First experiments using *N*-alkenyl-*N*-benzyl-*N*-(2-fluoroacryl)amides **200** instead of the corresponding *N*-(2-fluoroallyl)amines such as **179** revealed the usefulness of the former compounds for RCM reactions, leading to fluorinated α,β-unsaturated lactams **201** in the presence of 2 mol% of catalyst [Ru-II] at 80 °C in toluene (Scheme 61). Initial experiments showed that the yield for γ-lactams was slightly lower when compared to the corresponding δ-lactams, while a tetrasubstituted γ-lactam **201b** was formed in 43% yield.[108] The yield was not improved when 7 mol% of catalyst [Ru-II] were used at 100 °C.[117] Higher homologs such as seven- or eight-membered lactams were not formed,[108,117] while related non-fluorinated medium-sized rings could be synthesized by RCM.[37]

Scheme 61. Synthesis of Unsaturated *N*-Benzyl-2-Fluoro-γ- and δ-Lactams by RCM



In order to fathom the scope and limitation of this reaction a series of aryl-substituted *N*-benzyl derivatives **202** was synthesized form the corresponding alkenyl benzylamines either with 2-fluoroacrylic acid chloride in the presence of a base or with 2-fluoroacrylic acid and EDC/HOBT or DCC/DMAP. Afterwards, compounds **202** were subjected to RCM conditions with Grubbs-II catalyst [Ru-II] to form **203** in moderate to good yields; the results are summarized in Table 4.[108,112]

Table 4. Synthesized Unsaturated *N*-Benzyl-2-Fluoro-γ- and δ-Lactams and their RCM Precursors

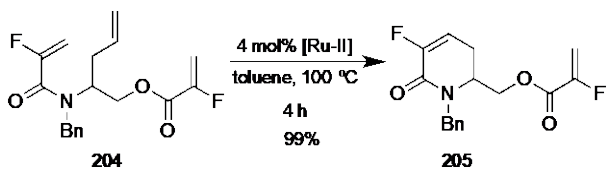


Entry	R^1	R^2	R^3	n	Products	**202**(%)	**203**(%)
1	H	H	Cl	1	**a**	30	73
2	H	Cl	H	1	**b**	40	65
3	Cl	H	H	1	**c**	43	76
4	H	H	F	1	**d**	95	70
5	H	H	F	2	**e**	57	76
6	H	F	H	1	**f**	40	77
7	H	H	CF_3	1	**g**	44	44
8	H	H	NO_2	1	**h**	46	33
9	H	CF_3	H	1	**i**	55	77
10	H	H	*t*-Bu	1	**j**	100[a)]	86
11	H	H	OMe	2	**k**	73	81
12	H	H	OMe	3	**l**	80	0
13	OMe	H	OMe	1	**m**	42	34

[a] Crude product

In compound **204**, with two alternatives for the RCM reaction, the formation of the δ-lactam **205** was favored over the formation of the fluorinated unsaturated ε-lactone (Scheme 62).[117]

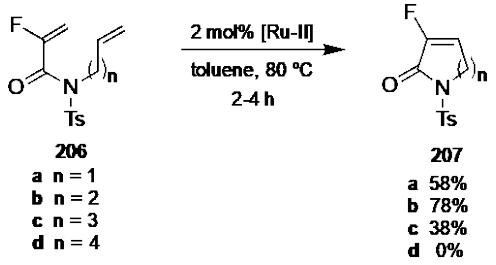
Scheme 62. Alternative Pathways for RCM



Attempts to use *N*-alkenyl-*N*-tosyl-*N*-(2-fluoroacryl)amides **206** were also successful. While the γ- and the δ-lactams **207a** and **207b** were isolated in moderate yields, the ε-lactam **207c** was

formed in a 38% share in addition to 23% of the ring-contracted δ-lactam **207b** and 39% of the 'homodimer' by heating the precursor **206c** with catalyst [Ru-II] in toluene at 80 °C for 16 h (Scheme 63). The ring-contracted **207b** was probably formed by initial isomerization of the non-fluorinated double bond and cleavage of propylene in the RCM step. The eight-membered lactam was not identified among the products. Only 6% of the 'homodimer' was found by GC/MS.[112]

Scheme 63. Synthesis of Unsaturated *N*-Tosyl-2-Fluoro-γ-, δ- and ε-Lactams

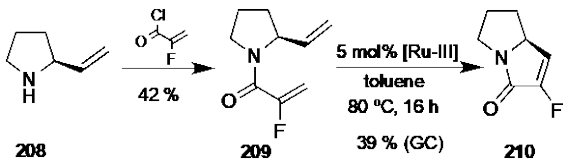


206
a n = 1
b n = 2
c n = 3
d n = 4

207
a 58%
b 78%
c 38%
d 0%

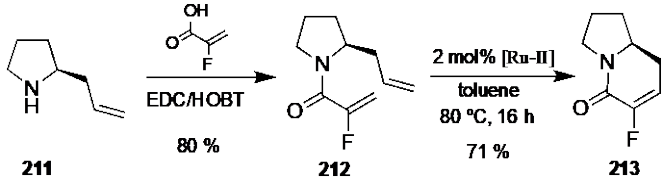
RCM application on suitably fluoroalkenyl-substituted heterocyclic systems would allow the formation of heterobicyclic analogs of alkaloids. Such reactions were already known for fluorine-free substrates.[121] Pyrrolizidine and indolizidine moieties are prevalent in natural products.[122] Thus, (*S*)-2-fluoro-5,6,7,7a-tetrahydro-pyrrolizin-3-one **210** was prepared using RCM of a vinyl fluoride as the key step.[112] Like in the synthesis of the non-fluorinated parent of **210**,[123] the starting material (*S*)-2-vinylpyrrolidine **208** was prepared in three steps from Boc-prolinol (Scheme 64). Schotten-Baumann amidation using 2-fluoroacrylchloride gave RCM precursor **209**, which was cyclized (39%, GC) with 5 mol% of Grubbs-Hoveyda catalyst [Ru-III]. However, the product could not be isolated in pure form (Scheme 64).[112]

Scheme 64. Synthesis of a Fluoro-Pyrrolizidinone



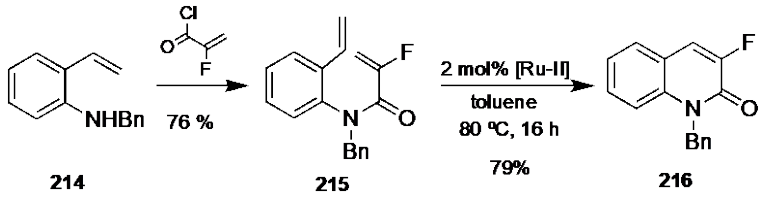
In a very similar way, the next homolog (*S*)-6-fluoro-2,3,8,8a-tetrahydroindolizin-5(1*H*)-one **213** was synthesized. First, (*S*)-2-allylpyrrolidine **211** was prepared from Boc-prolinol in three steps according to the literature[124] and coupled with 2-fluoroacrylic acid using the peptide coupling reagent EDC/HOBT to form RCM precursor **212**. With 2 mol% of Grubbs-II catalyst [Ru-II] the target indolizidine derivative **213** was isolated in 71% yield (Scheme 65).[112]

Scheme 65. Synthesis of a Fluoro-Indolizinone



Another class of biologically relevant compounds are quinolines. The fluorinated *N*-benzyl-3-fluoroquinolone **216** had been synthesized earlier by Schlosser in an eight-step sequence.[125] Starting from the commercially available 2-nitrophenylethanol, 2-(*N*-benzylamiono)styrene **214** was prepared and transferred to precursor **215** according to Schotten-Baumann amidation with 2-fluoroacrylchloride. RCM of **215** with 2 mol% of catalyst [Ru-II] in toluene at 80 °C provided the target compound **216** in 79% yield (Scheme 66).[112]

Scheme 66. Synthesis of a Fluorinated *N*-Benzyl-3-Fluoroquinolone

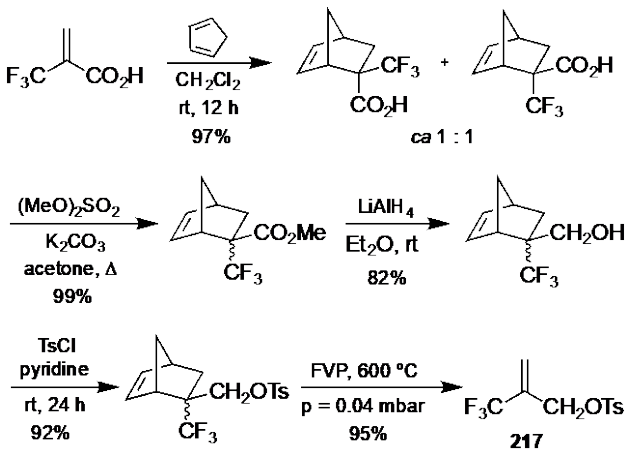


2.3.2. Ring closing metathesis reactions involving 2-(trifluoromethyl)allyl moieties

Among the fluorinated building blocks for pharmaceutical and agrochemical applications trifluoromethyl substituted compounds are particularly important. While there are numerous methods for the preparation of CF_3-aromatics[126] and of compounds available by trifluoromethylation methodologies,[127] it is still a challenge to introduce trifluoromethyl groups into non-aromatic carbo- and heterocycles using alternative ways.[128] Therefore, ring closing metathesis might serve as an efficient approach to prepare suitable basic structures.

Rutjes *et al.* published pioneering work in this field a decade ago.[110] A key precondition for this type of chemistry is the preparation of a suitable 2-(trifluoromethyl)allyl electrophile. Efforts to reduce the commercially available 2-(trifluoromethyl)acrylic acid or its derivatives to the corresponding allylic alcohol were not practicable. Therefore, the authors developed a high yielding (up to 3g scale) five-step procedure for tosylate **217** (Scheme 67).

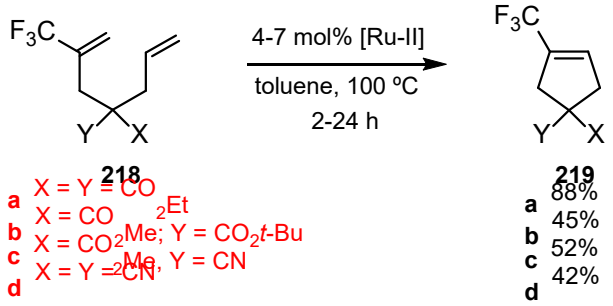
Scheme 67. Synthesis of (2-Trifluoromethyl)-Allyltosylate (216)

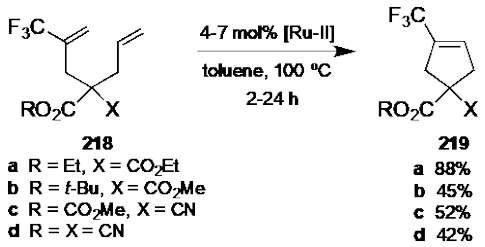


2.3.2.1. Synthesis of unsaturated, trifluoromethylated carbocycles and dihydrofuran derivatives

The malonate and malonitrile precursors **218** were prepared *via* consecutive alkylation with allyl bromide and tosylate **217** under standard conditions. Ring closing metathesis reactions were successful by portion-wise addition of Grubbs II catalyst [Ru-II] under the conditions shown in Scheme 68 within 2-24 hours.[110]

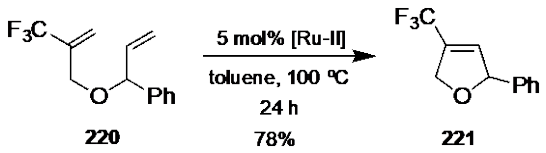
Scheme 68. Synthesis of Substituted Trifluoromethylcyclopentenes





As the only example for the preparation of an unsaturated, trifluoromethyl substituted oxygen heterocycle, ether **220** prepared from 3-phenylprop-1-en-3-ol and tosylate **217**, underwent an RCM reaction to form dihydrofuran derivative **221** (78% yield) in the presence of 5 mol% [Ru-II] in toluene at 100 °C within 24 hours (Scheme 69).[110]

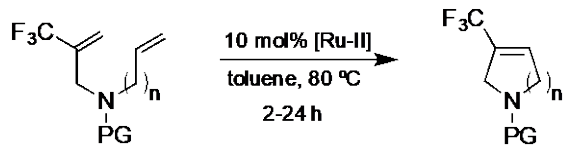
Scheme 69. Synthesis of a 3-(Trifluoromethyl)-Dihydrofuran



2.3.2.2. Synthesis of unsaturated, trifluoromethylated nitrogen heterocycles

Nitrogen heterocycles are particularly interesting from a synthetic point of view. Therefore, Rutjes and co-workers made an effort to prepare trifluoromethylated pyrrolines and dihydropyridines by RCM reactions. In this way, allyl derivatives **222a,b** cyclized to form **223a,b** in the presence of 10 mol% of Grubbs II catalyst **B**. In contrast, the reaction failed in the case of the *N*-benzyl derivative **222c**. The corresponding dihydropyridine **223c** was not detected even after 48 hours (Scheme 70). The more basic *N*-benzyl moiety might prevent RCM. Also, the corresponding trifluoromethyl substituted *N*-benzyl acrylates did not cyclize (not shown).[110]

Scheme 70. Synthesis of *N*-Protected 3-(Trifluoromethyl)-Pyrrolines

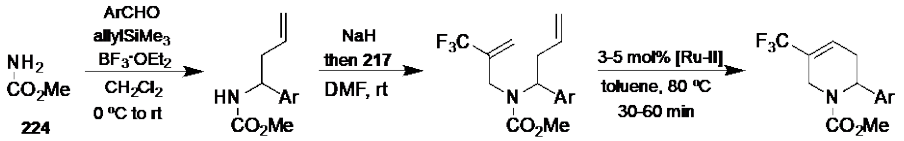


222
a n = 1, PG = Bz
b n = 1, PG = Boc
c n = 2, PG = Bn

223
a 68%
b 97%
c 0%

On the other hand, a series of carbamates **226** bearing a substituted aryl ring in the α-position of the homoallyl moiety in addition to the 2-(trifluoroallyl)group were cyclized to the corresponding 3-(trifluoromethyl)-*N*-carbamoyl-3,4-dihydropyridines **227**. RCM precursors **226** were prepared from methylcarbamate **224** *via* 4-arylbut-1-enes **225** as shown in Scheme 71.[129]

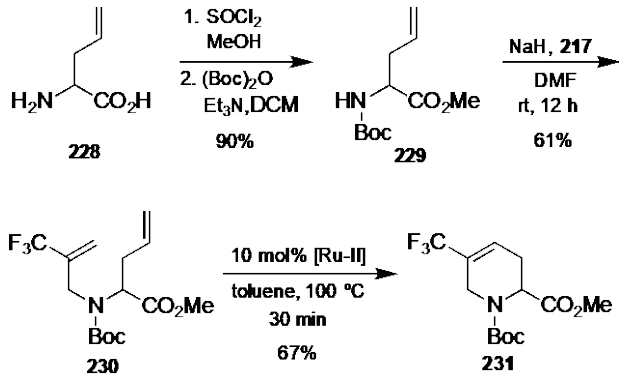
Scheme 71. Synthetic Sequence towards *N*-Protected 3-(Trifluoromethyl)-6-Aryl-Tetrahydropyridines



	225	**226**	**227**
a Ar = 4-F-C_6H_4	50%	56%	80%
b Ar = 2,4-Cl_2-C_6H_3	68%	60%	63%
c Ar = 3,5-Cl_2-C_6H_3	51%	70%	79%
d Ar = 4-MeO-C_6H_4	30%	46%	80%

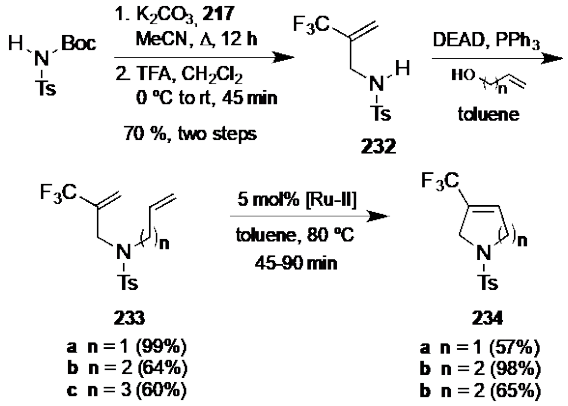
Starting from racemic allyl glycine **228**, after protection of both the amino and the carboxylic functions, RCM precursor **230** was prepared from **229** in fair yield. Upon RCM in the presence of 10 mol% of catalyst [Ru-II] the pipecolic acid derivative **231** was isolated in 67% yield (Scheme 72).[129]

Scheme 72. Synthetic Sequence to Form an *N*-Boc-3-(Trifluoromethyl)-Pipecolic Acid Ester



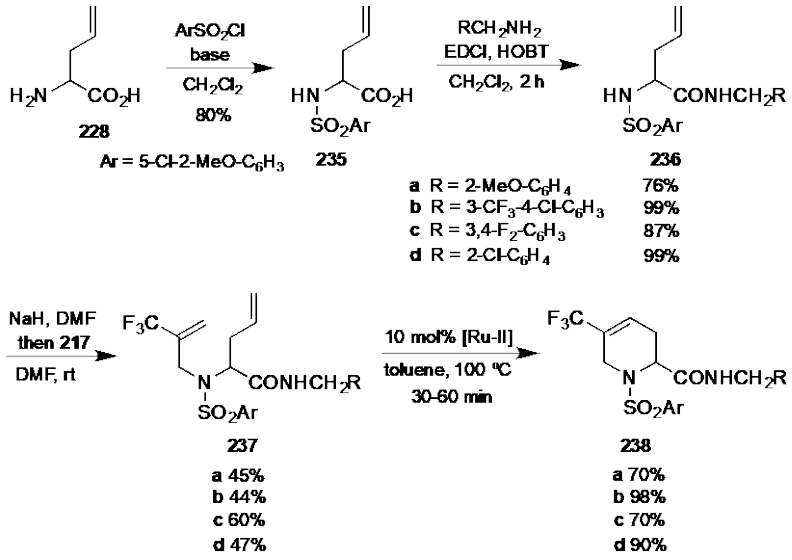
N-Tosyl protected bis-alkenylamines have been shown to be suitable precursors for olefin metathesis reactions. Thus, *N*-alkenyl-*N*-(2-trifluoromethyl)allyl sulfonamides **233** were synthesized by alkylation of *tert*-butyl tosylcarbamate with 2-(trifluoromethyl)allyl tosylate **217** to form **232** and underwent a subsequent reaction with ω-hydroxyalkenes. Upon treatment with 5 mol% of catalyst [Ru-II] in toluene at 80 °C, the expected pyrroline and dihydropyridine derivatives **234** were formed in fair to excellent yields (Scheme 73).[118]

Scheme 73. Synthesis of *N*-Tosyl-3-(Trifluoromethyl)-Pyrroline and Tetrahydropyridines



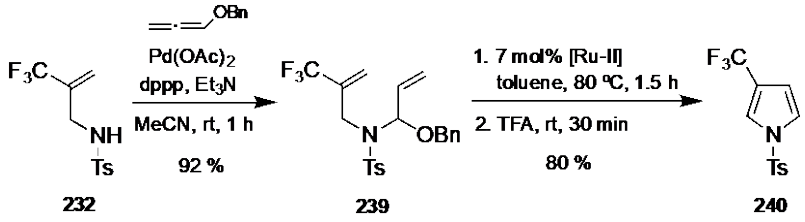
In a similar way, a small library of *N*-arenesulfonyl-pipecolic acid *N*-benzylamides **238** was prepared in four steps (Scheme 74**)**.[129]

Scheme 74. Synthesis of Unsaturated *N*- Arylsulfonyl-3-(Trifluoromethyl)-Pipecolic Acid Amides



By attachment of a potential leaving group in the α-position of the alkenyl substituent, *N*-tosyl-3-(trifluoromethyl)pyrrol **240** was prepared by alkylation of tosylate **232** with benzyloxyallene to provide aminal **239**, which on RCM with 7 mol% of catalyst [Ru-II] and subsequent treatment with TFA gave the target pyrrol **240** in 74% overall yield (Scheme 75).[118]

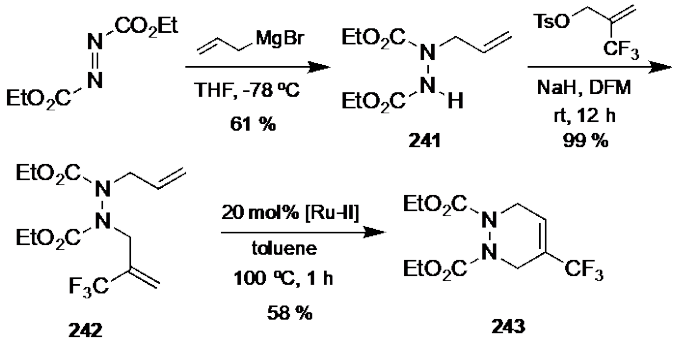
Scheme 75. Synthesis of *N*-Tosyl-3-(Trifluoromethyl)-Pyrrol



A similar methodology was also used for trifluoromethyl-substituted piperazine derivatives. The monoallylated hydrazo ester **241** was prepared starting from diethyl azodicarboxylate. In a second alkylation step, the 2-(trifluoromethyl)allyl substituent was introduced providing RCM

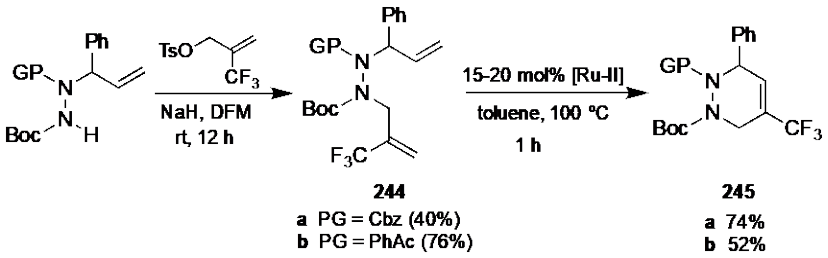
precursor **242** in excellent yield. Under the conditions shown in Scheme 72, cyclization product **243** was formed in 58% yield (Scheme 76).[120]

Scheme 76. Synthetic Sequence towards Trifluoromethylated Tetrahydropyridazine Derivative 243



In a similar way, the cyclic hydrazine derivatives **245** were also synthesized from the dienes **244**, available from the corresponding trisubstituted hydrazines (Scheme 77).[120]

Scheme 77. Synthesis of Phenylsubstituted (Trifluoromethyl)-Tetrahydropyridazines



In this section, it has been shown that RCM reactions are suitable for the straightforward synthesis of a variety of unsaturated carbocyclic and *O*- and *N*-heterocyclic vinylfluorides and the corresponding trifluoromethyl-substituted alkenes including lactones and lactams. While five- and six-membered compounds can generally be prepared in good yields, seven-membered

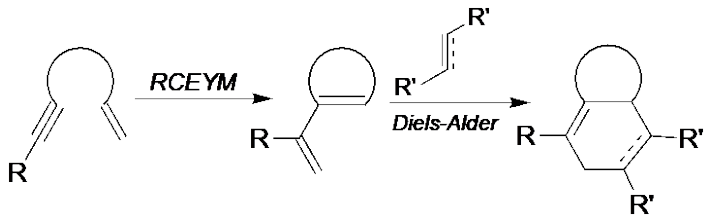
compounds are accessible, if at all, in low yields, and larger rings in general can not be synthesized, in contrast to their non-fluorinated analogs.

2.4. Ring-Closing Enyne Metathesis (RCEYM) with Fluorinated Derivatives

Enyne Metathesis has widely been used alone or in combination with Diels Alder reactions to prepare various interesting synthetic and natural products including amino acids, heterocycles etc. Enyne Metathesis can be divided into two categories: (a) Intermolecular or cross enyne metathesis (CEYM). (b) Intramolecular or ring-closing enyne metathesis (RCEYM).

As opposed to RCM, RCEYM gives rise to products bearing the same number of carbon atoms as the substrates (in RCM two carbon atoms are lost, usually forming ethylene), thus it can be considered as a cycloisomerization.[130] The reaction affords unsaturated cycles bearing a pendant-conjugated double bond (the two extra carbon atoms with respect to RCM). In turn, the thus formed 1,3-dienes are usually coupled in tandem processes, frequently in Diels-Alder reactions (Chart 2).[131]

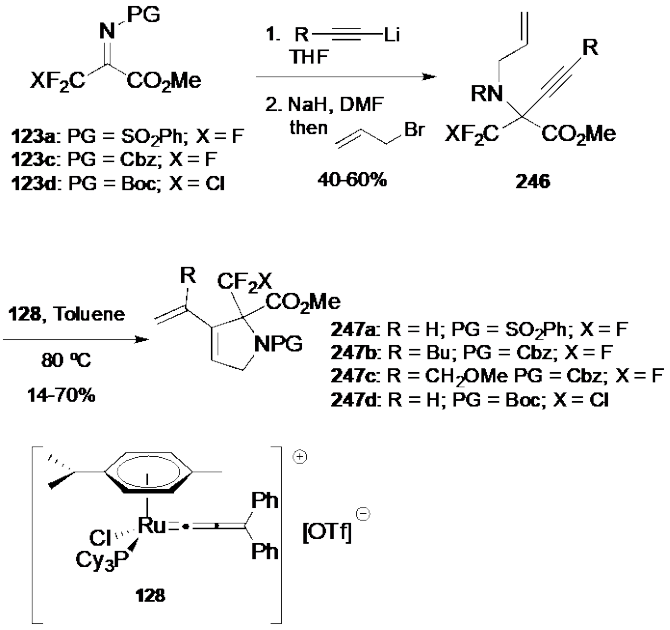
Chart 2. General scheme of an RCEYM / DA sequence



There are only few examples of RCEYM using fluorinated derivatives to be found in the literature. In this sense, in a closely related study to the one depicted in Schemes 34-37,[84] Osipov and Dixneuf described the behavior of *N*-tethered trifluoromethyl enynes towards ruthenium based metathesis catalysts.[132] The reaction sequence started with the addition of a variety of

lithium acetylides to electrophilic imines derived from fluorinated pyruvates **123a,c,d** followed by *N*-allylation under standard conditions (Scheme 78).[844a] Intermediates 1,6-enynes **246** were in turn cyclized with the same cationic allenylidene ruthenium complex **128** depicted in Scheme 35, to obtain **247** in variable yields (Scheme 78).

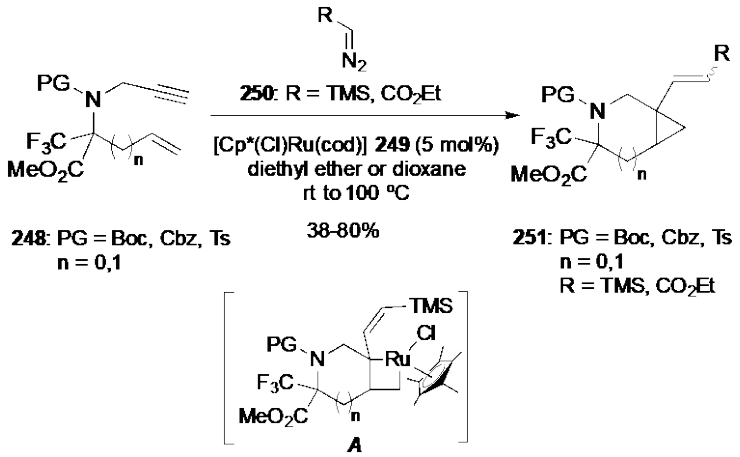
Scheme 78. RCEYM on *N*-Tethered Trifluoromethyl 1,6-Enynes



The addition of vinyl- or allylmagnesium bromide to imines **123** (Scheme 34) followed by *N*-propargylation afforded closely related 1,6- and 1,7-enynes **248** (Scheme 79).[84b,c] However, these intermediates were not used in "normal" RCEYM. Instead, they were treated with the ruthenium pre-catalyst **249**, in the presence of a diazocompound **250**, affording fluorinated bicycle [3.1.0]hexane and [4.1.0]heptanes amino esters, respectively (Scheme 79). The only difference between this carbene insertion–cyclopropanation tandem reaction and an RCEYM, besides the initial carbene insertion step, was the last step of the catalytic cycle on intermediate ***A***. The

authors suggested that *the Cp*(Cl)Ru moiety favors reductive elimination with respect to the (IMes)Cl$_2$Ru moiety leading to metathesis* (Scheme 79).

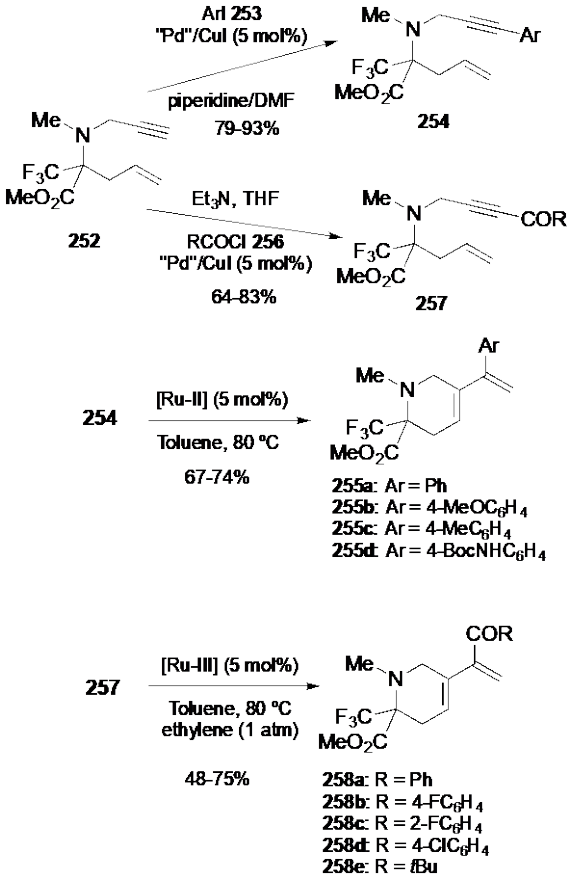
Scheme 79. Carbene Insertion / Cyclopropanation Tandem Reaction



By using the aforementioned tandem ylide formation–[2,3]-sigmatropic rearrangement strategy (see Scheme 37)[84c] the same authors synthesized 1,7-enyne **252** analogous to **248**.[84d] After observing that the RCEYM on terminal enyne **252** invariably led to considerable amounts of self cross-metathesis of the RCEYM product, the authors decided to introduce a substitutent on the triple bond by means of a palladium-catalyzed Sonogashira cross-coupling with different aryl iodides **253** (Scheme 80). Treatment of the new substituted enynes **254** with second generation Grubbs catalyst in toluene at 80 ºC afforded RCEYM products **255a-d** in good yields (Scheme 80). Interestingly, enynes derived from *ortho*-substituted aryl iodides resulted completely inert to RCEYM under various reaction conditions. The authors attributed this observation to a steric effect that would shield the triple bond, thus preventing coordination to the ruthenium center. In addition, terminal enyne **252** was cross-coupled, under palladium-catalysis, with acid chlorides **256** affording enynones **257**, which were in turn cyclized using

Hoveyda-Grubbs second generation catalyst under an atmosphere of ethylene to obtain **258a-e** (Scheme 80).

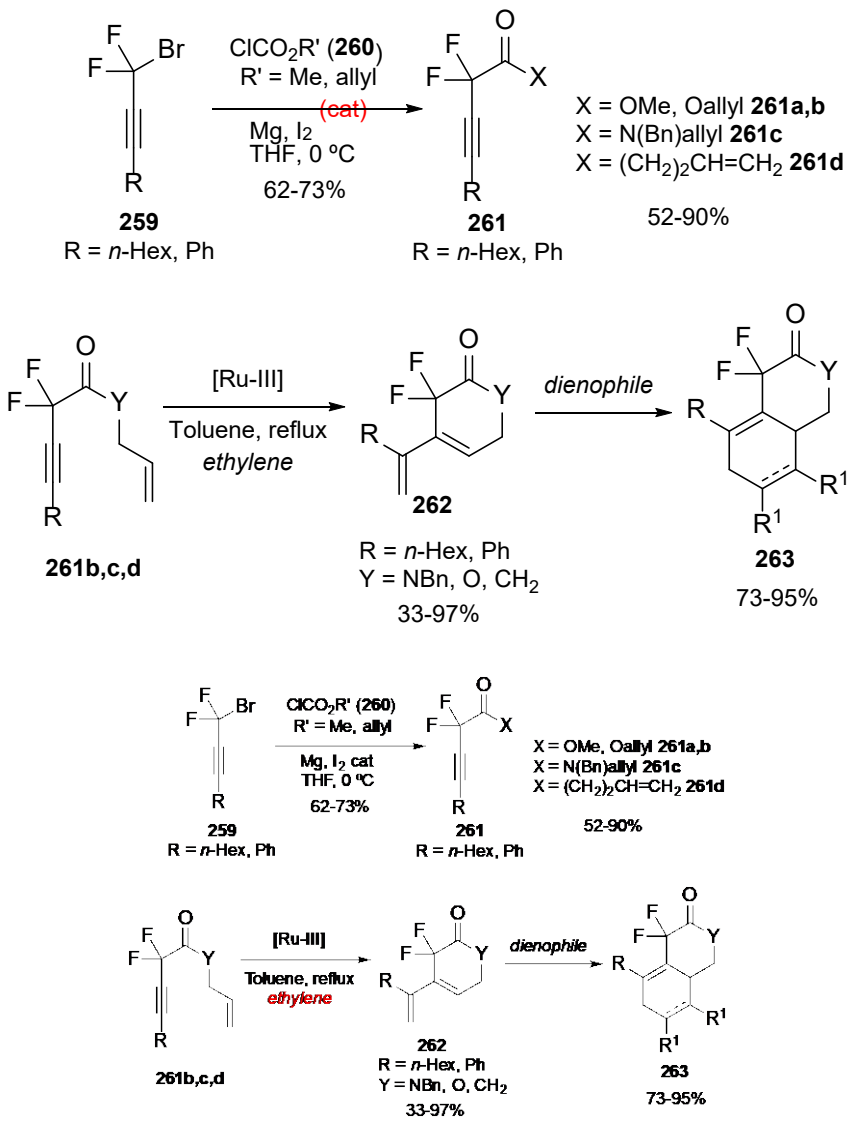
Scheme 80. RCEYM on Substituted Fluorinated 1,7-Enynes



In the context of a longstanding collaboration in the field of fluorinated β- and γ-lactams,[133,29] Hammond and Fustero reported the synthesis of *gem*-difluoromethylene containing 6-membered carbo- and heterocycles by means of RCEYM.[134] The reaction sequence began with the Grignard addition of difluoropropargyl derivatives **259** to chloroformates **260** giving rise to 2,2-difluorohomopropargyl esters **261a,b** (X = OMe, Oallyl) (Scheme 81). The corresponding amides **261c** were obtained by treatment of the latter intermediates with suitable amines in the presence

of $AlMe_3$, while the ketone **261d** required for the synthesis of the carbocycle was obtained from the corresponding Weinreb amide by treatment with homopropargylmagnesium bromide (Scheme 81). Cyclization towards lactam, lactone or cyclohexene derivatives **262** was finally accomplished using Hoveyda-Grubbs second-generation catalyst in refluxing toluene, under an atmosphere of ethylene (Scheme 81). These 2,2-difluorohomopropargyl carbonyl compounds proved to be good cycloaddition partners. Thus, the enyne metathesis of fluorinated 1,7-enyne carbonyl compounds **261** furnished the six-membered diene ring, which proved to be an efficient diene in a Diels-Alder reaction to afford fluorinated carbo- and heterocycle derivatives **263**. If the reaction is carried out in the presence of an extra olefin an additional CM/RCEYM tandem process takes places (Scheme 81).[134b]

Scheme 81. RCEYM on *gem*-Difluoropropargyl Derivatives



In this process, the *crucial importance* of ethylene in the RCEYM of 1,7-enynes synthesized from substituted difluoropropargyl bromides was demonstrated. The beneficial effect of ethylene was discovered by Mori *et al.* enabling for the preparation of 1,3-dienes, suitable for either inter- or intramolecular Diels-Alder reactions in a sequential or tandem manner.[135] Mori *et al.* were the first to envisage that ethylene gas could be employed as one of the reaction partners in the intermolecular enyne metathesis reaction.

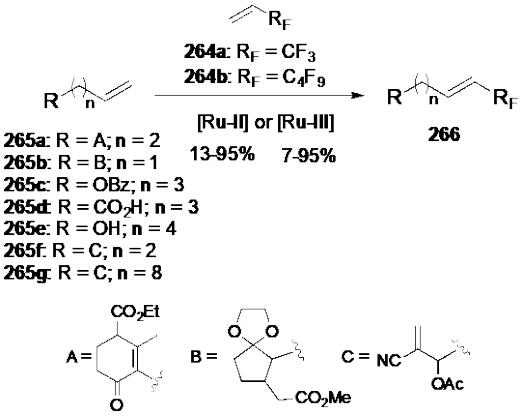
3. CROSS METATHESIS (CM)

Intermolecular olefin metathesis (cross-metathesis, CM) has found narrower applications than its intramolecular counterpart (ring-closing metathesis, RCM) discussed in the previous section.[136] This general trend is probably even more pronounced for fluorine containing olefins. In this section, the results obtained with regard to cross-metathesis with fluorinated olefins will be divided in three subsections: 3.1. CM with fluorinated derivatives; 3.2. CM in fluorous synthesis and 3.3. CEYM (cross enyne metathesis).

3.1. Cross Metathesis (CM) with Fluorinated Derivatives

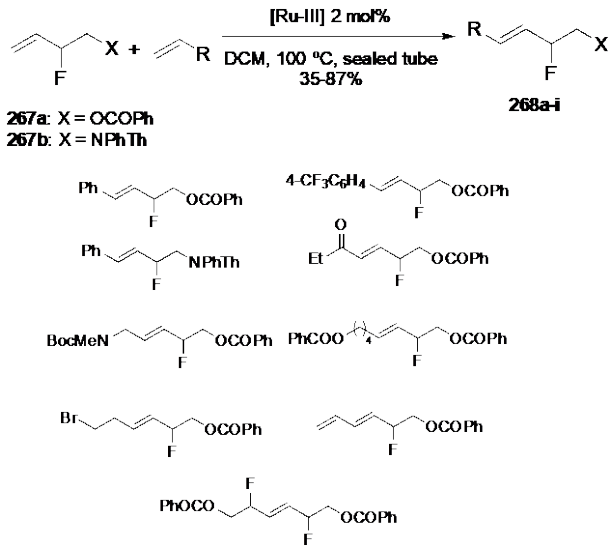
The first examples of a cross-metathesis with fluorinated olefins were reported by Grubbs and Uneyama in 2000.[137,138] However, in Grubbs' report only an isolated example proceeding in rather poor yield (34%) was described;[137a] while Uneyama also observed low yields (9-35%) for vinyl *gem*-difluorocyclopropanes when the double bond is in the proximity of the ring.[137b] The pioneer study specifically devoted to cross metathesis with fluorinated olefins was reported by Blechert one year later.[139] The authors carried out reactions between two model fluorinated olefins **264a,b** and an assorted library of functionalized olefins **265** (Scheme 82). The first interesting observation was that a large excess of the electron deficient fluorinated olefin must be used in order to suppress dimerization of the more electron rich counterpart. Regarding the catalyst, first generation Grubbs catalyst [Ru-I] proved inactive in these systems, while Hoveyda-Grubbs second generation [Ru-III] led to better yields and milder conditions than second generation Grubbs catalyst [Ru-II] to obtain **266** (Scheme 82). Another salient feature was the complete *E* selectivity achieved in all cases.

Scheme 82. Cross Metathesis with Fluorinated Olefins



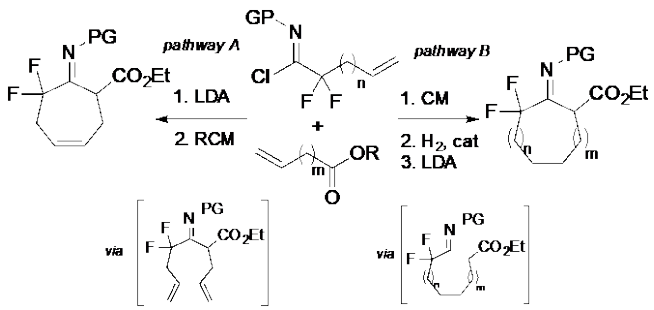
Gouverneur reported a second study of cross metathesis on allylic fluorides several years later.[140] The starting terminal allylic fluorides **267a,b** were prepared by a sequential two-step procedure developed by the same authors one year before.[141] Optimal reaction conditions were identified as 5 equivalents of the partner olefin and 2 mol% of second generation Grubbs catalyst in DCM at 100 ºC in a sealed tube (Scheme 83). Under these reaction conditions a small library of internal allylic fluorides **268** was obtained in moderate to good yields and high *E* selectivity (Scheme 83). It was found that styrene derivatives, unsubstituted or electron deficient ones, enones, aliphatic olefins bearing several functional groups were good olefinic partners for this transformation (Scheme 83).

Scheme 83. Cross Metathesis of Allylfluorides



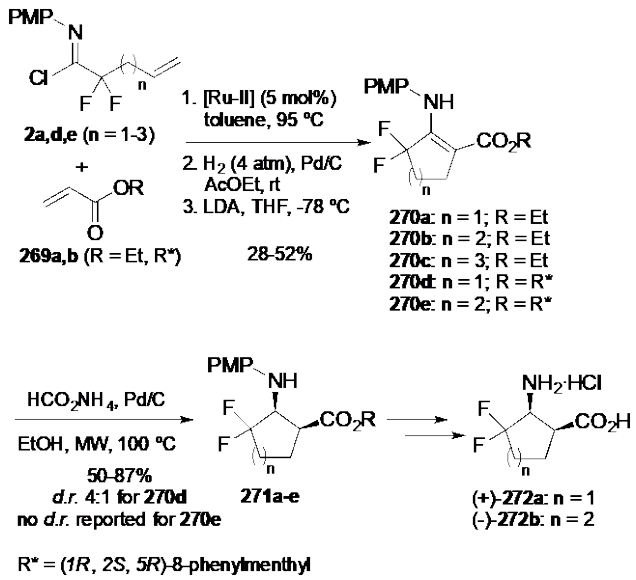
After a few years of inactivity in this field, Fustero reported the first synthetic applications using a cross-metathesis of a fluorinated olefin as key step in the synthesis of fluorinated cyclic β-amino acids[142] and lactams,[143] respectively. The first study aimed at to circumventing an intrinsic limitation of the previously reported methodology by the same group (see, Schemes 6-8).[28b] The first generation approach was limited to seven-membered analogs **22a** (*pathway A*, Scheme 84), while competitive side reactions were obtained when the synthesis of 5- or 6-membered derivatives was attempted. For that reason, the authors found that by switching the order of the reaction sequence this limitation could be overcome (*pathway B*, Scheme 84).

Scheme 84. Second Generation Strategy for the Construction of Fluorinated Cyclic β-Amino Acid Derivatives



The starting fluorinated imidoyl chlorides **2d,e** (n = 2, 3) were synthesized applying Uneyama's method as depicted in Scheme 3. First, the cross-metathesis step was studied using several fluorinated imidoyl chlorides and unsaturated esters, including some methyl substituted ones like ethyl methacrylate (in Scheme 85 only those carried out through the whole reaction sequence are depicted). The reaction proceeded in moderate to good yields in either refluxing DCM or toluene (for less reactive acrylates **269a,b**, see, Scheme 85). In view of the high *E*/*Z* selectivity observed (>20:1 for acrylates **269a,b**), hydrogenation of the double bond needed to be carried out prior to intramolecular Dieckman-type cyclization (Scheme 85). The obtained products **270a-e** were in equilibrium with the corresponding imine forms, the major tautomer being the depicted enamine. After some optimization, diastereoselective *syn* double bond hydrogenation was carried out with ammonium formate as hydrogen surrogate by means of palladium catalyzed transfer hydrogenation under microwave irradiation (Scheme 85). In order to obtain enantiomerically enriched products, the authors tried two complementary strategies, *i.e.* placing a chiral auxiliary either at the imine or at the ester groups. The use of (*S*)-phenylglycinol methyl ester as chiral auxiliary for the imine failed to control the stereochemical outcome during the reduction step under a variety of experimental conditions. On the other hand, (*1R,2S,5R*)-8-phenylmenthol derivatives **270d,e** allowed obtaining moderate facial selectivity of separable *cis*-diastereoisomers (Scheme 85). Enantioenriched **271d,e** were transformed into the completely unprotected β-amino acids by standard functional group interconversion chemistry (Scheme 85). It is worth noting that derivative (+)-**272a** was a fluorinated analog of the antifungal *ent*-cispentacin.[144]

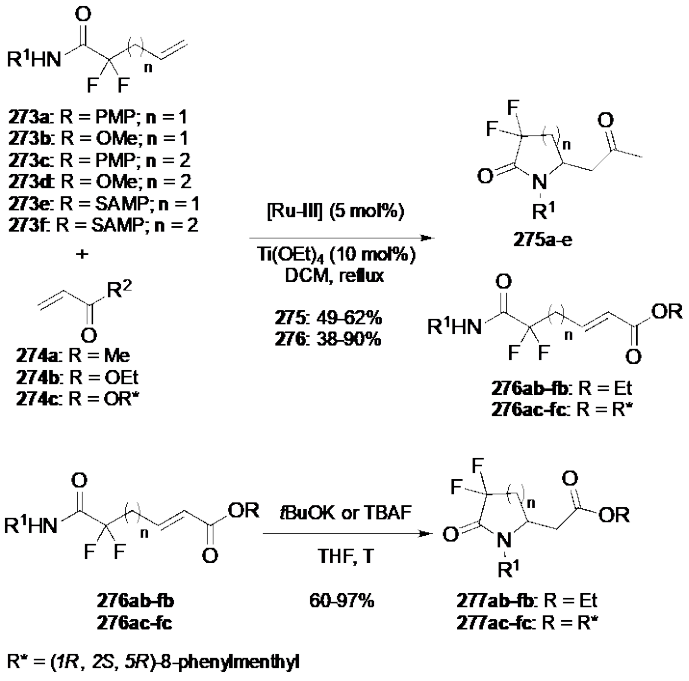
Scheme 85. CM-Intramolecular Dieckman-Type Reaction for the Synthesis of Fluorinated Cyclic β-Amino Acids



Continuing their work on CM / intramolecular *aza*-Michael reaction (IMAMR) tandem processes,[145] Fustero and del Pozo developed an analogous tandem process affording fluorinated γ- and δ-lactams.[143] The cross-metathesis between fluorinated amides **273a-d** and Michael acceptors **274a,b** was carried out in refluxing toluene using Hoveyda-Grubbs second generation catalyst and a Lewis acid [$Ti(OEt)_4$ in most cases] as co-catalyst (Scheme 86). Thus, the reactions with methyl vinyl ketone (MVK) (**274a**) proceeded in a tandem fashion, giving rise to lactones **275ab-db** in moderate yields, while ethyl acrylate (**274b**) renders cross-metathesis products **276aa-da**, into good yields (Scheme 86). The latter were converted in the corresponding lactams by treatment with potassium *tert*-butoxide in THF (Scheme 86). Similarly to the aforementioned results for the synthesis of cyclic β-amino acids (see, Scheme 85), the asymmetric version of this process was examined by placing suitable chiral auxiliaries on both the nucleophilic and the electrophilic moieties of the molecule (Scheme 86). The use of a SAMP-derived amide gave rise to 5- and 6-membered lactams when subjected to metathesis conditions towards MVK, although in very poor stereocontrol (Scheme 86). As expected, the reaction with ethyl acrylate stopped at the cross-metathesis stage making a careful optimization of the *aza*-Michael cyclization step

possible. It was found that for the formation of both 5- and 6-membered lactams the use of TBAF as a base in refluxing THF resulted in the best balance between chemical yield and diastereoselectivity (Scheme 86).[146] Not surprisingly, the reactions with chiral ester **274** did not proceed spontaneously towards the tandem lactam products. Once again, careful optimization of the IMAMR allowed identifying TBAF as the base of choice, although at -78 ºC (Scheme 86). This dramatic difference in the reaction temperature suggested that the reactions with SAMP derivatives occur under thermodynamic control, while the ones with 8-phenylmenthol proceed under kinetic control.

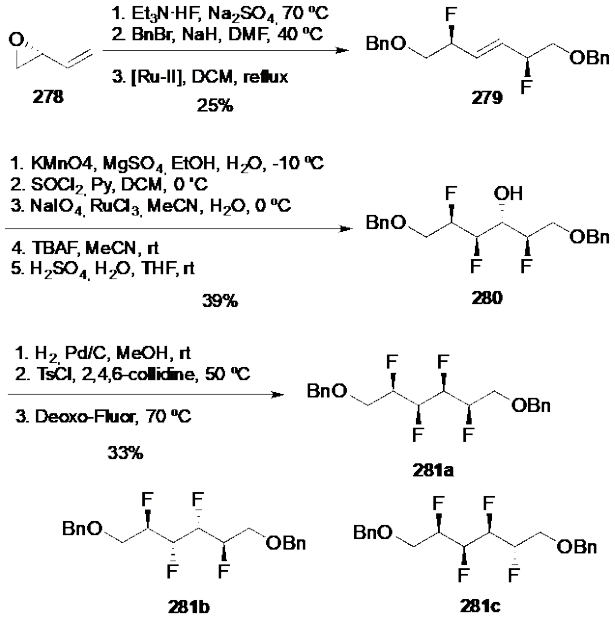
Scheme 86. Synthesis of Fluorinated γ- and δ-Lactams by a Cross Metathesis/IMAMR Tandem Process



In a series of reports, O'Hagan studied the conformational properties of multi-vicinal fluoroalkanes.[147,148] These compounds, intermediates between the corresponding alkanes and perfluoroalkanes, represent a synthetic challenge owing to their stereochemical complexity. In

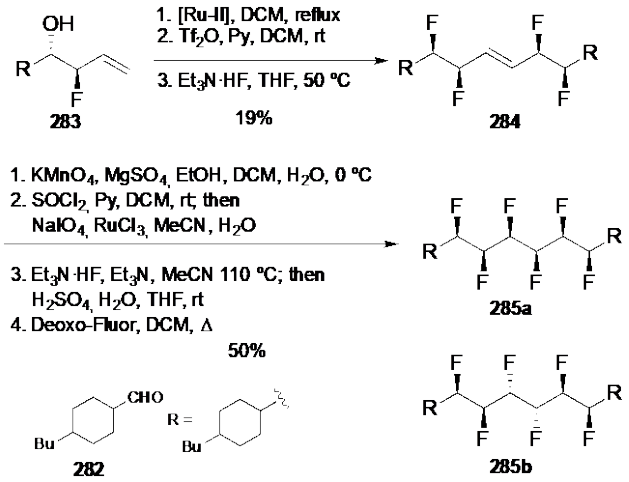
addition, the different stereoisomers exhibit diverse conformational behavior, influenced by the well-established stereoelectronic *gauche* effect.[149] For the synthesis of the even members of the family (tetra-[147d,g] and hexafluoroalkanes [147i]), the authors used *E*-selective cross-metathesis as key step (Schemes 87, 88). Thus, starting from readily available (*R*)-butadiene monoxide **278**, difluoroolefin **279** was obtained in three steps, *i.e.* regioselective epoxide ring-opening, protection of the corresponding fluorohydrin and cross-metathesis (Scheme 87). Dihydroxylation of the double bond followed by formation of the corresponding cyclic sulfate and ring opening of the latter afforded trifluoroalcohol **280** (Scheme 87). Finally, the nature of the protecting group at the terminal hydroxyl groups proved crucial for the successful introduction of the last fluorine atom, which was accomplished by treatment of the bis(tosyl) derivative with Deoxo-Fluor affording all-*syn* isomer **281a** (Scheme 87). The reaction sequence was also adapted to the synthesis of the *anti-syn-anti* and the *syn-syn-anti* isomers **281b** and **281c**, respectively.

Scheme 87. Stereoselective Synthesis of Tetrafluoroalkanes



A similar cross-metathesis/olefin dihydroxylation/cyclic sulfate ring-opening strategy was then used for the synthesis of the hexafluoroalkanes **285a,b** (Scheme 88). Starting from fluorohydrin **283** (obtained in 6 conventional steps from **282**) the target compounds were synthesized in 7 steps (Scheme 88). The conformational preferences of tetra- and hexafluoro derivatives **281a-c** and **285a,b** were then studied in solid state (X-ray) as well as in solution (^{1}H and ^{19}F NMR) and further reinforced by molecular modeling. Summarizing, all-*syn* diastereoisomers showed a preferred conformation placing the fluorine atoms in a helical disposition, while mixed *syn*- *anti*-diastereoisomers exhibited more linear zigzag conformations.

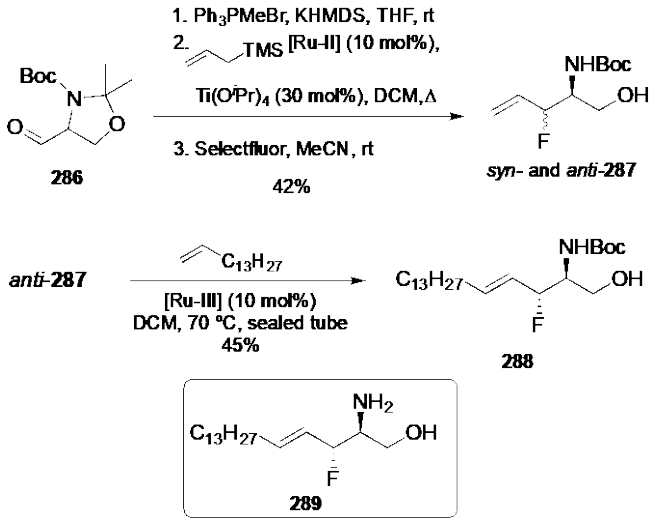
Scheme 88. Stereoselective Synthesis of Hexafluoroalkanes



Two cross-metathesis reactions (one of them on a fluorinated substrate) were used in Gouverneur's synthesis of a fluorinated sphingosine analog.[150] After methylenation of Garner's aldehyde **286**, the sequential cross-metathesis electrophilic fluorodesilylation process developed by the same authors for the synthesis of functionalized allylic fluorides was carried out giving rise to **287** as a 1:1 mixture of separable diastereoisomers (Scheme 89).[141] After some optimization, Hoveyda-Grubbs second-generation catalyst was identified as the catalyst of choice

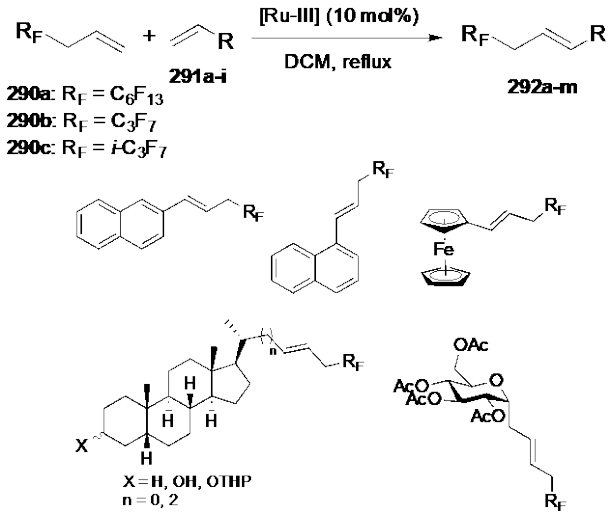
for the subsequent cross-metathesis with 1-pentadecene affording **288** with complete *E*-selectivity and accomplishing the formal total synthesis of the desired fluorinated sphingosine analog **289** (Scheme 89).

Scheme 89. Cross Metathesis Approach towards Sphingosine Analog



Kotora and coworkers carried out a study on the cross-metathesis reaction between perfluoroalkyl olefins and a number of aromatic and aliphatic olefins including steroid and saccharide derivatives.[151] The reaction was effectively carried out using 2 equivalents of perfluoropropene derivatives **290a-c**, Hoveyda–Grubbs second generation catalyst (10 mol%) in refluxing dichloromethane and olefins **291** affording poor (for aromatic olefins) to good chemical yields (for aliphatic ones) and moderate to complete *E*-selectivity of **292** (Scheme 90).

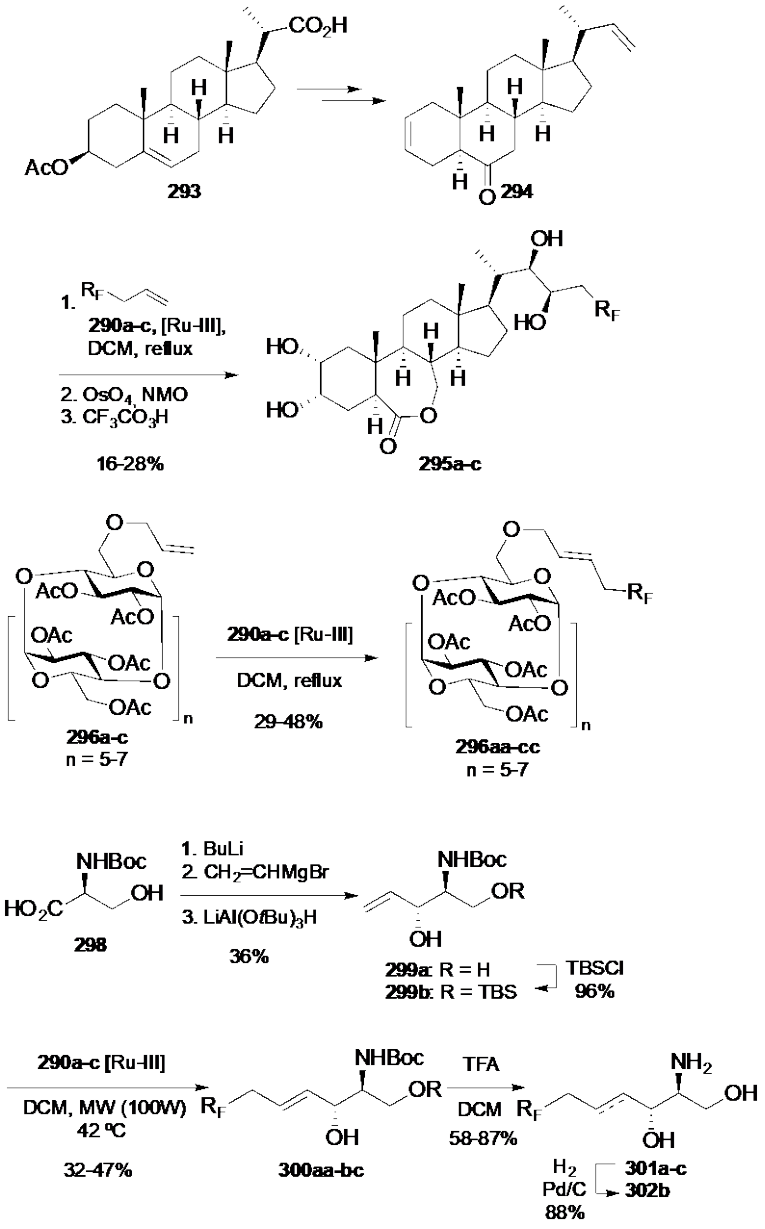
Scheme 90. Cross Metathesis with Perfluoro Olefins



The study on these model substrates was then applied to perfluorinated natural product analogs: brassinosteroids, β-cyclodextrines[152] and sphingosines (Scheme 91).[153] The coupling partner required for the synthesis of brassinosteroid analogs **294** was obtained in 10 conventional steps from commercially available acid **293**.[153a] Cross-metathesis with perfluoropropene derivatives **290a-c**, under the aforementioned reaction conditions, afforded fluorinated analogs, which were in turn converted into the targeted brassinosteroid derivatives **295a-c** by bis-double bond dihydroxylation followed by trifluoroperacetic acid-mediated Baeyer-Villiger oxidation (Scheme 91). Regarding cyclodextrin derivatives, starting allylcyclodextrins **296a-c** were prepared according to reported procedures in two steps[154] and subjected to cross-metathesis under the typical reaction conditions affording fluorinated derivatives **297aa-cc** in moderate yields (Scheme 91).[153b] Finally, the synthesis of perfluoroalkylated sphingosine derivatives started with the two-step synthesis of suitable olefinic cross-metathesis partners **299a,b** from *N*-Boc-*L*-serine **298** (Scheme 91).[153c] After some struggling with the vinylmagnesium addition to the corresponding Weinreb's amide, the authors found that treatment of *N*-Boc-*L*-serine with excess BuLi followed by Grignard addition and diastereoselective enone reduction afforded the required substrate (Scheme 91). Cross-metathesis with perfluoroalkyl propene derivatives **290a-c**

proceeded in similar, moderate yields regardless of the protection or non-protection of the hydroxy group (Scheme 91). Here, the use of microwave irradiation instead of conventional heating proved crucial in order to achieve reasonable conversions (Scheme 91). *N*-Boc deprotection of **300** led to sphingosine derivatives **301a-c**, which were converted into clavaminol H derivative **302** by catalytic hydrogenation of the double bond (Scheme 91).

Scheme 91. Cross Metathesis based Synthesis of Brassinosteroid, Cyclodextrine and Sphingosine Derivatives

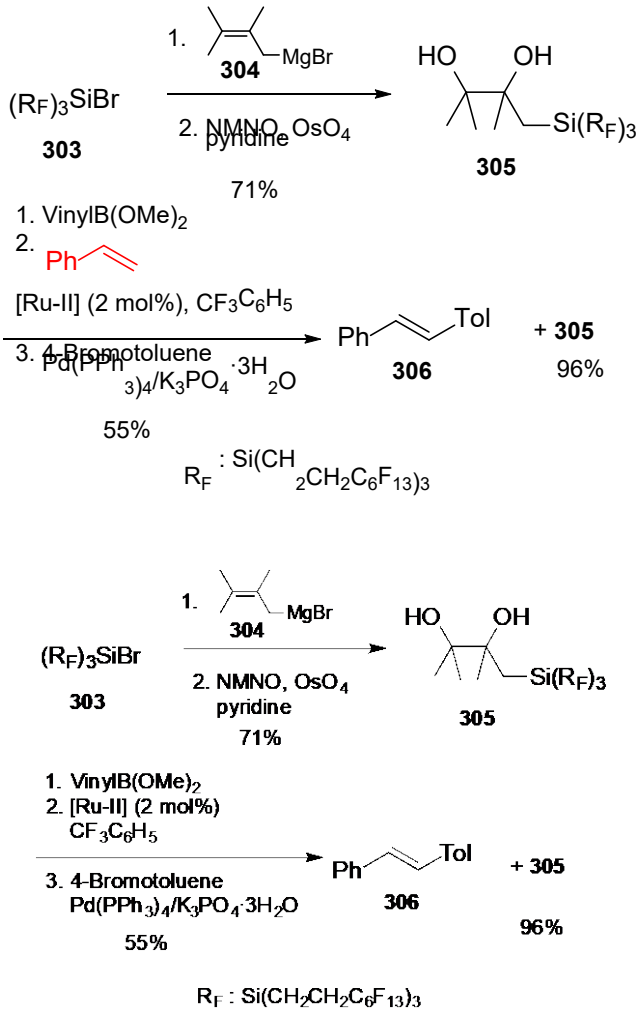


3.2. Cross Metathesis (CM) in Fluorous Synthesis

More than 10 years ago, Qing reported the first example of a cross-metathesis reaction on a fluorous substrate.[155] In this report, the authors described the synthesis and applications of fluorous boronates. A heavy fluorous analog of pinacol **305** was prepared in two steps from Grignard reagent **304** and fluorous bromosilane **303** (Scheme 92). This, in turn, was used to synthesize a fluorous analog of the vinylboronic acid pinacol ester derivative, which was then

subjected to cross metathesis with styrene and final palladium-catalyzed Suzuki cross-coupling with 4-bromotoluene giving rise to stylbene derivative **306** and allowing recovery of **305** in excellent yield by means of fluorous extractive work-up using the FC-77/DCM biphasic system (Scheme 92).

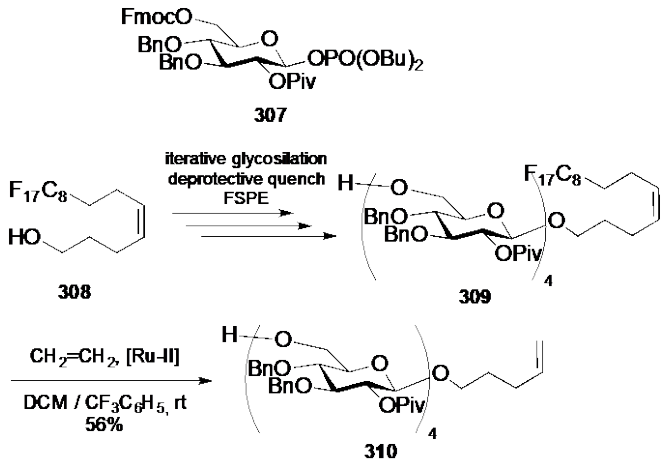
Scheme 92. Synthesis and Applications of Heavy Fluorous Boronates



Seeberger used a cross metathesis reaction with ethylene as detagging step for fluorous tetrasaccharide **309** synthesized by iterative glycosilations in a microfluidic reactor using Fmoc-protected glycosylphosphate **307** and fluorous linker **308**, obtained in 3 steps from the

corresponding fluorous alcohol (Scheme 93).[156] The subsequent cross metathesis with ethylene proceeded in moderate 56% conversion to the desired *n*-pentenyl glycoside **310**, while remaining starting material **309** was recovered in 44% yield by fluorous solid phase extraction (FSPE) (Scheme 93).

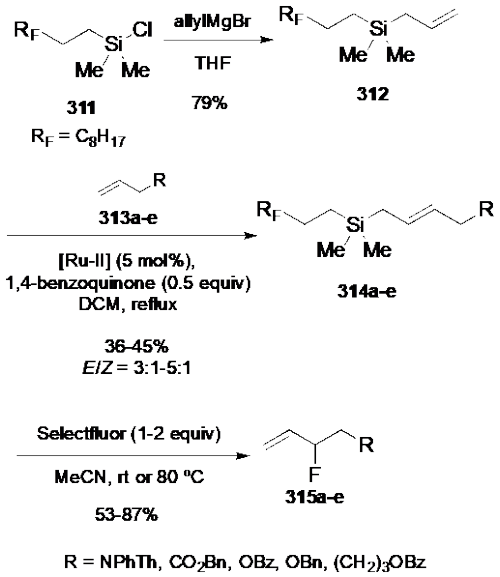
Scheme 93. Detagging of Fluorous Tetrasaccharide by CM with Ethylene



In the context of an extensive study on the electrophilic fluorination of allylsilanes,[157] Gouverneur reported an elegant fluorous version in which the C-F bond formation event takes place simultaneously with the detagging process.[158] Key for the success of the strategy was the preparation, for the first time, of a light fluorous allylsilane **312** by reaction of the commercially available fluorous-tagged dimethylchlorosilane **311** with allylmagnesium bromide (Scheme 94). Optimization of the cross-metathesis of the new fluorous allylsilane **312** using a model olefinic partner showed that the use of 1,4-benzoquinone as an additive was required in order to suppress the formation of an undesired side-product arising from isomerization of the allylsilane towards the corresponding crotylsilane prior to CM (this processes was not observed when using non-fluorous precursors [141]). With the optimized conditions in hand, the scope of the reaction was studied using a series of functionalized olefinic partners **313a-e**, including unsaturated esters or

ethers, obtaining the corresponding fluorous allylsilanes **314a-e** in moderate yields and *E*/*Z* ratios (Scheme 94). Next, the electrophilic fluorination / detagging process was carried out attaining allylic fluorides **315a-e** in moderate to good yields (Scheme 94). Intermediates **314** as well as final allylfluorides **315** were purified by means of FSPE.

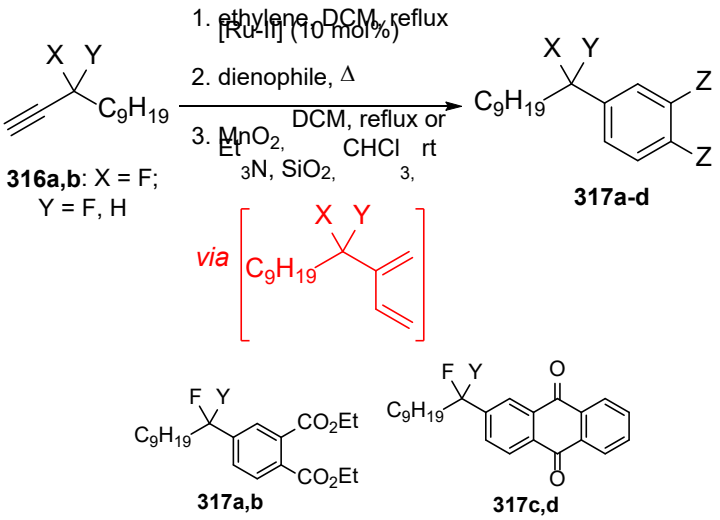
Scheme 94. Fluorous Synthesis of Allylic Fluorides by Sequential Cross Metathesis / Electrophilic Fluorination

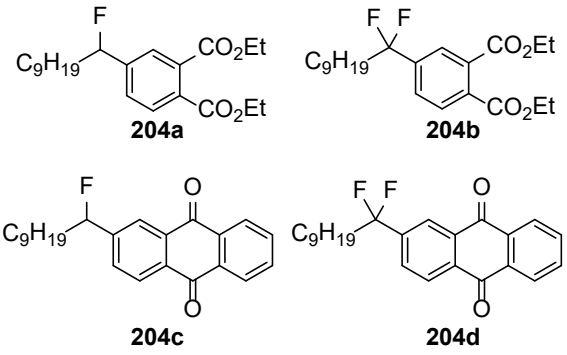


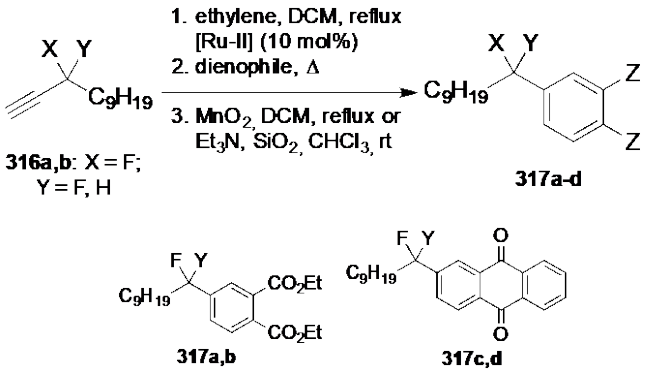
3.3. Cross Enyne Metathesis (CEYM) with fluorinated derivatives

CEYM has barely been applied to fluorinated substrates.[159] The first report in this field [159a] describes the CEYM between mono- and difluoropropargyl derivatives **316a,b**, readily available by treatment with DAST of the corresponding propargyl alcohol and ketone, respectively, and ethylene giving rise to fluorinated dienes, that were used in a subsequent Diels-Alder reaction followed by aromatization towards the corresponding mono- and difluorobenzyl derivatives **317a-d** (Scheme 95). The reaction sequence was also applied to enantioenriched derivative (+)-**316a** (Y = H) affording (+)-**317a** with minimal erosion of optical purity (<4%).

Scheme 95. CEYM between Fluorinated Propargyl Derivatives and Ethylene

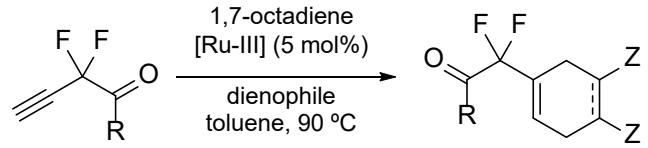

1. ethylene, DCM, reflux
[Ru-II] (10 mol%)
2. dienophile, Δ
DCM, reflux or
3. MnO2, Et3N, SiO2, CHCl3, rt
X Y
C9H19
316a,b: X = F;
Y = F, H
Z
317a-d
via
317a,b
317c,d
CO2Et
O


F
F F
C9H19
CO2Et
O
204a
204b
204c
204d



Recently, Fustero and del Pozo described the use of 1,7-octadiene as a useful ethylene surrogate in tandem multicomponent CEYM/Diels-Alder reactions.[159b,c] This tandem protocol was applied to *gem*-difluoropropargyl amides and ketones **318a-d** as well as a variety of dienophiles giving rise to cyclohexene and cyclohexadiene derivatives **319a-o** in moderate to good yields (Scheme 96).

Scheme 96. 1,7-Cyclooctadiene-Assisted Tandem Multicomponent CEYM/Diels-Alder Reactions

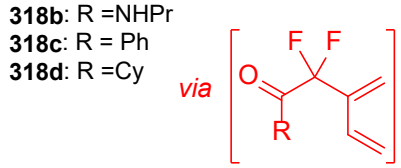


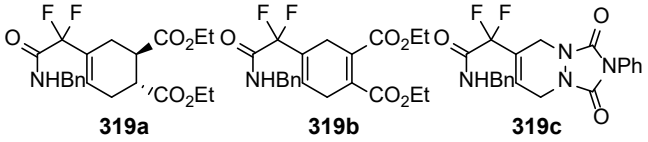
318a: R = NHBn
318b: R =NHPr
318c: R = Ph
318d: R =Cy

28-87%

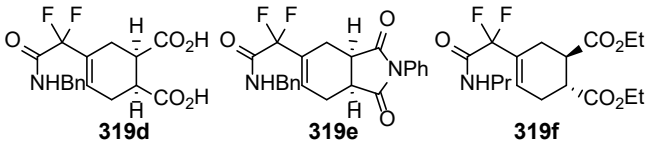
319a-k

via

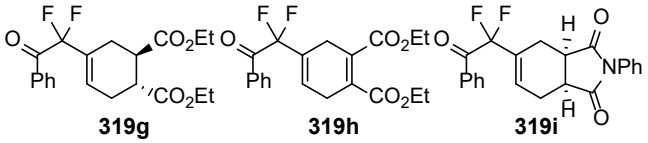




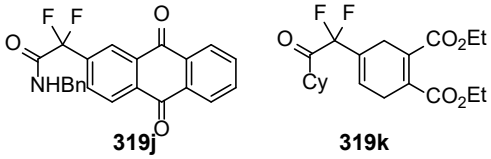
319a **319b** **319c**



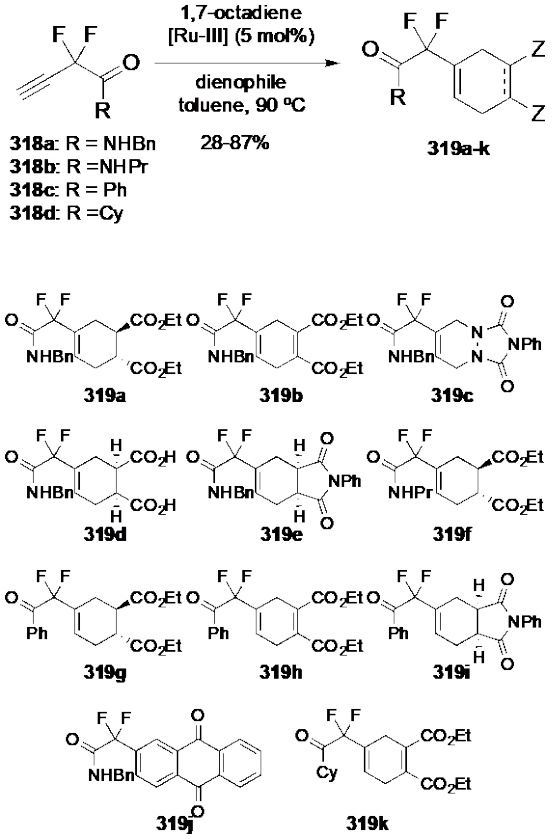
319d **319e** **319f**



319g **319h** **319i**



319j **319k**



4. RING OPENING METATHESIS POLYMERIZATION (ROMP) AND ACYCLIC DIENE METATHESIS (ADMET) IN FLUORINE CHEMISTRY

4.1. Ring Opening Metathesis Polymerization (ROMP)

The use of olefin metathesis reactions in polymer science has complemented the closely related Ziegler-Natta polymerization process.[160] It is not surprising that the field of metathesis polymerization of fluorinated olefins has been very active for the last 35 years due to the huge impact that fluorine-containing polymers have had on society.[161]

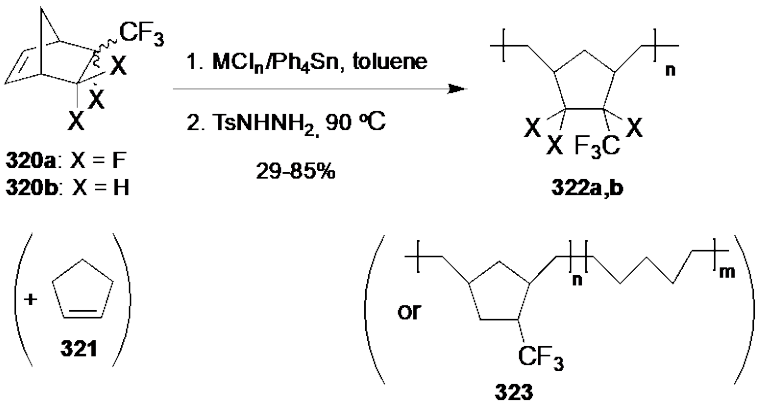
Trying to combine the low glass transition temperatures of polypentylenes with the thermal stability and solvent resistance associated with fluorocarbon polymers was the starting point of a longstanding research line carried out in Durham by the Feast's group. After twenty years of

research in the field, Feast gathered the results obtained by his group (occasionally in collaboration with Schrock's) in ROMP of fluorinated substrates, most frequently fluorinated norbonene and norbonadiene derivatives, in a review.[162] Consequently, only the bibliography on the topic starting from 1999 will be covered in this section.[163,164]

Continuing their interest in ROMP of fluorinated norbornene derivatives, Feast and co-workers reported the first contributions of the present century in this field.[165] The authors described the hydrogenation of fluorinated polymers or copolymers as an approach to highly polar polymers with low glass transition temperatures (T_g). In their first report,[165a] 5,5,6-trifluoro-6-trifluoromethylbicyclo[2.2.1]hept-2-ene (F_3CF_3-NB, **320a**) and 5-trifluoromethyl bicyclo[2.2.1] hept-2-ene (CF_3-NB, **320b**), both synthesized in one step by means of a Diels-Alder reaction between cyclopentadiene and the corresponding fluorinated olefin, were polymerized from a "classical" ill-defined WCl_6/Ph_4Sn or $MoCl_5/Ph_4Sn$ initiation (Scheme 97). The polymers obtained in that manner were in turn hydrogenated by treatment with diimide *in situ* generated from *p*-toluensulfonylhydrazide, in variable conversions (Scheme 97). For the two of these materials whose T_g could be determined an expected lowering in T_g (36/37 ºC) was observed. However, thermogravimetric studies indicated that the hydrogenated polymers **322a,b** displayed a lower thermal stability than their unsaturated precursors. Polymers having a low *Tg* and fluorine content as high as possible were obtained by ROMP co-polymerization of **320b** with cyclopentene **321** followed by hydrogenation (Scheme 97). Key for the success of this strategy was the determination of the optimum monomer ratio (2.5:1) leading to a low *Tg* (-22 ºC), while keeping high fluorine content (*ca*. 27wt.%, 60 mol% of fluorinated monomer). In addition, this material **323** did not present lower thermal stability than its precursor. In both contributions, the

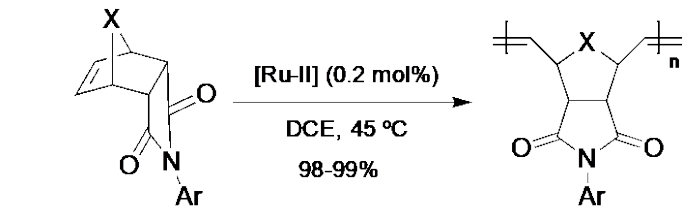
authors carried out a thorough NMR characterization of the polymeric materials, reaching beyond the scope of the present review.

Scheme 97. Low T_g Fluorinated Polymers by ROMP/Hydrogenation



In addition, improved gas permeability towards several gases (He, CO_2, O_2, N_2, CH_4) was reported for fluorine containing polynorbornene dicarboximide **325a,b**.[166] Large permeability coefficients and high selectivity for gas separation are desirable features for a membrane to be used in gas separation processes.[167] Based upon their own experience in the field of carboximide functionalized polynorbornenes[168] and the reported beneficial effect on gas permeability and selectivity by introduction of fluorine in polynorbornene derivatives,[169] the authors ring-opened trifluoromethyl-containing carboximide norbornenes derivatives **324a,b** with Grubbs catalysts (first and second generation catalysts displayed very similar reactivity, the former achieving higher *E*-selectivity) in a very efficient manner (Scheme 98). The authors reported the formation in excellent yield of the corresponding polymers **325a,b**, displaying a high *Tg* (182 ºC for **325b**) and one of the largest gas permeability, diffusion and solubility coefficients reported for glassy polynorbornene dicarboximides (in the range of CF_3 containing polynorbornenes). Lower polymer chain packing would account for these improved properties.

Scheme 98. ROMP of Fluorine-Containing Polynorbornene Dicarboximide Derivatives

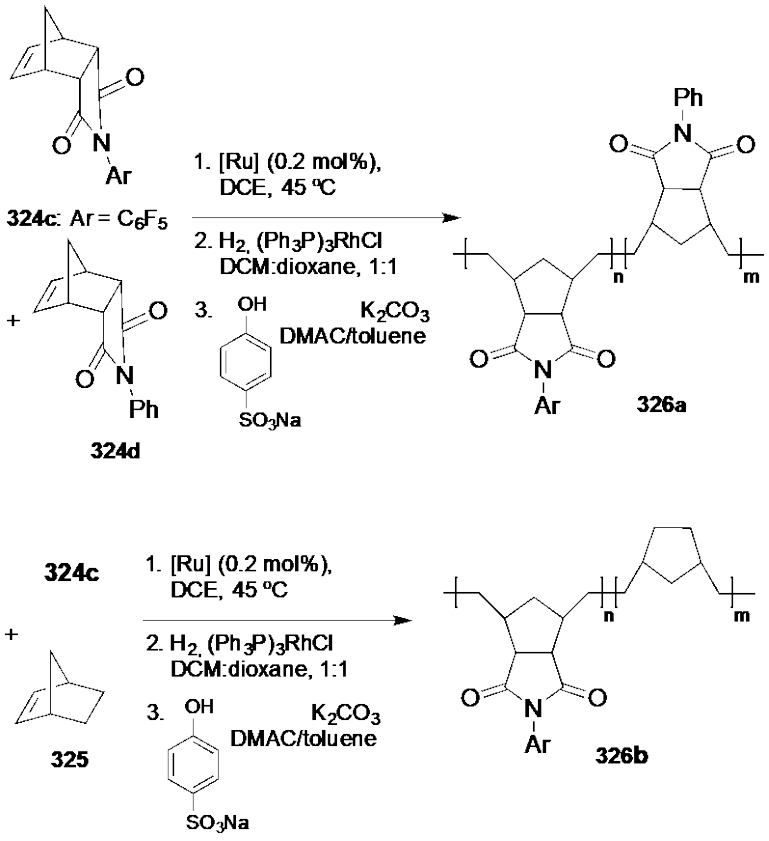


324a: X = CH_2; Ar = 4-$CF_3C_6H_4$
324b: X = O; Ar = 3,5-di$CF_3C_6H_3$

325a,b

A few years later, the same authors reported the use of the *N*-perfluorophenyl derivative **324c** for the synthesis of copolymers with *N*-phenyl derivative **324d** and norbornene **325** (Scheme 99).[170] The pentafluorophenyl moiety was further modified, after hydrogenation of the double bonds, by nucleophilic aromatic substitution, affording sulfonated derivatives **326a,b** (Scheme 99) behaving as thermally stable ionomers and exhibiting a high cationic permselectivity at low electrolyte concentrations.

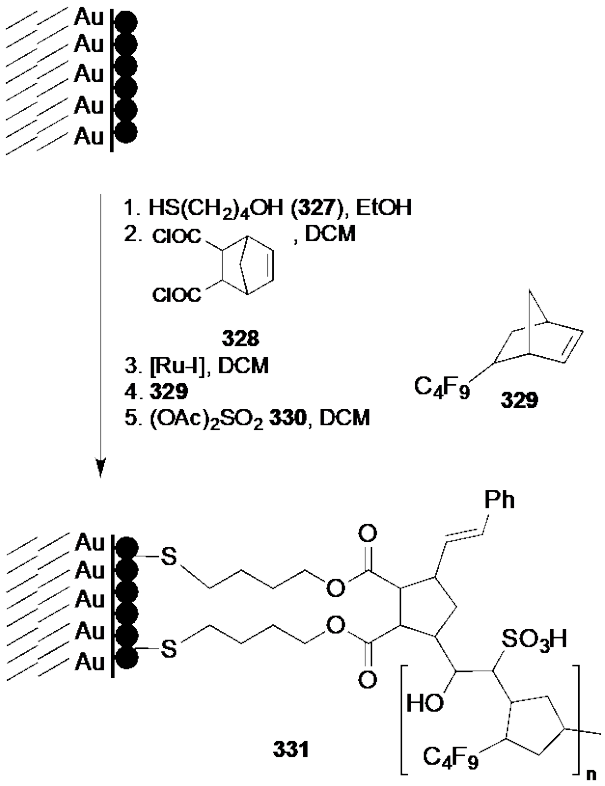
Scheme 99. Synthesis of Ionomers by S_NAr on *N*-Pentafluorophenyl co-Polymers



Finally, fluoroalkylnorbornenes have been used in *surface-initiated ROMP* (SI-ROMP) for growing ionomer films from gold substrates.[171] The electrochemical performance of a proton exchange membrane was improved by chemisorption of the ionomer at the electrode surface resulting in a more efficient transfer of protons and oxygen. SI-ROMP offers the advantage of polymer growth from the electrode surface by reacting the monomer with a surface-tethered initiator or, as in this case, a polymerization catalyst.[172] In the first of the three reports,[171a] Jennings and coworkers described the SI-ROMP growth of ionomer films from platinum-modified gold electrodes. After deposition of a monolayer of platinum on the gold surface, the film was functionalized with 4-mercapto-1-butanol **327** followed by condensation with norbornenyl diacid chloride **328** (Scheme 100). Ring opening of the norbornene units allowed tethering the catalyst to the surface for the subsequent SI-ROMP process with a variety of

norbornene derivatives, including perfluorobutylnorbornene **329** (Scheme 100). Finally, sulfonation of the polymer double bonds afforded ionomer films directly wired to the electrode surface (Scheme 100). The resulting electrodes showed higher anodic potentials for oxygen reduction but increased resistances against proton transfer than norbornene derived or unfunctionalized ones. In addition, the authors showed that the platinum monolayer remained unaltered on the gold surface along the reaction sequence and that the non-tethering unreactive short-chain thiolates could be removed electrochemically (by oxidation towards the corresponding non-coordinating sulfonates) without affecting the ionomer film.

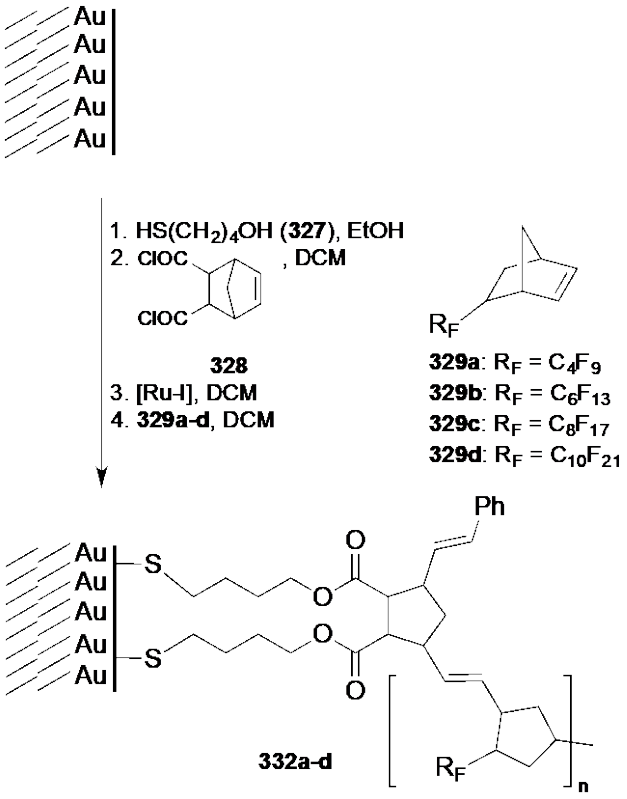
Scheme 100. SI-ROMP Preparation of Ionomer Films from Pt-Modified Gold Electrodes



Continuing their interest in combining the advantages of SI-ROMP and the technological importance of partially fluorinated films, the same authors showed the rapid growth of films with

critical surface tensions and ultimate thickness dependent on the length of the fluorocarbon chain.[171b] Following a reaction sequence analogous to the one depicted in Scheme 100 (excluding the sulfonation step), four partially fluorinated polynorbornene derivatives **332a-d** were obtained (Scheme 101). The structure, morphology and surface properties of materials **332a-d** were described in detail, but that discussion is beyond the scope of this review.

Scheme 101. SI-ROMP of Perfluoroalkylnorbornenes from Gold Surfaces



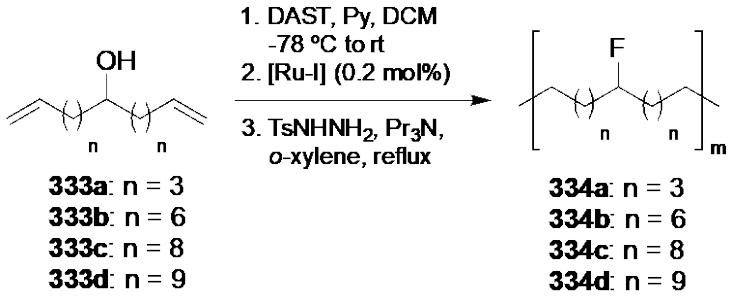
In order to increase the thickness of the coating, Jennings reported the combination of SI-ROMP with a previous step of surface-initiated atom-transfer polymerization (SI-ATRP) to grow a macroinitiator, promoting a rapid growth of dense partially fluorinated coatings.[171c] The success of this approach relied on the immobilization of a higher number of catalyst molecules in a modified poly(2-hydroxyethyl methacrylate) (PHEMA) macroinitiator, resulting in an enhanced

polymerization rate when compared with the monolayer initiation procedure described above (1-2 orders of magnitude). A similar reaction sequence as depicted in Scheme 100 and 101 was carried out on a PHEMA pre-coated gold surface-giving rise to partially fluorinated films, having a thickness of 4-12 μm.[1711c] The obtention of thick coatings may improve the blocking properties and robustness of the film, and thus hamper undesirable species from reaching the surface.

4.2. Acyclic Diene Metathesis (ADMET)

The outstanding importance of polyethylene (PE) and some of its halogenated derivatives (PVC, PTFE) is undoubtable. Polymer structure, specifically semicrystalline morphology, plays a crucial role in the physical-chemical properties of the material and, therefore, in its applications. The production of PE structures by ADMET allows introducing pendant groups in precise positions and thus the fine-tuning of their properties. In a series of reports, Wagener reported the synthesis of halogen-containing polyolefins, including fluorine.[173] This strategy allowed obtaining well-defined precision ethylene/vinyl fluoride polymers and studying their crystalline properties. The synthesis of the halogenated dienes started with a common alcohol **333** that was converted into the corresponding halide, polymerized with Grubbs first generation catalyst and hydrogenated with diimide affording partially fluorinated polyethylenes **334** (Scheme 102).[173a,c]

Scheme 102. Synthesis of Fluorine Containing Polyethylenes by ADMET

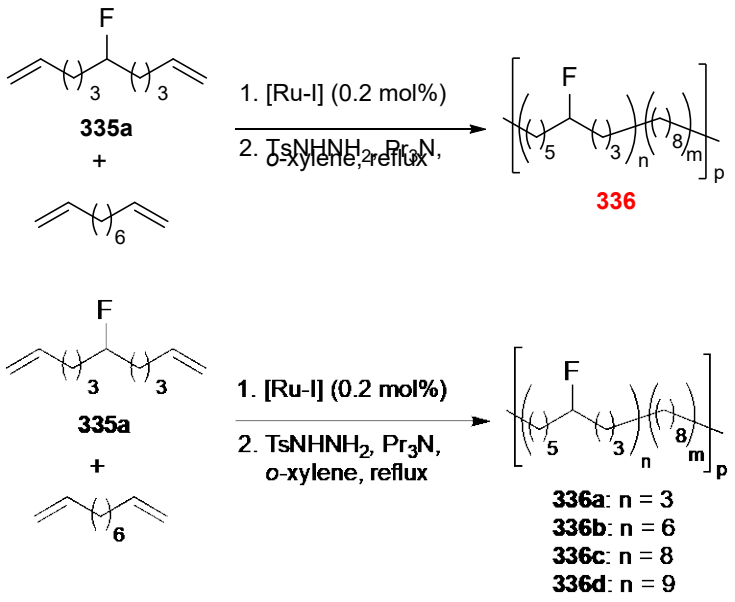


333a: n = 3
333b: n = 6
333c: n = 8
333d: n = 9

334a: n = 3
334b: n = 6
334c: n = 8
334d: n = 9

Random, defect-free ethylyne/vinyl fluoride (and other halides) copolymers **336** were also obtained by co-polymerization of **335a** with 1,9-decadiene (Scheme 103).

Scheme 103. Co-Polymerization of 335a with 1,9-Decadiene



5. FLUORINE CONTAINING CATALYSTS FOR METATHESIS REACTIONS

5.1. Applications of fluorine-containing Schrock-type molybdenum catalysts

The first and still most frequently used fluorine-containing olefin metathesis catalyst is Schrock's molybdenum carbene complex [Mo-I] (see Figure 1). Generally this catalyst is more reactive than Grubbs catalysts [Ru-I] and [Ru-IV]. The electron withdrawing trifluoromethylated alkoxide ligands increase the electrophilicity of the metal, which is beneficial for its catalytic performance. Hence, [Mo-I] is particularly useful for electron-rich olefins bearing heteroatoms in the α-position and for sterically demanding systems, like intermediates for the synthesis of complex structures including natural products. An excellent review on the synthesis, structure, reactivity and synthetic application of molybdenum and tungsten imido alkylidene complexes as

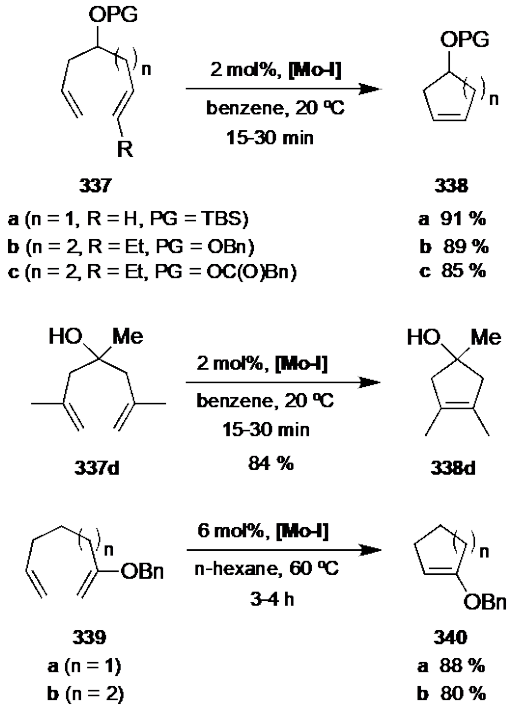
efficient olefin metathesis catalysts was provided by Schrock and Hoveyda,[174] which was supplemented by Schrock and Czekelius several years ago.[175] Although [Mo-I] is quite sensitive to oxygen and moisture it tolerates a variety of substituents in the substrates, such as keto groups, esters, amides, epoxides, acetals, silyl ethers, some amines and sulfides.[17b] [Mo-I] was successfully applied in the synthesis of carbocycles and particularly in *O*- and *N*-heterocycles, but also in cross metathesis and in polymerization reactions under inert reaction conditions.[174,175] Generally, five- and six-membered rings are produced in high yields, while the formation of seven-membered and especially medium-sized rings is generally less efficient (apart from a few exceptions) due to entropic and enthalpic reasons. Macrocyclic compounds, on the other hand, could be formed in several cases. In spite of the discovery and development of the very robust and highly active second-generation Ru-catalysts [Ru-II] and Hoveyda-Grubbs catalyst [Ru-III], the [Mo-I] catalyst continues to be frequently used for olefin metathesis reactions. Advantages and disadvantages of Mo- and Ru-based catalysts can best be explored using a side-by-side comparison of a particular reaction.[175] It is not the intention of the following sections to comprehensively demonstrate the applicability particularly of [Mo-I] in synthesis, but to present typical examples for the formation of carbocycles, *O*- and *N*-heterocycles (and a few *S*- and *P*-heterocycles) by RCM or by cross metathesis, respectively.[174,175,176]

5.1.1. Formation of carbocycles

Doubtlessly, cycloalkenes belong to a versatile class of basic chemicals having found manifold applications in the synthesis of complex organic molecules. Therefore, such compounds were among the first to be prepared by RCM reactions. Fu and Grubbs, in 1993, reported the high yielding synthesis of *O*-protected cyclopent-3-enol- and cyclohex-3-enol derivatives **338a-c** from the precursors **337a-c** by reaction with 2 mol% of [Mo-I] in benzene at 20 °C.[177] Even the

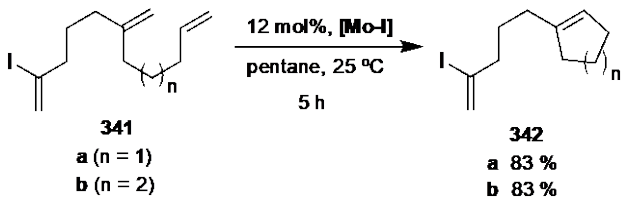
tetrasubstituted cyclopentene **338d** with a free OH group was prepared with 84% yield. Moreover, also the enolethers **339a,b** gave the expected products **340a,b** on treatment with the same catalyst in hexane at 60 °C for 3-4 hours (Scheme 104).[178]

Scheme 104. Synthesis of Substituted Cyclopentenes and Cyclohexenes by RCM



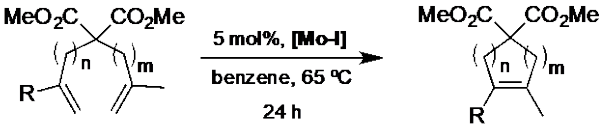
The building blocks **342a,b** useful for the total synthesis of terpenoide natural products were prepared in high yields (Scheme 105).[179] Later investigations (see chapter 2.3) confirmed that halogen-substituted double bonds are less reactive, which partially explains the chemoselectivity of the metathesis reaction.

Scheme 105. Synthesis of Terpenoide Building Blocks



RCM substrates **343a-d** containing a *gem*-diester moiety in the tether of the α,ω-diene system were shown to be very reactive and underwent smooth cyclization to the target 5-, 6-, and 7-membered cycloalkenes **344a-d** in excellent yields. Other substrates with alkyl as well as phenyl, methoxycarbonyl and acetoxymethyl substituents attached to one of the double bonds were successfully cyclized towards the normal rings, too. Cyclooctenes such as **343e**, however, were not obtained neither with [Mo-I] nor with [Ru-I]. Moreover, the five and six-membered products **344f,g** containing a tetrasubstituted double bond were also synthesized from the corresponding precursors **343f,g** in fair or excellent yields, respectively (Scheme 106).[180] Later on, α,ω-dienes with *gem*-dicarboxylates in the tether of the diene and no, one, or two methyl groups in α+1 or/and ω-1-position were used to test the quality of fluorous catalysts (see section 5.2).

Scheme 106. Synthesis of C_5-C_7 *gem*-Disubstituted Cycloalkenedicarboxylates by RCM



343

a (n = 1, m = 1, R = H)
b (n = 1, m = 2, R = H)
c (n = 2, m = 2, R = H)
d (n = 3, m = 1, R = H)
e (n = 3, m = 2, R = H)
f (n = 1, m = 1, R = Me)
g (n = 1, m = 2, R = Me)

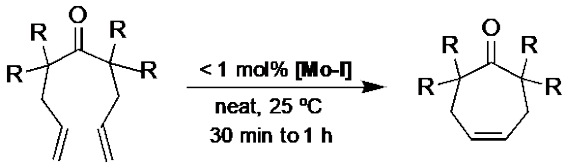
344

a 100 %[a]
b 100 %[a]
c 100 %[a]
d 96 %[b]
e 0 %
f 93 %[b]
g 61 %[b]

[a] Conversion.
[b] Isolated yield

Another example that supports the Thorpe-Ingold effect in RCM reactions is visualized in Scheme 107. While the reaction of **345a** (R=H) with <1 mol% [Mo-I] led to polymerization and no cyclic products were observed, the reaction of **345b** (X = Me) afforded 95% of the desired cycloheptenone **346b**; the *gem*-dimethyl moiety steering the diene conformation towards the RCM reaction. In more flexible systems ring formation did not benefit from the *gem*-dimethyl effect and medium-sized rings were not formed.[181]

Scheme 107. Synthesis of a Cycloheptenone Derivative

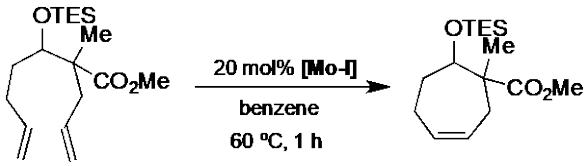


345
a (R = H)
b (R = Me)

346
a 0 %
b 95 %

Schrock's [Mo-I] was also successfully applied in the synthesis of other seven-membered rings. In the context of these studies for structural elucidation of some liverwort diterpenes, the RCM of the nona-1,8-diene **347** with [Mo-I] depicted in Scheme 108 gave >98% yield of **348**.[182]

Scheme 108. Synthesis of Cycloheptenecarboxylic Ester

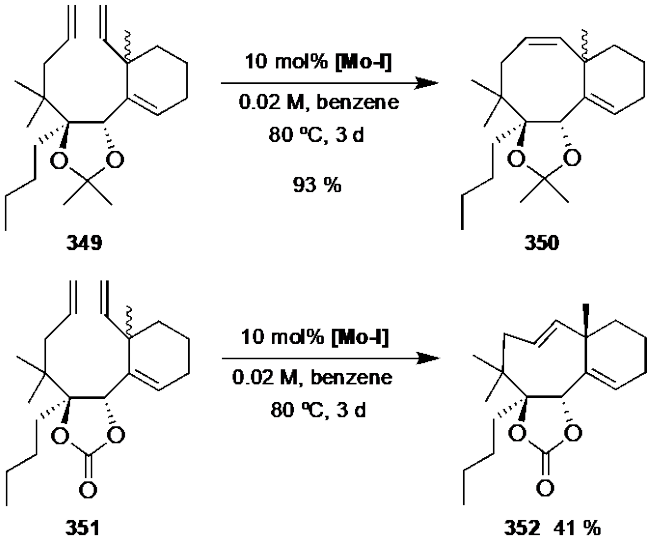


347 **348**

In contrast, within the frame of synthetic investigations towards taxol total synthesis, some eight-membered compounds have been synthesized in excellent yields. As examples, two of such transformations are depicted in Scheme 109. While the two diastereoisomers of the acetonide **349** underwent RCM to obtain a mixture of the diastereomeric *cis*-cyclooctene derivatives **350**, the corresponding cyclic carbonate **351** surprisingly delivered only one diastereoisomer of the *trans*-cyclooctene derivative **352**. The other diastereoisomer of **349** did not undergo cyclization and was isolated in 34% yield. It appeared that the reaction did not proceed to complete thermodynamic equilibrium. A plausible explanation for the different reaction outcomes from acetonide **349** and carbonate **351** is the possible involvement of the carbonyl group chelating the catalyst. This assumption is supported by the fact that in the presence of 1 equivalent of titanium

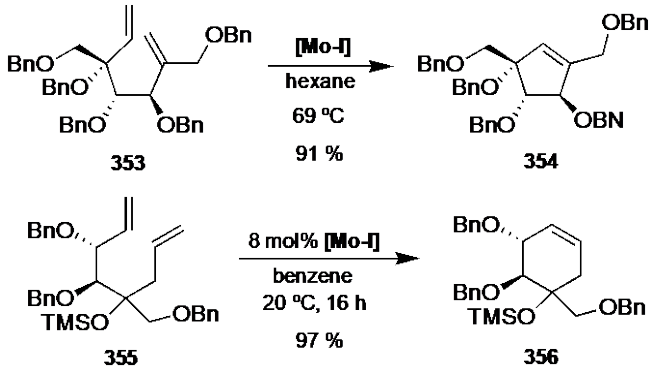
isopropoxide (as demonstrated by Fürstner and Langemann)[183] the *cis*-isomer of **349** is formed in addition to the unreacted second diastereisomer of **351**. [184]

Scheme 109. Synthesis of Cyclooctene Derivatives within the Frame of a Taxol Total Synthesis



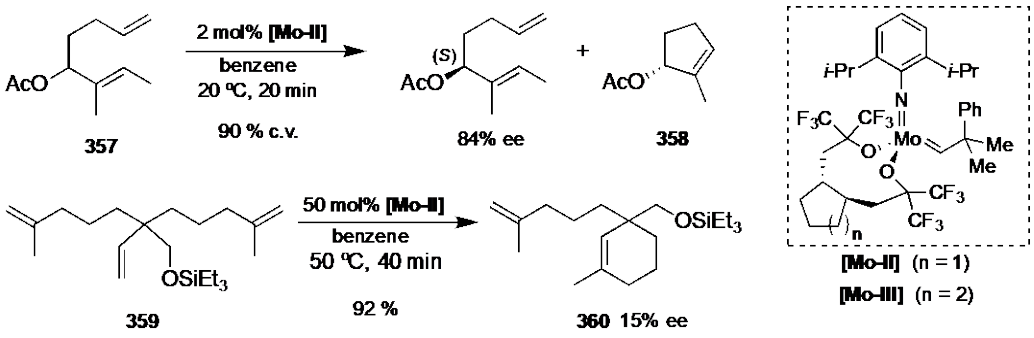
Schrock's molybdenum complex [Mo-I] has also been used for the preparation of several highly functionalized cyclopentane and cyclohexane derivatives. Thus, from the hepta-1,6-diene **353** and the octa-1,7-diene **355** the corresponding RCM products **354** and **356** were obtained in excellent yield under the conditions shown in Scheme 110.[185]

Scheme 110. Synthesis of Highly Functionalized Cyclopentane and Cyclohexane Derivatives



Several years ago, catalytic asymmetric olefin metathesis reactions were reviewed.[186] Among the used catalysts, there are also two fluorinated [Mo-I]-based ones, [Mo-II] and [Mo-III].[187] The enantioselectivity of [Mo-II] was generally slightly higher than that of [Mo-III], which might be due to the more flexible nature of the six-membered ring present in the latter catalyst. However, the enantioselectivity of these fluorinated catalysts was far below that of fluorine-free binaphthol-based catalysts. One of the best examples for kinetic resolution was published by Fujimura and Grubbs, who found that the enantiomeric excess determined for the unreacted acetate **357** after 90% conversion was 84% ee, but was much lower after 60% conversion.[187a] The RCM of the prochiral **359** proceeded with partial desymmetrization and delivered 92% of product **360** after 40 min with an enantiomeric excess of 15% (Scheme 111). [187b]

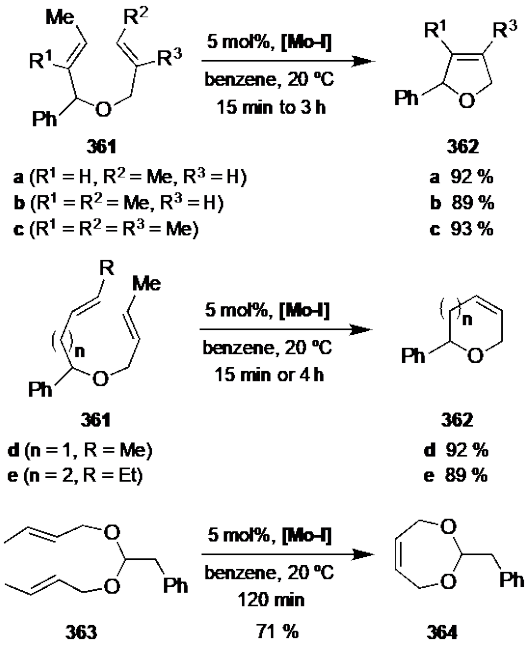
Scheme 111. RCM Reactions Proceeding by Kinetic Resolution of Deracemization



5.1.2. Formation of O-heterocycles

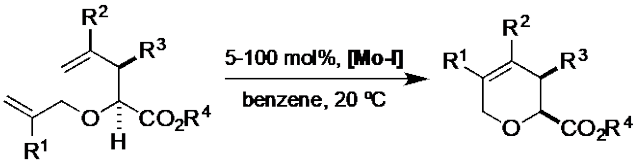
Cyclic ethers are of great importance in several classes of natural products. Grubbs *et al.* previously reported the potential of RCM reactions for the synthesis of dihydrofurans, dihydropyrans and tetrahydrooxepins. Thus, a series of cyclic α-phenylethers **362** was synthesized from **361** in very high yields. Also, compounds with additional methyl groups at the double bond and even a dihydrofuran with a tetrasubstituted double bond were prepared in excellent yield. Moreover, a *cis*-4,7-dihydro-1,3-dioxepin **364** was prepared in the same way (Scheme 112).[188]

Scheme 112. Synthesis of a Series of Unsaturated *O*-Heterocycles



In order to obtain oxygen heterocyclic scaffolds for solid-phase combinatorial synthesis, a series of glycolate-based tetrahydropyranecarboxylic esters were prepared by RCM using [Mo-I]. While for the cyclization of **365a-c** 5 mol% of the catalyst was sufficient, the transformation of **365d** and **365e** required 50 or even 100 mol% of [Mo-I] (Scheme 113).[189]

Scheme 113. Synthesis of Glycolate-based *O*-Heterocycles

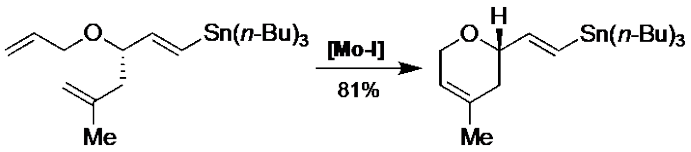


365 **366**

a (R^1 = Me, R^2 = H, R^3 = Me, R^4 = *i*-Pr) **a** 79 %
b (R^1 = CH_2OMe, R^2 = H, R^3 = Me, R^4 = *n*-Bu) **b** 92 %
c (R^1 = H, R^2 = Me, R^3 = Me, R^4 = *i*-Pr) **c** 83 %
d (R^1 = H, R^2 = Ph, R^3 = H, R^4 = Bn) **d** 56 %
e (R^1 = H, R^2 = $SiMe_3$, R^3 = H, R^4 = Bn) **d** 70 %

One of the key intermediates in a total synthesis of (-)-Laulimalide, which is a potent inhibitor of cellular proliferation in a number of cancer cell lines,[190] was prepared by RCM with [Mo-I]. Thus, the reaction (conditions not given) of the tributyltin-substituted compound **367** gave 81% of the target dihydropyran **368** (Scheme 114), which in turn was transformed into the macrocyclic target lactone.[191]

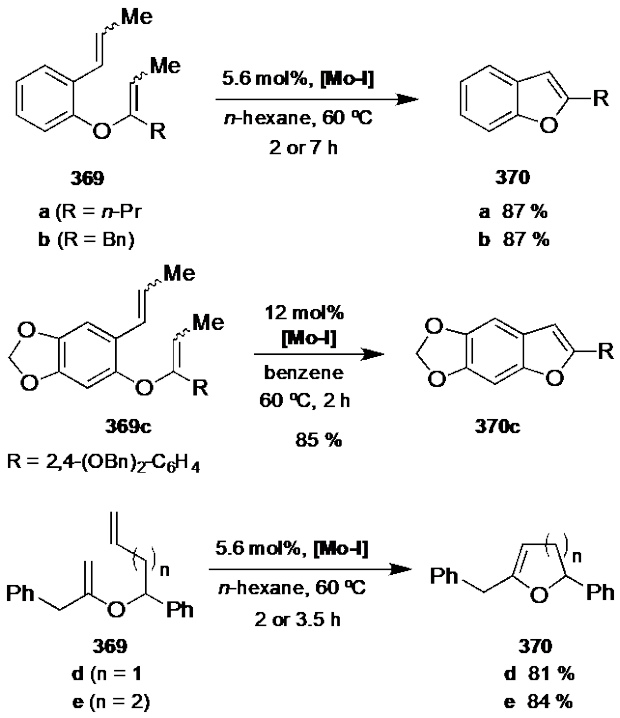
Scheme 114. Synthesis of an Intermediate of a (-)-Laulimalide Total Synthesis



367 **368**

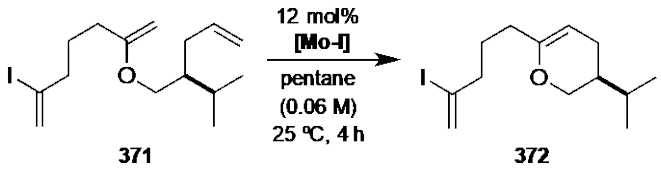
Synthesis of cyclic enol ethers by RCM was first described by Grubbs *et al.* in 1994, who synthesized several benzofurans **370a-e**, including a protected precursor for the antifungal phytoalexine Sophora Compound I (**370c**), from the corresponding oxa-diene precursors **369a-e** (Scheme 115).[178]

Scheme 115. [Mo-I]-Catalyzed Synthesis of Benzofurans by RCM



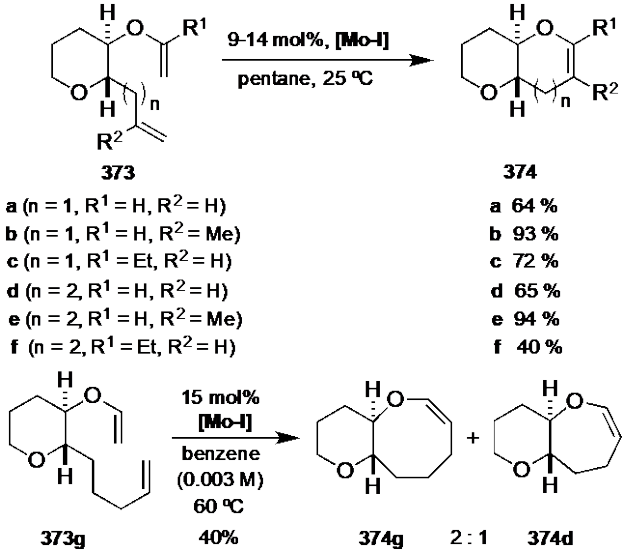
Within a formal total synthesis of the racemic pheromone components of the American cockroach Periplanone-B and Germacrene-D, the sensitive dihydropyran **372** was prepared (Scheme 116) and directly submitted for the subsequent step.[179]

Scheme 116. Synthesis of Dihydropyran 372 within a Formal Pheromone Synthesis



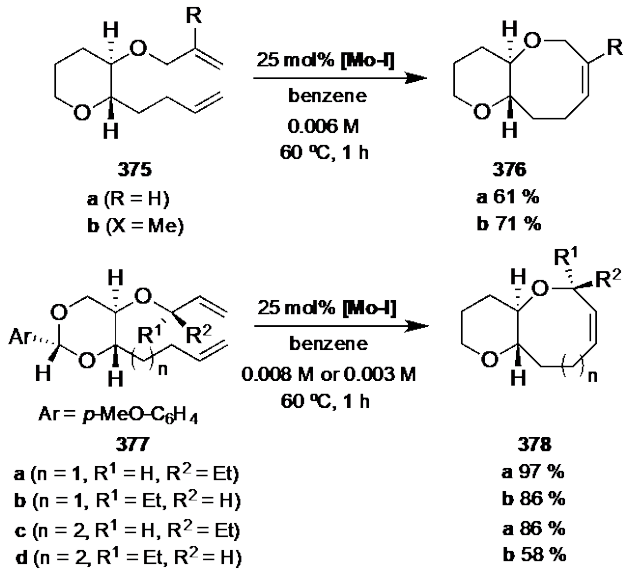
Clark and coworkers explored the construction of cyclic ethers using RCM as one of the key steps in fused-polyether syntheses. Thus, from the enolethers **373a-f** the acid-sensitive 2,7-dioxa-bicyclo[4.4.0]dec-3-enes **374a-c** or 2,8-dioxa-bicyclo[5.4.0]undec-3-enes **374d-f** were prepared in fair to excellent yields. Even **374g** containing an eight-membered ring could be prepared as a 2:1 mixture with **374d** under high dilution conditions (Scheme 117).[192]

Scheme 117. Synthesis of Dioxabicycloalk-3-enes 374a-g



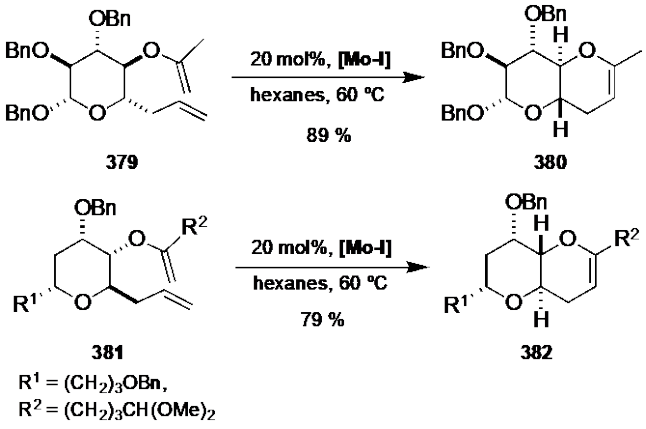
Conformational constrains induced by oxygen atoms seem to be responsible for the facilitation of oxacyclooctene system formation, as for example the RCM reactions of **375a,b** to form **376a,b**. In this case, an additional methyl group attached to the double bond seems to support the cyclization.[193] Furthermore, eight and even nine-membered rings were available when conformational constrains were forced by a condensed 1,3-dioxolane ring and a larger substituent adjacent to the ether function like in **377a-d** to form **378a-d**.[1933] Occasionally, the formation of cyclic ethers competes with isomerization or dimerization [1922a] and the reactions become sluggish and low yielding. This problem can be overcome by portion-wise addition of the catalyst (Scheme 118).[194] More examples of RCM towards cyclic ethers are given in Schrock and Hoveyda's excellent review.[174]

Scheme 118. Formation of Oxacyclooctene and Oxacyclononene Derivatives



A series of polyfunctional analogs **380** was synthesized from **379** by Rainier *et al.* applying [Mo-I]. These RCM reactions did generally not work with Grubbs-I catalyst [Ru-I], but were successful with Grubbs-II [Ru-IV] as well. Thus, with 20 mol% of [Mo-I] the 3-oxa-octa-1,7-dienes **379** and **381** gave the 2,7-dioxa-bicyclo[4.4.0]dec-3-enes **380** and **382** in high yields (Scheme 119).[195]

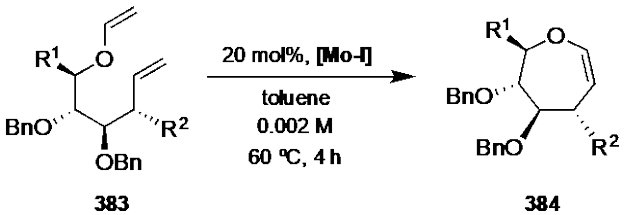
Scheme 119. Synthesis of Substituted 2,7-Dioxa-bicyclo[4.4.0]dec-3-enes



Moreover, this strategy was also successful for the preparation of the basic skeleton of glycals and also its seven-membered homologs were available in high yields. Glycals are versatile

building blocks for the preparation of a variety of carbohydrates and carbohydrate mimics. The synthesis of a series of fully protected seven-membered homologs of glycals using [Mo-I] was described by Peczuh and Snyder in 2003. Thus, the precursors **383a-c** were reacted with 20 mol% of this catalyst in toluene to give **384a-c** in excellent yields (Scheme 120). Other protection patterns were also employed for the preparation of such tetrahydrooxepines.[196]

Scheme 120. Synthesis of Tetrahydrooxepines 384



383

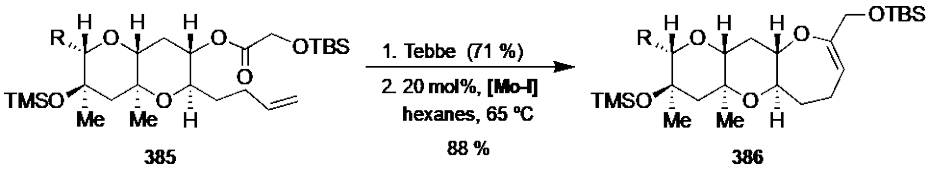
a (R^1 = H, R^2 = OBn)
b (R^1 = CH_2OBn, R^2 = OBn)
c (R^1 = CH_2OBn, R^2 = H)

384

a 82 %
b 92 %
c 86 %

A [Mo-I]-catalyzed RCM was used by Rainier *et al.* within the total synthesis of Gambierol, a marine ladder neurotoxin. In that case, the Schrock's catalyst showed to be more efficient than Grubbs-II catalyst [Ru-IV] (Scheme 121).[197]

Scheme 121. Synthesis of a Polycylic Polyether 386

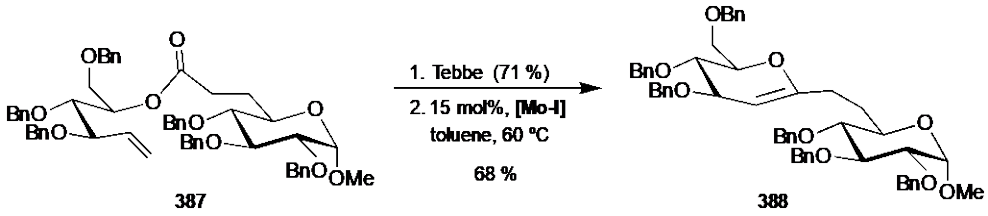


385 **386**

Glycals are versatile building blocks for the preparation of a variety of carbohydrates and carbohydrate mimics. In a series of papers, Postema and coworkers described the preparation of such compounds by RCM using [Mo-I] as a very active catalyst for this type of transformation. In a key experiment, Postema and Calimente demonstrated the transformation of **387** to **388**,

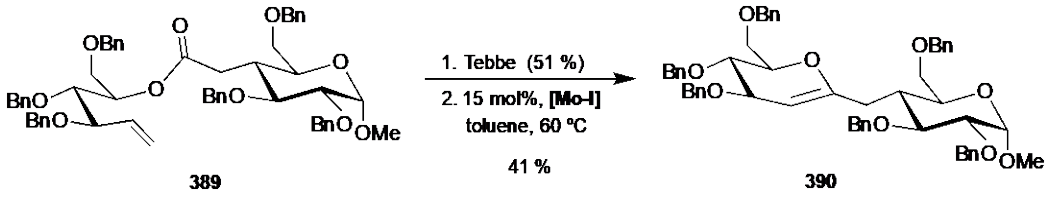
having an ethane spacer between the two monosaccharide-like parts of the target 1,6-glycal molecule (Scheme 122).[198]

Scheme 122. Synthesis of a (1→6)-C-Disaccharide Glycal Derivative by RCM



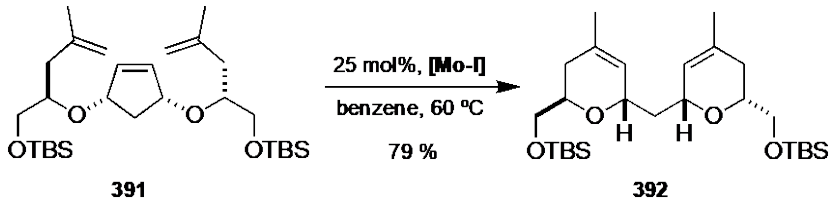
Later the same research group described the synthesis of several analogs with different monosaccharide components. Moreover, also glycols **389** with only one CH_2-group as a spacer between the glycosidic position of the glycal and the 4-position of the second carbohydrate were also prepared, but in lower yield (Scheme 123). Furanose derivatives were also prepared in an analogous manner.[199]

Scheme 123. Synthesis of the (1→4)-C-Disaccharide Glycal Derivative 390 by RCM



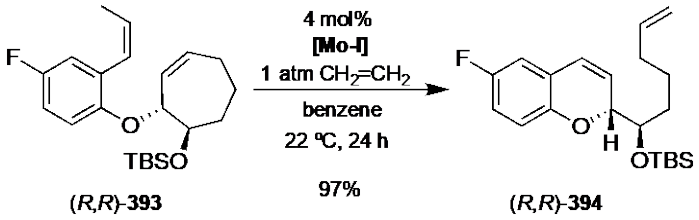
Multi-RCM reactions constitute a powerful tool for the efficient assembly of complex polycyclic polyethers. Thus, the TBS-protected cyclopentene derivative **391** with a bis-3-oxa-octa-1,7-diene structure underwent a double-RCM reaction by ring opening/ring closure to give the bis(dihydropyran) **392**, an intermediate in the total synthesis of Halichondrin B, in high yield despite the high steric encumbrance of the involved olefins (Scheme 124).[200]

Scheme 124. Synthesis of an Intermediate of a Halichondrin B Total Synthesis



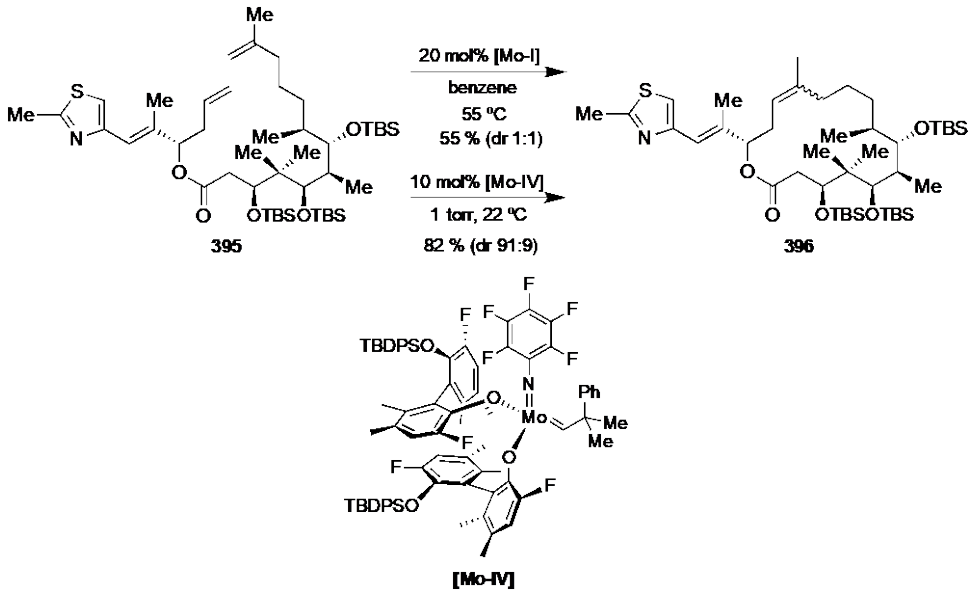
A similar strategy was applied by Hoveyda *et al.* within an enantioselective total synthesis of the therapeutically important antihypertensive agent (*S*,*R*,*R*,*R*)-Nebivolol. After kinetic resolution of the RCM precursor **393**, the [Mo-I]-catalyzed cyclization in the presence of 1 atm of ethylene afforded the target compound **394** in high yield (Scheme 125).[201] The presence of ethylene was shown to improve the selectivity and the yield of the RCM. The corresponding (*S*,*R*)-epimer was synthesized under identical conditions.[2011]

Scheme 125. Synthesis of an Intermediate of a Nebivolol Total Synthesis



As an example of the formation of a macrocyclic lactone by a [Mo-I]-catalyzed RCM, the synthesis of an advanced intermediate of a total synthesis of (-)-epothilone B **396** is depicted in Scheme 126.[202]

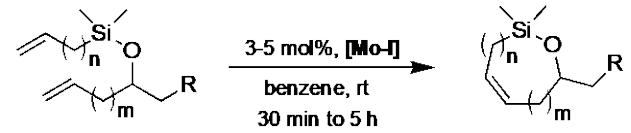
Scheme 126. Synthesis of Macrolide 396 by [Mo-I]-Catalyzed RCM Reaction



A general shortcoming of most of the commonly used olefin metathesis catalysts is the lack of kinetic control over the stereochemistry of the newly formed double bond. Recently there was significant progress to solve this issue of utmost importance.[16m] In addition to fluorine-free pre-catalysts, there are also several fluorine-containing Mo-complexes developed by Schrock, Hoveyda and their co-workers for RCM of the macrocyclic 17-membered lactone **396**. Most selective was the polyfluorinated bis-biphenyl complex [Mo-IV] delivering 82% of a 91:9 *Z*/*E* mixture. [203]

Within a synthetic sequence of polyhydroxylated long chain alkenes, the silylethers **397a-c** were subjected to RCM using [Mo-I] in benzene to give the cyclic silylethers **398a-c** in high yields (Scheme 127). Subsequent oxidation with H_2O_2 provided the target unsaturated polyols.[204] Later the same strategy was used to prepare other long chain alcohols.[205]

Scheme 127. Synthesis of Cyclic Silylethers by RCM with [Mo-I]



397

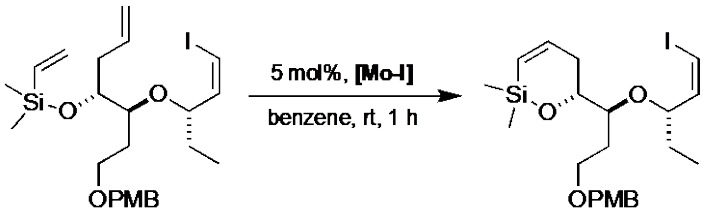
a (n = 1, m = 0, R = Me)
b (n = 2, m = 0, R = CH_2OPh)
c (n = 4, m = 1, R = CH_2OPh)

398

a 84 %
b 91 %
c 73 %

A silicon-assisted RCM reaction of **399** was also used to produce **400**, an important intermediate in the total synthesis of Brasilenyne (Scheme 128).[206]

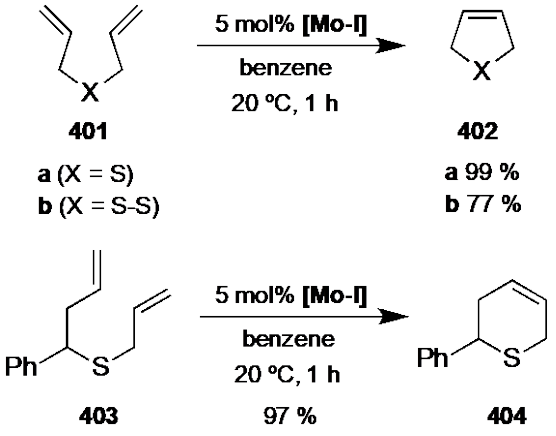
Scheme 128. Synthesis of Cyclic Silylethers by RCM with [Mo-I]



399 **400**

During initial studies of metathesis reactions, thioethers proved to be problematic at least with most ruthenium-based catalysts.[207] Therefore, it was most welcome that [Mo-I] was compatible with sulfides such as **403**, which gave 97% of the desired dihydrothiopyran **404** as depicted in Scheme 129.[208]

Scheme 129. Formation of Dihydrothiofurans and Dihydrothiopyrans



401

a (X = S)
b (X = S-S)

402

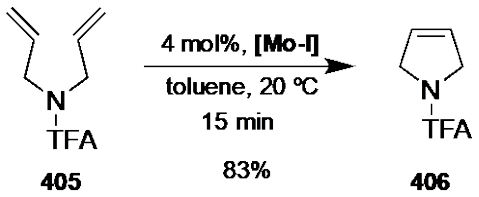
a 99 %
b 77 %

403 97 % **404**

5.1.3. Formation of N-heterocycles

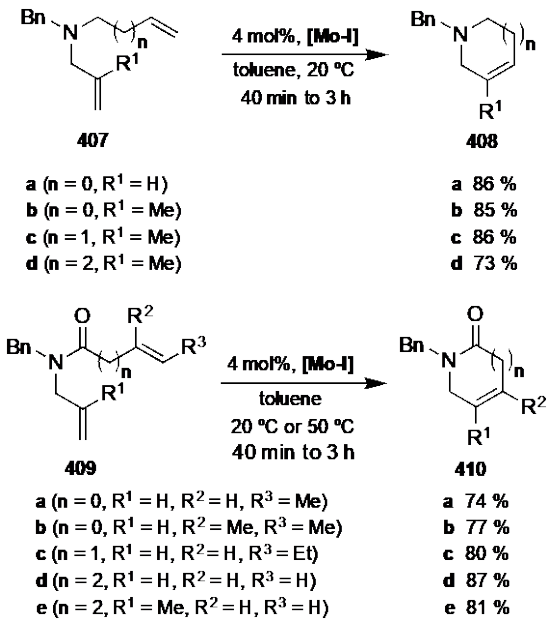
Another important class of heterocycles available applying [Mo-I] are nitrogen heterocycles, including mostly dihydropyrrols and tetrahydropyridines, some tetrahydroazepines and unsaturated γ-, δ- and ε-lactams. The first example of such a reaction was described by Fu and Grubbs in 1992 using [Mo-I] to cyclize *N*-trifluoroacetyl-4-azahepta-1,6-diene **405** to give the dihydropyrrol **406** in 83% yield (Scheme 130).[209]

Scheme 130. Synthesis of TFA Protected Dihydropyrrol 406



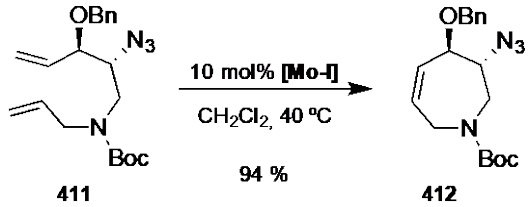
With the benzyl protecting group on the nitrogen the corresponding five- to seven-membered rings were synthesized and the corresponding lactams were also available using this system (Scheme 131).[209]

Scheme 131. Synthesis of Five-, Six-, and Seven-Membered *N*-Heterocycles



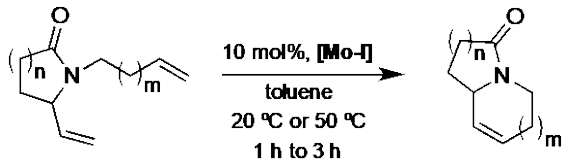
This exciting first result stimulated a number of research groups to apply this catalyst to construct a variety of *N*-heterocycles, including complex molecules. For instance, the RCM of the 4-azanona-1,8-diene **411** to form **412** was a key step in the total synthesis of Balanol (Scheme 132). While the target compound was obtained in 94% yield with the [Mo-I] catalyst, [Ru-I] led to non-metathesis products.[210]

Scheme 132. Synthesis of the Tetrahydroazepin 412 by RCM with [Mo-I]



Also, fused *N*-heterocyclic systems such as the basic skeletons of alkaloids **414** were prepared by Martin *et al*.[211] (Scheme 133).

Scheme 133. Synthesis of Fused *N*-Heterocycles



413

a (n = 1, m = 1)
b (n = 1, m = 2)
c (n = 1, m = 3)
d (n = 2, m = 1)
e (n = 2, m = 2)
f (n = 2, m = 3)

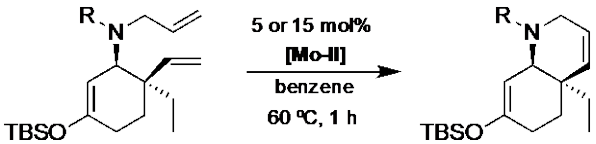
414

a 92 %
b 81 %
c 47 %
d 91 %
e 84 %
f 50 %

This method was also successful for the preparation of analogs with a vinylic trisubstituted double bond, *i.e.* a methyl group in 2-position of the longer alkenyl chain.[2111]

As one of the key steps in the total synthesis of Aspidosperma alkaloids, exhibiting anticancer activity, a [Mo-II]-catalyzed RCM reaction was applied (see, Scheme 111). Thus, the precursor **415a** was heated in benzene in the presence of 5 mol% of Schrock's catalyst to yield target compound **416a**. The cyclization was also successful when *N*-methyl derivative **416b** was used to afford the corresponding hydroquinoline **416b** in the presence of 15 mol% of the catalyst (Scheme 134).[212]

Scheme 134. Synthesis of a Hydroquinoline Building Block for Alkaloid Synthesis



415

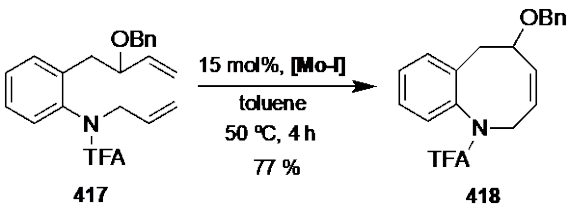
a (R = CO_2Me)
b (R = Me)

416

a 88 %
b 75 %

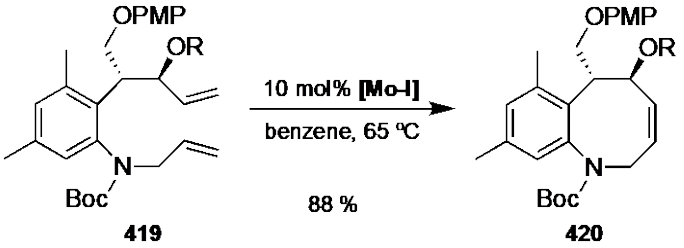
When precursor **417**, containing a TFA protected nitrogen and a rigid benzene backbone, was used the eight-membered derivative **418** was formed in good yield (Scheme 135).[2111]

Scheme 135. Synthesis of a Benzo-Tetrahydroazocine



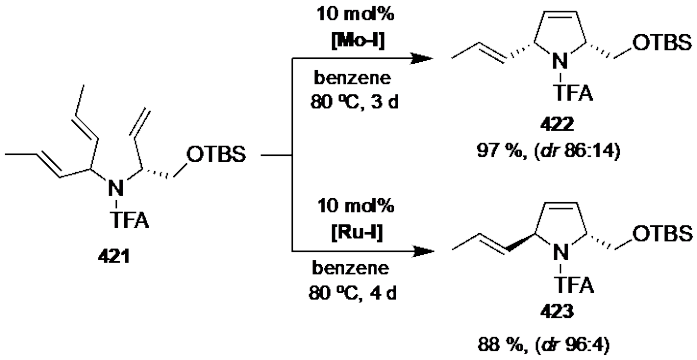
Similarly, the substituted 4-azadeca-1,9-diene **419** delivered target benzo-tetrahydroazocine **420** in the presence of 10 mol% of **[Mo-I]** (Scheme 136).[213]

Scheme 136. Synthesis of a Benzo- Tetrahydroazocine 420



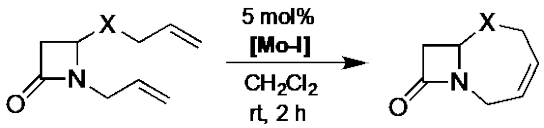
When the stereoselectivity of RCM was investigated, it was found that it may depend on the type of the catalyst used. While triene **421** gave the *cis*-configurated product **422** with 10 mol% of [Mo-I], the [Ru-I]-catalyzed reaction led to the other diastereoisomer **423** both in high yield and diastereoselectivity (Scheme 137). Several more of such examples including the formation of dihydropyridines, which proceeded with lower diastereoselectivity, were reported.[214]

Scheme 137. Different Diastereoselectivity of RCM Depending on the Used Catalyst



Most interestingly, also bicyclic β-lactams were prepared using RCM with [Mo-I]. For example, from precursors **424** with X = S, NTs homocephem **425a** or homo-azacephem **425b** were formed in high yields (Scheme 138).[215]

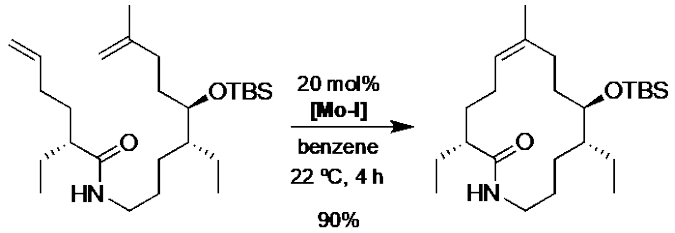
Scheme 138. Synthesis of Bicyclic β-Lactams



424a (X = S) **425a** (78 %)
424b (X = NTs) **425b** (91 %)

A [Mo-I]-catalyzed macrocyclization was one of the key steps in the asymmetric total synthesis of the antifungal agent Sch 38516 (Fluvirucin B_1). Hoveyda *et al.* first investigated the cyclization step using the OTBS protected model compound **426** (Scheme 139) contaning the skeleton of the target product and then also cyclized the glycosylated precursor with the same efficiency of the RCM step, illustrating that multifunctional macrocyclic structures are accessible by RCM during the late stages of multi-step total synthesis.[216]

Scheme 139. Synthesis of the Model Compound 427 for Fluvirucin B_1

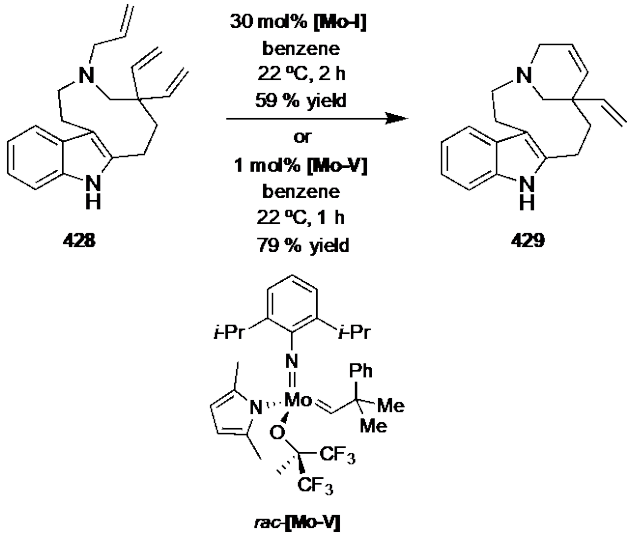


426 **427**

The RCM of the indol derivative **428** using the achiral [Mo-I] formed the basis of an asymmetric RCM reaction with enantiopure fluorine-free Mo-catalysts. Thus, with 30 mol% of [Mo-I] 98% conversion was reached at 22 °C after 2 h to give 59% yield of the target product **429**. Subsequently, Hoveyda, Schrock and their coworkers demonstrated that the chiral (racemic)

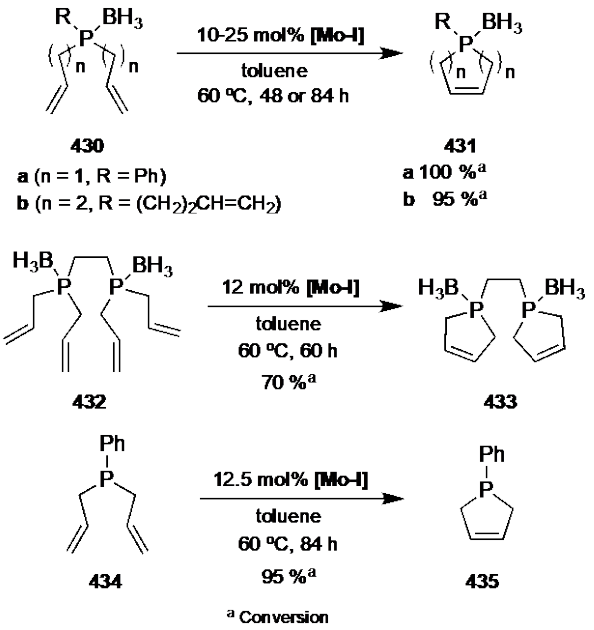
catalyst [Mo-V] is much more efficient, delivering the same product in the presence of 1 mol% of [Mo-V] at 22 °C after 1 h with 79% yield (Scheme 140). Ru-Catalysts, on the other hand, were less efficient and gave rise to the formation of side products resulting in lower yields of 35-65%. Finally, the enantioselective synthesis of both enantiomers of **429** was accomplished using binaphthol-based enantiopure Mo-catalysts.[217]

Scheme 140. Chiral (racemic) Catalyst [Mo-V] was more Efficient than Achiral [Mo-I]



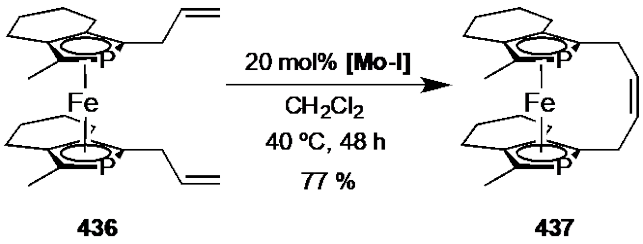
In addition to *N*-heterocyclic compounds, some phosphaheterocycles were prepared using [Mo-I] (Scheme 141).[218]

Scheme 141. Synthesis of Phosphaheterocycles



The meso- as well as the racemic 1,1'-diphospha[4]ferrocenophanes **437** were prepared in good to moderate yield with the interannular ring-closing metathesis reaction of diallyl-1,1'-diphosphaferrocenes **436** using Schrock's molybdenum-carbene catalyst [Mo-I] (Scheme 142). Moreover, also a corresponding double-bridged diphosphaferrocenophane was synthesized.[219]

Scheme 142. Mo-Catalyzed RCM Route to Diphospha[4]ferrocenophanes

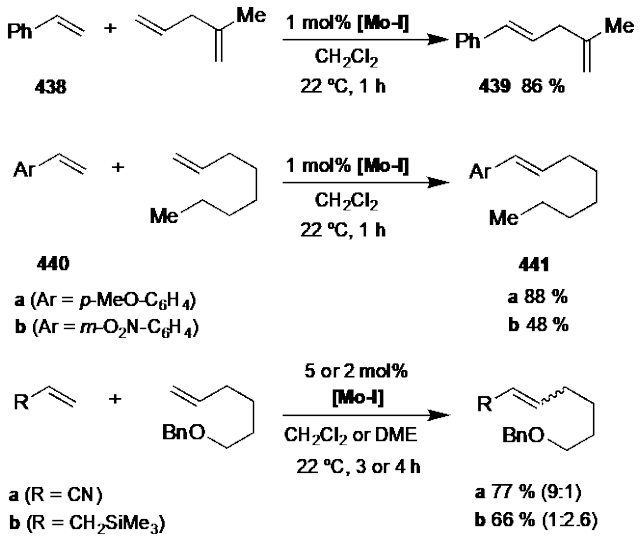


5.1.4. Cross Metathesis with Schrock's catalyst

In addition to the cyclizing metathesis reactions discussed in the previous chapters, there are also some applications of Schrock's catalyst [Mo-I] in cross metathesis (CM) reactions. One of the problems, which had to be overcome, was to find olefins, not tending towards extensive self-metathesis with the formation of so-called homodimers in the presence of other alkenes. At the

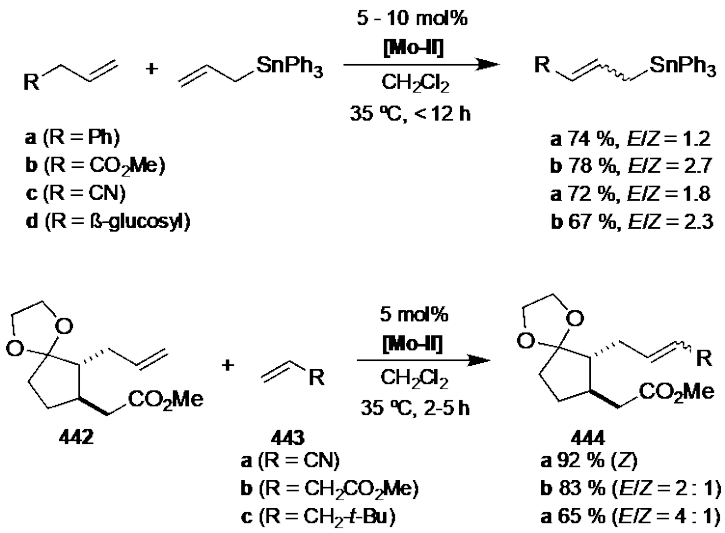
beginning of the 1990s, Crowe and Zhang described a series of such experiments with substituted arenes **438** and **440a,b** with terminal alkenes 2-methyl-penta-1,4-diene and oct-1-ene, showing that the electronic nature of the involved double bonds do significantly determine the success of CM to form **439** and **441a,b**.[220] Furthermore, acrylonitrile and allyl trimethylsilane by reaction with benzyl protected hex-5-en-1-ol provided the corresponding alkenes as mixtures of (*Z*)/(*E*)-isomers (Scheme 143).[221]

Scheme 143. Cross Metathesis of Electronically Different Terminal Alkenes



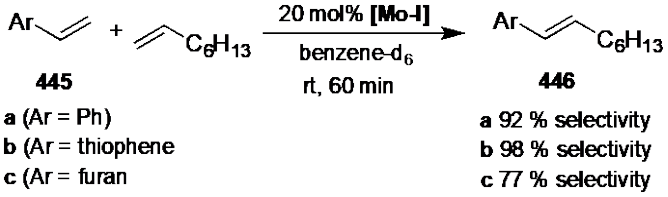
Blechert *et al.* discovered allyltributyl and allyltriphenyl stannanes as potent cross metathesis substrates. Generally, the yield was higher with the latter stannanes (Scheme 144).[222]

Scheme 144. Cross Metathesis of Alkenes with Allyl Triphenylstannan



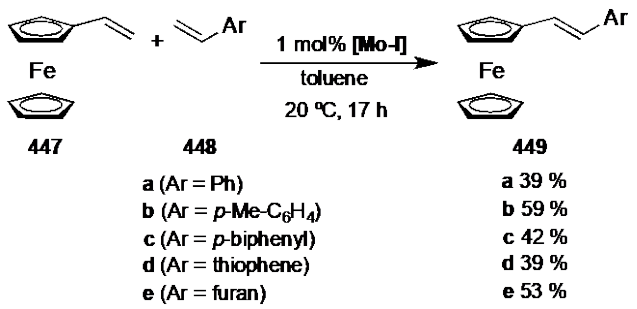
CM reactions were also successful with the (2-allylcyclopentyl)-acetate **442**, which did not undergo self-metathesis probably due to steric constrains, and a series of terminal alkenes **443a-c** (Scheme 144).[223] Moreover, a series of 2-vinyl aromatic compounds such as styrene, 2-vinylthiophene and 2-vinylfuran **445a-c** were reacted with oct-1-ene in the presence of 20 mol% of [Mo-I] in benzene affording the corresponding 1-aryloct-1-enes **446** in good selectivities (Scheme 145).[224]

Scheme 145. Synthesis of 1-Aryloct-1-enes by Cross Metathesis with [Mo-I]



A series of π-conjugated 1-arenyl-2-ferrocenylethylenes **449a-e** was synthesized from vinylferrocene **447** and a series of vinylarenes **448a-e** in the presence of 1 mol% of [Mo-I] in toluene at 20 °C. In all cases the *trans*-double bond was generated (Scheme 146).[225]

Scheme 146. Cross Metathesis of Vinylferrocene with a Variety of Vinylarenes

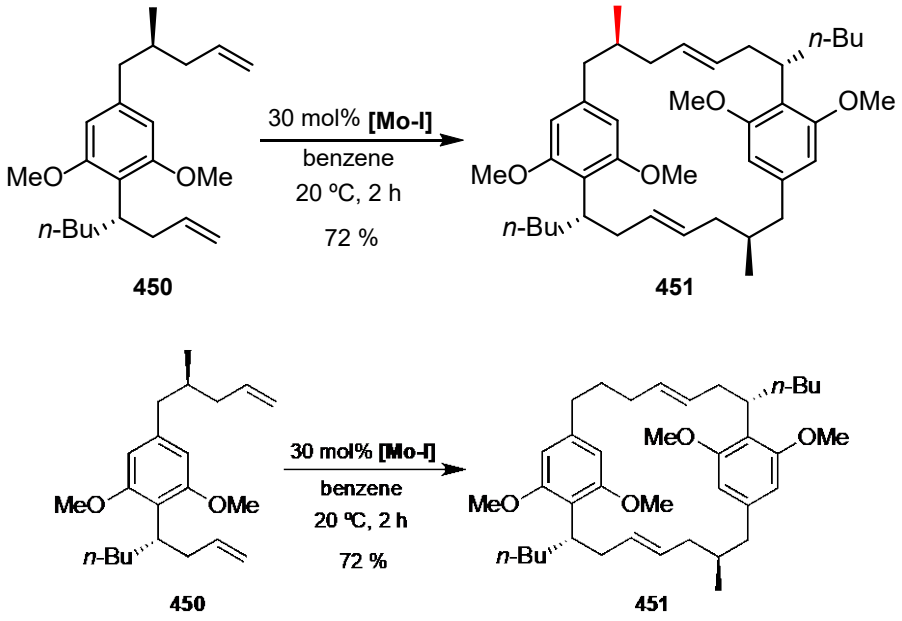


447 **448** **449**

a (Ar = Ph)	**a** 39 %
b (Ar = *p*-Me-C_6H_4)	**b** 59 %
c (Ar = *p*-biphenyl)	**c** 42 %
d (Ar = thiophene)	**d** 39 %
e (Ar = furan)	**e** 53 %

Smith *et al.* accomplished a remarkable high-yielding tandem CM/RCM reaction leading to a macrocyclic compound. Thus, as one of the final steps in the total synthesis of (-)-cylindrocyclophane F, treatment of **450** with 30 mol% of [Mo-I] afforded the target macrocycle **451** as the only region- and stereoisomer probably due to the reversible nature of the olefin metathesis reaction (Scheme 147).[226] The Ru-II catalyst was less efficient.

Scheme 147. Tandem CM/RCM Reaction to Obtain the Macrocyclophane 451



450 **451** **450** **451**

At the end of this section we like to mention another class of multiple trifluoromethylated molybdenum and tungsten imidazolin-2-iminato alkylidyne complexes, which were recently developed and governed by Tamm *et al.*[227] based on earlier work reviewed by Schrock and

Czekelius [175] and approved to be very useful alkyne metathesis catalysts (Figure 8). The synthesis and application of catalysts such as [Mo-VI] and [W-Ia,b] have been reviewed very recently.[228] These catalysts have been shown to be almost equally active in ring-closing alkyne metathesis (RCAM) to form macrocycles, alkyne cross metathesis (ACM) and ring-opening alkyne metathesis polymerization (ROAMP).

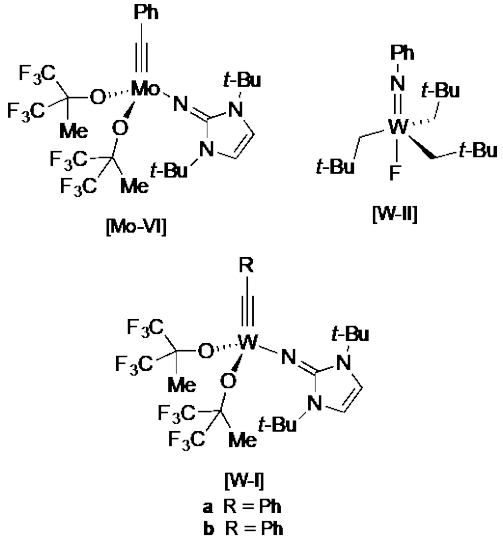


Figure 8. Types of Mo- and W-based fluorine-containing catalysts used for alkyne or olefin metathesis reactions

In a recent patent the application of the fluorine-containing tungsten complex [W-II] was used for self-metathesis of propylene to deliver a 1:1 mixture of ethylene and the diastereomeric but-2-enes.[229]

5.2. Olefin Metathesis Reactions with Fluorous Catalysts

The preceding section reviewed applications of Schrock's [Mo-I] catalyst containing four CF_3-groups for the preparation of various carbocycles and heterocycles. In other previous sections we have discussed applications of different catalysts for the preparation of fluorinated molecules by RCM, CM or polymerization. In general, the used catalysts cannot be recovered after workup of

the reaction mixtures. Another major drawback is the difficult separation of traces of the metal complexes or fragments from the target products, which is particularly important when synthesizing biologically/medicinally relevant target molecules. Different immobilization techniques have been developed to overcome the latter issues (see multi author special issues on that topic in *Chem. Rev.* and *Adv. Synth. Catal.*).[230] One of the more recent of such technologies is the application of perfluoro-tagged catalysts in perfluorinated solvents.[231] Since these solvents are immiscible with most organic solvents (at room temperature), the reactions proceed under fluorous biphasic conditions. The perfluoro-tagged catalyst can subsequently be separated under mild conditions by liquid-liquid extraction. In many cases, the catalyst is suitable for consecutive runs. In this sense, usually more than 60% of fluorine content in the molecule is required.[232] Therefore, multiple substitution has to be combined with perfluorinated ponytails of substituent chain lengths. However, a compromise has to be found including the solubility of the catalysts and substrates in typical solvents for metathesis reactions. Thus, the perfluorinated ponytail should, in general, not exceed 10 carbon atoms.

Despite these advantages there are also two major shortcomings, namely (*i*) the elevated cost of fluorous solvents and (*ii*) their persistence in nature. These disadvantages can be overcome by "light fluorous technology" developed by Curran and coworkers.[233] This technology is characterized by the following parameters: (*i*) reactions proceed in organic solvents and (*ii*) the polyfluoro-tagged compounds (including fluorous catalysts) are separated from the products by solid-phase extraction on fluorous silica gel.[234] Another advantage of this method is that lower fluorine content is required when compared to fluorous biphasic applications.

In order to place polyfluorinated moieties in metathesis catalysts four principal options were followed with respect to catalysts derived from Grubbs II or Hoveyda-Grubbs' catalysts (Figure

8). The polyfluorinated chains can be bound to the phosphine ligand (**A**); can be attached as a substituent in the Ru-binding aromatic ring (**B**); can be placed and in the *N*-heterocyclic carbene ligands (**C**); or can replace one or two chlorine atoms at ruthenium (**D**), e.g., with perfluoroalkoxylates. These types of catalysts will be discussed in this and the next two chapters. The R_F substituents in the structures shown in Figure 9 represent not necessarily a perfluoroalkyl or perfluoroaryl group, i. e., that this group contains a fluorine atom or a fluorinated fragment. In section 5.2 "R_F" stands for fluorous groups.

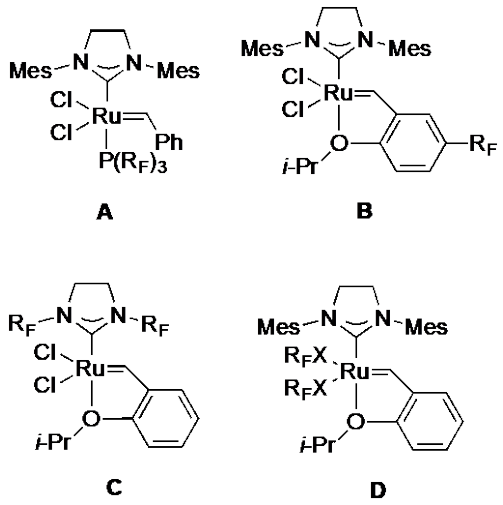


Figure 9. Types of Ru-based fluorine-containing catalysts used for metathesis reactions in sections 5.2. to 5.4.

Matsugi and Curran applied light fluorous strategy for the preparation of first and second-generation derivatives of Hoveyda-Grubbs catalysts [Ru-F1]/[Ru-F2] and [Ru-F3] (Figure 10), which are air stable over several days either as solids or in solvents, but do slowly decompose in $CDCl_3$ at 80 °C.[235]

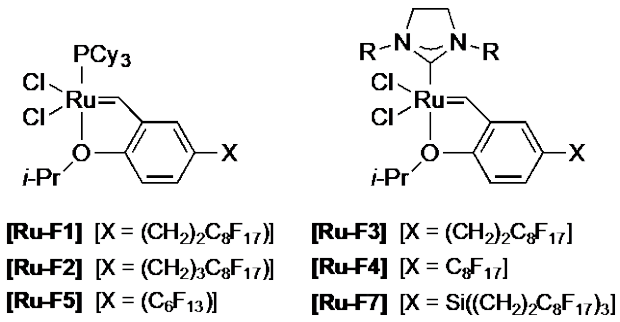
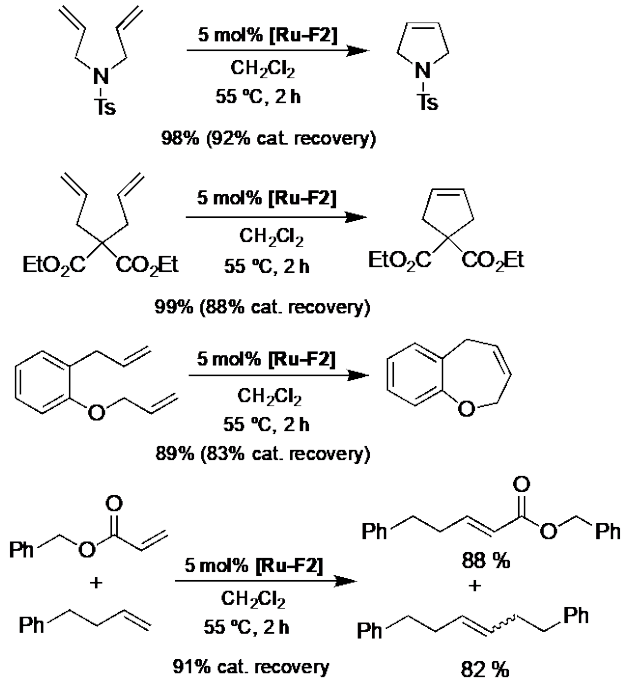


Figure 10. First and second generation light fluorous Ru-catalysts

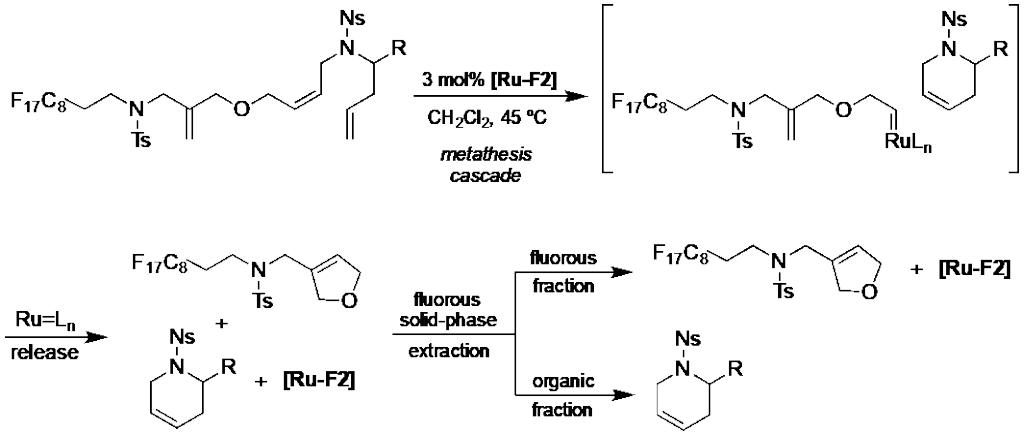
These catalysts exhibited a similar reactivity profile as the fluorine-free parent catalysts in several RCM and CM model reactions, but could readily be recovered by fluorous solid phase extraction and reused five or more times with only partial loss of activity. The catalysts have been used both in a stand-alone fashion or supported on fluorous silica gel as, for example, for the benchmark RCM and CM reactions depicted in Scheme 148.[235]

Scheme 148. RCM and CM Reactions with [Ru-F2] with Catalyst Recovery



The [Ru-F2] catalyst was later used by Nelson *et al.* to synthesize an additional series of normal-, medium- and large-sized *N*-heterocycles, some carbo- and *O*-heterocycles as well as several more complex molecules. These authors attached a fluorous-tagged substituent to the nitrogen atom in order to couple the "cyclization release" of the heterocyclic products with liberation of the active catalyst as depicted in Scheme 149.[236]

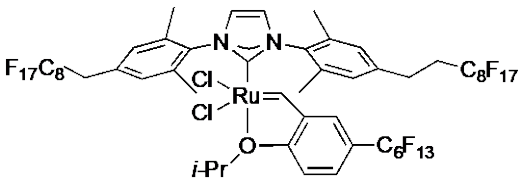
Scheme 149. RCM with a Fluorous Tagged Substituent in the Substrate and Catalyst Recovery



Based on these findings, a combinatorial chemistry approach was used by the same research group to produce a library of different scaffolds spanning large tracts of biologically relevant chemical space in chemical biology.[237]

Recently, a modified light fluorous catalyst [Ru-F4] was designed, which exhibited higher catalytic activity than the original Hoveyda-Grubbs catalyst [Ru-III] or the parent light fluorous Curran's catalyst [Ru-F3] in several of the above-mentioned model reactions (Figure 10). Once again, the light fluorous tag served as both a catalyst activator and a handle for separation and recovery with fluorous solid phase extraction.[238]

Soon after, Kvíčala and coworkers demonstrated that a light fluorous variation [Ru-F5] of Hoveyda-Grubbs 1st generation catalyst was more reactive than the parent complex in RCM of diethyl hepta-1,6-diene-4,4-dicarboxylate.[239] [Ru-F5], however, was less reactive than 2nd generation Hoveyda-Grubbs catalyst [Ru-II] and much less reactive than [Ru-F4] in RCM of diethyl 2-methylhepta-1,7-diene-4,4-dicarboxylate leading to the corresponding 1-methylcyclopentene derivative. This was also true for a heavy fluorous catalyst [Ru-F6] with additional perfluorooctyl moieties instead of the methyl groups in the *para*-position of the mesitylene groups in the unsaturated heterocyclic carbene ligand (Figure 11). Kvíčala *et al.* also demonstrated that [Ru-F4] was the most reactive catalyst to form the tetrasubstituted double bond of diethyl 1,2-dimethylcyclopentene-4,4-dicarboxylate by RCM.[239]



[Ru-F6]

Figure 11. Heavy fluorous ruthenium carbene complex [Ru-F6]

An unsymmetrical complex of this type, bearing a *para*-$(CH_2)_2C_6F_{13}$ side chain at one of the mesitylene groups instead of the third methyl group, was prepared by Fürstner *et al.* in order to increase the solubility of the catalyst in supercritical CO_2.[240]

A similar type of fluorous Hoveyda-Grubbs-type metathesis catalyst [Ru-F7] (Figure 10) was designed by Bannwarth *et al.* and it has been used for RCM reactions of benchmark dienes to form carbocyclic as well as *N*- and *O*-heterocyclic compounds.[241a] This catalyst bears a tris(polyfluoroalkyl)silyl tag[241b,c] for efficient noncovalent attachment of fluorous silica gel and can also be used in aqueous phase.[241d]

In another approach, Yao and Zhang prepared a poly(fluoroalkylacrylate)-supported Hoveyda-Grubbs -type catalyst [Ru-F8] and compared the reactivity in RCM model reactions similar to those mentioned above as well as the recyclability with a corresponding PEG-supported and ionic liquid modified Ru-catalyst (Figure 12). All catalysts were evaluated using three test dienes and showed similar reactivity and recycling was possible by fluorous extraction in case of the fluorine polymer modified catalyst [Ru-F8]. The loading capacity of this catalyst was quite low (0.19 mmol/g). In all cases very low residual ruthenium levels (average 7 ppm per run) were detected.[242] Liquid/liquid biphasic recovery/reuse of soluble polymer-supported catalysts was recently reviewed.[243]

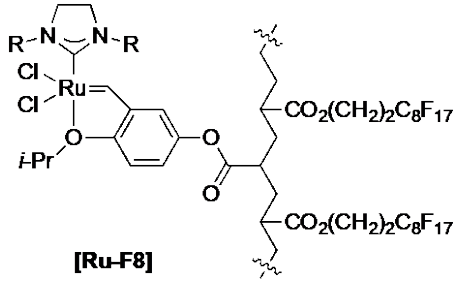


Figure 12. Poly(fluoroalkylacrylate)-supported Grubbs-Hoveyda-type catalyst [Ru-F8]

In 2006, Gladysz *et al.* disclosed that Grubbs-II-type catalysts [Ru-F9a-c] containing fluorous phosphine moieties were active for RCM under organic monophasic and fluorous/organic biphasic conditions (Figure 13). The latter protocol was more efficient, which was believed to arise from phase transfer of the dissociated fluorous phosphine into the fluorous phase. The most fluorophilic catalyst [Ru-F9c] was recycled by extracting the reaction mixture with perfluoro(methylcyclohexane) and it was reused for RCM of diethyl hepta-1,6-diene-4,4-dicarboxylate without loss of yield in three cycles.[244]

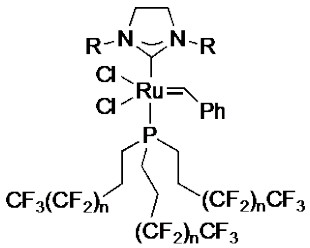


Figure 13. Fluorous phosphine containing Grubbs-II-type olefin metathesis catalysts

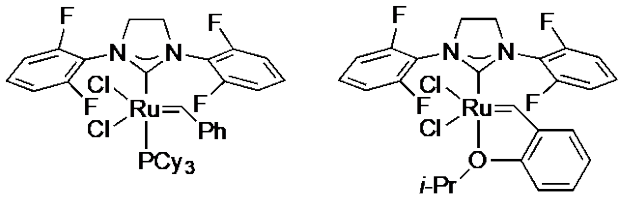
Recently, Gladysz and coworkers demonstrated that [Ru-F9b] catalyzes ring opening metathesis polymerization of norbornene at essentially the same rate as Grubbs 2nd generation catalyst [Ru-II] in $CDCl_3$ at room temperature. However, in the presence of a fluorous solvent [perfluoro(methylcyclohexane)] a dramatic rate acceleration was observed. Similar effects were found with a 7-oxanorbornene-based *N*-butylsuccinimide.[245] X-Ray structural analysis of [Ru-F9b] revealed that the perfluoroalkyl groups adopt helical conformations aligning in pairs with opposite helical chirality.[246] Consequences of these structural features for olefin metathesis reactions have not been discussed so far.

5.3. Olefin Metathesis Reactions with Fluorine-containing Dichloro-Ru-Catalysts

In addition to the light and heavy fluorous catalysts discussed in the preceding section, many other ruthenium-based olefin metathesis catalysts including those with fluorine substituents in many different positions (catalyst types **A**-**C**, see Figure 8) have been prepared and their chemistry has been reviewed recently.[247]

A number of analogs of Grubbs 2nd generation [Ru-II] and Hoveyda-Grubbs catalysts [Ru-III] with fluorine substituents at the heterocyclic carbene (NHC) part have been compared with their parents with regard to their activity to catalyze olefin metathesis reactions. Thus, the phosphine

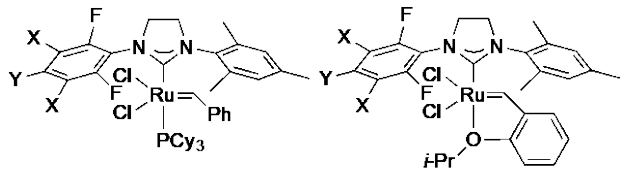
containing catalyst [Ru-F10] (Figure 14) with *ortho*,*ortho'*-difluorinated aryl groups in both of the NHC substituents accelerated the RCM of diethyl diallylmalonate compared to [Ru-II] and Hoveyda-Grubbs catalyst [Ru-III], while the analog of the latter [Ru-F11] was slower than both [Ru-II] and [Ru-III]. This different influence of fluorine substitution was attributed to an unprecedented, quite close proximity of fluorine and ruthenium found in X-ray structural analysis.[248] [Ru-F10] was successfully used in the RCM of several benchmark dienes, for ROMP of norbornene, cyclooctene and cycloocta-1,5-diene as well as for a CM reaction.[249]



[Ru-F10] **[Ru-F11]**

Figure 14. Ruthenium carbene complexes [Ru-F10] and [Ru-F11] fluorinated in the NHC

Furthermore, a series of unsymmetrically fluorinated catalysts such as [Ru-F12a-c] and [Ru-F13a-c] were prepared (Figure 15).[250] All phosphine complexes suggest phosphine dissociation as the rate-determining step, while phosphine-free catalysts are indicative of an associative mechanism.[247] Thus, the catalytic activity in RCM, CM, and ROMP reactions of [Ru-F12] is higher than either [Ru-II] and [Ru-III], while [Ru-F13] has a similar or lower activity than either [Ru-II] and [Ru-III] due to slow initiation.[250]



[Ru-F12]
a X = Y = H
b X = H, Y = F
c X = Y = F

[Ru-F13]
a X = Y = H
b X = H, Y = F
c X = Y = F

Figure 15. Ruthenium carbene complexes [Ru-F12a-c] and [Ru-F13a-c] unsymmetrically fluorinated in the NHC

Blechert and coworkers investigated the influence of fluorine and a CF_3 group in the *para*-position of the alkylidene ligand of first and second generation ruthenium-based catalysts on the rate and the yield of RCM reactions of *N,N*-diallyl-*N*-tosylamine and *N,N*-dipent-4-en-1-yl-*N*-tosylamine with 1 mol% of the catalysts [Ru-F14b,c] and [Ru-F15b,c] (Figure 16). While [Ru-F14b,c] slightly accelerated the conversion of both of the mentioned aza-dienes when compared to [Ru-F14a] bearing an electron donating substituent, almost no difference was found for [Ru-F15b,c] when compared to [Ru-F15a].[251]

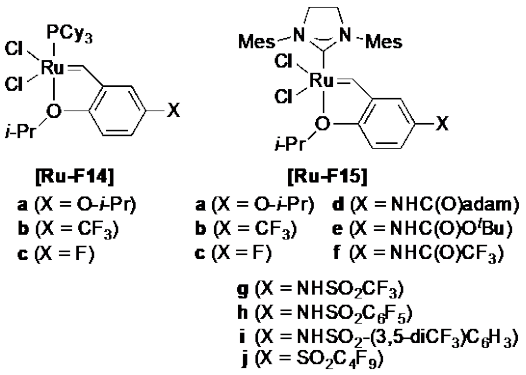


Figure 16. Blechert's phosphine and NHC Ru-based metathesis catalysts

Posterior studies led to the discovery of other [Ru-15]-type catalysts bearing fluorine-free or various fluorine-containing moieties in the *para*-position of the alkylidene part of NHC catalysts (Figure 16). Within this series [Ru-F15d-f], the CF_3-derivative [Ru-F15f] was the best performing one (0.3 mol% catalyst loading) in a series of benchmark ring closing olefin metathesis reactions to obtain carbocycles, *N*- and *O*-heterocycles, cross metathesis reactions as well as in enyne heterocyclization reactions.[252] Recently, the variety of such catalysts was broadened and fluorine containing sulphonamides such as [Ru-F15g-i] have been used for the RCM of benchmark dienes

to form carbocycles, *N*- and *O*-heterocycles, CM reactions and enyne metathesis reactions. These catalysts are at least as active as the parent [Ru-III] or more active, while [Ru-F15i] was the most active one in this series.[253] Furthermore, the potential perfluorobutyl sulfone catalyst [Ru-F15j] was synthesized by Grela and coworkers but, to the best of our knowledge, has not been applied in metathesis reactions so far.[254]

Very recently, newly designed Ru-benzylidene-oxazinone catalysts [Ru-F16a,b] (Figure 17) were prepared in connection with mechanistic investigations on the selectivity of olefin metathesis reactions. These catalysts decreased the initiation rate relative to other Hoveyda-Grubbs-type catalysts considerably. Particularly, [Ru-F16b] is a highly efficient catalyst both for RCM and for CM reactions.[255]

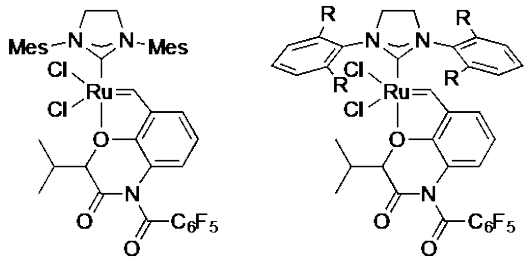
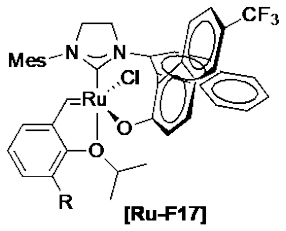


Figure 17. Ru-benzylidene-oxazinone catalysts [Ru-F16a,b]

In 2002, Hoveyda *et al.* prepared a series of chiral, non-racemic catalysts with a binaphthyl moiety bearing the chirality.[256] Attachment of a CF_3 group at one of the naphthyl rings led to a 1:3 rate acceleration of [Ru-F17a] with regard to the parent binaphthyl catalyst of the asymmetric ring opening metathesis/cross metathesis (AROM/CM) cascade of norbornenedicarboxylic anhydride **452** both with styrene **453a** and with oct-1-ene **453b**, respectively, to give **454a,b** with 55-74% ee. Introduction of an additional phenyl group into the *ortho*-position of the alkylidene aryl ring led to a dramatic rate acceleration of 1:130 (for the fluorine free binaphthyl catalyst) or

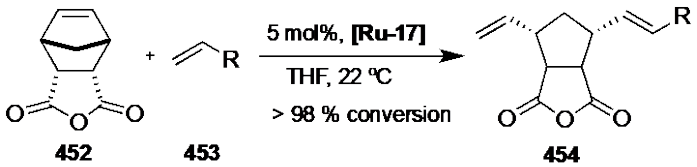
1:160 for [Ru-F17b], respectively, with regard to the unsubstituted parent catalyst (Figure 18 and Scheme 150). The enantioselectivity of the reaction was not significantly influenced by the catalysts.[256b]



[Ru-F17]
a R = H
b R = Ph

Figure 18. Chiral binaphthyl-based Ru-catalyst

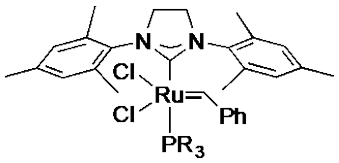
Scheme 150. Asymmetric Ring Opening Metathesis/Cross Metathesis of Norbornenedicarboxylic Anhydride (452) with Styrene (453a) and Oct-1-ene (453b)



452 **453** **454**

a (R = Ph)	**[Ru-17a]**, 22 h	**a** 55 %
b (R = *n*-C_6H_{13})	**[Ru-17a]**, 14 h	**b** 74 %
a (R = Ph)	**[Ru-17b]**, 25 min	**a** 55 %
b (R = *n*-C_6H_{13})	**[Ru-17b]**, 20 min	**b** 74 %

Last but certainly not least, Grubbs 2nd generation catalyst [Ru-II] was also modified with fluorine substituents in the phosphine part, i.e. with *p*-F- and *p*-CF_3-phenyl groups [Ru-F18a,b] (Figure 19). These as well as other *p*-substituted analogs can serve as significantly more reactive catalysts for both ROMP and RCM.[257]



[Ru-F18]

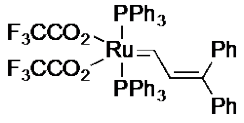
a R = *p*-FC_6H_4
b R = *p*-$CF_3C_6H_4$

Figure 19. Grubbs II catalysts [Ru-F18] fluorine modified in the phosphine

5.4. Olefin Metathesis Reactions with Ru-based Polyfluorocarboxylate and Perfluoromethanesulfonate Catalysts

In sections 5.2 and 5.3, the influence of fluorinated moieties on the reactivity and selectivity of Ru-based catalysts bearing fluorine in the alkylidene, in the phosphine ligand or in the NHC ligand was summarized. This section gives an overview on homogeneous and heterogeneous Ru-catalysts containing fluorinated ligands replacing one or both of the anionic chloride ligands in Grubbs and particularly in Hoveyda-Grubbs-type catalysts.[258]

In 1995, Grubbs and coworkers published the synthesis and application of the first anion exchanged Ru-complex of this type [Ru-F19] in olefin metathesis reactions (Figure 20). However, this complex gave only stoichiometric reactions with electron-rich olefins such as enolethers or enamines.[259] Several analogous complexes with more bulky perfluoroalkoxy groups were also prepared, but were not reactive in metathesis because of steric congestion.[260]



[Ru-F19]

Figure 20. Grubbs-I-type bis-trifluoroacetate complex [Ru-F19]

In 1999 and 2001, Mol and coworkers synthesized a novel type of ruthenium carbene dimers from Grubbs catalysts [Ru-I] and [Ru-II] by reaction with silver trifluoroacetate or silver pentafluorobenzoate, respectively (Figure 21). The complexes [Ru-F20a-d], characterized by X-ray as dimeric carboxylate-bridged and one water containing molecules, were shown to be active in metathesis reactions, *e.g.* with methyl *cis*-oleate to produce *trans*-octadec-9-ene and dimethyl *trans*-octadec-9-ene-1,18-dioate. The catalysts were also active in RCM of diethyl diallylmalonate. Metathesis was assumed to first proceed through dissociation of the bridging ligands to form monomeric catalysts, which together with their low stability limited their applicability.[261]

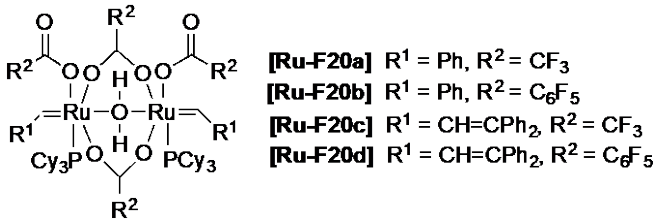
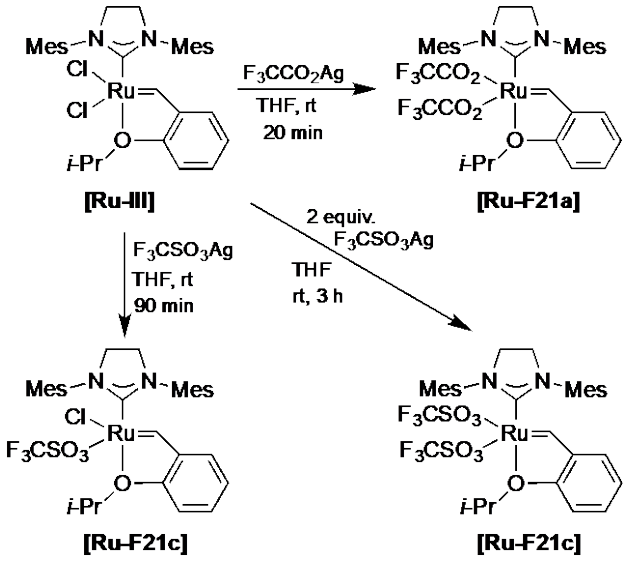


Figure 21. Trifluoroacetate-bridged Grubbs I-type ruthenium carbene dimers ~~of~~

The applicability of similar catalysts derived from Hoveyda-Grubbs catalyst [Ru-III] was significantly developed by Buchmeiser and his coworkers.[262] They synthesized monodentate perfluorocarboxylate and perfluoroalkylsulfonate complexes [Ru-F21a-c] (Scheme 151), which are among the most useful ones within this series for RCM, CM and ROCM (ring openin/cross-metathesis) reactions and some of them are also useful for enyne RCM and CM.[247]

Scheme 151. Synthesis of Ruthenium Trifluoroacetate and Trifluoromethanesulfonate Catalysts [Ru-F21a-c]



Buchmeiser *et al.* found that the bis-TFA catalyst [Ru-F21a] was the most active one in this series, comparable to the original Hoveyda-Grubbs catalyst [Ru-III], and the activity could be drastically increased by introduction of a nitro group in the *para*-position of the alkylidene part of the complex.[262c] In contrast, the mono-triflate [Ru-F21b] and the bis-triflate catalyst [Ru-F21c] were slightly less reactive in RCM reactions with diethyl diallylmalonate, octa-1,7-diene and other benchmark dienes.[263] [Ru-F21a] was also found to be a very active enyne cross metathesis catalyst.[262a]

Subsequently, a series of homolog to [Ru-F21a] complexes [Ru-F21d-h] with longer chain perfluoroalkylcarboxylate, pentafluorobenzoate and pentafluorophenolate ligands were prepared and their activity in benchmark RCM reactions proved to be comparable or lower than that of the parent catalyst [Ru-III] (Figure 22).[264,265] Braddock *et al.* showed that the ligand exchange is reversible by adding a different perfluorocarboxylate to one of the complexes [Ru-F21a] or [Ru-F21b].[266] A number of other analogs with different axial ligands were also prepared and successfully applied in RCM reactions to form carbocyclic and heterocyclic products including macrocyclic lactones.[267]

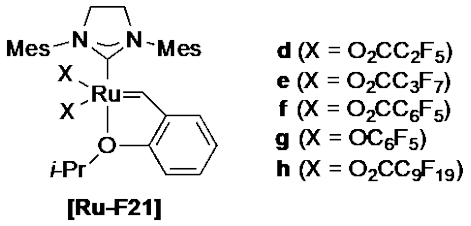
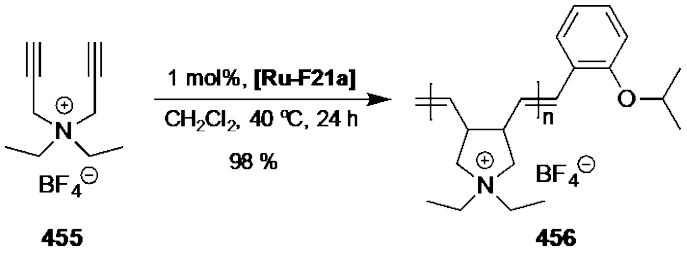


Figure 22. Bis-perfluorocarboxylate analogs [Ru-F21d-h] of Hoveyda-Grubbs catalyst

The bis-TFA catalyst [Ru-F21a] (Scheme 151) was demonstrated to be a highly efficient and active catalyst not only in RCM and enyne CM, but also for cyclopolymerizations of *e.g.* diethyl dipropargylmalonate and other 1,6-heptadiynes.[268] Moreover, catalysts like [Ru-F21a] (*vide supra*) and its *p*-nitro derivative were used for regioselective cyclopolymerization of *N*,*N*-dipropargylamines, *N*,*N*-dipropargylammoninum salts, and dipropargylethers to form the corresponding polymers. In this sense, the gross reaction of *N*,*N*-diethyl-*N*,*N*-dipropargylammonium tetrafluoroborate **455** in the presence of 1 mol% [Ru-F21a] in methylenechloride at 40 °C gave the *N*,*N*-diethyl 3,4-(1*H*-2,5-dihydropyrrylenium)vinylene **456** (M_n 35,300; M_w 55,200; PDI 1.56) in 98% yield (Scheme 152).[269]

Scheme 152. Cyclopolymerization of *N*,*N*-Diethyl-*N*,*N*-Dipropargylammonium tetrafluoroborate 455 in the Presence of 1 mol% of [Ru-F21a]



455 **456**

By substitution of one or both of the chlorides of [Ru-III], Blechert and coworkers synthesized a series of perfluoroglutaric anhydride-based complexes, functionalized at the fluorinated ligand. In RCM reactions of benchmark dienes and CM reactions of olefins disubstituted catalysts [Ru-

F22b,d,e] were less active than monosubstituted ones [Ru-F22a,c,f]; with [Ru-F22a] as the most reactive in this series showing a similar activity to [Ru-III] (Figure 23).[270]

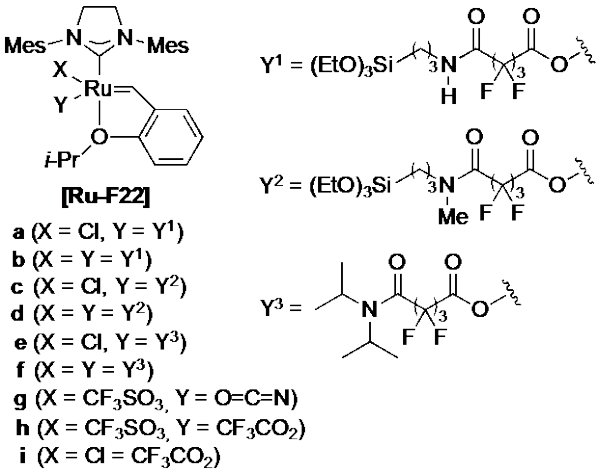


Figure 23. Partially fluorinated monosubstituted and disubstituted analog s of [Ru-III]

Ru-alkylidenes with other mixed anionic ligands [Ru-F22g-i] (Figure 23) and homologs of [Ru-F23a,b] (Figure 24) were synthesized recently and [Ru-F23b] was shown to be an active initiator for ROMP and also a good polymerization catalyst for regioselective cyclopolymerization (CP) of dipropargyl diethyl malonate.[271] The experimental findings on the role of the anionic ligands in the Ru-alkylidene catalysed CP of 1,6-heptadiynes were elucidated with quantum chemical calculations.[272]

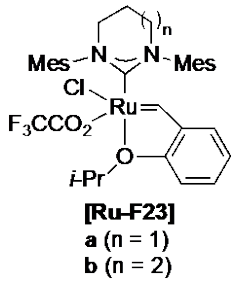
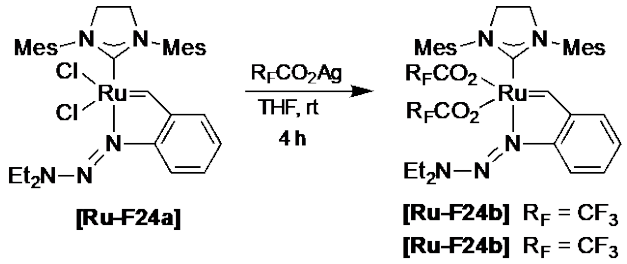


Figure 24. Homologs in the ring size of the NHC ligand [Ru-F23a,b]

Trifluoroacetate and pentafluorobenzoate-modified ruthenium-triazene complexes [Ru-F24a-c] were synthesized (Scheme 153) and tested as latent catalysts for UV-induced ROMP of *cis*-

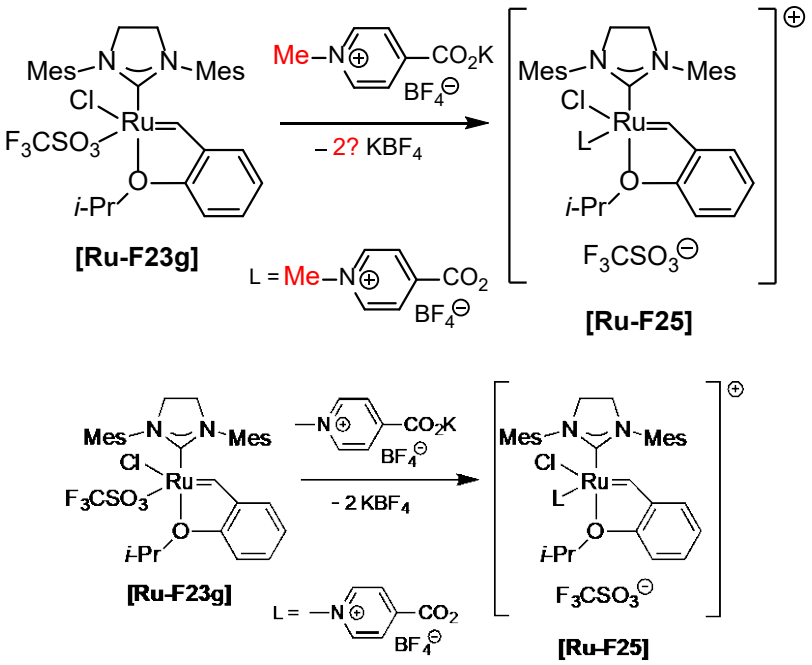
cyclooctene and dicyclopentadiene. However, the original dichloro complex was the only one showing significant photo-ROMP activity.[273]

Scheme 153. Synthesis of Ru-Triazene Complexes [Ru-F24a-c] as Potential Metathesis Catalysts



Very recently, novel pyridinium cationic metathesis catalysts such as [Ru-F25] containing a triflate as counter ion (Scheme 154) were shown to be active in the ROMP of norbornene-based monomers, with *cis*-cyclooctene and dicyclopentadiene providing the corresponding polymers in good yields and with a low metal content in the products.[274]

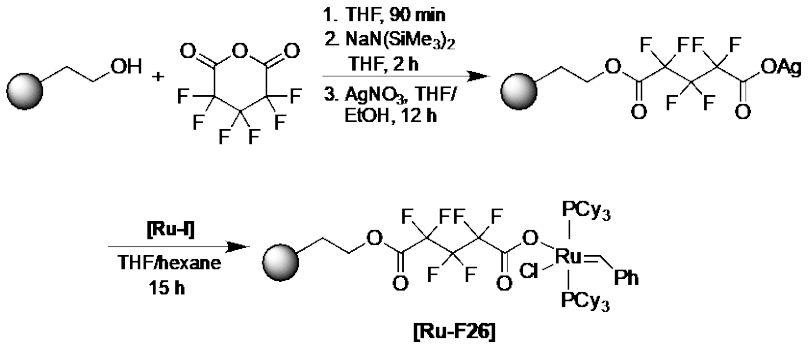
Scheme 154. Synthesis of Ru-Based Pyridiniumionic Metathesis Catalysts [Ru-F25] with Triflate Counter Ion



In the introduction to section 5.2, the immobilization of metathesis catalysts was already mentioned to be desirable for three reasons: (*i*) contamination of products with metal ions must be avoided, particularly in medicinally relevant compounds, (*ii*) regeneration and reuse of catalysts are important for cost reasons, and (*iii*) supported catalysts are suitable for high-throughput synthesis and continuous flow techniques. Therefore, a number of variations of chloride exchanged Grubbs-I and Hoveyda-Grubbs-type catalysts were bound to polymeric resins or solid supports.[275,258]

Initially, Mol and coworkers synthesized the first poly(styrene-*co*-divinylbenzene) (PS-DVB) supported version of Grubbs-I catalyst [Ru-F26]. They first reacted the hydroxyethyl-PS-DVB (1 mol% DVB) with hexafluoroglutaric anhydride followed by conversion of the formed acid into its silver salt, which was finally coupled with Grubbs-I catalyst [Ru-I] (Scheme 155). This catalyst was shown to be slightly more active than the homogenous [Ru-I] in self metathesis of internal alkenes such as *trans*-dec-4-ene or methyl oleate and was also active in RCM of diethyl diallylmalonate in 1 mol% concentration.[276]

Scheme 155. Synthesis of the First Polymer Supported Grubbs-I-type Catalyst [Ru-F26]



Most of the next generation of supported, fluorine-containing Ru-catalysts were developed by Buchmeiser's group.[275] They reported the first Hoveyda-Grubbs-based catalysts on a monolithic support [Ru-F27], which was used heterogeneously in a continuous flow reactor for the RCM of diethyl diallylmalonate (Figure 25).[277]

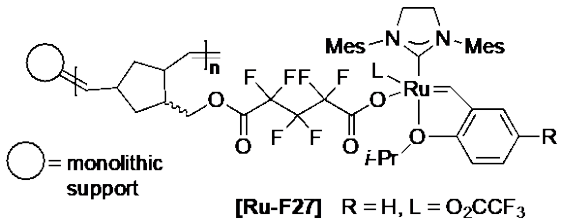


Figure 25. First Hoveyda-Grubbs-based catalysts on a monolithic support [Ru-F27]

Buchmeiser *et al.* also prepared Hoveyda-Grubbs-I [Ru-F28] and Grubbs-II [Ru-F29] analogs both immobilized on PS-DVB (Figure 26) and tested them in RCM reactions of five benchmark dienes. In terms of reactivity, no general trend was observed for these catalysts. With [Ru-F28], a significant loss of reactivity was found, as well as for the monomeric form of this catalyst. [Ru-F29] showed equal or slightly better activity than monomeric catalyst [Ru-II]. Leaching of ruthenium into the reaction mixture was < 85 ppb (ng/g) in the final RCM derived products.[264]

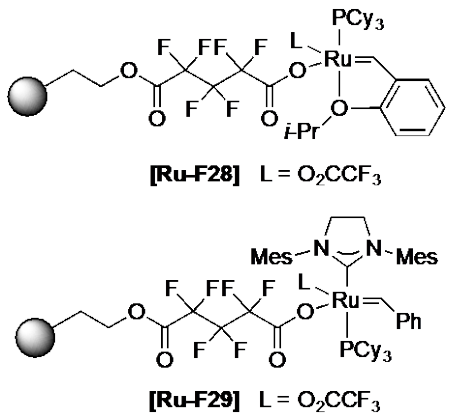


Figure 26. Hoveyda-Grubbs-I [Ru-F28] and Grubbs-II [Ru-F29] analogs immobilized on PS-DVB

Finally, Buchmeiser's group also synthesized some supported analogues of Hoveyda-Grubbs-II-type catalysts, *i.e.* [Ru-F30a-c] (Figure 27). Not a big difference in reactivity was found for catalyst [Ru-F30a] and [Ru-F30b] in RCM reactions with the dienes mentioned above.[262a] The catalyst [Ru-F30c] with a six-membered NHC ligand and a *p*-nitro group in the alkylidene substituent exhibited excellent reactivity (up to 3200 TON) in the PS-DVB supported form and was somewhat less reactive in the monolith supported form.[262c] Braddock *et al.* converted [Ru-F21a] into a 4-bromopolystyrene supported (1% DVB, 1.9 mmol g^{-1}) catalyst [Ru-F30d]. The activity of this catalyst with the standard RCM diene diethyl diallylmalonate was found to be much lower when compared to the homogeneous counterpart,[266b] this being in agreement with the results of other authors.[262c,2644,276]

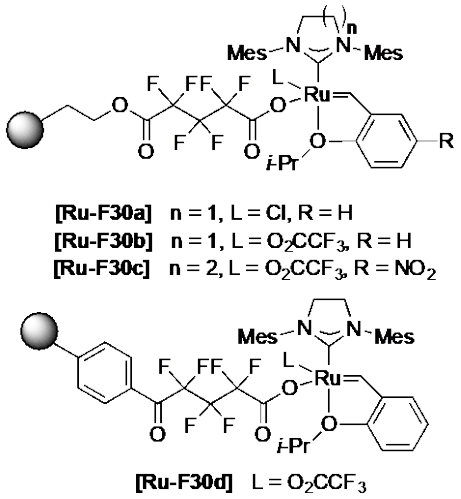


Figure 27. Hoveyda-Grubbs-II-type catalyst supported analogs [Ru-F30a-c]

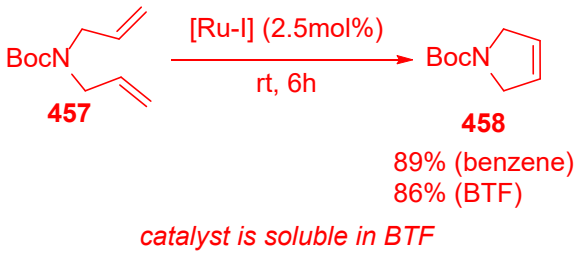
The catalyst [Ru-F30b] was also active for polymerization of diethyl dipropargylmalonate in water. Under micellar conditions, the required reaction times were reduced to 30 min, as compared to 2 hours with the monomeric catralyst [Ru-F21a], due to a higher concentration of the substrate within the micelles. However, lower polydispersity indexes < 1.40 compared to [Ru-F21a] were observed.[278]

In addition to the metathesis catalysts presented in sections 5.2 through 5.4 there are a number of alkylidene-free ruthenium complexes including fluorine-containing ones, which do carry ligands such as nitrile or isonitrile groups. Moreover, also *N*-heterocyclic carbene coordinated (η^6-arene)ruthenium complexes are suitable as metathesis catalysts. These complexes have been part of an excellent recent review by Vougioukalakis and Grubbs[247] and therefore will not be repeated in this review.

6. METATHESIS REACTIONS IN FLUORINATED SOLVENTS

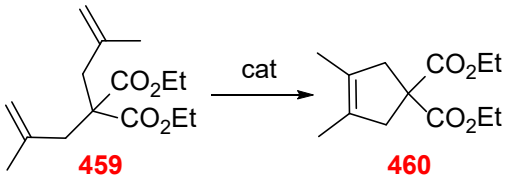
The first example of an olefin metathesis reaction carried out in a fluorinated solvent was described by Curran in 1999.[279] In this report, the use of benzotrifluoride (BTF) in several types of organic transformations as an alternative to chlorinated solvents is discussed. Among many others, the RCM of N,N-bisallylamine derivative **457** to the corresponding pyrrolidine **458** is achieved in comparable yield by using benzene or BTF as solvent (Scheme 156).

Scheme 156. First Olefin Metathesis Reaction in a Fluorinated Solvent

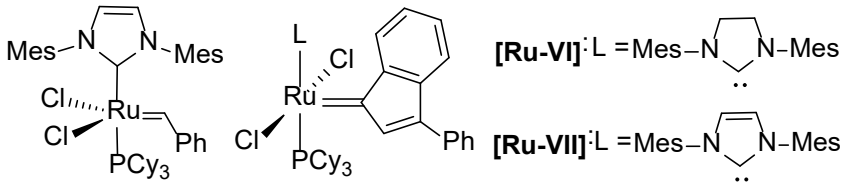


After many years of inactivity in this field,in 2008, Grela and Blechert independently reported the beneficial effect of fluorinated aromatic hydrocarbons (FAH) in olefin metathesis reactions of challenging substrates using standard commercially available ruthenium catalysts.[280,281,282] This effect seemed to be specially pronounced for RCM leading to tetrasubstituted olefins, as exemplified in Table 5. Also, other research groups reached similar conclusions in related studies.[283]

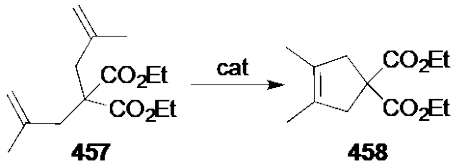
Table 5. The Doping Effect of FAH in RCM



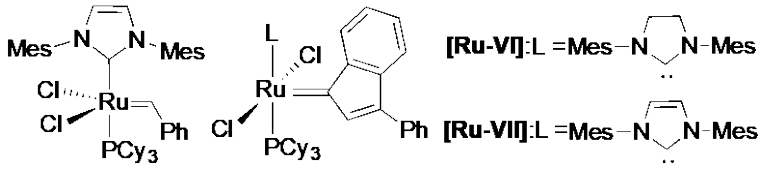
459 460



[Ru-V]



457 **458**

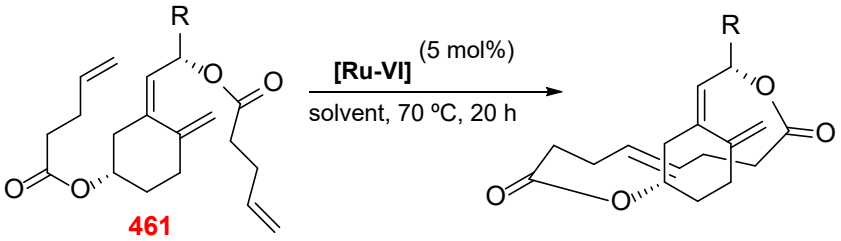


[Ru-V]

		Yield (%)				
Entry	Solvent	[Ru-II]	[Ru-V]	[Ru-VI]	[Ru-VII]	[Ru-III]
1	DCE	21	n.d.	26	36	4
2	toluene	20	n.d.	27	56	33
3	C_6F_6	61	77	91	74	56
4	F8-toluene	72	nd	94	85	72

The same authors applied these improved reaction conditions to RCM of natural products such as the compounds depicted in Scheme 157.

Scheme 157. Application of FAH Enhanced RCM Conditions to the Vitamin D_2 Derivative 462

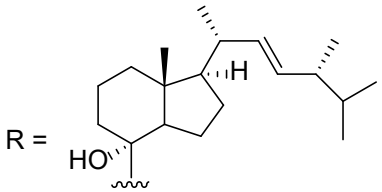


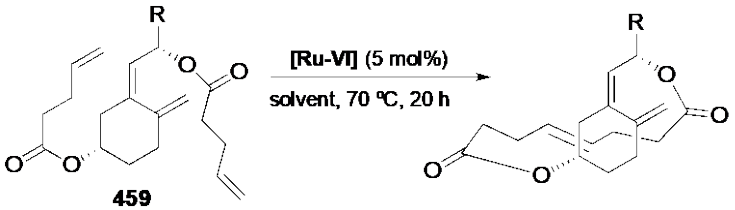
461

462

$C_2H_4Cl_2$	30 (52)[a]
C_6F_6	71 (95)

[a] Isolated yields. Conversions calculated by ^{1}H NMR are in parentheses



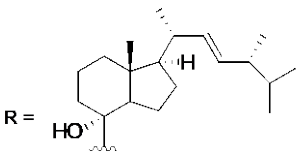


459

460

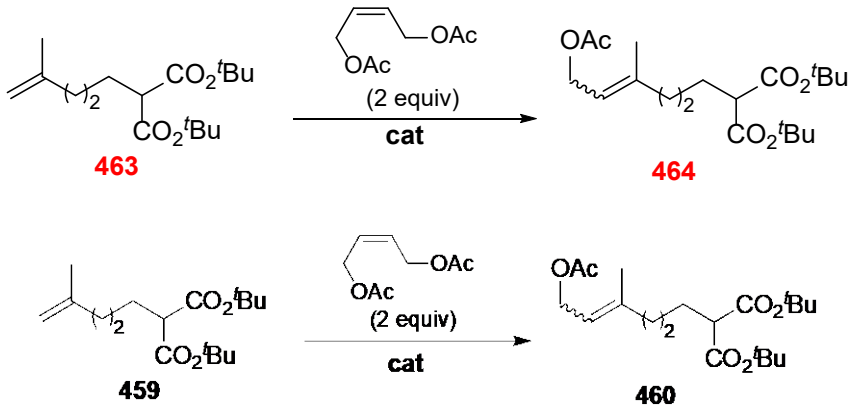
$C_2H_4Cl_2$	30 (52)[a]
C_6F_6	71 (95)

[a] Isolated yields. Conversions calculated by ^{1}H NMR are in parentheses



This beneficial effect seemed to be less pronounced in CM reactions with sterically demanding 1,1-disubstituted olefins (Table 6).

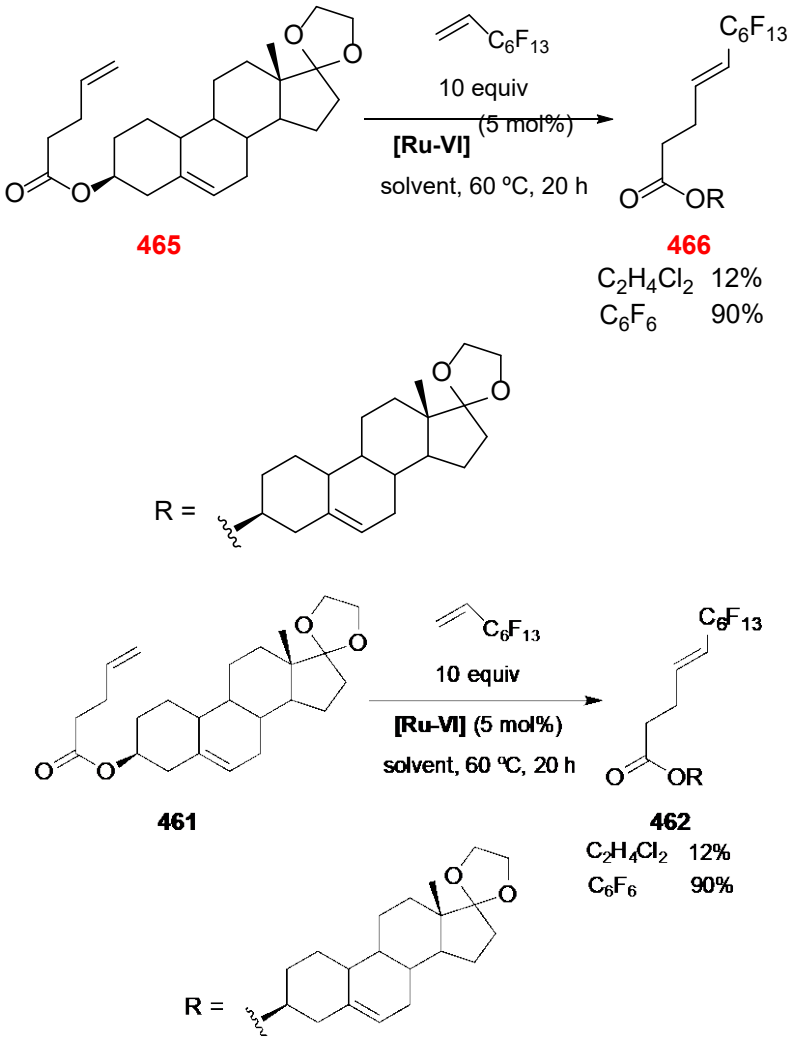
Table 6. Doping Effect of Fluorinated Solvents on Cross Metathesis



Entry	solvent	Yield (%) [Ru-II]	[Ru-VI]	[Ru-III]
1	DCE	27	25	7
2	toluene	37	38	20
3	C_6F_6	45	47	39
4	F8-toluene	50	51	44

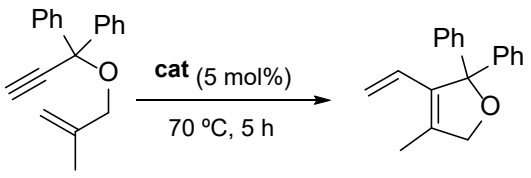
However, the CM between two monosubstituted olefins benefitted from the use of hexafluorobenzene (HFB) as solvent as showcased by the reaction of steroid derivative **465** and a perfluoroalkylated ethylene derivative shown in Scheme 158.[280a]

Scheme 158. HFB Enhanced CM of 465 with a Perfluoroalkylated Ethylene Derivative

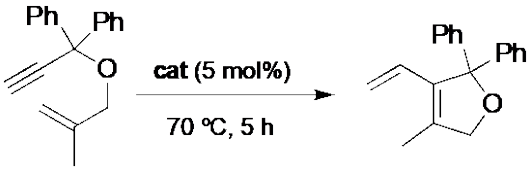


In a subsequent report,[284] Grela studied another class of challenging metathesis processes like the RCEYM of enyne **467** (Table 7) or the CM of 1,1-disubstituted electron-deficient alkenes (Table 8), observing again a much more pronounced effect in the intramolecular reaction. Simultaneously, the same authors reported that RCM, CM and RCEYM processes of difficult substrates were enhanced when the activating effects of FAH were combined with microwave irradiation in the presence of commercially available Ru-based pre-catalysts; moreover, it was also observed that HFB prevented the quick degradation of the Ru propagating species.[285]

Table 7. Doping Effect of FAH in RCEYM



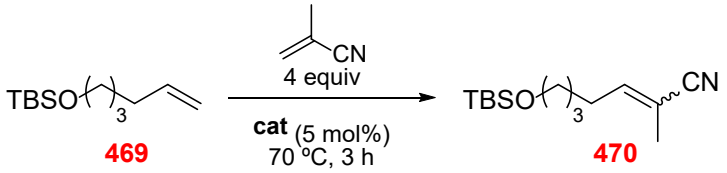
467 468



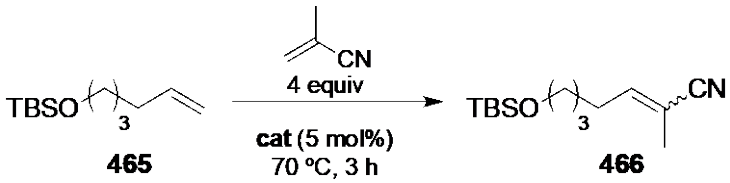
463 464

		Yield (%)	
Entry	solvent	[Ru-II]	[Ru-VI]
1	DCE	16	4
2	toluene	57	20
3	C_6F_6	88	37
4	F8-toluene	96	53

Table 8. Doping Effect of FAH in CM with metacrylonitrile



469 470



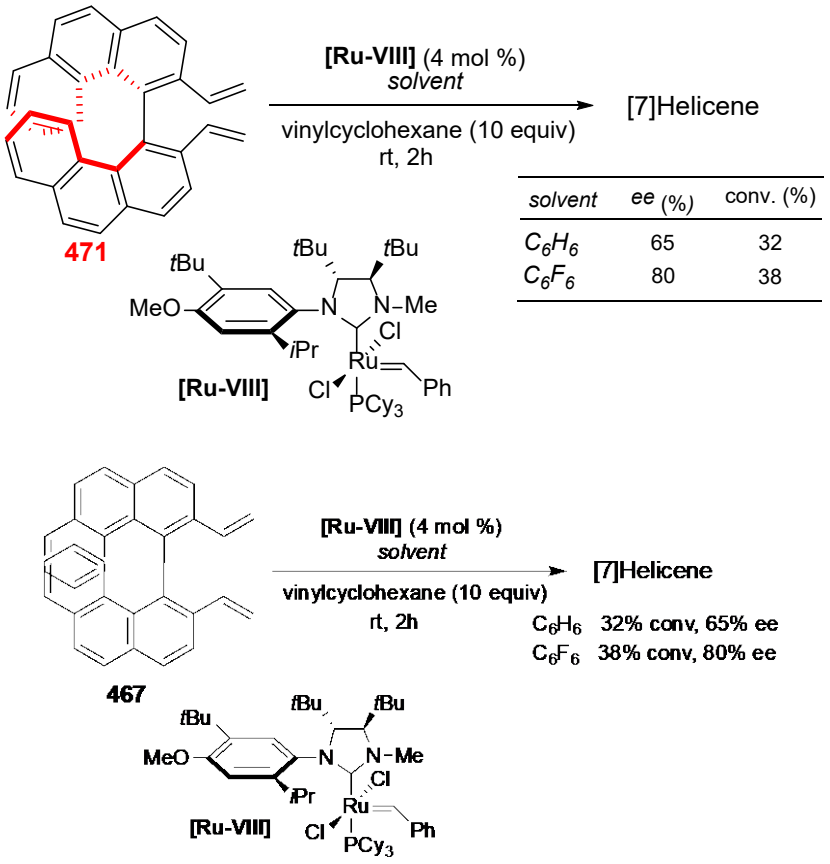
465 466

		Yield (%)		
Entry	Solvent	[Ru-II]	[Ru-VI]	[Ru-VII]
1	toluene	13	12	16
2	F8-toluene	41	40	25
3	C_6F_6	50	55	39

The role of fluorinated solvents in reaction enhancement is not fully understood. On the one hand, Nolan and coworkers concluded that the catalytic performance of a Ru-indenylidene complex in HFB was caused more by its physical properties than by a fluorine-ruthenium interaction.[283] However, from both X-ray structure analysis and computational results of interactions between FAH and the Ru catalysts, Grela concluded that the formation of $\pi - \pi$ stacking interactions between the *N*-mesityl groups of the NHC ligand present in the catalyst and the fluorinated solvent molecules would be responsible for the improved efficiency of the initiation step.[284] The interactions of an aromatic solvent molecule with a Ru complex would protect the 14-electron species by direct coordination to the Ru center, and thus, contribute to the higher stability of the active ruthenium species

Finally, Collins and Grandbois[286] communicated that the use of HFB as a solvent was one of the three key factors that contributed to the success in the synthesis of [7]helicene (80% ee, 38% conversion) through kinetic resolution by means of asymmetric olefin metathesis, in the presence of a Ru catalyst [Ru-VIII] bearing a chiral NHC ligand (Scheme 159).

Scheme 159. Solvent Effects on Kinetic Resolution



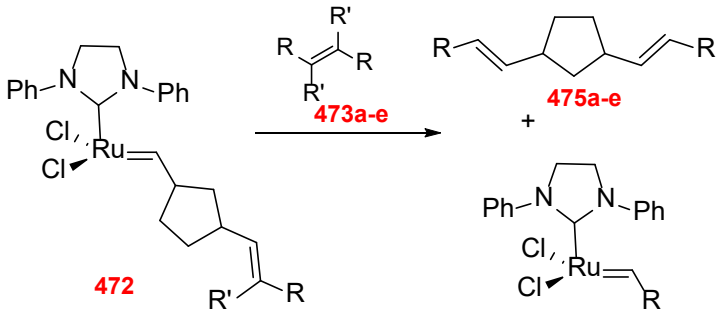
7. THEORETICAL STUDIES

Since the pioneering report on the mechanism of the olefin metathesis reaction by Chauvin,[287] numerous theoretical studies have been published.[288] However, studies of that kind on fluorinated substrates are scarce.[289]

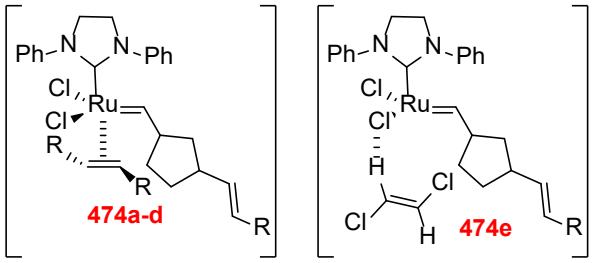
In the first of them,[289a] the relative performance of ethylene **473a**, *trans*-1,2-difluoroethylene **473b** and *trans*-1,4-dichloro-2-butene **473c** as chain transfer agents for ROMP of norbornene (NB) catalyzed by a second generation Grubbs like catalyst was studied (Scheme 160). The energetic profile for each reaction was determined using DFT calculations at B3LYP/6-31G* level of theory. Assuming coordination of the olefin to the ruthenium center to be rate-determining, the relative stability of the corresponding π-complexes **474a-c** was crucial for the

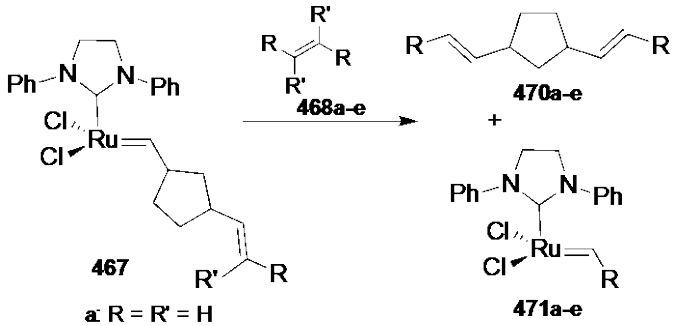
kinetics of the process. The molecular volumes of **473a-c** (31.6, 37.5 and 43.6 Å^3, respectively) correlated with the total Gibbs activation energies (10.2, 17.3 and 18.7 kcal/mol, respectively), which could be explained by unfavorable steric interactions upon olefin complexation to the metal center. On the other hand, the electrophilicity indexes (ω) showed **473b** to be the most nucleophilic olefin, in other words, the π-electron-donating effect of fluorine would overwhelm its σ-electron-withdrawing one. The authors concluded that the activation energy would mostly be determined by steric factors, **473a** being the most favorable olefin (kinetically); while stability of the final ruthenium carbene complex **476a-c** could be attributed to the electron-donating ability of the methylidene moiety, the reaction with **473b** being the only exothermic one, owing to *the extraordinary stability of fluorine carbene complex* **476b** *due to the strong π-electron-donating effect of the fluorine atom* (Scheme 160).[105,106,290] These conclusions were further supported by a following report by the same authors,[289b] in which the studied olefinic partners were ethylene **473a**, *trans*-1,2-difluoroethylene **473b**, tetrafluoroethylene **473d** and *trans*-1,2-dichloroethylene **473e (**Scheme 160). Again, the most sterically demanding olefin **473e** (molecular volume 61.5 Å^3) showed the highest activation energy (actually this olefin did not form a π-complex with ruthenium at all, but initial binding took place by electrostatic interaction of one hydrogen atom of the olefin with one chloride ligand of the complex), while the strong +M effect of the fluorine atoms accounted for the stability of the difluorocarbene complex arising from the reaction with **473d** (the calculated ΔG for the reaction with **473d** was -31.6 kcal/mol), that effect *slowed down the reactions with participation of these complexes* (Scheme 160). In this sense, Grubbs and others showed that difluorocarbene derivatives of the second-generation catalyst are ineffective catalysts in metathesis reactions, while the corresponding monofluorocarbene analogs displayed diminished catalytic activity in RCM.[290]

Scheme 160. ROMP Reaction of NB, Key Intermediates

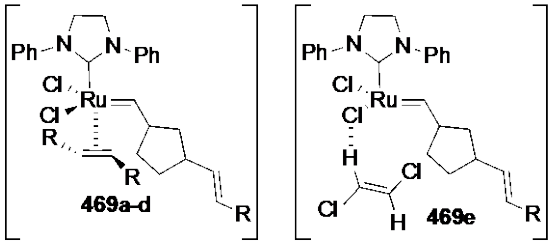


a: R = R' = H
b: R = F; R' = H
c: R = CH_2Cl; R' =H
d: R = R' = F
e: R = Cl; R' = H





a: R = R' = H
b: R = F; R' = H
c: R = CH_2Cl; R' =H
d: R = R' = F
e: R = Cl; R' = H



Recently, O'Hagan and Nolan studied the accelerating influence of the *gem*-difluoromethylene moiety in RCM.[289c] The "Thorpe-Ingold" effect is a well established kinetic phenomenon consisting of the acceleration of a cyclization due to the replacement of hydrogen atoms with alkyl groups on the carbons tethering the two reacting centers.[291,292] The first explanation of this experimental observation was given one century ago by Ingold and Thorpe in terms of repulsion between the *gem*-disubstituents resulting in a decrease of the angle between the two reacting centers.[293] An alternative explanation was later suggested by introducing the concept of the "reactive rotamer effect", meaning that the introduction of the *gem*-disubstitution increases the population of the *gauche* rotamer with the two ends properly oriented for cyclization.[294] In their report, the authors extensively analyzed structures as those depicted in Figure 28 in the Cambridge Structural Database (CSD) and concluded that *geminal electronegative functional groups have the opposite hybridization characteristics (wider C-CR$_2$-C angle) to other substituents required to promote a classical Thorpe-Ingold effect (narrower C-CR$_2$-C angle)*.

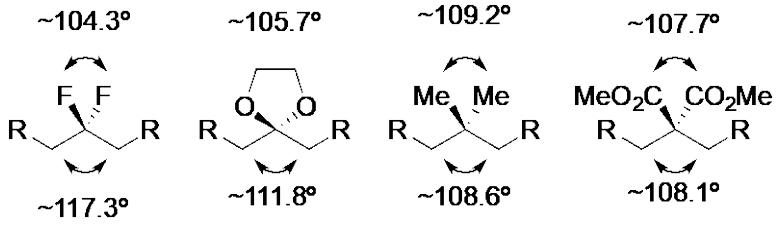
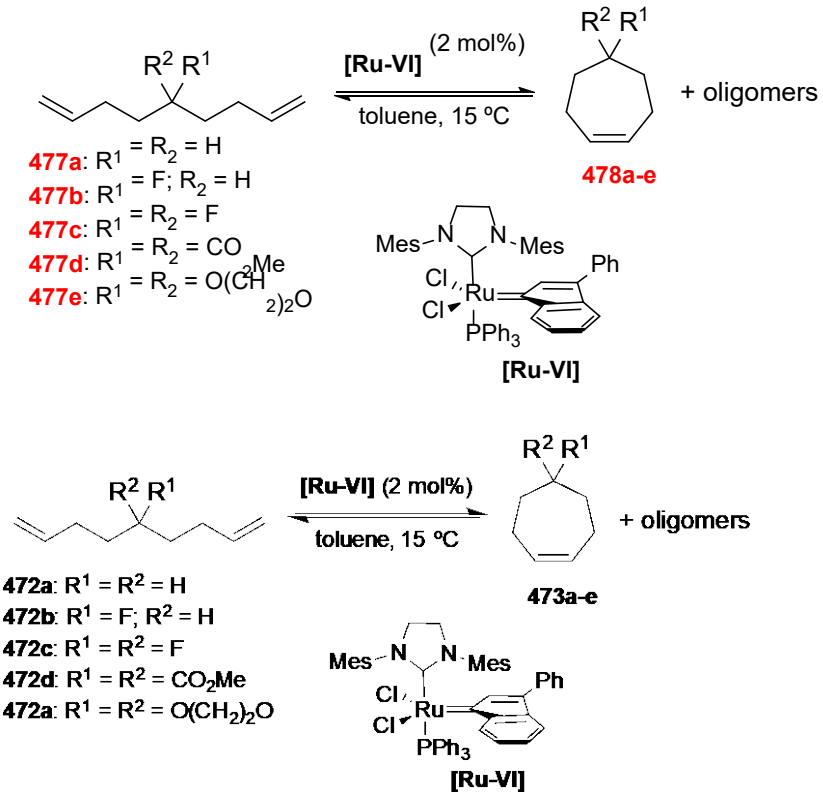


Figure 28. Representative C-CR$_2$-C angles

Joining the interests of both research groups in the mechanistic aspects of the olefin metathesis reaction [288f,295] and the geometric perturbation at CF_2 containing molecules,[296] respectively, the authors studied the non-obvious behavior of the CF_2 unit as *gem*-disubstituent, in view of the high electronegativity and small size of fluorine, in RCM towards cycloheptenes **478a-e**. The

reaction conversion profiles of the RCM of 1,8-nonadienes **477a-e** showed that while **477a,b** tended to oligomerize, **477c-e** efficiently cyclized to the corresponding cycloheptene derivatives **478a-e** (Scheme 161).

Scheme 161. RCM of Dienes 472a-e



DFT calculations showed that for dienes **477a-c** the *anti* rotamer was preferred over the reactive *gauche* one. This result, together with the expected wider C-CF_2-C angle ruled out a classical kinetic effect to explain the increased efficiency of **477c** over **477a,b**. DFT structures of cycloheptenes **478a-e** showed a CH_2-CR_2-CH_2 angle wider than the tetrahedral geometry for compounds **478a-e**. The ring strain is reduced in **478c** as the CF_2 moiety can absorb the angle widening. Additionally, **478c** would benefit from $\sigma_{CH}/\sigma_{CF^*}$ hyperconjugative stabilizing interactions between the axial C-H bonds antiperiplanar to the axial C-F bond. In view of these

results, the authors concluded that the observed increase of the efficiency of the RCM through the introduction of a *gem*-difluoromethylene unit would have a thermodynamic origin owing to the hybridization of the CF_2 group and stereoelectronic stabilizing interactions on the final product rather than a kinetic one due to a classical Thorpe-Ingold effect (angle narrowing) or a reactive rotamer effect.

8. CONCLUSIONS

Since Feast's pioneering reports 35 years ago on ROMP of fluoroalkylnorbornene derivatives using classical ill-defined metathesis catalysts,[297] both fields namely, olefin metathesis and organofluorine chemistry have witnessed an impressive development. The discovery of well-defined ruthenium and molybdenum based alkylidene complexes has made such catalysts much more available while greatly increasing the functional group tolerance, among other virtues. Simultaneously, the availability of suitable fluorinated building blocks, including vinyl fluorides, has been broadened enormously by the discovery of more efficient strategies for their preparation. Perhaps, the synthesis of fluorine containing heterocycles, including cyclic amino acid derivatives, saccharide analogs and other biologically relevant skeletons, has undergone the most dramatic impact of olefin metathesis in organofluorine chemistry. Cross-metathesis has enabled the synthesis of natural product analogs and vicinal fluoroalkanes, otherwise inaccessible by current methodologies. The search for increasingly sophisticated materials has redoubled efforts in the field of metathesis polymerization (ROMP and ADMET), fluorinated substrates playing a major role due to the unique properties exhibited by fluorine containing polymers. In addition to the great applicability that fluorinated substrates have found in olefin metathesis reactions, the introduction of fluorine atoms in the catalysts' ligand framework has also proven beneficial in many cases. An example is the development of fluorous catalysts that can easily be separated

yielding metal-free products. Finally, fluorine-containing solvents have also shown an accelerating effect in certain metathesis reactions.

The liaison between these two central branches of organic synthesis has given rise to a fruitful harvest, gathered in this review.

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

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For excellent books on organofluorine chemistry, see: (a) Hiyama, H. *Organofluorine Compounds: Chemistry and Applications*; Springer: Berlin, 2000. (b) R. D. Chambers, R. D. *Fluorine in Organic Chemistry*, Blackwell Publishing Ltd., Oxford, 2004. (c) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, Wiley-VCH, Weinheim, 2004. (d) Uneyama, K. *Organofluorine Chemistry*, Blackwell Publishing Ltd., Oxford, 2006.

(2) (a) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (b) Wang, J.; Sáchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432.

(3) (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (b) In *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; Wiley-Blackwell: Chichester, 2009.

(4) (a) Banks, R. E:; Smart, B.E.; Tatlow, J. C. *Organofluorine Chemistry: Principles and Commercial Applications*, Plenum Press, New York, 1994. (b) Giornal, F.; Pazenok, S.; Rodefeld, L.; Lui, N.; Vors, J.-P.; Leroux, F. R. *J. Fluorine Chem.* **2013**, *152,* 2.

(5) Berger, R.; Resnati, G.; Metrangolo, P.; Weber, E.; Hulliger, J. *Chem. Soc. Rev.* **2011**, *40*, 3496.

(6) For an outstanding review, see: O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308

(7) Schlosser, M. *Angew. Chem. Int. Ed.* **1998**, *110*, 1496.

(8) For recent reviews on the use of ^{19}F NMR spectroscopy in chemical biology, see: (a) Cobb, S. L.; Murphy, C. D. *J. Fluorine Chem.* **2009**, *130*, 132. (b) Chen, H.; Viel, S.; Ziarellic, F.; Peng, L. *Chem. Soc. Rev.* **2013**, *42*, 7971.

(9) For reviews on the synthesis and applications of ^{18}F-radiolabelled organic compounds in positron emission tomography (PET), see: (a) Le Bars, D. *J. Fluorine Chem.* **2006**, *127*, 1488. (b) Miller, P. W.; Long, N. J.; Vilar, R.; Gee, A. D. *Angew. Chem. Int. Ed.* **2008**, *47*, 8998. (c) Littich, R.; Scott, P. J. H. *Angew. Chem. Int. Ed.* **2012**, *51*, 1106. (d) Tredwell, M.; Gouverneur, V. *Angew. Chem. Int. Ed.* **2012**, *51*, 11426. For recent examples, see: (e) Lee, E.; Hooker,J. M.; Ritter, T. *J. Am. Chem. Soc.* **2012**, *134*, 17456. (f) Huiban, M.; Tredwell, M.; Mizuta, S.; Wan, Z.; Zhang, X.; Collier, T. L.; Gouverneur, V.; Passchier, J. *Nat. Chemistry* **2013**, *5*, 941. (g) Gao, Z.; Gouverneur, V.; Davis, B. G. *J. Am. Chem. Soc.* **2013**, *135*, 13612.

(10) Paul, E. A.; Huang, P. M. *Chemical aspects of soil*. In Handbook of Environmental Chemistry, Hutzinger, O., Ed. Springer-Verlag, Berlin, 1980; pp 69−86.

(11) For a review on fluorine containing natural products, see: (a) O'Hagan, D.; Harper, D. B. *J. Fluorine Chem.* **1999**, *100*, 127. For recent examples, see: (b) Xu, X.-H.; Yao, G.-M.; Li, Y.-M.; Lu, J.-H.; Lin, C.-J.; Wang, X.; Kong C.-H. *J. Nat. Prod.* **2003**, *66*, 285. (c) Jaivel, N.; Uvarani, C.; Rajesh, R.; Velmurugan, D.; Marimuthu, P. *J. Nat. Prod.* **2014**, *77*, 2.

(12) For reviews on different fluorination methodologies including nucleophilic, electrophilic, transition-metal-catalyzed and organocatalytic, see: (a) Singh, R. P.; Shreeve, J. M. *Synthesis* **2002**, 2561. (b) Singh, R. P.; Shreeve, J. M. *Acc. Chem. Res.* **2004**, *37*, 31. (c) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119. (c) Bobbio, C.; Gouverneur, V. *Org. Biomol. Chem.* **2006**, ***4***, 2065. (d) Kirk, K. L. *Org. Proc. Res. Dev.* **2008,** *12,* 305. (e) Grushin, V. V. *Acc. Chem. Res.*

2010, *43*, 160. (e) Lectard, S.; Hamashima, Y.; Sodeoka, M. *Adv. Synth. Catal.* **2010**, *352*, 2708. (f) Cahard, D.; Xu, X.; Couve-Bonnaire, S.; Pannecoucke, X. *Chem. Soc. Rev.* **2010**, *39*, 558. (g) Hollingworth, C.; Gouverneur, V. *Chem. Commun.* **2012**, *48*, 2929. (h) Zhao, Y.; Pan, Y.; Sim, S.-B. D.; Tan, C. H. *Org. Biomol. Chem.* **2012**, *10*, 479. (i) Liann, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214.

(13) For reviews on the synthesis and applications of fluorinated building blocks, see: (a) Percy, J. M. *Top. Curr. Chem.* **1997**, *193*, 131. (b) Fustero, S.; Sanz-Cervera, J.-F.; Piera, J.; Sánchez-Roselló, M.; Chiva, G.; Simón-Fuentes, A. *J. Fluorine Chem.* **2004**, *125*, 621. (c) Pacheco, M. C.; Purser, S.; Gouverneur, V. *Chem. Rev.* **2008**, *108*, 1943. (d) Fustero, S.; Sanz-Cervera, J.-F.; Aceña, J. L.; Sánchez-Roselló, M. *Synlett* **2009**, 525. (e) Wu, J.; Cao, S. *Curr. Org. Chem.* **2009**, *13*, 1791. (f) Landelle, G.; Bergeron, M.; Turcotte-Savard M.-O.; Paquin, J.-F. *Chem. Soc. Rev.* **2011**, *40*, 2867. (g) Qing, F.-L.; Zheng, F. *Synlett* **2011**, 1052. (h) Dmowski, W. *J. Fluorine Chem.* **2011**, *132*, 504. (i) David, E.; Milanole, G.; Ivashkin, P.; Couve-Bonnaire, S.; Jubault, P.; Pannecoucke, X. *Chem. Eur. J.* **2012**, *18*, 14904. (j) Dmowski, W. *J. Fluorine Chem.* **2012**, *142*, 6. (k) Kuehnel, M. F.; Lentz, D.; Braun, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 3328.

(14) Calderon, N.; Chen, H. Y.; Scott, W. K. *Tetrahedron* **1967**, *34*, 3327.

(15) For Mo-based, see: (a) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875. For Ru-based, see: (b) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974. (c) Johnson, L. K.; Grubbs, H. R.; Ziller, J. W. *J. Am. Chem. Soc*. **1993**, *115*, 8130. (d) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **1995**, *34*, 2039.

(16) For "classical" reviews see: (a) Schuster, M.; Blechert, S. *Angew. Chem. Int. Ed. Engl.* **1997**, *109*, 2124. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) Fürstner, A. *Angew. Chem. Int. Ed.* **2000**, *112*, 3140. (d) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (e) Hoveyda, A. H.; Schrock, R. R. *Chem. Eur. J.* **2001**, *7*, 945. (f) Grubbs, R. H. *Tetrahedron* **2004**, *60,* 7117. (g) Hoveyda, A. H.; Zhigralin, A. R. *Nature* **2007**, *450*, 243. For recent reviews, see: (h) Hoveyda, A. H.; Malcolmson, S. J.; Meek, S. J.; Zhugralin, A. R. *Angew. Chem. Int. Ed.* **2010**, *49*, 34. (i) Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010,** *110,* 1746. (j) Nolan, S. P.; Clavier, H. *Chem. Soc. Rev.* **2010**, *39*, 3305. (k) Kress, S.; Blechert, S. *Chem. Soc. Rev.* **2012**, *41*, 4389. (l) Kotha, S.; Dipak, M. K. *Tetrahedron* **2012**, *68*, 397. (m) Fürstner, A. *Science* **2013**, *341*, 1357.

(17) Reviews: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Phillips, A. J.; Abell, A. D. *Aldrichim. Acta* **1999**, *32*, 75. (c) Fürstner, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3012. (d) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (e) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (f) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2189.

(18) For a review, see: (a) Osipov, S. N.; Dixneuf, P. *Russ. J. Org. Chem.* **2003**, *39*, 1211. For a recent example, see: (b) Nash, A.; Soheili, A.; Tambar, U. K. *Org. Lett.* **2013**, *15*, 4770.

(19) For recent reviews, see: (a) Brik, A. *Adv. Synth. Catal.* **2008**, *350*, 1661. (b) Jiang, S.; Li, Z.; Ding, K.; Roller, P. P. *Curr. Org. Chem.* **2008**, *12*, 1502. (c) Wakchaure, S.; Einsiedel, J.; Waibel, R.; Gmeiner, P. *Synthesis* **2012**, *44*, 2682.

(20) For reviews, see: (a) Brenneman, J. B.; Martin, S. F. *Curr. Org. Chem.* **2005**, *9*, 1535. (b) Gaich, T.; Mulzer, J. *Curr. Top. Med. Chem.* **2005**, *5*, 1473. (c) Martin, W. H. C.; Blechert, S.

Curr. Top. Med. Chem. **2005**, *5*, 1521. (d) Dragutan, I.; Dragutan, V.; Demonceau, A.; Vosloo, H. C. M. *Curr. Org. Chem.* **2013**, *17*, 2721.

(21) Review: (a) Plumet, J.; Gomez, A. M.; Lopez, J. C. *Mini-Reviews in Organic Chemistry* **2007**, *4*, 201. (b) Roy, R.; Das, S. K. *Chem. Commun.* **2000**, 519.

(22) (a) Feature Article: Fürstner, A. *Synthesis* **1997**, 792. (b) Hassan, H. M. A. *Chem. Commun.* **2010**, *46*, 9100.

(23) Review: Paek, S.-M. *Molecules* **2012**, *17*, 3348.

(24) Reviews: (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem.* **2005**, *117*, 4516. (b) Fürstner, A. *Chem. Commun.* **2011**, *47*, 6505.

(25) For recent reviews on selected types of fluorinated organic molecules, see: for amino acids (a) Tarui, A.; Sato, K.; Omote, M.; Kumadaki, I.; Ando, A. *Adv. Synth. Catal.* **2010**, *352*, 2733. (b) Mikami, K.; Fustero, S.; Sánchez-Roselló, M.; Aceña, J. L.; Soloshonok, V.; Sorochinsky, A. *Synthesis* **2011**, 3045. (c) Qiu, X.-L.; Qing, F.-L. *Eur. J. Org. Chem.* **2011**, 3261. (d) Salwiczek, M.; Nyakatura, E. K.; Gerling, U. I. M.; Ye, S.; Koksch, B. *Chem. Soc. Rev.* **2012**, *41*, 2135. For carbohydrates and nucleosides, see: (e) Miethchen, R. *J. Fluorine Chem.* **2004**, *125*, 895. (f) Hein, M.; Miethchen, R. *Advances in Organic Synthesis: Modern Organofluorine Chemistry–Synthetic Aspects (Vol 2)* **2006**, *2*, 381. Atta–ur–Rahman, Ed.; Bentham Sci. Publi. Ltd. (g) Qiu, X.-L.; Xu, X.-H.; Qing, F.-L. *Tetrahedron* **2010**, *66,* 789. (h) Cheng, Y.; Guo, A.-L.; Guo, D.-S. *Curr. Org. Chem.* **2010**, *14*, 977.

(26) Feast, W. J.; Khosravi, E. *J. Fluorine Chem.* **1999**, *100*, 117.

(27) (a) Grubbs, R. H. Ed. *Handbook of Metathesis* Vol 1-3, 2003 Wiley-VCH, Weinheim. (b) Chattopadhyay, S. K.; Karmakar, S.; Biswas, T.; Majumdar, K.C. *Tetrahedron* **2007**, *63*, 3919. (c) Alcaide, B.; Almendros, P.; Luna, A. *Chem. Rev.* **2009,** *109,* 3817. (d) van Otterlo, W. A. L.; de Koning Ch. B. *Chem. Rev.* **2009,** *109,* 3743. (d) An special issue dedicated to carbenes including metathesis reactions was also published: see, *Chem. Rev.* **2009,** *109,* issue 8, pp 3209-3884.

(28) (a) Fustero, S.; Navarro, A.; Pina, B.; García Soler, J.; Bartolomé, A.; Asensio, A.; Simón, A.; Bravo, P.; Fronza, G.; Volonteiro, A.; Zanda, M. *Org. Lett.* **2001**, *3*, 2621. (b) Fustero, S.; Bartolomé, A.; Sanz-Cervera, J. F.; Sánchez-Roselló, M.; García Soler, J.; Ramírez de Arellano, C.; Simón Fuentes, A. *Org. Lett.* **2003**, *5*, 2523. (c) Fustero, S.; Sánchez-Roselló, M.; Rodrigo, V.; del Pozo, C.; Sanz-Cervera, J. F.; Simón, A.; Ramírez de Arellano, C. *Org. Lett.* **2006**, *8*, 4129. (d) Fustero, S.; Fernández, B.; Sanz-Cervera, J. F.; Mateu, N.; Mosulén, S.; Carbajo, R. J.; Pineda-Lucena, A.; Ramírez de Arellano, C. *J. Org. Ch*em. **2007**, *72*, 8716. (e) Fustero, S.; Sánchez-Roselló, M.; Rodrigo, V.; Sanz-Cervera, J. F.; Piera, J.; Simón-Fuentes, A.; del Pozo, C. *Chem. Eur. J.* **2008**, *14*, 7019.

(29) Fustero, S.; Sánchez-Roselló, M.; Jiménez, D.; Sanz-Cervera, J. F.; del Pozo, C.; Aceña, J. L. *J. Org. Chem.* **2006**, *71*, 2706.

(30) Fustero, S.; Catalán, S.; Piera, J.; Sanz-Cervera, J. F.; Fernández, B.; Aceña, J. L. *J. Org. Chem.* **2006**, *71*, 4010.

(31) Cuñat, A. C.; Flores, S.; Oliver, J.; Fustero, S. *Eur. J. Org. Chem.* **2011**, 7317.

(32) (a) Fustero, S.; Navarro, A.; Pina, B.; Asensio, A.; Bravo, P.; Crucianelli, M.; Volonteiro, A.; Zanda, M. *J. Org. Chem.* **1998**, *63*, 6210. (b) Bravo, P.; Cavicchio, G.; Crucianelli, M.; Markovsky, A. L.; Volonterio, A.; Zanda, M. *Synlett* **1996**, 887.

(33) (a) Greuter, H.; Lang, R. W., Romann, A. J. *Tetrahedron Lett.* **1988**, *29*, 3291. (b) Xu, F.; Simmons, B.; Amstrong, J., III; Murry, J. *J. Org. Chem.* **2005**, *70*, 6105.

(34) Crucianelli, M.; Bravo, P.; Arnone, A.; Corradi, E.; Meille, S. V.; Zanda, M. *J. Org. Chem.* **2000**, *65*, 2965.

(35) Apple, R.; Warning, K.; Ziehn, K. D. *Chem. Ber.* **1973**, *106*, 2093.

(36) Tamura, K.; Mizukami, H.; Maeda, K.; Watanabe, H.; Uneyama, K. *J. Org. Chem.* **1993**, *58*, 32.

(37) Review: Maier, M. E. *Angew. Chem. Int. Ed.* **2000**, *39*, 2073.

(38) This effect is more pronounced for Ru- than for Mo-based catalysts, for a comparative review, see: Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371.

(39) Amii, H.; Kishikawa, Y.; Kageyama, K.; Uneyama, K. *J. Org. Chem.* **2000**, *65*, 3404.

(40) (a) Osipov, S. N.; Golubev, A. S.; Sewald, N.; Michel, T.; Kolomiets, A. F.; Fokin, A. V.; Burger, K. *J. Org. Chem.* **1996**, *61*, 7521. (b) Asensio, A.; Bravo, P.; Crucianelli, M.; Farina, A.; Fustero, S.; Garcia Soler, J.; Meille, S: V.; Panzeri, W.; Viani, F.; Volonteiro, A.; Zanda, M. *Eur. J. Org. Chem.* **2001**, 1449.

(41) For substrate **27d** derived from (*S*)-1-phenylethylamine only moderate diastereoselectivity was observed. The better performance of the phenylglycinol derivative is justified by the presence of a second heteroatom, which allows a better metal chelation-giving rise to a more rigid transition state.

(42) (a) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **1996**, *118*, 8489. (b) Hanessian, S.; Yang, R. Y. *Tetrahedron Lett.* **1996**, *37*, 8997.

(43) See, for example: (a) Vidal, A.; Nefti, A.; Houghten, R. A. *J. Org. Chem.* **2001**, *66*, 8268. (b) Volonteiro, A.; Chiva, G.; Fustero, S.; Piera, J.; Sánchez-Roselló, M.; Sani, M.; Zanda, M. *Tetrahedron Lett.* **2003**, *44*, 7019. (c) Fustero, S.; Piera, J.; Sanz-Cervera, J.-F.; Catalán, S.; Ramírez de Arellano, C. *Org. Lett.* **2004**, *6*, 1417.

(44) For the application of fluorous synthesis to the preparation of partially modified retropeptides, see: (a) Fustero, S.; García Sancho, A.; Chiva, G.; Sanz-Cervera, J.-F.; del Pozo, C.; Aceña, J. L. *J. Org. Chem.* **2006**, *71*, 3299. For fluorinated uracils, see: (b) Fustero, S.; Catalán, S.; Flores, S.; Jiménez, D.; del Pozo, C.; Aceña, J. L.; Sanz-Cervera J.-F.; Merida, S. *QSAR Comb. Sci.* **2006**, *25*, 753.

(45) (a) Studer, A.; Hadida, S.; Ferritto, R.; Kim, S.-Y.; Jeger, P.; Wipf, P.; Curran, D. P. *Science* **1997**, *275*, 823. (b) *Handbook of Flourous Chemistry* (Eds.: J. A. Gladysz, D. P. Curran, I. T. Horvát), Wiley-VCH, Weinheim, **2004**. (c) Zhang, W. *Chem. Rev.***2004**, *104*, 2531.

(46) Curran, D. P. *Synlett* **2001**, 1488.

(47) Trimethylsilylethanol (TMSE) is a widely employed protecting group for carboxylic acids due to its mild cleavage upon treatment with TBAF (See: Kocienski, *Protecting Groups*, 3rd. ed., Thieme, Stuttgart, **2005**).

(48) Fustero, S.; Rodrigo, V.; Sánchez-Roselló, M.; Mojarrad, F.; Vicedo, A.; Moscardó, T.; del Pozo, C. *J. Fluorine Chem.* **2008**, *129*, 943.

(49) (a) Frizler, M.; Stirnberg, M.; Sisay, M. T.; Gütschow, M. *Curr. Top. Med. Chem.* **2010**, *10*, 294. (b) Löser, R.; Frizler, M.; Schilling, K.; Gütschow, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 4331. (c) Palmer, J. T.; Bryant, C.; Wang, D. X.; Davis, D. E.; Setti, E. L.; Rydzewski, R. M.; Venkatraman, S.; Tian, Z. Q.; Burril, L. C.; Mendoca, R. V.; Springman, E.; McCarter, J.; Chumg, T.; Cheung, H.; Janc, J. W.; McGrath, M.; Somoza, J. R.; Enriquez, P.; Yu, Z. W.; Strickley, R. M.; Liu, L.; Venuti, M. C.; Percival, M. D.; Falgueyret, J. P.; Prasit, P.; Oballa, R.; Riendeau, D.; Young, R. N.; Wesolowski, G.; Rodan, S. B.; Johnson, C:; Kimmel, D. B.; Rodan, G. *J. Med. Chem.* **2005**, *48*, 7520. (d) Fustero, S.; Rodrigo, V.; Sánchez-Roselló, M.; del Pozo, C.; Timoneda, J.; Frizler, M.; Sisay, M. T.; Bajorath, J.; Calle, L. P.; Cañada, F. J.; Jiménez-Barbero, J.; Gütschow, M. *Chem. Eur. J.* **2011**, *17*, 5256.

(50) (a) Vasiljeva, O.; Reinheckel, T.; Peters, C.; Turk, D.; Turk, B. *Curr. Pharm. Des.* **2007**, *13*, 387. (b) Mohamed, M. M.; Sloane, B. F. *Nat. Rev. Cancer* **2006**, *6*, 764. (c) Black, W. C. *Curr. Top. Med. Chem.* **2010**, *10*, 294.

(51) Cuñat, A. C.; Flores, S.; Oliver, J.; Fustero, S. *Eur. J. Org. Chem.* **2011**, 7317.

(52) Peterlin-Mašič, L.; Kikelj, D. *Tetrahedron* **2001**, *57*, 7073.

(53) Berlinck, R. G. S.; Burtuloso, A. C. B.; Kossuga, M. H. *Nat. Prod. Rep.* **2008**, *25*, 919.

(54) Vassilev, L. T.; Vu, B. T.; Graves, B.; Carvajal, D.; Podlaski, F.; Filipovic, Z.; Kong, N.; Kammlott, U.; Lucacs, C.; Klein, C.; Fotouhi, N.; Liu, E. A. *Science* **2004**, *303*, 844.

(55) Coles, M. P. *Dalton Trans.* **2006**, 985.

(56) See, for example: Fustero, S.; Jiménez, D.; Sánchez-Roselló, M.; del Pozo, C. *J. Am. Chem. Soc.* **2007**, *129*, 6700.

(57) For reports on the synthesis of fluorinated cyclooctenone derivatives, see: (a) Kariuki, B. M.; Owton, W. M.; Percy, J. M.; Pintat, S.; Smith, C. A.; Spencer, N. S.; Thomas, A: C.; Watson, M. *Chem. Commun.* **2002**, 228. (b) Griffith, G. A.; Percy, J. M.; Pintat, S.; Smith, C. A.; Specer, N.; Uneyama, E. *Org. Biomol. Chem.* **2005**, *3*, 2701. (c) Mitchell, L.; Parkinson, J. A.; Percy, J. M.; Singh, K. *J. Org. Chem.* **2008**, *73*, 2389.

(58) For applications of fluorinated cyclooctenones in the synthesis of conformationally-locked difluorosugar analogs, see: (a) Fawcett, J.; Griffith, G. A.; Percy, J. M.; Pintat, S.; Smith, C. A.; Spencer, N. S.; Uneyama, E. *Chem. Commun.* **2004**, 302. (b) Fawcett, J.; Griffith, G. A.; Percy, J. M.; Uneyama, E. *Org. Lett.* **2004**, *6*, 1277. (c) Miles, J. A. L.; Mitchell, L.; Percy, J. M.; Singh, K.; Uneyama, E. *J. Org. Chem.* **2007**, *72*, 1575. (d) Ashworth, I. W.; Miles, J. A. L.; Nelson, D. J.; Percy, J. M.; Singh, K. *Tetrahedron* **2009**, *65*, 9637. (e) Kyne, S. H.; Miles, J. A. L.; Percy, J. M.; Singh, K. *J. Org. Chem.* **2012**, *77*, 991.

(59) For the synthesis of difluoro carbasugar analogs, see: (a) Audouard, C.; Fawcett, J.; Griffith, G. A.; Kérourédan, E.; Miah, A.; Percy, J. M.; Yang, H. *Org. Lett.* **2004**, *6*, 4269. (b)

Kérourédan, E.; Percy, J. M.; Rinaudo, G.; Singh, K. *Synthesis* **2008**, 3903. (c) Anderl, T.; Audouard, C.; Miah, A.; Percy, J. M.; Rinaudo, G.; Singh, K. *Org. Biomol. Chem.* **2009**, *7*, 5200.

(60) (a) Patel, S. T.; Percy, J. M.; Wilkes, R. D. *Tetrahedron* **1995**, *51*, 9201. (b) Patel, S. T.; Percy, J. M.; Wilkes, R. D. *J. Org. Chem.* **1996,** *61,* 166. (c) Balnaves, A. S.; Gelbrich, T.; Hursthouse, M. B.; Light, L. E.; Palmer, M. J.; Percy, J. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2525. (d) Broadhurst, M. J.; Brown, S. J.; Percy, J. M.; Prime, M. E. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3217.

(61) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130.

(62) Jung, M. E.; Piizi, G. *Chem. Rev.* **2005**, *105*, 1735.

(63) Commeureuc, A. G. J.; Murphy, J. A.; Dewis, M. L. *Org. Lett.* **2003**, *5*, 2785.

(64) Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 1123.

(65) Most of the kinetic studies published at that time on RCM dealt with five and six membered rings formation and cyclization is not rate-determining. For some examples, see: (a) Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887. (b) Bassetti, M.; Centola, F.; Semeril, D.; Bruneau, C.; Dixneuf, P. H. *Organometallics* **2003**, *22*, 4459. (c) Guo, X.; Basu, K.; Cabral, J. A.; Paquete, L. A. *Org. Lett.* **2003**, *5*, 789.

(66) Fogg has reported expected values for RCM EMs for the formation of several ring sizes: Conrad, J. C.; Eelman, M. D.; Duarte Silva, J. A.; Monfette, S.; Pamas, H. H.; Snelgrove, J. L.; Fogg, D. E. *J. Am. Chem. Soc.* **2007**, *129*, 1024.

(67) (a) Briggs, A.; Evans, C. M.; Glenn, R.; Kirby, A. J. *J. Chem. Soc., Perkin Trans. 2,* **1983**, 1637. (b) Bleriot, Y.; Vadivel, S. K.; Greig, I. R.; Kirby, A. J.; Sinay, P. *Tetrahedron Lett.* **2003**, *44*, 6687.

(68) (a) van Hooft, P. A. V.; Litjens, R.; van der Marel, G. A.; van Boeckel, C. A. A.; van Boom, J. H. *Org. Lett.* **2001**, *3*, 731. (b) Wang, W.; Zhang, Y. M.; Sollogoub, M.; Sinay¨, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2466. (c) Lorthiois, E.; Meyyappan, M.; Vasella, A. *Chem. Commun.* **2000**, 1829.

(69) (a) Hart, D. O.; He, S. M.; Chany, C. J.; Withers, S. G.; Sims, P. F. G.; Sinnott, M. L.; Brumer, H. *Biochemistry* **2000**, *39*, 9826. (b) Gibson, R. P.; Tarling, C. A.; Roberts, S.; Withers, S. G.; Davies, G. J. *J. Biol. Chem.* **2004**, *279*, 1950.

(70) For reviews on carbasugars, see: (a) Sears, P.; Wong, C. H. *Angew. Chem. Int. Ed.* **1999**, *38*, 2301. (b) Compain, P.; Martin, O. R. *Bioorg. Med. Chem.* **2001**, *9*, 3077.

(71) Kirby, A. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer-Verlag, Berlin, 1983.

(72) (a) Vasella, A.; Davies, G. J.; Bohm, M. *Curr. Opin. Chem. Biol.* **2002**, *6*, 619. (b) Ünligil, U. M.; Rini, J. M. *Curr. Opin. Struct. Biol.* **2000**, *10*, 510.

(73) Barchi, J. J.; Karki, R. G.; Nicklaus, M. C.; Siddiqui, M. A.; George, C.; Mikhailopulo, I. A.; Marquez, V. E. *J. Am. Chem. Soc.* **2008**, *130*, 9048.

(74) Gerig, J. T. *Magn. Reson. Chem.* **1999**, *37*, 647.

(75) (a) Ellaghdach, A.; Echarri, R.; Matheu, M. I.; Barrena, M. I.; Castillon, S.; Garcia, J. *J. Org. Chem.* **1991**, *56*, 4556. (b) Barrena, M. I.; Matheu, M. I.; Castillon, S. *J. Org. Chem.* **1998**,

63, 2184. (c) Aghmiz, M. L.; Diaz, Y.; Jana, G. H.; Matheu, M. I.; Echarri, R.; Castillon, S.; Jimeno, M. L. *Tetrahedron* **2001**, *57*, 6733.

(76) (a) Percy, J. M.; Pintat, S. *Chem. Commun.* **2000**, 607. (b) Audouard, C.; Fawcett, J.; Griffith, G. A.; Percy, J. M.; Pintat, S.; Smith, C. *Org. Biomol.Chem.* **2004**, *2*, 528. (c) You, Z.-W.; Wu, Y.-Y.; Qing, F.-L. *Tetrahedron Lett.* **2004**, *45*, 9479. (d) You, Z.-W.; Zhang, X.-G.; Qing, F.-L. *Synthesis* **2006**, 2533.

(77) For previous total syntheses, see: Grupta, P.; Naidu, S. V.; Kumar, P. *Tetrahedron Lett.* **2004**, *45*, 849; and references cited therein.

(78) You, Z.-W.; Jiang, Z.-X.; Wang, B. L.; Qing, F.-L. *J. Org. Chem.* **2006**, *71*, 7261.

(79) For reviews, see: (a) Ferrero, M.; Gotor, V. *Chem. Rev.* **2000**, *100*, 4319. (b) Wu, Q.; Simons, C. *Synthesis* **2004**, 1533. (c) Casu, F.; Chiacchio, M. A.; Romeo, R.; Gumina, G. *Curr. Org. Chem.* **2007**, *11*, 999.

(80) (a) Yang, Y.-Y.; Meng, W.-D.; Qing, F.-L. *Org. Lett.* **2004**, *6*, 4257. (b) Yang, Y.-Y.; Xu, J.; You, Z.-W.; Xu, X.-h.; Qiu, X.-L.; Qing, F.-L. *Org. Lett.* **2007**, *9*, 5437. (c) Yang, Y.; Zheng, F.; Qing, F.-L. *Tetrahedron* **2011**, *67*, 3388.

(81) Cao, Y.; Hidaka, A.; Tajima, T.; Fuchigami, T. *J. Org. Chem.* **2005**, *70*, 9614.

(82) (a) Darrow, J. W.; Drueckhammer, D. G. *J. Org. Chem.* **1994**, *59*, 2976-2985. (b) Hannessian, S.; Galeotti, N.; Rosen, P.; Olva, G.; Babu, S. *Bioorg. Med. Chem.* **1994**, *23*, 2763.

(83) Purser, S.; Claridge, T. D. W.; Odell, B.; Moore, P. R.; Gouverneur, V. *Org. Lett.* **2008**, *10*, 4263.

(84) (a) Osipov, S. N.; Bruneau, C.; Picquet, M.; Kolomiest, A. F.; Dixneuf, P. H. *Chem. Commun.* **1998**, 2053. (b) Osipov, S. N.; Artyushin, O. I.; Kolomiets, A. F.; Bruneau, C.; Dixneuf, P. H. *Synlett* **2000**, 1031. (c) Osipov, S. N.; Kobelíkova, N. M.; Shchetnikov, G. T.; Kolomiest, A. F.; Bruneau, C.; Dixneuf, P. H. *Synlett* **2001**, 621. (d) Osipov, S. N.; Artyushin, O. I.; Kolomiest, A. F.; Bruneau, C.; Picquet, M.; Dixneuf, P. H. *Eur. J. Org. Chem.* **2001**, 3891. (e) Vorobyeva, D. V.; Mailyan, A. K.; Peregudov, A. S.; Karimova, N. M.; Vasilyeva, T. P.; Bushmarinov, I. S.; Bruneau, C.; Dixneuf, P. H.; Osipov, S. N. *Tetrahedron* **2011**, *67*, 3524.

(85) Maguer, G.; Legros, J.; Meyer, F.; Ourévitch, M.; Crousse, B; Bonnet-Delpon, D. *Eur. J. Org. Chem.* **2005**, 1258.

(86) (a) Legros, J.; Meyer, F.; Coliboeuf, M.; Crousse, B.; Bonnet-Delpon, D.; Bégué, J.-P. *J. Org. Chem.* **2003**, *68*, 6444. (b) Bonnet-Delpon, D.; Bégué, J.-P.; Legros, J.; Crouse, B.; Meyer, F. (Rhodia Chimie, Fr.) PCT Int. Appl., **2003**, WO 2003095415.

(87) Billard, T.; Langlois, B. R. *J. Org. Chem.* **2002**, *67*, 997.

(88) Gille, S.; Ferry, A.; Billard, T.; Langlois, B. R. *J. Org. Chem.* **2003**, *68*, 8932.

(89) Fustero, S.; Jiménez, D.; Sanz-Cervera, J. F.; Sánchez-Roselló, M.; Esteban, E.; Simón-Fuentes, A. *Org. Lett.* **2005**, *7*, 3433.

(90) Fustero, S.; Esteban, E.; Sanz-Cervera, J. F.; Jiménez, D.; Mojarrad, F. *Synthesis* **2006**, 4087.

(91) Grellepois, F.; Kikelj, V.; Coia, N.; Portella, C. *Eur. J. Org. Chem.* **2012**, 509.

(92) Grellepois, F.; Timoshenko, V. M.; Shermolovich, Y. G.; Portella, C. *Org. Lett.* **2006**, *8*, 4323.

(93) Komatsu, Y.; Sakamoto, T.; Kitazume, T. *J. Org. Chem.* **1999**, *64*, 8369.

(94) (a) Sattler, A.; Haufe, G. *Liebigs Ann. Chem.* **1994**, 921. (b) Sattler, A.; Haufe, G. *Tetrahedron* **1996**, *52*, 5469. (c) Runge, M.; O'Hagan, D.; Haufe, G. *J. Polym. Sci. A, Polym. Chem.* **2000**, *38*, 2004.

(95) (a) Runge, M.; Haufe, G. *J. Org. Chem.* **2000**, *65*, 8737. (b) Haufe, G.; Bruns, S.; Runge, M. *J. Fluorine Chem.* **2001**, *112*, 55.

(96) Bruns, S.; Haufe, G. *J. Fluorine Chem.* **2000**, *104*, 247.

(97) (a) Lequeux, T. P.; Percy, J. M. *Synlett* **1995**, 361. (b) Blades, K.; Lequeux, T. P.; Percy, J. M. *Chem. Commun.* **1996**, 1457. (c) Blades, K.; Lapôrte, D.; Percy, J. M. *Tetrahedron* **1997**, *38*, 5895. (d) Blades, K.; Lequeux, T. P.; Percy, J. M. *Tetrahedron* **1997**, *53*, 10623. (e) Blades, K.; Percy, J. M. *Tetrahedron Lett.* **1998**, *39*, 9085. (f) Blades, K.; Butt, H.; Cockerill, G. S.; Easterfield, H. J.; Lequeux, T. P.; Percy, J. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3609.

(98) Butt, A. H.; Percy, J. M.; Spencer, N. S. *Chem. Commun.* **2000**, 1691.

(99) Reviews: (a) Hara, S., Stereoselective synthesis of monofluoroalkenes using cross-coupling reactions, in: *Fluorine-Containing Synthons*, Soloshonok, V. A. (Ed.), ACS Symposium Series 911, American Chemical Society, Washington, DC, 2005, 120-134. (b) Haufe, G., Vinyl Fluorides in Cycloadditions, in: *Fluorine-Containing Synthons*, Soloshonok, V. A. (Ed.), ACS Symposium Series 911, American Chemical Society, Washington, DC, 2005, 155-172. (c) Landelle, G.; Bergeron, M.; Turcotte-Savard, M.-O.; Paquin, J.-F. *Chem. Soc. Rev.* **2011**, *40*, 2867, and references cited therein.

(100) (a) Laue, K. W.; Mück-Lichtenfeld, C.; Haufe, G. *Tetrahedron* **1999**, *55*, 10413. (b) Shendage, D. M.; Fröhlich, R.; Bergander, K.; Haufe, G. *Eur. J. Org. Chem.* **2005**, 719. (c) Lübke, M.; Jung, M.; Haufe, G. *J. Fluorine Chem.* **2013**, *152*, 144.

(101) Reviews: (a) Welch, J. T.; Lin, J.; Boros, L. G.; DeCorte, B.; Bergmann, K.; Gimi, R., in *Biomedical Frontiers of Fluorine Chemistry,* ACS Symposium Series, Vol. 639, Ojima, I.; McCarthy, J. R.; Welch, J. T. (Eds.), American Chemical Society, Washington, **1996**, 129-142. (b) Taguchi T.; Yanai, H., in *Fluorine in Medicinal Chemistry and Chemical Biology*, Ed. I. Ojima, Blackwell Publishing Inc, **2009**, 257. Original papers: (c) Allmendinger, T.; Felder, E.; Hungerbühler, E. *Tetrahedron Lett*. **1990**, *31*, 7297. (d) Allmendinger, T.; Furet, P.; Hungerbühler, E. *Tetrahedron Lett*. **1990**, *31*, 7301. (e) Bartlett, P. A.; Otake, A. *J. Org. Chem.* **1995**, *60*, 3107. (f) Welch, J. T.; Lin, J. *Tetrahedron* **1996**, *52*, 291. (g) Veenstra, S. J.; Hauser, K.; Felber, P. *Bioorg. Med. Chem. Lett.* 1997, 7, 351. (h) Zhao, K.; Lim, D. S.; Funaki, T.; Welch, J. T. *Bioorg. Med. Chem.* **2003**, *11*, 207.

(102) (a) Asahina, Y.; Iwase, K.; Iinuma, F.; Hosaka, M.; Ishizaki, T. *J. Med. Chem.* **2005**, *48*, 3194. (b) Edmondson, 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. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2409. (c) Oishi, S.; Kamitani, H.; Kodera, Y.; Watanabe, K.; Kobayashi, K.; Narumi, T.; Tomita, K.; Ohno, H.; Naito, T.; Kodama, E.; Matsuoka, M.; Fujii, N. *Org. Biomol. Chem.* **2009**, *7*, 2872. (d) Osada, S.; Sano, S.; Ueyama, M.; Chuman, Y.; Kodama, H.; Sakaguchi, K. *Bioorg. Med. Chem.* **2010**, *18*, 605.

(103) Halle, L. F.; Armentrout, P. B.; Beauchamp, J. L. *Organometallics* **1983**, *2*, 1829.

(104) (a) Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem*. **1997**, *62*, 7310. (b) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783.

(105) Trnka, T. M.; Day, M. W.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2001**, *40*, 3441.

(106) (a) Macnaughtan, M. L.; Johnson, M. J. A.; Kampf, J. W. *Organometallics* **2007**, *26*, 780. (b) Macnaughtan, M. L.; Gary, J. B.; Gerlach, D. L. Johnson, M. J. A.; Kampf, J. W. *Organometallics* **2009**, *28*, 2880.

(107) Connon, S. J.; Blechert, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 1900-1902.

(108) Marhold, M.; Buer, A.; Hiemstra, H.; van Maarseveen, J. H.; Haufe, G. *Tetrahedron Lett.* **2004**, *45*, 57.

(109) Fürstner; A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204.

(110) De Matteis, V.; van Delft, F. L.; de Gelder, R.; Tiebes, J.; Rutjes, F. P. J. T. *Tetrahedron Lett.* **2004**, *45*, 959.

(111) Salim, S. S.; Bellingham, R. K.; Satcharoen, V.; Brown, R. C. D. *Org. Lett.* **2003**, *5*, 3403.

(112) Marhold, M.; Stillig, C.; Fröhlich, R.; Haufe, G. *submitted*.

(113) (a) Laue, K. W.; Haufe G. *Synthesis* **1998**, 1453. (b) Shendage, D. M.; Fröhlich, R.; Bergander, K.; Haufe G. *Eur. J. Org. Chem.* **2005**, 917.

(114) Stillig, C. *PhD Thesis*, University of Münster, **2010**, 169.

(115) TFA was added because it had been reported earlier for non-fluorinated compounds that free amines might be problematic, while the corresponding ammonium salts could be cyclized. See, for example: (a) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856. (b) Felpin, F.-X.; Girard, S.; Vo-Thanh, G. Robins, R. J.; Villieras, J.; Lebreton, J. *J. Org. Chem.* **2001**, *66*, 6305. However, Brown and co-workers obtained similar results with free amines **179** and **181**.

(116) Cadot, C.; Dalko, P. I.; Cossy, J. *Tetrahedron Lett.* **2002**, *43*, 1839.

(117) De Matteis, V.; van Delft, F. L.; Tiebes, J.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **2006**, 1166.

(118) De Matteis, V.; Dufay, O.; Waalboer, D. C. J.; van Delft, F. L.; Tiebes, J.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **2007**, 2667.

(119) (a) Tae, J.; Hahn, W.-D. *Tetrahedron Lett*. **2004**, *45*, 3757-3760. (b) Kim, Y. J.; Lee, D. *Org. Lett*. **2004**, *6*, 4351.

(120) De Matteis, V.; van Delft, F. L.; Tiebes, J.; Rutjes, F. P. J. T. *Synlett* **2008**, 351.

(121) (a) Manzoni, L.; Colombo, M.; Scolastico, C. *Tetrahedron Lett.* **2004**, *45*, 2623. (b) Sattely, E. S.; Cortez, G. A.; Moebius, D. C.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 8526. (c) Review: Brenneman, J. B.; Martin, S. F. *Curr. Org. Chem.* **2005**, *9*, 1535.

(122) Southon, I. W.; Cordell, G. A.; Buckingham, J. *Dictionary of Alkaloids*, Chapman & Hall, London 1989, 890.

(123) Arisawa, M.; Takezawa, E.; Nishida, A.; Mori, M.; Nakagawa, M. *Synlett* **1997**, 1179.

(124) Park, S. H.; Kang, H. J.; Ko, S.; Park, S.; Chang, S. *Tetrahedron: Asymmetry* **2001**, *12*, 2621.

(125) Shi, G.; Takagishi, S.; Schlosser, M. *Tetrahedron* **1994**, *50*, 1129.

(126) (a) McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555. (b) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475. (c) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Asian. J.* **2012**, *7*, 1744.

(127) (a) Ma, J.-A.; Cahard, D. *J. Fluorine Chem.* **2007**, *128*, 975. (b) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1-PR43. (c) Shibata, N.; Matsnev, A.; Cahard, D. *Beilstein J. Org. Chem.* **2010**, *6*, No. 65, 1. (d) Studer, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8950.

(128) Review: Lin, P.; Jiang, J.-L. *Tetrahedron*, **2000**, *56*, 3635.

(129) De Matteis, V.; van Delft, F. L.; Jakobi, H.; Lindell, S.; Tiebes, J.; Rutjes, F. P. J. T. *J. Org. Chem.* **2006**, *71*, 7527.

(130) For general reviews on enyne metathesis, see: (a) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317. (b) Hansen, E. C.; Lee, D. *Acc. Chem. Res.* **2006**, *39*, 509. (c) Mori, M. *Adv. Synth. Catal.* **2007**, *349*, 121. For specific reviews on RCEYM, see: (d) Maifeld, S. V.; Lee, D. *Chem. Eur. J.* **2005**, *11*, 6118. (e) Villar, H.; Frings, M.; Bolm, C. *Chem. Soc. Rev.* **2007**, *36*, 55.

(131) For reviews on enyne metathesis in tandem processes, see: (a) Kotha, S.; Meshram, M.; Tiwari, A. *Chem. Soc. Rev.* **2009**, *38*, 2065. (b) Li, J.; Lee, D. *Eur. J. Org. Chem.* **2011**, 4269.

(132) (a) Semeril, D.; Le Nôtre, J.; Bruneau, C.; Dixneuf, P. H.; Kolomiets, A. F.; Osipov, S. N. *New. J. Chem.* **2001**, *25*, 16. (b) Eckert, M.; Monnier, F.; Shchetnikov, G. T.; Titanyuk, I. D.; Osipov, S. N.; Toupet, L.; Dérien, S.; Dixneuf, P. H. *Org. Lett.* **2005**, *7*, 3741. (c) Eckert, M.; Moulin, S.; Monnier, F.; Titanyuk, I. D.; Osipov, S. N.; Roisnel, T.; Dérien, S.; Dixneuf, P. H. *Chem. Eur. J.* **2011**, *17*, 9456. (d) Mailyan, A. K.; Krylov, I. M.; Bruneau, C.; Dixneuf, P. H.; Osipov, S. N. *Eur. J. Org. Chem.* **2013**, 5353.

(133) (a) Fustero, S.; Fernández, B.; Bello, P.; del Pozo, C.; Arimitsu, S.; Hammond, G. B. *Org. Lett.* **2007**, *9*, 4251. (b) Arimitsu, S.; Bottom, R. L.; Hammond, G. B. *J. Fluorine Chem.* **2008**, *129*, 1047. (d) Fustero, S.; Bello, P.; del Pozo, C.; Hammond, G. B. *J. Org. Chem.* **2009**, *74*, 7690.

(134) (a) Arimitsu, S.; Fernández, B.; Carlos, C.; Fustero, S.; Hammond, G. B. *J. Org. Chem.* **2008**, *73*, 2656. (b) Arimitsu, S.; Hammond, G. B. *Beilstein J. Org. Chem.* **2010**, *6*, Nº 48 (Special Issue Organo-fluorine chemistry II).

(135) Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082.

(136) For reviews on cross-metathesis, see: (a) Connon, S. J.; Blechert, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 1900. (b) Aljarilla, A.; López, J. C.; Plumet, J. *Eur. J. Org. Chem.* **2010**, 6123. (c) Donohoe, T. J.; Bower, J. F.; Chan, L. K. M. *Org. Biomol. Chem.* **2012**, *10*, 1322.

(137) (a) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000,** *122,* 3783. (b) Itoh, T.; Mitsukura, K.; Ishida, N.; Uneyama, K. *Org. Lett.* **2000***, 2*, 1431.

(138) For a non-catalytic example with difluoroethylene, see reference 108.

(139) Imhof, S.; Randl, S.; Blechert, S. *Chem. Commun.* **2001**, 1692.

(140) Thibaudeau, S.; Fuller, R.; Gouverneur, V. *Org. Biomol. Chem.* **2004**, *2*, 1110.

(141) Thibaudeau, S.; Gouverneur, V. *Org. Lett.* **2003**, *5*, 4891.

(142) (a) Fustero, S.; Sánchez-Roselló, M.; Sanz-Cervera, J. F.; Aceña, J. L.; del Pozo, C.; Fernández, B.; Bartolomé, A.; Asensio, A. *Org. Lett.* **2006**, *8*, 4633. (b) Fustero, S.; Sánchez-Roselló, M.; Aceña, J. L.; Fernández, B.; Asensio, A.; Sanz-Cervera, J.-F.; del Pozo, C. *J. Org. Chem.* **2009**, *74*, 3414.

(143) Fustero, S.; Báez, C.; Sánchez-Roselló, M.; Asensio, A:; Miró, J.; del Pozo, C. *Synthesis* **2012**, *44*, 1863.

(144) (a) Oki, T.; Hirano, M.; Tomatsu, K.; Numata, K.; Kamei, H. *J. Antibiot.* **1989**, *42*, 1756. (b) Kawabata, K.; Inamoto, Y.; Sakane, K.; Iwamoto, T.; Hashimoto, S. *J. Antibiot.* **1990**, *43*, 513. (c) Benedeck, G.; Palkó, M.; Wéber, E.; Martinek, T. A.; Forró, E.; Fülöp, F. *Eur. J. Org. Chem.* **2008**, 3724.

(145) (a) Fustero, S.; Jiménez, D.; Sánchez-Roselló, M.; del Pozo, C.; *J. Am. Chem. Soc.* **2007**, *129*, 6700. (b) Fustero, S.; Monteagudo, S.; Sánchez-Roselló, M.; Flores, S.; Barrio, P.; del Pozo, C. *Chem. Eur. J.* **2010**, *16*, 9835.

(146) For other reports on the use of TBAF as a superior base in intramolecular Michael and *aza*-Michael processes, see: (a) Fustero, S.; Rodríguez, E.; Herrera, L.; Asensio, A.; Maestro, M. A.; Barrio, P. *Org. Lett.* **2011**, *13*, 6564. (b) Fustero, S.; Herrera, L.; Lázaro, R.; Rodríguez, E.; Maestro, M. A.; Mateu, N.; Barrio, P. *Chem. Eur. J.* **2013**, *19*, 11776.

(147) (a) Tavasli, M.; O'Hagan, D.; Pearson, C.; Petty, M. C. *Chem. Commun.* **2002**, 1226. (b) Schüler, M.; O'Hagan, D.; Slawin, A. M. Z. *Chem. Commun.* **2005**, 4324. (c) Nicoletti, M.;

O'Hagan, D.; Slawin, A. M. Z. *J. Am. Chem. Soc.* **2005**, *127*, 482. (d) Hunter, L.; O'Hagan, D.; Slawin, A. M. Z. *J. Am. Chem. Soc.* **2006**, *128*, 16422. (e) Nicoletti, M.; Bremer, M.; Kirsch, P.; O'Hagan, D. *Chem. Commun.* **2007**, 5075. (f) Gooseman, N. E. J.; O'Hagan, D.; Peach, M. J. G.; Slawin, A. M. Z.; Tozer, D. T.; Young, R. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 5904. (g) Hunter, L.; Slawin, A. M. Z.; Kirsch, P.; O'Hagan, D. *Angew. Chem. Int. Ed.* **2007**, *46*, 7887. (h) Hunter, L.; Kirsch, P.; Hamilton, J. T. G.; O'Hagan, D. *Org. Biomol. Chem.* **2008**, *6*, 3105. (i) Hunter, L.; Kirsch, P.; Slawin, A. M. Z.; O'Hagan, D. *Angew. Chem. Int. Ed.* **2009**, *48*, 5457.

(148) For a review, see: Hunter, L.; O'Hagan, D. *Org. Biomol. Chem.* **2008**, *6*, 2843.

(149) Craig, N. C.; Chen, A.; Suh, K. H.; Klee, S.; Mellau, G. C.; Winnewisser, B. P.; Winnewiseser, M. *J. Am. Chem. Soc.* **1997**, *119*, 4789.

(150) Teare, H.; Huguet, F.; Tredwell, M.; Thibeudeau, S.; Luthra, S.; Gouverneur, V. *Arkivoc* **2007**, 232.

(151) Eignerova, B.; Dračínský, M.; Kotora, M. *Eur. J. Org. Chem.* **2008**, 4493.

(152) For a precedent on the use of cross-metathesis for the synthesis of perfluorinated cyclodextrin analogs, see: Ghera, B. B.; Fache, F.; Parrot-Lopez, H. *Tetrahedron* **2006**, *62*, 4807.

(153) (a) Eignerova, B.; Slavíková, B.; Buděšinský, M.; Klepetářová, B.; Šťastna, E.; Kotora, M. *J. Med. Chem.* **2009**, *52*, 5753. (b) Řezanka, M.; Eignerová, B.; Jindřich, J.; Kotora, M. *Eur. J. Org. Chem.* **2010**, 6256. (c) Prchalová, E.; Votruba, I.; Kotora, M. *J. Fluorine Chem.* **2012**, *141*, 49.

(154) (a) Jindřich, J.; Tišlerová, I. *J. Org.Chem.* **2005**, *70*, 9054. (b) Hanessian, S.; Benali, A.; Laferriere, C. *J. Org. Chem.* **1995**, *60*, 4786. (c) Jindrich, J.; Pitha, J.; Lindberg, B.; Seffers, P.; Harata, K. *Carbohydr. Res.* **1995**, *266*, 75. (d) Maksimov, A. L.; Sakharov, D. A:; Filippova, T. Y.; Zuchkova, A. Y.; Karakhanov, E. A. *Ind. Eng. Chem. Res.* **2005**, *44*, 8644.

(155) Huang, Y.; Chen, D.; Qing, F.-L. *Tetrahedron* **2003**, *59*, 7879.

(156) Carrel, F. R:; Geyer, K.; Codée, J. D. C:; Seeberger, P. H. *Org. Lett.* **2007**, *9*, 2285.

(157) (a) Lam, Y.-H.; Bobbio, C.; Cooper, I. R.; Gouverneur, V. *Angew. Chem. Int Ed.* **2007**, *46*, 5106. (b) Purser, S.; Odell, B.; Claridge, T. D: W.; Moore, P. R.; Gouverneur, V. *Chem.-Eur. J.* **2006**, *12*, 9176. (c) Tredwell, M.; Gouverneur, V. *Org. BIomol. Chem.* **2006**, *4*, 26.

(158) Boldon, S.; Moore, J. E.; Gouverneur, V. *Chem. Commun.* **2008**, 3622.

(159) (a) Pujari, S. A.; Kaliappan, K. P.; Valleix, A.; Grée, D.; Grée, R. *Synlett* **2008**, 2503. (b) Fustero, S.; Bello, P.; Miró, J.; Simón, A.; del Pozo, C. *Chem. Eur. J.* **2012**, *18*, 10991. (c) Fustero, S.; Bello, P.; Miró, J.; Sánchez-Roselló, M.; Haufe, G.; del Pozo, C. *Beilstein J. Org. Chem.* **2013**, *9*, 2688.

(160) For recent reviews on ROMP, see: (a) Schrock, R. R. *Dalton Trans.* **2011**, *40*, 7484. (b) Leitgeb, A.; Wappel, J.; Slugovc, C. *Polymer* **2010**, *51*, 2927. (c) Nomura, K.; Abdellatif, M. M. *Polymer* **2010**, *51*, 1861. (d) Buchmeiser, M. R. *Chem. Rev.* **2000**, *100*, 1565. For recent reviews on ADMET, see: (e) Atallah, P.; Wagener, K. B.; Schulz, M. D. *Macromolecules* **2013**, *46*, 4735. (f) Mutlu, H.; Montero de Espinosa, L.; Meier, M. A. R. *Chem. Soc. Rev.* **2011**, *40*, 1404.

(161) For recent reviews on fluorinated polymers, see: (a) Krafft, M. P.; Riess, J. G. *J. Polym. Sci., Part A: Polym. Chem.* **2007**, *45*, 1185. (b) Narita, T. *J. Polym. Sci., Part A: Polym. Chem.* **2004**, *42*, 4101. (c) Kostov, G.; Ameduri, B.; Boutevin, B. *J. Fluorine Chem.* **2002**, *114*, 171.

(162) Feast, W. J.; Khosravi, E. *J. Fluorine Chem.* **1999**, *100*, 117.

(163) For some isolated examples of polymerization of fluorinated norbornene derivatives prior to 1999 and not published by the Feast's group and therefore not included in reference 165, see: (a) Seehof, N.; Risse, W. *Makromol. Chem., Rapid Commun.* **1991**, 1*2*, 107. (b) Bazan, G. C.; Renak, M. L.; Sun, B. J. *Macromolecules* **1996**, *29*, 1085. (c) Bazan, G. C.; Schrock, R. R.; Cho, H.-N.; Gibson, V. C. *Macromolecules* **1991**, *24*, 4495. For an isolated example of perfluoroalkyl-ended block polyethylenes, see: McLain, S. J.; Sauer, B. B.; Firment, L. E. *Macromolecules* **1996**, *29*, 8211.

(164) Feast also introduced the use of a fluorinated monomer as acetylene surrogate for the preparation of polyenes. As the final products did not contain fluorine, these publications have been excluded. See: (a) Edwards, J. H.; Feast, W. J. *Polymer* **1980**, *21*, 595. (b) Edwards, J. H.; Feast, W. J.; Bott, D. C. *Polymer* **1984**, *25*, 395. (c) Feast, W. J.; Winter, J. N. *J. Chem. Soc., Chem. Commun.* **1985**, 202. (d) Knoll, K.; Krouse, S. A:; Schrock, R. R. *J. Am. Chem. Soc.* **1988**, *110*, 4424. (e) Knoll, K.; Schrock, R. R. *J. Am. Chem. Soc.* **1989**, *111*, 7989.

(165) (a) Feast, W. J.; Gimeno, M.; Khosravi, E. *Polymer* **2003**, *44*, 6111. (b) Feast, W. J.; Gimeno, M.; Khosravi, E. *J. Mol. Catal. A: Chem.* **2004**, *213*, 9.

(166) (a) Vargas, J.; Martínez, A.; Santiago, A. A.; Tlenkopatchev, M. A.; Aguilar-Vega, M. *Polymer* **2007**, *48*, 6546. (b) Vargas, J.; Martínez, A.; Santiago, A. A.; Tlenkopatchev, M. A.; Gaviño, R.; Aguilar-Vega, M. *J. Fluorine Chem.* **2009**, *130*, 162.

(167) Freeman, B. D.; Pinnau, I. Polymer membranes for gas and vapor separatin: chemistry and materials science. Washington, DC: American Chemical Society; 1999.

(168) (a) Vargas, J.; Sánchez, E.; Tlenkopatchev, M. A. *Eur. Polym. J.* **2004**, *40*, 1325. (b) Tlenkopatchev, M. A.; Vargas, J.; López-González, M. M.; Riande, E. *Macromolecules* **2003**, *36*, 8483. (c) Tlenkopatchev, M. A.; Vargas, J.; Almaráz-Girón, M. A.; López-González, M. M.; Riande, M. *Macromolecules* **2005**, *38*, 2696.

(169) Yampol'skii, Y. P.; Bespalova, N. B.; Finkel'shtein, E. S.; Bondar VI, P. A. V. *Macromolecules* **1994**, *27*, 2872.

(170) Santiago, A. A.; Vargas, J.; Cruz-Gómez, J.; Tlenkopatchev, M. A.; Gaviño, R.; López-González, M.; Riande, E. *Polymer* **2011**, *52*, 4208.

(171) (a) Berron, B. J.; Faulkner, C. J.; Fischer, R. E.; Payne, P. A.; Jennings, G. K. *Langmuir* **2009**, *25*, 12721. (b) Faulkner, C. J.; Fischer, R. E.; Jennings, G. K. *Macromolecules* **2010**, *43*, 1203. (c) Escobar, C. A.; Harl, R. R.; Maxwell, K. E.; Mahfuz, N. N.; Rogers, B. R.; Jennings, G. K. *Langmuir* **2013**, *29*, 12560.

(172) Jennings, G. K.; Brantley, E. L. *Adv. Mater.* **2004**, *16*, 1983.

(173) (a) Boz, E.; Wagener, K. B.; Ghosal, A:; Fu, R.; Alamo, R. G. *Macromolecules* **2006**, *39*, 4437. (b) Boz, E.; Ghiviriga, I.; Nemeth, A. J.; Jeon, K.; Alamo, R. G.; Wagener, K. B.

Macromolecules **2008**, *41*, 25. (c) Boz, E.; Nemeth, A. J.; Wagener, K. B.; Jeon, K.; Smith, R.; Nazirov, F, Bockstaller, M. R.; Alamo, R. G. *Macromolecules* **2008**, *41*, 1647.

(174) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592.

(175) Schrock, R. R.; Czekelius, C. *Adv. Synth. Catal.* **2007**, *349*, 55.

(176) Van de Weghe, P.; Bisseret, P.; Blanchard, N.; Eustache, J. *J. Organomet. Chem.* **2006**, *691*, 5078.

(177) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 3800.

(178) Fujimura, O.; Fu, G. C.; Grubbs, R. H. *J. Org. Chem.* **1994**, *59*, 4029.

(179) Hodgson, D. M.; Foley, A. M.; Lovell, P. J. *Synlett* **1999**, 744.

(180) Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310.

(181) Forbes, M. D. E.; Patton, F. T. Mayers, T. L.; Manard, H. D.; Smith, D. W., jr.; Schulz, G. R.; Eagener, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 10978.

(182) Nakashima, K.; Inoue, K.; Sono, M.; Tori, M. *J. Org. Chem.* **2002**, *67*, 6034.

(183) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130.

(184) (a) Bourgeois, D.; Pancrazi, A.; Ricard, L.; Prunet, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 725. (b) Bourgeois, D.; Mahuteau, J.; Pancrazi, A.; Nolan, S.- P.; Prunet, J. *Synthesis* **2000**, 869.

(185) Seepersaud, M.; Al-Abed, Y. *Org. Lett.* **1999**, *1*, 1463.

(186) Hoveyda, A. H.; Schrock, R. R. *Chem. Eur. J.* **2001**, *7*, 945.

(187) (a) Fujimura, O.; Grubbs, R. H. *J. Am. Chem Soc.* **1996**, *118*, 2499. (b) Fujimura, O.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 824.

(188) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426.

(189) Miller, J. F.; Termin, A.; Koch, K.; Piscopio, A. *J. Org. Chem.* **1998**, *63*, 3158.

(190) Mooberry, S. L.; Tien, G.; Hernandez, A. H.; Plubrukarn, A.; Davidson, B. S. *Cancer Res.* **1999**, *59*, 653.

(191) Nelson, G. S.; Cheung, W. S.; Kassick, A. J.; Hilfiker, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 13654.

(192) (a) Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 123. (b) Clark, J. S.; Kettle, J. G. *Tetrahedron* **1999**, *55*, 8231.

(193) Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 127.

(194) (a) Clark, J. S.; Trevitt, G. P.; Boyall, D.; Stammen, B. *Chem. Commun.* **1998**, 2629. (b) Clark, J. S.; Freeman, R. P.; Cacho, M.; Thomas, A. W.; Swallow, S.; Wilson, C. *Tetrahedron Lett.* **2004**, *45*, 8639.

(195) (a) Rainier, J. D.; Allwein, S. P. *J Org. Chem.* **1998**, *63*, 5310. (b) Rainier, J. D.; Allwein, S. P. Cox, J. M. *Org. Lett.* **2000**, *2*, 231. (c) Rainier, J. D.; Cox, J. M.; Allwein, S. P. *Tetrahedron Lett.* **2001**, *42*, 179. (d) Rainier, J. D.; Allwein, S. P. Cox, J. M. *J. Org. Chem.* **2001**, *66*, 1380. (e) Allweil, S. P.; Cox, J. M.; Howard, B. E.; Johnson, H. W. B.; Rainier, J. D. *Tetrahedron* **2002**, *58*, 1997.

(196) (a) Peczuh, M. W.; Snyder, N. L. *Tetrahedron Lett.* **2003**, *44*, 4057. (b) Peczuh, M. W.; Snyder, N. L.; Fyvie, W. S. *Carboh. Res.* **2004**, *339*, 1163.

(197) Majumder, U.; Cox, J. M.; Johnson, H. W. B.; Rainier, J. D. *Chem. Eur. J.* **2006**, *12*, 1736.

(198) (a) Postema, M. H. D.; Calimente, D. *Tetrahedron Lett.* **1999**, *40*, 4755. (b) Postema, M. H. D.; Calimente, D. Liu, L.; Behrmann, T. L. *J. Org. Chem.* **2000**, *65*, 6061.

(199) Postema, M. H. D.; Piper, J. L.; Betts, R. L. *Synlett* **2005**, 1345.

(200) Burke, S. D.; Quinn, K. J.; Chen, V. J. *J Org. Chem.* **1998**, *63*, 8626.

(201) Johannes, C. W.; Visser, M. S.; Weatherhead, G. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 8340.

(202) May, S. A.; Grieco, P. A. *Chem. Commun.* **1998**, 1597

(203) Wang, C.; Haeffner, F.; Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2013**, *52*, 1939.

(204) Chang, S.; Grubbs, R. H. *Tetrahedron Lett*. **1997**, *38*, 4757.

(205) Ahmed, M.; Barrett, A. G. M.; Beall, J. C.; Braddock, D. C.; Flack, K.; Gibson, V. C.; Procopiou, P. A.; Salter, M. M. *Tetrahedron* **1999**, *55*, 3219.

(206) Denmark, S. E.; Yang, S. M. *J. Am. Chem. Soc.* **2002**, *124*, 15196.

(207) Spagnol, G.; Heck, M.-P.; Nolan, S. P.; Mioskowski, C. *Org. Lett.* **2002**, *4*, 1767.

(208) Shon, Y.-S.; Lee, T. R. *Tetrahedron Lett*. **1997**, *38*, 1283.

(209) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324.

(210) Fürstner, A.; Thiel, O. R. *J. Org. Chem.* **2000**, *65*, 1738.

(211) Martin, S. F.; Chen, H.-J.; Courtney, A. K.; Liao, Y.; Pätzel, M.; Ramser, M.; Wagman, A. S. *Tetrahedron* **1996**, *52*, 7251.

(212) Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 4628.

(213) Fellows, I. M.; Kaelin, D. E.; Martin, S. F. *J. Am. Chem. Soc.* **2000**, *122*, 10781.

(214) Huwe, C. M. Velder, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2376.

(215) Barrett, A. G. M.; Baugh, S. P. D.; Gibson, V. C.; Giles, M. R.; Marshall, E. L.; Procopiou, P. A. *Chem. Commun.* **1997**, 155.

(216) Xu, Z.; Johannes, C. W.; Houri, A. F.; La, D. S.; Cogan, D. A.; Hofilena, G. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 10302.

(217) (a) Malcomson, S. J.; Meek, S. J.; Sattely, E. S.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2008**, *456*, 933. (b) Sattely, E. S.; Meek, S. J.; Malcomson, S. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 943. (c) Meek, S. J.; Malcomson, S. J.; Li, B.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 16407.

(218) Slinn, C. A.; Redgrave, A. J.; Hind, S. L.; Edlin, C.; Nolan, S. P.; Gouverneur, V. *Org. Biomol. Chem.* **2003**, *1*, 3820.

(219) Ogasawara, M.; Nagano, T.; Hayashi, T. *Organometallics* **2003**, *22*, 1174.

(220) Cowe, W. E.; Zhang, Z. J. *J. Am. Chem. Soc.* **1993**, *115*, 10998.

(221) (a) Cowe, W. E.; Goldberg, D. R.; *J. Am. Chem. Soc.* **1995**, *117*, 5162. (b) Cowe, W. E.; Goldberg, D. R.; Zhang Z. J. *Tetrhedron Lett.* **1996**, *37*, 2117.

(222) Feng, J.; Schuster, M.; Blechert, S. *Synlett* **1997**, 129.

(223) Brümmer, O.; Rückert, A.; Blechert S. *Chem. Eur. J.* **1997**, *3*, 441.

(224) Kawai, T.; Komaki, M.; Iyoda, T. *J. Mol. Catal. A* **2002**, *190*, 45.

(225) Yasuda, T.; Abe, J.; Yoshida, H.; Iyoda, T.; Kawai, T. *Adv. Synth. Catal.* **2002**, *344*, 705.

(226) Smith, A. B.; Kozmin, S. A.; Adams, C. M.; Paone, D. V. *J. Am. Chem. Soc.* **2000**, *122*, 4984.

227 Beer, S.; Hrib, C. G.; Jones, P.G.; Brandhorst, K.; Grunenberg, J.; Tamm, M. *Angew. Chem. Int Ed.* **2007**, *46*, 8890.

(228) Wu, X.; Tamm, M. *Beilstein J. Org. Chem* **2011**, *7*, 82.

(229) Taoufik, M.; Mazoyer, E.; Nicholas, C. P.; Basset, J.-M. US-Pat. 2012/0316374 A1.

(230) (a) Gladysz, J. A., Guest Editor, Special issue, *Chem. Rev.* **2002**, *102*, pp 3215-3892. (b) Tzschucke, C. C.; Markert, C.; Bannwarth, W.; Roller, S.; Hebel, A.; Haag, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3964. (c) Baker, R. T.; Kobayashi, S.; Leitner, W., Guest Editors, Special issue, *Adv. Synth. Catal.* **2006**, *348*, 1337-1771. (d) Liu, S.; Xiao, J. *J. Mol. Catal. A* **2007**, *270*, 1. (e) Benanglia, M., Ed.; Recoverable and recyclable catalysts, Wiley-Blackwell: Oxford, UK, **2009**.

(231) *Handbook of Fluorous Chemistry,* Gladysz, J. A.; Curran, D. P.; Horvát, I. T., Eds., Wiley-VCH, Weinheim, **2004**.

(232) (a) Gladysz, J. A. in: *Catalysis involving fluorous phases: fundamentals and directions for greener methodology*, Handbook of Green Chemistry: Green Catalysis, Anastas, P. T.; Crabtree, R. H., Eds., Wiley-VCH, Weinheim, **2004**, pp 17-38. (b) Curran, D. P. *Aldrichim. Acta* **2006**, *39*, 3-9. (c) Gladysz, J. A. *Science* **2006**, *313*, 1249-1250. (d) Hobbs, H. R.; Thomas, N. R. *Chem. Rev.* **2007**, *107*, 2786-2820. (e) Zhang, W. *Green Chem.* **2009**, *11*, 911-920.

(233) Curran, D. P., *Light fluorous chemistry – a user's guide*, in: ref. [231a], pp. 128-155.

(234) Curran, D. P., *Separations with fluorous silica gel and related materials*, in: ref. [231a], pp. 101-127.

(235) Matsugi, M.; Curran, D. P. *J. Org. Chem.* **2005**, *70*, 1636.

(236) Leach, S.; Cordier, C. J.; Morton, D.; McKierman, G. J.; Warriner, S.; Nelson, A. *J. Org. Chem.* **2008**, *73*, 2753.

(237) Morton, D.; Leach, S.; Cordier, C.; Warriner, S.; Nelson, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 104.

(238) Matsugi, M.; Kobayashi, Y.; Suzumura, N.; Tsuchiya, Y.; Shioiri, T. *J. Org. Chem.* **2010**, *75*, 7905.

(239) Kvíčala, J.; Schindler, M.; Kelbichová, V.; Babuněk, M.; Rybáčková, M.; Kvíčalová, M.; Cvačka, J.; Březinová, A. *J. Fluorine Chem.* **2013**, *153*, 12-25.

(240) Fürstner, A.; Ackermann, L.; Gabor, B.; Goddard, R.; Lehmann, C. W.; Mynott, R.; Stelzer, F.; Thiel, O. R. *Chem. Eur. J.* **2001**, *7*, 3236.

(241) (a) Michalek, F.; Bannwarth, W. *Helv. Chim. Acta* **2006**, *89*, 1030. (b) Andrushko, V.; Schwinn, D.; Tzucke, C. C.; Michalek, F.; Horn, J.; Mössner, C.; Bannwarth, W. *Helv. Chim. Acta* **2005**, *88*, 936. (c) Lim, J.; Lee, S. S.; Ying, J. Y. *Chem. Commun.* **2008**, 4312. (d) Hensle, E. M.; Tobis, J.; Tiller, J. C.; Bannwarth, W. *J. Fluorine Chem.* **2008**, *129*, 968.

(242) Yao, Q.; Zhang, Y. *J. Am. Chem. Soc.* **2004**, *126*, 74.

(243) (a) Bergbreiter, D. E.; Sung, S. D. *Adv. Synth. Catal.* **2006**, *348*, 1352. (b) Miao, W.; Chan, T. H. *Acc. Chem. Res.* **2006**, *39*, 897.

(244) (a) Da Costa, R. C.; Gladysz, J. A. *Chem. Commun.* **2006**, 2619. (b) Da Costa, R. C.; Gladysz, J. A. *Adv. Synth. Catal.* **2007**, *349*, 243.

(245) Tuba, R.; da Costa, R. C.; Bazzi, H. S.; Gladysz, J. A. *ACS Catalysis* **2012**, *2*, 155.

(246) Tuba, R.; Brothers, E. N.; Reibenspies, J. H.; Bazzi, H. S.; Gladysz, J. A. *Inorg. Chem.* **2012**, *51*, 9943.

(247) Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746.

(248) Ritter, T.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 11768.

(249) Siano, V.; d'Auria, I.; Grisi, F.; Costabile, C.; Longo, P. *Cent. Eur. J. Chem.* **2011**, *9*, 605.

(250) (a) Vougioukalakis, G. C.; Grubbs, R. H. *Organometallics* **2007**, *26*, 2469. (b) Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Eur. J.* **2008**, *14*, 7545.

(251) Zaja, M.; Connon, S. J.; Dunne, A. M.; Rivard, M.; Buschmann, N.; Jiricek, J.; Blechert, S. *Tetrahedron* **2003**, *59*, 6545.

(252) (a) Rix, D.; Caijo, F.; Laurent, I.; Boeda, F.; Clavier, H.; Nolan, S. P. Mauduit, M. *J. Org. Chem.* **2008**, *73*, 4225. (b) Clavier, H.; Caijo, F.; Borré, E.; Rix, D.; Boeda, F.; Nolan, S. P.; Mauduit, M. *Eur. J. Org. Chem.* **2009**, 4254.

(253) Borré, E.; Caijo, F.; Crévisy, C.; Mauduit, M. *Beilstein J. Org. Chem.* **2010**, *6*, 1159.

(254) Michrowska, A.; Bujok, R.; Harutyunyan, S.; Sashuk, V.; Dolgonos, G.; Grela, K. *J. Am. Chem. Soc.* **2004**, *126*, 9318.

(255) Nelson, D.; Queval, P.; Rouen, M.; Magrez, M.; Toupet, L.; Caijo, F.; Borré, E.; Laurent, I.; Crévisy, C.; Baslé, O.; Mauduit, M.; Percy, J. M. *ACS Catalysis* **2013**, *3*, 259.

(256) (a) Van Veldhuizen, J. J.; Garber, S. B.; Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 4954. (b) Van Veldhuizen, J. J.; Gillingham, D. G.; Garber, S. B.; Kataoka, O.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 12502.

(257) Love, J. A.; Sanford, M. S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 10103.

(258) Reviews: (a) Buchmeiser, M. R. *Chem. Rev.* **2009**, *109*, 303. (b) Anderson, E. B.; Buchmeister, M. R. *Synlett* **2012**, *23*, 185.

(259) Wu, Z.; Nguyen, S. B.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1995**, *117*, 5503.

(260) Conrad, J. C.; Snelgrove, J. L.; Eeelman, M. D.; Hall, S.; Fogg, D. E. *J. Mol. Catal. A* **2006**, *254*, 105.

(261) (a) Buchowitz, W. ; Mol, J. C.; Lutz, M.; Spek, A. L. *J. Organomet. Chem.* **1999**, *588*, 205-210. (b) Buchowitz, W. ; Ingold, F.; Mol, J. C.; Lutz, M.; Spek, A. L. *Chem. Eur. J.* **2001**, *7*, 2842.

(262) (a) Krause, J. Nuyken, O.; Wurst, K.; Buchmeiser, M. R. *Chem. Eur. J.* **2004**, *10*, 777. (b) Krause, J. Nuyken, O.; Buchmeiser, M. R. *Chem. Eur. J.* **2004**, *10*, 2029. (c) Yang, L.; Mayr, M.; Wurst, K.; Buchmeiser, M. R. *Chem. Eur. J.* **2004**, *10*, 5761.

(263) Vehlow, K.; Köhler, K.; Blechert, S.; Dechert, S.; Meyer, F. *Eur. J. Inorg. Chem.* **2005**, 2727.

(264) Halbach, T. S.; Mix, S.; Fischer, D.; Maechling, S.; Krause, J. O.; Sievers, C.; Blechert, S.; Nuyken, O.; Buchmeiser, M. R. *J. Org. Chem.* **2005**, *70*, 4687.

(265) Mingotaud, A.-F.; Krämer, M.; Mingotaud, C. *J. Mol. Catal. A* **2007**, *263*, 39.

(266) (a) Tanaka, K.; Böhm, V. P. W.; Chadwick, D.; Roeper, M.; Braddock, D. C. *Organometallics* **2006**, *25*, 5696. (b) Braddock, D. C.; Tanaka, K.; Chadwick, D.; Böhm, V. P. W.; Roeper, M. *Tetrahedron Lett.* **2007**, *48*, 5301.

(267) (a) Conrad, J. C.; Amoroso, D.; Czechura, P.; Yap, G. P. A.; Fogg, D. E. *Organometallics* **2003**, *22*, 3634. (b) Conrad, J. C.; Parnas, H. H.; Snelgrove, J. L.; Fogg, D. E. *J. Am. Chem. Soc.* **2005**, *127*, 11882.

(268) (a) Krause, J. O.; Zarka, M. T.; Anders, U.; Weberskirch, R.; Nuyken, O.; Buchmeiser, M. R. *Angew. Chem., Int Ed.* **2003**, *42*, 5965. (b) Krause, J. O.; Wang, D.; Anders, U.; Weberskirch, R.; Zarka, M. T.; Nuyken, O.; Jäger, K.; Haarer, D.; Buchmeiser, M. R. *Macromol. Symp.* **2004**, *217*, 179. (c) Halbach, T.; Krause, J. O.; Nuyken, O.; Buchmeiser, M. R. *Macromol. Rapid Commun.* **2005**, *26*, 784.

(269) Kumar, P. S.; Wurst, K.; Buchmeiser, M. R. *J. Am. Chem. Soc.* **2009**, *131*, 387.

(270) (a) Vehlow, K.; Maechling, S.; Köhler, K.; Blechert, S. *J. Organomet. Chem.* **2006**, *691*, 5267. (b) Vehlow, K.; Maechling, S.; Köhler, K.; Blechert, S. *Tetrahedron Lett.* **2006**, *47*, 8617.

(271) (a) Kumar, P. S.; Wurst, K.; Buchmeiser, M. R. *Organometallics* **2009**, *28*, 1785. (b) Buchmeiser, M. R.; Ahmad, I.; Gurram, V.; Kumar, P. S. *Macromolecules* **2011**, *44*, 4098.

(272) Naumov, S.; Buchmeiser, M. R. *Organometallics* **2012**, *31*, 847.

(273) Wang, D.; Unold, J.; Bubrin, M.; Elser, I.; Frey, W.; Kaim, W.; Xu, G.; Buchmeiser, M. R. *Eur. J. Inorg. Chem.* **2013**, 5462.

(274) Ferraz, C.; Autenrieth, B.; Frey, W.; Buchmeiser, M. R. *ChemCatChem* **2014**, *6*, 191.

(275) Sommer, W. J.; Weck, M. *Coord. Chem. Rev.* **2007**, *251*, 860.

(276) Nieczypor, P.; Buchowsicz, W. Meester, W. J.; Rutjes, F. P. J. T.; Mol, J. C. *Tetrahedron Lett.* **2001**, *42*, 7103.

(277) Krause, J. O.; Lubbad, S. H.; Nuyken, O.; Buchmeiser, *Macromol. Rapid Commun.* **2003**, *24*, 875.

(278) Korte, T.; Zarka, M. T.; Krause, J. O.; Buchmeiser, M. R. *Macromol. Symp.* **2004**, *217*, 203.

(279) Maul, J. J.; Ostrowski, P. J.; Ublacker, G. A.; Linclau, B.; Curran, D. P. in Topics in current chemistry, "Modern Solvents in Organic Synthesis", Knochel, P., Ed. Springer-Verlag: Berlin, 1999; Vol. 206, pp 80-104

(280) (a) Samojlowicz, C.; Bieniek, M.; Zarecki, A.; Kadyrov, R.; Grela, K. *Chem. Commun.* **2008**, 6282. (b) Rost, D.; Porta, M.; Gessler, S.; Blechert, S. *Tetrahedron Lett.* **2008**, *49*, 5968.

(281) For a previous report by Grela, see: Kadyrov, R.; Bieniek, M.; Grela, K. DE Patent Application 102007018148.7, April, 11, 2007.

(282) Such a doping effect was never reported before in metathesis reactions conducted in FAH. For examples in trifluoromethylbenzene (TFMB), see: (a) Imhof, S.; Randl, S.; Blechert, S. *Chem. Commun.* **2001**, 1692. (b) Yao, Q.; Zang, Y. *J. Am. Chem. Soc.* **2004**, *123*, 74. For examples in hexafluorobenzene (HFB), see: (c) Conrad, J.C.; Amoroso, D.; Czechura, P.; Yap, G.P.A.; Fogg, D.E *Organometallics* **2003**, *22*, 3634.

(283) (a) Vieille-Petit, L.; Luan, X.; Gatti, M.; Blumentritt, S.; Linden, A.; Clavier, H.; Nolan, S. P.; Dorta, R. *Chem. Commun.* **2009**, 3783. (b) Clavier, H.; Urbina-Blanco, C. A.; Nolan, S. P. *Organometallics* **2009**, *28*, 2848.

(284) Samojlowicz, C.; Bieniek, M.; Pazio, A.; Makal, A.; Vozniak, K.; Poater, A.; Cavallo, L.; Vójcik, J.; Zdanowski, K.; Grela, K. *Chem. Eur. J.* **2011**, *17*, 12981.

(285) Samojlowicz, C.; Borré, E.; Mauduit, M.; Grela, K. *Adv. Synth. Catal.* **2011**, *353*, 1993.

(286) Grandbois, A.; Collins, S.K. *Chem. Eur. J.* **2008**, *14*, 9323.

(287) Chauvin, Y.; Herisson, J. *Makromol. Chem.* **1971**, *141*, 161.

(288) For recent reviews, see: (a) du Toit, J. I.; van Sittert, C.G.C.E.; Vosloo, H.C.M. *J. Organomet. Chem.* **2013**, *738*, 76. (b) Handzlik, J.; Kurleto, K. *Curr. Org. Chem.* **2013**, *17*, 2796. (c) Credendino, R.; Poater, A.; Ragonea, F.; Cavallo, L. *Catal. Sci. Technol.* **2011**, *1*, 1287. (d) Zhao, Y.; Truhlar, D. G. *Acc. Chem. Res.* **2008**, *41*, 157. For an recent examples, see: (e) Chu, Y.; Heyndrickx, W.; Occhipinti, G.; Jensen, V. R.; Alsberg, B. K. *J. Am. Chem. Soc.* **2012**, *134*, 8885. (f) Urbina-Blanco, C. A.; Poater, A.; Lebl, T.; Manzini, S.; Slawin, A. M. Z.; Cavallo, L.; Nolan, S. P. *J. Am. Chem. Soc.* **2013**, *135*, 7073.

(289) (a) Fomine, S.; Vargas Ortega, J.; Tlenkopatchev, M. A. *J. Organomet. Chem.* **2006**, *691*, 3343. (b) Fomine, S.; Tlenkopatchev, M. A. *Appl. Catal A: Gen.* **2009**, *355*, 148. (c) Urbina-Blanco, C. A.; Skibiński, M.; O'Hagan, D.; Nolan, S. P. *Chem. Commun.* **2013**, *49*, 7201.

(290) Di- and monofluorocarbene complexes have been isolated from stoichiometric reactions with 1,1-difluoroethene and β-fluorostyrene. For an additional citation to references 108 and 109, see: Macnaughtan, M. L.; Johnson, M. A. J.; Kampf, J. W. *J. Am. Chem. Soc.* **2007**, *129*, 7708.

(291) For an excellent review, see: Jung, M. E.; Pizzi, G. *Chem. Rev.* **2005**, *105*, 1735.

(292) Often this term and the "*gem*-dialkyl effect" are often used interchangeably, but to be more precise the "Thorpe-Ingold effect" refers specifically to the angle change upon substitution, whereas the "*gem*-dialkyl effect" refers to the overall acceleration.

(293) (a) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080. (b) Ingold, C. K. *J. Chem. Soc.* **1921**, *119*, 305. (c) Ingold, C. K.; Sako, S.; Thorpe, J. F. *J. Chem. Soc.* **1922**, *120*, 1117.

(294) (a) Bruice, T. C.; Pandit, U. K. *J. Am. Chem. Soc.* **1960**, *82*, 5858. (b) Bruice, T. C.; Pandit, U. K. *Proc. Natl. Acad. Sci. U.S.A.* **1960**, *46*, 402.

(295) (a) Clavier, H.; Urbina-Blanco, C. A.; Nolan, S. P. *Organometallics* **2009**, *28*, 2848. (b) Urbina-Blanco, C. A.; Bantreil, X.; Clavier, H.; Slawin, A. M. Z.; Nolan, S. P. *Beilstein J. Org. Chem.* **2010**, *6*, 1120. (c) Urbina-Blanco, C. A.; Leitgreb, A.; Slugovc, C.; Bantreil, X.; Clavier, H.; Slawin, A. M. Z.; Nolan, S. P. *Chem.-Eur. J.* **2011**, *17*, 5045. (d) Manzini, S.; Urbina-Blanco, C. A.; Slawin, A. M. Z.; Nolan, S. P. *Organometallics* **2012**, *31*, 6514.

(296) (a) Skibiński, M.; Wang, Y.; Slawin, A. M. Z.; Lebl, T.; Kirsch, P.; O'Hagan, D. *Angew. Chem. Int. Ed.* **2011**, *50*, 10581. (b) O'Hagan, D.; Wang, Y.; Skibiński, M.; Slawin, A. M. Z. *Pure Appl. Chem.* **2012**, *84*, 1587.

(297) Feast, W. J.; Wilson, B. *Polymer* **1979**, *20*, 1182.