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Very Important Publication

Access to Trisubstituted Fluoroalkenes by Ruthenium-Catalyzed Cross-Metathesis

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Abstract: Although the olefin metathesis reaction is a well-known and powerful strategy to get alkenes, this reaction remained highly challenging with fluororalkenes, especially the Cross-Metathesis (CM) process. Our thought was to find an easy accessible, convenient, reactive and post-functionalizable source of fluoroalkene, that we found as the methyl 2-fluoroacrylate. We reported herein the efficient ruthenium-catalyzed CM reaction of various terminal and internal alkenes with methyl 2-fluoroacrylate giving access, for the first time, to trisubstituted fluoroalkenes stereoselectively. Unprecedent TON for CM involving fluoroalkene, up to 175, have been obtained and the reaction proved to be tolerant and effective with a large range of olefin partners giving fair to high yields in metathesis products.

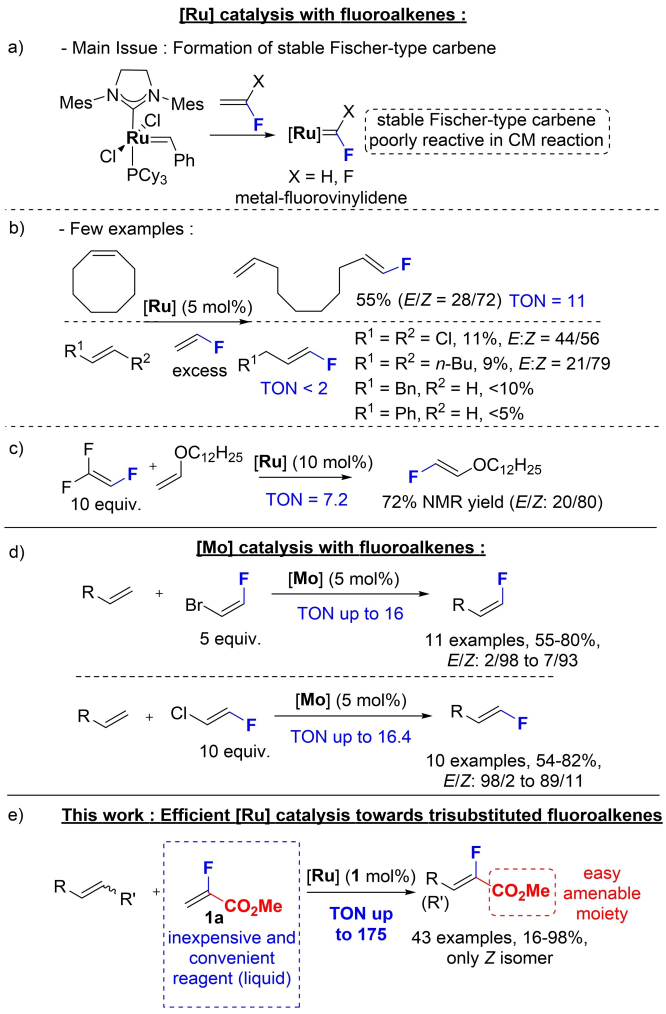
Keywords: Fluoroalkene; Metathesis; Ruthenium; Catalysis

Introduction

Organofluorine chemistry has blossomed over the past decade to become one of the most active research areas in organic synthesis. One of the main reasons of this impressive rise lies in the strong implications of fluorinated molecules in several areas such as medicinal chemistry, medical imaging, agrochemistry, materials…[1] Among the organofluorinated compounds, fluorinated alkenes have emerged as an important class of molecules, which was notably used to build up unavoidable materials[1c,2] (Teflon® for instance), as well as interesting bioactive compounds.[3] Another feature of the fluoroalkene moiety is its isosteric and isoelectronic mimicry with the amide bond, explaining its use as a bioisostere in structure-activity relationship studies in the agrochemical or pharmaceutical domains[4] or to overcome problems associated to the instability of peptides.[5]

A straightforward access to new fluoroalkenes is the use of the metathesis reaction. Indeed, the metathesis, which possesses enormous industrial potential and stands at the top of the class of olefin production,[6] appears as an ideal solution to produce fluoroalkenes. Unfortunately, despite the tremendous studies reported over the past two decades toward the development of efficient metathesis processes to synthesize alkenes, the relevant combination of metathesis and fluoroalkene has been scarcely studied. Several reasons could explain this poorly documented reaction: i) the vinyl fluoride and more generally vinyl halides are known to be reluctant substrate for metathesis;[7] ii) the main issue with ruthenium catalyst is the formation of stable metal-fluorovinylidene – a Fischer type carbene – hampering its catalytic activities.[7c,8] Indeed, early reports from Grubbs *et al.*[8a] and later from the Johnson's group[8b] showed that the reaction between di- or monofluoroethylene with the Grubbs II precatalyst formed a stable complex with a low propensity to act as a catalytically active species (Scheme 1.a).

Very few examples of CM with fluoroalkenes have been described. Among them, the Johnson's group reported few examples of successful ring opening/cross-metathesis reactions using the gaseous fluoroethylene (boiling point: −72 °C) as the fluorinated olefin reaction partner. Low stereoselectivities and low



Scheme 1. Cross-Metathesis with fluoroalkenes: state of the art & this work.

yields were reported, except for the constrained cyclooctene and resulting release of ring strain by metathesis (Scheme 1.b).[7c]

More recently, Morizawa and Takahira succeeded in the CM of tetrafluoroolefins and derivatives via an elegant strategy based on a Fischer carbenes interconversion.[9] Nevertheless, only few examples have been described including one leading to a fluoroalkene product with good NMR yield (72%), albeit without isolated yield and with low stereoselectivity (Scheme 1.c). Moreover the enol ether partner, not so convenient for further post-functionalization, was the sole possible reaction partner, while the fluorinated substrates used for this reaction were hazardous gases.

To date, the only efficient CM processes involving fluoroalkenes are mediated by Molybdene precatalyst. In 2016, Hoveyda and Schrock reported astonishing works concerning the stereoselective synthesis of (*E*)-[10a] or (*Z*)-[10b] terminal halogenoalkenes, including fluorinated ones (Scheme 1.d). Several molybdenum based monoaryloxide pyrrolide (MAP) complexes were designed and used in combination with either (*E*)-1-chloro-2-fluoroethene (boiling point: −4 °C; 5.23 $/mmol[11]) or the liquid (*Z*)-1-bromo-2-fluoroethene (boiling point: +36 °C; 5.62 $/mmol[11]) to produce efficiently and selectively the (*E*)- or (*Z*)-fluoroalkenes, respectively.[10] However, these reactions are restricted to the production of terminal fluoroalkene, hardly post-functionalizable and require glovebox manipulation with the air-sensitive Mo catalysts, which constitutes a practical constraint.

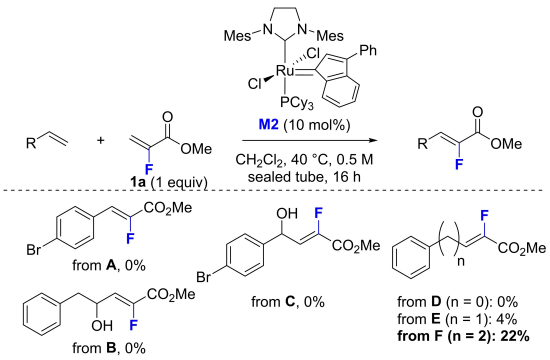
To our knowledge, i) no efficient general CM reaction with Ru-catalyst has been reported yet and ii) the CM reaction producing trisubstituted fluoroalkenes remains elusive and still remains a major challenge in the metathesis area. Our first idea was to identify a reactive fluorinated substrate, convenient to use (at least a liquid), inexpensive and commercially available, which could ideally be classified as a type III[12] olefin for CM reaction. The ideal candidate showed up as one of the common fluorinated reagents used in our lab, the methyl 2-fluoroacrylate **1a**. Although it belongs to the acrylate derivatives family, which has been extensively used in CM reactions,[13] this reagent has, to our knowledge, never been used in such reaction. Moreover, it showcases several advantages: i) it is an inexpensive commercially available liquid (boiling point: +95 °C, 0.52 $/mmol[11]) convenient to use, ii) the ester group can be easily further manipulated, iii) whereas acrylate belongs to type II olefin, the 1,1-disubstituted olefin **1a** should fall into the type III olefin for CM with catalyst of type II,[12] and finally iv) the steric hindrance resulting from *gem*-disubstitution along with the electronic deactivation of the alkene by both the fluorine atom and the ester moiety would disfavor the first coordination of the olefin with the precatalyst, preventing the formation of an inactive metal-fluorovinylidene species.

Herein, we reported the unprecedented efficient CM reaction of methyl-2-fluoroacrylate **1a** with Ru-precatalyst, leading to the stereoselective production of trisubstituted fluoroalkenes (Scheme 1.e).

Results and Discussion

Our first attempts were made with three different alkenes, giving high yields in standard CM with methyl acrylate, *para*-bromostyrene **A**,[14] a type I olefin and two allylic alcohols **B** and **C**,[15] type II olefins. None of them led to the formation of the desired compound (Scheme 2).

Taking into account the difficulty of cross-metathesis involving our 1,1-*gem*-disubstituted fluorinated substrate **1a**, we postulated that the introduction of higher flexibility and implicitly less steric hindrance on the olefinic partner would favor the approach of **1a**

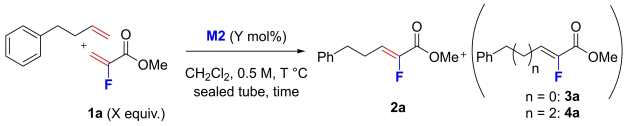


Scheme 2. Preliminary attempts.

on the ruthenium-alkylidene complex and allow the cross-metathesis reaction.[16] Whereas the use of styrene **D** was inefficient, some traces (4%) of the desired product were detected starting from 3-phenyl-prop-1-ene **E** as partner. To our delight, the more flexible 4-phenylbut-1-ene **F** furnished an encouraging 22% ^{19}F NMR yield of the desired product (Scheme 2). This result served as starting point for further optimization of the reaction conditions (Table 1).

Increasing the temperature from 40 °C to 60 °C or 80 °C allowed the formation of the desired product **2 a** in 52% and 58%, respectively (Table 1, entries 1–3). During the course of the reaction, two major side-products **3 a**, with a subtracted carbon, and **4 a**, with an additional carbon, in low percentages, were identified as a result of the alkene isomerization during the CM process.[6,17] Conventional additives,[18] such as benzo-

Table 1. Optimization of the CM reaction.



entry	X (equiv.)	Y (mol%)	T (°C)	Time (h)	Yield (%)[a]	Ratio[b] **2 a**:(**3 a** + **4 a**)
1	1	10	40	15	22	n.d.
2	1	10	60	15	52	82:18
3	1	10	80	15	58	83:17
4	1	1	80	15	61	92:8
5	2	1	80	15	94 (85)	97:3
6	2	1	100	15	74 (69)	95:5
7	2	1	80	1	30	n.d.
8	2	1	80	7	86 (77)	97:3
9[c]	1	1	80	15	Traces	–

[a] Determined by ^{19}F NMR with fluorobenzene as internal standard. Isolated yield into brackets.
[b] Determined by ^{19}F NMR and correlated by GC-FID.
[c] 4 equiv. of 4-phenylbut-1-ene.

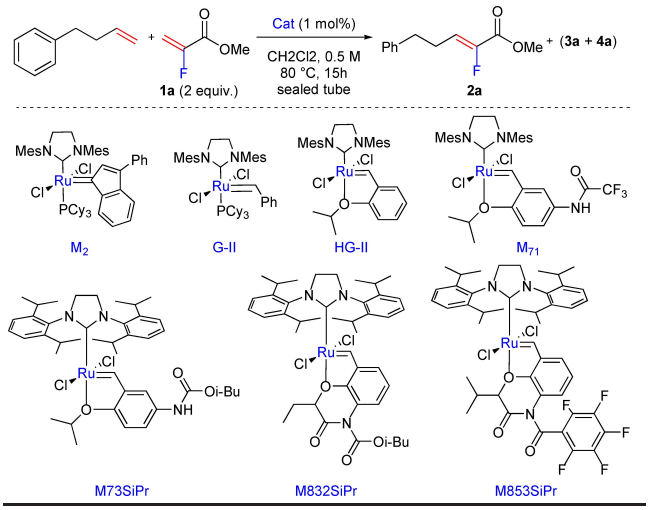
quinone or acetic acid, have been used to circumvent this side-process involving ruthenium hydride species, but the reaction yield decreased without suppressing the formation of compounds **3 a** and **4 a**.[19] Hence, to decrease the formation of these side-products, we decided to reduce the catalyst loading in order to prevent or reduce the formation of ruthenium hydride. With 1 mol% of the precatalyst, a similar yield of the desired product **2 a** was obtained and the side-products were still detected, albeit in lower amount (Table 1, entry 4). Using 2 equiv. of methyl 2-fluoroacrylate **1 a** led to our best results with 94% NMR yield, 85% of isolated yield and a **2 a**:(**3 a** + **4 a**) ratio of 97:3 (Table 1, entry 5). Using more than 2 equiv. of **1 a** did not improve the yield in **2 a**. Increasing the temperature to 100 °C gave a lower yield probably due to the faster decomposition of the catalyst at higher temperature (Table 1, entry 6). The reaction was incomplete after 1 h or 7 h of reaction (Table 1, entries 7–8), showing that this reaction is rather slow but the catalyst is stable in our experimental conditions, as it was still active between 1 h and 15 h.[19] Finally, the use of an excess of non-fluorinated alkene was detrimental for the reaction as only the dimer of the non-fluorinated alkene was produced, whereas no desired product was obtained (Table 1, entry 9).

In the Table 2 are presented selected results obtained with different type 2 precatalysts.[19] In our case the phosphine-containing ruthenium indenylidene precatalyst **M2**[20] proved to be the most active one (Table 2, entry 1). This result differs to the cross-metathesis with acrylate, in which chelating benzylidene-ether precatalyst gave usually better result in CM reaction because no side-reactions triggered by the ancillary PCy_3 ligand could occur.[21] A presumable reason is the poor reactivity of methyl 2-fluoroacrylate **1 a** as Michael acceptor, precluding the formation of poisonous enolate for metathesis from a phospha-Michael addition reaction.[22]

We recently showed, inspired by previous reports,[23] the beneficial effect of an aryl substitution on the fluoroalkene partner in RCM reaction.[24] Indeed, this modification regenerates a more stable ruthenium-arylidene instead of ruthenium-methylidene after a catalytic cycle. So, under the conditions from the entry 5, trisubstituted fluoroacrylates **1 b** ((*Z*)-methyl 2-fluoro-3-phenylacrylate), **1 c** ((*Z*)-methyl 2-fluoro-3-(4-methoxyphenyl)acrylate) and **1 d** ((*E*)-methyl 2-fluoro-3-phenylacrylate), were tested in CM reaction but without success. The increase of the bulkiness should preclude the approach of these substrates **1 b**–**d**, which were categorized as reluctant fluoroalkenes in CM process.[19]

Many other parameters (solvent, temperature, etc.) were screened to optimize the reaction without improvement.[19] Worthy of note that under our optimal reaction conditions, a TON (turnover number) of 85

Table 2. Screening of catalysts.



entry	Cat	Yield (%)[a]	Ratio[b] **2a**:(**3a**+**4a**)
1	M2	94 (85)	97:3
2	G-II	15	–
3	HG-II	77	90:10
4	M71	6	–
5	M73SiPr	72	81:19
6	M832SiPr	–	–
7	M853SiPr	–	–

[a] Determined by ^{19}F NMR with fluorobenzene as internal standard. Isolated yield into brackets.
[b] Determined by ^{19}F NMR and correlated by GC-FID.

was reached, which is unprecedented for the cross-metathesis involving fluoroalkenes. Moreover, the reaction proved to be highly *Z* selective, since no trace of the *E*-isomer of **2a** has been observed in ^{19}F NMR of the crude mixture.[19]

Having settle the optimized reaction conditions, we studied the scope of the reaction (Scheme 3). With terminal alkenes (Scheme 3.a), although side-products **3** and **4** were often produced during the CM process, the desired products **2** were always the major compound with a ratio **2**:(**3**+**4**) varying from 89:11 to 99:1.

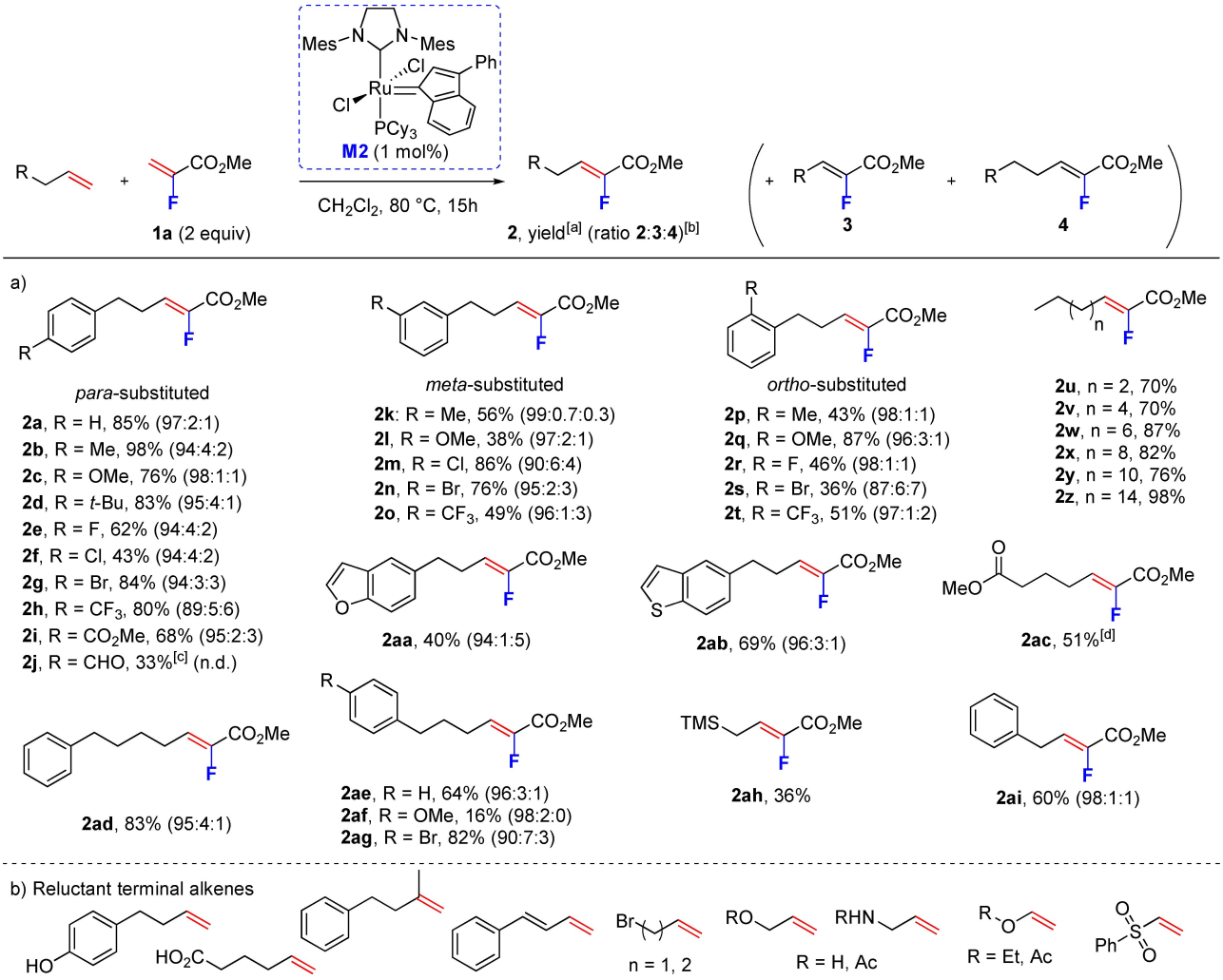
Importantly, whatever the metathesis partner of **1a**, only the *Z*-product **2** was obtained. Pleasingly, different substituents on the aromatic residue of 4-phenylbut-1-ene were suitable for the reaction, whatever its position (*para*, *meta* or *ortho*) and its electron-donating or -withdrawing feature. Interestingly, products bearing a chlorine (**2f**, **2m**) or bromine (**2g**, **2n**, **2s**) atom as well as an ester moiety (**2i**), valuable anchors for further post-functionalizations, were compatible furnishing fair to very good yields (36–86%). Product **2j** containing a relevant carboxaldehyde moiety, was obtained as a 1:1 mixture with the dimer of non-fluorinated olefin partner representing a yield of 33% and 66% for **2j** and the dimer, respectively. The reaction was then extended to aliphatic alkenes, furnishing the desired trisubstituted fluoroacrylates **2u–z** in good to excellent yields without the formation of side-products (70–98%). Heterocyclic derivatives, such as benzofuran or benzothiophene, were also compatible with the CM process leading to the corresponding products **2aa** and **2ab** in 40% and 69% yields, respectively. The methyl 5-hexenoate displayed a fair reactivity furnishing the diester **2ac** with 51% yield. The use of longer alkyl chain (6-phenylhex-1-ene and 5-phenyl-pent-1-ene) was possible, leading to the corresponding products **2ad–ae**, **2ag** in good yields (64–83%), while compound **2af** was surprisingly obtained with a low 16% yield. The use of more constrained 3-phenylprop-1-ene was also suitable leading to the corresponding **2ai** in 60% yield. Conversely, the bulkier allyltrimethylsilane only led to 36% yield in the corresponding **2ah**.

Unfortunately, some substrates remained reluctant in our hand. Alkenes bearing an acidic hydrogen (phenol or carboxylic acid), 1,1-*gem*-disubstituted alkenes, conjugated alkene, allyl-bromide, alcohol or amine (free or acetylated), vinyl-sulfone or -acetate were unreactive probably, for most of them, because of steric congestion (Scheme 3.b).

Importantly, the formation of the homodimer of methyl 2-fluoroacrylate **1a** has never been witnessed, while the homodimer of 4-phenylbut-1-ene was observed, as expected for type I olefin. The latter, known to be able to enter in CM reaction, could indeed be used directly in CM reaction furnishing the desired product **2a** in 58% yield (see Scheme 4.a). From this observation, we carried out the reaction with various cyclic alkenes (Scheme 4.b) as well as internal alkenes (Scheme 4.c).

The use of constrained cyclooctene allowed the ring opening CM with **1a**, the release of the ring strain led to the formation of three compounds incorporating respectively one (**2aj**) or two fluoroalkene moieties (**2ak**, **2al**) in 97% overall yield. Similarly, the ring-opening CM of the more stable cyclohexene occurred, albeit in low yield.[25] Then, the ring-opening CM of cyclododecene only furnished the bis-fluoroacrylate **2ao** in a fair 32% yield.

Finally, we valorized our method using fatty acid esters (Scheme 4.c). Indeed, the use of renewable feedstock in olefin metathesis gave birth to new chemical platforms dedicated to surfactants or polymers.[26] The combination of fluoroacrylate **1a** with renewable raw materials by metathesis could give rise to original and versatile fluorinated building-blocks. The use of 1 equiv. of **1a** with methyl (*Z*)-oleate being not a selective process, we used 2 equiv. of **1a** in order to maximize the yield of the both targeted products. Thus, 75% of α,ω-diester **2ap** could be obtained along with the formation of the monofluoroacrylate **2w** in 55% yield. The geometry of the

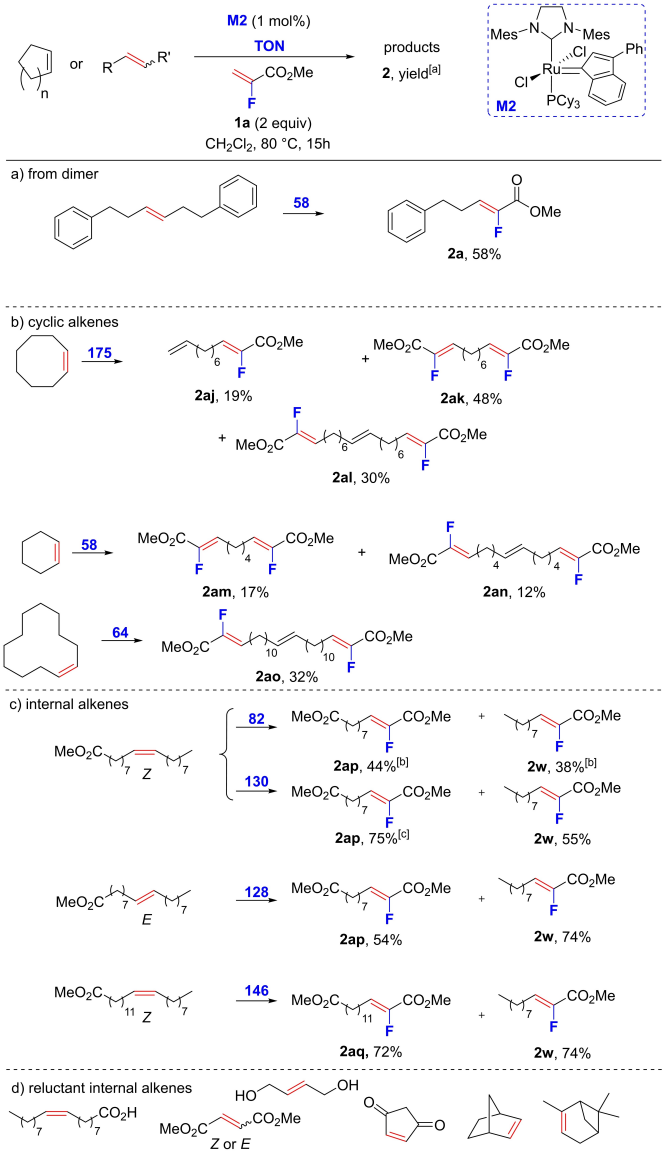


Scheme 3. Scope of the reaction with terminal alkenes. Reaction conditions: alkene (0.25 mmol), **1** (0.50 mmol, 2 equiv.) and **M2** precatalyst (2.5 µmol, 1 mol%) in CH_2Cl_2 (0.5 mL) at 80 °C for 15 h in a sealed tube. n.d., not determined; TON (turnover number) = yield value. [a] Isolated yield in fluorinated compounds (**2** + **3** + **4**). [b] Ratio between products **2**, **3** and **4** was determined by GC/FID. [c] Inseparable mixture of **2 j**/dimer of non-fluorinated olefin partner in 1:1 ratio. [d] Inseparable mixture of **2 ac**/dimer of non-fluorinated olefin partner in 3:1 ratio.

double bond had no influence on the reaction process as the methyl (*E*)-oleate furnished similar results. The use of bigger fatty ester like methyl erucate allowed the formation of both α,ω-diester **2 aq** and monofluoroalkene **2 w** in good 72% and 74% yields, respectively. The fluorinated α,ω-diester **2 ap** and **2 aq** could serve, for example, as relevant monomer for polycondensation and production of polyester and polyamide with new properties.

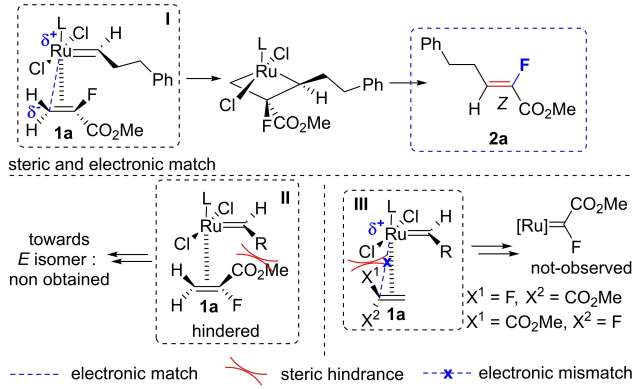
The use of 1,2-disubstituted alkenes bearing acid or alcohol moiety, as well as more constrained internal alkenes proved to be reluctant substrates for the CM reaction (Scheme 4.d).

To explain the high selectivity of our developed process the following scenario was suggested (Scheme 5). After the initiation of the reaction and the formation of the active olefin complex with the less hindered and more electron-rich non-fluorinated alkene, a new alkylidene complex is generated from which several approaches of the fluorinated alkenes, according to the preferential bottom-bound pathway for propagation,[27,28] could be envisioned. For the CM reaction between the 4-phenyl-but-1-ene and the methyl 2-fluoroacrylate **1 a**, the complex **I** is the less hindered and therefore favored, furnishing exclusively the *Z*-product. Moreover, there is also an electronically match between the more electronegative carbon at position 3 of **1 a** (strong π donation from the fluorine atom) and the electron deficient Ru in the $14e^-$ alkylidene complex. Nevertheless, when the hindrance is increased on the alkylidene moiety, the approach of **1 a** is rather unlikely and could explain the lower yield



Scheme 4. Scope of the reaction with internal alkenes. Reaction conditions: alkene (0.25 mmol), **1** (0.50 mmol, 2 equiv.) and **M2** precatalyst (2.5 µmol, 1 mol%) in CH_2Cl_2 (0.5 mL) at 80 °C for 15 h in a sealed tube. n.d., not determined; TON, turnover number. [a] Isolated yield in fluorinated compounds **2**. [b] Results obtained with 1 eq of **1a**. [c] contaminated with 5% of the dimer of methyl oleate.

obtained with the allyltrimethylsilane and the lack of reactivity with even more constrained alkenes. In the complex **II**, the approach is hampered by the steric hindrance between the ester and the R group. The involvement of this complex **II** is unlikely as no trace of *E*-isomer was detected at the end of the reaction. The formation of complex **III** was also disfavored by steric hindrance between the bigger chlorine atom and the fluorine atom or the ester group as well as



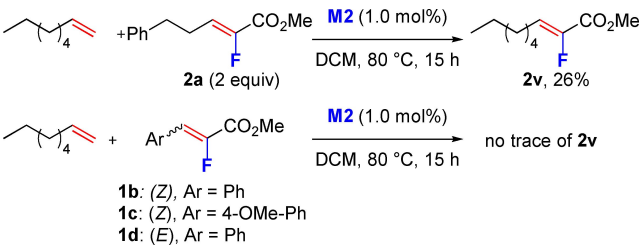
Scheme 5. Proposed bottom-bound olefin complexes.

electronically mismatch. The Ru-fluoroacrylatevinylidene was not observed by NMR analysis.

Interestingly, when trisubstituted **2a** was submitted to the reaction condition with *n*-oct-1-ene as the olefin partner, we could obtain the CM product **2v** in 26% isolated yield (Scheme 6). Although the yield remains low, this experiment showed that the introduction of flexibility on the fluorinated partner allowed a fluoracrylate moiety exchange by CM reaction.[29] By comparison, reaction of 4-phenylbut-1-ene or *n*-oct-1-ene with more constrained **1b–d** did not produce **2a** or **2v**, respectively.[19]

Conclusion

In summary, we reported the first formation of trisubstituted fluoroalkenes by cross-metathesis using methyl 2-fluoroacrylate **1a** as an inexpensive and convenient fluoroalkene source. The reaction was successfully achieved under ruthenium catalysis proving their viability in CM involving fluoroalkene without fast deactivation. The reaction was exemplified on more than forty terminal and internal alkenes, giving exclusively the *Z*-isomer in fair to excellent yields with unprecedented turnover number with fluoroalkene (up to 175). The used catalyst loading of 1 mol% might appear high and consequently TON somehow low, however it is the first time that such low catalyst



Scheme 6. CM of *n*-oct-1-ene with trisubstituted fluoroacrylate.

loading has been used and high TON have been obtained with fluoroalkenes. Nevertheless, some side-isomerization reaction occurred, implying the formation of undesired products in low proportion (ranging from 0 to 11%). Investigations to improve the process with more constrained alkene partner as well as the use of other fluorinated sources are currently under progress and will be reported in due course.

Experimental Section

General Procedure for cross-metathesis with 2-Fluoroacrylate 1a. In a 10 mL oven dried reaction tube, the olefin (0.25 mmol, 1.0 eq.) and the methyl 2-fluoroacrylate **1a** (0.5 mmol, 2.0 eq.) were added under argon atmosphere. Then, 0.5 mL of a prepared catalyst solution of M2 in DCM (5.0 µmol.mL^{-1}, 1.0 mol%) was added and the tube was sealed. The reaction mixture was stirred at 80 °C for 15 hours. After coming back to room temperature, 23 µL of fluorobenzene was added as internal standard. ^{19}F NMR with a d1 parameter of 8 seconds was performed to determine the ^{19}F NMR yield. Then, the crude mixture was purified by flash column chromatography on silica gel to afford the desired product **2**.

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