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Access to Fluorinated Lactams through Ring-Closing Metathesis of Reluctant Fluoroalkenes Promoted by Appropriate Substitution of a Double Bond

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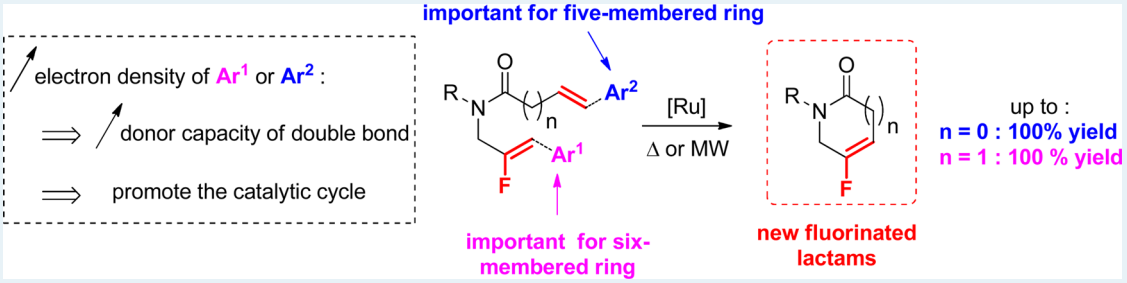
Supporting Information



ABSTRACT: Challenging homogeneous ring-closing metathesis reaction has been developed with reluctant fluorinated substrates. The combination of various parameters, such as the use of fluorinated aromatic solvent and appropriate substitution of the double bonds, allowed us to reach high levels of reactivity, leading to high yields of both new relevant five- and six-membered lactams containing a fluorinated double bond. The electron density of the substituted double bond seems to play a crucial role in the reaction. The formation of six-membered rings proved to be highly efficient, even at low catalyst loading and low temperature.

KEYWORDS: *fluoroalkene, ruthenium, olefin metathesis, N-heterocyclic carbenes*

Organofluorine chemistry is an area experiencing tremendous expansion, and the market for organofluorine fine chemicals keeps growing every year. Fluorinated molecules have applications in almost all areas of science and clearly have a crucial impact on everyday life and on modern societies.[1] Of particular relevance is the emergence of fluoroalkenes, versatile compounds that have found many applications as, for example, peptidomimetics,[2] bioactive compounds,[3] and materials.[4] Different methods have been reported for the synthesis of fluoroalkenes;[5] nevertheless, numerous reactions have limitations, such as narrow substrate scope, the presence of inseparable *E*/*Z* isomers, harsh experimental conditions, moderate yields, or the need for a multistep preparation of the fluorinated reagent, which restrict the further development of these useful building blocks. There is therefore a strong need for new processes that would tackle this major challenge in chemical synthesis.

Of the numerous catalytic reactions allowing the synthesis of olefins and possessing enormous industrial potential, the olefin metathesis reaction stands at the top of the class.[6] Nevertheless, whereas the ring-closing metathesis (RCM) reaction is a well-known powerful and largely developed approach for the preparation of cyclic alkenes, the use of fluoroalkenes as RCM substrates has been scarcely studied, mainly because of the inherent challenges associated with the use of these reluctant substrates.[7] Recently, an astonishing breakthrough has been reported by Dorta's group in the challenging RCM synthesis of bromo- and chloroolefins. The substitution of the reluctant halogenated olefin by a phenyl group allowed achieving high yields in the expected product with only 2−5 mol % of the well-defined Grubbs II catalyst.[8] Applied to the synthesis of fluoroolefin derivatives, this strategy was easy to manage and economically friendly, as discussed later in the article. To date, only six publications[9−11] have reported metathesis reactions on fluoroalkene derivatives limited to a few carbon and nitrogen links between the two alkene moieties, with the highest TON

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of 43 reported by Haufe[10] (Figure 1). It is worthy of note that very few five-membered rings have been synthesized by RCM

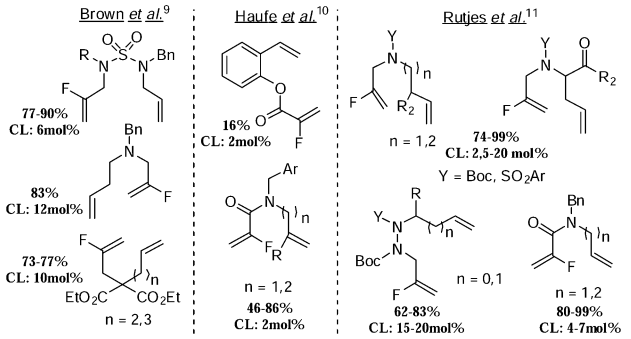
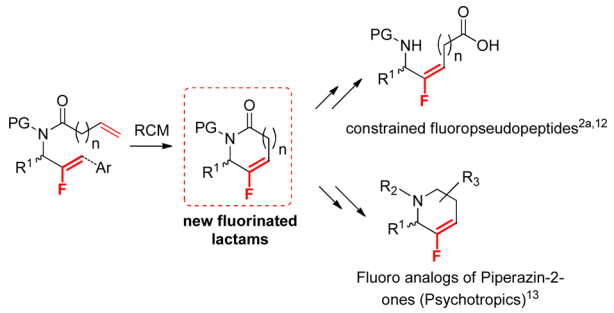


Figure 1. A few examples of fluoroalkenes involved in the RCM reaction with Grubbs II catalyst (% indicates the yield of the reaction; CL = catalyst loading).

reaction, probably due to the low reactivity of the fluoroolefin combined with steric constrain during the metathesis process.

In this Letter, we address the challenges associated with the use of fluoroalkenes in homogeneous RCM reactions toward the production of relevant γ- and δ-lactams. In our substrates, olefin moieties are separated by an amide linker that has, to our knowledge, never been used efficiently in RCM reaction in such a position. Indeed, Haufe discussed the importance of an amide link in vicinal position to the fluoroolefin and in conjugation with the carbonyl moiety for efficiency of the RCM reaction.[10] In our case, the amide link is disconnected from the fluoride vinylic group. Scheme 1 presents the strategy developed and

Scheme 1. Fluorinated Lactams and Potential Applications



some potentialities of the fluorinated intermediates to be further converted into fine fluorine chemicals, such as constrained fluoropseudopeptides[2a,12] or bioactive heterocycles.[13]

First, we investigated the formation of versatile six-membered ring **3** by RCM reaction of substrate **1** under microwave irradiation with 2 mol % of commercially available Umicore M2 complex **4a**,[14] which already has proved its efficiency with reluctant substrates[15] (Table 1). The use of toluene as the solvent appeared to be inappropriate, leading to only 6% yield in **3a** and a lot of side-products (66%). The replacement of toluene by its fluorinated analogue, octafluorotoluene, allowed us to significantly enhance the yield of the reaction to 40% along with a decrease in the formation of side-products (entry 1). This result constitutes another proof of the synergistic effect between fluorinated aromatic solvents and a second-generation catalyst for RCM reaction.[16]

The use of a higher temperature (140 °C) or a higher concentration (0.4 M) favored the formation of side products, as did longer reaction times (see SI for full list of experiments). The decrease in the concentration was highly beneficial with almost no side reactions and better catalytic activity (entry 2). Doubling the catalyst loading to 4 mol % under diluted conditions (0.02 M), allowed attaining 88% yield in **3a** with only 7% side products (entry 3). Amazingly, in a dilute system, under conventional heating with 4 mol % catalyst loading, only 2% side products was generated, resulting in a high yield of 98% in **3a** (entry 4), better than that observed under microwave irradiation.

To further improve the process, we next decided to modify the substrate to increase its reactivity[8,17] on the basis of relevant works reported by Grubbs[17a,b] and Dorta,[8] who have shown that convenient substitution of the terminal olefin could be highly beneficial for the efficiency of the reaction by regenerating, at the end of each catalytic cycle, a more stable Ru-alkylidene instead of the Ru-methylidene that is formed in the case of a terminal alkene. Thus, we synthesized a set of substrates substituting the terminal position of the fluoroolefin with an aryl moiety in the *Z* configuration following a five- or six-step procedure[18] from arylaldehyde (see the Supporting Information for the synthesis of the substrates).

As shown in Table 1, the reaction carried out with **2a** gave improved results (entry 5) in comparison with those previously obtained with **1** (entry 1). Indeed, a full conversion was obtained, leading to a high yield in **3a** (87%) along with lesser amounts of side products (13%). We next screened the temperature, the catalyst loading, and the dilution with substrate **2a**. The best results were obtained at a concentration of 0.02 M, affording a complete conversion, even at rather low temperature (80 °C) with a catalyst loading as low as 1 mol % (TON = 100), which constitutes the best TON ever reported with fluoroalkenes (entry 6).

Even at a lower temperature (70 °C), a full conversion has been obtained, but at the expense of a higher catalyst loading (2 mol %) (entries 7, 8). The transposition to conventional heating afforded similar results, with a full cyclization at 80 °C (entry 9). The RCM of substrate **2b** bearing a *p*-methoxybenzyl (PMB) as an N-protecting group was also successful, giving similar results (entries 10, 11).

The contribution of the phenyl substitution to the fluorinated double bond appeared to be tremendous for the formation of six-membered ring **3a**. Indeed, the use of trisubstituted **2** instead of disubstituted **1** afforded excellent results with one-fourth the catalyst amount and especially with a decrease in the temperature of 50 °C. The protocol used for the synthesis of a trisubstituted fluoroalkene such as **2** was easy to manage, compared to gem-disubstituted α-fluoroalkenes,[5] and could be performed on a large substrate set with inexpensive fluorinated reagents, which constitutes another main advantage of this substitution methodology for RCM of fluoroalkenes.

To have insight into the influence of the phenyl ring substitution, a kinetic study was performed at 70 °C to follow the formation of **3a** starting from RCM precursors **1**, **2a**, **5a**, and **5c** (Figure 2a). This study showed that a precursor bearing an electron-withdrawing group, such as CF_3 (**5a**), was less efficient than **2a**. Interestingly, the most reactive substrate was the electron-donating substituted **5c**. Compared with non-substituted substrate **1**, this study confirmed the beneficial influence of the use of substituted fluoroolefin **2**, which

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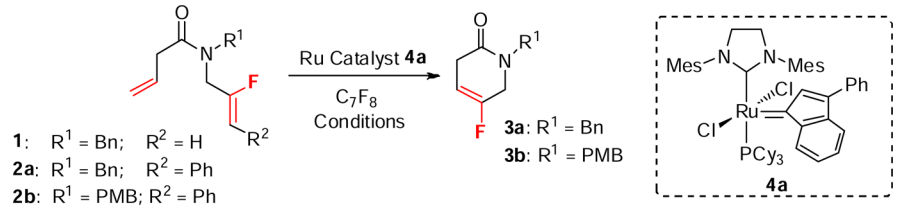
Table 1. RCM Leading to Six-Membered Ring 3



entry	substrate	concn, M	4a (mol %)	conditions[a]	side products (%)[b]	yield (%)[c]
1	**1**	0.2	2	120 °C, MW	26	41
2	**1**	0.02	2	120 °C, MW	1	46
3	**1**	0.02	4	120 °C, MW	7	88
4	**1**	0.02	4	reflux[d], Δ	2	98
5	**2a**	0.2	2	120 °C, MW	13	87
6	**2a**	0.02	1	80 °C, MW	0	100
7	**2a**	0.02	2	70 °C, MW	0	100
8	**2a**	0.02	1	70 °C, MW	0	20
9	**2a**	0.02	2	80 °C, Δ	0	100 (86)[e]
10	**2b**	0.02	2	80 °C, MW	0	100
11	**2b**	0.02	2	80 °C, Δ	0	100 (100)[e]

[a]MW (microwave irradiation, 15 min, 200W) or Δ (conventional heating, 30 min). [b]Percent of side products refers to numerous undesired not-characterized compounds produced during the RCM process. [c]Yields were determined by ^{1}H NMR spectroscopy using 2,4-dinitrofluorobenzene as internal standard. [d]C_7F_8, bp = 105 °C. [e]Isolated yield.

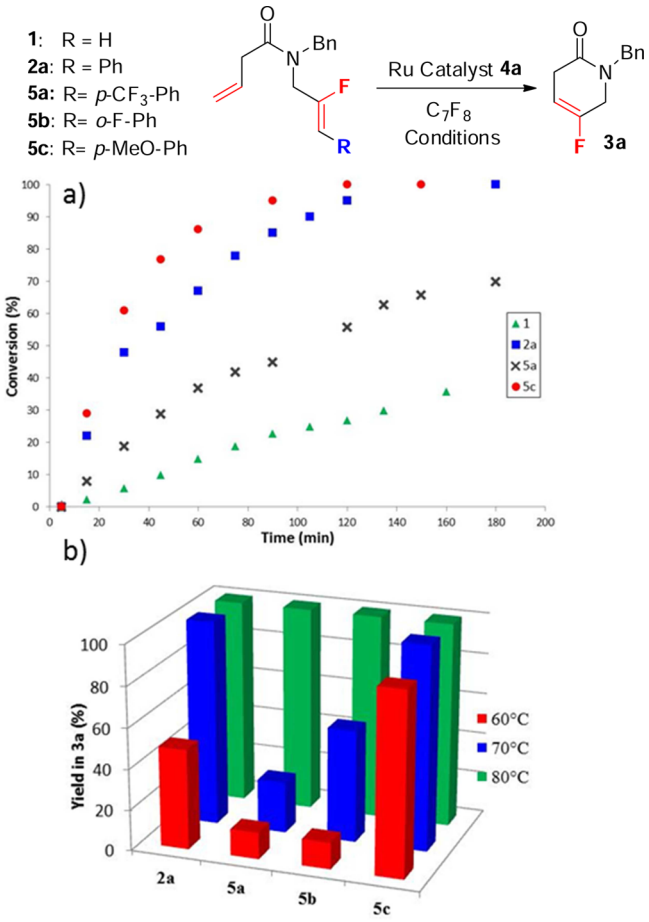


Figure 2. (a) Kinetic study with fluorinated RCM precursors (70 °C, 2 mol % of **4a**, 0.02 M); (b) RCM leading to **3a** with EWG- and EDG-substituted *Z*-phenylated precursors (*T* °C, 15 min MW (200 W), 2 mol % of **4a**, 0.02 M).

generates a more stable and active Ru-arylidene catalyst upon each catalytic cycle. On the basis of this kinetic study, we decided to test the efficiency of these precursors in the RCM reaction at various temperatures (60, 70, and 80 °C, Figure 2b). All substrates proved to be highly reactive at 80 °C; however, at lower temperature, both substrates bearing electron-withdrawing groups (CF_3 or F; **5a** and **5b**) appeared to be significantly less reactive in comparison with their phenylated or methoxyphenylated counterparts (**2a** and **5c**). This difference in reactivity was more pronounced at 60 °C because only the electronically enriched fluoroolefin **5c** proved to be reactive, yielding **3a** in 91%.

Recently, Plenio reported a nice study in line with our results pointing out the higher stability of catalyst containing an electron-donating group, which prevents the catalyst deactivation compared with electron-withdrawing congeners.[19] In addition to the beneficial generation of more stable catalyst, the electron density of the fluoroalkene should also play a crucial role in the reaction. The electron-donating group *p*-methoxy gave improved reactivity compared with electron-withdrawing derivatives and a simple phenyl group, probably thanks to the enhancement in the electron density on the fluoroalkene partner that increases its donor capacity as a ligand and its ability to enter in the catalytic cycle, favoring and promoting the formation of the second metallacyclobutane. This is the first time, to our knowledge, that this observation has been reported from a substrate.

Encouraged by these satisfactory results obtained in the formation of the versatile six-membered rings, we decided to study the RCM reaction for the production of five-membered ring **9** (Table 2). As expected, a higher ring strain resulted in a more difficult cyclization than for the 6-membered ring. Indeed, application of the optimized conditions determined for substrate **1** to precursor **6** gave only 18% yield for a similar level of side product formation (entry 1). Better results with this precursor were obtained through the increase in the catalyst loading to 10 mol % (entry 2), leading to 80% yield in **9**. Under reflux of the solvent, as expected, the decrease in

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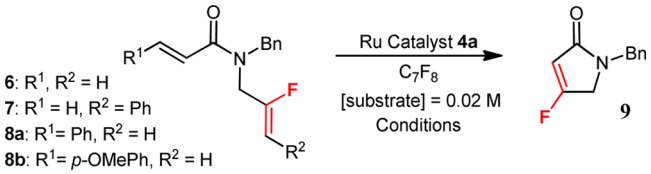
Table 2. RCM of Five-Membered Ring Precursors



entry	substrate	4a (mol %)	conditions[a]	side products (%)[b]	yield (%)[c]
1	**6**	4	120 °C, MW	7	18
2	**6**	**10**	120 °C, MW	0	80
3	**6**	10	**reflux**[d], 60 min, **Δ**	33	41
4	**6**	**2 × 5**	reflux[d], 2 × 15 min, **Δ**	0	70
5	**6**	**3 × 5**	reflux[d], 3 × 5 min, **Δ**	20	80 (75)[e]
6	7	10	120 °C, MW	19	66
7	**8a**	10	120 °C, MW	0	100
8	**8a**	**6**	120 °C, MW	0	97
9	**8a**	4	120 °C, MW	0	80
10	**8b**	4	120 °C, MW	0	100
11	**8b**	2	120 °C, MW	0	57

[a]MW (microwave irradiation, 15 min, 200W) or Δ (conventional heating). [b]Percent of side products refers to numerous undesired not-characterized compounds produced during the RCM process. [c]Yields were determined by ^{1}H NMR spectroscopy using 2,4-dinitrofluorobenzene as internal standard. [d]C_7F_8, bp = 105 °C. [e]Isolated yield.

temperature resulted in a decrease in yield (entry 3). To circumvent the deactivation due to the lower temperature, split additions of catalyst **4a** were performed, allowing attainment of a high yield, up to 80% in **9** (entries 4−5). In contrast with what was observed in the case of six-membered ring **3a**, trisubstituted fluoroolefin **7** did not give better results than substrate **6** (entry 6), perhaps because reaction of the precatalyst at the nondeactivated olefin generates a sterically hindered metallacyclobutane as a result of the inherent constrained geometry of the five-membered lactam precursor.

Taking into account this problem, we tried to favor the first step[20] of the catalytic cycle by stabilizing the poorly reactive terminal olefin (deactivated by electronwithdrawing effect of the carbonyl moiety), hoping for an improvement in both the reactivity and the catalyst stability in the media. For that purpose, we synthesized precursors **8** by simply coupling an appropriate amine with (*E*)-cinnamic acid derivatives. As a matter of fact, the substitution of olefin **8a** seemed to favor the first step of the catalytic cycle, furnishing the five-membered ring **9** in 100% yield with a 10 mol % catalyst loading (entry 7). This phenyl substitution of the nonfluorinated terminal olefin allowed us to decrease the catalyst loading from 10 to 6 and even to 4 mol % with still high yields in **9** (entries 8−9). This result clearly indicated that the RCM process for the production of **9** involving the cyclization between 1,2-disubstituted and gem-disubstituted olefins was more efficient than between terminal and gem-disubstituted olefins, which is quite unusual and rather difficult to explain at the moment. In this case, the phenyl substitution did not play a role in the regeneration of a more active catalyst after a turnover.

Although it is difficult to deconvolute the electronic and steric effects provided by the phenyl group, this study showed that an appropriate substitution of olefin partners can lead to an improvement of the RCM process, which constitutes an original breakthrough for this reaction. To go further, we synthesized precursor **8b** bearing an electron-donating *p*-methoxy group to boost the electron density of the alkene and favor the reaction. The result is astonishing because it has been possible to reach quantitative yield with this electronically enriched substrate with only 4 mol % as catalyst loading and 57% yield with only 2 mol % as catalyst loading.

In summary, we have developed efficient homogeneous conditions for the RCM reaction of various fluorinated substrates in which the alkene partners are for the first time linked by an amide fragment not conjugated to the fluoroalkene. The syntheses of relevant six- and five-membered rings were performed in quantitative yields under microwave or conventional heating conditions. The use of trisubstituted fluoroolefins proved to be a nice strategy for the production of the six-membered ring to promote the reaction under mild conditions, that is, 80 °C and even 70 °C with low catalyst loading, results that are clearly unprecedented.

During this study, we have also investigated the influence of electron-donating and -withdrawing groups on the phenylated fluoroalkene. We have shown, for the first time, the beneficial effect of a substrate bearing an electron-donating group in the catalytic process, which allowed the reaction to occur efficiently at a temperature as low as 60 °C.

Moreover, interestingly, the design of new substrates allowed us to succeed in the formation of a highly constrained five-membered ring through the substitution of the nonfluorinated olefin, which is the first to enter in the catalytic cycle. All together, these results indicated that the modification of the substrates, not only at the most deactivated olefin, could lead to a significant improvement of the metathesis process. Whereas numerous of studies about tuning the catalyst have been done so far, these results pave the way to a further methodological study (mechanistic insight, DFT calculations, etc.) and prove that an appropriate structural modification of the substrate can have a huge impact on the RCM process.

■ ASSOCIATED CONTENT

Supporting Information

Details concerning materials, full experimental procedures, substrates syntheses, full RCM optimization tables and kinetic experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(20) The high stability of fluorocarbene complexes (see ref 7) combined with deactivation of the double bond by the fluorine atom preclude the first coordination of the precatalyst with the fluoroalkene as a plausible scenario for RCM process. A control experiment carried out with a bisfluoroalkene ($(CF{=}CH{-}CH_2)_2{-}NBn$) led to complete recovery of the substrate and degradation of the catalyst in the media.