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Synthesis of vinyl fluorides by ring-closing metathesis

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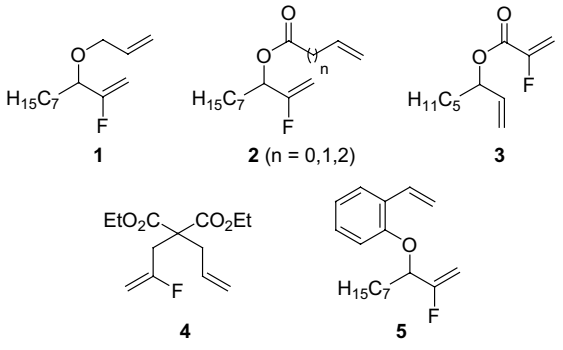
Abstract—The first ring-closing olefin metatheses of alkenyl α-fluoroacrylamides or acrylates incorporating a fluorinated double bond are reported. Several *N*-benzyl-*N*-alkenyl-α-fluoroacrylamides were cyclized in the presence of 2 mol% of Grubbs II catalyst at room temperature to form an unsaturated γ-lactam, and at 80 °C to form the corresponding δ-lactams bearing a fluoro vinyl moiety. At elevated temperature, cyclization of an *N*-methallyl 2-fluoroacrylamide to form a fluorinated, tetrasubstituted double bond was achieved. Similarly, 3-fluorocoumarin was prepared from (2-vinylphenyl)-α-fluoroacrylate.

Vinyl fluorides are versatile building blocks and are widely used in organic and medicinal chemistry, for example, as isosteres of peptides or amides.[1] Recently, synthesis of different types, particularly of terminal vinyl fluorides has been reviewed.[2] In principle, internal fluoro-substituted double bond systems should be accessible either by intermolecular cross-coupling metathesis (CM)[3] of a 2-fluoroalkene and an α-olefin or, for cyclic systems, by intramolecular ring-closing metathesis (RCM) of monofluorinated α,ω-dienes.[4] However, no example of this type of C=C-bond formation was known until very recently.[5] In 2000, Grubbs and co-workers[6] reported their unsuccessful attempts to cross-couple vinyl halides with olefins. Earlier, Beauchamp et al. speculated about the metathesis of directly fluorinated olefins with nickel or manganese complexes[7] and experiments by Grubbs and co-workers[8] to incorporate a 1,1-difluoroethylene in a metathesis reaction led to a stable ruthenium difluorocarbene complex. A recent paper by Chao and Weinreb[9] on the synthesis of vinyl chlorides by RCM led us to report our results on ring-closing olefin metathesis involving fluorinated double bonds.[10]

Unsaturated fluorinated carbocycles bearing fluorine substituents in positions remote from the double bond have already been prepared by RCM.[6,11] Our first attempts to synthesize vinyl fluorides by this methodology were not successful. Reactions of the ether **1** and esters **2** of 2-fluorodec-1-en-3-ol, which is available in a three-step synthesis starting from dec-1-ene,[12] in the presence of 2 mol% of Grubbs' II or Hoveyda's catalysts resulted in very slow reactions and if any, only minor amounts of homodimeric[3b] products were detected. These compounds were formed in reactions of the non-fluorinated double bonds. Products of RCM were not detected, while similar non-fluorinated dienes are known to cyclize in moderate to good yields using the same catalyst.[13]



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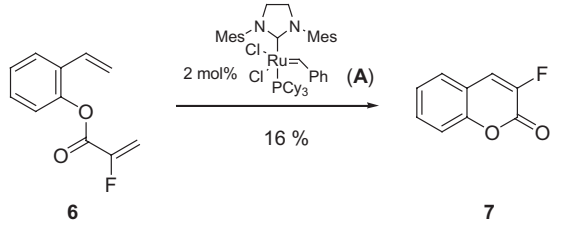
Also the reverse substitution pattern, namely the oct-1-en-3-yl ester of α-fluoroacrylic acid **3**, could not be cyclized in the presence of Grubbs' or Hoveyda's metathesis catalysts.

It was also shown that the corresponding carbocycles could not be synthesized and that the Thorpe–Ingold effect did not help to force a RCM reaction with the fluorinated 1,6-diene **4**, even though the cyclization of the corresponding non-fluorinated compound was successful in high yields using different Ru-catalysts.[14]

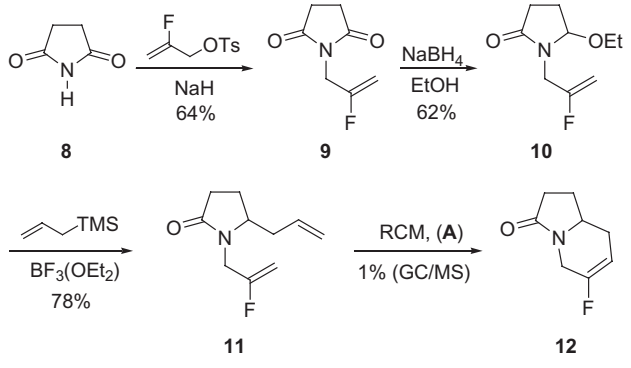
Furthermore, attempts to profit from the effect of a rigid aromatic system, were not successful in the case of the 2-fluorodecenyl ether of *o*-vinyl phenol **5**, which did not lead to the expected fluorinated dihydrobenzopyran derivative. In contrast, a rigid backbone was helpful in the reaction of the α-fluoroacrylate **6** to give 3-fluorocoumarin **7** (16% isolated yield) in a Grubbs II (**A**) catalyzed RCM reaction.[15] Additionally, 44% of a homodimer involving the non-fluorinated double bonds was isolated (Scheme 1).[15]



Scheme 1. RCM to 3-fluorocoumarin **7**.

In attempts to favor the RCM product, we performed high dilution experiments. However, from 0.5 M down to 0.05 M solutions there was no significant change in the product ratio.

We then carried out experiments with nitrogen heterocycles. In analogy to the non-fluorinated system,[16] we synthesized the monofluorinated metathesis precursor **11** according to Scheme 2.

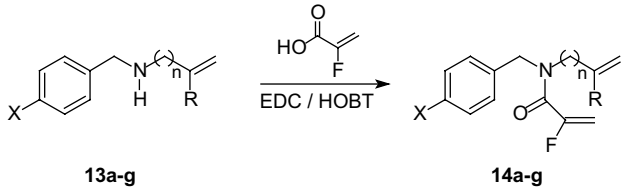


Scheme 2. Synthesis of amide **11** as an RCM precursor.

Alkylation of succinimide **8** with 2-fluoropropenol tosylate gave the imide **9**, which was reduced to the aminal derivative **10**. Allylation with allyl trimethylsilane gave the monofluorinated 4-aza-1,7-diene **11**. Treatment of this compound with 2 mol% of Grubbs II catalyst **A**, in contrast to the corresponding reaction of the non-fluorinated parent compound,[16] gave only traces of the RCM product **12**.

This low-yielding reaction and our experience with different ester-type α,ω-diene systems (see above) demonstrated that vinyl fluorides that are part of an α,β-unsaturated carbonyl system seem to be more suitable for RCM reactions. Therefore, in the following investigations, we focused on α-fluoroacrylamides, which have a decreased π-electron density about the fluorinated double bond.

Several examples of RCM reactions of *N*-alkenyl acrylamides[17] and the corresponding allylglycine derivatives[18] have been reported and used in the frame of natural product synthesis.[19] In several cases reactions with *N*-protected compounds of this type were more successful.[20] We synthesized a number of terminal *N*-alkenyl-*N*-benzyl-α-fluoroacrylamides **14**[21] by acylation of compounds **13** with α-fluoroacrylic acid (Scheme 3). Some derivatives bearing fluorine or a methoxy group in the phenyl ring of the protecting group were also prepared (Table 1).



Scheme 3. Synthesis of *N*-alkenyl-*N*-benzyl-α-fluoroacrylamides **14**.

The compounds **14** were reacted in the presence of 2 mol% of Grubbs II catalyst (**A**) to give good yields of the unsaturated fluorinated γ-lactam **15a** at room temperature and of the corresponding δ-lactams **15b**,**f** and **15g** at 80 °C.[22] Conversion was >95% in all cases. Pure products were isolated in 76–86% yields (Table 1). Corresponding seven and eight-membered *N*-heterocycles were not formed under identical conditions, while related non-fluorinated medium-sized rings could be synthesized (Scheme 4).[19]

Scheme 4. RCM of *N*-alkenyl-*N*-benzyl-α-fluoroacrylamides **14**.

Furthermore, the *N*-methallyl-2-fluoroacrylamide **14e** could be cyclized under the same conditions to form the γ-lactam **15e**[22] with a fluorinated tetrasubstituted double bond in 46% isolated yield.

Table 1. Formation and RCM reactions of *N*-alkenyl-*N*-benzyl-α-fluoroacrylicamides **14**

Entry	Educts **13**	R	X	*n*	Products **14**	Yield [%]	Time [min]	Temperature [°C]	Products **15**	Yield [%]
1	**13a**	H	H	1	**14a**	70	10	rt	**15a**	79
2	**13b**	H	H	2	**14b**	48	120	80	**15b**	86
3	**13c**	H	H	3	**14c**	52	240	80	**15c**	Not detected[a]
4	**13d**	H	H	4	**14d**	52	240	80	**15d**	Not detected[a]
5	**13e**	CH_3	H	1	**14e**	77	480	80	**15e**	46
6	**13f**	H	OMe	2	**14f**	73	240	80	**15f**	81
7	**13g**	H	F	2	**14g**	57	240	80	**15g**	76

[a] Only a homodimeric product involving the non-fluorinated double bond was found.

In conclusion, the first ring-closing olefin metatheses of alkenyl α-fluoroacrylamides or acrylates incorporating fluorinated double bonds were realized. These reactions seem to profit from the combined but opposite action of fluorine and the carbonyl group on the electronic properties of the double bond. We are continuing our investigations in this direction.

Typical procedure for RCM reactions of α-fluoroacrylamides: In a flame-dried Schlenk tube *N*-but-4-enyl-*N*-benzyl-2-fluoroacrylamide **14b** (163.3 mg, 0.7 mmol) in dry toluene (1.4 mL) was degassed under argon before Grubbs II catalyst (**A**) (11.9 mg, 2 mol%) was added. After the mixture had been heated at 80 °C for 2 h, the solvent was removed under reduced pressure and the black residue was purified by column chromatography (diethyl ether) to give 123 mg (86%) of pure colorless crystals of compound **15b**.

Acknowledgements

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References and Notes

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15. Spectroscopic data of **7**: ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 7.13–7.65 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): δ 116.7 (d, C-8), 118.0 (s, $^3J_{C,F} = 3.7$ Hz, C-4a), 121.1 (d, $^2J_{C,F} = 16.4$ Hz, C-4), 125.2 (d, C-6), 127.7 (d, $^4J_{C,F} = 6.2$ Hz, C-5), 130.7 (d, C-7), 146.5 (s, $^1J_{C,F} = 259.1$, C-3), 147.6 (s, C-8a), 154.2 (s, $^2J_{C,F} = 32.9$ Hz, C-2). ^{19}F NMR ($CDCl_3$, 282 MHz, ppm): δ −129.8 (d, $^3J_{F,H} = 9.9$ Hz).
Spectroscopic data of the 'homodimer': ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 5.54 (dd, $^3J_{H,F} = 12.9$ Hz, $^2J_{H,H} = 3.3$ Hz, 2H, H_{cis}), 5.94 (dd, $^3J_{H,F} = 42.6$ Hz, $^2J_{H,H} = 3.3$ Hz, 2H, H_{trans}), 7.13–7.65 (m, 10H); ^{13}C NMR ($CDCl_3$,

75 MHz, ppm): δ 104.6 (t, $^2J_{C,F} = 15.0$ Hz, =CH_2), 122.4 (d), 124.5 (d), 126.8 (d), 127.1 (d), 129.0 (d), 129.6 (d), 147.6 (s), 152.7 (s, $^1J_{C,F} = 260.3$ Hz, =C–F), 158.5 (s, $^2J_{C,F} = 36.8$ Hz, C=O); ^{19}F NMR ($CDCl_3$, 282 MHz, ppm): δ −116.8 (dd, $^3J_{F,H} = 12.4$ Hz, $^3J_{F,H} = 42.6$ Hz).

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21. Spectroscopic data of **14b**: ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 2.32 (dt, $^3J_{H,H} = 7.2$ Hz, $^3J_{H,H} = 7.2$ Hz, 2H), 3.37 (t, $^3J_{H,H} = 7.2$ Hz, 2H), 4.62 (s, 2H), 5.05 (dd, $^2J_{H,H} = 1.5$ Hz, $^3J_{H,F} = 18.6$ Hz, 1H, H_{cis}), 5.08 (m, 2H), 5.30 (d, $^3J_{H,F} = 47.4$ Hz, 1H, H_{trans}), 5.73 (m, 1H), 7.23–7.37 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): δ 30.9 (t), 47.0 (t), 49.1 (t), 99.3 (t), 117.1 (t), 127.6 (d), 128.6 (d), 128.7 (d), 134.3 (d), 136.4 (s), 157.9 (s, $^1J_{C,F} = 274.4$ Hz, C-F), 162.5 (s, $^2J_{C,F} = 30.7$ Hz); ^{19}F NMR ($CDCl_3$, 282 MHz, ppm): δ −104.2 (d, $^3J_{F,H} = 38.8$ Hz), −105.6 (d, $^3J_{F,H} = 38.8$ Hz).
Spectroscopic data of **14e**: ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 1.69 (s, 3H), 3.87 (s, 2H), 4.58 (s, 2H), 4.81 (s, 1H, H_{cis}), 4.97 (s, 1H, H_{trans}), 5.10 (dd, $^2J_{H,H} = 3.5$ Hz, $^3J_{H,F} = 17.1$ Hz, 1H, H_{cis}), 5.31 (dd, $^2J_{H,H} = 3.3$ Hz, $^3J_{H,F} = 47.4$ Hz, 1H, H_{trans}), 7.24–7.35 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): δ 19.8 (q), 47.9 (t), 52.6 (t), 99.2 (t, $^2J_{C,F} = 17.3$ Hz), 112.9 (t), 127.6 (d), 128.3 (d), 128.6 (d), 136.2 (s), 139.6 (s), 157.5 (s, $^1J_{C,F} = 271.8$ Hz, C-F), 162.7 (s, $^2J_{C,F} = 32.9$ Hz); ^{19}F NMR ($CDCl_3$, 282 MHz, ppm): δ −103.9 (d, $^3J_{H,F} = 45.1$ Hz), −104.5 (d, $^3J_{F,H} = 45.1$ Hz, $^3J_{F,H} = 11.6$ Hz).
22. Spectroscopic data of **15b**: ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 2.37 (m, 2H), 3.33 (t, $^3J_{H,H} = 7.0$ Hz, 2H), 4.63 (s, 2H), 5.99 (dt, $^3J_{H,H} = 4.5$ Hz, $^3J_{H,F} = 10.5$ Hz, 1H), 7.25–7.37 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): δ 21.3 (t, $^3J_{C,F} = 6.4$ Hz), 44.6 (t), 49.8 (t), 112.7 (d, $^2J_{C,F} = 15.1$ Hz), 127.7 (d), 128.1 (d), 128.1 (d), 136.7 (s), 149.9 (s, $^1J_{C,F} = 251.2$ Hz, C–F), 159.8 (s, $^2J_{C,F} = 30.3$ Hz); ^{19}F NMR ($CDCl_3$, 282 MHz, ppm): δ −127.1 (m).
Spectroscopic data of **15e**: ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 1.91 (d, $^3J_{H,F} = 2.1$ Hz, 3H), 3.61 (d, $^3J_{H,F} = 5.7$ Hz, 2H), 4.59 (s, 2H), 7.22–7.36 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): δ 9.6 (q), 46.5 (t), 48.9 (t, $^3J_{C,F} = 5.0$ Hz), 124.3 (s, $^2J_{C,F} = 4.9$ Hz), 127.7 (d), 128.0 (d), 128.8 (d), 136.5 (s), 148.2 (s, $^1J_{C,F} = 267.6$ Hz, C-F), 163.4 (s, $^2J_{C,F} = 30.3$ Hz); ^{19}F NMR ($CDCl_3$, 282 MHz, ppm): δ −147.4 (s).