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Synthesis of Heterocyclic and Carbocyclic Fluoro-olefins by Ring-Closing Metathesis

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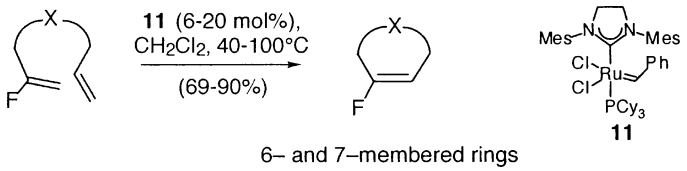
ABSTRACT



Ring-closing metathesis (RCM) of vinyl fluoride-containing dienes in the presence of ruthenium alkylidene carbene complex 11 proceeded efficiently to give six- and seven-membered cyclic vinyl fluorides. The RCM reaction was used to prepare amine- and sulfamide-linked cycloolefins, as well as carbocyclic systems, from a simple commercial fluoro-olefin.

Fluoro-olefins have been recognized as hydrolytically stable, nonclassical isosteric replacements for the carboxamide group.[1] In contrast to simple double bonds, which are generally considered to behave as noninteracting conformationally constrained spacers,[2] fluoro-olefins have been suggested as superior isosteric replacements and are therefore of considerable interest in the synthesis of peptidomimetics and other biologically active molecules.[3] Consequently, mild and general methods that allow the straightforward introduction of fluorinated double bonds into acyclic and cyclic systems would constitute valuable synthetic methods.[4] Here we describe our preliminary studies concerning the ring-closing metathesis (RCM) reactions of monofluorinated dienes linked by various carbon and heteroatom-containing chains to provide cyclic vinyl fluorides.[5]

Initial investigations focused on the RCM reactions of sulfamide-linked diene substrates, as these provided the seven-membered cyclic scaffold present in a series of highly potent HIV protease inhibitors (Figure 1).[6] Indeed, Hanson

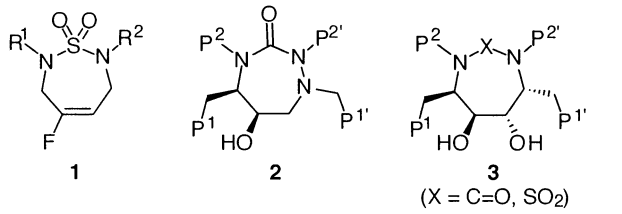


Figure 1. Structure of sulfamide fluoro-olefin RCM products and related small-molecule HIV protease inhibitors.

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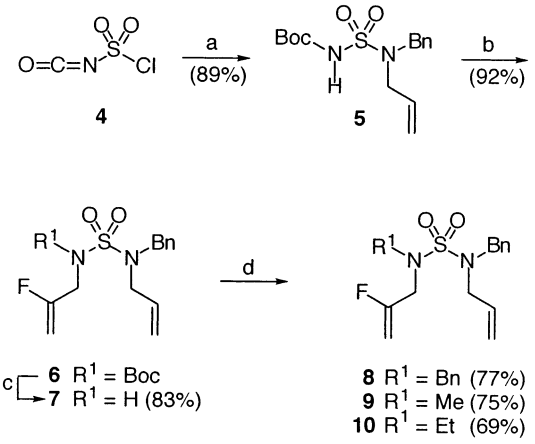
et al. had previously demonstrated that analogues of the cyclic sulfamide protease inhibitors could be prepared efficiently by a RCM-based approach,[7,8] and we felt that extension of the method to fluoro-olefins might provide access to novel analogues with potentially interesting properties. Impetus for the synthesis of fluorinated seven-membered sulfamides was augmented further by the fact that previous efforts to interconvert hydroxyl groups to halogens in cyclic HIV protease inhibitors **3** had been complicated by ring-contraction reactions.[9]

Sulfamide-linked RCM precursors were prepared using established procedures,[10] the only point of note being the relatively low reactivity of 1-chloro-2-fluoroprop-2-ene as an alkylating agent (Scheme 1). This minor complication in the synthesis was readily resolved by conversion of the chloride to the corresponding allylic iodide, either in situ or prior to the reaction.

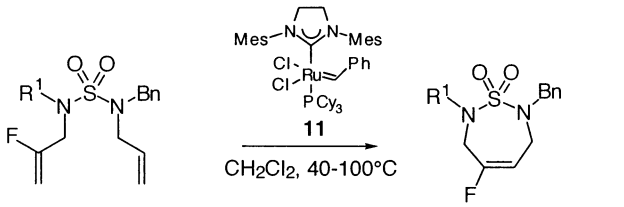
Scheme 1[a]



[a] Reagents: (a) *t*-BuOH, CH_2Cl_2, Et_3N, then allylbenzylamine; (b) $CH_2{=}CFCH_2Cl$, NaI, *t*-BuOK, THF; (c) TFA, CH_2Cl_2; (d) *t*-BuOK, THF, BnBr/MeI/EtBr, rt.

RCM was first carried out on the Boc-protected sulfamide **6**, which cyclized smoothly (3 h) in refluxing CH_2Cl_2 with 6 mol % ruthenium complex **11** (Scheme 2). The monosubstituted sulfamide **7** also underwent ring-closure in refluxing CH_2Cl_2 (7 h), whereas the *N*-alkyl sulfamides **8**−**10** were slower to cyclize and required higher temperatures. We found it convenient to use sealed, crimped-cap vials immersed in a heated bath at 100 °C, retaining CH_2Cl_2 as the solvent. It is noteworthy that no special high-dilution conditions were required to avoid cross-metathesis, and all of the desired N,N′-disubstituted sulfamides were obtained in good to excellent yields.[11] The difference in reaction rates between the Boc-, H-, and alkyl-substituted sulfamides is not immediately apparent but may be a consequence of conformational preferences of the intermediate ruthenium alkylidene complexes.

Scheme 2. RCM Reactions of Sulfamides



6 R^1 = Boc
7 R^1 = H
8 R^1 = Bn
9 R^1 = Me
10 R^1 = Et

12 R^1 = Boc (90%)
13 R^1 = H (79%)
14 R^1 = Bn (78%)
15 R^1 = Me (77%)
16 R^1 = Et (85%)

During the course of this work, literature searches failed to reveal any previously successful examples of RCM of fluoro-olefins to give cyclic vinyl fluorides. However,

(3) For general reviews of peptidomimetics: Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789. Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699. Gainnis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244.

(4) For reviews on the synthesis of fluoro-olefins: Gouverneur, V.; Greedy, B. *Chem. Eur. J.* **2002**, *8*, 766. Taylor, S. D.; Kotoris, C. C.; Hum, G. *Tetrahedron* **1999**, *55*, 12431. Silvester, M. J. *Aldrichimica Acta* **1995**, *28*, 45. See also ref 1 for selected examples.

(5) For general reviews of olefin metathesis: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. (b) Schuster, M.; Blechert S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2037. (c) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (d) Phillips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75. (e) Fürstner A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (f) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900.

(6) For a review of cyclic HIV protease inhibitors: De Lucca, G. V.; Erickson-Viitanen, S.; Lam, P. Y. S. *Drug Discovery Today* **1997**, *2*, 6. Cyclic ureas **3** (X = CO): Lam, P. Y. S.; Jadhav, P. K.; Eyermann, C. J.; Hodge, C. N.; Ru, Y.; Bacheler, L. T.; Meek, J. L.; Otto, M. J.; Rayner, M. M.; Wong, N. Y.; Chang, C. H.; Weber, P. C.; Jackson, D. A.; Sharpe, T. R.; Erickson-Viitanen, S. *Science* **1994**, *263*, 380. Sulfamides **3** (X = SO_2), see ref 10 and: Hultén, J.; Bonham, N. M.; Nillroth, U.; Hansson, T.; Zuccarello, G.; Bouzide, A.; Åqvist, J.; Classon, B.; Danielson, U. H.; Karlén, A.; Kvarnström, I.; Samuelsson, B.; Hallberg, A. *J. Med. Chem.* **1997**, *40*, 885. Bäckbro, K.; Löwgren, S.; Österlund, K.; Atepo, J.; Unge, T.; Hultén, J.; Bonham, N. M.; Schaal, W.; Karlén, A.; Hallberg, A. *J. Med. Chem.* **1997**, *40*, 898. Triazacyclic ureas **2**: Sham, H. L.; Zhao, C.; Stewart, K. D.; Betebenner, D. A.; Lin, S.; Park, C. H.; Kong, X.-P.; Rosenbrook, W. Jr.; Herrin, T.; Madigan, D.; Vasavanonda, S.; Lyons, N.; Molla, A.; Kempf, D. J.; Plattner, J. J.; Norbeck, D. W. *J. Med. Chem.* **1996**, *39*, 392.

(7) For olefin RCM approaches to sulfamides: Dougherty, J. M.; Probst, D. A.; Robinson, R. E.; Moore, J. D.; Klein, T. A.; Snelgrove, K. A.; Hanson, P. R. *Tetrahedron* **2000**, *56*, 9781.

(8) For olefin RCM approaches to related (*S*)-heterocycles: Cyclic sulfonamides (sultams): (a) Hanson, P. R.; Probst, D. A.; Robinson, R. E.; Yau, M. *Tetrahedron Lett.* **1999**, *40*, 4761. (b) Brown, R. C. D.; Castro, J. L.; Moriggi, J. D. *Tetrahedron Lett.* **2000**, *41*, 3681. (c) Long, D. D.; Termin, A. P. *Tetrahedron Lett.* **2000**, *41*, 6743. Sultones: (d) Karsch, S.; Schwab, P.; Metz, P. *Synlett* **2002**, 2019.

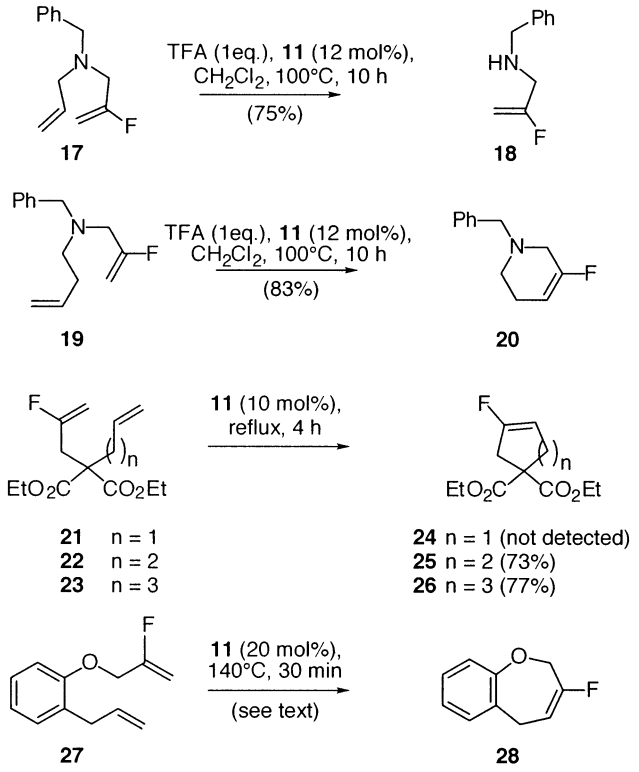
(9) De Lucca, G. V. *J. Org. Chem.* **1998**, *63*, 4755.

(10) See ref 7 and: Dewynter, G.; Aouf, N.; Criton, M.; Montero J. L. *Tetrahedron* **1993**, *49*, 65.

(11) **Procedure for the Preparation of Compound 12.** To a stirring solution of the sulfamide **6** (60 mg, 0.16 mmol) in CH_2Cl_2 (5 mL) was added Grubbs' ruthenium complex **11** (8.0 mg, 0.009 mmol). The reaction mixture was stirred for 5 h at reflux. The solvent was removed under reduced pressure to afford a brown oil, which was purified by column chromatoraphy (Et_2O/hexane, 1:4) to yield the title compound **12** as a pale yellow oil (50.0 mg, 0.14 mmol, 90%). ^1H NMR (400 MHz, $CDCl_3$): δ 1.56 (9H, s, CH_3), 3.78 (2H, t, J = 5.0 Hz, NCH_2), 4.46 (2H, s, NCH_2), 4.48 (2H, d, J_{H-F} = 11.3 Hz, NCH_2), 5.31 (1H, td, J = 5.0, 17.8 Hz, =CH), 7.38−7.33 (5H, m, Ar). ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 28.1 (CH_3), 41.2 (d, J_{C-F} = 11 Hz, CH_2), 45.3 (d, J_{C-F} = 42 Hz, CH_2), 52.1 (CH_2), 85.0 (C), 102.8 (d, J_{C-F} = 20 Hz, CH), 128.5 (CH), 128.6 (CH), 129.1 (CH), 135.0 (C), 151.3 (CO), 161.9 (d, J_{C-F} = 264 Hz, CF). IR (CCl_4): υ_{max} 2978, 2935, 2864, 1725, 1370, 1327, 1130 cm^{-1}. HRMS ($C_{16}H_{21}FN_2O_4S$): calcd, 379.1098; found, 379.1099.

Blechert et al. and Grubbs had reported on the cross-metathesis of perfluoroalkyl-substituted olefins,[12−14] attributing their success to the use of later-generation ruthenium N-heterocyclic carbene complexes.[15] In the same work, Grubbs et al. noted that vinyl halides had failed to give cross-metathesis products.[13,14] Given the dearth of examples of RCM involving halo-olefins, we set out to establish if the RCM of fluoro-olefins could be more widely applicable (Scheme 3).

Scheme 3. Further RCM Reactions of Vinyl Fluorides



A variety of monofluorinated dienes, with carbon and heteroatoms in the linking chain, were prepared. Amine and ether substrates **17**, **19**, and **27** were obtained by fluoro-allylation of *N*-benzylallylamine, *N*-benzyl-4-aminobutene, and 2-allyl-phenol, respectively. The malonate derivatives **21**−**23** were synthesized by alkylation of the sodium salt of diethyl (2-fluoro-allyl)malonate in DMF at 100 °C in the presence of NaI.

RCM reactions of the amines **17** and **19** were carried out on both the free 3° amines and their corresponding ammonium salts with similar results.[16] We were surprised to observe that in the case of the five-membered ring precursor **17**, deallylation occurred rather than the desired ring closure. Recently, Cadot et al. have reported that allyl and homoallyl groups can undergo isomerization in the presence of the ruthenium alkylidene complex **11**.[17] It therefore seems likely that isomerization of allylic amine **17**, followed by in situ hydrolysis of the resulting enamine, accounts for the formation of **18**. However, the structure of the ruthenium species mediating the isomerization remains unknown. Gratifyingly, the homologous amine **19** provided the six-membered vinyl fluoride **20** in good yield.

In the carbocyclic series, RCM also proceeded smoothly to provide the six- and seven-membered products **25** and **26**, respectively. However, we were unable to close the five-membered ring **24**, and in this case starting material was recovered.

RCM of the ether-linked diene **27** required more forcing conditions and did not proceed as cleanly as the above examples. The characteristic signals of the desired seven-membered product **28** were observed in the ^{1}H NMR spectra of the crude reaction mixture, and a partially purified sample (40%, see Supporting Information) was obtained after chromatography. Unfortunately, isolation of a pure sample of the product was not possible due to its instability and volatility.[18]

A general observation made on the work described here is that RCM reactions of fluoro-olefins are typically slower than their nonfluorinated analogues. We therefore suggest that the first step along a productive reaction pathway would be reaction at the more electron-rich olefin to form a ruthenium alkylidene complex **A** (Figure 2). Coordination

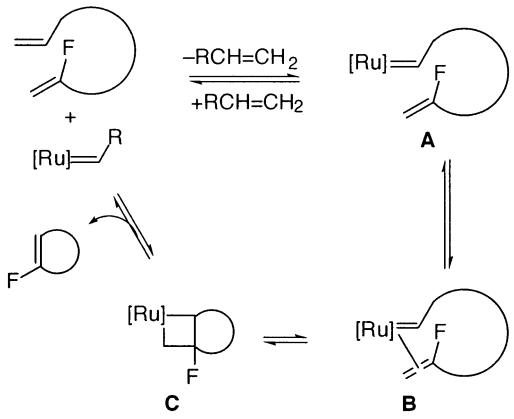


Figure 2. Proposed reaction pathway for the RCM of fluoro-olefin-containing dienes

of the poorer σ-donor fluoro-olefin and formal [2 + 2]

(12) Imhof, S.; Randl, S.; Blechert, S. *Chem. Commun.* **2001**, 1692.
(13) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783. See also: Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310.
(14) RCM of chloro-olefins has recently been realized using the ruthenium complex **11** to provide five- to seven-membered products. Chao, W.; Weinreb, S. M. *Org. Lett.* **2003**, *5*, 2505.
(15) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.
(16) Early reports in the literature suggested that RCM reactions of substrates containing free basic nitrogen atoms could be problematic, whereas the corresponding ammonium salts could be cyclized. Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856. Felpin, F.-X.; Girard, S.; Vo-Thanh, G.; Robins, R. J.; Villiéras, J.; Lebreton, J. *J. Org. Chem.* **2001**, *66*, 6305. In the current work, we initially formed TFA salts of **17** and **19** prior to submission to the RCM conditions but subsequently found that the reactions of free amines **17** and **19** with ruthenium complex **11** gave similar results.

cycloaddition can then occur to provide the intermediate metallacyclobutane **C** when a suitable linking group is present. We believe that the failure of the RCM reactions to give five-membered rings is a reflection of the lower reactivity of the fluoro-olefin double bond, combined with a greater ring strain energy developing in the formation of an intermediate such as **B** or the transition state en route to **C**. Thus, competing side-reactions (deallylation of **17**) or recovered starting material are observed.

In conclusion, we have shown that RCM of fluoro-olefins provided a convenient approach to a variety of carbocyclic and heterocyclic vinyl fluorides in good to excellent yields using a commercially available fluoro-olefin fragment. Current effort in our laboratory is focused on the development of solid-phase cyclization−cleavage approaches to fluoro-olefins.[8b]

Acknowledgment. We thank GlaxoSmithKline for a CASE award (S.S.S.), the Royal Society (R.C.D.B.) for a University Research Fellowship, and Merck Sharp and Dohme, Syngenta, AstraZeneca, and Pfizer for unrestricted grants. We also thank Professor S. Weinreb for helpful discussions during the preparation of this manuscript.

Supporting Information Available: Experimental procedures, data for **7**−**10**, **13**−**23**, and **25**−**27**, and copies of ^{1}H NMR spectra for **6**−**10**, **12**−**23**, and **25**−**28**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035065W

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

(18) Partial purification of **28** was possible on base-washed (Et_3N) SiO_2, although some decomposition still occurred. An NMR sample enriched in **28** also underwent substantial decomposition on standing in $CDCl_3$ overnight (see Supporting Information).