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Sequential Cross-Metathesis/ Electrophilic Fluorodesilylation: A Novel Entry to Functionalized Allylic Fluorides

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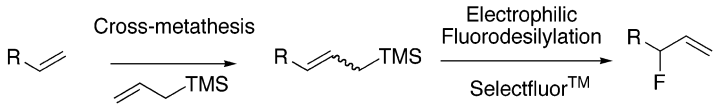
ABSTRACT



Various allylic fluorides were prepared using a two-step process involving a cross-metathesis of allyltrimethylsilane with different olefinic partners followed by a fluorodesilylation of the corresponding functionalized allylsilanes with Selectfluor.

The ability of fluorine to alter the physical and chemical properties of organic molecules has been used in the design of fluorine-containing materials and bioactive compounds.[1] General methodologies to access fluorine-substituted targets are still limited, probably because of the abnormal reactivity often displayed by fluorine and fluorine-containing groups when compared with other halo substituents. Surprisingly, only a few methodologies are available for the preparation of allylic fluorides despite the enormous synthetic potential of this functional group.

Allylic fluorides are often prepared by nucleophilic displacement of allylic alcohols with reagents such as (diethylamino)sulfur trifluoride (DAST), but this transformation suffers from the formation of side products as a result of allylic transposition.[2] The ring opening of tertiary cyclopropyl silyl ethers with DAST provides an alternative route to allylic fluorides, but this technology lacks generality and requires starting materials that are not readily available.[3]

With the appearance of electrophilic sources of fluorine, the concept of electrophilic fluorodesilylation[4] has emerged and our group has reported on how this concept can be applied to vinylsilanes and allylsilanes as an entry to fluoroolefins[5] and enantioenriched non functionalized allylic fluorides, respectively.[6] This letter will further report on the synthetic applications of electrophilic fluorodesilylation of allylsilanes and will elaborate on the scope and limitations of an improved strategy combining a cross-metathesis (CM) reaction with a fluorodesilylation process as a direct entry to various functionalized allylic fluorides.

As an alternative to the Wittig olefination using the Seyferth−Fleming phosphorane[7] $Ph_3P{=}CHCH_2SiMe_3$, cross-

(1) For general reviews on the physical properties of fluorinated compounds: (a) Smart, B. E. In *Chemistry of Organic Fluorine Compounds II: A Critical Review*; Hudlicky, M., Pavlath, A. E., Eds.; ACS Monograph 187; American Chemical Society: Washington, DC, 1995; pp 979−1010. (b) Smart, B. E. In *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum Publishing Corp.: New York, 1994; pp 57−88. For applications of organofluorine compounds in pharmaceutical development, see, for example: (c) Edwards, P. N. In *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum Publishing Corp.: New York, 1994; pp 501−541. (d) Ojima, I., McCarthy, J. R. ,Welch, J. T., Eds. *Biomedical Frontiers of Fluorine Chemistry*; ACS Symposium Series 639; American Chemical Society: Washington, DC, 1996. (e) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley and Sons: New York, 1991.

(2) (a) Middleton, W. J., US Patent 3914265, 1975. (b) Blackburn, G. M.; Kent, D. E. *J. Chem. Soc., Chem. Commun.* **1981**, 511. (c) Piva, O. *Synlett* **1994**, 729. (d) Grée, D. M.; Kermarrec, C. J. M.; Martelli, J. T.; Grée, R. L.; Lellouche, J.-P.; Toupet, L. J. *J. Org. Chem.* **1996**, *61*, 1918. (e) Kermarrec, C. J. M.; Madiot, V.; Grée, D.; Meyer, A.; Gree, R *Tetrahedron Lett.* **1996**, *61*, 1918.

(3) Kirihara, Masayuki; Kambayashi, Toshihiro; Momose, Takefumi *Chem. Commun.* **1996**, *10*, 1103.

(4) Gouverneur, V.; Greedy, B. *Chem. Eur. J.* **2002**, *8*, 766.

(5) Greedy, B.; Gouverneur, V. *Chem. Commun.* **2001**, 233.

(6) Greedy, B.; Paris, J.-M.; Vidal, T.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 3291.

(7) Seyferth, D.; Wursthorn, K. R.; Mammarella, R. E. *J. Org. Chem.* **1977**, *42*, 3104. (b) Seyferth, D.; Wursthorn, K. R.; Lim, T. F. O.; Sepelak, D. J. *J. Organomet. Chem.* **1979**, *181*, 293. (c) Fleming, I.; Paterson, I. *Synthesis* **1979**, 446.

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metathesis has recently gained increasing significance as a novel process for the preparation of various allylsilanes due to the availability of catalysts with varied activities such as **1** and **2**.[8] We reasoned that the CM reaction should allow direct access to various allylsilanes which, upon fluorination using an electrophilic source of fluorine such as F-TEDA (also called Selectfluor), might lead to the regioselective preparation of structurally diverse allylic fluorides that are difficult to prepare by other means. In this strategy, the trimethylsilyl group enhances the reactivity of the alkene toward the addition of F-TEDA and controls the regioselectivity of the addition by virtue of the stabilization of the cation β to the silicon (Scheme 1).

Scheme 1. General Strategy toward Allylic Fluorides

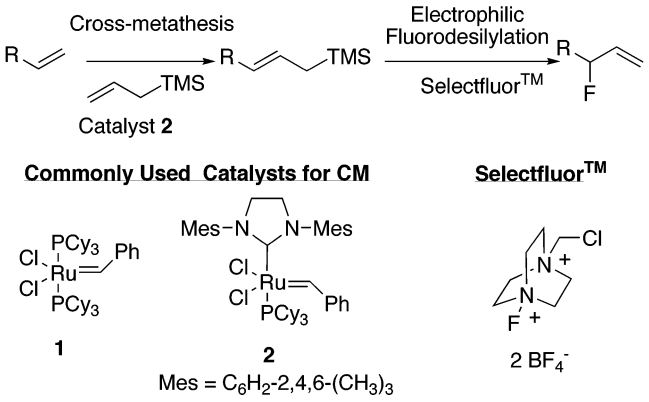


Table 1. CM of Allyltrimethylsilane with Various Olefins[a]

entry	CM partner	product	yield *E*/*Z* ratio
1	**3a**	**4a**	58% 4/1
2	**3b**	**4b**	84% 4/1
3	**3c**	**4c**	54% 5/1
4	**3d**	**4d**	82% 3/1
5	**3e**	**4e**	70% 9/1
6	**3f**	**4f**	89% 3/1
7	**3g**	**4g**	62%(lit: 50%)[8e] > 95/5
8	**3h**	**4h**	75% >95/5
9	**3i**	**4i**	13% 1/1

[a] 3 equiv of allyltrimethylsilane, 5 mol % of **2**, DCM, reflux, 48 h.

Our study began by subjecting allyltrimethylsilane to the CM reaction with a series of functionalized olefinic partners, including various protected alcohols and allylic amines, 2-vinyl-1,3-dioxolane, as well as unsaturated carbonyl derivatives such as esters, ketones, or imides. Typically, the CM reactions were performed in dichloromethane at reflux in the presence of 5 mol % of catalyst **2**. Our results are summarized in Table 1.

The reaction of the benzyl-protected allylic alcohol **3a** with 3 equiv of allyltrimethylsilane afforded the desired product **4a** with an isolated chemical yield of 58% as an inseparable mixture of *E* and *Z* isomers (*E*/*Z* = 4:1). Similarly, unsaturated esters **3b**, **3c**, and **3d** reacted with allyltrimethylsilane to give the desired cross-metathesis products **4b**−**d** as inseparable mixtures of *E* and *Z* stereoisomers with chemical yields ranging from 54% to 84%. The major stereoisomer for all these transformations was consistently the *E*-isomer. The stereoselectivity of the product **4e** resulting from a cross-metathesis with the protected allylamine **3e** was superior with an *E*/*Z* ratio of 9/1. This product was obtained with a chemical yield of 70%. The *N*-allylphthalimide **3f** was also found to be a good olefinic partner for the CM reaction with allyltrimethylsilane. This transformation afforded the desired allylsilane **4f** with a chemical yield of 89% and a *E*/*Z* ratio of 3/1.

For the reactions resulting in the formation of a single stereoisomer such as the cross-metathesis of ethylvinyl ketone **3g** and of the vinyl-2,3-dioxolane **3h**, the *Z*-isomer was not detected in the crude mixtures by either ^{1}H or ^{13}C NMR, suggesting a greater than 95:5 selectivity in favor of the *E*-olefin. Finally, a cross-metathesis was attempted with the *gem*-substituted olefin **3i** in order to produce the trisubstituted allylsilane **4i.** Unfortunately, the chemical yield for this transformation never exceeded 13% suggesting that this substrate should be prepared according to one of the multistep procedures reported in the literature.[9] For all the reactions that gave the products as the *E*- and *Z*-isomers, the mixture of stereoisomers was engaged in the next step.

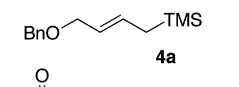
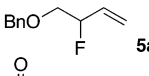
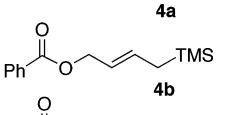
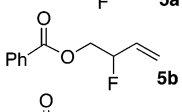
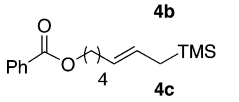
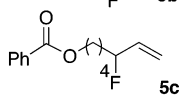
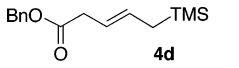
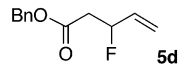
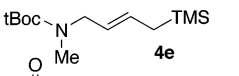
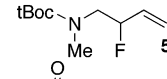
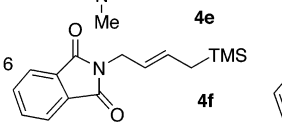
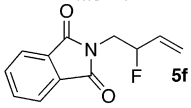
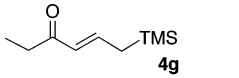
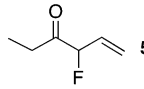
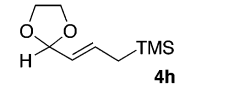
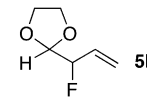
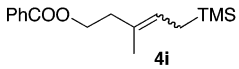
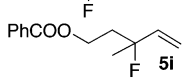
Our next goal was to validate the feasibility of the electrophilic fluorodesilylation of the functionalized allylsilanes **4a**−**i**. These transformations were carried out in acetonitrile at room temperature in the presence of 1 equiv of Selectfluor (Table 2).

Allylsilane **4a** possessing an ether functionality was smoothly converted into the corresponding allylic fluoride

(8) For general reviews on cross-metathesis: (a) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360. (b) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036. (c) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900. For references on CM of allyltrimethylsilane, see, for example: (d) Crowe, W. E.; Goldberg, D. R.; Zhang, Z. J. *Tetrahedron Lett.* **1996**, *37*, 2117. (e) Bouzbouz, S.; De Lemos, E.; Cossy, J. *Adv. Synth. Catal.* **2002**, *344*, 627. (f) Engelhardt, F. C.; Schmitt, M. J.; Taylor, R. E. *Org. Lett.* **2001**, *3*, 2209..

(9) See for example: Vidari, G.; Lanfranchi, G.; Masciaga, F.; Moriggi, J.-D. *Tetrahedron: Asymmetry* **1996**, *7*, 3009.

Table 2. Fluorodesilylation of **4a**−**i** with Selectfluor[a]

entry	starting material	product	yield
1	 **4a**	 **5a**	71%
2	 **4b**	 **5b**	74%
3	 **4c**	 **5c**	33%
4	 **4d**	 **5d**	69%
5	 **4e**	 **5e**	52%
6	 **4f**	 **5f**	82%
7	 **4g**	 **5g**	0%
8	 **4h**	 **5h**	100%[b]
9	 **4i**	 **5i**	79%

[a] 1 equiv of Selectfluor, acetonitrile, room temperature, 48 h. [b] Conversion.

with an isolated chemical yield of 71% (entry 1). It is not clear why the ester **4b** was found to be a better substrate than **4c** for the fluorodesilylation (chemical yield of 74% for **5b** but only 33% for the formation of **5c**). Indeed, no other products could be detected by ^{1}H NMR of the crude reaction mixture of the allylsilane **4c** with Selectfluor suggesting that **5c** might be sensitive to purification. The β-fluorinated ester **5d** was easily accessible using our methodology (entry 4, yield 69%) with no detectable side product resulting from an elimination process, a result that reflects the mildness of the conditions used for the fluorination step. The vicinal fluorinated protected amines **5e** and **5f** were also obtained from the corresponding allylsilanes in respectable yields (entries 5 and 6). To the best of our knowledge, the methodology reported here is the most expeditious route to these compounds. Indeed, products similar to **5e** or **5f** are more often prepared by treating the corresponding allylic amino alcohol with DAST but these reactions suffer from poor selectivity as a result of allylic transposition.[10] Our technology circumvents this problem with the trimethylsilyl group controlling the regioselectivity of the addition of the fluorinating agent efficiently. Allylsilane **4g** did not react with Selectfluor (entry 7). Only starting material was recovered after prolonged reaction time. For this substrate, the presence of the necessary cation stabilizing group (CH_2SiMe_3) is not sufficient to overcome the electron withdrawing effect of the carbonyl functionality. In contrast, allylsilane **4h** possessing the acetal-protected aldehyde could be cleanly converted into the corresponding allylic fluoride **5h**. No yield was reported for this product due to its volatility making its purification difficult (entry 8). Nevertheless, the ^{1}H NMR of the crude mixture revealed solely the presence of the desired product (entry 8). Finally, we have also applied the methodology to the formation of the quaternary fluorinated allylic compound **5i** which was isolated with a chemical yield of 79% (entry 9).

In conclusion, the versatility of the technology described herein makes this chemistry a useful and highly practical alternative to other methods for the construction of allylic fluorides from alkenes. Most importantly, this investigation sets the stage for the application of more elaborated targets as numerous functional groups are compatible with this sequential CM/electrophilic fluorodesilylation process, thus allowing the introduction of the fluorine at a later stage of a synthetic plan.

Acknowledgment. This work was generously supported by The Cancer Research UK (grant to S.T.) and AstraZeneca (research grant to V.G.).

Supporting Information Available: Experimental details and spectroscopic data for all allylsilanes **4a**−**i** and the allylic fluorides **5a**−**i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Van Overmeire, I.; Boldin, S. A.; Venkatamaran, K.; Zisling, R.; De Jonghe, S.; Van Calenbergh, S.; De Keukeleire, D.; Futerman, A. H.; Herdewijn, P. *J. Med. Chem.* **2000**, *43*, 4189.