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Fluorous synthesis of allylic fluorides: C–F bond formation as the detagging process†‡

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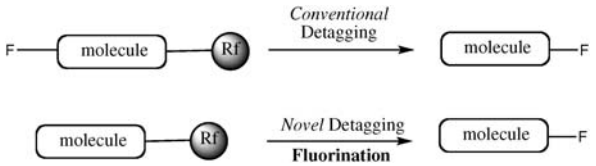
A novel fluorous tagging–detagging strategy has been developed featuring a fluorination as the detagging process; fluorous allylsilanes were prepared by cross-metathesis and subsequently subjected to electrophilic fluorodesilylation; Selectfluor was used as the detagging reagent; the resulting allylic fluorides were successfully purified by fluorous solid phase extraction.

The ability of fluorine to alter the physical and chemical properties of organic molecules has been used in the design of fluorine-containing bioactive compounds.[1] Rapid and efficient protocols for the purification of fluorinated compounds are therefore in high demand. Radiochemists working in the area of positron emission tomography would also greatly benefit from the availability of fast purification strategies for the production of short half-life fluorinated ^{18}F-radiotracers. Fluorous chemistry emerges as a particularly attractive technology since the unique separation properties of molecules containing a highly perfluorinated domain allows for the rapid purification of crude reaction mixtures using fluorous solid phase extraction (FSPE).[2,3] This technique has proved to be valuable in the context of medicinal chemistry. Surprisingly, radiolabelling strategies relying on the use of fluorous soluble supports are extremely scarce, notable exceptions being the preparation of ^{125}I-labelled benzamides and ^{35}S-labelled sulfonamides.[4,5] In recognition of the importance of fluorinated pharmaceuticals, the need to develop rapid purification protocols for ^{18}F-radiotracers, and the advantages of fluorous chemistry, fluorous-tagged precursors should be regarded as highly valuable for the preparation and purification of fluorinated products. Examples of functional manipulation of fluorinated fluorous reactants followed by a conventional detagging process were reported in the literature.[6] A more challenging approach is the detagging of a fluorous-tagged precursor based on a fluorination process. In the context of ^{18}F-radiochemistry, this approach is potentially very powerful as it allows for the FSPE separation of the ^{18}F-labelled radiotracers from the large excess of fluorous starting material, the fluorination conveniently taking place late in the radiosynthetic sequence (Scheme 1).

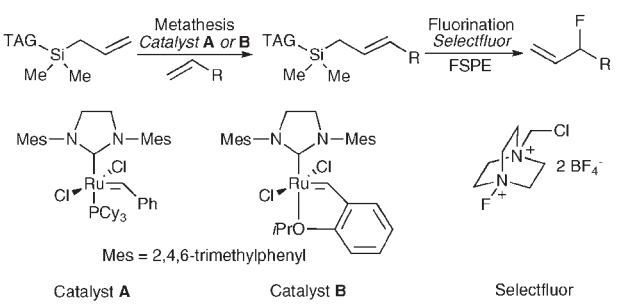


Scheme 1 C–F Bond formation, a new detagging process.

In this paper, we report the first detagging process relying on a C–F bond forming event. For proof of concept, we validated the feasibility of this unprecedented strategy with the electrophilic fluorination of allylsilanes, a well-documented reaction for the preparation of allylic fluorides.[7]

We opted for a light fluorous approach as it advantageously requires minimal optimisation and allows for the use of FSPE for the purification protocol. We reasoned that tagged allyltrimethylsilanes may be amenable to cross-metathesis (CM) and subsequent detagging upon fluorination with Selectfluor. This reaction sequence raised two main points of interest, the feasibility of cross-metathesis reactions involving a fluorous olefin and the validation of the key fluorination-detagging process (Scheme 2).

As no light fluorous allylsilanes are reported in the literature,[8] our study began with the preparation of a model light fluorous allylsilane. Allylsilane **1** was selected for further functional manipulation as the incorporation of the ethylene spacer insulates the silicon from the tag, thereby minimising any electronic perturbation that could otherwise affect the reactivity of the fluorous allylsilane for the cross-metathesis reaction and subsequent electrophilic substitution. The reaction of the commercially available fluorous-tagged dimethylchlorosilane **2** with allyl magnesium bromide afforded the fluorous-tagged allylsilane **1** in an isolated yield of 79% (Scheme 3).[9]



Scheme 2 Fluorous approach to allylic fluorides.

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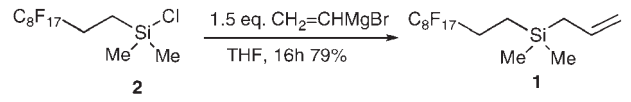
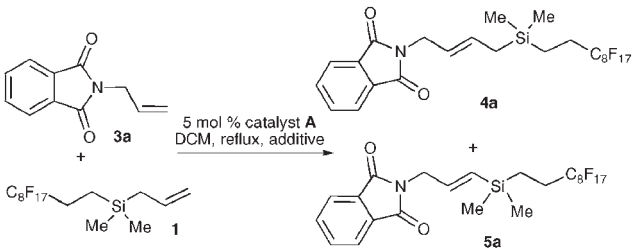
† Dedicated to Professor Andrew B. Holmes on the occasion of his 65th birthday.
‡ Electronic supplementary information (ESI) available: Experimental section. See DOI: 10.1039/b804484h



Scheme 3 Preparation of the fluorous allylsilane **1**.



Scheme 4 Cross-metathesis of fluorous allylsilane **1** with **3a**.

With allylsilane **1** in hand, we optimised the CM reaction using *N*-allylphthalimide **3a** as the olefinic partner (Scheme 4, Table 1). The reaction conditions previously reported for this transformation in non-fluorous series[7a] (5 mol% catalyst **A**, DCM, reflux) led to the formation of the desired product **4a** along with a side-product not observed using non-fluorous precursors (entry 1, Table 1). The structure of this side product was unambiguously determined to be the truncated vinylsilane **5a** (Scheme 4). This was confirmed through an independent synthesis.[9] Compound **5a** is likely the result of an isomerisation process followed by alkene exchange. The formation of **5a** was eradicated when the reaction was performed in the presence of 0.5 eq. of 1,4-benzoquinone, the reaction time being limited to 12 h.[10] Under these conditions, **4a** was isolated in 45% yield (entry 2, Table 1). Increasing the reaction time did not improve conversion or *E*/*Z* selectivity but resulted in detectable isomerisation (entry 3, Table 1).

With the initial studies completed, we prepared various fluorous allylsilanes by cross-metathesis with a series of functionalised olefinic partners including unsaturated esters and ethers (Table 2). The reaction of the unsaturated ester **3b** with 3 eq. of allylsilane **1** afforded the desired product **4b** with an isolated chemical yield of 40% (entry 2). Similar yields were obtained when using as the olefinic partner, the benzylic ester derivative **3c** or the benzyl-protected allyl alcohol **3e** (entries 3 and 5). When applying our standard conditions, the benzoyl-protected allyl alcohol **3d** delivered the product of cross-metathesis **4d** as the major product along with up to 20% of the undesired vinylsilane **5d** (Fig. 1). Further optimisation of this reaction was therefore required and revealed that the formation of **5d** was suppressed when the metathesis was carried out in the presence of 5 mol% of the Hoveyda–Grubbs catalyst **B** instead of catalyst **A**. All reactions delivered the product as mixtures of *E* : *Z* isomers. The purification of all CM adducts was performed using silica gel chromatography or FSPE.

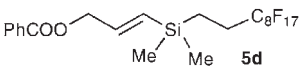
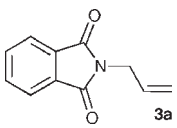
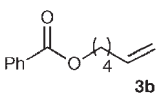
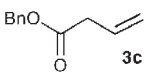
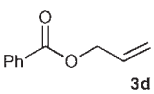
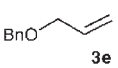


Fig. 1 Side-product formed upon CM of **3d** and **1** using catalyst **A**.

The electrophilic fluorination of the fluorous allylsilanes **4a–e** were carried out in acetonitrile at room temperature in the presence of 2 equivalents of Selectfluor (Scheme 5). The results are summarised in Table 3.

All fluorous allylsilanes **4a–e** underwent fluorodesilylation and delivered the corresponding allylic fluorides **6a–e** resulting from clean transposition of the double bond. The allylic fluorides were all purified by FSPE and using this purification protocol, isolated in chemical yields ranging from 53 to 87% (entries 1–5). The fluorous tag positioned two methylene groups away from the silicon did not affect the reactivity of the fluorous allylsilanes. Indeed, similar reaction times were necessary for complete conversion using either the fluorous or the corresponding non-fluorous allylsilanes.[7a] An additional experiment revealed that the reaction time for the fluorination of **4c** can be significantly reduced from 24 h to only 30 min. when the reaction was carried out at 80 °C. Using these conditions, **6c** was formed in 70% yield after FSPE (entry 3). Notably, when the fluorination of **4c** was carried out with a sub-stoichiometric amount of Selectfluor, the excess allylsilane

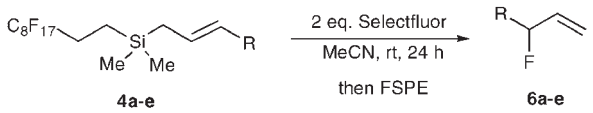
Table 2 Cross-metathesis of **1** with various olefins[a]

Entry	CM partner	Product	Yield (%) [*E* : *Z* ratio]
1		**4a**	45 [4 : 1]
2		**4b**	40[b]
3		**4c**	39 [3 : 1]
4		**4d**	36 [5 : 1][c]
5		**4e**	42 [5 : 1]

[a] 3 eq. fluorous allylsilane **1**, 5 mol% catalyst **A**, 0.5 eq. 1,4-benzoquinone, DCM, reflux, 12 h. [b] *E* : *Z* ratio could not be determined unambiguously from NMR. [c] 5 mol% catalyst **B**.

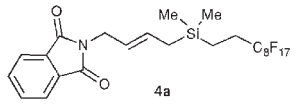
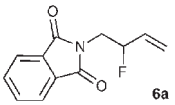
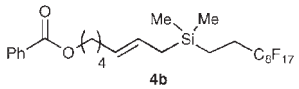
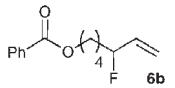
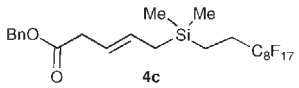
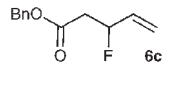
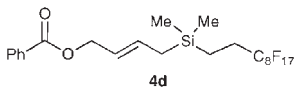
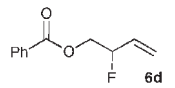
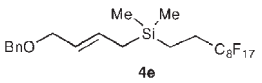
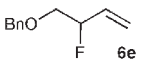
Table 1 Optimisation of CM of allylsilane **1** with N-allylphthalimide **3a**

Entry	Additive	Eq.	*t*/h	Ratio of **4a** : **5a**	Yield **4a** (%) [*E* : *Z* ratio]
1	—	—	48	4 : 1	60 [3 : 1]
2	1,4-Benzoquinone	0.5	12	**4a** only	45 [4 : 1]
3	1,4-Benzoquinone	0.5	48	8 : 1	43 [4 : 1]



Scheme 5 Electrophilic fluorination of **4a–e** with Selectfluor.

Table 3 Fluorodetagging of **4a–e** with Selectfluor

Entry	Allylsilane	Allylic fluoride	Yield (%)
1	 **4a**	 **6a**	53[a]
2	 **4b**	 **6b**	79[b]
3	 **4c**	 **6c**	87 70[c]
4	 **4d**	 **6d**	63
5	 **4e**	 **6e**	87

[a] 1 eq. Selectfluor. [b] **6b** contaminated with ~5% of an unidentified impurity. [c] 1 eq. Selectfluor, MeCN, 80 °C, 30 min.

was easily separated by FSPE, a result further demonstrating the potential of fluorous chemistry in radiochemistry.

In conclusion, we have applied light fluorous chemistry for the preparation and manipulation of allylsilanes. Since allylsilanes are widely used in organic synthesis through electrophilic, radical or organometallic processes, numerous fluorous variants are likely to appear in the near future. To the best of our knowledge, this is the first reported example of light fluorous olefins used in a cross-metathesis reaction.[8,11] Although a complete and rigorous study on the use of fluorous olefins in cross-metathesis will be necessary, the results reported herein validate the feasibility of such a process. Significantly, this is also the first example of a fluorous detagging process featuring a C–F bond forming reaction. We are currently developing other novel fluorination–detagging processes for applications in medicinal chemistry and in ^{18}F-radiochemistry.

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