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Stereoselective synthesis of internal allylic fluorides

Sébastien Thibaudeau, Robert Fuller and Véronique Gouverneur *
University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford, UK OX1 3TA.
E-mail: veronique.gouverneur@chem.ox.ac.uk

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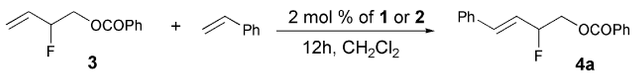
Ru-based catalysts can be used in *E*-selective cross metathesis (CM) reactions to synthesise various functionalised internal allylic monofluorides.

Introduction

In the pharmaceutical and agrochemical sectors, selectively fluorinated products are increasingly common. Introducing F and CF_3 substituents could affect lipophilicity, and suppresses metabolic detoxification processes to increase the *in vivo* lifetime of drugs.[1] Amongst marketed fluorine-containing drugs, only a minority contain a stereogenic (sp^3-hybridised) carbon atom bearing fluorine, probably because of the lack of practical methods for their synthesis. Compared to other fluorinated functionalities, the development of novel methodologies for the preparation of allylic fluorides has been neglected despite the enormous synthetic potential of this functional group. The most obvious route to these compounds is the dehydroxyfluorination of allylic compounds with diethylaminosulfur trifluoride (DAST) but this reaction is neither regiocontrolled, as a result of allylic transposition, nor stereocontrolled. This problem has been elegantly overcome by using alternative strategies such as the protection of the alkene as a transition metal complex prior to the nucleophilic displacement, or the stereoselective reduction of the corresponding propargylic fluoride that can be produced with high regio- and stereoselectivity by fluorination of the propargylic alcohol with DAST.[2] Recently, our group has demonstrated that enantioenriched allylic fluorides can be easily obtained by regio- and enantioselective fluorodesilylation of the corresponding allylsilanes in the presence of chiral N–F reagents.[3] We have also reported an easy two-step procedure for the preparation of various functionalised allylic fluorides involving the cross-metathesis of readily available functionalised alkenes with allyltrimethylsilane, followed by the electrophilic fluorodesilylation of the corresponding allylsilanes in the presence of Selectfluor™. So far, only terminal allylic fluorides have been prepared using this new reaction.[4] In an extension of our efforts to develop new practical syntheses for the preparation of important fluorinated building blocks, we sought to study the scope and limitation of the cross-metathesis reaction of terminal allylic monofluorides with various olefinic partners for the regio- and stereoselective preparation of internal allyl monofluorides. To the best of our knowledge, the ruthenium catalysed cross-metathesis of only two commercially available polyfluorinated alkane olefins (3,3,3-trifluoropropene and 3,3,4,4,5,5,6,6,6-nonafluorohexene) has been reported in the literature.[5] The methodology has not been applied to allylic monofluorides probably because, until our recent report,[4] general and practical synthetic methods for their preparation were not available. In this communication, we wish to report that intermolecular cross-metathesis of these terminal monosubstituted allylic monofluorides with various olefinic partners provides a rapid entry for the regio- and stereocontrolled preparation of various functionalised disubstituted allylic monofluorides. Catalysts **1** and **2** have been selected for this study as these catalysts have expanded the variety of functional groups amenable to CM (Scheme 1).[6]

Table 1 Optimisation studies for the cross-metathesis of allylic fluoride **3** with styrene

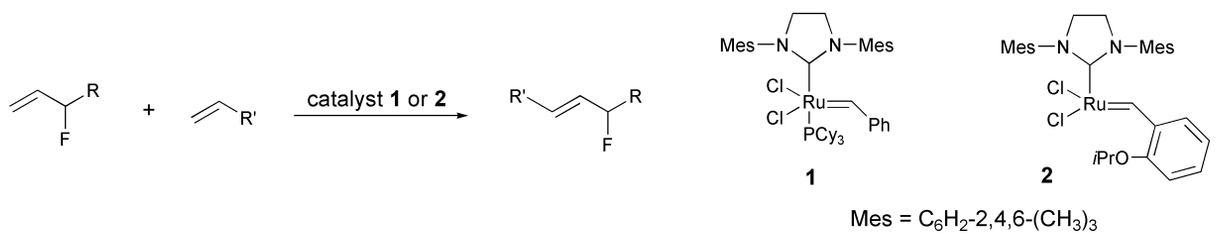


Entry	Styrene	Temperature/°C	Catalyst	Yield **4a**[c]
1	5 eq.	40	**1**	30%
2	5 eq.	25	**2**	30%
3	5 eq.	100[a]	**1**	69%
4	1 eq.	100[a]	**1**	43%[b]

[a] Reaction performed in a sealed tube. [b] The side product of this reaction is *E*-stilbene (21%). [c] *E* isomer exclusively.

Results and discussion

We set out to study first the reactivity of the allylic fluoride **3** with styrene in the presence of the Ru-based catalysts **1** or **2** (Table 1). A preliminary experiment was carried out in DCM at reflux with 2 mol% of the ruthenium catalyst **1**, one equivalent of the allylic fluoride **3** and five equivalents of styrene. We found that under these conditions, the desired product **4a** was obtained in 30% yield (entry 1). In the presence of catalyst **2** in place of catalyst **1**, the reaction took place slowly at room temperature to afford the desired compound with a similar yield (entry 2). Optimal results were obtained by performing the reaction in a sealed tube at 100 °C in the presence of catalyst **1** and an excess of styrene. Under these conditions, the CM product **4a** was isolated as a single stereoisomer (*E* only) in 69% yield (entry 3). The use of only one equivalent of styrene resulted in the formation of only 43% of product **4a** along with 21% of *E*-stilbene formed upon homodimerisation of styrene (entry 4). Therefore, subsequent CM reactions were performed in a sealed tube at 100 °C with catalyst **1** (2–10 mol%) and an excess of the non-fluorinated olefinic partner.



Scheme 1

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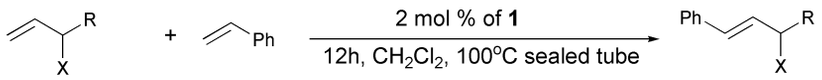


3 X = F, R = CH_2OCOPh
allyl chloride X = Cl, R = H
allyl bromide X = Br, R= H

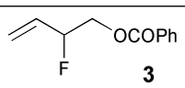
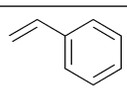
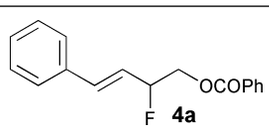
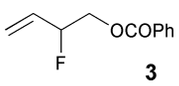
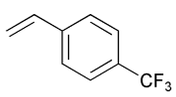
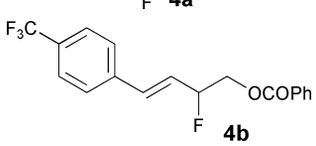
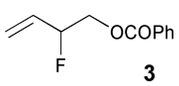
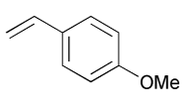
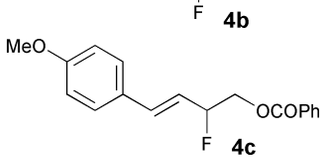
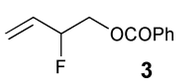
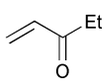
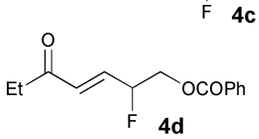
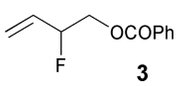
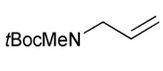
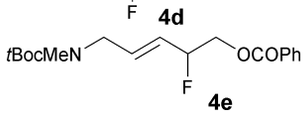
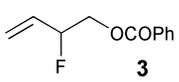
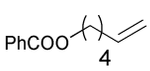
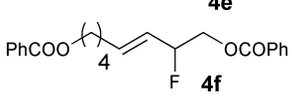
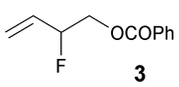
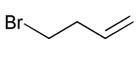
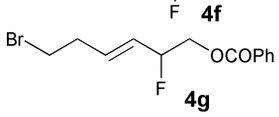
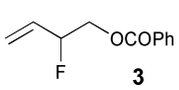
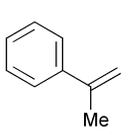
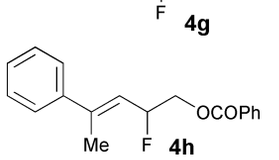
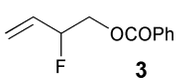
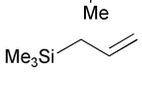
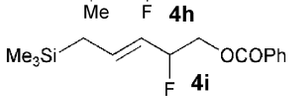
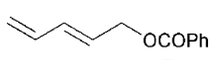
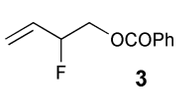
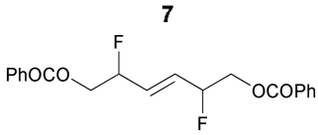
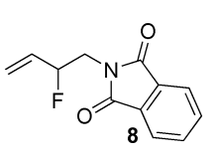
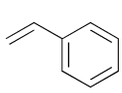
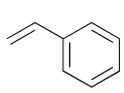
4a X = F, R = CH_2OCOPh 100% conversion
5 X = Cl, R = H 65% conversion
6 X = Br, R = H 54% conversion

Scheme 2 Cross-metathesis of allylic fluoride **3**, allyl chloride and allyl bromide with styrene.

During the course of this preliminary study, we also assessed the difference of reactivity of the allyl fluoride **3**, allyl chloride and allyl bromide towards styrene. The reactions were performed in $CDCl_3$ at 100 °C (sealed tube). The conversion of the starting material into the cross-metathesis product was determined after 12 hours by ^{1}H NMR analysis of the crude mixture. We found that allyl bromide was the less effective substrate with 54% conversion into the desired cross-metathesis product **6**. Both the allyl fluoride **1** and allyl chloride gave products **4a** and **5** with 100% and 65% conversion, respectively. These results strengthen the hypothesis that the presence of allylic halide such as fluorine, chlorine and bromine, of increased coordinating ability toward ruthenium, induces a decrease in efficiency for the cross-metathesis reaction (Scheme 2).[7]

The scope and limitation of this reaction has been explored with one representative allylic fluoride **3** combined with several olefins. The results are listed in Table 2.[8] Particularly note-

Table 2 Cross-metathesis of allylic fluoride **3** and **8** with various CM partners

Entry	Allylic fluoride	Cross partner	Product	mol% **2**, time	Yield (%)	*E* : *Z* ratio
1	 **3**		 **4a**	2, 12 h	69	>95 : 5
2	 **3**		 **4b**	3, 16 h	70	>95 : 5
3	 **3**		 **4c**	6, 48 h	Decomposition	
4	 **3**		 **4d**	10, 72 h	35	>95 : 5
5	 **3**		 **4e**	4, 48 h	53	>95 : 5
6	 **3**		 **4f**	4, 24 h	67	6 : 3
7	 **3**		 **4g**	2, 12 h	85	9 : 1
8	 **3**		 **4h**	6, 24 h	0	—
9	 **3**		 **4i**	2, 16 h	0	—
			 **7**		40	>95 : 5
10	 **3**	none		4, 48 h	78	—[a]
11	 **8**			4, 24 h	87	>95 : 5

[a] 1 : 1 mixture of diastereomers.

worthy is the difference of reactivity of 4-trifluoromethylstyrene and 4-methoxystyrene (entries 2 and 3). Indeed, 70% yield of the desired cross-metathesis product **4b** was attained by reacting compound **3** with 4-trifluoromethylstyrene in the presence of only 3 mol% of catalyst **2** but only decomposition was observed when **3** was reacted with 4-methoxystyrene. For this electron rich partner, lowering the reaction temperature did not prove beneficial. Compound **3** also reacted with ethyl vinyl ketone albeit less efficiently (entry 4). For this transformation, 35% of the cross-metathesis product **4d** was obtained, despite extended reaction time and an increased catalyst loading (up to 10 mol%). Nevertheless, the stereoselectivity was excellent with only the *E*-isomer observed in the crude mixture and after purification. The only other compound that could be isolated from this reaction was the product resulting from homodimerisation of ethyl vinyl ketone (traces only) along with 27% of recovered starting material. The reaction of the allylic fluoride **3** with the N-tBoc protected allylmethylamine afforded the cross-metathesis product **4e** in 53% yield as a single *E* stereoisomer (entry 5). In reaction with 6-benzoyloxyhexene and 4-bromobutene, the desired internal allylic monofluorides **4f** and **4g** were isolated as a mixture of stereoisomers in 67% and 85% yield respectively (entries 6 and 7). The major isomer was the *E* alkene with a better selectivity for the halogenated olefin ($E : Z = 9 : 1$) in comparison with the oxygenated olefin ($E : Z = 6 : 3$).

We have also found that the cross-metathesis reaction of allylic monofluoride presents some limitations. The reaction did not allow us to observe the formation of the trisubstituted internal allylic monofluoride **4h** in the presence of the more sterically demanding 2-methylstyrene, nor did it allow us to isolate the product **4i** resulting from a cross-metathesis with allyltrimethylsilane (entries 8 and 9). However, side products were formed and isolated for these two transformations. Some homodimerisation of the allylic fluoride **3** was observed in the reaction with α-methylstyrene, an alkene categorised as a type III olefin according to the classification of Grubbs *et al.* because of its inability to homodimerise in the presence of catalyst **1**.[6a] A control experiment was performed exposing **3** as the sole reagent in the presence of catalyst **1**, and confirmed the ability of this compound to self-dimerise under these conditions (78% yield, entry 10). When allyltrimethylsilane was used as the olefinic partner, a reaction took place as reflected by the disappearance of the allylic fluoride **3**, but no trace of the desired CM product **4i** was detected. However, compound **7** was isolated in 40% yield as a single *E* isomer. This product could be formed upon the anticipated cross-metathesis followed by an elimination process to give the corresponding diene. In this elimination process, the formation of fluoride ions can promote, *via* a desilylation process, the conversion of the cross-metathesis product **4i** into the observed diene **7**.

A cross-metathesis reaction of the terminal allylic fluoride **8**[4] bearing a phthalimido protecting group was also performed in the presence of five equivalents of styrene and allowed the formation of compound **9** as a single *E* stereoisomer with 87% yield (entry 11).

Although some yields were modest, the overall good to excellent stereoselectivities obtained makes this method synthetically practical. Numerous factors control the stereochemistry of the ultimate products, with simple steric arguments providing a first level of rational. In light of the long lifetime of the catalysts used for this study and the reaction conditions applied, one should not exclude the possibility of isomerisation of the initial products. Compared to other methodologies currently available for the synthesis of internal allylic fluorides, this simple disconnective strategy presents the advantage of circumventing the problem of allylic transposition encountered when one used a nucleophilic source of fluoride in reaction with allylic compounds. Further studies on the synthesis and the use of fluorinated olefins are under way in our laboratories and will be reported in due course.

Acknowledgements

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8 Typical procedure for the preparation of **4a**. Fluorinated protected alcohol **3** (35 mg, 0.18 mmol) and styrene (0.1 ml, 5 eq.) were solubilised in freshly distilled dichloromethane under N_2 atmosphere in a sealed tube. Catalyst **2** (2 mol%, 3 mg) was added as a solid. Then the reaction mixture was allowed to stir for 12 hours at 100 °C. The reaction mixture was then allowed to cool to room temperature, then concentrated under vacuum. Purification by flash chromatography (1/99 diethyl ether/hexane, then 3/97 diethyl ether/hexane) afforded 34 mg of the benzoic acid 2-fluoro-4-phenyl but-3-enyl ester **4a** (*E*/*Z* ratio >95%) as a white oil (69%). ^{1}H NMR (400.132 MHz, $CDCl_3$, ppm): 4.51 (1H, ddd, J = 19.6 Hz, J = 12.4 Hz, J = 7.0 Hz, H_1), 4.61 (1H, ddd, J = 26.4 Hz, J = 12.4 Hz, J = 3.2 Hz, H_1), 5.43 (1H, dddd, J = 49.2 Hz, J = 7.0 Hz, J = 3.2 Hz, J = 1.2 Hz, H_2), 6.30 (1H, ddd, J = 16.0 Hz, J = 13.2 Hz, J = 7.0 Hz, H_3), 6.84 (1H, dd, J = 16.0 Hz, J = 3.2 Hz, H_4), 7.27–7.61 (8H, m, H_{arom}), 8.10 (2H, d, J = 5.6 Hz, H_{arom}). ^{13}C NMR (100.624 MHz, $CDCl_3$, ppm): 66.1 (CH_2, d, J = 24 Hz, C_1), 90.8 (CH, d, J = 172 Hz, C_2), 122.5 (CH, d, J = 18 Hz, C_3), 126.8 (CH, C_{arom}), 128.4 (CH, C_{arom}), 128.6 (CH, C_{arom}), 128.7 (CH, C_{arom}), 129.6 (CH, C_{arom}), 133.2 (CH, C_{arom}), 134.9 (CH, d, J = 11 Hz, C_4), 135.6 (C_{arom}), 166.3 (CO). ^{19}F{^{1}H} NMR (376.508 MHz, $CDCl_3$, ppm): −178.9. MS (GCT, CI^+): *m*/*z* (relative intensity %) 268 $[M - HF + NH_4]^+$ (40), 251 $[M]^+$ (100). HRMS (GCT, CI^+): Calc for $C_{17}H_{18}NO_2$: 268.1338, found 268.1326.