Ready Synthetic Access to Enantiopure Allylic α(F)-Branched Fluoroalkenes

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ABSTRACT
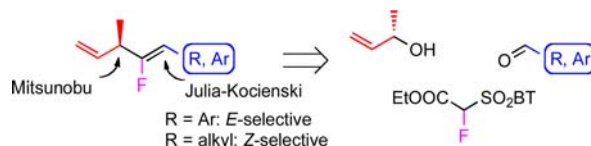
Convenient access to homochiral fluoroalkenes is described via a Julia–Kocienski olefination reaction. The required homochiral fluorosulfone is synthesized by a Mitsunobu reaction from readily available enantiopure secondary alcohols.

Fluorination of bioactive compounds is now a routine consideration in the drug development process.[1] Apart from preventing metabolic degradation, fluorine is often introduced to alter particular properties of adjacent functional groups (e.g., pK_a/pK_b, and hydrogen bonding properties), which then typically also has an effect on molecular properties including conformation and lipophilicity.[2] In addition, fluorine can replace a functional group (e.g., alcohols), or fluorine-containing groups can be used as functional group isosteres. Perhaps the most known example is fluoroalkenes as amide

Scheme 1. Synthetic Approaches towards Enantioenriched Allylic α(F)-Chiral Fluoroalkenes
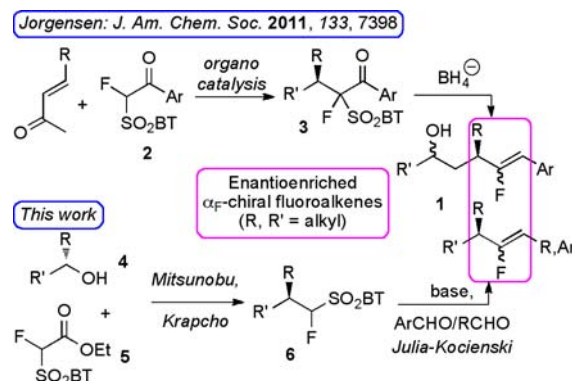
isosteres, mimicking their dipolar nature while being hydrolytically stable.[3] Fluoroalkenes are isoelectronic with enolates, leading to additional applications as enolate isosteres.[4]

As a consequence, there are many methods for the synthesis of fluoroalkenes.[5] Nevertheless, the enantioselective

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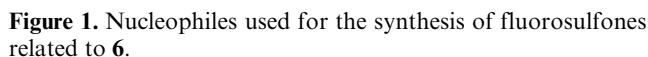[‡] University of Southampton.

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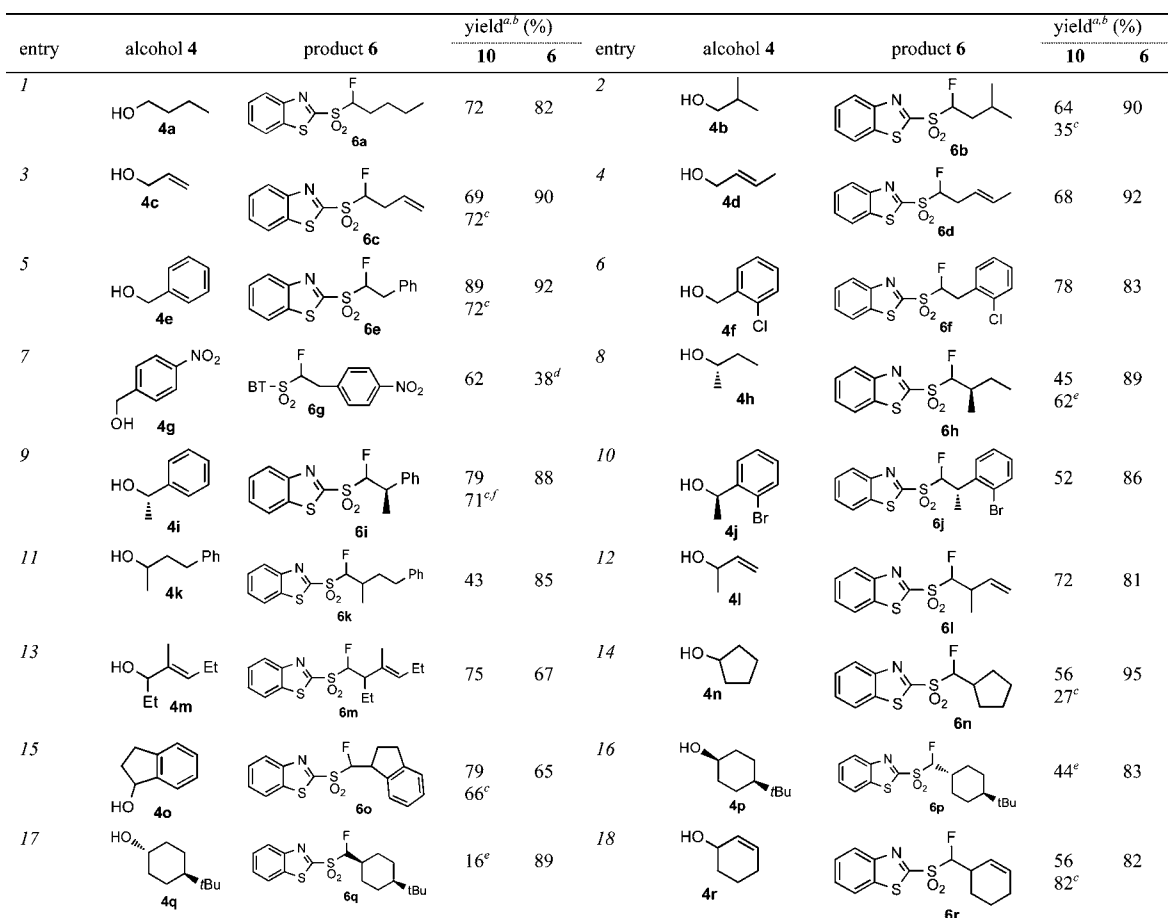
(5) Recent reviews: (a) Landelle, G.; Bergeron, M.; Turcotte-Savard, M.-O.; Paquin, J.-F. *Chem. Soc. Rev.* **2011**, *40*, 2867–2908. (b) Yanai, H.; Taguchi, T. *Eur. J. Org. Chem.* **2011**, 5939–5954. (c) Zajc, B.; Kumar, R. *Synthesis* **2010**, 1822–1836.

synthesis of fluoroalkenes having a chiral allylic center is much less well-developed, especially for chiral centers that do not contain a heteroatom.[6] We are only aware of one enantioselective synthetic method toward acyclic fluoroalkenes **1** with such a chiral center next to the =CF moiety ($\alpha_{(F)}$), recently reported by Jorgensen et al.[7] Organocatalyzed Michael addition involving readily available **2** leads to

Figure 1. Nucleophiles used for the synthesis of fluorosulfones related to **6**.

enantioenriched **3** in excellent *ee* (Scheme 1). Elegantly, reduction of **3** induces alkene formation, with *E* or *Z* fluoroalkenes accessible in good selectivities (~4:1) depending on the presence or absence of a chelating agent.

The Julia−Kocienski olefination reaction is now a popular method for fluoroalkene synthesis.[5] Nevertheless, to the best of our knowledge this method has not yet been reported for the synthesis of α_F-branched fluoroalkenes **1** (except one isolated example involving a cyclopropyl group).[8]

We report a general synthesis of $\alpha_{(F)}$-branched allylic fluoroalkenes, including homochiral fluoroalkenes, via the Julia−Kocienski reaction using a benzothiazolyl (BT) based fluorosulfone **6**. Crucially, this methodology relies on an effective synthesis of the required homochiral fluorosulfone **6**, which is also described here.

There are a number of possible syntheses of fluorosulfones **6**, such as opening of internal epoxides or conjugate additions to 3-substituted enones, both of which have been

Table 1. Synthesis of the Julia−Kocienski Substrate **6** by Mitsunobu and Krapcho Reactions

entry	alcohol 4	product 6	yield[a,b] (%)		entry	alcohol 4	product 6	yield[a,b] (%)	
			10	**6**				**10**	**6**
1	4a	6a	72	82	2	4b	6b	64 35[c]	90
3	4c	6c	69 72[c]	90	4	4d	6d	68	92
5	4e	6e	89 72[c]	92	6	4f	6f	78	83
7	4g	6g	62	38[d]	8	4h	6h	45 62[e]	89
9	4i	6i	79 71[c,f]	88	10	4j	6j	52	86
11	4k	6k	43	85	12	4l	6l	72	81
13	4m	6m	75	67	14	4n	6n	56 27[c]	95
15	4o	6o	79 66[c]	65	16	4p	6p	44[e]	83
17	4q	6q	16[e]	89	18	4r	6r	56 82[c]	82

a Isolated yield. *b* Secondary alcohols lead to a mixture of diastereomers; see text and SI. *c* At 20 °C. *d* 3% of 3-aryl-2-fluoroacrylate elimination product. *e* At reflux temp. *f* Racemic substrate.

reported by Hu using nucleophiles derived from **7a** (*n*-BuLi, HMPA) or **8** (Cs/K$_2$CO$_3$) (Figure 1).[9] To the best of our knowledge, alkylation reactions starting from **5**,[10] **7a**–**b**,[11] and **8**[12] using secondary halides have not been reported.[13] Our attempts starting from **5** only led to product **10** in low yield (eq 1). Moreover, a likely *in situ* halide-mediated racemization of starting material will preclude formation of homochiral derivatives **6**. Finally, direct fluorination leading to **6** is also a possibility. Relevant precedence was published by Zajc,[8] which showed however that complete fluorination was difficult to achieve. In addition, the required starting substrate would require similar efforts to obtain.

$$5 + 9 \xrightarrow[\substack{\text{MeCN, 100 °C, 5 h} \\ (39\%)}]{\text{Cs}_2\text{CO}_3 \text{ (2 equiv)}} 10 \quad (1)$$
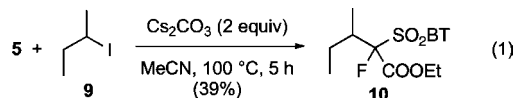
We have achieved a successful alkylation approach for the synthesis of fluorosulfone precursors **6** starting from secondary alcohols **4** instead of halides, using a modified Mitsunobu reaction (Scheme 1). Importantly, homochiral fluorosulfones **6** become accessible due to the ready availability of homochiral secondary alcohols. The required subsequent Krapcho decarboxylation reaction was recently reported by us,[10b] and significant improvements of this reaction are reported herein.

The Mitsunobu reaction was first optimized for primary alcohols (Table 1, entries 1−7). It was found that an azodicarboxamide reagent (azodicarbonyldipiperidide, ADDP)[14] was necessary to provide a basic enough intermediate to allow deprotonation of sulfone **5**, and reaction in toluene at elevated temperature gave the best yields. The reaction worked well with both benzothiazolyl (BT) and pyrimidyl sulfones, but no reaction was obtained using a pyridyl sulfone (see Supporting Information). All further optimization was carried out using BT-sulfones. From **5**, the Mitsunobu process with primary (including allylic, benzylic) alcohols gave good yields, which are comparable with the corresponding alkylation process with halides to give **10**.[10a,b] Nevertheless, more sterically hindered side chains such as isobutyl were more efficiently incorporated via the Mitsunobu process (41% via alkylation vs 64%, entry 2). In addition, reaction with *p*-nitrobenzyl alcohol

(6) Example of racemic methodology: Lin, X.; Zheng, F.; Qing, F.-L. *J. Org. Chem.* **2012**, *77*, 8696–8704.

(7) Jacobsen, C. B.; Nielsen, M.; Worgull, D.; Zweifel, T.; Fisker, E.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2011**, *133*, 7398–7404.

(8) Ghosh, A. K.; Zajc, B. *J. Org. Chem.* **2009**, *74*, 8531–8540.

(9) (a) Ni, C.; Li, Y.; Hu, J. *J. Org. Chem.* **2006**, *71*, 6829–6833. (b) Ni, C.; Zhang, L.; Hu, J. *J. Org. Chem.* **2008**, *73*, 5699–5713.

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(11) For **7a**: Asakura, N.; Usuki, Y.; Iio, H.; Tanaka, T. *J. Fluorine Chem.* **2006**, *127*, 800–808. (b) For **7b**: Zhu, L.; Ni, C.; Zhao, Y.; Hu, J. *Tetrahedron* **2010**, *66*, 5089–5100.

(12) Surya Prakash, G. K.; Chacko, S.; Vaghoo, H.; Shao, N.; Gurung, L.; Mathew, T.; Olah, G. A. *Org. Lett.* **2009**, *11*, 1127–1130.

(13) The alkylation reaction of **7b** with hindered halides such as isobutyl iodide has been described in 62% yield; see ref 11b.

(14) (a) Tsunoda, T.; Yamamiya, Y.; Ito, S. *Tetrahedron Lett.* **1993**, *34*, 1639–1642. (b) Lai, J.-Y.; Yu, J.; Hawkins, R. D.; Falck, J. R. *Tetrahedron Lett.* **1995**, *36*, 5691–5694.

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Table 2. The Julia−Kocienski Reaction Leading to Allylic α$_{(F)}$-Branched Fluoroalkenes

entry	product	yield (%)[a] (Z/E ratio)[b]
1	**1a**	63 (29:71)
2	**1b**	68 (25:75)
3	**1c**	66 (31:69)
4	**1d**	72 (40:60)
5	**1e**	57 (49:51)
6	**1f**	58 (83:17)
7	**1g**	49 (24:76)
8	**1h**	87 (26:74)
9	**1i**	51 (29:71)
10	**1j**	51 (62:38)

[a] Isolated yield. [b] Determined by ^{19}F NMR analysis.

gave a good yield (entry 7), while the corresponding alkylation using *p*-nitrobenzyl bromide gave no reaction. Alternatively, Pd-catalyzed allylation of **5** with cinnamyl methyl carbonate has also been described (85% yield) as a way to introduce allylic groups.[15]

(15) Zhao, X.; Liu, D.; Zheng, S.; Gao, N. *Tetrahedron Lett.* **2011**, *52*, 665–667.

The reaction of secondary alcohols (entries 8−18) proceeded generally in good to very good yields. In all cases, a mixture of fluoride epimers was produced (see table in the SI), which however ultimately is inconsequential for the Julia−Kocienski olefination. The clean inversion of configuration was unambiguously proven by chiral HPLC for the Mitsunobu reaction with homochiral (*S*)-2-butanol and (*S*)-1-phenyl ethanol (entries 8−9). In each case a mixture of homochiral fluoride epimers **10h−i** was obtained (see SI). Benzylic and allylic secondary alcohols react in higher yields compared to saturated secondary alcohols, though with the latter a higher temperature can be employed to increase the yield. Of note is the formation of **10l** (entry 12), which was only accompanied by < 5% of S_N2' adduct. This is in stark contrast to the corresponding alkylation reaction of **5** with secondary allylic bromides, which exclusively led to the corresponding S_N2' product,[10b] and is further illustration of the expanded scope provided by the Mitsunobu process. The reaction has also been demonstrated on cyclic alcohols, with the benzylic **4o** leading to a higher yield than **4n**. Given the large size of the nucleophile, the Mitsunobu reaction with *cis*-4-*t*Bu cyclohexanol **4p** is higher yielding compared with the *trans* stereomer **4q**. Compared to the saturated cyclohexanols, a much higher yield was obtained using 2-cyclohexenol (at 20 °C).

The next step is a decarboxylation reaction to give the desired Julia−Kocienski fluorosulfone precursors **6**, which was generally achieved in good to excellent yields under Krapcho decarboxylation conditions.[10b] A considerable improvement in yield and purity was achieved by replacing NaCl by KBr and increasing the amount of water to 100 equiv. The less basic bromide significantly decreased the amount of sulfone elimination, which is a side reaction with allylic and benzylic substrates (see SI).

The Julia−Kocienski reaction involving fluorosulfones **6** gave low yields and incomplete conversions with *t*BuOK as base (not shown). To avoid HMPA as the additive, NaHMDS was then employed as the base (Table 2),[16] leading to good yields. With aromatic aldehydes *E*-alkenes were obtained as the major isomer, but aliphatic aldehydes gave the *Z*-alkene as the major isomer.[17] The structure of *E*-**1i** was unambiguously determined by X-ray crystallography (see SI). Interestingly, while the observed diastereoselectivity could result from the stereoselectivity and possible reversibility of the initial aldehyde addition step leading to **11**, the relative rates of the subsequent Smiles rearrangement of the up to four possible diastereomers of **11** (M = Na), or even the precise subsequent elimination mechanism,[5,18] the Jorgensen fluoroalkene *E/Z* ratios arise from a different stereodefining step. In that case, the selectivity of the borohydride β-ketosulfone reduction (Scheme 1), also leading to **11** (M = Li), appears to be translated into the fluoroalkene *E/Z* ratio.

In conclusion, we report the first synthesis of homochiral α-fluorinated BT-sulfones with a chiral center in the β-position, based on a successful modified Mitsunobu reaction. It was shown that the Mitsunobu process has a much wider structural scope compared to the equivalent alkylation starting from alkyl halides. Both enantiomeric forms are readily accessible thanks to the wide availability of homochiral alcohols. The application of this reaction, together with an optimized procedure for the required subsequent Krapcho decarboxylation, results in a convenient method for the synthesis of homochiral fluoroalkenes with a branched alkyl group next to the =CF center, using a Julia−Kocienski reaction. The procedure allows a wide substrate scope, with regard to both substitution of the fluorinated benzothiazole and the nature of the aldehyde (aliphatic and aromatic aldehydes). Interestingly, the former leads to fluoroalkenes predominantly with *Z*-configuration, while the latter leads to *E*-alkenes as the major isomer. Nevertheless, the observed diastereoselectivity levels are within the range usually observed for Julia−Kocienski mediated fluoroalkene formation.

Supporting Information Available. General reaction procedures (including optimization of the Krapcho decarboxylation); characterization of all compounds; confirmation of optical purity of **6i**, **10h**, and **10i**; X-ray structure of **6o**; copies of NMR spectra of all compounds (^{1}H, ^{13}C, ^{19}F). This material is available free of charge via the Internet at http://pubs.acs.org.

(16) Chevrie, D.; Lequeux, T.; Demoute, J. P.; Pazenok, S. *Tetrahedron Lett.* **2003**, *44*, 8127–8130.

(17) These results are consistent with observations by Zajc; see ref 8.

(18) (a) Aissa, C. *Eur. J. Org. Chem.* **2009**, 1831–1844. (b) Robiette, R.; Pospisil, J. *Eur. J. Org. Chem.* **2013**, 836–840.