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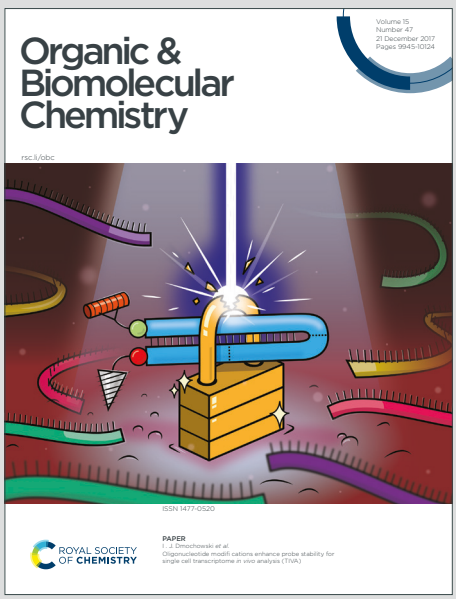

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COMMUNICATION

Stereodivergent synthesis of alkenes by controllable *syn*-/*anti*-fragmentation of β-hydroxysulfonyl intermediates

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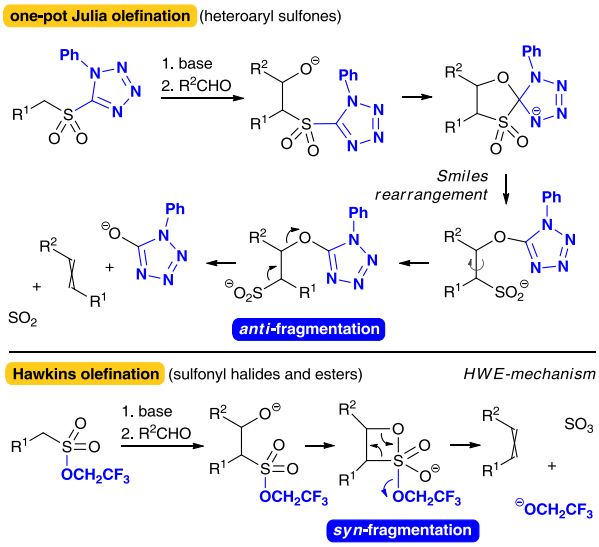
Reduction of the carbonyl group in acylated trifluoroethyl alkanesulfonates follows the Felkin-Ahn selectivity, and so-formed diastereomeric β-hydroxysulfonyl intermediates undergo *syn*- and *anti*-fragmentation, depending on the reaction conditions. In effect, isomeric *E*- and *Z*-alkenes are formed in a stereodivergent manner, which mimics mechanistic manifold of the Peterson olefination.

Formation of the C=C bonds play a key role in construction of the molecular frameworks, and numerous methods, based on reactions of heteroorganic derivatives of phosphorus, silicon and sulfur, have been developed.[1] In the most prominent variants, phosphonium (Wittig reaction) and phosphonate (Horner-Wadsworth-Emmons reaction) precursors add to the carbonyl compounds to produce four-membered ring oxaphosphetanes, which spontaneously *syn*-fragment to the olefins.[2] A more diverse process can be realized with silyl-stabilized carbanions (Peterson olefination), where β-hydroxysilanes undergo controllable *syn*- and *anti*-fragmentations. In effect, each of the diastereomeric intermediates can be transformed into *E*- or *Z*-alkene, depending on the reaction conditions.[3] In turn one-pot Julia olefination with heteroaryl sulfones usually runs by the initial aldol-type addition, followed by Smiles rearrangement and *anti*-fragmentation with release of SO_2 and aryloxide byproducts (Scheme 1, top).[4] Recently, we systematically studied[5,6] another sulfur-based olefination reaction, mechanistically similar to the phosphorus-based transformations. The method, pioneered many years ago by Hawkins,[7] utilizes sulfonyl halides and esters, which add to the carbonyl compounds, cyclize to four-membered ring intermediates, and spontaneously *syn*-fragment to the olefins (Scheme 1, bottom). Although yields of the olefinic products were usually high, attempts at control of the *E*/*Z*-isomer ratio[6]



Scheme 1. One-pot Julia olefination with heteroaryl sulfones (top), and Hawkins olefination with activated alkanesulfonates (bottom).

were only moderately successful, due to poor selectivity of the initial aldol-type addition, and limited equilibration of adducts formed with unstabilized alkanesulfonates.[5] Therefore, to improve the selectivity we considered alternative generation of β-hydroxysulfonates by acylation and diastereoselective reduction of the carbonyl group. A similar approach was reported by Jørgensen[8] on acylated benzothiazoyl sulfones, which were selectively reduced to isomeric alcohols. Next, Smiles rearrangement and *anti*-fragmentation of the intermediates led to isomeric alkenes. Analogously, Warren[9] applied the acylation-reduction approach to perform *E*-selective Horner-Wittig reaction with phosphine oxides. Importantly in the mentioned reports diastereomerically pure intermediates were transformed into single isomer of the olefins, following specific mechanism of the fragmentation step. In the present report we demonstrate Felkin-Ahn reduction of acylated trifluoroethyl alkanesulfonates, followed by controllable *syn*- and *anti*-fragmentation of the

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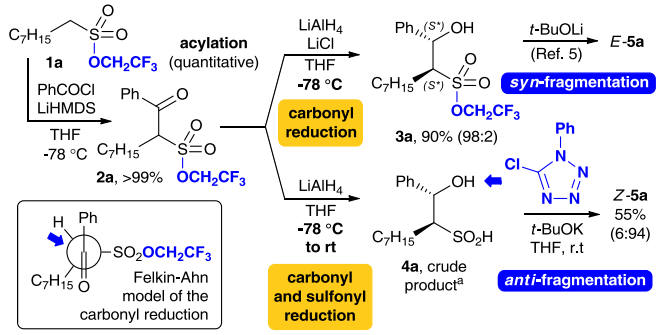
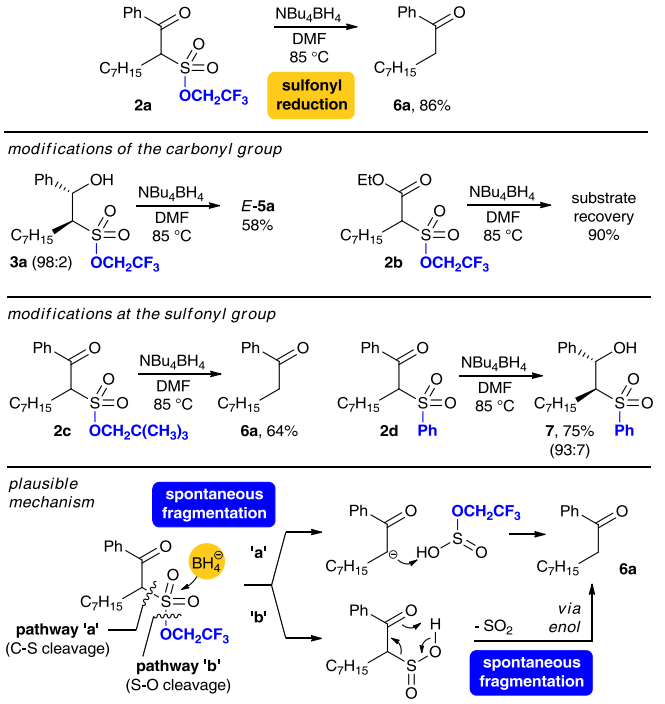
intermediates to both isomers of the alkenes, that mimics mechanistic manifold of the Peterson reaction.

In a preliminary experiment mixture of carbanion precursor **1a**[5,6] and benzoyl chloride was treated with LiHMDS in THF at -78 °C.[10] After aqueous workup acylated product **2a** was isolated in a quantitative yield with excellent purity (see the Supporting Information for details). Next, we tested various reducing agents of **2a**, and identified a combination of $LiAlH_4$/LiCl[‡] in THF at -78 °C as optimal for the carbonyl reduction, giving β-hydroxysulfonate **3a** in 90% of yield with high diastereoselectivity (98:2, based on ^{1}H NMR, Scheme 2, top).



Scheme 2. Synthesis, $LiAlH_4$ reductions, and further transformations of acylated sulfonate **2a** to the *E*-alkene (top), and to the *Z*-alkene (bottom). [a] The β-hydroxysulfinic acid **4a** decomposed on attempt of chromatographic purification on a silica gel.

The observed stereochemical course of the reaction followed the Felkin-Ahn model of selectivity, where large electronegative sulfonyl group is located perpendicularly to the carbonyl moiety, as observed earlier by Jørgensen,[8] and Marcantoni and Bartoli.[11] The produced *S*,S**-isomer of the alcohol **3a** was known to selectively *syn*-fragment on treatment with *tert*-BuOLi in THF at rt, giving *E*-1-phenyl-1-nonene (*E*-**5a**).[5] Indeed, when we repeated the three-step sequence of acylation→reduction→fragmentation, with single chromatographic purification of the final mixture, alkene **5a** was isolated as a predominant *E* isomer (98:2) in overall yield 85%, based on **1a**. Interestingly, we observed also that reduction of **2a** with equimolar amount of $LiAlH_4$ at -78 °C, followed by warming of the reaction mixture to rt, gives β-hydroxysulfinic acid **4a**, as a main product (Scheme 2, bottom). Although stereochemical structure of **4a** was not unequivocally established, we assumed that the sulfonyl reduction is a secondary process, which does not affect the relative *S*,S** configuration at the stereogenic centers, controlled by the initial Felkin-Ahn attack on the carbonyl group.[§] Importantly formation of **4a** paved the way to the alternative fragmentation mechanism, inspired by the last step of the one-pot Julia olefination (Scheme 1, top). We reckoned that basic treatment of **4a** with 5-chloro-1-phenyl-1*H*-tetrazole can activate the hydroxyl group toward *anti*-fragmentation,[§§] giving alkene of opposite configuration, as compared with reaction of **3a**. Indeed, using the activating agent and *tert*-BuOK in THF, alkene **5a** was formed as a predominant *Z*-isomer (6:94) in 55% of yield (based on **1a**, Scheme 2, bottom). The stereochemical course of the reaction confirmed our expectations, concerning of the complementary fragmentation mechanisms, where single diastereomer of the intermediate translates into both isomers of the alkene.[12] Amazingly, in further studies we discovered yet another transformation of acylated sulfonate **2a**, in which carbonyl group remains intact, but the $SO_2OCH_2CF_3$ group is selectively cleavaged, giving ketone **6a**. The chemoselective reduction-fragmentation of the sulfonyl group was performed using equimolar amount of NBu_4BH_4 in DMF at 85 °C (Scheme 3, top).



Scheme 3. Reductive cleavage of the sulfonyl group in acylated sulfonate **2a** (top), mechanistic studies (middle), and plausible reaction mechanism (bottom).

To elucidate mechanism of the formation of **6a** we tested β-hydroxysulfonate **3a** and modified substrates **2b-d** under the same conditions (Scheme 3, middle). Reaction of alcohol **3a** gave only alkene *E*-**5a** instead of ketone that ruled out reduction of the carbonyl group, as a first step of the transformation. Thus, we assumed that in the polar aprotic solvent (DMF) sulfonyl group is preferably attacked by the borohydride, and nucleophilic substitution at the sulfur atom releases ketone enolate (pathway 'a', Scheme 3, bottom), or 2,2,2-trifluoroethoxide ('pathway 'b', Scheme 3, bottom),[13] as a leaving group. To obtain more insights into the process we tested ester derivative **2b** and *neo*-pentyl sulfonate **2c**. Basicity considerations suggested that leaving group ability of ester enolate in **2b**, and *neo*-pentoxide in **2c** should be reduced, as compared with the parent structure of **2a**. Interestingly, in our hands only the first modification inhibited the reaction, whereas sulfonate **2c** gave ketone **6a** in 64% of yield, supporting mechanism, in which the C-S bond is preferentially cleavaged (pathway 'a'). However, reaction of β-ketosulfone **2d** was more difficult to interpret, suggesting a subtle balance

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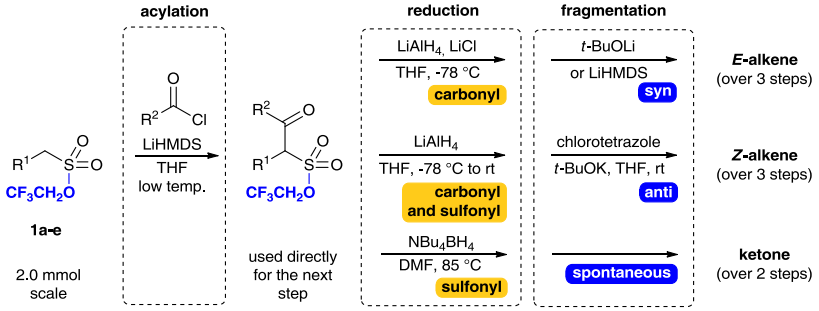
between electrophilic properties of carbonyl and sulfonyl groups, which seemed to be beyond the scope of the current studies.

Finally, after careful optimization of the reaction conditions of acylation, reduction and fragmentation for a broad palette of substrates we performed a series of 3-step (for alkenes) or 2-step (for ketones) transformations of alkanesulfonates **1a-e**, with single chromatographic purification of the final products (see the Supporting Information for details). The results are presented in Table 1.



Entry	Sulfonate R^1=	Acyl chloride R^2=	*E*-alkenes		*Z*-alkenes		Ketones
			Isolated yields[a]	*E*/*Z*[b]	Isolated yields[a]	*E*/*Z*[b]	Isolated yields[a]
1	Me, **1b**	1-naphthyl	**5b**, 82%	97:3	53%	8:92	**6b**, 73%
2	Et, **1c**		**5c**, 73%	94:6	51%	8:92	**6c**, 68%
3	*i*-Pr, **1d**		**5d**, 76%	>99:1	39%	48:52	**6d**, 61%
4	*c*-C_6H_{11}, **1e**	*n*-C_7H_{15}	**5e**,[c] 65%	87:13	34%	26:74	**6e**, 66%
5		*c*-C_6H_{11}	**5f**, 66%	97:3	[d]	–	**6f**, 62%
6		Ph	**5g**, 79%	>99:1	40%	62:38	**6g**, 70%
7	C_7H_{15}, **1a**	CH_2=$CHCH_2CH_2$	**5h**, 61%	90:10[e]	35%	8:92[e]	**6h**, 70%
8		*n*-C_7H_{15}	**5i**, 69%	90:10	53%	7:93	**6i**, 73%
9		*c*-C_6H_{11}	**5e**,[c] 74%	97:3	25%	7:93	**6e'**, 67%
10		*tert*-Bu	**5j**, 39%	>99:1	[d]	–	**6j**, 53%
11		$Ph(CH_2)_2$	**5k**, 66%	89:11	41%	10:90	**6k**, 79%
12		$PhCH_2$	**5l**, 46%	91:9	26%	12:88	**6l**, 59%
13		4-ClC_6H_4	**5m**, 87%	98:2	53%	8:92	**6m**, 83%
14		Ph	**5a**, 85%	98:2	55%	6:94	**6a**, 86%
15		1-naphthyl	**5n**, 81%	95:5	50%	16:84	**6n**, 66%
16		4-MeC_6H_4	**5o**, 82%	98:2	57%	37:63[f]	**6o**, 88%
17		4-$MeOC_6H_4$	**5p**, 71%	98:2	59%	90:10[f]	**6p**, 72%

Table 1. Syntheses of isomeric alkenes and ketones by divergent reduction-fragmentation of acylated trifluoroethyl alkanesulfonates (**1a-e**) at 2.0 mmol scale. [a] The yields were based on **1a-e**. [b] The E/Z-isomer ratio of alkenes was based on GC. [c] Alkene **5e** was formed from two combination of substrates (entries 4 and 9). [d] Yield of alkene was <10 %. [e] The approximate E/Z-isomer ratio was based on ^{13}C NMR (isomers of **5h** were inseparable by GC). [f] Selectivities of alkenes **5r,s** produced under tetrazole activation conditions resulted from use of β-hydroxysulfinic acids partially transformed to the E-alkenes (most likely by self-protonation and non-stereospecific decomposition via carbocations).

We observed that in most cases *E*-alkenes and ketones are formed in good to very good yields, and best results are obtained for a combination of linear-chain sulfonates (**1a-c**) and aroyl chlorides (highlighted in yellow at the Table 1). In turn yields and selectivities of the *Z*-alkenes were lower, in particular for branched sulfonates (**1d,e**) and for branched acyl chlorides (e.g. cyclohexanecarbonyl chloride). Noteworthy, in one-pot Julia olefination with heteroaromatic sulfones aromatic aldehydes preferably give *E*-alkenes,[14] that is attributed to a non-stereospecific elimination pathway.[4,15] In our studies 1-alkyl-2-arylethylenes **5a-c**,**m-p** were formed as predominant *Z*-isomers, and only for donor-substituted benzoyl chlorides intermediate β-hydroxysulfinic acids displayed limited stability and (prior to the tetrazole activation) underwent spontaneous non-stereospecific decomposition to the *E*-alkenes, that altered selectivities in entries 16 and 17.

In conclusion we presented chemoselective reductive transformations of acylated trifluoroethyl alkanesulfonates. Their reduction with $LiAlH_4$ leads to β-hydroxysulfonates or β-hydroxysulfinic acids, depending on the reaction conditions. In the following step the diastereomeric intermediates undergo base-induced *syn*- and *anti*-fragmentations to *E*- and *Z*-alkenes, respectively. The divergent transformations mimic mechanistic manifold of the Peterson olefination, with controllable switch between the fragmentation mechanisms. In addition we observed that reduction of the substrates with NBu_4BH_4 in DMF causes cleavage of the sulfonyl group, giving ketones.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

‡ $LiAlH_4$ reduction of **2a** in THF at -78 °C caused partial deprotonation of the substrate, which was recovered after aqueous workup (16%). Presence of two-fold molar excess of LiCl partially limited the process (to ca. 6%). See the Supporting Information for details.

§ The assumption was supported by the fact that treatment of **3a** with $LiAlH_4$ with warming of the reaction mixture to rt resulted in the same crude product **4a**. Interestingly yield of *Z*-**5a** prepared from **1a** by a four step procedure (with the reduction carried out as two individual steps **2a**→**3a**→**4a**) was even slightly higher (60%; 12:88), than obtained by a three-step sequence, shown at Scheme 2, bottom (55%; 6:94).

§§ Reaction of **4a** with 5-chloro-1-phenyl-1*H*-tetrazole was carried out in the presence of two equivalents of strong base (*t*-BuOK), so as both acidic groups (SO_2H and OH) were deprotonated. Therefore we reckoned that the activation concerns more nucleophilic *O*-anion of the hydroxyl group, and thus the following fragmentation process mimics the last step of the one-pot Julia olefination. However, alternative activation of the SO_2H group was attempted by reaction of (neutral) **4a** with *N,N'*-dicyclohexylcarbodiimide (DCC) in $CHCl_3$ at 0 °C→rt, which resulted in the formation of alkene **5a** of opposite (*E*) configuration (52%; 95:5). In the latter case the most likely scenario involves cyclization, followed by *syn*-fragmentation of four-membered ring intermediate, as in case of **3a**.

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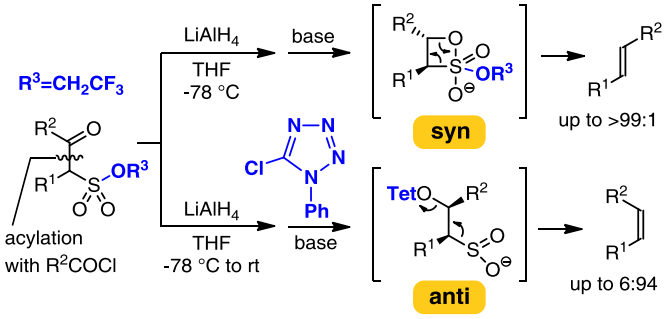

Text

Complementary fragmentation mechanisms of Hawkins and one-pot Julia olefinations were applied for stereodivergent synthesis of alkenes.

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