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Olefination with Sulfonyl Halides and Esters: Scope, Limitations, and Mechanistic Studies of the Hawkins Reaction

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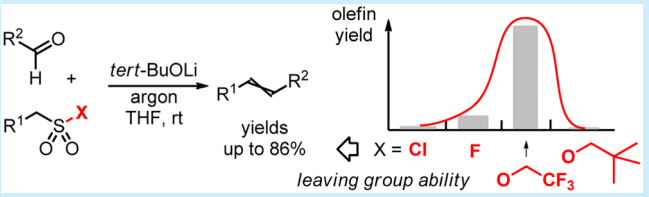
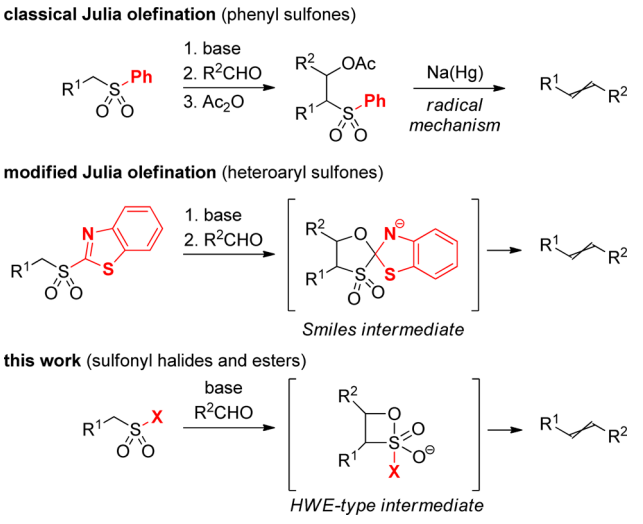
Supporting Information

ABSTRACT: Carbanions of alkanesulfonyl halides and esters react with nonenolizable carbonyl compounds to give olefins. Mechanistic studies reveal that initial aldol-type addition of the carbanions is followed by cyclization−fragmentation to alkenes, and the leaving group on the sulfonyl moiety (RSO_2X) controls carbanion stability and rate of the olefin formation.



Formation of the C=C bonds plays a fundamental role in organic synthesis, and numerous reactions of carbonyl compounds with derivatives of phosphorus, sulfur, and silicon were described in the literature. For sulfur-based olefinations the most common protocol, known as Julia olefination, involves addition of sulfone carbanion, acylation of so-formed aldol-type adduct, and reduction. The methodology was further improved with heteroaromatic sulfones, which add to carbonyl compounds and spontaneously undergo Smiles rearrangement, giving olefins in a one-pot transformation (Scheme 1, top).[1]

Scheme 1. Sulfur-Based Olefination Reactions[1]



Interestingly, both mechanistic schemes differ substantially from reactivity of phosphorus reagents (e.g., organic phosphonates in Horner−Wadsworth−Emmons reaction), which form intermediate 4-membered oxaphosphetanes.[2] A similar mechanism for sulfur-based olefinations is much less common, although important precedents were described by Hawkins,[3] Kagabu,[4] and Nader.[5] Process utilizing carbanions of alkanesulfonates as olefinating reagents was described for the first time by Hawkins,[3] who tested a series of mesylates. Indeed, some of them, namely 2,2,2-trifluoroethyl and aryl mesylates, deprotonated with *t*-BuLi at low temperature, underwent the expected transformation with benzophenone to give 1,1-diphenylethylene in moderate to goods yields. However, reaction of benzaldehyde with 2,2,2-trifluoroethyl ethanesulfonate (even used in excess) was much less efficient, giving alkene in only 23% of yield. Hawkins also performed preliminary mechanistic studies, but the limited scope of substrates, moderate yields of products, and superficial stereochemical studies made the report a proof of concept, with little practical application. Shortly thereafter, Kagabu[4] described reactions of semistabilized carbanions of arylmethanesulfonyl fluorides, generated with potassium carbonate under mild conditions. With substituted benzaldehydes, he synthesized a set of stilbenes in moderate to good yields and observed a correlation between electrophilicity of the carbonyl group and isomer ratio of the products. Unfortunately, under these conditions nonstabilized precursors, as mesyl fluoride, condensed only slightly with benzaldehyde. Interestingly, in a similar process, Nader[5] applied mesyl chloride in a reaction with potassium fluoride as base and as a source of fluoride ion for the conversion to mesyl fluoride in a one-pot process. The olefination was demonstrated only on electrophilic ketones and required very harsh reaction conditions (110−170 °C). To the best of our knowledge, further studies of the olefination reaction with precursors of nonstabilized carbanions were not reported in the literature.

In our report, we present a new convenient protocol, which makes the Hawkins olefination a useful methodology for the synthesis of selected alkenes.

Our studies began from preliminary experiments, in which 1-octanesulfonyl chloride (**1a**) was deprotonated with LiHMDS in THF at −78 °C (Scheme 2, top). So-formed carbanion

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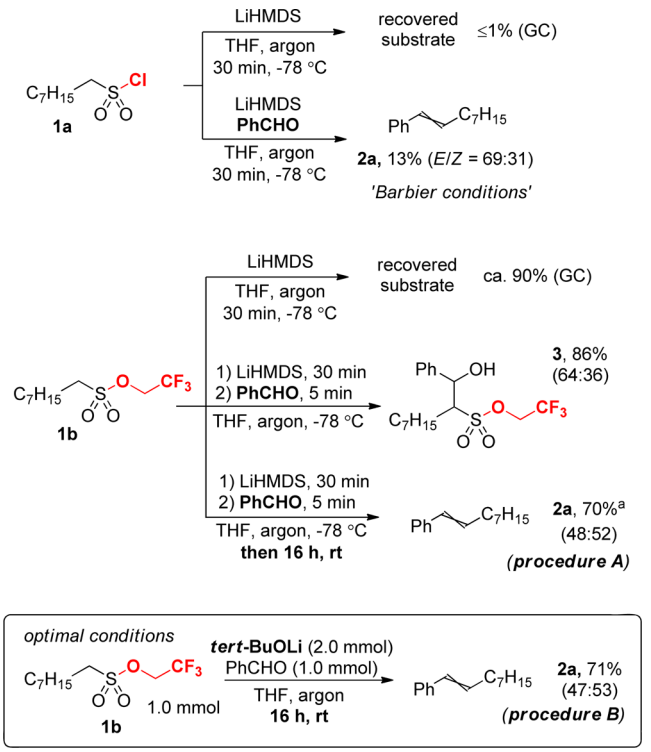
Scheme 2. Preliminary Experiments and Optimization[7]



[a]LiHMDS (1.3 mmol), PhCHO (1.5 mmol); with LiHMDS (1.0 mmol), PhCHO (1.0 mmol) the yield decreased to 57% (48:52).

appeared to be very unstable, and most likely eliminated to sulfene,[6] giving an ill-defined mixture of polar products. However, when the base was added to a mixture of **1a** and benzaldehyde (Barbier conditions), the expected 1-phenylnon-1-ene (**2a**) was isolated in 13% yield. The result proved the $E1_{cb}$ mechanism of the elimination, where the short-living carbanion was trapped in situ to form alkene. Then, under similar conditions we tested 2,2,2-trifluoroethyl 1-octanesulfonate (**1b**). The poor leaving group ability of trifluoroethoxide, as compared with chloride, increased the stability of the carbanion, and after 30 min at −78 °C we were able to recover unreacted ester **1b** with 90% of yield (GC). Interestingly, the same carbanion, trapped with benzaldehyde, led only to an aldol-type adduct **3**, with essentially no traces of alkene formed at low temperature. The data clearly demonstrated that the character of the leaving group influences both carbanion stability and rate of the olefin formation, and thus, the latter process may run at higher temperature. Indeed, when the reaction mixture was kept at rt for 16 h, alkene **2a** was isolated in 70% (procedure A). Attempts of application of sodium or potassium bases (*t*-BuOK, NaHMDS, etc.) under similar conditions led mainly to polar byproducts. However, after a short optimization, we recognized lithium *tert*-butoxide as an optimal base. With an equimolar proportion of substrates and a 2-fold excess of the base in anhydrous THF under argon, combination of the reagents at rt for 16 h led to alkene **2a** isolated in 71% of yield as a mixture of two isomers (*E*/*Z* = 47:53) (procedure B; Scheme 2, bottom). With the optimized procedure, we tested various aromatic aldehydes to obtain substituted alkenes (Figure 1).[8] Those substituted with electron-donating groups (entries **2c**−**g**) and a naphthalene core (**2h**,**i**) led to the corresponding alkenes in high yields

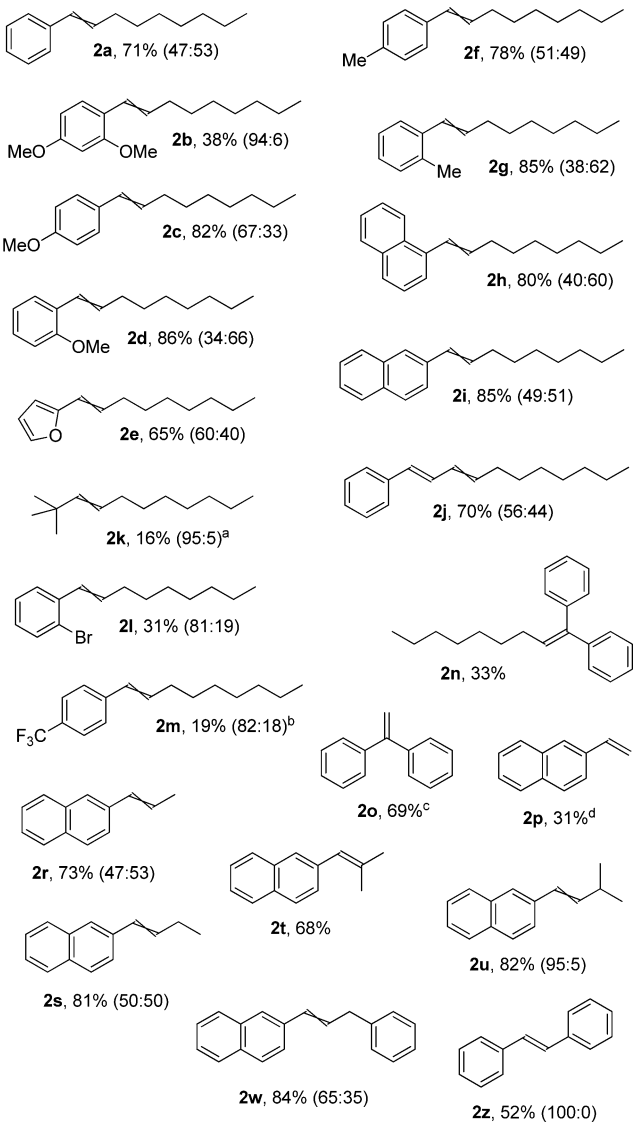


Figure 1. Alkenes **2a**−**z** synthesized form 2,2,2-trifluoroethyl alkanesulfonates under the conditions of procedure B.[7] Key: (a) procedure A, 39% (89:11); (b) procedure A, 30% (70:30); (c) procedure B at 65 °C, 71%; (d) byproducts were formed.

(65−86%), whereas the presence of acceptors as *o*-Br (**2l**, 31%), *p*-CF_3 (**2m**, 19%), and alkyl *tert*-butyl group (**2k**, 16%) decreased the yields. The reaction of benzophenone with **1b** was only moderately efficient (**2n**, 33%), but a higher yield was obtained in the reaction of 2-naphthaldehyde with 2-propanesulfonate (**2t**, 68%). Evidently, the combination of electrophilic aldehyde with secondary sulfonate appeared to be more efficient for the synthesis of trisubstituted olefin, as compared with ketone as a substrate. Finally, we also tested reactions of various 2,2,2-trifluoroethyl alkanesulfonates with 2-naphthaldehyde. Ethyl, propyl, isobutyl, and 2-phenylethylsulfonates led to the desired products in good yields, with the only exception of semistabilized phenylmethanesulfonate, which in reaction with benzaldehyde gave stilbene **2z** as a pure *E* isomer in 52% of yield. Limiting cases of the protocol were reactions of **1b** with *p*-(dimethylamino)benzaldehyde, pentafluorobenzaldehyde, and enolizable hydrocinnamaldehyde (3-phenylpropionaldehyde), which failed to give the expected alkenes. Besides, an attempt of a reaction between benzophenone and secondary

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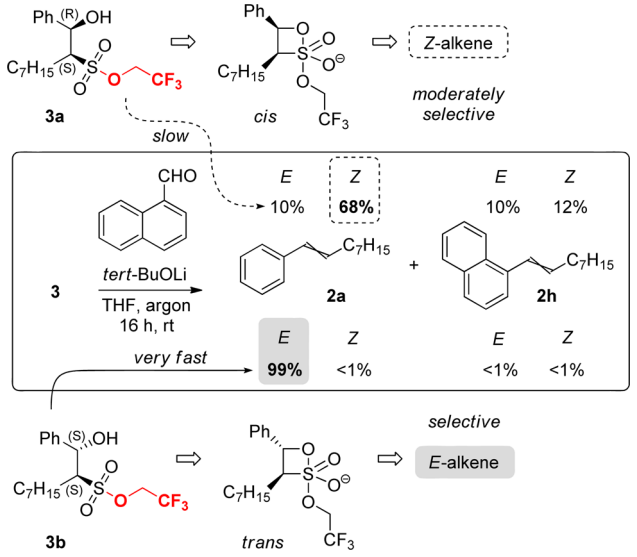
carbanion precursor 2,2,2-trifluoroethyl 2-propanesulfonate at 65 °C led only to traces of tetrasubstituted olefin.

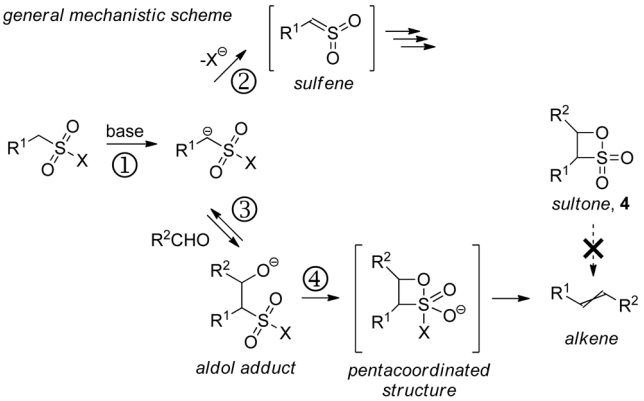
To better understand these factors, which control the reaction yield and stereoselectivity, we focused on the mechanism of the transformation. First, intermediate aldol-type adducts, isolated as single isomers **3a** and **3b** (for stereochemistry assignments, see the Supporting Information),[9] were subjected to conditions of procedure B with equimolar amounts of 1-naphthaldehyde (Scheme 3). The diasteroisomers

Scheme 3. Reactions of Aldol-Type Adducts 3 with 1-Naphthaldehyde under the Conditions of Procedure B[7]

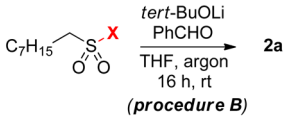


differed in reactivity in numerous points. A less polar, major isomer **3a** reacted slowly (ca. 1.5 h), giving a mixture of alkenes with predominant *Z* isomer of **2a** but also a substantial amount of *E*-**2a** and cross-products *E*- and *Z*-**2h**. In turn, reaction of **3b** was very fast (completed after 2 min at rt, as determined by ^{1}H NMR)[7] and led almost exclusively to *E*-**2a**. Most likely in the first case, the system had enough time for excessive equilibration of the aldol addition that it diminished overall selectivity, whereas in the latter fast stereospecific cyclization–fragmentation led to one isomer of the olefin. Consideration of the general mechanistic scheme of the reaction led to the following conclusions (Scheme 4, top). First, base deprotonates the precursor, giving a relatively stable carbanion (step 1). Then, two competitive processes can occur: intramolecular elimination to sulfene (step 2) and intermolecular addition to the carbonyl compound, giving a mixture of diastereoisomeric aldol-type adducts (as *O*-anions, step 3). As the first process seems to be irreversible (at least for **1a**), the second one is reversible, as demonstrated by the formation of cross-product with 1-naphthaldehyde (**2h**). Then, the diastereomeric adducts cyclize to pentacoordinated intermediates, which spontaneously fragment to alkene (step 4). Although the exact structure of the intermediates remains speculative, it is known that electronegative ligands present in apical positions tend to stabilize pentacoordinated sulfur compounds.[3,10] To support the hypothesis, we synthesized sultone **4** (R^1 = C_7H_{15}; R^2 = Ph) from **2a** and chlorosulfonic acid in CD_2Cl_2/dioxane-d_8, according to the procedure described by Cerfontain.[11] Although the product appeared to be too unstable for the isolation, we characterized it in solution with ^{1}H and ^{13}C NMR

Scheme 4. General Mechanistic Scheme of the Olefination Reaction (Top) and Reactions of 1-Octanesulfonyl Halides and Esters with Benzaldehyde under the Conditions of Procedure B (Bottom)



synthesis of alkene **2a** *from sulfonyl halides and esters*



	yield of **2a**	*E*/*Z* ratio
X = Cl	≤1%	73:27
F	13%	40:60
O CF3	**71%**	47:53
O	0%	
	(aldol adducts 55% + recovered ester 42%)	

and subjected it to conditions of procedure B.[7] Only traces of alkene **2a** were detected in the reaction mixture, supporting that sultone **4** is not an intermediate of the olefination reaction, at least for model alkene **2a**. Then, the formulated mechanism was justified by a series of reactions of 1-octanesulfonyl halides and esters with benzaldehyde under conditions of procedure B (Scheme 4, bottom). At rt, 1-octanesulfonyl chloride **1a** with *t*-BuOLi easily eliminated to sulfene, giving only traces of olefin **2a** (≤1%). 1-Octanesulfonyl fluoride, with a less nucleofugal fluoride group, gave 13% of alkene, whereas **1b** gave as much as 71%. In turn, under the same conditions, neopentyl 1-octanesulfonate led exclusively to a mixture of diastereomeric aldol adducts (55%) and unreacted substrate (42%). In this case, very stable carbanion adds to benzaldehyde (although equilibrium of the aldol-type addition seems to be less favored at rt), but further transformation displays a substantial barrier, and in effect, alkenes are not formed.

Finally, we carried out follow-up studies to demonstrate the potential of the method. Preparation of **2a** from **1b** and benzaldehyde was performed on a 100 mmol scale with nondried, commercially available THF and concentrated lithium *tert*-amoxide (2-methyl-2-butoxide), a cheaper alternative to *t*-BuOLi. After aqueous workup and filtration of the mixture through a pad of silica gel in cyclohexane, alkene **2a** of excellent purity was isolated in 79% yield (Scheme 5, top).

An interesting multistep process was performed on 2,2,2-trifluoroethyl 3-iodopropanesulfonate, **5** (Scheme 5, bottom). Reaction with a 2-fold excess of benzaldehyde and a corresponding amount of base led to intermediate aldol adduct, which cyclized to the tetrahydrofuran ring (path a,[12] instead of attacking the sulfonyl group, path b). In the following step, olefination with a second equivalent of benzaldehyde present in the reaction mixture completed the transformation to give functionalized product **6** as a single *E* isomer in 64% yield.

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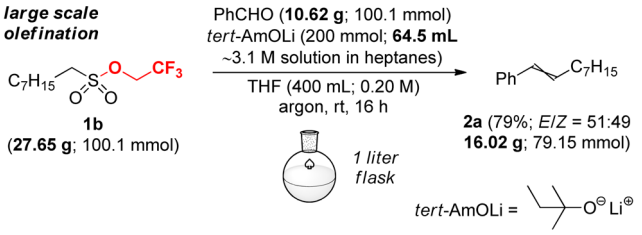
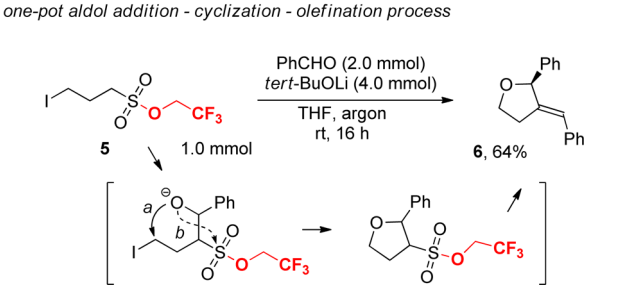
Scheme 5. Follow-up Studies: Large-Scale Olefination under Conditions of Procedure B (Top) and One-Pot Synthesis of Functionalized Alkene 6 (Bottom)[7]





In conclusion, we presented a convenient protocol, utilizing lithium *tert*-butoxide as a base, to perform olefination of carbonyl compounds with 2,2,2-trifluoroethyl alkanesulfonates. The process substantially differs in mechanism from the well-known methodology of the one-pot Julia olefination with heteroaromatic sulfones and mimics the reactivity of organic phosphonates. In addition, we demonstrated that the structure of the leaving group of the precursor displays a substantial effect on carbanion stability and rate of fragmentation of the sulfonyl group. The search of novel reactivities of the species is presently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00517.

Experimental procedures, stereochemistry assignments, characterization data, and NMR spectra of the synthesized compounds (PDF)

Structural data of X-ray studies (CIF)

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Notes

The authors declare no competing financial interest.

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(7) See the Supporting Information for details.

(8) In most of the olefin syntheses presented in Figure 1, in the reaction mixture we detected some amount of unreacted ester, while aldehyde was consumed. It is likely that low yields of alkenes with acceptor-substituted aldehydes may arise from competitive reaction of aldehydes with *t*-BuOLi (e.g., the Cannizzaro reaction).

(9) For the assignment of stereochemistry of diastereoisomeric aldol adducts **3a,b** we synthesized diastereoisomeric adducts of benzaldehyde with neopentyl phenylmethanesulfonate, one of which (**10b**) was characterized by X-ray studies (see the Supporting Information for details; CCDC 1530545).

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