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3,5-Bis(trifluoromethyl)phenyl Sulfones for the Highly Stereoselective Julia–Kocienski Synthesis of α,β-Unsaturated Esters and Weinreb Amides

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Dedicated to Professor Miguel Yus on the occasion of his 60th birthday

Keywords: Olefination / Esters / Amides / Sulfones

The 3,5-bis(trifluoromethyl)phenyl (BTFP) sulfones *tert*-butyl α-(BTFPsulfonyl)acetate (**4**) and Weinreb α-(BTFPsulfonyl)-acetamide (**5**) have successfully been employed in the Julia–Kocienski olefination of aldehydes with K_2CO_3 as the base at 120 °C in DMF under solid/liquid phase-transfer catalysis conditions to afford α,β-unsaturated esters and Weinreb amides, respectively. The corresponding products were obtained in good yields and with high *E* stereoselectivities (*E*/*Z* up to >99:1), especially in the case of the amides. A detailed computational study of the Julia–Kocienski olefination with BTFP sulfone **4** was carried out and confirmed the existence of an equilibrium in the initial addition of the sulfone enolate to the aldehyde and, in contrast to other proposed mechanisms, a non-concerted final elimination of SO_2 and 3,5-bis-(trifluoromethyl)phenoxide. A plausible explanation for the high *E* diastereoselectivity observed in the reaction has been suggested based on kinetic considerations at spirocyclic **TS2** and thermodynamic factors during the elimination after **TS2**. ESI-MS studies carried out during the olefination reaction of benzaldehyde with BTFP sulfone **4** were used to characterize the sulfone enolate and the intermediate assumed for the reaction mechanism.

Introduction

For several decades, a wide variety of approaches have been developed for the regio- and stereoselective synthesis of alkenes, the most generally applicable methods being those that involve the direct olefination of carbonyl compounds,[1] as in the Wittig,[2] Horner,[3] Wadsworth–Emmons,[4] Peterson,[5] Johnson[6] and classic Julia[7] reactions. A new variant of the classic Julia reaction, the Julia–Kocienski olefination, also called the modified or one-pot Julia olefination,[8] has recently emerged as a powerful tool in olefin synthesis. The process involves the replacement of the aryl sulfone moiety, traditionally used in the classic reaction, with different heteroaryl[8,9] sulfones, such as benzothiazol-2-yl sulfones (BT sulfones), 2-pyridyl sulfones (PYR sulfones), 1-phenyl-1*H*-tetrazol-5-yl sulfones (PT sulfones) and 1-*tert*-butyl-1*H*-tetrazol-5-yl sulfones (TBT sulfones), thus allowing direct olefination. The α,β-unsaturated ester[10] and Weinreb amide[11] functions are of great utility and versatility in organic synthesis as they serve as important synthetic intermediates. Very recently, BT sulfones **1a** and **1b** were reported as effective reagents for the one-pot Julia olefination of aldehydes in the synthesis of α,β-unsaturated esters[12] and Weinreb amides[13] employing DBU and NaH as the base, respectively (Figure 1). π-Deficient 4-nitrophenyl (NP) sulfone **2** (Figure 1) has also shown moderate reactivity towards the alkenylation of aromatic aldehydes with Cs_2CO_3 as the base.[14]

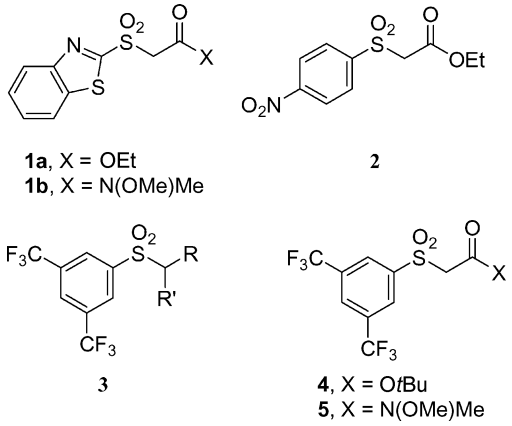

Figure 1. BT, NP and BTFP sulfones.

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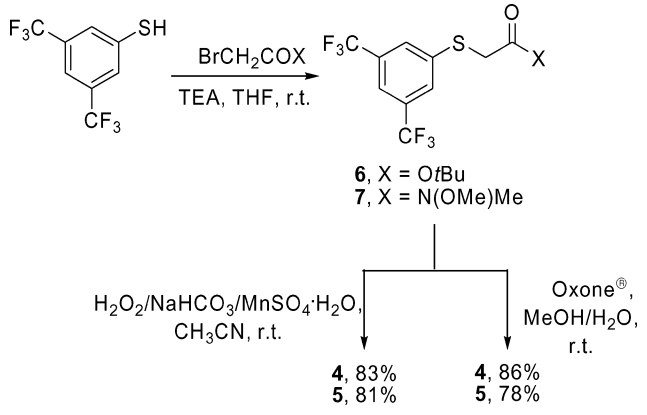
We have recently demonstrated that the 3,5-bis(trifluoromethyl)phenyl (BTFP) sulfone group is an excellent nucleofuge in base-promoted β-elimination processes.[15] On the other hand, 3,5-bis(trifluoromethyl)phenyl sulfones (BTFP sulfones) **3** (Figure 1) can undergo the Smiles rearrangement[8b] that is involved in the Julia–Kocienski olefination. Thus, they have been employed as excellent π-deficient partners for the stereoselective synthesis of di-, tri- and tetrasubstituted olefins by the Julia–Kocienski olefination of aliphatic and aromatic aldehydes as well as ketones under very simple reaction conditions by using KOH and phosphazenes as bases.[16] Herein we report the synthesis of *tert*-butyl α-(BTFPsulfonyl)acetate (**4**) (Figure 1) and Weinreb α-(BTFPsulfonyl)acetamide (**5**) (Figure 1) and their application as efficient reagents for the stereoselective synthesis of α,β-unsaturated esters and Weinreb amides by the Julia–Kocienski olefination of aldehydes.

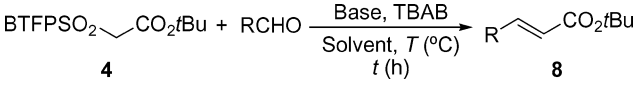
Results and Discussion

Commercially available 3,5-bis(trifluoromethyl)thiophenol[17] was *S*-alkylated with *tert*-butyl bromoacetate and pre-prepared 2-bromo-*N*-methoxy-*N*-methylacetamide[18] using triethylamine as base to afford sulfides **6** and **7** in 89 and 92% yields, respectively, after flash chromatography (Scheme 1). These compounds were submitted to oxidation without purification to yield the corresponding BTFP sulfones **4** and **5**, respectively. Oxidation with 30% H_2O_2/$NaHCO_3$/$MnSO_4$·H_2O[19] led to sulfones **4** and **5** in 83 and 81% overall yields, respectively. For multigram-scale synthesis, the oxidation of sulfides **6** and **7** was performed with Oxone® to provide the corresponding sulfones in 86 and 78% overall yields, respectively (Scheme 1).



Scheme 1. Synthesis of BTFP sulfones **4** and **5**.

With the olefination reagents in hand, we then focused on the stereoselective synthesis of α,β-unsaturated esters by Julia–Kocienski olefination of aldehydes with sulfone **4**. The synthesis of *tert*-butyl cinnamate (**8a**, R = Ph) was selected in order to identify the optimal reaction conditions (Scheme 2, R = Ph, and Table 1). The reaction was performed by the addition of a base to a mixture of sulfone **4** (2 equiv.) and benzaldehyde (Barbier conditions). Under the conditions previously employed for the Julia–Kocienski olefination of aldehydes with BT sulfone **1a**[12] and DBU as the base in CH_2Cl_2, sulfone **4** failed to react. However, in DMF at 120 °C over 48 h, **8a** was obtained in 15% yield and excellent selectivity (*Z*/*E* = 1:99) (Table 1, entries 1 and 2). The yield of the reaction was improved to 36% by using the phosphazene base P4-*t*Bu in DMF at the same temperature (Table 1, entry 3). By employing NaH as the base under THF reflux, sulfone **4** failed to react with benzaldehyde to any significant extent (Table 1, entry 4). The inorganic bases *t*BuOK and KOH gave modest yields of **8a** in DMF, even on heating at 120 °C. When the reaction was performed in the same solvent with a large excess (18 equiv.) of weaker ionic bases such as Cs_2CO_3 and K_2CO_3 at 120 °C under solid/liquid phase transfer catalysis (PTC) conditions (TBAB, 10 mol-%), *tert*-butyl cinnamate (**8a**) was obtained in high yields and excellent stereoselectivities (Table 1, entries 7 and 8). By using K_2CO_3 as the base and different solvents, such as DMSO, DMAc, acetonitrile, THF and toluene, lower yields than in DMF were obtained (Table 1, entries 8–13). When the amount of K_2CO_3 was decreased to 10 equiv., a lower yield of 49% was obtained (Table 1, entry 14). Finally, and to try to decrease the reaction time, the olefination was carried out under microwave irradiation (Table 1, entry 15). Unfortunately, BTFP methyl sulfone (**3**,



Scheme 2. Synthesis of α,β-unsaturated esters by Julia–Kocienski olefination.

Table 1. Synthesis of *tert*-butyl cinnamate (**8a**) by Julia–Kocienski olefination.[a]

Entry	Base (equiv.)	Solvent	*T* [°C]	*t* [h]	% Yield[b]	*Z*/*E*[c]
1	DBU (2.4)	CH_2Cl_2	Room temp.	48	<5	n.d.
2	DBU (2.4)	DMF	120	48	15	1:99
3	P4-*t*Bu (2.4)	DMF	120	18	36	4:96
4	NaH (3)	THF	76	48	<5	n.d.
5	*t*BuOK (4)	DMF	120	48	22	n.d.
6	KOH (9)[d]	DMF	120	18	26	n.d.
7	Cs_2CO_3 (18)[d]	DMF	120	48	71	3:97
8	K_2CO_3 (18)[d]	DMF	120	18	95	4:96
9	K_2CO_3 (18)[d]	DMSO	120	18	83	5:95
10	K_2CO_3 (18)[d]	DMAc	120	18	65	5:95
11	K_2CO_3 (18)[d]	MeCN	76	18	<5	n.d.
12	K_2CO_3 (18)[d]	THF	76	18	<5	n.d.
13	K_2CO_3 (18)[d]	PhMe	110	18	<5	n.d.
14	K_2CO_3 (10)[d]	DMF	120	18	49	1:99
15	K_2CO_3 (18)[d]	DMF	80[e]	0.5	45[f]	–

[a] The reaction was carried out under Barbier-type conditions [addition of the base to a solution of benzaldehyde and BTFP sulfone **4** (1:2)]. [b] Isolated yield after flash chromatography. [c] Determined by ^{1}H NMR of the crude reaction mixture. [d] The reaction was performed in the presence of TBAB (0.1 equiv.). [e] The reaction was performed under microwave irradiation (80 W). [f] Yield of BTFP methyl sulfone (**3**, R = R′ = H).

R = R′ = H) was the only product formed in 45% yield under these conditions as a consequence of the hydrolysis and decarboxylation of the starting *tert*-butyl ester.[20]

The scope of the olefination reaction with sulfone **4** (2 equiv.) with a range of different aldehydes was examined under the optimized reaction conditions, K_2CO_3 (18 equiv.) as base in DMF at 120 °C for 18 h under Barbier conditions (Scheme 2 and Table 2). All the aromatic and heteroaromatic aldehydes tested gave moderate-to-high yields of the corresponding olefins after flash chromatography (Table 2, entries 1–10). The diastereoselectivity of the process was excellent (*Z*/*E* up to > 1:99) irrespective of the steric demand and electronic character of the electrophile, except in the case of the alkenylation of 2-thiophenecarbaldehyde in which olefin **8i** was obtained with *Z*/*E* = 15:85 (Table 2, entry 9). In general, better yields were observed with electron-poor electrophiles such as 4-halobenzaldehydes and 4-trifluoromethylbenzaldehyde (Table 2, entries 2–4), the highest yield being obtained for the olefination of benzaldehyde and 4-pyridinecarbaldehyde (Table 2, entries 1 and 10).

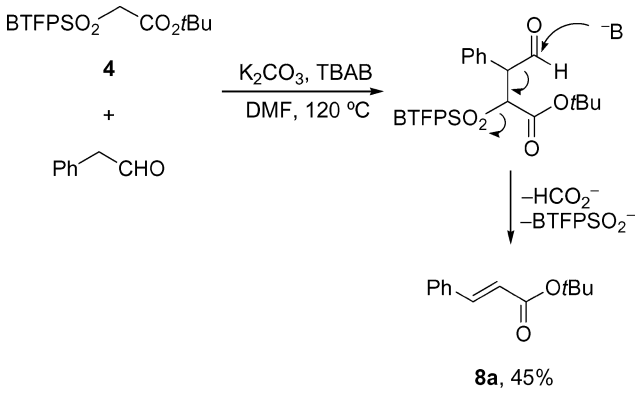
Table 2. Synthesis of α,β-unsaturated esters **8** by Julia–Kocienski olefination.[a]

Entry	RCHO	α,β-Unsaturated esters **8**		
			% yield[b]	*Z*/*E*[c]
1	C_6H_5CHO	**8a**	95	4:96
2	4-ClC_6H_4CHO	**8b**	56	>1:99
3	4-BrC_6H_4CHO	**8c**	62	>1:99
4	4-$CF_3C_6H_4CHO$	**8d**	74	>1:99
5	4-$MeOC_6H_4CHO$	**8e**	45	>1:99
6	2-ClC_6H_4CHO	**8f**	52	>1:99
7	2-naphthaldehyde	**8g**	48	5:95
8	6-MeO-2-naphthaldehyde	**8h**	31	5:95
9	2-thiophenecarbaldeyde	**8i**	46	15:85
10	4-pyridinecarbaldehyde	**8j**	96	4:96
11	*n*$C_9H_{19}CHO$	**8k**	14	32:68
12	*c*$C_6H_{11}CHO$	**8l**	15	25:75

[a] Reactions were performed under Barbier-type conditions: To a DMF solution of BTFP sulfone **4** (2 equiv.) and the corresponding aldehyde (1 equiv.), TBAB (10 mol-%) and K_2CO_3 (18 equiv.) were added and the resulting mixture was stirred at 120 °C for 18 h. [b] Isolated yield after flash chromatography. [c] Determined by ^1H NMR of the crude reaction mixture.

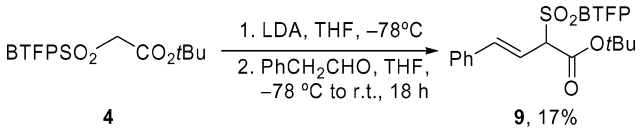
The results obtained with BTFP sulfone **4** in the one-pot Julia olefination of aromatic aldehydes are comparable, in terms of yield and selectivity, with those obtained with BT sulfone **1a**[12] even though this heteroaromatic sulfone reacts at room temp. with DBU as the base in CH_2Cl_2. In contrast, when compared with other non-heteroaromatic sulfones such as **2** (Cs_2CO_3, DMF, room temp. or 60 °C),[14] BTFP sulfone **4** affords higher yields in much shorter reaction times.

The stabilized α-sulfonyl carbanion of BTFP sulfone **4** showed very low reactivity in the alkenylation of aliphatic aldehydes such as decanal and cyclohexanecarbaldehyde, providing the corresponding olefins **8k** and **8l** in very low yields and with modest selectivities (Table 2, entries 11 and 12). The olefination reaction of phenylacetaldehyde unexpectedly led to the stereoselective formation of *tert*-butyl cinnamate (**8a**) in 45% yield. The formation of **8a** can be explained by an oxidative coupling between the BTFP sulfone **4** and aldehyde enolates[21] and β-elimination of BTFP sulfinate from the resulting 1,4-dicarbonyl intermediate under the basic reaction conditions (Scheme 3).



Scheme 3. Formation of *tert*-butyl cinnamate (**8a**) from phenylacetaldehyde and **4**.

On the other hand, when the reaction was carried out under kinetic conditions employing LDA as the base at a low temperature under Grignard conditions (addition of the electrophile to the previously generated sulfone enolate), the starting sulfone was mainly obtained, compound **9** also being isolated in a low yield of 17% (Scheme 4). The thermodynamically less stable β,γ-unsaturated ester **9** was formed as a result of the aldol reaction between the α-sulfonyl carbanion of **4** and phenylacetaldehyde followed by double bond isomerization.[22]

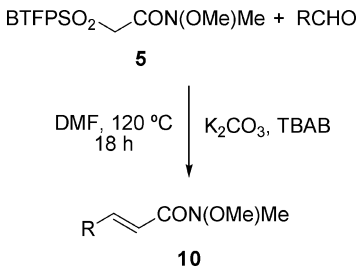


Scheme 4. Synthesis of the α-sulfonyl ester **9** from BTFP sulfone **4** and phenylacetaldehyde.

Finally, alkene formation from a representative α,β-unsaturated aldehyde such as *trans*-cinnamaldehyde with sulfone **4** afforded a complex mixture of products in which *tert*-butyl cinnamate (**8a**) was characterized as the major product and was isolated in a yield of 20%. In this case, the formation of **8a** could be a consequence of the Julia–Kocienski reaction between **4** and benzaldehyde, the latter obtained from *trans*-cinnamaldehyde by a retro-aldol process.

The synthesis of α,β-unsaturated Weinreb amides by the alkenylation of aldehydes with BTFP sulfone **5** was next investigated under the optimized reaction conditions (Scheme 5 and Table 3). Sulfone **5** reacted with aryl and heteroaryl aldehydes in moderate-to-good yields to give the corresponding diastereomerically pure *E* α,β-unsaturated Weinreb amides **10**. The stereochemistry was again independent of the electronic character or the steric demand of the aldehyde (Table 3, entries 1–10). However, the yield of the process was lower for electron-rich aldehydes, even with

longer reaction times, as in the case of 4-methoxybenzaldehyde, 2-naphthaldehyde and 6-methoxy-2-naphthaldehyde (Table 3, entries 5, 7 and 8).



Scheme 5. Synthesis of α,β-unsaturated Weinreb amides by Julia–Kocienski olefination.

Table 3. Synthesis of α,β-unsaturated Weinreb amides **10** by Julia–Kocienski olefination.[a]

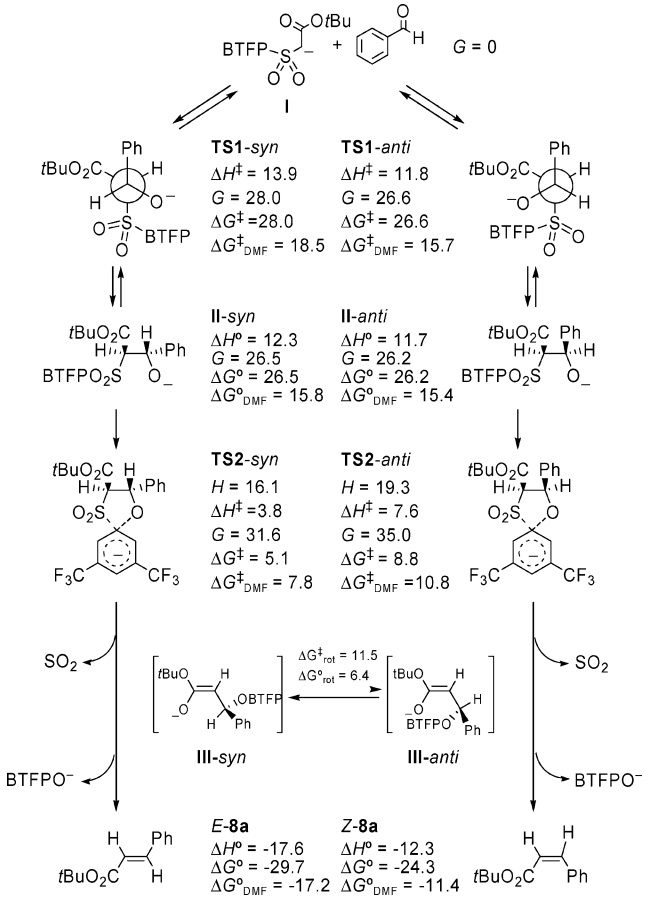
Entry	RCHO	Weinreb amides **10**	% yield[b]	*Z*/*E*[c]
1	PhCHO	**10a**	66	>1:99
2	4-ClC_6H_4CHO	**10b**	47	>1:99
3	4-BrC_6H_4CHO	**10c**	51	>1:99
4	4-$CF_3C_6H_4CHO$	**10d**	82	>1:99
5	4-$MeOC_6H_4CHO$	**10e**	20[d]	>1:99
6	2-ClC_6H_4CHO	**10f**	84	>1:99
7	2-naphthaldehyde	**10g**	30	>1:99
8	6-MeO-2-naphthaldehyde	**10h**	25	>1:99
9	2-thiophenecarbaldehyde	**10i**	49	>1:99
10	2-furancarbaldehyde	**10j**	50	>1:99

[a] The reaction was carried out under Barbier-type conditions with 2 equiv. of sulfone **5**. [b] Isolated yield after flash chromatography. [c] Determined by ^1H NMR of the crude reaction mixture. [d] Reaction time was 48 h.

In terms of yield and selectivity, BTFP sulfone **5** competes with other sulfones recently employed in the synthesis of α,β-unsaturated Weinreb amides from aromatic aldehydes by the one-pot Julia olefination, for example, BT sulfone **1b** (NaH, THF, room temp.),[13] the main advantage of the protocol presented here being the absence of anhydrous conditions, which is essential when using sulfone **1b**. On the other hand, **1b** has been shown to be an effective reagent for the olefination of aliphatic aldehydes, derivatives which are not reactive with BTFP sulfone **5** under the optimized reaction conditions.

With respect to the reaction mechanism, we have previously demonstrated that the Julia–Kocienski olefination of aromatic aldehydes employing stabilized benzyl BTFP sulfones may involve zwitterionic intermediates.[16b] However, the formation of zwitterionic betaine intermediates should not be so favoured for stabilized sulfones such as **4** and **5**. To add further insight into the reaction mechanism we computationally studied the reaction between *tert*-butyl ester **4** and benzaldehyde.

In order to ascertain the origin of the selectivity of the reaction, two diastereomeric pathways (*syn* and *anti*) were computed separately (Scheme 6). The reaction proceeds through a two-step mechanism. The first one (**TS1**) involves the nucleophilic addition of enolate **I** to benzaldehyde with the formation of a high-energy alkoxide intermediate (**II**). A second transition state (**TS2**) was located thereafter that corresponds to the nucleophilic aromatic substitution of the sulfonyl group by the incoming alkoxide. A preliminary extensive conformational search for **TS1**- and **II**-type structures was conducted at the B3LYP/6-31G* level of theory including all the possible *gauche* conformations around the forming C–C bond and all the different orientations of the ester and sulfonyl moieties. Two related lowest-lying transition-state structures (**TS1**-*syn* and **TS1**-*anti*) and two absolute minima (**II**-*syn* and **II**-*anti*) were located and reoptimized at the B3LYP/6-31++G** level of theory. The sum of the absolute free energies of anion **I** + benzaldehyde was taken as $G = 0$ and $H = 0$ for the gas-phase and solution-phase calculations. Thus, the activation barriers to **TS1** were measured as the difference between the energies of **TS1** and the separate starting reactants ($G = H = 0$), whereas the activation barriers to **TS2** were measured as the difference between the energies of **TS2** and the **II**-type intermediates ($\Delta G^{\ddagger} = G_{\mathbf{TS2}} - G_{\mathbf{II}}$, $\Delta H^{\ddagger} = H_{\mathbf{TS2}} - H_{\mathbf{II}}$). The solution-phase energies were treated in the same manner.



Scheme 6. Mechanism for the Julia–Kocienski olefination of benzaldehyde with BTFP sulfone **4** computed at the B3LYP/6-311++G** level of theory.

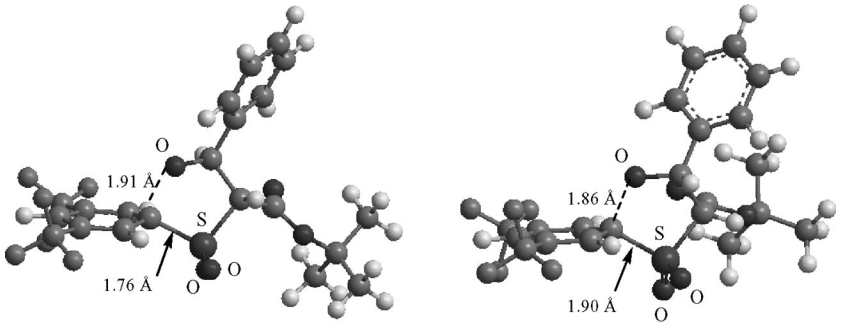
The initial nucleophilic addition of sulfone anion **I** to benzaldehyde occurs through **TS1**-type transition states; diastereomeric **TS1**-*syn* and **TS1**-*anti* were found to be the lowest-energy structures. In both cases, the phenyl ring of

the benzaldehyde appears *anti* to the sterically demanding arylsulfonyl moiety, whereas the developing alkoxide is situated *gauche* to the electron-deficient BTFP aromatic ring. Thus, the reaction seems to be faster for the *anti* attack and the activation energies for **TS1**-*anti* and **TS1**-*syn* in the gas-phase differ by around 2 kcal/mol ($\Delta\Delta H^{\ddagger}$ = 2.1 kcal/mol and $\Delta\Delta G^{\ddagger}$ = 1.4 kcal/mol). The nucleophilic attack generates a pair of alkoxide intermediates (**II**-*anti* or **II**-*syn*) that lie very close in energy to the corresponding transition states. The high energy of the **II**-type intermediates and the small barrier for the retro-addition reaction ($G_{\mathbf{TS1}\text{-}syn} - G_{\mathbf{II}\text{-}syn}$ = 1.5 kcal/mol and $G_{\mathbf{TS1}\text{-}anti} - G_{\mathbf{II}\text{-}anti}$ = 0.4 kcal/mol) suggest the existence of an equilibrium in the first step that is strongly displaced towards the starting materials. Interestingly, the very small energy difference in favour of **II**-*anti* over **II**-*syn* in both the gas phase and the solvent phase ($\Delta\Delta G°$ = 0.3 kcal/mol, $\Delta\Delta G°_{DMF}$ = 0.4 kcal/mol) is not enough to explain the high selectivity experimentally encountered in this particular reaction. The nucleophilic aromatic displacement of the sulfonyl group by the alkoxide **II**-type intermediates leads to a second transition state (**TS2**), which represents the highest-lying point along the reaction coordinate ($G_{\mathbf{TS2}\text{-}anti}$ = 35.0 kcal/mol, $G_{\mathbf{TS2}\text{-}syn}$ = 31.6 kcal/mol). The mechanism of related nucleophilic displacements has been theoretically studied and is well established.[23] In our case, the high relative energy of the **II**-type intermediates induces a fairly low activation barrier to **TS2** ($\Delta G^{\ddagger}_{\mathbf{TS2}\text{-}syn}$ = 5.1 kcal/mol, $\Delta G^{\ddagger}_{\mathbf{TS2}\text{-}anti}$ = 8.8 kcal/mol). These data correspond to a significant energy difference in favour of the less sterically demanding **TS2**-*syn* diastereomeric structure in which the ester and phenyl moieties are located in an *anti* relationship.

Both of the **TS2** transition states are very asynchronous (Figure 2); the partial formation of the C–O bond (ca. 1.9 Å) precedes the rupture of the C–S bond (ca. 1.7 Å), which means that during the formation of the transition state significant charge injection into the aromatic ring occurs that is facilitated by the highly electron-withdrawing CF_3 groups. Nonetheless, in accordance with previous related theoretical studies on aromatic substitution,[23] the corresponding Meisenheimer intermediates, in which both atoms (sulfur and oxygen) are covalently bound to the aromatic ring, were not located. Furthermore, IRC calculations show that the **TS2** transition states are undoubtedly connected to the final products (*E*)-**8a** and (*Z*)-**8a** as well as to the intermediates **II**-*anti* and **II**-*syn*. The final products are 61.3 (*syn*) and 59.3 kcal/mol (*anti*) lower in energy than **TS2**, and thus the second step (Smiles rearrangement) leads to the irreversible formation of the final products without the generation of intermediates. The IRC calculations also show that after **TS2**, the elimination of SO_2 and ArO^- is not a concerted process. A fast elimination of SO_2 occurs first, producing an anionic enolate species **III** that is not a minimum along the reaction coordinate. Thus, this species could not be detected and subsequent barrierless elimination of ArO^- leads directly to the final products. Note, elimination from **TS2**-*syn* leads to the *E* product, whereas the *Z* product is observed from **TS2**-*anti*.

Thus, in contrast to other proposed mechanisms,[24] the elimination of SO_2 and BTF-phenol is not a concerted process and does not occur in an *anti* fashion in our reaction system. The fact that a significant activation energy difference was computed in favour of **TS2**-*syn* over **TS2**-*anti* ($\Delta\Delta G^{\ddagger}$ = 3.7 kcal/mol, $\Delta\Delta G^{\ddagger}_{DMF}$ = 3.0 kcal/mol), leading to the formation of the experimentally encountered *E* isomer, suggests that **TS2** is the selectivity-determining step of this reaction. In addition, the introduction of solvent effects does not alter the overall picture described above. As found by others in related aromatic substitution reactions,[23] polar solvents (DMF in this study) induce a relative stabilization of the charged species, especially **II**-type intermediates, and hence, the **TS2** barriers are higher in the solvent-phase than in the gas-phase calculations.

We also considered the possibility that after elimination of SO_2 and prior to the elimination of ArO^- a fast rotation around the newly formed C–C bond could lead to equilibration of the **III**-type enolate species. The fact that they are not localizable stationary points along the reaction coordinate precludes a direct comparison of their energies, which were estimated by fixing the C–O bond at 1.45 Å to avoid elimination of ArO^- during the optimization. Thus, we could have an indirect measure of the relative energies of **III**-type species and the rotation barrier between them. Eventually, these could lead to the thermodynamic conver-



TS2-*syn* **TS2**-*anti*

Figure 2. Transition-state structures for the nucleophilic aromatic substitution step (second step) of the reaction between benzaldehyde and BTFP sulfone **4**.

gence of both pathways to the more stable *E* isomer through **III**-*syn*, which is 6.4 kcal/mol more stable than its isomer **III**-*anti*. The rotational barrier is 11.5 kcal/mol, which suggests that the rotation might be too slow in comparison to the barrierless elimination of phenoxide. The lack of detectable intermediates after **TS2** does not allow direct evaluation of its significance in the mechanism. Nonetheless, both kinetic considerations at **TS2** and thermodynamic factors during elimination after **TS2** merge at the formation of the same isomer [(*E*)-**8a**] and account for the high *E* diastereoselectivity observed in the process.

The formation of the enolate from sulfone **4** was confirmed by ESI-MS experiments (see the Supporting Information). Under typical reaction conditions, enolate **I** (*m*/*z* = 391.0, Scheme 6) was detected after stirring sulfone **4** (0.05 mmol), K_2CO_3 (62 mg, 0.45 mmol) and TBAB (1.5 mg, 10 mol-%) in DMF (300 μL) for 10 min at room temp. Benzaldehyde (3 μL, 0.025 mmol) was then added to this solution and the mixture was heated at 120 °C for 1 h. An aliquot of the reaction mixture was then dissolved in MeOH and injected after 0.2 min. The formation of intermediate **II** (Scheme 6) was detected in the mixture by ESI-MS.

Conclusions

We have shown that BTFP sulfones **4** and **5** are efficient reagents for the stereoselective synthesis of (*E*)-α,β-unsaturated esters and Weinreb amides by the Julia–Kocienski olefination of aromatic aldehydes under very convenient solid/liquid phase-transfer catalysis conditions employing K_2CO_3 as the base and TBAB in DMF at 120 °C. According to computational studies, the reaction mechanism, which involves two transition states, ends with a non-concerted elimination of SO_2 and 3,5-bis(trifluoromethyl)phenoxide, in contrast to other proposed mechanisms, with the generation of **TS2** being the selectivity-determining step in a step closely related to the Smiles rearrangement. Additional applications of BTFP sulfones in olefination and other reactions are currently under investigation.

Experimental Section

General: Melting points were obtained with a Reichert Thermovar apparatus and are not corrected. IR data were collected with a Nicolet Impact 400D FTIR apparatus. Only the structurally most important IR peaks have been listed. NMR spectra were recorded with a Bruker AC-300 spectrometer (300 MHz for H^1 NMR and 75 MHz for ^{13}C NMR) using $CDCl_3$ as the solvent and TMS as the internal standard unless otherwise noted. Low-resolution electron impact (EI) mass spectra were obtained at 70 eV with Shimadzu QP-5000 and Agilent 5973 spectrometers. HRMS were recorded with a Finnigan MAT 95S spectrometer. ESI-MS experiments were carried out with an Agilent 1100 Series LC/MSD Trap "SL" mass spectrometer equipped with an ESI source. Analytical TLC was visualized with UV light at 254 nm or with $KMnO_4$. Thin-layer chromatography was carried out with TLC aluminium sheets with silica gel 60 F_{254} (Merck). For flash chromatography, silica gel 60 (0.040–0.063 mm) was employed. Reactions under inert atmosphere (argon) were performed in oven-dried glassware sealed with a rubber septum using anhydrous solvents.

With respect to the computational studies, all stationary points along the reaction coordinate were optimized using the B3LYP functional[25] and the 6-311++G** basis set as implemented in Gaussian 03.[26] Use of the large basis set was described as being important for the correct energetic description of anionic species in computational studies of related reactions. All energy minima and transition states were characterized by frequency analysis. The energies reported in this work include unscaled electronic and thermal corrections to the enthalpy and Gibbs free energy. The stationary points were characterized by frequency calculations in order to verify that they have the right number of negative eigenvalues. The intrinsic reaction coordinate[27] (IRC) was followed to verify the energy profiles connecting each transition state to the correct local minima. DMF solvent effects have been considered by B3LYP/6-311++G** single-point calculations on the previously gas-phase-optimized structures with the self-consistent reaction field (SCRF) based on the polarizable continuum model PCM[28] (ε = 36.7, solvent radius = 3.48 Å).

Products **8a**,[29] **8b**,[30] **8c**,[30] **8d**,[30] **8e**,[30] **8f**,[31] **8g**,[32] **8h**,[33] **8i**,[34] **8j**,[35] **8k**,[29] **8l**,[29,36] **10a**,[37] **10b**,[38] **10c**,[39] **10d**,[40] **10e**,[38] **10f**,[41] **10g**,[42] **10h**,[43] **10i**,[43] and **10j**[43] have been described previously and gave satisfactory spectroscopic and physical data. Products **8a**, **10a** and **10d** are also commercially available.

General Procedure for the Synthesis of BTFP Sulfides 6 and 7: 3,5-Bis(trifluoromethyl)thiophenol (835 μL, 5 mmol) was added at room temperature to a solution of TEA (1.4 mL, 10 mmol) in MeCN (15 mL) under argon. After stirring for 15 min, the corresponding alkyl bromide (5.5 mmol) was added to the reaction and the resulting mixture was stirred at room temp. for 1 d. After quenching with H_2O (20 mL), the mixture was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to afford the corresponding 3,5-bis(trifluoromethyl)phenyl sulfides, which were used in the next step without further purification. They were purified by flash chromatography for characterization purposes.

***tert*-Butyl 2-[3,5-Bis(trifluoromethyl)phenylsulfanyl]acetate (6):** Yield 1.6 g, 89%, colourless oil; R_f (hexane/EtOAc, 4:1) = 0.68. IR: $\tilde{\nu}$ = 2984, 2936, 1731, 1617, 1354, 1277, 1133 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.81 (s, 2 H, ArH), 7.68 (s, 1 H, ArH), 3.69 (s, 2 H, CH_2S), 1.43 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.5 (CO), 139.6 (ArC), 132.0 (q, J_{CF} = 33.3 Hz, 2 CCF_3), 127.7 (ArCH), 122.9 (q, J_{CF} = 272.9 Hz, 2 CF_3), 119.5 (ArCH), 82.5 [$C(CH_3)_3$], 36.1 (CH_2S), 27.4 (3 CH_3) ppm. MS: *m*/*z* (%) = 360 (19) $[M]^+$, 304 (20), 285 (32), 260 (21), 259 (93), 239 (35), 57 (100). HRMS: calcd. for $C_{14}H_{14}F_6O_2S$ $[M]^+$ 360.0619; found 360.0613.

2-[3,5-Bis(trifluoromethyl)phenylsulfanyl]-*N*-methoxy-*N*-methylacetamide (7): Yield 1.1 g, 92%, yellow oil; R_f (hexane/EtOAc, 4:1) = 0.18. IR: $\tilde{\nu}$ = 1670, 1354, 1278, 1181, 1132 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.87 (s, 2 H, ArH), 7.66 (s, 1 H, ArH), 3.96 (s, 2 H, CH_2S), 3.78 (s, 3 H, OCH_3), 3.23 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.6, 139.6 (ArC), 131.8 (q, J_{CF} = 33.2 Hz, 2 CCF_3), 127.9 (ArCH), 122.8 (q, J_{CF} = 272.6 Hz, 2 CF_3), 119.4 (ArCH), 61.3 (OCH_3), 33.7 (CH_2S), 32.1 (CH_3) ppm. MS: *m*/*z* (%) = 347 (34) $[M]^+$, 260 (18), 259 (100), 239 (62), 195 (14), 61 (89). HRMS: calcd. for $C_{12}H_{11}F_6NO_2S$ $[M]^+$ 347.0415; found 347.0415.

General Procedure for the Synthesis of BTFP Sulfones 4 and 5: Oxidation reaction employing H_2O_2/$NaHCO_3$/$MnSO_4 \cdot H_2O$: An aque-

ous mixture of 30% H_2O_2 (5 mmol, 515 μL) and a 0.2 M buffer solution of $NaHCO_3$ (17 mL), prepared at 0 °C, was slowly added to solution of the corresponding crude sulfide **6** or **7** (1 mmol) and $MnSO_4$ monohydrate (2 mg, 1 mol-%) in MeCN (23 mL) stirred a room temp. After stirring for 1 d at room temp., the reaction was quenched with a saturated aqueous solution of NaCl (30 mL), extracted with EtOAc (2 × 20 mL) and dried ($MgSO_4$). Final evaporation of the solvents (15 Torr) afforded the corresponding pure crude sulfones **4** or **5**, which were recrystallized from diethyl ether/hexane.

Oxidation reaction employing Oxone®: Oxone® (50 mmol, 31 g) was slowly added to a 0 °C stirred solution of the corresponding sulfide **6** or **7** (5 mmol) in a 1:1 mixture of MeOH/H_2O (44 mL). The reaction was stirred at room temp. for 1 d. After this time, MeOH was evaporated and the residue was dissolved in CH_2Cl_2 (50 mL) and filtered through Celite. Water was added to the filtrate and the mixture was extracted with CH_2Cl_2 (2 × 25 mL) and washed with a saturated aqueous solution of NaCl (3 × 50 mL). The organic phase was then dried ($MgSO_4$), filtered and evaporated to afford the corresponding crude sulfones **4** and **5** which were recrystallized from diethyl ether/hexane.

***tert*-Butyl 2-{[3,5-Bis(trifluoromethyl)phenyl]sulfonyl}acetate (4):** White solid; m.p. 70–71 °C. IR: ṽ = 3104, 3082, 2984, 2940, 1734, 1282, 1164, 1133 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.41 (s, 2 H, ArCH), 8.18 (s, 1 H, ArCH), 4.13 (s, 2 H, SCH_2), 1.19 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.6 (CO), 141.4 (ArC), 133.0 (q, $J_{C–F}$ = 35.2 Hz, 2 *C*CF_3), 129.2, 127.7 (ArCH), 122.3 (q, $J_{C–F}$ = 274.5 Hz, 2 CF_3), 84.6 [*C*$(CH_3)_3$], 61.7 (CH_2S), 27.5 [C(*C*$H_3)_3$] ppm. MS: *m*/*z* (%) = 377 (15) $[M – CH_3]^+$, 317 (35), 277 (42), 213 (75), 57 (100). HRMS: calcd. for $C_{14}H_{14}F_6O_4S$ $[M]^+$ 392.0517, $[M – CO_2tBu]^+$ 276.9758; found 276.9757.

2-{[3,5-Bis(trifluoromethyl)phenyl]sulfonyl}-*N*-methoxy-*N*-methylacetamide (5): White solid; m.p. 98–100 °C. IR: ṽ = 3081, 1667, 1286, 1155, 1106 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.42 (s, 2 H, ArCH), 8.16 (s, 1 H, ArCH), 4.42 (s, 2 H, SCH_2), 3.81 (s, 3 H, OCH_3), 3.19 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.5 (CO), 141.7 (ArC), 132.7 (q, $J_{C–F}$ = 35.3 Hz, 2 *C*CF_3), 129.4, 127.6 (ArCH), 123.1 (q, $J_{C–F}$ = 274.5 Hz, 2 CF_3), 61.9 (CH_2S), 57.61 (OCH_3), 32.1 (CH_3) ppm. MS: *m*/*z* (%) = 377 (15) $[M]^+$, 277 (54), 213 (100), 149 (37), 61 (78), 43 (63). HRMS: calcd. for $C_{12}H_{11}F_6NO_4S$ $[M]^+$ 379.0313; found 379.0324.

General Procedure for the Julia–Kocienski Olefination of Aldehydes with BTFP Sulfones 4 or 5: K_2CO_3 (250 mg, 1.8 mmol) and TBAB (6 mg, 0.02 mmol) were added portionwise to a solution of sulfone **4** or **5** (0.2 mmol) and aldehyde (0.10 mmol) in DMF (4 mL) stirred at room temp under argon. The resulting mixture was stirred overnight at 120 °C and then quenched with a saturated aqueous solution of NH_4Cl (4 mL). The mixture was then extracted with EtOAc (2 × 10 mL). The organic phase was washed with H_2O (2 × 10 mL) and dried ($MgSO_4$). Filtration and evaporation of the solvent afforded the corresponding crude product **8** or **10**, which was purified by flash chromatography (see Tables 1, 2 and 3).

Synthesis of *tert*-Butyl (*E*)-2-{[3,5-Bis(trifluoromethyl)phenyl]-sulfonyl}-4-phenylbut-3-enoate (9): Freshly prepared LDA (0.3 mmol) was added dropwise to a solution of sulfone **4** (0.3 mmol) in anhydrous THF (6 mL) stirred at –78 °C under argon. The mixture was then stirred for 30 min at –78 °C and then phenylacetaldehyde (35 μL, 0.3 mmol) was added and the temperature allowed to rise to room temp. The resulting mixture was stirred overnight at room temperature and quenched with a saturated aqueous solution of NH_4Cl (10 mL). The mixture was extracted with EtOAc (2 × 15 mL) and the organic phase was dried ($MgSO_4$), filtered, the solvent evaporated and the residue purified by flash chromatography to afford 24.5 mg of the title compound (17% yield). White solid; m.p. 71–72 °C (EtOAc/hexane). IR: ṽ 2982, 1731, 1358, 1279, 1144, 1100 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.28 (s, 2 H, ArCH), 8.16 (s, 1 H, ArCH), 7.40–7.28 (m, 5 H, ArCH), 6.72 (d, $^3J_{H,H}$ = 15.9 Hz, 1 H, CH=C*H*Ph), 6.00 (dd, $^3J_{H,H}$ = 15.9, 9.2 Hz, 1 H, C*H*=CHPh), 4.67 (d, $^3J_{H,H}$ = 9.4 Hz, 1 H, CH), 1.46 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.3 (CO), 139.6 (CH=C*H*Ph), 138.5, 133.8 (ArC), 131.5 (q, $J_{C–F}$ = 33.7 Hz, 2 *C*CF_3), 129.46, 129.43, 128.3, 127.8, 125.9 (ArCH), 122.6 (2 CF_3), 113.7 (C*H*=CHPh), 83.7 [*C*$(CH_3)_3$], 74.1 (CH), 26.6 [C(*C*$H_3)_3$] ppm. MS: *m*/*z* (%) = 494 (0.04) $[M]^+$, 217 (20), 213 (10), 162 (10), 161 (95), 144 (15), 133 (44), 117 (22), 116 (24), 115 (100), 57 (44). HRMS: calcd. for $C_{22}H_{20}F_6O_4S$ $[M]^+$ 494.0986, $[M – tBuO]^+$ 421.0330; found 421.0325.

Supporting Information (see also the footnote on the first page of this article): Cartesian coordinates for transition states and reactant complexes as well as ESI-MS(–) spectra.

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