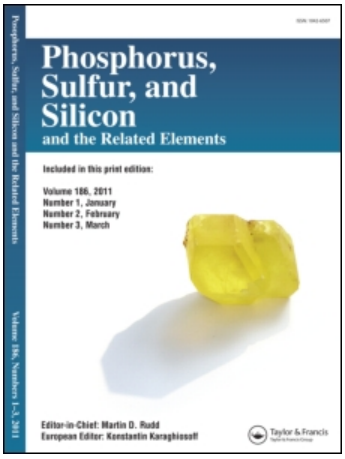


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# Synthetic Applications of π-Electron-Deficient Sulfones

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# Synthetic Applications of $\pi$-Electron-Deficient Sulfones

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*The use of $\pi$-electron-deficient aryl sulfones, especially 3,5-bis(trifluoromethyl) phenyl alkyl sulfones (BTFP-sulfones) as soft nucleophiles, as caboxylic acid protecting group and in Julia–Kocienski olefination reactions is described. In the case of $\alpha$-(arylsulfonyl)acetates dialkylation, reactions are performed under phase-transfer analysis (PTC) conditions using $K_2CO_3$ as base. Esters derived from 2-(arylsulfonyl)ethanol can be deprotected using aqueous $NaHCO_3$. Alkyl BTFP sulfones are coupled with carbonyl compounds using KOH or P4-t-Bu as bases to give the corresponding alkenes after Smiles rearrangement.*

**Keywords** Aconitates; elimination; olefination; protecting groups; stilbenoids; sulfones



## INTRODUCTION

The sulfone group is a well-established activating moiety for the construction of a C—C skeleton and other transformations.[1] In past decade the number of publications per year about the use of sulfones in organic chemistry has increased notably. They show a high reactivity especially for C—C bond formation reactions by regioselective formation of $\alpha$-sulfonyl carbanions followed by reaction with different types of electrophiles. Sulfones also allow the carbon-carbon double bond formation by elimination processes because of the good ability of the sulfonyl or the sulfur dioxide to be leaving groups. The sulfonyl group can be easily removed and can be oxidized to a carbonyl group.[2] The most important role of the sulfone group in total synthesis is based on the use of $\alpha$-sulfonyl carbanions, which can be related with the use of enolates. Generally, the sulfone is a synthetic tool that is introduced in

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an organic molecule, transformed into the carbanion to form the new C—C bond, and followed by final desulfonylation to afford the target molecule. For the generation of $\alpha$-sulfonyl carbanions, different reaction conditions can be used depending of the acidity of the hydrogen at the $\alpha$-position. As deprotonating conditions strong bases such alkyllithiums or lithium amides or alkoxides under anhydrous conditions, or hydroxides under aqueous phase-transfer conditions as well as organic bases such as amines or phosphazenes have been used. Convergent synthesis is based on a) alkylation-desulfonylation of $\alpha$-sulfonyl carbanions, b) aldol reaction-reductive elimination (Julia olefination), c) aldol reaction-Smiles rearrangement (Julia–Kocienski olefination), and d) acylation-reductive desulfonylation to give ketones.[1f]

Sulfones bearing an electron-withdrawing substituent can show a higher reactivity as leaving groups and a higher acidity. (Perfluoroalkyl) sulfonyl groups such as triflones, (trifluoromethyl sulfones),[3] and $\pi$-electron-deficient aryl sulfones are better candidates than simple sulfones for $\alpha$-sulfonyl carbanion stabilization and should favor desulfonylation processes. Triflones have a great tendency to decompose by sulfur dioxide extrusion. However, $\pi$-electron-deficient aryl sulfones are stable compounds easily prepared from the corresponding thiols. They have been used to increase the reactivity of $\alpha$-sulfonyl carbanions only in the case of the total synthesis of rhizoxin D, the phenyl sulfonyl being substituted by a 3,4-(dichlorophenyl)sulfonyl group to improve both the alkylation of the LDA-generated carbanion of compound **1** and the dehydrosulfinylation steps.[4] Acetal carbanions derived from **2** with a (4-nitrophenyl) sulfonyl group can be generated with KO-*t*-Bu and dialkylated with methyl iodide, whereas in the case of the phenysulfonyl substituent only monoalkylation is observed.[5] In the reductive desulfonylation of compounds **3** the (4-nitrophenyl)sulfonyl group increase the rate and the yield on the sodium amalgam reduction when compared with phenyl or *p*-tolylsufonyl groups.[6] Pyrimid-2-yl and pyridin-2-yl sulfones **4** are better desulfonylated than phenylsufones in the stannyl-radical mediated cleavage for the synthesis of $\alpha$-fluorinated esters and phosphonates.[7] In nucleophilic displacements pyridin-2-yl sulfones,[8] such as **5**, are transformed better than the *p*-tolyl derivatives into glycosides in the presence of samarium (III) triflate and alcohols.[9] 2-(Arylsulfonyl)ethanol derived carbamates **6** are used as base-labil amino-protecting groups as an alternative to the (9*H*-fluoren-9-ylmethoxy)carbonyl (Fmoc) group. Some representative examples are the 4-nitrophenyl (Msc), 4-bromophenyl (Bsc), and 2,4-(dinitrophenyl)sulfonyl derivatives.[10]

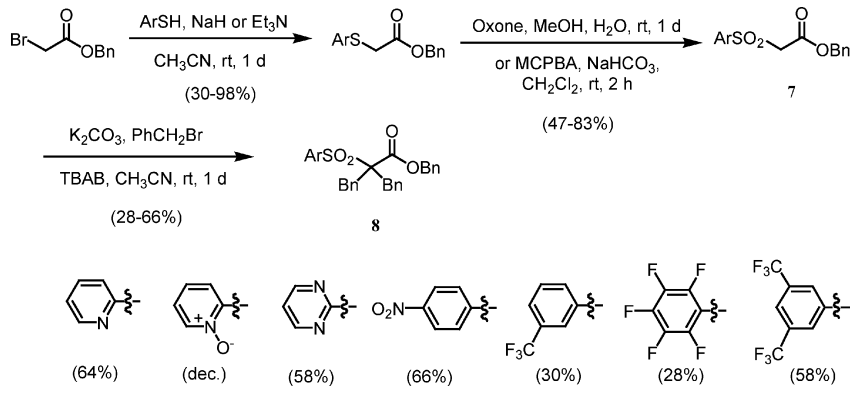
In this lecture we present our studies about the use of $\pi$-electron-deficient aryl sulfones, especially 3,5-bis(trifluoromethyl)phenyl alkyl

sulfones (BTFP sulfones) as soft nucleophiles, as a carboxylic acid protecting group and in Julia–Kocienski olefination reactions.

## RESULTS

### α-[3,5-Bis(trifluoromethyl)phenylsulfonyl]acetates as Soft Nucleophiles[11]

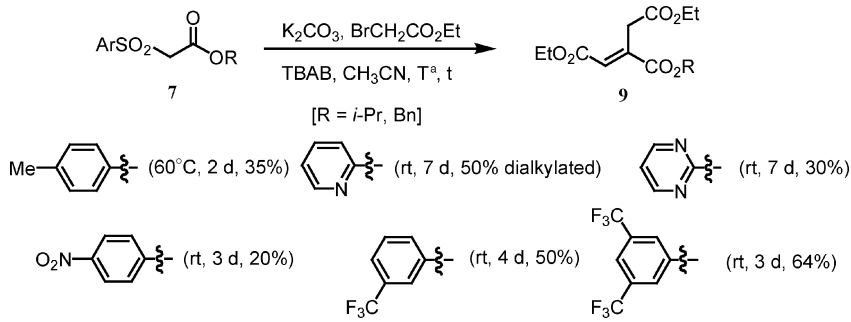
Different type of π-electron-deficient α-(arylsulfonyl)acetates **7** have been synthesized by an alkylation/oxidation sequence of the corresponding arylthiols (Scheme 1). The electron-withdrawing effect of the different arylsulfonyl groups was studied in the benzylation reaction using $K_2CO_3$ as base and tetra-*n*-butylammonium bromide (TBAB) as phase-transfer catalyst in acetonitrile for 1 d at room temperature. The *N*-oxido-2-pyridyl derivative decomposed under these reaction conditions and the 3,4-(dichlorophenyl) sulfone has to be alkylated using DBU as base. The rest of α-(arylsulfonyl)acetates suffered dibenzylation to give products **8** in good to moderate yields, whereas the α-(tosyl)acetate afforded a 1:1 mixture of mono and dibenzylated products in 60% yield. The best yields in the alkylation reaction were obtained with the 4-nitrophenyl, pyridin-2-yl, pyrimidin-2-yl and 3,5-bis(trifluoromethyl)phenyl sulfones (Scheme 1).




**SCHEME 1**

The alkylation-dehydrosulfinylation in situ sequence was performed with ethyl bromoacetate as electrophile under the aforementioned conditions in the presence of 6 equiv of $K_2CO_3$ to provide stereoselectively the corresponding (*E*)-aconitates **9** (Scheme 2). The integrated process was faster and in higher yields with α-[3,5-bis(trifluoromethyl)phenylsulfonyl]acetates. By contrast, the

$\alpha$-(tosyl)acetate must be treated at 60°C during 2 d to give the aconitate **9** in 35% yield. Trimethyl aconitate have been used as versatile synthetic building blocks in the synthesis of heterocycles.[12]




**SCHEME 2**

A variety of alkyl halides were found to undergo dialkylation reaction under these PTC conditions with the 3,5-bis(trifluoromethyl)phenyl (BTFP) sulfones **7**, which had been shown to be the best activating group. For the Michael diaddition, DBU and LiBr or $Si(OEt)_4$ and CsF were used as bases at 60°C for 1 d (Scheme 3). Cyclopentane annulations were carried out with 1,4-dihaloalkanes under PTC conditions in good yields.

Diallylated derivatives were submitted to the cyclopentannulation catalyzed by $Pd(OAc)_2$ in the HCl-saturated $CHCl_3$ solution at 60°C during 12 h to afford stereoselectively products **10** and **11** (Scheme 4). The dialkylation-desulfonylation of dibenzylated ester **8**

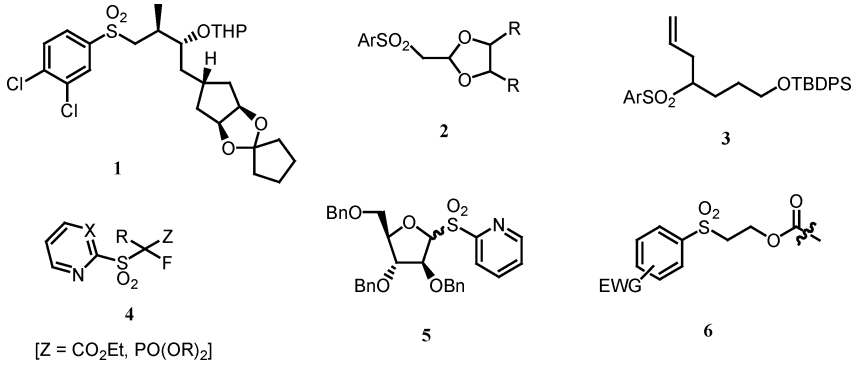
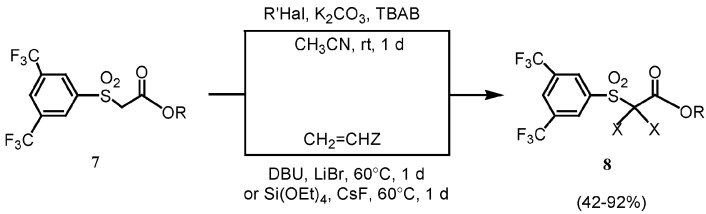



**FIGURE 1**



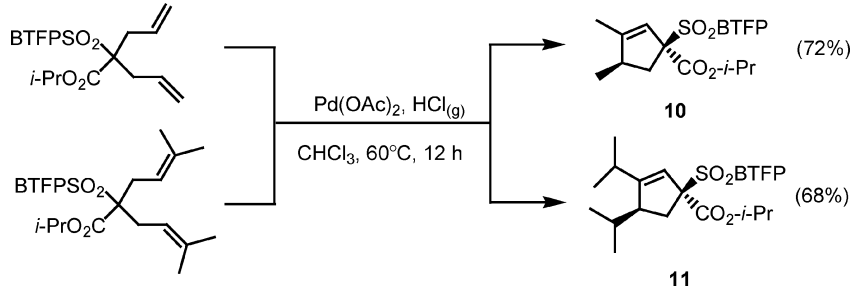

R'Hal: MeI, $CH_2$=CHCH$_2$Br, HCCCH$_2$Br, (*E*)-PhCH=CHCH$_2$Br, (*E*)-MeO$_2$CCH=CHCH$_2$Br, Me$_2$C=CHCH$_2$Br
HalR'Hal: I(CH$_2$)$_4$I, (*Z*)-BrCH$_2$CCH=CHCH$_2$Br, *o*-(CH$_2$Br)$_2$C$_6$H$_3$
$CH_2$=CHZ: $CH_2$=CHCO$_2$Et, $CH_2$=CHCO$_2$-*t*-Bu, $CH_2$=CHCOMe

**SCHEME 3**

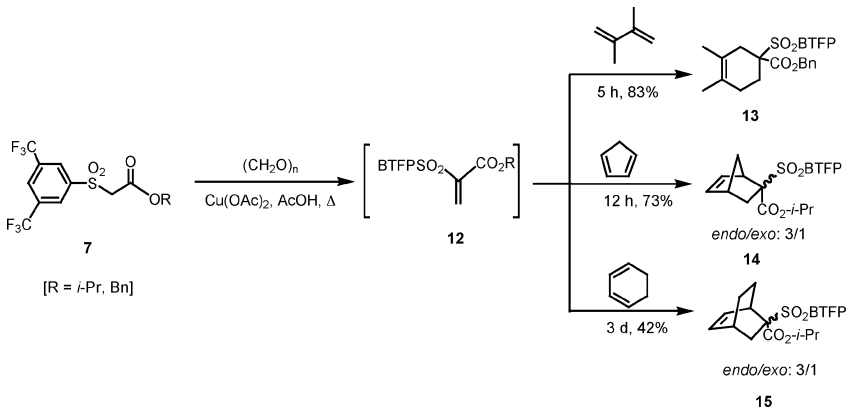
(R = Pr$^i$) was performed with Zn in the presence of $NH_4Cl$ in refluxing THF for 1 d to give isopropyl 2-benzyl-3-phenylpropanoate in 70% yield.

α-[Bis(3,5-trifluoromethyl)phenylsulfonyl]acrylates **12** were prepared by a Knoevenagel condensation of α-(BTFP-sulfonyl)acetates **7** with paraformaldehyde in the presence of $Cu(OAc)_2$ as catalyst in refluxing acetic acid.[13] This condensation was carried out in the presence of a diene to trap the unstable acrylates **12** and to give the corresponding Diels–Alder adducts **13–15** in moderate *endo*/*exo* diastereoselectivity (Scheme 5).

In conclusion, of all synthesized π-electron-deficient α-(arylsulfonyl)-acetates, the BTFP derivatives have been shown to be the best systems for dialkylation and dialkylation-β-elimination processes under very mild reaction conditions, allowing the stereoselective synthesis of (*E*)-aconitates. Reductive desulfonylation can be carried out with Zn and ammonium chloride. The corresponding α-(arylsulfonyl)acrylates underwent smooth Diels–Alder reaction with dienes.



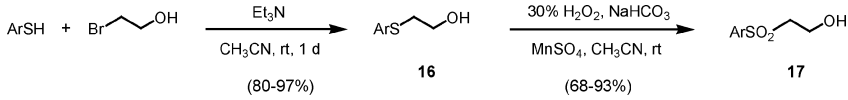

**SCHEME 4**




**SCHEME 5**

## $\alpha$-[3,5-Bis(trifluoromethyl)phenylsulfonyl]ethyl as Protecting Group[14]

The base labile protecting groups 2-(tosyl)ethyl (TSE) and 2-(phenylsulfonyl)ethyl (PSE) have been used as carboxylic acid protecting groups in several total syntheses.[15] These $\beta$-hydroxyethyl sulfone-derived esters are prepared by carbodiimide-mediated esterification and cleaved using organic bases such as DBU. Inorganic bases such as NaOH or $Na_2CO_3$ in aqueous dioxane or tetra-*n*-butylammonium fluoride in THF at 0°C can also be used for the dehydrosulfinylation process. We have studied several $\pi$-electron-deficient 2-(arylsulfonyl)ethyl groups for the protection-deprotection of carboxylic acids under mild reaction conditions. Diverse $\pi$-electron-deficient 2-(arylsulfanyl)ethanols **16** were prepared by reaction of thiophenols with 2-bromoethanol using $Et_3N$ as base in acetonitrile at rt to afford the corresponding sulfides. Their oxidation to 2-(arylsulfonyl)ethanols **17** was performed with $H_2O_2$ (30%) in the presence of a buffer solution of $NaHCO_3$ and a catalytic amount of $MnSO_4 \cdot H_2O$ (1 mol%) also in acetonitrile at room temperature (rt) (Scheme 6). These oxidation conditions of sulfides constitute a simple, economical, and environmentally friendly methodology for the synthesis of sulfones.[16] This method generates peroxymonocarbonate ion, which accelerates the low reactivity of hydrogen peroxide and was previously used for the epoxidation of olefins.[17]



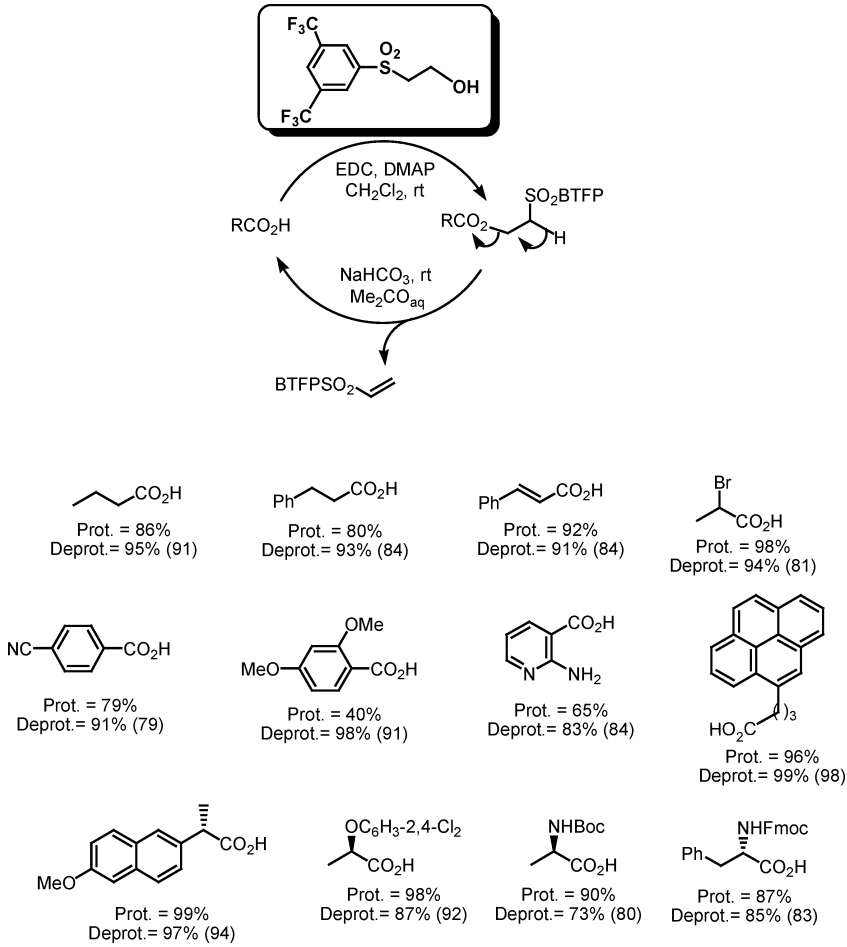

**SCHEME 6**

2-(Arylsulfonyl)ethanols **17** were used for the protection of cinnamic and hydroxycinnamic acids in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) and 4-(dimethylamino)pyridine (DMAP) in ethanol-free dichloromethane. The best results in this protection step were obtained with 2-[bis(3,5-trifluoromethyl)phenylsulfonyl]ethanol, 2-(4-nitrophenylsulfonyl)-ethanol and 2-(3,4-dichlorophenylsulfonyl)ethanol (79–92% yield), whereas 2-(phenylsulfonyl) and 2-[3-(trifluoromethyl)phenylsulfonyl]-ethanol gave lower (35–56%) yields. The deprotection step of 2-[3,5-bis(trifluoromethyl)phenylsulfonyl]ethyl (*E*)-3-phenyl-2-propenoate as a model substrate was studied with NaOAc, KOH, TBAF, TBAOH, and $NaHCO_3$. The best conditions for the deprotection step were the use of $NaHCO_3$ in acetone:$H_2O$ (1:1) yielding the vinylic sulfone and cinnamic acid in 87 and 96% yield, respectively. These deprotection conditions were studied with cinnamic and hydrocinnamic esters of different π-electron-deficient 2-(arylsulfonyl)ethanols, and the best results were obtained with the 2-[3,5-bis(trifluoromethyl)phenylsulfonyl]ethyl group. The 3-(trifluoromethyl) derivatives decomposed under these deprotection conditions. Different carboxylic acids were transformed into [3,5-bis(trifluoromethyl)phenylsulfonyl]ethyl esters by using EDC in high yields. The deprotection step was performed with $NaHCO_3$ in aqueous acetone to give the corresponding carboxylic acid and 3,5-bis(trifluoromethyl)phenyl vinyl sulfone in high yields (Scheme 7). Enantiomerically pure carboxylic acids were protected and deprotected with no loss in the optical purity. Aliphatic and aromatic carboxylic acids, even in the case of hindered substrates, were protected and deprotected in high yields.

In conclusion, 2-[3,5-bis(trifluoromethyl)phenylsulfonyl]ethanol is a new stable and crystalline reagent that has been shown as an efficient protecting system for carboxylic acids using very mild reaction conditions for the deprotection step.

## BTFP Sulfones in the Julia–Kocienski Olefination[18]

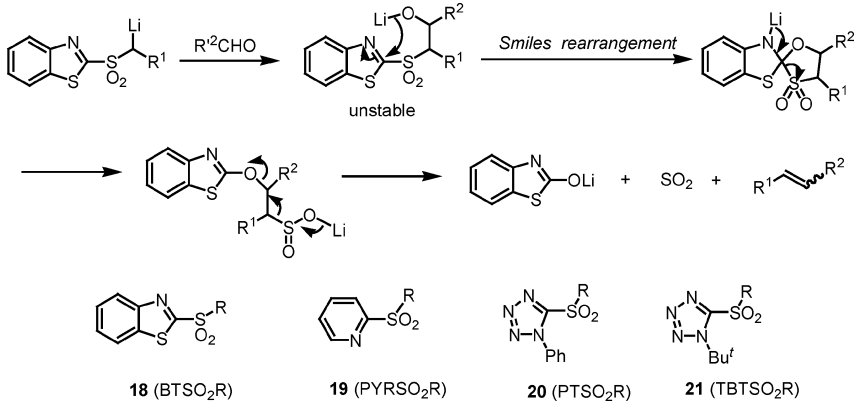
The *classical* Julia olefination is a connective olefination three-step procedure disclosed thirty years ago by Marc Julia and Jean-Marc Paris.[19] The method is an aldol condensation of a α-sulfonyl carbanion with a carbonyl compound, followed by acylation and final reductive elimination of the β-acyloxysulfone. The desulfonylation step is generally streoselective to give the *E*-alkene independent of the relative configuration of the β-acyloxysulfone, and depends on the increase of the chain branching about the newly formed double bond. The radical formed during the reduction step equilibrates to afford the stereochemical results.




**SCHEME 7**

A vinylic radical seems to be formed during the sodium amalgam reduction and a $\beta$-acyloxy radical is more likely under samarium(II) iodide desulfonylation.[20] The modified Julia olefination, also known as the Julia–Kocienski olefination,[21] is a new variant of the classical Julia–Lythgoe olefination, disclosed by Sylvestre Julia as a one-step procedure.[21] The reaction of metallated benzothiazol-2-yl sulfones with carbonyl compounds also affords a $\beta$-alkoxysulfone that is unstable and results in a facile Smiles rearrangement by addition of the alkoxide to the imine-like moiety. The resulting sulfinate salt suffers spontaneous sulfur dioxide elimination to afford the lithium benzothiazolone and the

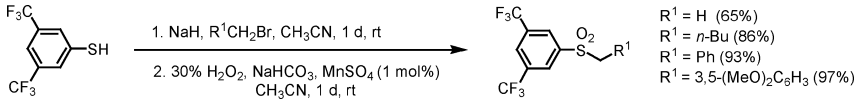
alkene (Scheme 8). Four heterocyclic sulfones have been used for the one-pot Julia olefination: benzothiazol-2-yl (BT) **18**, pyridin-2-yl (PYR) **19**, 1-phenyl-1*H*-tetrazol-5-yl (PT) **20** and 1-tert-butyl-1*H*-tetrazol-5-yl (TBT) **21**.[22]




**SCHEME 8**

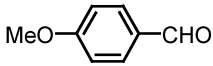
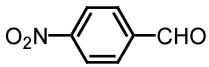
The deprotonation of these heterocyclic alkyl sulfones is performed by strong bases (LDA, *n*-BuLi, KHMDS) at very low temperatures (−60 to −78°C) under strict anhydrous conditions in THF or DME as solvents. Self-condensation of BT sulfones is a secondary process that can be avoided by using Barbier conditions, the addition of the base to a mixture of sulfone and aldehyde. For BT and PT sulfones, mainly *E*-isomers are formed and for PYR and TBT mainly *Z*-isomers are obtained. The increased stability of metallated TBT sulfones (**21**) as compared to PT (**20**) and BT (**21**) sulfones has been demonstrated by metallation of *n*-butyl derivatives with potassium hexamethyldisylazide (KHMDS) in DME at −60°C for 2 h. After final hydrolysis 0, 20, and 91% of the corresponding BT, PT, and TBT *n*-butyl sulfones were recovered, respectively.[23]

We envisioned that BTFP-sulfones could undergo the Smiles rearrangement necessary for the one-pot Julia–Kocienski olefination. The potent electron-withdrawing effect of the BTFP-sulfonyl group could allow us to use less strict reaction conditions for the deprotonation carbonyl addition process. Different alkyl and benzyl sulfones (Scheme 9) were prepared by alkylation of 3,5-bis(trifluoromethyl)thiophenol




**SCHEME 9**

**TABLE I**

| RCHO | Base | T(°C) | Yield (%) | *Z*/*E* ratio |
|---|---|---|---|---|
| PhCHO | P4-*t*-Bu | −78 | 78 (*E*) | 5:95 |
|  | P4-*t*-Bu | −78 | 67 (*E*) | 6:94 |
|  | P4-*t*-Bu | 0 | 76 (*Z*) | 70:30 |
| $C_6H_{11}CHO$ | P4-*t*-Bu | rt | 86 | 50:50 |
| $C_6H_{11}CHO$ | P2-Et | rt | 75 | 75:25 |

followed by oxidation with hydrogen peroxide as previously mentioned.[16] Initial studies about the stability of lithium diisopropylamide (BTFP)-sulfones were performed during 1 d with LDA/THF/−78°C, KHMDS/DME/−60°C, the phosphazene P4-*t*-Bu/THF/−78°C, or KOH/THF/TBAB/rt. In general these BTFP-sulfones showed high stability under these basic conditions even at rt with KOH with low self-condensation adducts formation. The stability of BT, PT, and TBT benzyl sulfones under these basic conditions has been studied. In the case of LDA, all of them present high stability, whereas when using KHMDS the BTFP and PT sulfones showed lower stability. In the case of P4-*t*-Bu similar survival was observed. However, very low stability was observed for BT, PT, and TBT sulfones under the aforementioned basic conditions (KOH).

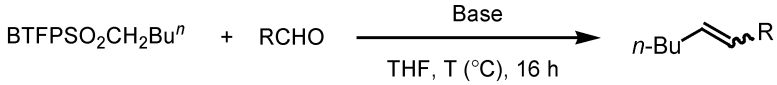
The olefination reaction was initially studied between the benzyl BTFP sulfone and benzaldehyde using different bases. Very low yield was obtained with KHMDS. In the presence of P4-*t*-Bu or P2-Et, higher yields and good *E*-stereoselectivities were obtained, whereas with the TBT benzyl sulfone, which showed the highest stability when was treated with P4-*t*-Bu, only 35% of stilbene was obtained. In the coupling mediated by KOH the best behavior was obtained with the BTFP benzyl sulfone. The olefination process was carried out between benzyl BTFP sulfone and aromatic aldehydes. Good yields and high *trans*-stereoselectivity using P4-*t*-Bu as base were obtained. However, in the case of 4-nitrobenzaldehyde and with aliphatic aldehydes, the reaction has to be performed at 0°C or rt with P4-*t*-Bu but with reverse selectivity (Scheme 10 and Table I).


**SCHEME 10**

**TABLE II**

| RCHO | Base | T (°C) | Yield (%) | *Z*/*E* ratio |
|---|---|---|---|---|
| PhCHO | KOH | rt | 70 | 33:67 |
| PhCHO | P4-*t*-Bu | rt | 45 | 25:75 |
| $C_6H_{11}CHO$ | P4-*t*-Bu | rt | 60 | 15:85 |
| $C_6H_{11}CHO$ | P2-Et | rt | 70 | 10:90 |

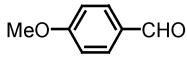
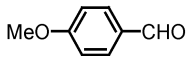
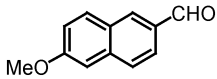
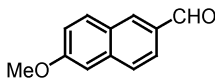
The coupling between *n*-butyl BTFP sulfone and aromatic or aliphatic aldehydes either with P4-*t*-Bu or KOH has to be carried out at rt and reasonable yields and *trans*-stereoselectivities were obtained (Scheme 11 and Table II). From Kocienski studies with PT and TBT sulfones using KHMDS as base and DME as solvent at −78°C, it is possible to compare to some extent with the results obtained with BTFP sulfones using P4-*t*-Bu as base in THF as solvent at rt. Similar results were observed concerning yields and also stereoselectitivy.



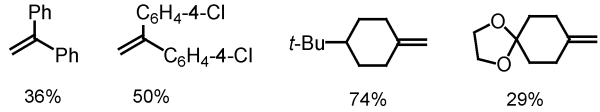

**SCHEME 11**

For the synthesis of terminal alkenes, the methyl BTFP sulfone was coupled with aldehydes using KOH or P4-*t*-Bu as base under Barbier conditions. In the case of ketones, P4-*t*-Bu was used as base, affording lower yields than when coupling aldehydes (Scheme 12 and Table III).[12]

**TABLE III**

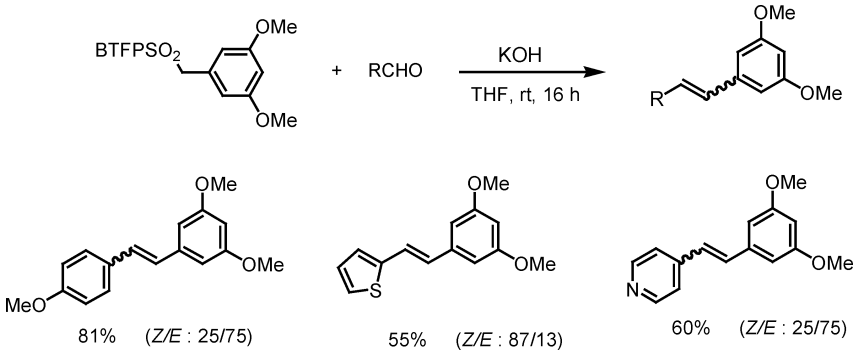
| RCHO | Base | T(°C) | Yield (%) |
|---|---|---|---|
|  | KOH[a] | rt | 60 |
|  | P4-*t*-Bu | −78°C to rt | 40 |
|  | KOH[a] | rt | 80 |
|  | P4-*t*-Bu[a] | −78°C to rt | 82 |
| | P4-*t*-Bu | −78°C to rt | 75 |

[a]The base was added to the mixture of reagents.




**SCHEME 12**

The coupling of 3,5-dimethoxybenzyl BTFP sulfone with different aromatic and heteroaromatic aldehydes using KOH as base allowed the synthesis of methoxylated stilbenoids including trimethylated resveratrol (Scheme 13).[18,24] These methoxylated stilbenoids are potent CYP1B1 inhibitors valuable for the development of a chemopreventing or therapeutic agent for cancer.[24,25]




**SCHEME 13**

We can concluded that BTFP sulfones are good substrates for the Julia–Kocienski olefination reaction working under mild and more simple reaction conditions than other heterocyclic sulfones and with comparable stereoselectivity. We are currently working in this olefination reaction and in other applications of BTFP sulfones in organic synthesis.

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