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# 3,5-Bis(trifluoromethyl)phenyl Sulfones in the Direct Julia−Kocienski Olefination

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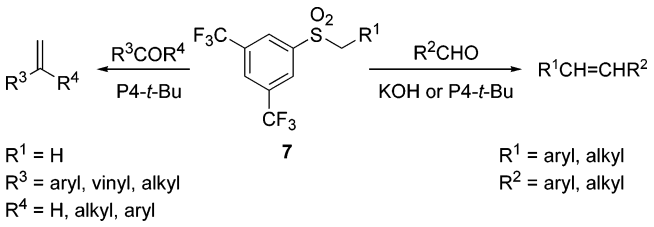


3,5-Bis(trifluoromethyl)phenyl (BTFP) sulfones **7** have been employed in the Julia−Kocienski olefination reaction with carbonyl compounds. Sulfones **7** are readily prepared in high yields (64−97%) from commercially available 3,5-bis(trifluoromethyl)thiophenol through an alkylation/oxidation two-step sequence. The stability of metalated BTFP sulfones has been studied and compared with heteroaryl benzothiazol-2-yl (BT), 1-phenyl-1*H*-tetrazol-5-yl (PT), and 1-*tert*-butyl-1*H*-tetrazol-5-yl (TBT) sulfones **9**−**11** under different reaction conditions. The Julia−Kocienski olefination between alkyl BTFP sulfones **7** and a wide variety of aldehydes affords the corresponding 1,2-disubstituted alkenes and dienes in good yields and stereoselectivities. This one-pot protocol can be performed using KOH at room temperature or the phosphazene bases P2-Et and P4-*t*-Bu at −78 °C or rt and has been successfully used in a high-yielding and stereoselective synthesis of various methoxylated stilbenes such as trimethylated resveratrol. These new reaction conditions for the Julia−Kocienski olefination reaction have been also studied with BT, PT, and TBT sulfones, giving poorer results. Methylenation of aliphatic and aromatic aldehydes, ketones, and 1,2-dicarbonyl compounds is carried out through the modified Julia olefination using BTFP methyl sulfone **7d** to give terminal alkenes and dienes. Mechanistic studies of the olefination reaction between benzyl BTFP sulfone **7a** and aromatic aldehydes performed by KOH-induced Smiles rearrangement of stereodefined *syn*- and *anti*-$\beta$-hydroxyalkyl BTFP sulfones indicate that the stereocontrol of the reaction is determined in the elimination step.

## Introduction

The stereoselective synthesis of alkenes has represented one of the long-standing challenges in organic chemistry. During several decades, a variety of approaches to the synthesis of olefins have been developed attempting to address their regio- and stereochemical demands. The most generally applicable methods involve the direct olefination of carbonyl compounds, as in the Wittig,[1] Horner,[2] Wadsworth−Emmons,[3] Peterson,[4] Johnson,[5] and classical Julia[6] reactions. These methodologies have played prominent roles in the synthesis of natural products containing the *E*- or *Z*-alkene moiety. The classical Julia olefination, also known as the Julia−Lythgoe olefination, was developed nearly 30 years ago and is based on a reductive elimination process of $\beta$-acyloxy alkyl sulfones.[7] Since its discovery, significant improvements have been made in the reaction, and it has become a crucial step in the synthesis of many natural products.[8] A new variant of the classical Julia reaction,

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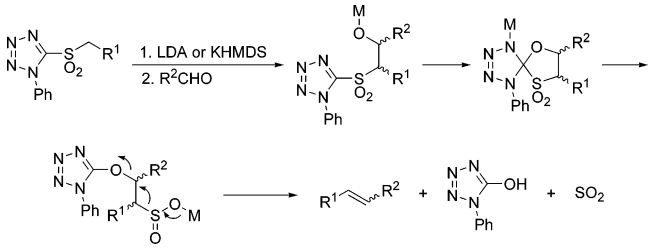
the Julia−Kocienski olefination, also called modified or one-pot Julia olefination,[9,10] has recently emerged as a powerful tool for olefin synthesis. The process involves the replacement of the aryl sulfone moiety, traditionally used in the classical reaction, with different heteroaryl sulfones, thus allowing the direct olefination process. Since the initial exploration by Julia and co-workers of the reaction of metalated benzothiazol-2-yl sulfones (BT sulfones, **1**) with carbonyl compounds,[9a] the versatility of these derivatives has been fully demonstrated through their application in the total synthesis of a large number of biologically active natural products[9c] such as rapamycin,[11] (+)-herboxidiene A,[12] (−)-[13] and (+)-lasonolide A,[14] rhizoxin D,[15] phorboxazole A[16] and B,[17] peridin,[18] (−)-colombiasin A,[19] and (−)-elisapterosin B.[19] In addition, other heterocyclic derivatives have also provided useful levels of stereoselectivity in the one-pot Julia olefination, such as pyridin-2-yl (PYR, **2**),[20] 1-phenyl-1*H*-tetrazol-5-yl (PT, **3**),[21] and 1-*tert*-butyl-1*H*-tetrazol-5-yl (TBT, **4**),[22] all of them developed with the aim of increasing the stability of the corresponding metalated sulfones and applied, especially in the case of the 1-phenyl-1*H*-tetrazol-5-yl derivatives, to the stereoselective synthesis of the alkene moiety in complex natural products.[23] The Julia−Kocienski reaction has also been used as a C−C coupling methodology in numerous total syntheses after hydrogenation of the newly formed double bond. The presence of an electrophilic imine-like moiety in the heterocyclic derivatives **1**−**4** is responsible for the different reactivity and reaction pathway observed in the one-pot Julia olefination, involving a Smiles rearrangement,[24] and spontaneous elimination of sulfur dioxide and the corresponding hydroxy-substituted heterocycle (Scheme 1). As depicted for PT derivatives in Scheme 1, the deprotonation of these sulfones must be carried out with strong anhydrous non-nucleophilic bases such as LDA or KHMDS. We have recently shown that the 3,5-bis(trifluoromethyl)phenylsulfonyl (BTFP sulfonyl), is a strong electron-withdrawing group and an excellent nucleofuge in base-promoted $\beta$-elimination processes. Thus, α-arylsulfonyl acetates **5** are very soft nucleophiles that can be easily dialkylated under very mild phase-transfer-catalyzed (PTC) conditions, and its reaction with ethyl bromoacetate allows the direct synthesis of (*E*)-aconitates via an alkylation−elimination integrated process.[25] On the other hand, $\beta$-arylsulfonyl ethanol **6** is an efficient protecting group for carboxylic acids, easily removed with aqueous $NaHCO_3$.[26] As part of a program aimed at developing useful applications of 3,5-bis(trifluoromethyl)-phenyl sulfones in organic synthesis, we have very recently communicated the successful use of alkyl BTFP sulfones **7a**−**c** in the Julia−Kocienski olefination reaction under very simple reaction conditions.[27] In this article, we report the full account on the evaluation and optimization of the synthetic applications of alkyl BTFP sulfones **7** in the Julia−Kocienski reaction of carbonyl compounds.

**SCHEME 1**



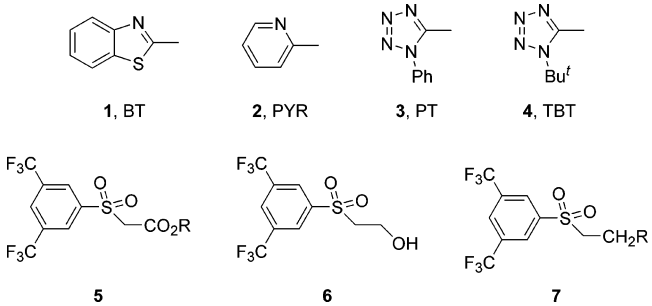




**FIGURE 1.** Heteroaryl groups and BTFP sulfones.

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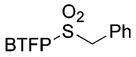
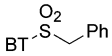
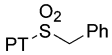
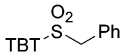
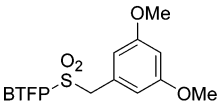
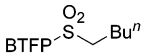
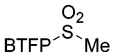
**SCHEME 2**


**7a**, R = Ph (93%)
**7b**, R = 3,5-$(MeO)_2C_6H_3$ (97%)
**7c**, R = $Bu^n$ (86%)
**7d**, R = H (65%)
**7e**, R = 4-$NO_2C_6H_4$ (64%)

**TABLE 1. Stability of Sulfones 7 and 9−11a**

| | reaction conditions | | | |
|---|---|---|---|---|
| sulfone recovery[a] | LDA, THF, -78ºC, 24h | KHMDS, DME, -60ºC, 24h | P4-*t*-Bu, THF, -78ºC, 24h | KOH, THF, TBAB, rt, 24h |
|  **7a** | >95[b] | 75(>95[b]) | 88 | 32[c] |
|  **9a** | >95[b] | 84 | 73 | 5[d] |
|  **10a** | >95[b] | 50 | 64 | -[e] |
|  **11a** | >95[b] | 99 | 78 | -[e] |
|  **7b** | 53 (>95[b]) | 60 (>95[b]) | 55 (>95[b]) | 20[f] |
|  **7c** | >95[b] | 53 (>95[b]) | 77 | 75 |
|  **7d** | >95[b] | 66 (>95[b]) | 70 | 45[g] |

[a] Isolated yield after flash chromatography. [b] Isolated crude yield, pure by $^1H$ NMR. [c] Isolated yields of 5 and 64% of 3,5-bis(trifluoromethyl)phenol and stilbene (**12aa**) (*Z*/*E*: 12/88), respectively, were also obtained. [d] Isolated yields of 25 and 26% of benzo[*d*]thiazol-2-ol and stilbene (**12aa**) (*Z*/*E*: 20/80), respectively, were also obtained. [e] Only decomposition products and small amounts of stilbene (*Z*/*E*: nd) were observed in the crude reaction mixture. [f] A 10% isolated yield of 1,2-bis(3,5-dimethoxyphenyl)ethene (**12ba**) (*Z*/*E*: 17/83) was also obtained. [g] 3,5-Bis(trifluoromethyl)phenol (55%) was also obtained.

## Results and Discussion

**BTFP Sulfones Preparation, Stability, and Reactivity under Basic Conditions**. Different representative $\pi$-deficient BTFP sulfones **7a**−**e** were prepared in high yields by reaction of 3,5-bis(trifluoromethyl)benzenethiol[28] with alkyl bromides or iodides using NaH as base in $CH_3CN$ at room temperature to afford the corresponding sulfides **8**, which were oxidized without further purification with 30% $H_2O_2$ in the presence of substoichiometric amounts of $MnSO_4 \cdot H_2O$ (1 mol %) and a buffer solution of $NaHCO_3$[29] to the corresponding sulfones **7** (Scheme 2).

On the basis of our previously reported studies of the α,α-dialkylation of α-arylsulfonyl acetates **5** under PTC conditions employing $K_2CO_3$ as base, we first carried out a stability analysis of the sulfonyl carbanions derived from the BTFP sulfones **7** under different basic conditions (Table 1). Benzylic heteroaryl sulfones **9a**−**11a**, prepared following literature methods,[21,22] were also included in the screening to compare their stability with 3,5-bis(trifluoromethyl)phenyl sulfones under the tested reaction conditions. As depicted in Table 1, sulfones **7** and **9a**−**11a** were treated with different bases such as LDA (1.1 equiv, THF, −78 °C), KHMDS (1.1 equiv, DME, −60 °C), the phosphazene (triaminoiminophosphorane) base P4-

(28) Alonso, D. A.; Nájera, C. 3,5-Bis(trifluoromethyl)benzenethiol. In *Encyclopedia of Reagents for Organic Synthesis*; Wiley & Sons. http://www.mrw.interscience.wiley.com/eros, in press.

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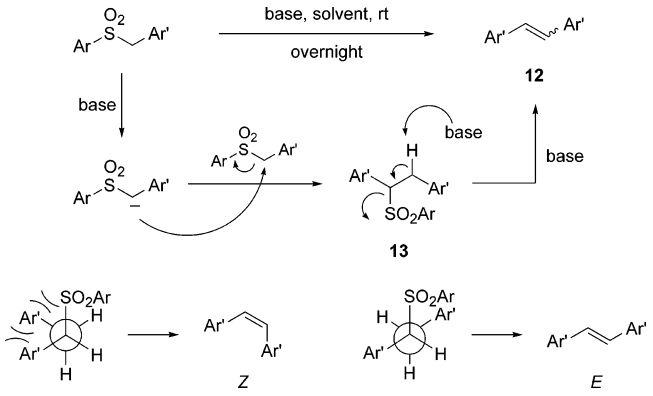
*t*-Bu[30] (1.2 equiv, THF, −78 °C), and KOH [9 equiv, THF, tetrabutylammonium bromide (TBAB, 10 mol %), rt], for 24 h, and the amount of remaining starting material after quenching the reaction with water was determined. When using metalated bases such as LDA and KHMDS, the sulfone recovery clearly showed that benzylic TBT sulfone **11a** was the most stable system under these conditions. With respect to BTFP sulfones **7**, the recovery of the crude material was also satisfactory, but a significant decrease in the isolated yield was observed after flash chromatography. This problem, which was also observed in the case of benzyl phenyltetrazolyl sulfone **10a**, was not detected when using P4-*t*-Bu as base in THF at −78 °C, all the systems giving place to recoveries between 55 and 88%. Furthermore, in no case were self-condensation products proceeding from an *ipso* reaction of the metalated carbanion of the BTFP sulfones with itself or with the starting material detected. This fact allows us to carry out the deprotonation step in the absence of the electrophile, thus extending the scope of the olefination reaction to base-sensitive carbonyl compounds. In addition, an inorganic base such as KOH under solid–liquid PTC conditions was also employed in the sulfone stability study. As shown in Table 1, the sulfone recovery after 24 h was much lower than that in the case of the previously mentioned bases. This behavior is in part due to the *ipso* nucleophilic substitution between the base and the arylsulfonyl moiety, leading to the corresponding hydroxy-BT, PT, and TBT derivatives, and 3,5-bis(trifluoromethyl)phenol in the case of the methyl BTFP sulfone **7d**. This unwanted side reaction was not observed in shorter metalation times, a 90% of sulfone recovery being obtained after stirring **7a** for 15–20 min in THF at room temperature in the presence of 9 equiv of KOH and TBAB (1 mol %). Furthermore, in the case of the benzyl BTFP sulfones **7a** and **7b**, the formation in variable amounts of symmetrical stilbenes **12** was also observed under the tested PTC reaction conditions. A plausible mechanism for the stereoselective formation of **12** would involve nucleophilic substitution on the benzylic sulfones by the formed α-sulfonyl carbanions to give intermediates **13**, which suffer a *β*-elimination of arylsulfinate under basic conditions to afford stereoselectively the corresponding stilbenes (Scheme 3).[31]

The oxidative homocoupling of metalated sulfones (mainly Li and Mg) has been previously reported under Cu-,[32] Ni-,[33] Te-,[34] Fe-,[35] and $O_2$[36]-catalyzed conditions.

**SCHEME 3**




With respect to benzylic sulfones, only the Ni- and Te-catalyzed protocols have been shown to be efficient for the preparation of the corresponding symmetrical stilbenes with moderate stereoselectivity. Furthermore, the homocoupling reactions are always carried out under inert atmosphere and either under reflux conditions[33] or employing substoichiometric amounts of catalyst.[34] We carried out an optimization study of the reaction with benzylic sulfone **7a** to improve the yield and stereoselectivity of the homocoupling reaction (Table 2). The optimization of the base, which was studied with THF as solvent at room temperature, showed *t*-BuOK (5 equiv) as the base of choice in terms of both yield and stereoselectivity (80% yield, *Z*/*E*: 3/97) (Table 2, entry 2). Other inorganic bases such a $K_2CO_3$ and organic bases such as 1,1,3,3-tetramethylguanidine (TMG), P4-*t*-Bu, or P2-Et failed to promote efficiently the reaction (Table 2, entries 3–6). With respect to the solvent, lower yields were obtained when the dimerization of sulfone **7a** was carried out in DME instead of in THF (Table 2, entries 2 and 8). BTFP sulfones **7b** and **7e** also afforded the corresponding *sym*-stilbenes **12bb** and **12ec** in 85 and 17% yields, respectively, when treated with *t*-BuOK in THF at room temperature in high *E*-selectivities (Table 2, entries 9 and 10). The low yield obtained with sulfone **7e** is due to the low stability of this sulfone under the reaction conditions. When the reaction with sulfone **7e** was carried out in DME, the yield was improved although the selectivity was lower (Table 2, entry 11). Finally, it is significant to mention that benzylic BT, PT, and TBT sulfones **9**–**11** did not afford significant amounts of stilbene under the optimized conditions (Table 2, entries 12–14). It can be concluded that benzyl BTFP sulfones are the most appropriate systems for the diastereoselective preparation of (*E*)-*sym*-stilbenes using *t*-BuOK as base and THF as solvent.

**Julia–Kocienski Olefination with BTFP Sulfones: Synthesis of 1,2-Disubstituted Olefins.** The Julia–Kocienski olefination of carbonyl compounds with BTFP sulfones **7** was first evaluated through the coupling between benzyl BTFP sulfone **7a** and PhCHO. In this study, different reaction conditions were employed: LDA, KHMDS, KOH, DBU, *t*-BuOK, and the phosphazene

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(31) Uguen has proposed the formation of carbene species from benzyl sulfone carbanions to explain the observed formation of stilbenes in very low yields in the reduction with sodium amalgam of benzyl sulfones: Jolivet, B.; Uguen, D. *Tetrahedron Lett.* **2002**, *43*, 7907–7911.

(32) Julia, M.; Le Thuillier, G.; Rolando, Ch.; Saussine, L. *Tetrahedron Lett*. **1982**, *23*, 2453–2456.

(33) (a) Julia, M.; Verpeaux, J.-N. *Tetrahedron Lett*. **1982**, *23*, 2457–2460. (b) Gai, Y.; Julia, M.; Verpeaux, J.-N. *Bull. Soc. Chim. Fr.* **1996**, *133*, 805–816.

(34) Engman, L. *J. Org. Chem.* **1984**, *49*, 3559–3563.

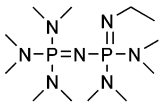
(35) Jin, L.; Julia, M.; Verpeaux, J. N. *Synlett* **1994**, 215–216.

(36) Heathcock has noticed the oxygen-catalyzed oxidative coupling of two alkyl sulfone anions to give an alkene after the reductive elimination of a bis sulfone intermediate: Heathcock, C. H.; Finkelstein, B. L.; Jarvi, E. T.; Radel, P. A.; Hadley, C. R. *J. Org. Chem.* **1988**, *53*, 1922–1942.

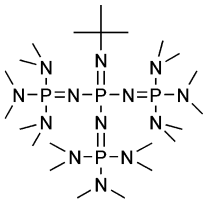
**TABLE 2. Synthesis of 1,2-Diarylethylenes 12**

| | | | | reaction conditions | | alkene | | |
|---|---|---|---|---|---|---|---|---|
| entry | Ar | Ar′ | sulfone No. | base (equiv) | solvent | No. | yield (%)[a] | *Z*/*E*[b] |
| 1 | BTFP | Ph | **7a** | KOH (9)[c] | THF | **12aa** | 65 | 12/88 |
| 2 | BTFP | Ph | **7a** | *t*-BuOK (5) | THF | **12aa** | 80 | 3/97 |
| 3 | BTFP | Ph | **7a** | $K_2CO_3$ (5)[c] | THF | **12aa** | <5 | nd |
| 4 | BTFP | Ph | **7a** | TMG (5) | THF | **12aa** | <5 | nd |
| 5 | BTFP | Ph | **7a** | P4-*t*-Bu (5) | THF | **12aa** | 10[d] | 50/50 |
| 6 | BTFP | Ph | **7a** | P2-Et (5) | THF | **12aa** | 8[d] | 50/50 |
| 7 | BTFP | Ph | **7a** | KOH (9)[c] | DME | **12aa** | 41 | 17/83 |
| 8 | BTFP | Ph | **7a** | *t*-BuOK (5) | DME | **12aa** | 25 | 1/99 |
| 9 | BTFP | 3,5-$(MeO)_2C_6H_3$ | **7b** | *t*-BuOK (5) | THF | **12bb** | 85 | 1/99 |
| 10 | BTFP | 4-$NO_2C_6H_4$ | **7e** | *t*-BuOK (5) | THF | **12ec** | 17 | 1/99 |
| 11 | BTFP | 4-$NO_2C_6H_4$ | **7e** | *t*-BuOK (5) | DME | **12ec** | 36 | 14/86 |
| 12 | BT | Ph | **9a** | *t*-BuOK (5) | THF | **12aa** | 0[e] | – |
| 13 | PT | Ph | **10a** | *t*-BuOK (5) | THF | **12aa** | 15[d] | 23/77 |
| 14 | TBT | Ph | **11a** | *t*-BuOK (5) | THF | **12aa** | <5[f] | nd |

[a] Isolated yield of (*E*)-**12** after flash chromatography. [b] Determined by GC over the crude reaction mixture. [c] TBAB (0.1 equiv) was added to the reaction mixture. [d] Mainly decomposition products were observed by $^1$HNMR in the crude reaction mixture. [e] A 100% conversion to benzo[*d*]thiazol-2-ol was observed by $^1$HNMR in the crude reaction mixture. [f] The starting sulfone **11a** was the main product observed by $^1$H NMR in the crude reaction mixture.



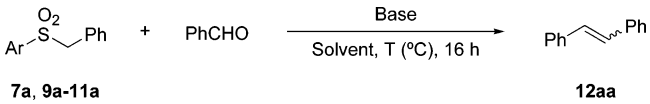
P2-Et



P4-*t*-Bu

bases P2-Et and P4-*t*-Bu,[37] either at room temperature (KOH, DBU, *t*-BuOK) or at low temperatures (−78 °C for LDA, P2-Et, and P4-*t*-Bu and −60 °C for KHMDS) in THF, $CH_2Cl_2$, and DME as solvents (Scheme 4, Table 3). For comparative purposes, the study was extended to sulfones **9a**−**11a**. The sulfone was treated with the corresponding base for 15−20 min prior to the addition of the aldehyde, except in the case of using *t*-BuOK where the reaction was carried out under Barbier-type conditions (slow addition of the base to a mixture of the aldehyde and sulfone), due to the propensity of sulfone **7a** to give stilbene (see Table 2), thus avoiding secondary reactions, especially in the case of using KOH as base (see Table 1). As shown in Table 3 (entries 1−8), the yields of the olefination reaction with KOH at room temperature and the Schwesinger bases at −78 °C were good. However, when 1.1 equiv of LDA, KHMDS, DBU, and *t*-BuOK were used as base, very low yields were obtained. No improvement was observed in the case of using LDA by adding 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) as additive or larger amounts of base (2.2 equiv). This could be explained by an aromatic metalation in the much-activated BTFP ring. However, after addition of $D_2O$ to a THF solution of metalated **7a**, only dideuteration in the benzylic position was observed (80% deuterium incorporation by $^1$H NMR). With respect to the (*E*)-stereoselectivity of the reaction, this was not sensitive to changes of base, and only in the presence of KOH (Table 3, entry 3) did it slightly

**SCHEME 4**




**7a**, **9a-11a** **12aa**

**TABLE 3. Julia−Kocienski Olefination of Benzaldehyde Employing Sulfones 7a and 9a−11a**

| | | reaction conditions | | | **12aa** | |
|---|---|---|---|---|---|---|
| entry | Ar | base (equiv) | solvent | *T* (°C) | yield (%)[a] | *Z*/*E*[b] |
| 1 | BTFP | LDA (1.1) | THF | −78 | <5[c] | nd |
| 2 | BTFP | KHMDS (1.1) | DME | −60 to rt | 20[c] | 1/99 |
| 3 | BTFP | KOH (9)[e] | THF | rt | 78 | 16/84 |
| 4 | BTFP | DBU (1.2) | $CH_2Cl_2$ | rt | <5 | nd |
| 5 | BTFP | *t*-BuOK (5) | THF | rt | <5 | nd |
| 6 | BTFP | P2-Et (2.2) | THF | −78 | 67[d] | 3/97 |
| 7 | BTFP | P4-*t*-Bu (1.2) | THF | −78 | 65[d] | 2/98 |
| 8 | BTFP | P4-*t*-Bu (1.2)[f] | THF | −78 | 78[d] | 5/95 |
| 9 | TBT | P4-*t*-Bu (1.2) | THF | −78 | 35 | 5/95 |
| 10 | TBT | KOH (9)[e] | THF | rt | 53 | 40/60 |
| 11 | BT | KOH (9)[e] | THF | rt | 45 | 25/75 |
| 12 | BT | P4-*t*-Bu (1.2) | THF | −78 | 55 | 15/85 |
| 13 | PT | KOH (9)[e] | THF | rt | 50 | 34/66 |
| 14 | PT | P4-*t*-Bu (1.2) | THF | −78 | 30 | 5/95 |

[a] Isolated yield of **12aa** after flash chromatography (hexane). [b] Determined by GC over the crude reaction mixture. [c] Similar results were obtained in the presence of 1.1 equiv of DMPU or using 2.2 equiv of LDA. [d] Isolated yield of (*E*)-stilbene. [e] TBAB (0.1 equiv) was added to the reaction mixture. [f] HMPA (1.2 equiv) was added to the reaction mixture.

decrease, probably due to the room temperature conditions. Both P2-Et (2.2 equiv) and P4-*t*-Bu (1.2 equiv) at −78 °C in THF gave satisfactory results in terms of yield and stereoselectivity (Table 3, entries 6 and 7). We also studied the effect of employing HMPA as an additive on the reaction behavior. The presence of this additive (1.2 equiv) in the reaction medium when using P4-*t*-Bu (1.2 equiv) as base involved an increase in the reaction yield, still with a high (*E*)-selectivity (Table 3, entry 8). Benzylic 1-*tert*-butyl-1*H*-tetrazol-5-yl TBT sulfone **11a** gave poorer results in terms of yield (P4-*t*-Bu as base, Table 3, entry 9) or selectivity (KOH, Table 3, entry 10). Under the same reaction conditions, BT and PT sulfones **9a** and **10a** also gave lower yields and stereoselectivities than the BTFP sulfone, as shown in Table 3, entries 11−14. From these

(37) Benzyl sulfones have been successfully deprotonated by phosphazene base P4-*t*-Bu in the diastereoselective aldol reaction with aldehydes: (a) Solladié-Cavallo, A.; Roche, D.; Fischer, J.; De Chian, A. *J. Org. Chem.* **1996**, *61*, 2690−2694. (b) Costa, A.; Nájera, C.; Sansano, J. M. *J. Org. Chem.* **2002**, *67*, 5216−5225.

**TABLE 4. Julia–Kocienski Olefination of Aldehydes with BTFP Sulfones 7**

| | sulfone | | | reaction conditions | | alkene | | |
|---|---|---|---|---|---|---|---|---|
| entry | No. | $R^1$ | $R^2CHO$ | base (equiv) | *T* (°C) | No. | yield (%)[a] | *Z*/*E*[b] |
| 1 | **7a** | Ph | PhCHO | KOH (9)[c] | rt | **12aa** | 78 | 16/84 |
| 2 | **7a** | Ph | PhCHO | P4-*t*-Bu (1.2) | −78 | **12aa** | 65[d] | 2/98 |
| 3 | **7a** | Ph | 4-$MeOC_6H_4CHO$ | KOH (9)[c] | rt | **12ad** | 52 | 14/86 |
| 4 | **7a** | Ph | 4-$MeOC_6H_4CHO$ | P4-*t*-Bu (1.2) | −78 | **12ad** | 76[d] | 6/94 |
| 5 | **7a** | Ph | 4-$NO_2C_6H_4CHO$ | KOH (9)[c] | rt | **12ac** | 12 | 34/66 |
| 6 | **7a** | Ph | 4-$NO_2C_6H_4CHO$ | P4-*t*-Bu (1.2) | 0 | **12ac** | 67 | 60/40 |
| 7 | **7a** | Ph | $C_6H_{11}CHO$ | KOH (9)[c] | rt | **12ae** | 14 | 66/34 |
| 8 | **7a** | Ph | $C_6H_{11}CHO$ | P2-Et (2.2) | rt | **12ae** | 75 | 75/25 |
| 9 | **7a** | Ph | $C_6H_{11}CHO$ | P4-*t*-Bu (1.2) | rt | **12ae** | 86 | 50/50 |
| 10 | **7c** | $Bu^n$ | PhCHO | KOH (9)[c] | rt | **12ca** | 70 | 33/67 |
| 11 | **7c** | $Bu^n$ | PhCHO | KOH (9)[c,e] | rt | **12ca** | 40 | 25/75 |
| 12 | **7c** | $Bu^n$ | PhCHO | P4-*t*-Bu (1.2) | rt | **12ca** | 45 | 25/75 |
| 13 | **7c** | $Bu^n$ | (*E*)-PhCH=CHCHO | KOH (9)[c] | rt | **12cf** | 30 | 88/12[f] |
| 14 | **7c** | $Bu^n$ | (*E*)-PhCH=CHCHO | P4-*t*-Bu (1.2) | −78 | **12cf** | 28 | 50/50[f] |
| 15 | **7c** | $Bu^n$ | $C_6H_{11}CHO$ | KOH (9)[c] | rt | **12ce** | 50[g] | 25/75 |
| 16 | **7c** | $Bu^n$ | $C_6H_{11}CHO$ | P2-Et (2.2) | rt | **12ce** | 70[g] | 10/90 |
| 17 | **7c** | $Bu^n$ | $C_6H_{11}CHO$ | P4-*t*-Bu (2.2) | rt | **12ce** | 60[g] | 15/85 |

[a] Isolated yield after flash chromatography (hexane). [b] Determined by GC over the crude reaction mixture. [c] TBAB (0.1 equiv) was added to the reaction mixture. [d] Isolated yield of (*E*)-isomer. [e] The reaction was carried out under Barbier-type conditions. [f] *EZ*/*EE* ratio determined by GC over the crude reaction mixture. [g] Conversion versus decane.

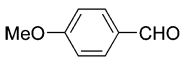
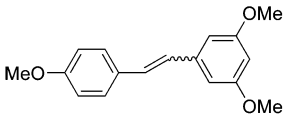
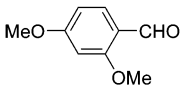
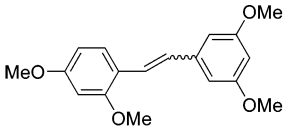
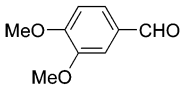
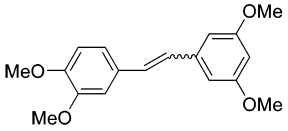
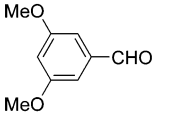
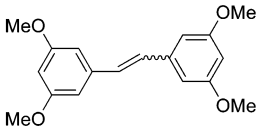
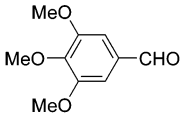
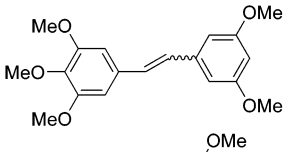
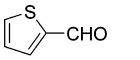
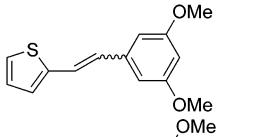
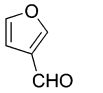
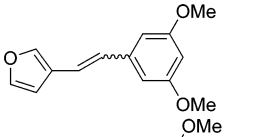
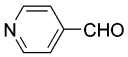
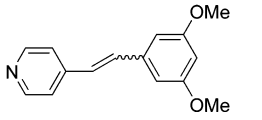
**SCHEME 5**


studies, it can be concluded that KOH is an appropriate base to carry out the Julia–Kocienski olefination between benzyl BTFP sulfone **7a** and benzaldehyde, even though higher selectivities are obtained using the phosphazene base P4-*t*-Bu in THF at −78 °C.

The olefination of different aromatic and aliphatic aldehydes with the benzyl sulfone **7a** and the pentyl sulfone **7c** was then performed according to the optimized conditions (Scheme 5, Table 4). The olefination process was successful when coupling benzyl sulfone **7a** with benzaldehyde and *para*-substituted electron-rich and electron-deficient benzaldehydes in the presence of P4-*t*-Bu or KOH as bases (Table 4, entries 1–6). With respect to the selectivity of the reaction, electron-rich *p*-methoxybenzaldehyde and benzaldehyde gave very similar results under these conditions (compare entries 1–4), affording better *E*-selectivities with P4-*t*-Bu as base. The olefination reaction with *p*-nitrobenzaldehyde employing KOH as base yielded the corresponding alkene **12ac** in a low 12% yield and as a 1/2 mixture of *Z*/*E* stereoisomers. The use of P4-*t*-Bu increased the yield of the reaction up to 67% and inverted the selectivity of the process in favor of the *Z*-isomer (Table 4, entry 6). The poor performance obtained with *p*-nitrobenzaldehyde has been previously observed with BT sulfones with LDA as base in THF, where the *E*-stereoselectivity of the process increases with the electron-donating ability of the *para* substituent on the benzaldehyde.[9c] Regarding aliphatic aldehydes, benzyl BTFP sulfone **7a** condensed with cyclohexanecarboxaldehyde in the presence of KOH in a low 14% yield and moderate selectivity (Table 4, entry 7). Higher *Z*-selectivity was obtained when using the phosphazene base P2-Et at room temperature (Table 4, entry 8), affording alkene **12ae** in a 75% yield. The reversed selectivity presented by an aliphatic aldehyde can be attributed to a diastereomeric equilibration between the *syn*- and *anti*-*β*-alkoxyalkyl sulfone intermediates via a retroaddition/addition process and a lower energy barrier for the syn isomer in the Smiles rearrangement, which drives to the *Z*-isomer. In fact, it has been demonstrated that the base-mediated elimination of *syn*-*β*-hydroxy-BT sulfones is more facile as compared with that of their *anti* counterparts (see below).[9b] The same reaction using P4-*t*-Bu as base at room temperature gave a 1/1 mixture of diastereoisomers (Table 4, entry 9). The olefination of (*E*)-cinnamaldehyde with sulfone **7a** was never successful irrespective of the base used, obtaining intractable crude reaction mixtures that were not analyzed.

The condensation of pentyl BTFP sulfone **7c** toward benzaldehyde, (*E*)-cinnamaldehyde, and cyclohexanecarboxaldehyde (Table 4, entries 10–17) was carried out employing KOH, P2-Et, and P4-*t*-Bu as bases. The (*E*)-selectivity of the olefination reaction with sulfone **7c** was in general good, except for the coupling with (*E*)-cinnamaldehyde. The reaction with benzaldehyde employing KOH as base was also carried out in the presence of the electrophile (Barbier-type conditions), with a small improvement in the *E*-selectivity, although a noticeable decrease in yield was also observed (Table 4, compare entries 10 and 11). When the same olefination reaction was performed in the presence of P4-*t*-Bu as base, a similar yield (45%) was obtained (Table 4, entry 12). Moderate yields were obtained in the olefination reaction of (*E*)-cinnamaldehyde with KOH and P4-*t*-Bu to give diene **12cf**, although in the former case a good *Z*-selectivity was obtained (Table 4, entries 13 and 14). High levels of *Z*-selectivity in the synthesis of conjugated 1,2-disubstituted alkenes via the condensation of metalated alkyl PYR sulfones with *α*,*β*-unsaturated aldehydes have also been observed.[20] With respect to the coupling of **7c** with cyclohexanecarboxaldehyde, the best result was obtained when the reaction was carried out at room temperature using 2.2 equiv of P2-Et (Table 4, entry 16). P4-*t*-Bu gave similar results (entry 17), and KOH afforded the lowest yield and selectivity (Table 4, entry 15). Unlike the coupling between sulfone **7a** and cyclohexanecarboxaldehyde, the reaction with sulfone **7c** was more stereoselective.

**TABLE 5. Synthesis of Resveratrol Analogues With BTFP Sulfone 7b**

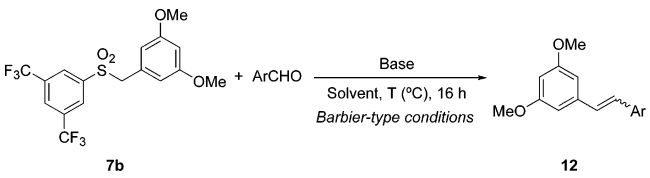
| | | reaction conditions[a] | | product | | | |
|---|---|---|---|---|---|---|---|
| entry | ArCHO | base (equiv.) | T (°C) | no. | structure | yield(%)[b] | *Z*/*E*[c] |
| 1 |  | KOH (9)[d] | rt | **12bd** |  | 81 (<5) | 25/75 |
| 2 | | P4-*t*-Bu (1.2) | -78 | | | 15[e] | 1/99 |
| 3 | | P4-*t*-Bu (1.2)[f] | -78 | | | 74[e] | 2/98 |
| 4 |  | KOH (9)[d] | rt | **12bg** |  | 35 (17) | 14/86 |
| 5 |  | KOH (9)[d] | rt | **12bh** |  | 40 (<5) | 14/86 |
| 6 |  | KOH (9)[d] | rt | **12bb** |  | 32 | 15/85 |
| 7 |  | KOH (9)[d] | rt | **12bi** |  | 25[e] (<5) | 4/96 |
| 8 |  | KOH (9)[d] | rt | **12bj** |  | 55[g] (<5) | 13/87 |
| 9 | | P4-*t*-Bu (1.2)[f] | -78 | | | 73 | 10/90 |
| 10 |  | KOH (9)[d] | rt | **12bk** |  | 40 (<5) | 29/71 |
| 11 |  | KOH (9)[d] | rt | **12bl** |  | 60 (<5) | 25/75 |

[a] The reactions were performed under Barbier-type conditions. [b] Isolated yield after flash chromatography (hexane). In parentheses isolated yield of (*E*)-1,2-bis(3,5-dimethoxyphenyl)ethene. [c] Determined by GC over the crude reaction mixture. [d] TBAB (0.1 equiv) was added to the reaction mixture. [e] Isolated yield of (*E*)-isomer. [f] HMPA (1.2 equiv) was added to the reaction mixture. [g] Isolated yield of (*E*)-isomer after isomerization of the mixture with $I_2$.

We can conclude with respect to the olefination of aliphatic and conjugated aldehydes with BTFP sulfones **7a** and **7c** that, under the studied reaction conditions, the benzyl sulfone **7a** performs better with aromatic aldehydes in the Julia−Kocienski reaction in terms of yield and selectivity with the phosphazene base P4-*t*-Bu at low temperature, giving the corresponding stilbenes with *E*-configuration. However, P2-Et at room temperature is the appropriate condition in the case of the coupling between benzyl sulfone **7a** and an aliphatic aldehyde. Regarding aliphatic sulfone **7c**, the olefination with aromatic aldehydes gives very similar results irrespective of the base used. However, α,β-unsaturated and aliphatic aldehydes afford better yields and selectivities when employing KOH and P2-Et at room temperature, respectively.

The benzyl BTFP sulfone **7b** was employed for the synthesis of methoxylated stilbenoids (Scheme 6, Table 5). Hydroxylated *E*-stilbenoids are natural polyphenols widely present in nature, especially in medicinal plants and food products, which have been shown to exhibit a

**SCHEME 6**




**7b** **12**

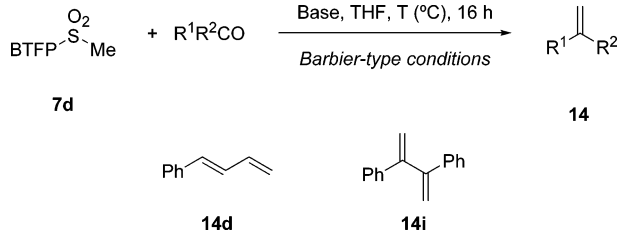
variety of unique and useful biological antioxidant, antimutagenic, and lifespan extension properties.[38] Methoxylated stilbenoids[39] such as the trimethylated resvera-

(38) (a) Siemann, E. H.; Creasy, L. L. *Am. J. Enol. Vitic.* **1992**, *43*, 49−52. (b) Soleas, G. J.; Diamandis, E. P.; Goldberg, D. M. *Clin. Biochem.* **1997**, *62*, 4821−4826. (c) Jang, M.; Cai, L.; Udenai, G. O.; Slowing, K. V.; Thomas, C. F.; Beecher, C. W. W.; Fong, H. H. S.; Farnsworth, N. R.; Kinghorn, A. D.; Mehta, R. G.; Moon, R. C.; Pezzuto, J. M. *Science* **1997**, *275*, 218−220. (d) Orsini, F.; Pelizzoni, F.; Verotta, L.; Aburjai, T.; Rogers, C. B. *J. Nat. Prod.* **1997**, *60*, 1082−1087. (e) Fremont, L. *Life Sci.* **2000**, *66*, 663−673. (f) Gusman, J.; Malonne, H.; Atassi, G. *Carcinogenesis* **2001**, *22*, 1111−1117. (g) Howitz, K. T.; Bitterman, K. J.; Cohen, H. Y.; Lamming, D. W.; Lavu, S.; Wood, J. G.; Zipkin, R. E.; Chung, P.; Kisielewski, A.; Zhang, L. L.; Scherer, B.; Sinclair, D. A. *Nature* **2003**, *425*, 191−196. (h) Lamming, D. W.; Wood, J. G.; Sinclair, D. A. *Mol. Microbiol.* **2004**, *53*, 1003−1009.

trol show higher activity against several human cancer cell lines than resveratrol itself.[40] After an extensive study of different bases, solvents, and temperatures, we found that the reaction between sulfone **7b** and *p*-methoxybenzaldehyde with KOH in the presence of TBAB yielded, under Barbier-type conditions, the corresponding trimethylated resveratrol **12bd** in a 81% yield and with a moderate *E*-selectivity (*Z*/*E* = 25/75) (Table 5, entry 1). This result could be a consequence of the presence of two electron-donating groups in BTFP sulfone **7b**, which may prevent the diastereomeric equilibration through a retroaddition/addition process, due to the lower stability of the corresponding benzylic carbanion, compared with **7a**. The reaction had to be carried out necessarily under Barbier-type conditions due to the low stability of sulfone **7b** under the basic reaction conditions (see Table 1). The phosphazene base P4-*t*-Bu in THF at −78 °C gave a very poor yield, although with an excellent selectivity (Table 5, entry 2). However, when this reaction was performed in the presence of HMPA, trimethylated resveratrol **12bd** was obtained with an excellent yield and selectivity (Table 5, entry 3). This strong positive effect of using HMPA in the reaction was not observed using other additives such as DMPU and is probably due to favorable interactions between the additive and the P4-*t*-Bu-derived carbanion, which could modify its structure and, hence, the reactivity of the system.[41] Several polymethoxylated stilbenes were synthesized following this protocol, although moderate yields were usually obtained (Table 5, entries 4−7), the best reaction conditions involving the use of KOH as base. The Julia−Kocienski olefination of 2,4-dimethoxybenzaldehyde afforded significant amounts of (*E*)-bis(2,4-dimethoxyphenyl)ethene (17%) even working under Barbier-type conditions (Table 5, entry 4). Better yields were obtained when sulfone **7b** was coupled with 2-thiophenecarboxaldehyde and 4-pyridine carboxaldehyde, substrates that afforded stilbenes **12bj** and **12bl**, respectively. These derivatives along with **12bg** present human cytochrome P450 1B1 inhibitory activity.[42] Even though both (*Z*/*E*) isomers of the corresponding stilbenes were obtained usually in different ratios following the Julia−Kocienski protocol with sulfone **7b**, it was possible to isomerize those mixtures after equilibration with catalytic iodine to furnish exclusively the *E*-stilbene, as shown for compound **12bj** (Table 5, entry 8). Therefore, the synthesis of resveratrol derivatives with sulfone **7b** employing KOH as base is a general process that works with a wide variety of aromatic aldehydes with moderate yields and good selectivities. The reaction has to be performed under Barbier-type conditions to avoid homocoupling of sulfone **7b** to the *sym*-stilbene **12bb**.

**Julia−Kocienski Methylenation of Aldehydes and Ketones with BTFP Sulfones.** The synthesis of terminal alkenes from carbonyl compounds is a very important reaction in organic synthesis.[43] The interest in the methylenation reaction of carbonyl compounds continues to generate many diverse methylenation reagents, such as Tebbe's reagent[44] and Grubbs' titanacyclobutane.[45] Recently, a few approaches to transition metal-catalyzed olefinations have also been disclosed.[46] We found out that BTFP methyl sulfone **7d** is a good reagent to perform methylenation reactions of carbonyl compounds through the Julia−Kocienski protocol[47] (Scheme 7, Table 6). In this case, the olefination reaction proved to be much more efficient when Barbier-type conditions were used. Thus, an equimolar mixture of BTFP sulfone **7d** and 4-methoxybenzaldehyde in THF at room temperature was treated with KOH (9 equiv) and a substoichiometric amount of TBAB (10 mol %) for 16 h to yield the corresponding alkene in a 60% isolated yield (Table 6, entry 1). In addition, 2-vinyl-6-methoxynaphthalene (**14b**), a key intermediate for the production of naproxen in the Albermale process, was obtained by reaction of sulfone **7d** with 6-methoxy-2-naphthaldehyde under similar reaction conditions in an 80% isolated yield (Table 6, entry 2). A comparable yield was obtained when the phosphazene base P4-*t*-Bu in THF was employed at −78 °C for 16 h (Table 6, entry 3). Moderate yields were obtained when either an aliphatic or an α,β-unsaturated aldehyde was submitted to the methylenation protocol employing P4-*t*-Bu or KOH as bases, respectively (Table 6, entries 4 and 5). In these particular reactions, the selection of the reaction conditions was based on the results obtained in the olefination reactions of similar substrates with pentyl BTFP sulfone **7c** (see Table 4). In the case of cinnamaldehyde, (*E*)-1-phenyl-1,3-butadiene (**14d**) was obtained as a single isomer in 50% yield (Scheme 7, Table 6, entry 5).

**SCHEME 7**




Several attempts to carry out the Julia−Kocienski olefination of acetophenone with benzyl BTFP sulfone **7a** employing different reaction conditions and bases (KOH,

(39) For a very recent synthesis of methoxylated stilbenoids employing Heck chemistry in our group, see: Botella, L.; Nájera, C. *Tetrahedron* **2004**, *60*, 5563−5570.

(40) (a) Pettit, G. R.; Grealish, M. P.; Jung, M. K.; Hamel, E.; Pettit, R. K.; Chapuis, J.-C.; Schmidt, J. M. *J. Med. Chem.* **2002**, *45*, 2534−2542. (b) Lion, C. J.; Matthews, C. S.; Stevens, F. G.; Westwell, A. D. *J. Med. Chem.* **2005**, *48*, 1292−1295.

(41) For a discussion about the nature of P4-*t*-Bu enolates, see: Fruchart, J.-S.; Gras-Masse, H.; Melnyk, O. *Tetrahedron Lett.* **2001**, *42*, 9153−9155.

(42) Kim, S.; Ko, H.; Park, J. E.; Jung, S.; Lee, S. K.; Chun, Y.-J. *J. Med. Chem.* **2002**, *45*, 160−164.

(43) Kelly, S. E. Alkene Synthesis. In *Comprehensive Organic Synthesis*; Trost, B. M. Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, p 729.

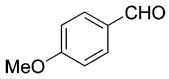
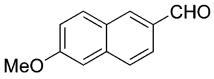
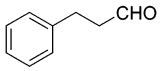
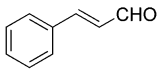
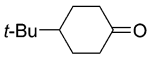
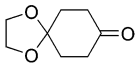
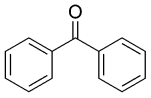
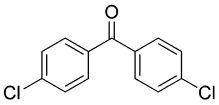
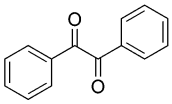
(44) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611−3613.

(45) Pine, S. H.; Zahier, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270−3272.

(46) (a) Mo-catalyzed: Lu, X. Y.; Fang, H.; Ni, Z. J. *J. Organomet. Chem.* **1989**, *373*, 77−84. (b) Re-catalyzed: Zhang, X. Y.; Chen, P. *Chem.−Eur. J.* **2003**, *9*, 1852−1859 and references therein. (c) Fe-catalyzed: Aggarwal, V. K.; Fulton, J. R.; Sheldon, C. G.; de Vicente, J. *J. Am. Chem. Soc.* **2003**, *125*, 6034−6035 and references therein. (d) Ru-catalyzed: Chen, Y.; Huang, L.; Ranade, M. A.; Zhang, X. P. *J. Org. Chem.* **2003**, *68*, 3714−3717 and references therein. (e) Rh-catalyzed: Lebel, H.; Paquet, V. *J. Am. Chem. Soc.* **2004**, *126*, 320−328 and references therein.

(47) For the methylenation reaction of carbonyl compounds employing $BTSO_2Me$, see refs 9a,c and Gueyrard, D.; Haddoub, R.; Salem, A.; Bavar, N. S.; Goekjian, P. G. *Synlett* **2005**, 520−522.

**TABLE 6. Julia–Kocienski Methylenation of Aldehydes and Ketones With Methyl BTFP Sulfone 7d**

| | | reaction conditions[a] | | product | |
|---|---|---|---|---|---|
| entry | $R^1R^2CO$ | base (equiv) | T (°C) | no. | yield (%)[b] |
| 1 |  | KOH (9)[c] | rt | **14a** | 60 |
| 2 |  | KOH (9)[c] | rt | **14b** | 80 |
| 3 | | P4-*t*-Bu (1.2) | -78 to rt | **14b** | 82[d] |
| 4 |  | P4-*t*-Bu (1.2) | -78 to rt | **14c** | 30 |
| 5 |  | KOH (9)[c] | rt | **14d** | 50[e] |
| 6 |  | KOH (9)[c] | rt | **14e** | 10[f,g] |
| 7 | | P4-*t*-Bu (1.2) | 0 to rt | **14e** | 74[g] |
| 8 |  | P4-*t*-Bu (1.2) | 0 to rt | **14f** | 41 |
| 9 |  | P4-*t*-Bu (1.2) | 0 to rt | **14g** | 36 (57[h]) |
| 10 |  | P4-*t*-Bu (1.2) | 0 to rt | **14h** | 50 |
| 11 |  | P4-*t*-Bu (1.2) | 0 to rt | **14i** | 45[i] |

[a] The reactions were carried out under Barbier conditions. [b] Isolated yield after flash chromatography (hexane). [c] TBAB (0.1 equiv) was added to the reaction mixture. [d] 75% yield was obtained when non-Barbier conditions were used. [e] (*E*)-isomer. [f] A 50% isolated yield of 3,5-(bistrifluoromethyl)phenol was also obtained. [g] Conversion versus decane. [h] Two equivalents of **7d** were used. [i] Four equivalents of **7d** were used.

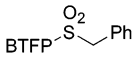
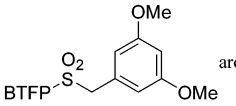
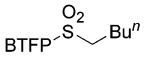
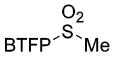
P4-*t*-Bu, P2-Et, KHMDS, and LDA) were unsuccessful, and sulfone recovery was always observed except when KOH was used, where significant amounts of 3,5-bis-(trifluoromethyl)phenol were obtained. However, under Barbier-type conditions, ketones could be condensed with BTFP methyl sulfone (**7d**). When the reaction was performed with 4-*tert*-butylcyclohexanone using KOH as base under Barbier conditions (Table 6, entry 6), very low yields of methylenated ketone were obtained due to the formation of 3,5-bis(trifluoromethyl)phenol as the main product. However, both aliphatic and aromatic ketones were converted into the corresponding terminal alkenes (**14e**–**h**) in moderate to good yields through methylenation with 1 equiv of **7d** and the phosphazene base P4-*t*-Bu at 0 °C to room temperature in THF. The observed low isolated yields of compounds **14c**–**f** appear associated with their volatility as indicated by the high reaction conversions observed. For the methylenation of benzophenone, the yield could be improved by increasing the amount of sulfone **7d** (Table 6, entry 9). Finally, it is worthy mentioning that 1,2-diketone derivatives such as benzil could be dimethylenated under the above-mentioned reaction conditions to the corresponding 1,3-diene **14i** using an excess of sulfone **7d** (Scheme 7, Table 6, entry 11). This type of diene-bearing aryl group has recently been studied as branched $\pi$-systems with potential applications in the development of materials with multiple conduction channels.[48]

Therefore, it can be concluded that the methylenation reaction of aromatic and $\alpha,\beta$-unsaturated aldehydes with sulfone **7d** gives good results when using KOH as base at room temperature. For aromatic aldehydes, the reaction can be carried out with P4-*t*-Bu, which also gives good isolated yields, whereas P4-*t*-Bu is the base of choice when a methylenation reaction with sulfone **7d** of aliphatic aldehydes and ketones is required.

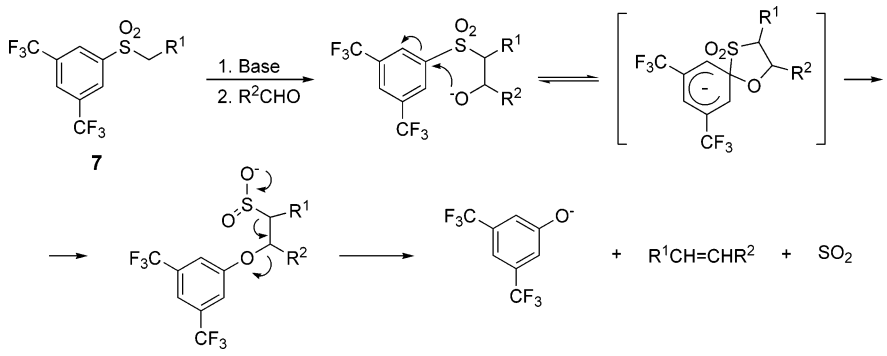
The olefination reaction of BTFP sulfones **7** can be performed with aromatic, $\alpha,\beta$-unsaturated, and aliphatic aldehydes, as well as aliphatic and aromatic ketones, the stereoselectivity of the process being influenced by a variety of factors, such as the carbonyl and sulfone structure, as well as the base, solvent, and additives employed (Table 7). In general, stabilized metalated benzyl sulfones **7a**,**b** stereoselectively afforded (*E*)-olefins when neutral or electron-rich aromatic aldehydes are employed in the reaction, whereas lower or reversed stereoselectivities were observed when using electron-poor aromatic or aliphatic aldehydes. The benzylic sul-

(48) Van der Wiel, B. C.; Williams, R. M.; van Walree, C. A. *Org. Biomol. Chem.* **2004**, *2*, 3432–3433.

**TABLE 7. Selected Olefination Conditions for BTFP Sulfones**

| sulfone | carbonyl compound | base | Barbier conditions | T (°C) | alkene yield | alkene diastereoselectivity |
|---|---|---|---|---|---|---|
|  **7a** | aliphatic aldehydes | P2-Et | no | rt | good | moderate *Z*-selectivity |
| | neutral or electron-rich aromatic aldehydes | P4-*t*-Bu | no | –78 | good | high *E*-selectivity |
| | electron-poor aromatic aldehydes | P4-*t*-Bu | no | 0 | good | moderate *Z*-selectivity |
|  **7b** | aromatic aldehydes | KOH | yes | rt | moderate | moderate to high *E*-selectivity |
|  **7c** | aliphatic aldehydes | KOH or P2-Et | no | rt | good | moderate to good *E*-selectivity |
| | aromatic aldehydes | KOH | no | rt | good | moderate *E*-selectivity |
| | α,β-unsaturated aldehydes | KOH | yes | rt | low | good *Z*-selectivity |
|  **7d** | aliphatic aldehydes | P4-*t*-Bu | yes | –78 to rt | low | – |
| | aromatic aldehydes | KOH or P4-*t*-Bu | yes | rt or –78 to rt | high | – |
| | α,β-unsaturated aldehydes | KOH | yes | rt | moderate | – |
| | aliphatic and aromatic ketones | P4-*t*-Bu | yes | 0 to rt | moderate | – |

**SCHEME 8**

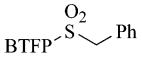
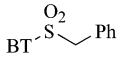
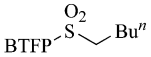
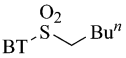
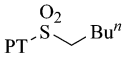
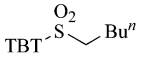
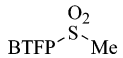
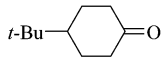
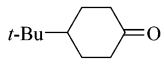



fone **7b** has been successfully used in the stereoselective synthesis of a wide variety of methoxylated stilbenes using KOH as base and working under Barbier-type conditions. Pentyl BTFP sulfone **7c**, which does not afford a stabilized carbanion intermediate, usually showed low stereoselectivity, the observed *E*/*Z* ratio being very dependent on the reaction conditions. BTFP methyl sulfone **7d** has been shown to be a good methylenation reagent for aliphatic and aromatic aldehydes, ketones, and 1,2-dicarbonyl compounds, working under Barbier-type conditions and employing P4-*t*-Bu as base.

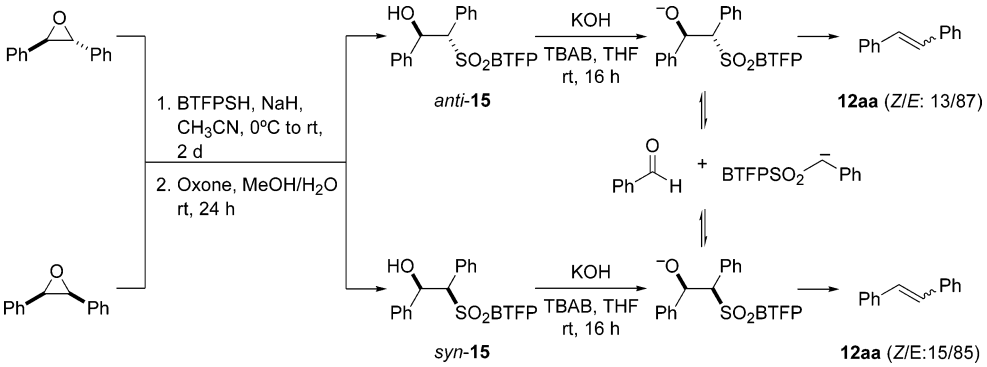
Table 8 includes a comparison among the results obtained for selected examples with BTFP sulfones with those for related BT, PT, and TBT sulfones under the particular conditions that have been optimized for these sulfones. With respect to benzylic sulfones **7a** and **9a**,[9c] better yields and similar or higher (*E*)-selectivities were obtained when employing BTFP sulfone **7a** with cyclohexanecarboxaldehyde and 4-methoxybenzaldehyde. In the case of pentyl sulfones **7c**–**11c**, good yields and excellent selectivities have been obtained in the olefination reaction of cyclohexanecarboxaldehyde and benzaldehyde with the phenyltetrazolyl derivative **10c** employing KHMDS as base.[22] BTFP sulfone **7c** afforded moderate to good yields and selectivities with these substrates working under room temperature conditions and using phosphazene base P2-Et and KOH as bases, respectively. When comparing BTFP and BT methyl sulfones **7d** and **9d**, their reaction with the aromatic 4-methoxybenzaldehyde afforded good yields in both cases of the terminal olefin. However, BTFP sulfone **7d** gives much better yields in the case of the olefination reaction of cyclic ketones such as 4-*tert*-butylcyclohexanone.

**Mechanistic Studies.** As mentioned above, after completion of the olefination reaction, we have observed in the crude reaction mixtures the formation of 3,5-bis(trifluoromethyl)phenol as a side product, which supports the postulated pathway for the modified Julia olefination (Scheme 8): addition of the sulfonyl carbanion to the

**TABLE 8. Olefination Conditions for Selected Examples With BT, PT, TBT, and BTFP Sulfones**

| sulfone | carbonyl compound | base | Barbier conditions | T (°C) | alkene yield (%) | alkene *Z*/*E* | ref. |
|---|---|---|---|---|---|---|---|
|  **7a** | $C_6H_{11}CHO$ | P2-Et | no | rt | 75 | 25/75 | |
| | 4-$MeOC_6H_4CHO$ | P4-*t*-Bu | no | –78 | 76 | 6/94 | |
|  **9a** | $C_6H_{11}CHO$ | LDA | yes | –78 to rt | 67 | 40/60 | *9c* |
| | 4-$MeOC_6H_4CHO$ | LDA | no | –78 to rt | 57 | 2/98 | *9c* |
|  **7c** | $C_6H_{11}CHO$ | P2-Et | no | rt | 70 | 10/90 | |
| | PhCHO | KOH | no | rt | 70 | 33/67 | |
|  **9c** | $C_6H_{11}CHO$ | KHMDS | no | –78 to rt | 32 | 25/75 | *21* |
| | PhCHO | LDA | yes | –78 to rt | 68 | 6/94 | *10* |
|  **10c** | $C_6H_{11}CHO$ | KHMDS | no | –60 to rt | 75 | 1/99 | *22* |
| | PhCHO | KHMDS | no | –60 to rt | 48 | <1/99 | *22* |
|  **11c** | $C_6H_{11}CHO$ | KHMDS | no | –60 to rt | 88 | 11/89 | *22* |
| | PhCHO | KHMDS | no | –60 to rt | 80 | 21/79 | *22* |
|  **7d** | 4-$MeOC_6H_4CHO$ | KOH | yes | rt | 60 | – | |
| |  | P4-*t*-Bu | yes | 0 to rt | 74 | – | |
|  **9d** | 4-$MeOC_6H_4CHO$ | LDA | yes | –78 to rt | 64 | – | *9c* |
| |  | LDA | yes | –78 to rt | 21 | – | *9c* |

**SCHEME 9**

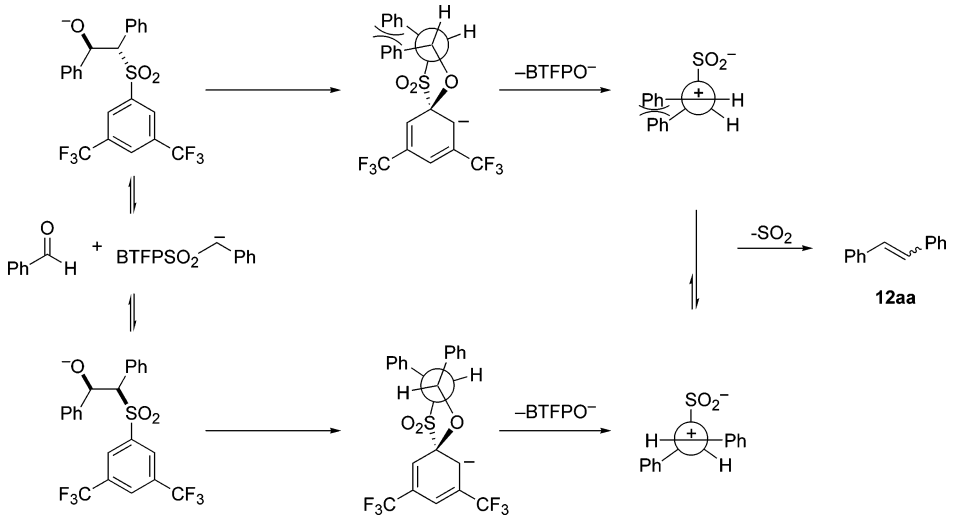



aldehyde, Smiles rearrangement, and spontaneous sulfur dioxide and 3,5-bis(trifluoromethyl)phenolate eliminations.[9c]

Regarding the stereoselectivity of the Julia–Kocienski reaction employing BTFP sulfones, an investigation of the base-mediated elimination of stereodefined *anti*- and *syn*-*β*-hydroxyalkyl BTFP sulfones **15** was carried out (Scheme 9). Hydroxyalkyl sulfones **15**, which were prepared from *trans*- and *cis*-stilbene epoxides in 40 and 30% isolated yields, respectively (Scheme 9),[49] gave place stereoselectively to the same results obtained in the olefination process under the tested reaction conditions (see Table 4, entry 1): a 13/87 and 15/85 mixtures of (*Z*)- and (*E*)-stilbene (**12aa**), respectively. These results and the presence of PhCHO and 3,5-bis(trifluoromethyl)-phenol in the crude reaction mixture demonstrate an equilibration between the *syn*- and *anti*-*β*-alkoxyalkyl sulfone diastereomers via a retroaddition/addition process with the carbonyl compound.

(49) All attempts to isolate or detect *β*-hydroxy sulfones **15** from the reaction between sulfone **7a** and benzaldehyde under different conditions were unfruitful due to the fast Smiles rearrangement and elimination of $SO_2$ that these systems suffer from.

**SCHEME 10**




The lack of total stereospecificity, although affording mostly the (*E*)-alkene, seems to involve zwitterionic intermediates created by direct loss of 3,5-bis(trifluoromethyl)-phenolate, as proposed by Julia.[9c] Conformational equilibration of these betaine intermediates favors the formation of the *trans*-alkene upon loss of $SO_2$ (Scheme 10).

In the case of the reaction between pentyl BTFP sulfone **7c** with aliphatic aldehydes (Table 4, entries 15−17), the $\beta$-alkoxyalkyl sulfone intermediate does not suffer a retroaddition/addition process due to the lower stability of the α-metalated sulfone, and therefore, the *E*/*Z* ratio of the product olefin accurately reflects the anti/*syn* ratio of the initial nucleophilic addition.

## Conclusions

The 3,5-bis(trifluoromethyl)phenyl sulfonyl (BTFP sulfonyl) group has been shown to be a very stable and excellent activator for the synthesis of olefins through the Julia−Kocienski olefination reaction using very simple reaction conditions. From studies on the stability and reactivity of BTFP sulfones in different reactions, it can be concluded that KOH and the phosphazene derivatives P2-Et and P4-*t*-Bu are the most appropriate bases for this type of coupling. Under these reaction conditions, BTFP sulfones were better substrates than the heteroaryl BT, PT, and TBT sulfones in terms of stability and reactivity. The olefination reaction of BTFP sulfones **7** could be performed with aromatic, α,$\beta$-unsaturated, and aliphatic aldehydes, as well as aliphatic and aromatic ketones, the stereoselectivity of the process being influenced by a variety of factors, such as the carbonyl and sulfone structure, as well as the base, solvent, and additives employed. The stereochemical behavior of BTFP sulfones in the olefination reaction seemed to be very similar to that presented by BT sulfones. Thus, the $\beta$-alkoxyalkyl sulfone intermediates from benzyl sulfones such as **7a** equilibrated via a retroaddition/addition process involving a zwitterionic sulfinate generated by direct loss of 3,5-bis(trifluoromethyl)phenolate in the spirocyclic intermediates. Additional applications of BTPF sulfones in olefination and other reactions are currently under investigation.

## Experimental Section

**Typical Procedure for the Synthesis of *sym*-(*E*)-1,2-Diarylethylenes 12.** To a stirred solution of *t*-BuOK (56 mg, 0.5 mmol) in anhydrous THF or DME (1 mL) under argon atmosphere was added dropwise a previously prepared solution of the corresponding sulfone (0.1 mmol) in anhydrous THF or DME (1 mL). After being stirred at room temperature for 16 h, the reaction mixture was quenched with a saturated aqueous $NH_4Cl$ solution (5 mL) and extracted with EtOAc (2 × 10 mL), the organic phase was dried ($Na_2SO_4$), and the solvent was evaporated, affording crude *sym*-olefins **12**, which were purified by flash chromatography (hexane).

**(*E*)-1,2-Bis(3,5-dimethoxyphenyl)ethene (12bb):**[42] Solid; $R_f$ (hexane/EtOAc: 2/1) 0.66; mp 129−131 °C; IR (KBr) $\nu_{max}$ 1616, 1461, 1425, 1282, 1058; $^1$H NMR $\delta$ 7.01 (s, 2H), 6.66 (d, $J$ = 2.3, 4H), 6.40 (t, $J$ = 2.2, 2H), 3.83 (s, 12H); $^{13}$C NMR $\delta$ 160.9, 139.1, 129.2, 104.6, 100.1, 55.4; MS *m*/*z* 300 ($M^+$, 100), 270 (11), 269 (29), 254 (12).

**General Olefination Procedure with BTFP Sulfones in THF.** To a stirred solution of the corresponding sulfone (0.1 mmol) in THF (2 mL) at the corresponding temperature (see Tables 3−6) under argon atmosphere (except for KOH) was added the suitable base (see Tables 3−6). After being stirred at the same temperature for 30 min, the corresponding aldehyde (0.11 mmol) was added. The reaction mixture was stirred overnight, quenched with a saturated aqueous $NH_4Cl$ solution (5 mL), and extracted with EtOAc (2 × 10 mL), and the organic phase was dried ($Na_2SO_4$). The solvent was evaporated to give crude olefins, which were purified by flash chromatography (hexane) to afford pure compounds **12aa**, **12ac**, **12ad**, **12ae**, and **12ca**. In the case of compound **12cf** the THF was distilled off and the residue was washed with pentane, which was evaporated, and the obtained residue was purified by flash chromatography (pentane) to afford pure compound **12cf**. For compounds **12ce** and **14e** the conversion of the reaction was determined by GLC over the crude reaction mixture by adding 0.1 mmol of internal standard (decane). In the case of compound **14d** the THF was distilled off, the residue was washed with pentane, and distillation of pentane afforded pure compound **14d**. For compounds of Tables 5 and 6, the reaction was carried out under Barbier conditions, that is, addition of the base to a stirred mixture of the sulfone and the corresponding carbonyl compound in THF (2 mL).

**(*E*)-2-[2-(3,5-Dimethoxyphenyl)vinyl]thiophene (12bj):**[42] Oil; $R_f$ (hexane/EtOAc: 2/1) 0.72; IR (KBr) $\nu_{max}$ 3055, 2951, 2918, 2847, 1580, 1454, 1421, 1279, 1203, 1159, 1061, 957, 837, 689; $^1$H NMR $\delta$ 7.17−7.10 (m, 2H), 6.99 (d, $J$ = 3.3, 1H), 6.92 (dd, $J$ = 3.5, 5.1, 1H), 6.78 (d, $J$ = 16.1, 1H), 6.54 (d, $J$ = 2.2,

2H), 6.31 (t, $J = 2.2$, 1H), 3.74 (s, 6H); $^{13}$C NMR $\delta$ 160.9, 142.6, 138.9, 128.2, 127.6, 126.3, 124.5, 122.3, 104.3, 100.0, 55.3; MS *m/z* 246 ($M^+$, 17), 245 (100), 244 (26), 230 (71), 215 (24), 199 (16), 187 (27), 171 (21), 115 (13), 97 (15).

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**Supporting Information Available:** General experimental methods and analytical and spectral characterization data for compounds **7a**−**d**, **8a**−**d**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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