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Mechanistic Manifold and New Developments of the Julia–Kocienski Reaction

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The Julia–Kocienski reaction has become indispensable in the synthetic organic chemist's olefination toolbox. Although the stereochemical outcome of the transformation is sometimes difficult to predict, some trends can be explained by an array of mechanistic hypotheses which have been put forward since the initial disclosure of the reaction. Moreover, several important developments have been recently reported and are summarised in this microreview.

Introduction

The versatility of aryl and heterocyclic sulfones for the preparation of carbon–carbon double bonds from carbonyl compounds is well documented (Figure 1).[1] Coincidently, two homonymous authors have given their name to two different reactions, which should not be mistaken.

The *classical Julia reaction*[2] was first disclosed by Marc Julia in 1973 and relies on a multi-step sequence comprised of nucleophilic attack of α-metallated aromatic sulfones on aldehydes affording β-hydroxy sulfones, functionalisation of the hydroxyl group, and reductive elimination.[3] After a first modification of the reaction by Kende,[4] who introduced 1-methylimidazol-2-yl sulfones and suppressed the necessity of the functionalisation step, another fundamental change in the original design appeared in 1991, when Sylvestre Julia described a seminal study which resulted in the one-pot preparation of olefins from carbonyl compounds and benzothiazol-2-yl sulfones (BT sulfones)[5] upon Smiles rearrangement[6] of the intermediate lithium alkoxide (see section 1). This reaction is commonly known as *the modified Julia reaction*. Whilst the enhanced electrophilic character of BT sulfones is advantageous, since it allows performing the olefination in a single and operationally simple step, it also makes BT sulfones more sensitive to self-condensation under basic conditions.[7] However, many examples of high-yielding couplings are regularly reported in the literature. S. Julia also disclosed the reaction of pyridin-2-yl sulfones (PYR sulfones) and pyrimidin-2-yl sulfones.[5]

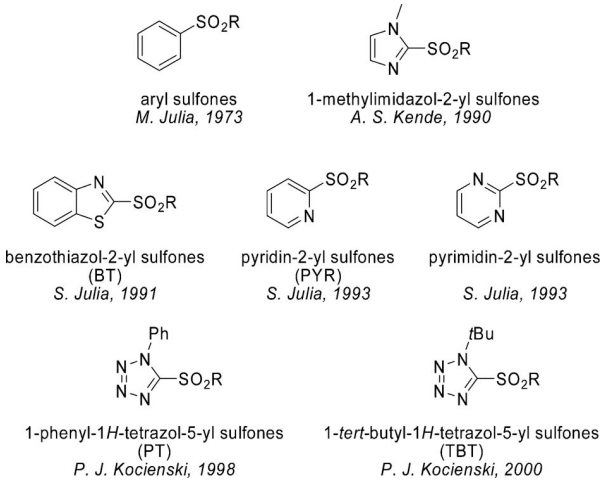

Figure 1. Sulfones used in olefination reactions.

The modified Julia reaction was further studied by Kocienski, who introduced 1-phenyl-1*H*-tetrazol-5-yl sulfones (PT sulfones),[8] and 1-*tert*-butyl-1*H*-tetrazol-5-yl sul-

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fones (TBT sulfones).[9] By virtue of enhanced steric hindrance, PT sulfones are more resistant to self-condensation than BT sulfones but still very reactive in olefination reactions. Both BT and PT sulfones are by far the most frequently employed heterocyclic sulfones in total synthesis. Accordingly, the modified Julia reaction is also commonly named *Julia–Kocienski reaction*. The mechanism of the modified Julia reaction is complex. However, stereochemical trends reported in the literature may enable a reasonable mechanistic rationale to be proposed.

1. Stereochemical Trends for Heteroaryl Sulfones

The commonly accepted mechanistic manifold of the modified Julia reaction is illustrated in Figure 2.[5c] For the sake of clarity only BT sulfones are depicted, but this rationale probably also applies to other heterocyclic sulfones. However, important differences between the various heterocyclic sulfones do exist and deserve comment.

According to this general mechanistic rationale, metallated sulfones would first react with aldehydes to give alkoxides **A1** (*anti*) and **A2** (*syn*). The irreversibility of this addition has been demonstrated experimentally in the case of aliphatic PT sulfones,[1a] and we will discuss how the adjustment of the reaction conditions may influence the ratio of alkoxides **A1** and **A2**. Conversely, the reversibility of this initial addition has been unambiguously established in the case of aromatic BT sulfones.[1a]

In order to undergo the Smiles rearrangement, **A1** and **A2** would fold into conformations **B1** and **B2** respectively. Noteworthy, metal coordination by one nitrogen atom of the heterocyclic moiety, as depicted for **B1** and **B2**, is plausible for BT sulfones but less likely for tetrazolyl sulfones, since it would presumably induce unfavourable steric interactions between the substituent of the tetrazole ring and one oxygen atom of the sulfone (Figure 3). Nevertheless, irreversible Smiles rearrangement through spirocyclic intermediates **C1** and **C2** would lead to **D1** and **D2** respectively. Importantly, by virtue of the *gauche* interaction in **B1** and eclipse interaction in **C1** between R^1 and R^2, it is likely that **A1** should undergo the Smiles rearrangement more slowly than **A2** ($k_1 < k_2$). This decreased rate of rearrangement for the *anti* metallated alkoxide has been unambiguously demonstrated in the case of PYR sulfones using isolated *syn* and *anti* β-hydroxy sulfones intermediates.[5c] Moreover, in the case of BT sulfones, only *anti* β-hydroxy sulfones could be isolated before their collapse into olefins [$R^1 = R^2$ = Ph or R^1 = Ph, $R^2 = (CH_3)_2C{=}CH$].[5c] After another change of conformation of intermediates **D1** and **D2**, **E1** and **E2** would be poised to undergo antiperiplanar β-elimination of the heterocyclic moiety via extrusion of sulfur dioxide.

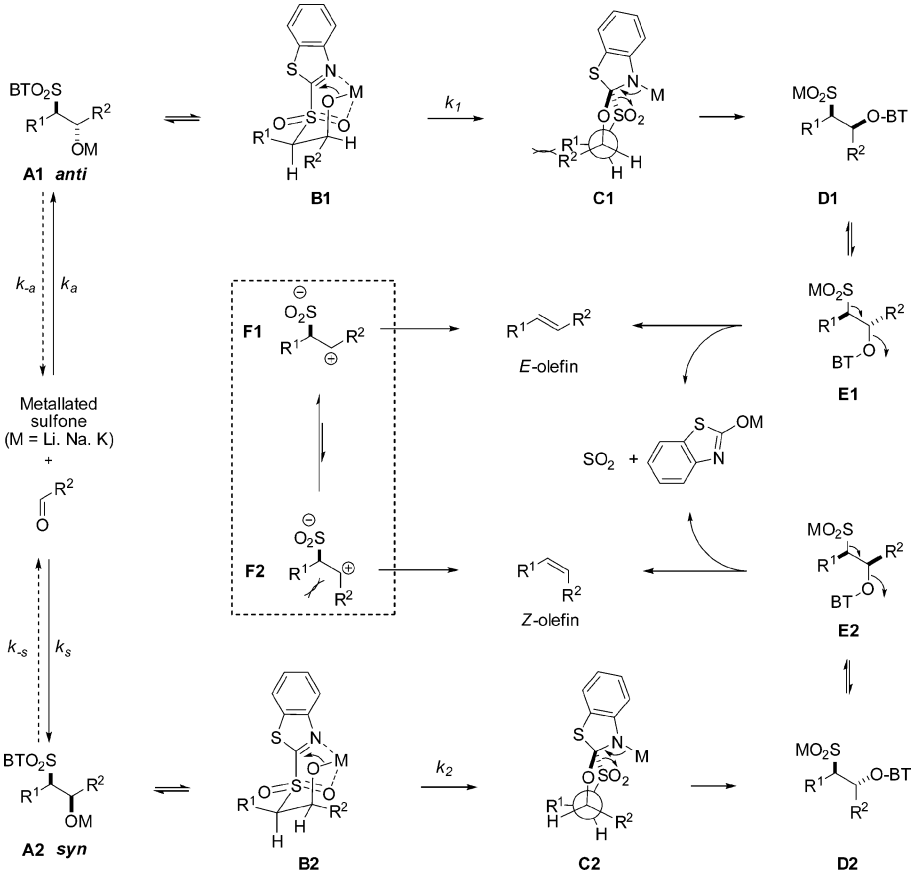


Figure 2. Commonly accepted mechanistic manifold.

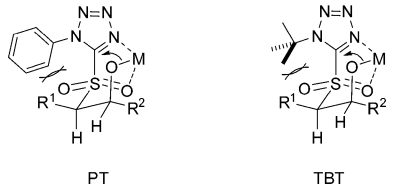
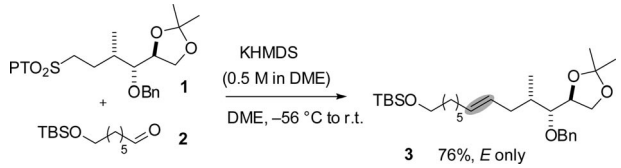


Figure 3. Steric hindrance during metal coordination.

Accordingly, in the case of an irreversible reaction between metallated sulfones and aldehydes, the final olefins ratio would be determined by the k_a/k_s ratio. In the case of a reversible reaction between metallated sulfones and aldehydes, the final olefins ratio would be dictated by a larger set of kinetic constants (k_a, k_{-a}, k_s, k_{-s}, k_1, and k_2). Notably, if $\{k_1, k_2\} << \{k_a, k_{-a}, k_s, k_{-s}\}$, then the stereochemical outcome would be dictated only by the relative rate of Smiles rearrangement of **A1** and **A2** (k_1/k_2) and the formation of *Z*-olefins would then be favoured, since $k_1 < k_2$. However, this mechanistic rationale does not suffice to explain all the results gathered. As we will discuss in section 1.3, the intermediary of zwitterions **F1** and **F2** have been considered in some reactions of aromatic and α,β-unsaturated aldehydes. In cases when zwitterionic pathways prevail, steric repulsion between R^1 and R^2 should favour the formation of *E*-olefins.

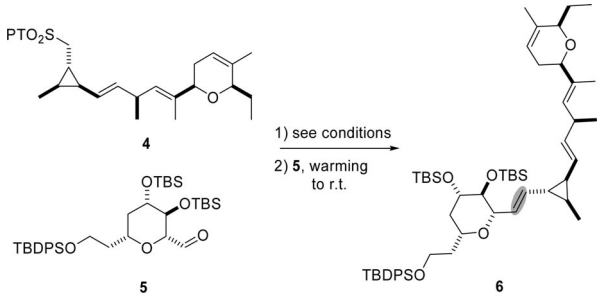
1.1. Irreversible Addition of Aliphatic Sulfones

Kocienski showed that the counterion of the base and the polarity of the solvents could have a strong influence on the stereochemical outcome of the reaction between aliphatic PT sulfones and aliphatic aldehydes.[8] Among the solvents and bases tested, pairing of KHMDS and DME afforded *E*-olefins almost exclusively in all cases studied. However, NaHMDS or LiHMDS are now often used in the coupling of α-branched PT sulfones to ensure high yields, sometimes at the expense of lower stereoselectivities. Hence, reaction of linear PT sulfone **1** and aldehyde **2** afforded compound **3** in good yield and exclusive stereoselectivity under Barbier-type conditions[10] (Scheme 1) and constitute a prototypical example of efficient coupling.[11]



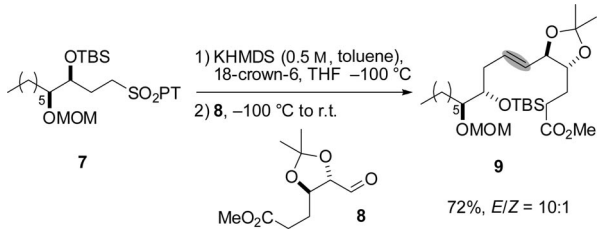
Scheme 1.

Moreover, Jacobsen has also established that the stereochemical outcome of the coupling between PT sulfone **4** and aldehyde **5** was strongly dependent on the polarity of the solvent (Scheme 2).[12] Upon metallation of **4**, **5** was added immediately and **6** was isolated in yields superior to 90% in all conditions indicated. In this specific case, the nature of the counterion was perhaps not the most influential factor, since very polar and strongly coordinating solvents such as DMF, HMPA and DMPU likely annihilated the possible differences between lithium, sodium and potassium cations. Hence, the *E*/*Z* ratio correlated well with the increasing polarity and coordinating ability of the solvents. More recently, 18-crown-6 was also used to coordinate K^+ in the coupling of **7** and **8** (Scheme 3).[13] Effects of this additive on the stereochemistry of **9** were remarkable and superior to those observed with HMPA. Interestingly, the authors postulated that some chelation between K^+ and oxygen functional groups in **7** and **8** was responsible for the lack of stereoselectivity without additive (*E*/*Z* = 3:1).



conditions	*E*/*Z*
NaHMDS, THF, –78 °C	1:8
KHMDS, DME, 18-crown-6, –60 °C	1:3
KHMDS, DMF, –60 °C	1:1
LiHMDS, THF:HMPA = 4:1, –60 °C	3:1
LiHMDS, DMF:HMPA = 4:1, –35 °C	> 30:1
LiHMDS, DMF:DMPU = 1:1, –35 °C	> 30:1

Scheme 2.



Scheme 3.

Several features could be considered in order to explain the enhancement of stereoselectivity in favour of *E*-isomers observed in more polar solvents.[14] The structure of lithium aryl sulfone carbanions has been extensively studied and it is established that Li–O contacts are preferred to Li–C contacts in monomeric and dimeric species **10** and **11** (Figure 4).[15,16] Dimeric structures are predominant in the solid state whilst monomeric species are observed in THF. Moreover, the hybridisation of the carbon atom bearing the negative charge depends on the nature of substituents: sp^3 if R is an alkyl group and sp^2 if R is a phenyl group. In all crystalline structures, the electron pair of the carbanion is in a *gauche* conformation relative to both oxygen atoms of the sulfone. In addition, the structure of free alkyl-substituted α-sulfonyl carbanion **12** has also been reported.[17] It is tempting to consider similar structures for aliphatic PT sulfones carbanions (Figure 5). Presumably, transition states minimising the steric repulsion between R^1 and R^2 are more populated. Hence, intermediates **13**–**15** would lead to chelated transition states, which would afford *syn* inter-

mediates **A2**. As discussed in the mechanistic manifold above, irreversible Smiles rearrangement would then give *Z*-olefins. On the opposite, coordination of base counterions by more polar solvents, especially big cations like K^+, might favour dissociated carbanions **16** or **17**, which would afford *anti* intermediates **A1** through open transition states, and *E*-olefins would be eventually obtained.

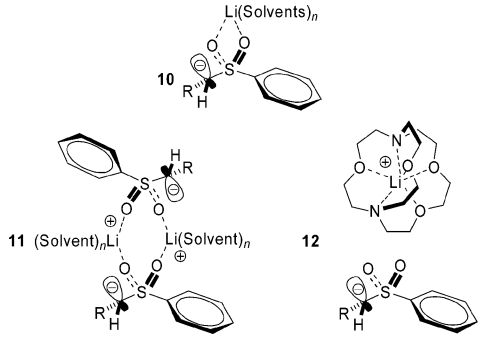


Figure 4. Lithium aryl sulfone carbanions.

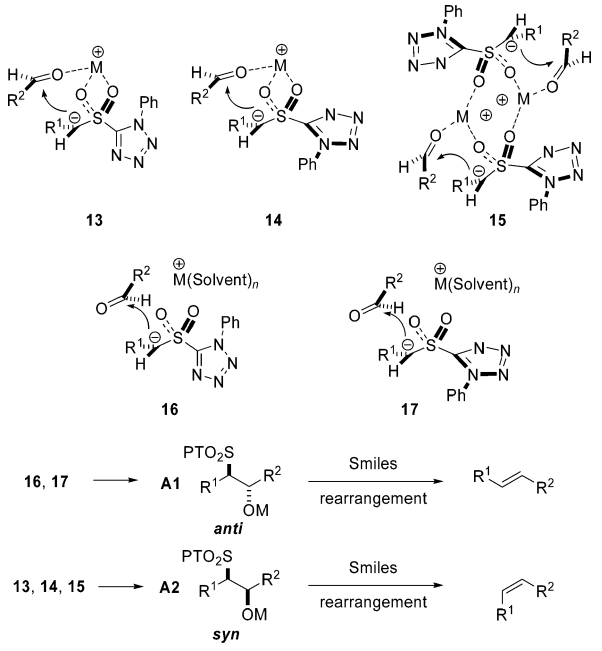
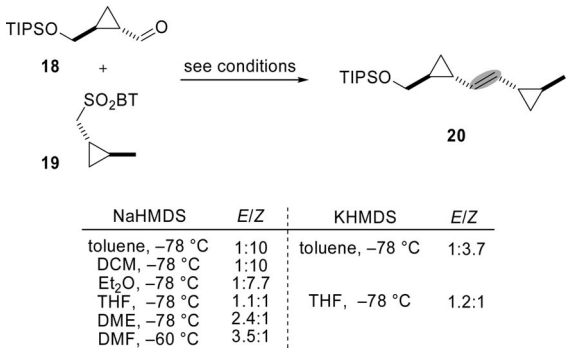


Figure 5. Putative structure of metallated PT sulfones.

The application of the same rationale to aliphatic BT sulfones is not straightforward. With respect to stereoselectivity, Kocienski showed that reactions of non-branched BT sulfones and aldehydes did not display any strong dependence on the nature of the base counterion.[8] Conversely, Charette's total synthesis of (+)-U-106305 brought evidence of strong solvent effects on the stereochemical outcome of the reaction (Scheme 4).[18] The authors established that in the coupling between aldehyde **18** and BT sulfone **19** under Barbier-type conditions, the *E*/*Z* ratio of olefins **20** was inverted by replacement of toluene with THF and then further increased to reach an optimal level in DMF. Polar but non-coordinating DCM had the same effect as toluene. Moreover, the *E*-stereoselectivity was increased by replacing NaHMDS with KHMDS in apolar toluene but not in THF. In all cases, yields were greater to 90%.



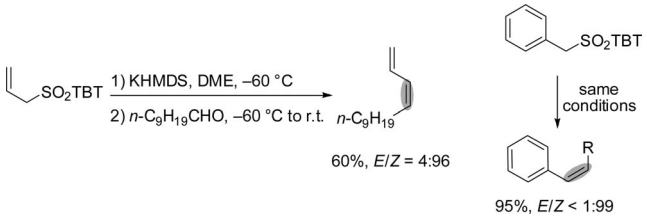
NaHMDS	*E*/*Z*	KHMDS	*E*/*Z*
toluene, –78 °C	1:10	toluene, –78 °C	1:3.7
DCM, –78 °C	1:10		
Et_2O, –78 °C	1:7.7		
THF, –78 °C	1.1:1	THF, –78 °C	1.2:1
DME, –78 °C	2.4:1		
DMF, –60 °C	3.5:1		

Scheme 4.

Although the stereoselectivity of reactions involving aliphatic BT sulfonyl carbanions is less predictable than those involving their PT counterparts, *E*-olefins can be obtained in high yield when α-branched substrates are employed.[19]

1.2. Reversible Addition of Allylic and Benzylic Sulfones

The stereochemical outcome of the reaction between allylic or benzylic sulfones and saturated aldehydes can be strongly dependent on the heterocyclic sulfone moiety. Hence, Kocienski showed that the formation of *E*,*Z*-dienes is strongly favoured upon reaction of allylic and benzylic TBT sulfones with nonanal (Scheme 5).[9] This result could be explained by considering the initial reaction between TBT sulfonyl carbanions and aldehydes as reversible. If k_1 and k_2 are much more smaller than k_a, k_{-a}, k_s, and k_{-s} ($\{k_1, k_2\} << \{k_a, k_{-a}, k_s, k_{-s}\}$), then the stereoselectivity of the reaction would be only determined by the k_1/k_2 ratio (Figure 6). Since *syn* alkoxide **21** should undergo the Smiles rearrangement towards *E*,*Z*-dienes faster than *anti* alkoxide **22** towards *E*,*E*-dienes ($k_1 < k_2$), *E*,*Z*-dienes would be formed predominantly. Moreover, the bulky *tert*-butyl group of TBT sulfones would ensure the proper kinetic ratio between sulfonyl carbanion addition and Smiles rearrangement by decreasing the rate of the latter process.



Scheme 5.

Similarly, reversibility of the initial condensation of allylic and benzylic sulfonyl carbanions could also be invoked in the case of benzylic and allylic BT and PT sulfones. However, the Smiles rearrangement is faster for BT and PT sulfones than for TBT sulfones. Therefore, the balance between

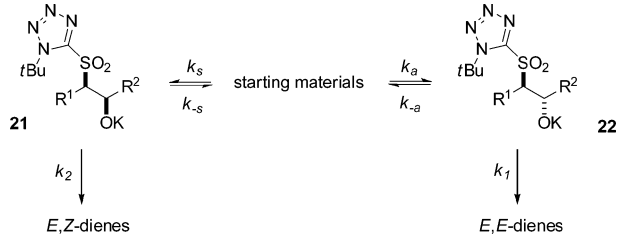
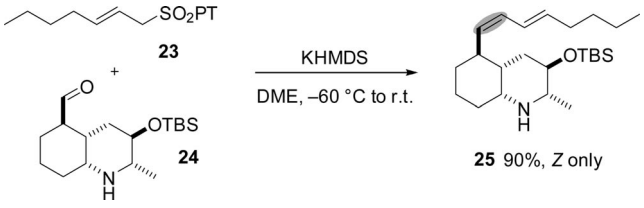


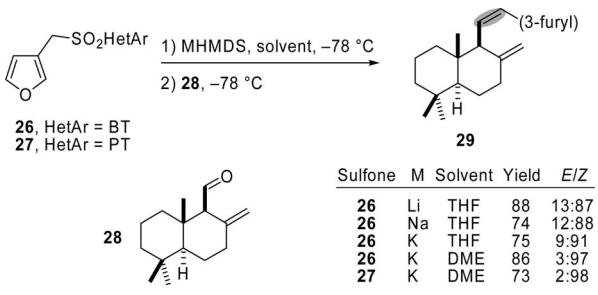
Figure 6. Stereocontrol in the case of reversible addition.

$\{k_1, k_2\}$ and $\{k_a, k_{-a}, k_s, k_{-s}\}$ can be more subtle and the stereochemical outcome of the reaction more case-dependent.[20]

For example, the reaction between sulfone **23** and aldehyde **24** afforded diene **25** in excellent yield as single diastereomer (Scheme 6).[21] This result could be explained assuming that the stereoselectivity is determined only by the Smiles rearrangement ($\{k_1, k_2\} << \{k_a, k_{-a}, k_s, k_{-s}\}$) upon reversible attack of the sulfonyl carbanion onto the adehyde. Moreover, the steric hindrance displayed by **24** could maximise unfavourable *gauche* and eclipse interactions during the Smiles rearrangement and enable an enhanced rate differentiation ($k_1 << k_2$), which would clearly favour the formation of *Z*-olefins. This rationale would be in good accordance with examples which have been reported recently with BT and PT sulfones **26** and **27** (Scheme 7).[22] Compound **29** was always obtained with good to excellent *Z*-selectivity upon reaction with **28**.

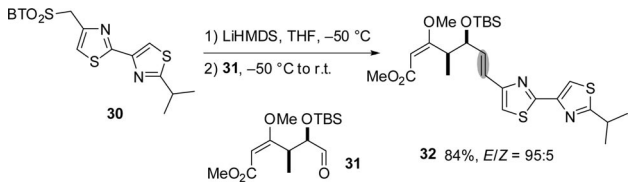


Scheme 6.



Scheme 7.

Conversely, exclusive formation of *E*,*E*-dienes upon reaction between allylic BT and PT sulfones and α-branched aliphatic aldehydes has been often reported during the synthesis of complex natural products,[23] and similar *E*-selectivity has been observed upon reaction of sterically hindered aldehydes with benzylic sulfones. For example, reaction of sulfone **30** and aldehyde **31** afforded *E*-olefin **32** in excellent yield (Scheme 8).[24] In those cases, the initial attack of the sulfonyl carbanion is likely to be reversible but the stereoselectivity cannot be determined during the Smiles rearrangement, as it would favour the formation of *Z*-olefins. Instead, one could tentatively explain the results by assuming one or several of the following hypotheses: 1) *syn* alkoxides are formed only transiently and their collapse into starting materials is much faster than the Smiles rearrangement; 2) mainly *anti* alkoxides are formed and undergo the Smiles rearrangement; 3) other mechanistic pathways toward *E*-olefins are energetically accessible to *syn* alkoxides.



Scheme 8.

1.3. Zwitterionic Intermediates

1.3.1. Reactions with Aliphatic Sulfones

Early investigations reported by S. Julia clearly demonstrated that the stereoselective formation of *E*-olefins with BT sulfones was accentuated by electron-donating substituents on the benzene ring of benzaldehydes.[5] Accordingly, the authors postulated the creation of a positive charge at the benzylic position during the course of the reaction through rapid collapse of intermediates **33** or **34** to form zwitterions **35** and **36** upon E_1 elimination (Figure 7). Steric repulsion between R^1 and R^2 groups would then favour **36** and the subsequent formation of the *E*-olefin upon final extrusion of sulfur dioxide.

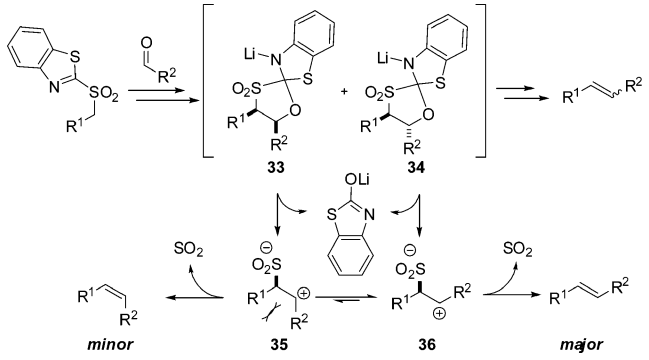
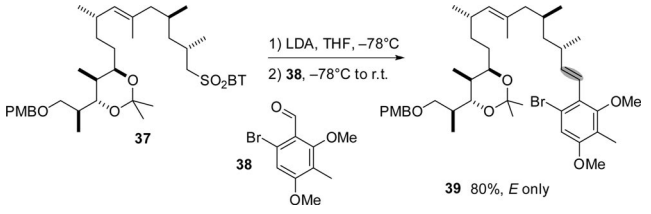


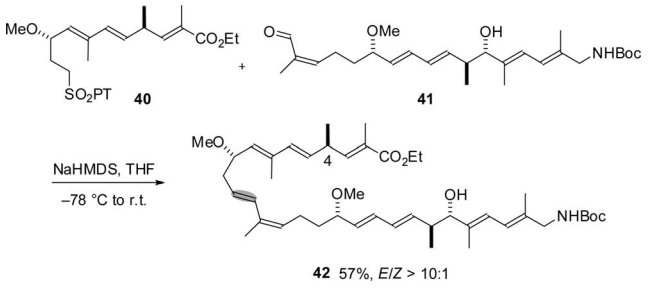
Figure 7. Zwitterionic reaction pathways.

Hence, the predominant formation of *E*-olefins upon reaction of aromatic aldehydes with aliphatic BT and PT sulfones is well documented. For example, treatment of sulfone **37** with LDA and subsequent addition of aldehyde **38** afforded **39** in excellent yield as a single diastereomer (Scheme 9).[25]



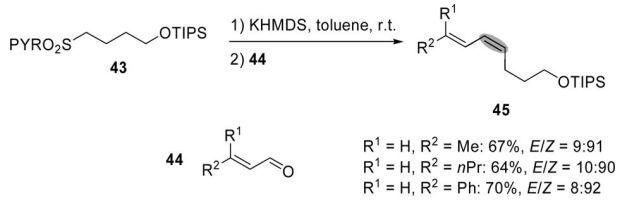
Scheme 9.

Similarly, the zwitterionic pathway could also be invoked in the reaction of α,β-unsaturated aldehydes with BT and PT sulfones to explain the predominant formation of *E*,*E*-dienes.[26] Recent examples were reported during the synthesis of iejimalide B (Scheme 10).[27] Under Barbier-type conditions, aldehyde **40** and PT sulfone **41** afforded compound **42** with good stereoselectivity.



Scheme 10.

Conversely, Charette reported a valuable olefination protocol for the selective preparation of *E*,*Z*-dienes.[28] After extensive optimisation, the authors found that metallation of PYR sulfone **43** in toluene with KHMDS (0.5 M in toluene) at room temperature, followed by addition of aldehydes **44** afforded predominantly the desired *E*,*Z*-dienes **45** in good yields (Scheme 11). Noteworthy, the PYR-sulfonyl carbanion generated from **43** was stable at room temperature for at least 5 minutes, which underpins the weak electrophilic character of PYR sulfones. These results are reminiscent of those obtained with TBT sulfones (see section 1.2, Scheme 5) and could be explained in the same manner by assuming a reversible addition of the PYR-sulfonyl carbanion onto **44** and a control of the stereoselectivity during the Smiles rearrangement ($\{k_1, k_2\} << \{k_a, k_{-a}, k_s, k_{-s}\}$ and $k_1 < k_2$). Moreover, the zwitterionic pathway is presumably disfavoured in apolar toluene.

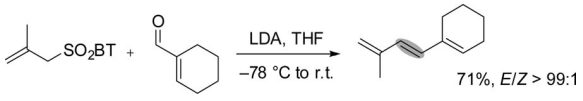


Scheme 11.

1.3.2. Reactions with Allylic Sulfones

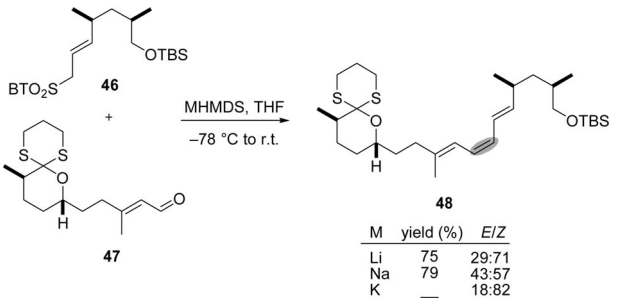
As explained above, reactions involving α,β-unsaturated aldehydes or benzaldehyde derivatives tend to give predominantly *E*-olefins when the zwitterionic pathway prevails. However, Charette's stereoselective preparation of *E*,*Z*-dienes shows that this mechanistic pathway can be bypassed when the initial addition of sulfonyl carbanions onto aldehydes is reversible and faster than the Smiles rearrangement.[28] Accordingly, the stereochemical outcome of the reaction between α,β-unsaturated aldehydes or benzaldehyde derivatives and allylic sulfones is substrate-dependent.

Early examples reported by S. Julia showed that *E*-olefins were formed exclusively using β-substituted allylic sulfones (Scheme 12).[5] This result could indicate the predominance of the zwitterionic pathway.

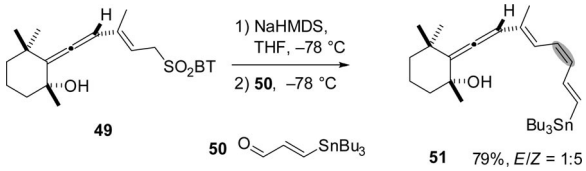


Scheme 12.

However, in most cases reported in the literature, reactions between allylic sulfones and α,β-unsaturated aldehydes show a strong stereochemical preference in favour of *E*,*Z*,*E*-trienes, which could indicate that the zwitterionic pathway does not play an important role in these cases. Hence, in a synthetic approach to rapamycin, Kocienski described that coupling of BT sulfone **46** and aldehyde **47** gave preferentially *E*,*Z*,*E*-triene **48** (Scheme 13).[29]As reported for aliphatic BT sulfones, the stereoselectivity did not show a linear dependence to the size of base counterion. Similarly, coupling of **49** and **50** gave preferentially *E*,*Z*,*E*-triene **51** (Scheme 14).[30] Interestingly, the reactivity of sulfone **49** with several aldehydes has been recently investigated and *E*,*Z*,*E*-trienes were always obtained preferentially.[31] Moreover, reactions of aldehyde **50** with various allylic sulfones showed the same stereoselectivity.[32] Therefore, the preferred formation of *E*,*Z*,*E*-**51** was likely favoured by both coupling partners in a synergetic manner upon reversible addition of the sulfonyl carbanions onto the aldehydes and stereocontrol during the Smiles rearrangement.[33]



Scheme 13.



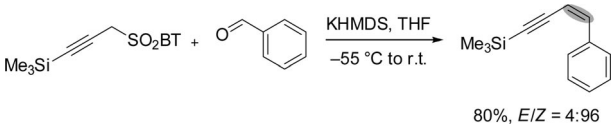
Scheme 14.

1.3.3. Reactions of Benzylic Sulfones

Although the addition of benzylic sulfonyl carbanions onto α,β-unsaturated and aromatic aldehydes is likely reversible, the stereochemical outcome of the reaction is not determined during the Smiles rearrangement. Instead, the zwitterionic pathway normally prevails and *E*-olefins are generally obtained with excellent stereoselectivity.[5]

1.3.4 Reactions of Propargylic Sulfones

Examples of reaction of propargylic sulfones are rare. However, available data suggest that the reactions of propargylic sulfonyl carbanions with α,β-unsaturated and aromatic aldehydes are reversible and that the stereoselectivity of the reaction is dictated by the faster Smiles rearrangement of *syn* alkoxide intermediates and not by a zwitterionic mechanism, as it could be assumed in regards to the structure of aldehydes.[5] Accordingly, *Z*-olefins were formed predominantly or exclusively in all examples reported to date (Scheme 15).[34]

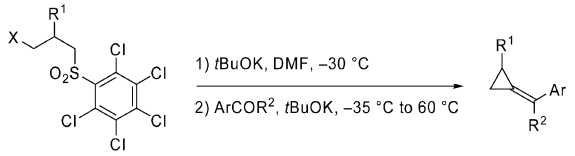


Scheme 15.

2. Electron-Poor Aryl Sulfones

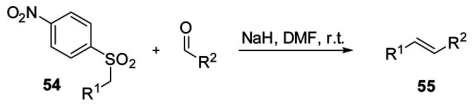
Recently, new olefination reactions relying on electron-poor aryl sulfones have been disclosed and these endeavours attest to the strong current interest in the Julia–Kocienski reaction.

Hence, Makosza reported that pentachlorophenyl sulfones **52** could afford benzylidenecyclopropanes **53** upon treatment with potassium *tert*-butoxide and reaction with aromatic aldehydes and ketones (Scheme 16).[35] Compounds **53** were obtained in satisfactory yields both with electron-rich and electron-poor aldehydes.[36] In addition, formation of *Z*-isomers was preferred in the case of substituted cyclopropane rings.

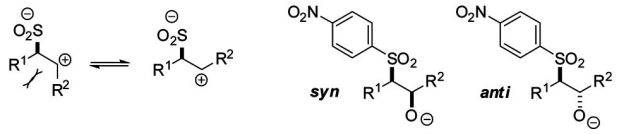


Scheme 16.

Moreover, Zhu has recently described the reactivity of *para*-nitrophenyl sulfones with aromatic aldehydes (Scheme 17).[37] Under optimised reaction conditions, mixtures of sulfones **54** and aromatic aldehydes were treated at room temperature with NaH in DMF. As a general trend, reactions involving *n*-hexyl-*para*-nitrophenyl sulfone gave lower isolated yields of expected olefins **55** than reactions involving benzyl-*para*-nitrophenyl sulfone, but stereoselectivities were better and favoured the formation of *E*-olefins. It is noteworthy that aliphatic aldehydes were not tolerated as substrates of the reaction due to competitive aldol reactions.



Entry	Result R^1 = *n*-C_5H_{11}	Entry	Result R^1 = Ph
1	R^2 = Ph: 43%, *E*/*Z* = 94:6	5	R^2 = Ph: 73%, *E*/*Z* = 63:37
2	R^2 = 4-$NO_2C_6H_4$: 68%, *E*/*Z* = 80:20	6	R^2 = 4-$NO_2C_6H_4$: 97%, *E*/*Z* = 70:30
3	R^2 = 4-$MeOC_6H_4$: 78%, *E*/*Z* = 81:19	7	R^2 = 4-$MeOC_6H_4$: 78%, *E*/*Z* = 53:47
4	R^2 = 2,4,6-$(MeO)_3C_6H_2$: 54%, *E*/*Z* > 99:1	8	R^2 = 2,4,6-$(MeO)_3C_6H_2$: 97%, *E*/*Z*>99:1

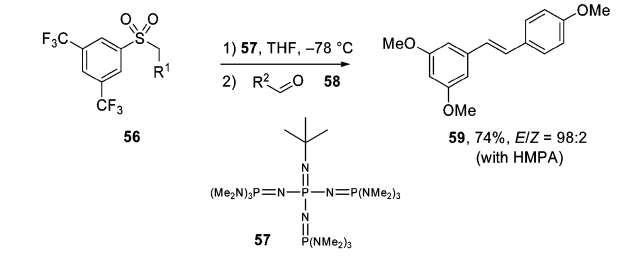


Scheme 17.

Importantly, electron-rich aromatic aldehydes did not give better *E*-selectivity than electron-poor aldehydes (Entries 2 and 3), and tended to give almost equimolar mixtures (Entries 6 and 7). The authors postulated that electron-rich aldehydes favoured the zwitterionic pathway. However, in constrast to the common assumption, they also postulated that this pathway would not be stereoselective, except in the case of sterically hindered aldehydes (Entries 4 and 8). Moreover, in order to explain the *E*-selectivity obtained with neutral or electron-poor aromatic aldehydes, the authors postulated that the Smiles rearrangement could be faster for the *anti* alkoxide intermediates than for their *syn* isomers, in contrast to the normally accepted mechanism of the Julia–Kocienski reaction (see section 1).

Prior to these disclosures, Nájera introduced 3,5-bis(trifluoromethyl)phenyl sulfones **56** (BTFP sulfones) (Scheme 18).[38] The stability of BTFP sulfones under basic conditions was quickly established. Both aliphatic and benzylic BTFP sulfones could be recovered in good yields upon treatment with either KOH at room temperature or phosphazene **57** at –78 °C in THF. The authors demonstrated that the initial attack of benzylic BTFP-sulfonyl carbanions on aldehydes **58** is reversible, since benzaldehyde was isolated upon treatment of β-hydroxysulfones with KOH in the presence of nBu_4NBr (Figure 8).[38b] Moreover, since *E*-stilbene was obtained predominantly both from *syn* and *anti* β-hydroxysulfones, zwitterionic intermediates have been postulated. Finally, isolation of 3,5-bis(trifluoromethyl)phenol could further support the reasonable assumption that BTFP sulfones react in this modified Julia olefination according the commonly accepted mechanistic manifold. Hence, under typical reaction condition, coupling of benzylic BTFP sulfones and electron-rich aromatic aldehydes strongly favoured the formation of *E*-olefins **59**. On the other hand, electron-poor aldehydes led preferentially to *Z*-

olefins. These results are in good accordance with a competition for the stereocontrol between the Smiles rearrangement (*Z*-selectivity) and the zwitterionic pathway (*E*-selectivity), as discussed in section 1.3. Noteworthy, HMPA (1.2 equiv.) had a beneficial effect on the yield of the reaction in the case of benzylic BTFP sulfones. Hence, trimethoxyresveratrol **59** was obtained in only 15% yield without this crucial additive.



Scheme 18.

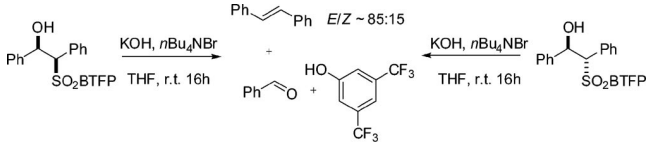
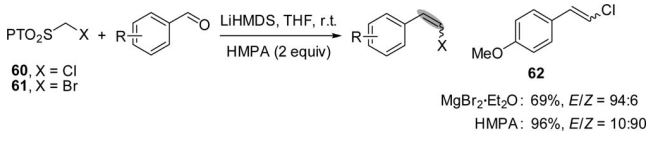


Figure 8. Reversible attack of BTFP sulfones.

3. α-Halogenated BT and PT Sulfones

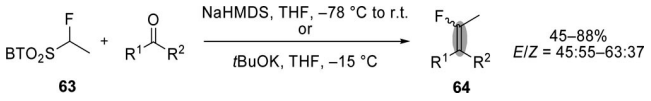
The scope of the Julia–Kocienski reaction has been extended to the preparation of halogenated olefins. Hence, Berthelette investigated the reactivity of α-monohalogenated PT sulfones **60** and **61** (Scheme 19).[39] Under optimised reaction conditions, addition of two equivalents of HMPA enabled the preparation of *Z*-alkenyl bromides and chlorides in a reproducible manner, although erosion of the stereoselectivity with 2-chloroquinone-3-carbaldehyde, 2-chloro-5-nitrobenzaldehyde and 3-phenylpropanal was observed. Conversely, addition of two equivalents of $MgBr_2{\cdot}Et_2O$ complex led preferentially to *E*-**62**. However, this effect could not be generalised to the reaction of other aromatic aldehydes. Interestingly, S. Julia disclosed in his early report that the reaction of paranisaldehyde with $ClCH_2SO_2BT$ yielded **62** in 95% as a 83:17 *E*/*Z* mixture, upon treatment of reactants with LDA at –78 °C and warming to room temperature.[5c]



Scheme 19.

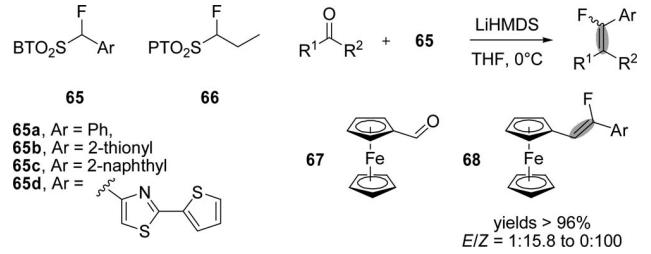
Although the predominant formation of *Z*-alkenyl halides from aromatic aldehydes could be explained by assuming that the initial attack of sulfonyl carbanions onto aldehydes is reversible and that *syn* alkoxides undergo the Smiles rearrangement faster than *anti* alkoxides (see sections 1.2 and 1.3), the role of additives in these particular examples has not been fully elucidated yet.

Lequeux and Pazenok were the first to describe the reactivity of α-monofluorinated BT sulfone **63** and obtained vinyl fluorides **64** upon reaction with aromatic and α,β-unsaturated aldehydes and ketones under Barbier-type conditions (Scheme 20).[40] Isolated yields were moderate to very good but stereoselectivity remained poor. Interestingly, when NaHMDS was used as base, ketones turned out to be suitable substrates.



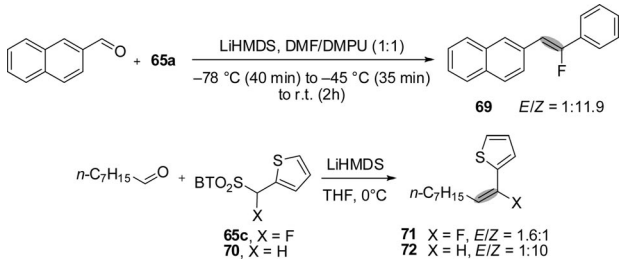
Scheme 20.

Further investigations have been conducted by Zajc with sulfones **65** and **66** (Scheme 21).[41] Reactions of sulfones **65** with aromatic and aliphatic aldehydes or with cinnamaldehyde were only moderately stereoselective, except with aldehyde **67** which afforded olefins **68** as major or single isomer. In all cases, yields were excellent, even using ketones as substrates. Similarly, reaction of **66** with naphthaldehyde afforded the expected product in high yield but without stereochemical preference.



Scheme 21.

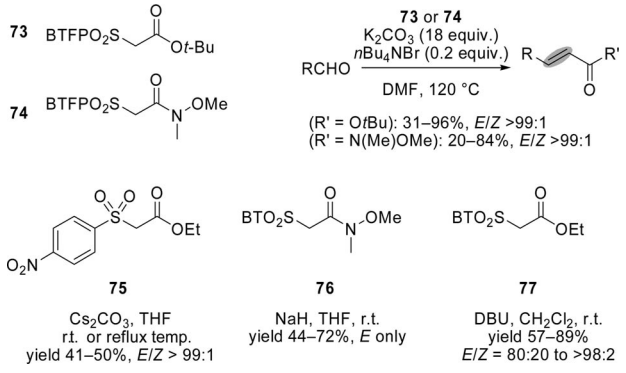
The stereochemical outcome of the reactions involving sulfones **65** was strongly influenced by the reaction conditions. Hence, treating naphthaldehyde and **65a** with LiHMDS under Jacobsen's conditions[12] afforded as expected **69** as a 1:11.9 (*E*/*Z*) mixture of diastereomers, whilst replacing the strongly coordinating solvents (DMF and HMPU) with THF and carrying the reaction at 0 °C led to a 2.3:1 (*E*/*Z*) mixture of diastereomers (Scheme 22). As discussed in section 1.1, Jacobsen's conditions likely favour the formation of an *anti* alkoxide intermediate through an open transition state and the subsequent Smiles rearrangement would then place the naphthyl and phenyl groups in a *trans*-relationship. In contrast, in THF, both *syn* and *anti* alkoxides can be formed through chelated and open transition states respectively and deliver the final products upon Smiles rearrangement. Moreover, Zajc demonstrated with one example that the fluorine atom can influence the stereoselectivity of the reaction. Hence, upon treatment of octanal and **65c** with LiHMDS in THF at 0 °C, **71** was isolated as a mixture of diastereomers, whilst octanal and **70** afforded predominantly *Z*-**72** when treated under identical reaction conditions.



Scheme 22.

4. 2-Sulfonylacetamide and 2-Sulfonylacetate

Another extension of the scope of the Julia–Kocienski olefination concerns the stereoselective formation of α,β-unsaturated esters and Weinreb amides. Hence, Nájera and co-workers reported that BTFP sulfones **73** and **74** can be employed towards this goal (Scheme 23).[42] *E*-olefins were obtained almost exclusively upon reaction with aromatic aldehydes under drastic reaction conditions in very variable yields, significant erosion of the stereoselectivity was observed upon reaction with aliphatic aldehydes.



Scheme 23.

Similar results have been obtained by other authors with sulfones **75**–**77**. Hence, premetallation of **75** with Cs_2CO_3 in DMF and subsequent treatment with aromatic aldehydes afforded *E*-olefins exclusively, albeit in modest yields.[37] The use of BT sulfone **76** enabled milder conditions, which were applied to a broader scope of aromatic and functionalised aliphatic aldehydes.[43] Once again, only *E*-olefins were isolated. Finally, the use of BT sulfone **77** resulted in the stereoselective formation of *E*-α,β-unsaturated esters in good yields from aromatic aldehydes and α-branched aliphatic aldehydes under mild reaction conditions.[44]

Interestingly, electron-rich and electron-poor aromatic aldehydes gave similar results, which could be in contradiction with a zwitterionic pathway. This striking feature prompted Nájera to investigate the mechanism with computational methods in the case of BTFP sulfones,[42] which revealed the possibility of a non-concerted final elimination of sulfur dioxide and 3,5-bis(trifluoromethyl)phenoxide (Figure 9). According to these calculations, after reversible attack of the stabilised sulfonyl carbanions onto aldehydes, *syn* alkoxide **78** would undergo reaction rapidly to give spirocyclic intermediate **79**, which would first liberate sulfur dioxide and form enolate **80** before final elimination of phenoxide and formation of *E*-olefins.

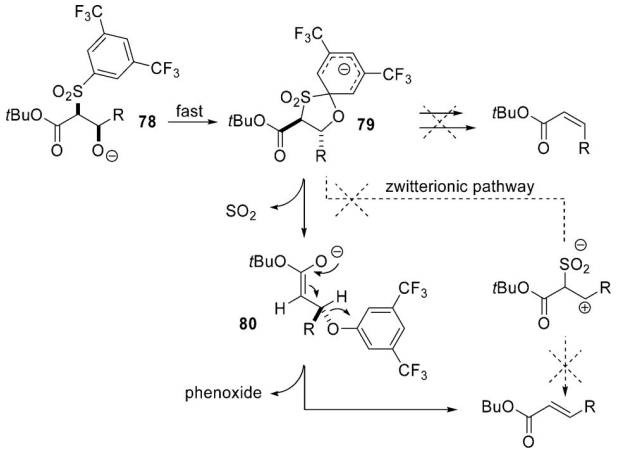
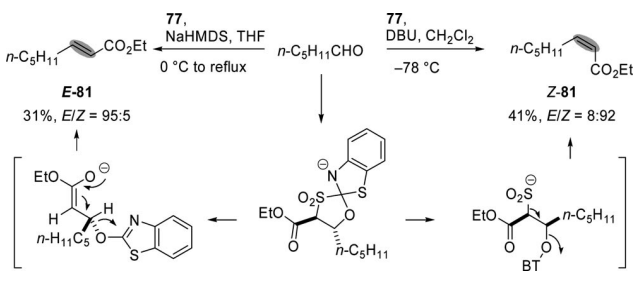
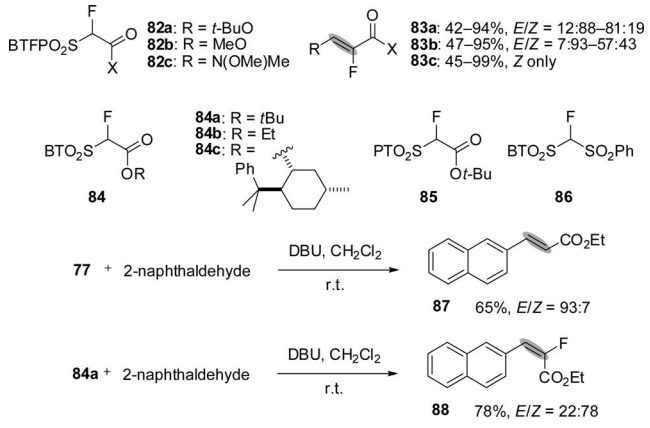


Figure 9. Non-concerted elimination of SO_2.

Importantly, Blakemore has shown that the carbanion of **77** reacts with an aliphatic aldehyde under kinetic conditions (DBU, CH_2Cl_2, –78 °C) to give *Z*-**81** as the major isomer, whilst thermodynamic conditions (NaHMDS, THF, 0 °C then reflux) ensured the stereoselective formation of *E*-**81** (Scheme 24).[44] This stereocontrol could perhaps be explained by assuming that at low temperature, the classical Smiles rearrangement followed by a concerted antiperiplanar elimination would give *Z*-**81**, whilst raising the temperature could enable collapse of the spirocyclic intermediate into an enolate and the subsequent formation of *E*-**81**. This rationale would be in good accordance with the findings reported by Nájera that enolate **80** was not an energy minimum along the reaction coordinate. Interestingly, Nájera and Alonso have recently reported that 2-fluoro-2-sulfonylacetate and 2-fluoro-2-sulfonylacetamide **82** can give fluorinated olefins **83** in good yields under mild reaction conditions (premetallation with K_2CO_3 in DMF in the presence of TBAB at room temp.) (Scheme 25).[45] The authors invoked an enolate intermediate similar to **80** to explain the *Z*-stereoselectivity, which was exquisite with Weinreb amides **82c**. Hence, the fluorine atom seems to have only little influence on the stereochemical outcome of the reaction if one compares these results with those obtained with **73** and **74**.



Scheme 24.



Scheme 25.

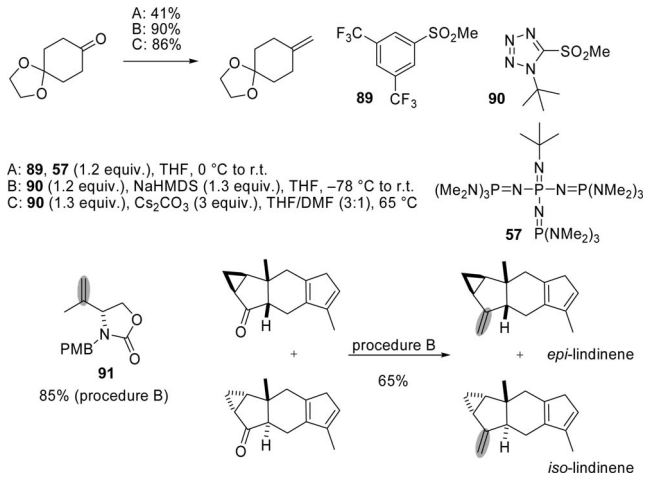
In contrast, Zajc has recently reported an inversion of stereoselectivity upon reaction of 2-fluoro-2-sulfonylacetate **84** with aromatic and α-branched aliphatic aldehydes (Scheme 25).[46] Hence, reaction of non-fluorinated 2-sulfonylacetate gave **87** whilst reaction of **84a** under identical conditions afforded **88**. Interestingly, the influence of the ester moiety of **84** on the stereochemical outcome of the reaction with aromatic aldehydes and α-branched aliphatic aldehydes was limited, since similar results were obtained with *tert*-butyl, ethyl or 8-phenylmenthyl esters. Preliminary results obtained with **85**[46] and **86**[47] were identical to those obtained with **84** with respect to the stereoselectivity.

Zajc explained this inversion of stereoselectivity with fluorinated substrates by assuming that the zwitterionic pathway is not operative, since the fluorine atom would destabilise the positive charge on the adjacent carbon atom. Instead, the stereoselectivity of the reaction involving **84** would be controlled by a combination of reversible attack of the sulfonyl carbanion, faster Smiles rearrangement of the *syn* alkoxide intermediate, and final antiperiplanar elimination, in accordance with the commonly accepted mechanistic manifold (see section 1.2).

Finally, the reactivity of **84a** was independently examined by Lequeux,[48] who reported the stereoselective preparation of *Z*-α-fluoroalkenoates upon treatment of aromatic and aliphatic aldehydes and **84a** with DBU in the presence of $MgBr_2$.

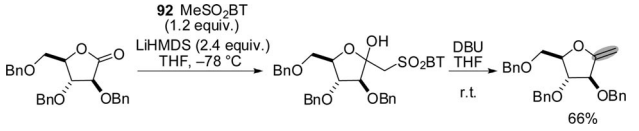
5. Methylenation

Until recently, the methylenation of carbonyl compounds under Julia–Kocienski conditions had been studied only briefly by S. Julia.[5,49] Nájera reported moderate yields when aliphatic, α,β-unsaturated and aromatic aldehydes or ketones were treated with BTFP sulfone **89** and phosphazene **57** (Scheme 26, procedure A).[38b] Independently, Aïssa disclosed two improved procedures for the methylenation of aldehydes and ketones (procedures B and C).[50] Both aromatic and aliphatic substrates were converted smoothly in high yields upon treatment with TBT sulfone **90**. It is noteworthy that substrates prone to enolisation could be submitted to procedure B without compromising the integrity of labile stereocentres, as illustrated with **91**, which was obtained from the corresponding ketone. This procedure has recently been employed in the racemic synthesis of *epi*-lindenene and *iso*-lindenene.[51] Importantly, the stability of sulfonyl carbanions prepared from **89** and **90** under the different reaction conditions was crucial to the success of the reaction.



Scheme 26.

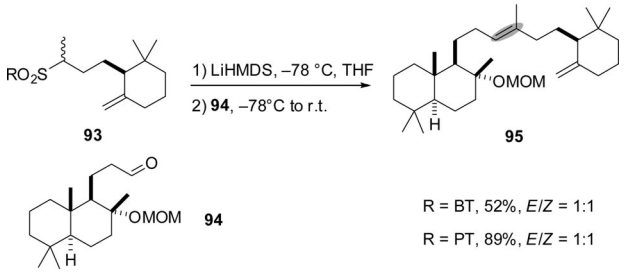
Moreover, Gueyrard also reported the synthesis of methylene exoglycals using a modified Julia reaction.[52] Hence, a two-step protocol comprised of a first reaction between the sulfonyl carbanion of BT sulfone **92** and sugar-derived lactones at –78 °C, isolation of the β-hydroxysulfone intermediate, and its treatment with DBU at room temp. ensured the formation of the desired products in moderate to good yields (Scheme 27).[53]



Scheme 27.

6. Miscellaneous

Access to trisubstituted olefins through Julia–Kocienski reaction between ketones and primary alkyl sulfones or between aldehydes and secondary alkyl sulfones was until recently limited, and although good yields were obtained, stereoselectivities remained poor.[5,54] More recent examples have confirmed these trends with both PT and BT sulfones.[55,56] Hence, Akita studied the reactivity of BT and PT sulfones **93** which upon premetallation and reaction with aldehyde **94** afforded compound **95** in moderate to excellent yield as an equimolar ratio of isomers (Scheme 28).[55e]



Scheme 28.

Pursuing their investigations on the reactivity of BTFP sulfones in the presence of phosphazene **57**,[38] Nájera and co-workers have recently disclosed some very interesting results concerning the preparation of tri- and tetrasubstituted olefins through Julia–Kocienski reaction (Figure 10).[57] The authors showed it was possible to obtain trisubstituted olefins in moderate to excellent yields under mild Barbier-type conditions upon reaction between BTFP sulfones **96** and aldehydes. Using unsymmetrical BTFP sulfones, they also demonstrated that the reaction can be stereoselective, favouring the formation of the *Z*-isomer. The stereoselectivity could be improved if the reaction temperature was maintained at –78 °C, but the yield was then lower. Alternatively, trisubstituted olefins could also be obtained upon reaction between ketones and primary alkyl BTFP sulfones. Moreover, this methodology enabled the formation of tetrasubstituted olefins, albeit in a more limited scope. For example, **97** was obtained in good yield from 4,4′-dichlorobenzophenone whilst **98** was obtained in much lower yield from 4,4′-dimethoxybenzophenone.

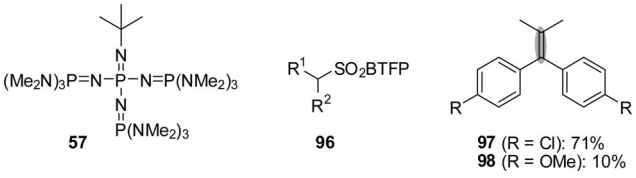
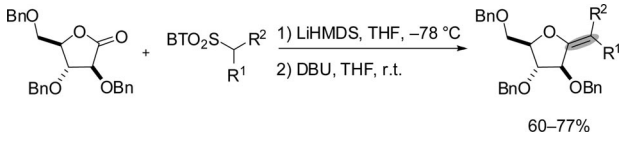


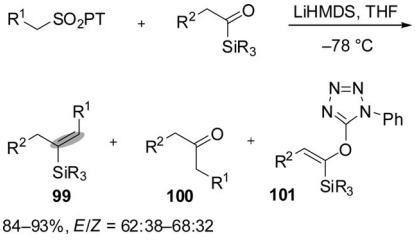
Figure 10. BTFP sulfones to access tetrasubstituted olefins.

Moreover, following their work on the methylenation of lactones,[52] Gueyrard and co-workers used the same two-step procedure for the preparation of tri- and tetrasubstituted exoglycals (Scheme 29).[58] Noteworthy, yields were good in the furanose series but significantly lower in the pyranose series. In the former series, unsymmetrical olefins were obtained with good stereoselectively, the *E*-isomer being favoured.



Scheme 29.

With respect to electrophiles, the scope of the Julia–Kocienski reaction has been recently extended to acylsilanes. Hence, Wicha reported the preparation of vinylsilanes **99** upon reaction of aliphatic PT sulfones and aliphatic acylsilanes (Scheme 30).[59] Yields were excellent but the stereoselectivity rather poor. It is noteworthy that ketones **100** were also isolated as minor side product when R is a methyl group or as sole product when R is a phenyl group. Moreover, when the sulfonyl carbanion was generated with KHMDS in DME at –78 °C, PT enol ether **101** was isolated in 68% yield.



Scheme 30.

The authors rationalised these results as illustrated in Figure 11. After initial condensation of the sulfonyl carbanion and the aldehyde, the two isomeric alkoxides **102** and **103** could undergo the Smiles rearrangement. However, this rearrangement is likely compromised for **102**, since two unfavourable *gauche* interactions involving R^1 would considerably raise the energy barrier. In contrast, only one *gauche* interaction between R^1 and SiR_3 would be generated in **103**. Hence, classical Smiles rearrangement followed by antiperiplanar elimination of sulfur dioxide would then ensure the formation of *E*-**99**. Alternatively, the authors postulated that a concerted fragmentation of the spirocyclic intermediate would give *Z*-**99**. This concerted fragmentation would become more favourable in apolar solvents like toluene, which would induce a tighter binding of the Li cation and therefore restrict the bond rotations, which are necessary for the antiperiplanar elimination. Moreover, when the size of the silicon-centred group becomes too large, a Brook rearrangement[60] becomes energetically more favourable and also explains the predominant formation of ketone **100**. Finally, the formation of enol ether **101** could be explained by α-deprotonation of the acylsilane and reaction of the thus generated enolate with the electrophilic tetrazole ring.

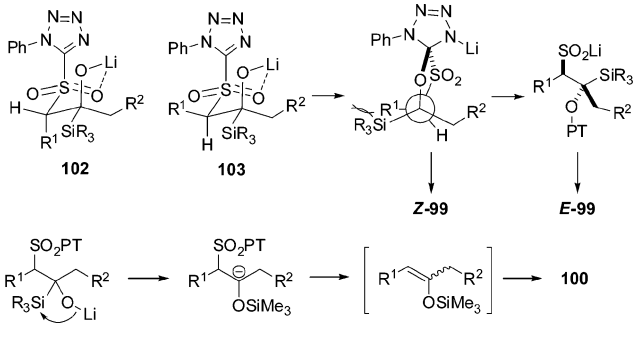
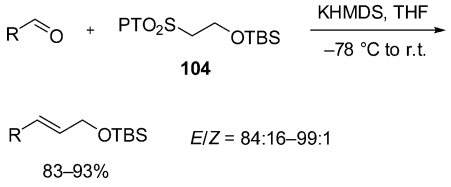


Figure 11. Competition between Brook and Smiles rearrangement.

Finally, Markó has recently reported an efficient and stereoselective preparation of allylic ethers and alcohols.[61] The authors used PT sulfones **104** to prepare the desired olefins in excellent yields, starting from aliphatic, aromatic and α,β-unsaturated aldehydes (Scheme 31). In all cases, *E*-isomers were obtained predominantly. Noteworthy, the choice of *tert*-butyldimethylsilyloxy as poor leaving group was crucial to the success of the reaction. Hence, these results must be put in perspective by considering the propensity of sulfonyl carbanions adjacent to a C–O bond to undergo β-elimination.[62–64] Accordingly, these results hold promise to find numerous applications in total synthesis and increase further the versatility of the modified Julia reaction.



Scheme 31.

Conclusions

The Julia–Kocienski olefination is operationally simple and enables the straightforward assembly of advanced and functionalised intermediates in the course of total syntheses. The scope of the reaction has been recently extended to the preparation of terminal olefins, tri- and tetrasubstituted olefins, halogenated olefins, and α,β-unsaturated esters and amides. Moreover, beyond aldehydes and ketones, the scope of electrophiles has been extended to lactones and acylsilanes. Although it is difficult to generalise with a high a level of predictability, some stereochemical trends have emerge for BT, PT and PYR sulfones. 1) *E*-olefins are obtained predominantly from reactions between aliphatic aldehydes and aliphatic sulfones, especially with PT sulfones if a polar solvent (DME, DMF) and a large base counterion (K^+) are used. Moreover, trapping additives like 18-crown-6 may induce the same effect. 2) The isomer ratio is more substrate dependent in the reactions between allylic or benzylic sulfones and aliphatic aldehydes. However, *Z*-stereoselectivity will probably prevail if the initial addition of α-sulfonyl carbanions is reversible and if the stereoselectivity is dictated by the Smiles rearrangement. 3) The reactions of aliphatic BT or PT sulfones with aromatic or α,β-unsaturated aldehydes should give predominantly the *E*-isomers, if carried out in standard polar solvents (THF, DME). However, the use of PYR sulfones in toluene should chiefly afford *Z*-olefins. 4) All reported reactions of propargylic sulfones gave *Z*-olefins. 5) Most reported reactions between allylic sulfones and α,β-unsaturated aldehydes gave conjugated trienes embedding a central *Z*-configured C=C bond.

Whilst the mechanistic manifold proposed by S. Julia during his seminal investigations seems in good accordance with results gathered since then, the recent disclosure of reactions involving α-sulfonylacetates suggest the possibility of alternative reaction pathways.

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