REVIEW

The modified Julia olefination: alkene synthesis *via* the condensation of metallated heteroarylalkylsulfones with carbonyl compounds

Paul R. Blakemore

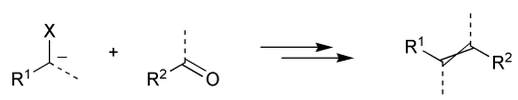
Department of Chemistry, University of Leeds, Leeds, West Yorkshire, UK LS2 9JT.
E-mail: P.R.Blakemore@chemistry.leeds.ac.uk

Received (in Cambridge, UK) 19th August 2002
First published as an Advance Article on the web 4th November 2002

Covering: until May 2002.

1 Introduction †

Connective olefination reactions capable of linking together advanced fragments *en route* to alkene containing biologically active natural products are highly valued synthetic methods. The great complexity of natural product molecules now routinely tackled by total synthesis[1] demands that the olefination methods employed in such endeavours must not only be highly regio- and stereoselective, but also compatible with the requisite multifunctional fragments. A variety of fundamentally different approaches to alkene synthesis have been developed which attempt to address these stringent demands; however, no single method yet provides a universal solution to the problem.[2] Arguably, the most efficient and generally applicable methods for alkene synthesis remain those involving direct olefination of carbonyl compounds.[3] Such methods are best exemplified by the venerable Wittig reaction[4,5] and also include the well known Horner–Wittig,[5c,6] Horner–Wadsworth–Emmons (HWE),[5c,7] Peterson,[8,9] Johnson,[10] and classical Julia[11,12] olefinations (Fig. 1).



X	Reaction	X	Reaction
R_3P^+	*Wittig*	R_3Si	*Peterson*
$R_2P(=O)$	*Horner-Wittig*	ArS(=O)(=NMe)	*Johnson*
$(RO)_2P(=O)$	*Horner-Wadsworth -Emmons (HWE)*	$ArS(=O)_2$	*classical Julia*
		$HetS(=O)_2$	***modified Julia***

Het = heteroaryl

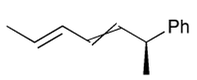
Fig. 1 Selected methodologies for the olefination of carbonyl compounds.

A new variant of the classical Julia olefination, the so-called *one-pot* or *modified* Julia olefination,[13] has recently emerged as a powerful tool for advanced fragment linkage and is the focus of this Review. Specifically, the article covers all aspects of direct alkene synthesis *via* the reactions of metallated heteroarylsulfones with carbonyl compounds. The material is subdivided as outlined above and begins with brief introductions to the classical and modified Julia reactions for the uninitiated. The major types of heteroarylsulfones currently available for alkene synthesis *via* the modified Julia olefination are surveyed in Section 2 accompanied by a more detailed analysis of reaction mechanism. Methods for incorporating heteroarylsulfone moieties into synthetic fragments are covered in Section 3 and a comprehensive survey of all applications of the modified Julia olefination in the synthesis of biologically active natural product molecules is provided in Section 4.

1.1 The classical Julia olefination

The *classical* Julia olefination (also commonly known as the Julia–Lythgoe olefination) was disclosed nearly thirty years ago by Marc Julia and Jean-Marc Paris in a short paper outlining a connective olefination procedure which utilised the reductive elimination of β-acyloxysulfones as an alkene forming step.[11] The method was later significantly developed by Lythgoe and Kocienski[14–17] and has since found pivotal use in the synthesis of many natural product molecules.[18] Alkene formation *via* the classical Julia reaction is a relatively cumbersome affair and typically requires four distinct synthetic operations (Scheme 1): metallation of a phenylsulfone **1**, addition of the metallate **2** to an aldehyde, acylation of the resulting β-alkoxysulfone **3**, and

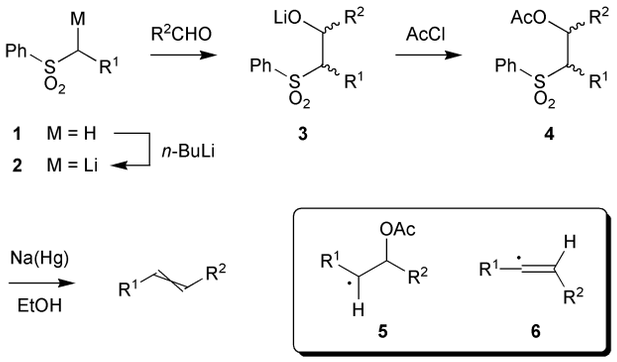
† Throughout this Review a crossed double bond denotes the site of a newly introduced alkene and *E* : *Z* ratios refer to isomeric mixtures about such bonds, *e.g.* **i**. Indicating double bond isomerisation in this manner removes the potential ambiguity of traditional representations, *e.g.* **ii**.



i

ii

DOI: 10.1039/b208078h



Scheme 1 The classical Julia olefination.

reductive elimination of the β-acyloxysulfone **4** with a single electron donor to afford alkene products. All four steps can be carried out in a single reaction vessel, although in practice the overall yield of the process is found to benefit from isolation of the intermediate β-hydroxysulfone and functionalisation of the hydroxy group in a separate step.

The classical Julia olefination is generally highly stereoselective and favours formation of the *trans* alkene. The geometry of the alkene product is independent of the relative configuration of the intermediate β-acyloxysulfone[14,15] and *trans* selectivity rises with increased chain branching about the newly formed double bond, *e.g.* *E* : *Z* (**9**) > *E* : *Z* (**8**) > *E* : *Z* (**7**)

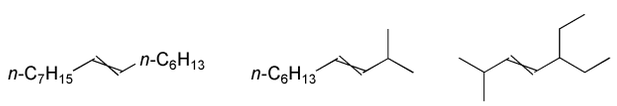
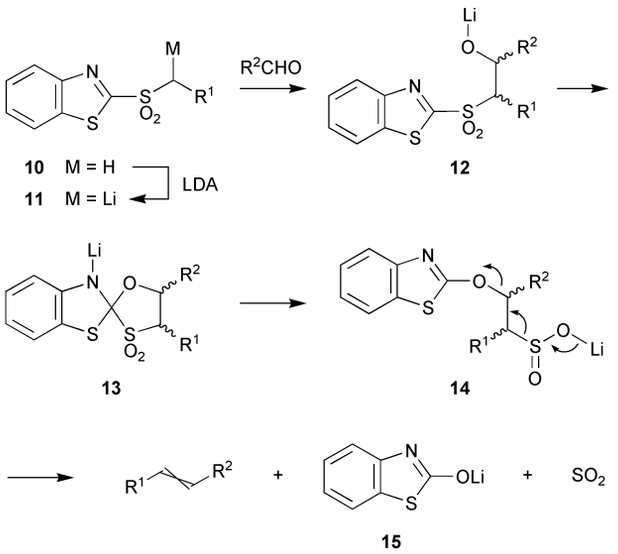


Fig. 2 Effects of chain branching on the stereochemical outcome of the classical Julia olefination.[16]

(Fig. 2).[16] The generation of intermediate radical species capable of stereochemical equilibration during the reduction step accounts for the above findings. Deuterium labelling studies by Keck implicate the formation of a vinylic radical **6** during sodium mercury amalgam reduction,[19] while the traditionally accepted radical intermediate **5**[16,20] is more likely formed during analogous reductions with samarium diiodide in HMPA or DMPU.[19] ‡

1.2 The modified Julia olefination

Replacement of the phenylsulfones traditionally used in the classical Julia olefination with certain heteroarylsulfones profoundly alters the reaction manifold. Sylvestre Julia and co-workers employed this ingenious device and explored the reactions of metallated benzothiazol-2-ylsulfones, hereafter denoted as BT-sulfones,§ with carbonyl compounds.[13] The presence of an electrophilic imine-like moiety within the heterocycle opens a new mechanistic pathway which is responsible for the transformed reactivity (Scheme 2). The addition of a metallated BT-sulfone **11** to an aldehyde proceeds in analogous fashion to the first step of the classical Julia olefination; however, the resulting β-alkoxysulfone **12** is inherently unstable and experiences a facile Smiles rearrangement.[23] The rearrangement occurs *via* a putative spirocyclic intermediate **13** and results in transfer of the heterocycle from sulfur to oxygen to yield sulfinate salt **14**. Spontaneous elimination of sulfur dioxide and lithium benzothiazolone (**15**) from **14** yields the alkene products directly. We refer to the above reaction as the *modified* Julia

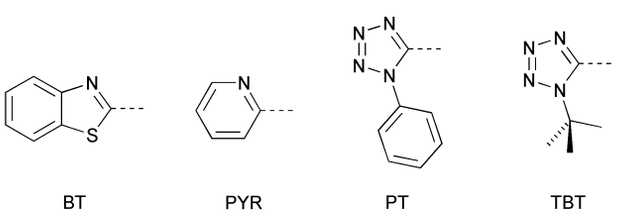


Scheme 2 The modified Julia olefination.

olefination but it is also commonly named the *one-pot* Julia olefination for obvious reasons.

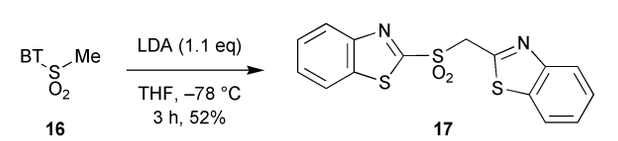
2 Heterocyclic sulfones for alkene synthesis

Four heterocyclic activators of the modified Julia olefination have been identified which provide useful levels of stereoselectivity in certain scenarios: benzothiazol-2-yl (BT), pyridin-2-yl (PYR), 1-phenyl-1*H*-tetrazol-5-yl (PT) and 1-*tert*-butyl-1*H*-tetrazol-5-yl (TBT). The methodological development of BT-, PYR-, PT- and TBT-sulfones for alkene synthesis and their associated mechanistic particulars are discussed below. A brief survey of other types of heteroarylsulfones which have also been used in the modified Julia olefination follows in Section 2.5.



2.1 Benzothiazol-2-yl sulfones

BT-sulfones are particularly susceptible to nucleophilic attack at C2 and readily participate in *ipso* substitution reactions with loss of a sulfinate nucleofuge.[24] Deprotonation of BT-sulfones must be effected with appropriate non-nucleophilic bases, *e.g.* lithium diisopropylamide (LDA), if *ipso* substitution is to be avoided. The donor–acceptor nature of metallated BT-sulfones can lead to self-condensation, a problem which is particularly acute for sterically unencumbered sulfones, *e.g.* treatment of methyl BT-sulfone **16** with LDA at low temperature gave adduct **17** in 52% yield.[25] A reverse addition protocol, *i.e.* adding the BT-sulfone to the base, does not prevent such behaviour.



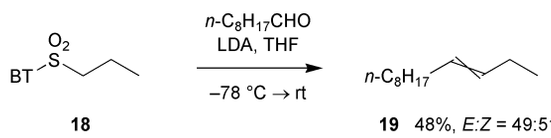
Self-condensation of BT-sulfones is inimical to the olefination process and in many cases yields can be improved by adopting so-called *Barbier* conditions. Under a Barbier protocol the base is added to a mixture of sulfone and aldehyde. *In situ* metallation of the sulfone and its subsequent addition to

‡ The reduction of β-benzoyloxyphenylsulfones by samarium diiodide in HMPA occurs *via* a β-sulfonyl radical, see ref. 21.

§ Use of Bt to denote benzothiazol-2-yl should be avoided as this abbreviation is already extensively used in the literature to signify benzotriazol-1-yl, see ref. 22.

the carbonyl compound compete against a self-condensation mechanism. Complex aldehyde substrates may not be compatible with the Barbier protocol; however, for the majority of fragment linkage reactions negligible self-condensation occurs at low temperature and the sulfone may be metallated before the addition of the aldehyde (*premetallation*) without penalty.

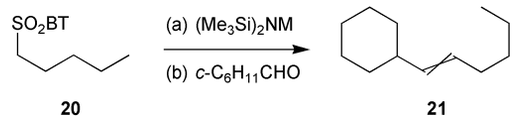
The stereochemical outcome of the BT-variant of the modified Julia olefination is substrate controlled but can also be influenced by the reaction conditions.[26–28] Julia and co-workers conducted the first systematic study of the process and investigated reactions between a variety of BT-sulfone structural types and a range of carbonyl compounds.[25] The coupling reactions were conducted predominantly *via* the Barbier mode in THF solvent with LDA as base. Under the selected reaction conditions of the survey, simple alkyl BT-sulfone metallates reacted with saturated aliphatic aldehydes to yield non-conjugated 1,2-disubstituted alkenes with little or no stereochemical bias, *e.g.* **18** ⟶ **19**.



18 **19** 48%, *E*:*Z* = 49:51

Subsequent studies have revealed that a degree of stereocontrol is achievable for such substrates if the coupling reaction is conducted under alternative conditions (*vide infra*).[28,29] For example, the stereochemical outcome of the reaction between metallated 2-(pentylsulfonyl)benzothiazole (**20**) and cyclohexanecarbaldehyde was dependent on the polarity of the reaction solvent and **21** was generated with moderate *trans* selectivity in DME solvent (Table 1).[29] Independence of stereoselectivity from base counter-cation, as illustrated in Table 1, is not a general phenomenon.

An investigation of the base mediated elimination of stereodefined β-hydroxy-BT-sulfones revealed that simple β-alkoxy-BT-sulfones (*i.e.* **22**, **25** with R^1 and R^2 alkyl) break down stereospecifically to give olefin products.[30] The *anti* diastereoisomer **22** yields an (*E*)-alkene while the *syn* diastereoisomer **25** yields a (*Z*)-alkene. An antiperiplanar arrangement of electrofuge and nucleofuge in the final elimination step is implied by the findings (Scheme 3). The disappointing geometrical selectivities in the aforementioned examples are therefore a consequence of poor diastereocontrol in the initial nucleophilic addition event and the *E* : *Z* ratio of the product olefins



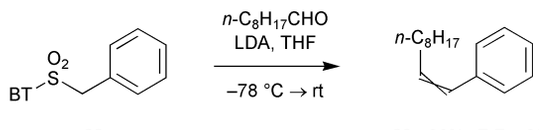
20 **21**

Table 1 Effects of solvent and base on the coupling of BT-sulfone **20** with cyclohexanecarbaldehyde.[29]

E : *Z* (**21**)	Reaction solvent			
M	Toluene	Et_2O	THF	DME
Li	50 : 50	49 : 51	66 : 34	70 : 30
Na	54 : 46	50 : 50	62 : 38	75 : 25
K	54 : 46	51 : 49	54 : 46	76 : 24

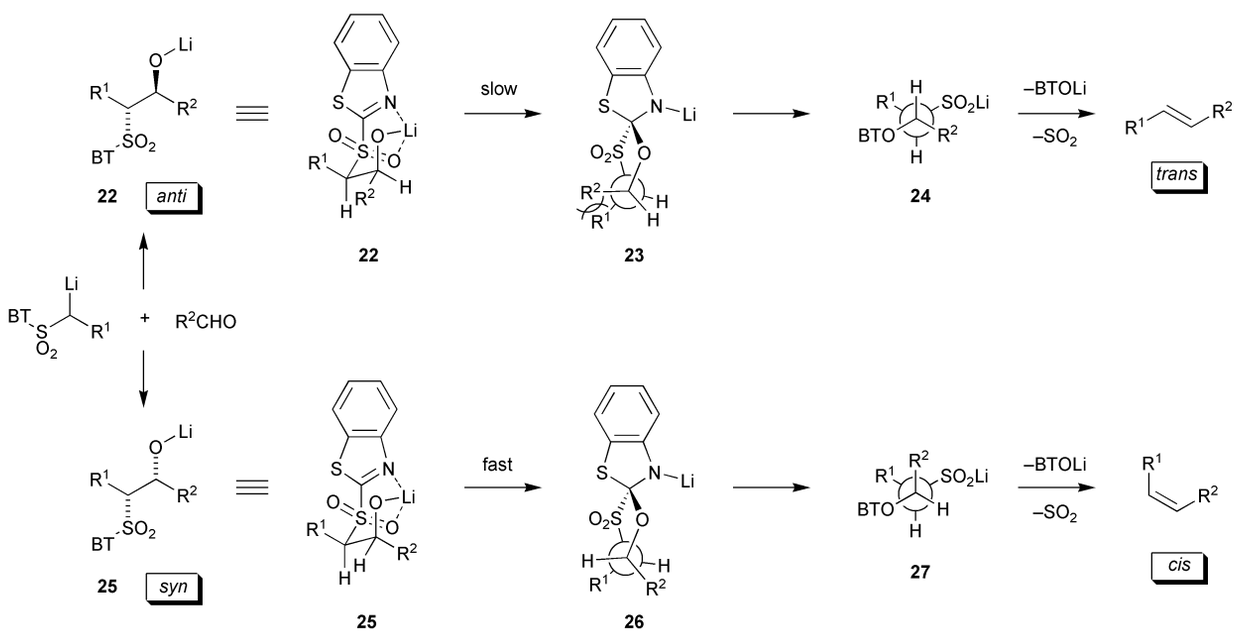
accurately reflects the *anti* : *syn* ratio of the intermediate β-alkoxysulfones.

Metallated β,γ-unsaturated BT-sulfones condense with unbranched non-conjugated aliphatic aldehydes to give olefins with low to moderate *cis* stereoselectivity, *e.g.* **28** ⟶ **29**.[25] In this instance, the intermediate β-alkoxy-BT-sulfones (*i.e.* **22**, **25** with R^1 unsaturated group) do not transform stereospecifically into olefins.[30] The lack of stereochemical fidelity is attributable to the ready fragmentation of such β-alkoxysulfones into resonance stabilised α-metallated sulfones and carbonyl compounds followed by subsequent re-addition. The possibility of addition/retroaddition in the reactions of stabilised metallated BT-sulfones with aldehydes has been established experimentally. The formation of a substantial quantity of cross-over adduct **32** was noted when *trans*-stilbene oxide derived *anti*-β-hydroxy-BT-sulfone **30** was treated with LDA in the presence of 4-nitrobenzaldehyde.[31] Sulfones resulting from the fragmentation of similar β-alkoxy-BT-sulfones have also been directly isolated.[30]

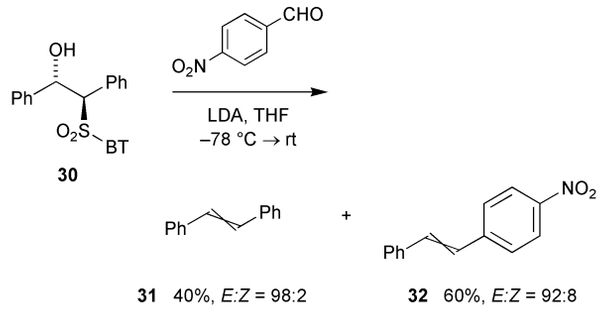


28 **29** 80%, *E*:*Z* = 23:77

A mechanism for equilibration between intermediate *syn*- and *anti*-β-alkoxysulfone diastereoisomers *via* retroaddition/addition is thus enabled for the reactions of metallated β,γ-unsaturated BT-sulfones with carbonyl compounds. The energy



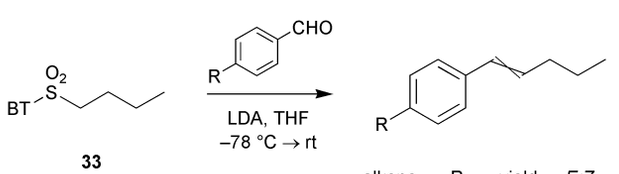
Scheme 3 Proposed mechanism for the modified Julia olefination.[25,30]



barrier to Smiles rearrangement for the *anti* isomer **22** is presumably higher than that for the corresponding *syn* isomer due to the eclipsed/*gauche* arrangement of R^1 and R^2 in the appropriate transition state for spirocyclisation. Indeed, the more facile base mediated elimination of *syn*-β-hydroxy-BT-sulfones as compared to their *anti* congeners has been noted.[30] Equilibration between **22** and **25** together with faster Smiles rearrangement/elimination for the latter provides a not unreasonable explanation for the aforementioned *cis* selectivity. However, the situation is certainly more complex than the above treatment may suggest since benzylic BT-sulfones react with α-branched unsaturated aliphatic aldehydes to give (*E*)-alkenes with high stereoselectivity.[25] There are also a number of more complex examples from total synthesis wherein β,γ-unsaturated BT-sulfones also give high levels of *trans* stereoselectivity (*vide infra*).

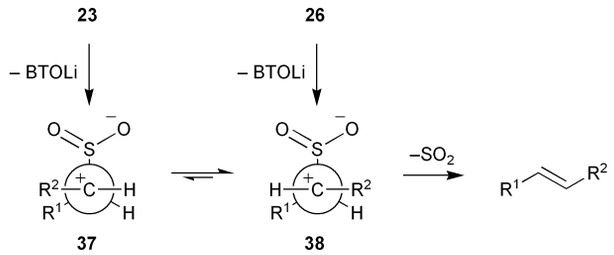
The most synthetically useful reactions of BT-sulfones involve the generation of conjugated 1,2-disubstituted (*E*)-alkenes. Metallated BT-sulfones of most structural types react with α,β-unsaturated aldehydes (including aromatic aldehydes) to yield (*E*)-olefins with high stereoselectivity. The reactions are particularly successful between simple alkyl BT-sulfones and electron-rich conjugated aldehydes. For example, lithiated 2-(butylsulfonyl)benzothiazole (**33**) was olefinated with a series of *para* substituted benzaldehydes and gave the expected styrene derivatives **34**, **35**, **36** with moderate to excellent stereoselectivity. Stereoselectivity increased with the electron donating ability of the *para* substituent on the benzaldehyde.

β-Alkoxy-BT-sulfones, **22** and **25**, with R^2 vinyl/aryl do not breakdown stereospecifically to olefins. The lack of stereospecificity remains whether or not R^1 is a group that can promote equilibration between the distereomeric alkoxides. It has also been demonstrated that some *syn*-β-alkoxy-BT-sulfones with R^2 vinyl/aryl collapse to predominantly (*E*)-alkenes.[30] Clearly a direct pathway for the transformation of *syn*-β-



alkene	R	yield	*E*:*Z*
34	OMe	95%	99:1
35	H	68%	94:6
36	Cl	51%	77:23

alkoxy-BT-sulfones **25** into (*E*)-alkenes must be available for these substrates. A plausible hypothesis concerning such a pathway has been forwarded by Julia.[25] Direct loss of lithiobenzothiazolone from intermediates **23** and **26** (or a similar event immediately following spirocycle opening) may yield zwitterionic conformers, **37** and **38**, respectively. Conformational equilibration of the betaine intermediates will favour **38** which yields an (*E*)-alkene product upon loss of sulfur dioxide. Unsaturated residues in R^2 provide stabilisation for the carbenium ion present in **37**/**38** and therefore, it is argued, promote the unusual pathway. The influence of benzaldehyde substituents on the stereochemical outcome of Julia olefination (*i.e.* **33** ⟶ **34**, **35**, **36**) is also accounted for by the hypothesis.

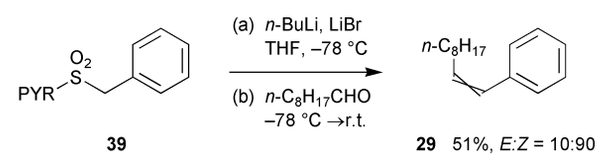


The condensation of metallated β,γ-unsaturated BT-sulfones with α,β-unsaturated aldehydes represents a hybrid scenario to those previously discussed above and consequently any prediction of stereochemical outcome is difficult. (*E*)-Alkenes are typically generated from such couplings, but this result is by no means assured and many examples exist where the (*Z*)-alkene was generated with excellent stereoselectivity (see Section 4).

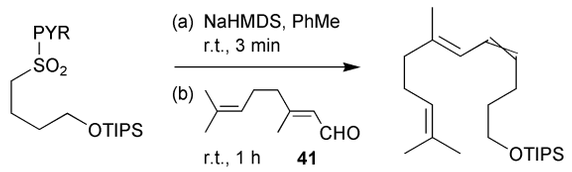
2.2 Pyridin-2-yl sulfones

PYR-sulfones are less susceptible to *ipso* substitution reactions than analogous BT-sulfones and simple derivatives may be cleanly metallated with *n*-butyllithium at low temperature. The comparative lack of electrophilicity of the pyridyl nucleus lends excellent stability to PYR-sulfone metallates and self-condensation problems are obviated. Charette has reported that the potassium metallate of a PYR-sulfone was stable for periods of at least 5 minutes at room temperature.[32,33] Metallated PYR-sulfones add readily to aldehydes to give the expected β-alkoxy-PYR-sulfones; however, the ensuing Smiles rearrangement is not particularly facile and β-hydroxy-PYR-sulfones may be easily isolated from the reaction mixture after protonolysis at low temperature. The reactions of a range of representative metallated PYR-sulfones, including simple alkyl and benzylic derivatives, with benzaldehyde yielded β-hydroxy-PYR-sulfones with little or no diastereoselectivity.[25,30]

PYR-sulfones generally give lower yields of olefin products than analogous BT-sulfones despite the impressive stability of PYR-sulfone metallates. However, β,γ-unsaturated PYR-sulfones give higher levels of *cis* selectivity in their reactions with aldehydes than the corresponding BT-sulfones (**39** ⟶ **29** *c.f.* **28** ⟶ **29**).[25] The recalcitrance of β-alkoxy-PYR-sulfones to undergo Smiles rearrangement no doubt enhances diastereomeric equilibration of these intermediates *via* a retroaddition/addition mechanism and thus favours the (*Z*)-alkene for the reasons discussed previously above.



Charette and co-workers have recently reported high levels of *cis* selectivity in the synthesis of conjugated 1,2-disubstituted alkenes *via* the condensation of metallated simple alkyl PYR-sulfones with α,β-unsaturated aldehydes, *e.g.* **40** ⟶ **42**.[32,33] The sense of stereoselectivity is contrary to that expected from the BT variant of the Julia olefination employing analogous substrates. The generality of the method remains to be established; however, Charette's development promises to be highly significant and increases still further the versatility of the modified Julia olefination. Particularly noteworthy is the fact that all stages of the coupling may be conducted at room temperature.

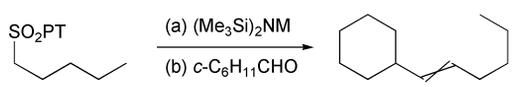


40 **42** 73%, *E*:*Z* = 17:83

2.3 1-Phenyl-1*H*-tetrazol-5-yl sulfones

PT-sulfones were introduced for the modified Julia olefination by Kocienski and co-workers in 1998 and provide a useful alternative to BT-sulfones in many instances.[29] The PT variant of the modified Julia olefination is distinguished by the ability to provide high levels of *trans* selectivity in the absence of biasing electronic or steric factors. In addition, the carbanions of PT-sulfones exhibit a reduced propensity to self-condense as compared to analogous BT-sulfones.

The *trans* selectivity of reactions involving PT-sulfones and leading to simple non-conjugated 1,2-disubstituted alkenes increases with both solvent polarity and the electropositivity of base counter-cation (Table 2).[29] A combination of 1,2-

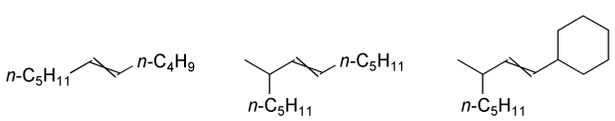


43 **21**

Table 2 Effects of solvent and base on the coupling of PT-sulfone **43** with cyclohexanecarbaldehyde[29]

E : *Z* (**21**)	Reaction solvent			
M	Toluene	Et_2O	THF	DME
Li	51 : 49	61 : 39	69 : 31	72 : 28
Na	65 : 35	65 : 35	73 : 27	89 : 11
K	77 : 23	89 : 11	97 : 3	99 : 1

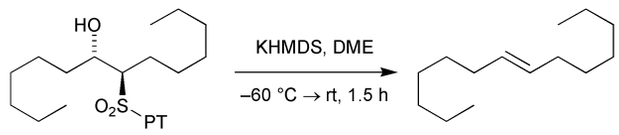
dimethoxyethane (DME) as solvent and potassium hexamethyldisilazide (KHMDS) as base often provides optimal conditions for the synthesis of simple *trans* alkenes *via* PT-sulfones. The level of stereoselectivity is impressive and, unlike in the case of the classical Julia olefination, is not markedly dependent on chain branching, *e.g.* *E* : *Z* (**44**) ≈ *E* : *Z* (**45**) ≈ *E* : *Z* (**46**) (Fig. 3).[29]



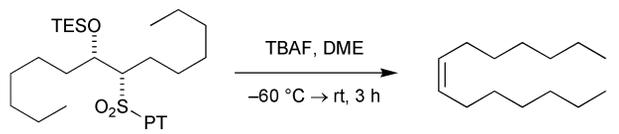
44 *E*:*Z* = 94:6 **45** *E*:*Z* = 96:4 **46** *E*:*Z* = 99:1

Fig. 3 Effects of chain branching on the stereochemical outcome of the PT-sulfone based variant of the modified Julia olefination.[29]

Experiments probing the breakdown of stereodefined β-alkoxy-PT-sulfones established that the aforementioned *trans* selectivity is the result of kinetically controlled diastereoselective addition of simple alkyl PT-sulfone metallates to non-conjugated aldehydes to yield *anti*-β-alkoxysulfones.[31] Thus, treatment of *anti*-β-hydroxy-PT-sulfone **47** with KHMDS in DME at −60 °C gave exclusively *trans*-tetradec-7-ene (**48**), while fluoride mediated desilylation of *syn*-β-(triethylsilyl)oxy-PT-sulfone **49** gave exclusively *cis*-tetradec-7-ene (**50**) under similar conditions.¶ Repetition of the experiments in the presence of 4-nitrobenzaldehyde gave comparable results with no trace of cross-over products indicating the irreversible nature of the addition of simple alkyl PT-sulfone metallates to aldehydes. PT-sulfones do not generally offer an advantage over their BT-sulfone counterparts for the synthesis of conjugated *trans* olefins from α,β-unsaturated aldehydes, although this is not without exception (*vide infra*).



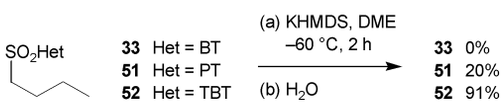
47 **48** 91%, *E*:*Z* = 98:2



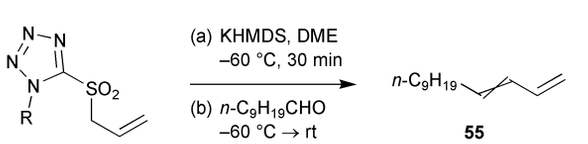
49 **50** 95%, *E*:*Z* = 2:98

2.4 1-*tert*-Butyl-1*H*-tetrazol-5-yl sulfones

The increased stability of metallated PT-sulfones as compared to analogous metallated BT-sulfones is presumably attributable to the 1-phenyl appendage which can sterically shield the key electrophilic sulfone-bearing carbon atom from intermolecular nucleophilic attack. Replacement of the phenyl moiety on the tetrazole ring with a bulkier *tert*-butyl group further improves sulfone metallate stability.[34] A collection of *n*-butyl heteroaryl-sulfones **33**, **51**, **52** were metallated under standard conditions and the amount of sulfone remaining following protonolysis two hours later was assessed. Over 90% of the TBT-sulfone **52** was recovered while only a meagre amount of the corresponding PT-sulfone **51** (20%) was found and none of the BT-sulfone **33**. Self-condensation adducts accounted for the mass balance.[34]



The synthesis of non-conjugated 1,2-disubstituted alkenes *via* TBT-sulfones is significantly less *trans* selective than *via* the analogous PT-sulfones; however, metallated allylic, or benzylic TBT-sulfones condense with aldehydes to afford conjugated 1,2-disubstituted (*Z*)-olefins with exquisite stereocontrol, *e.g.* **54** ⟶ **55**.[34] The bulky *tert*-butyl moiety presumably promotes equilibration between *syn*- and *anti*-β-alkoxysulfone intermediates by raising the energy barrier to Smiles rearrangement and consequently leads to high levels of *cis* selectivity for those metallated sulfones for which retroaddition is feasible. For the illustrated example, the level of *cis* selectivity was far greater than that obtained with the analogous BT-sulfone (*E* : *Z* = 32 : 68).[35] It is noteworthy that allyl PT-sulfone **53** afforded trideca-1,3-diene (**55**) with the opposite sense of stereoselectivity (*E* : *Z* = 67 : 33).[34]



53 R = Ph
54 R = Bu^t

R = Ph 39%, *E*:*Z* = 67:33
R = Bu^t 60%, *E*:*Z* = 4:96

2.5 Miscellaneous heterocyclic sulfones

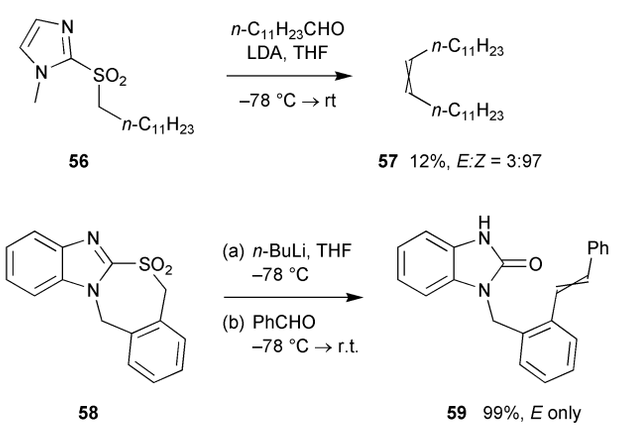
Aside from the four major variants of the modified Julia olefination discussed above, a variety of other heterocyclic sulfones

¶ Attempted synthesis of the *syn* diastereoisomer of **47** by oxidation of the corresponding β-hydroxysulfide led to spontaneous elimination of SO_2 and PTOH. The more facile elimination of *syn*-β-hydroxy-heteroarylsulfones had already been noted by Julia in the BT and PYR series, see ref. 30.

have been briefly examined as potential mediators of the process. Alternative heterocyclic sulfones investigated to date include: pyrimidin-2-yl,[25,31] 1-methylimidazol-2-yl,[31] benzimidazol-2-yl,[32] 1-methylbenzimidazol-2-yl,[32] 4-methyl-1,2,4-triazol-3-yl,[31] and isoquinolin-1-yl[31] sulfones. All of the aforementioned sulfones participate in the one-pot olefination process to some extent; however, too few reactions have been conducted to fully assess the particular advantages and disadvantages of a given system.

Heteroarylsulfones had been employed as substrates in the classical Julia olefination before the one-pot BT-sulfone mediated process was discovered. Kende introduced 1-methylimidazol-2-ylsulfones for use in the classical Julia olefination in 1990.[36] Imidazolyl sulfones have a low reduction potential and the reductive elimination of β-hydroxyimidazolylsulfones to yield olefin products is readily accomplished by treatment with samarium(II) iodide in THF. The operational simplicity of the Kende variant of the classical Julia olefination has led to its exploitation in a number of total synthesis efforts.[37–39] Interestingly, we have observed that simple metallated 1-methylimidazol-2-ylsulfones react with aldehydes to afford small quantities of olefin products directly if the intermediate β-alkoxyimidazolylsulfones are allowed to warm to room temperature, *e.g.* **56** ⟶ **57**.[31] The low yield of the olefin products obtained and the accompanying high levels of *cis* stereoselectivity presumably reflect a near total resistance of *anti*-β-alkoxyimidazolylsulfones to undergo Smiles rearrangement at ambient temperatures.

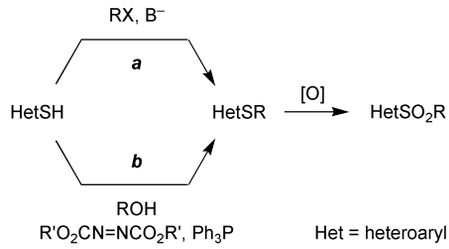
Kim and Yoon reported the synthesis of a series of benzimidazolinones from a modified Julia olefination sequence employing benzimidazolylsulfone **58**.[40] Metallation of **58** was accomplished with *n*-butyllithium in THF solvent and subsequent addition of a variety of aldehydes and ketones gave the expected products in good to excellent yields, *e.g.* **58** ⟶ **59**.



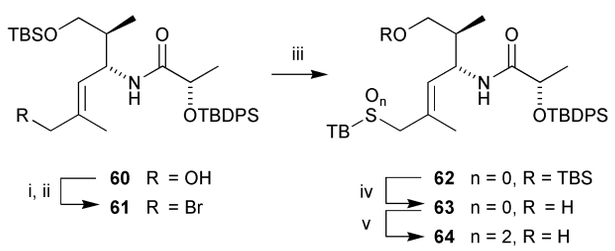
3 Synthesis of heterocyclic sulfone intermediates

The heterocyclic sulfone intermediates required for the modified Julia olefination are typically prepared by a two step *S*-alkylation/*S*-oxidation sequence commencing from the appropriate heterocyclic thiol and progressing *via* the corresponding thioether.‖ The heteroarylthiol starting materials are inexpensive odourless solids which are widely available from commercial suppliers.**

The alkylation reaction may be carried out under a classical Williamson-type protocol whereby the heteroarylthiol is

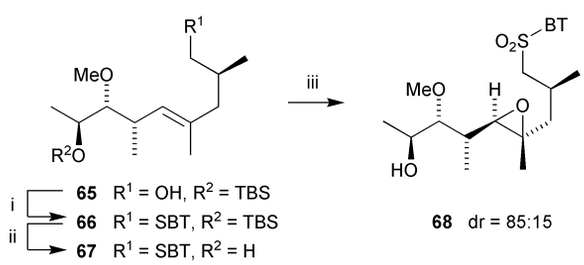


condensed with an alkyl halide or pseudo-halide under basic conditions (route *a*).[42] Alternatively, the intermediate sulfides may be conveniently prepared *via* Mitsunobu reaction between an aliphatic alcohol and the heteroarylthiol (route *b*).[43,44] The latter method has been extensively applied in total synthesis since high yielding coupling occurs under very mild conditions and the requisite alcohols are attractive synthetic intermediates. The following examples are illustrative of the above strategies: Williams and co-workers employed the classical alkylation route to access BT-sulfide **62** *en route* to the carbocyclic antibiotic lankacyclinol (Scheme 4),[45] while Kocienski and co-



Scheme 4 *Reagents and conditions:* i, MsCl, 2,6-lutidine, CH_2Cl_2; ii, LiBr, THF, r.t., 97% (2 steps); iii, *n*-BuLi, BTSH, THF, −78 °C, then **61**, −78 °C ⟶ r.t., 97%; iv, PPTS, MeOH–H_2O, 85%; v, $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, H_2O_2, EtOH, 0 °C ⟶ r.t., 89%.

workers took advantage of the Mitsunobu process to prepare **66**, an intermediate in a synthesis of the herbicidal polyketide herboxidiene (Scheme 5).[46]



Scheme 5 *Reagents and conditions:* i, BTSH, DIAD, Ph_3P, THF, 0 °C ⟶ r.t., 2 h, 99%; ii, TBAF, THF, r.t., 32 h, 98%; iii, MCPBA, $NaHCO_3$, CH_2Cl_2, r.t., 20 h, 46%.

The comparative ease with which a heteroarylthioether may be introduced into an advanced synthetic intermediate makes the Julia olefination a particularly attractive methodology.†† The precursors for many other types of carbonyl olefination chemistry are not always easily prepared or purified. For example, the phosphonium salt precursors necessary to prepare ylides for the Wittig reaction can be very awkward to access, particularly if the alkyl halide starting material is sterically encumbered.‡‡ In contrast, a heteroarylthioether unit can often be introduced into relatively hindered positions *via* the Mitsunobu reaction without great difficulty.[49]

‖ An attempted single step preparation of BT-sulfones *via* the alkylation of sodium benzothiazol-2-ylsulfinate was unsuccessful, see ref. 25.

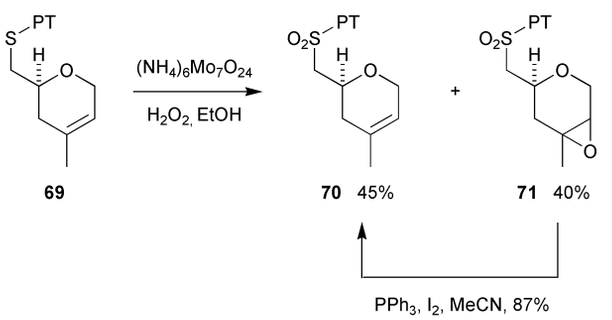
** 2-Mercaptobenzothiazole (BTSH), 2-mercaptopyridine (PYRSH) and 1-phenyl-1*H*-tetrazole-5-thiol (PTSH) are available from Aldrich at 0.05, 1.51 and 0.49 £ g^{-1}, respectively (2000–2001 catalogue). 1-*tert*-Butyl-1*H*-tetrazole-5-thiol (TBTSH) is not commercially available but is easily prepared by the addition of sodium azide to *tert*-butyl isothiocyanate, see ref. 41.

†† For a selection of representative experimental procedures for the introduction of a heteroarylthioether into a given substrate, see: classical alkylation, ref. 25; Mitsunobu, refs. 26,46,47.

‡‡ For a contemporaneous example illustrating the potential pitfalls incurred in forming phosphonium salts from moderately hindered functionalised alkyl halides, see ref. 48.

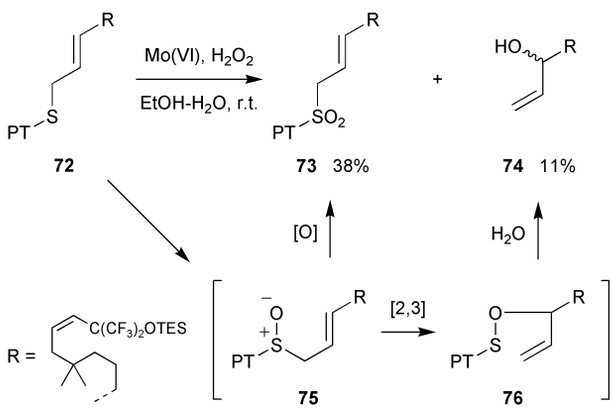
Conversion of heteroarylthioethers to the necessary sulfone intermediates has been accomplished with a variety of oxidants.§§ Most of the standard reagents commonly employed for *S*-atom oxidation effect the conversion satisfactorily and exactly which protocol is adopted depends largely on the desired degree of chemoselectivity.[54,55] Oxidation of the heteroatoms within the heterocyclic unit is not generally encountered. Peracid reagents, particularly 3-chloroperoxybenzoic acid (MCPBA),[56] have been extensively employed for the oxidation of heteroarylthioethers which are bereft of other easily oxidisable functional groups. Alkene containing heteroarylthioethers should not be converted to sulfones with peracid oxidants unless concomitant epoxidation is desired. Kocienski and co-workers deliberately explored this tactic to synthesise epoxy BT-sulfone **68** (Scheme 5).[46]

Mo(VI) catalysed oxidation has proven the most popular method for accessing more complex heteroarylsulfones. Treatment of heteroarylthioethers with $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$–$H_2O_2$[57] generally results in highly chemoselective *S*-atom oxidation, *e.g.* **63** ⟶ **64** (Scheme 4),[45] although epoxidation has been observed as a side reaction in at least one example. Davidson reported the formation of a substantial quantity of epoxysulfone **71** during the synthesis of sulfone **70** from sulfide **69**.[58] Other heteroarylthioethers possessing very similar or identical dihydropyran moieties have been converted to sulfones under the same conditions without competing epoxidation.[59–61] In any event, epoxide **71** was successfully deoxygenated with triphenylphosphine and iodine to bolster the overall yield of sulfone **70** which was later converted to a C15–C28 fragment of laulimalide.[58]



Charette and co-workers recently reported that W(VI) catalysed oxidation of heteroarylthioethers offers superior chemoselectivity for sulfone generation compared to other methods.[32] A variety of thioethers derived from geraniol (including BT- and PYR-thioethers) were cleanly oxidised to the expected sulfones using $Na_2WO_4\cdot 2H_2O$–H_2O_2 without competing oxidation of the heterocyclic unit or the olefinic sites. It is noteworthy that oxidation of an analogous PT-thioether under identical conditions was not successful.[32] Heteroarylsulfones have also been prepared from thioethers by oxidation with Oxone®,[34,53,62] peroxyacetic acid,[63–65] monoperoxyphthalic acid,[66] potassium permanganate,[67,68] sodium perchlorate,[69] and oxygen–isobutyraldehyde.[70]

The synthesis of allylic heteroarylsulfones by an oxidative route may be complicated by the intervention of [2,3]-sigmatropic rearrangement of the intermediate sulfoxides.[71] Hilpert and co-worker observed the formation of a significant quantity of allylic alcohol **74** during an attempted synthesis of PT-sulfone **73**.[51] The alcohol presumably resulted from hydrolysis of sulfenate ester **76**, itself the sigmatropic rearrangement product of intermediate sulfoxide **75**. The side reaction was not observed in the synthesis of the analogous BT-sulfone **228**. The difference in reactivity was attributed to the greater electron withdrawing ability of PT *vs.* BT moieties, the former accelerating rearrangement.[51] A related problem concerning [2,3]-sigmatropic rearrangment of an allylic BT-sulfoxide thwarted the attempted synthesis of a vitamin D_3 A-ring fragment.[49] In that case, two consecutive [2,3]-sigmatropic rearrangements reconfigured a dienyl sulfoxide system to a thermodynamic minimum.

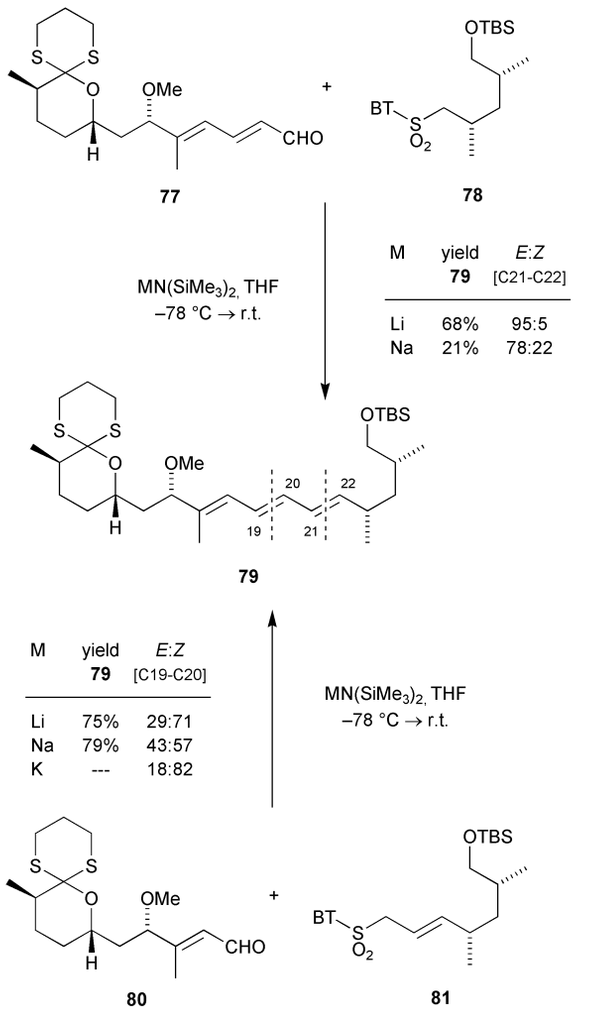


4 Applications of the modified Julia olefination in the total synthesis of biologically active natural product molecules

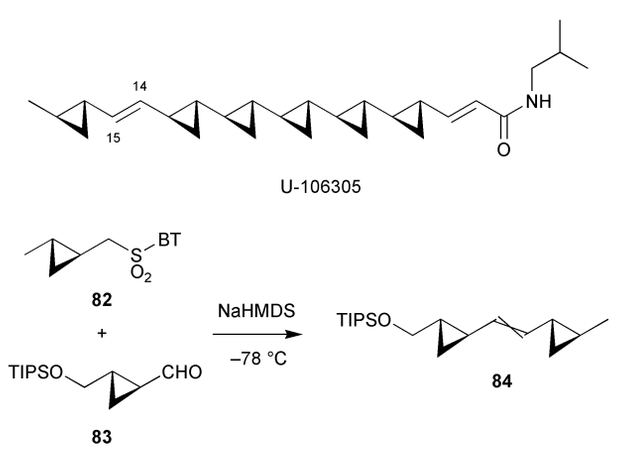
Applications of the modified Julia olefination in target directed synthesis began to appear soon after its disclosure. Kocienski and co-workers were the first to apply the new methodology to a *bona fide* synthetic target and used the reaction to synthesise the conjugated triene segment of the potent immunosuppressant rapamycin.[26] A C10–C26 rapamycin fragment **79** was prepared by the addition of lithiated BT-sulfone **78** to conjugated dienal **77** in THF solvent. Based on the earlier observations of Julia (see Section 2.1),[25] it was anticipated that the reaction would favour formation of the desired (*E*)-alkene. In the event, triene **79** was isolated in good yield and with excellent stereoselectivity (*E* : *Z* = 95 : 5) about the newly formed C21–C22 alkene (the all *trans* stereochemistry of the existing double bonds within **77** was retained in the product). Further investigations revealed that the stereochemical outcome of the coupling reaction was influenced by the nature of the base used to effect sulfone deprotonation.[26] Under otherwise identical reaction conditions to the above, the sodium metallate of sulfone **78** yielded triene **79** with a much reduced stereoselectivity (*E* : *Z* = 78 : 22). Base counter-cation was also observed to markedly affect stereoselectivity when fragment **79** was accessed *via* an alternative route. Coupling of allylic BT-sulfone **81** and enal **80** yielded triene **79** with predominantly *cis* stereochemistry about the C19–C20 alkene. Again, the sense of the stereoselectivity was not totally unexpected for such a sulfone (see Section 2.1), but the controlling influence of metal cation on the degree of selectivity was noteworthy. Much subsequent work has amply demonstrated that base effects in the modified Julia olefination are a general phenomenon.

That stereocontrol in the modified Julia olefination can also be tuned by solvent effects was discovered during another early application of the methodology. Charette and co-worker required a connective olefination methodology to form the C14–C15 alkene unit of the multi-cyclopropane containing natural product U-106305.[28] The alkene in question joins two separate cyclopropane containing domains and traditional olefination methods failed to realise the double bond. The carbanion of cyclopropyl BT-sulfone **82** proved a viable reagent (ring opening pathways were not observed) and its addition to model aldehyde **83** gave the expected alkene products **84** in excellent yield (> 90%). Stereocontrolled formation of non-conjugated 1,2-disubstituted alkenes *via* the modified Julia

§§ For a selection of representative experimental procedures for HetSR ⟶ $HetSO_2R$ conversions with particular oxidants, see: MCPBA, refs. 26,46,50; $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$–$H_2O_2$, refs. 47,51,52; Oxone®, ref. 53; $Na_2WO_4\cdot 2H_2O$–H_2O_2, ref. 32.



olefination was unprecedented at the time of Charette's study, and a range of reaction conditions were surveyed to optimise the $E:Z$ ratio of **84**. Significantly, the nature of the solvent had a profound effect on stereoselectivity. Relatively non-polar solvents favoured formation of the (Z)-alkene, while in co-ordinating polar media the desired (E)-alkene was preferred. Some limited effects of base counter-cation were also noted during the study.[28] Optimised reaction conditions were later used to conjoin sulfone **82** and an aldehyde (**151**) containing five contiguous cyclopropane rings to complete a synthesis of the antipode of U-106305 (see Table 3).



solvent	toluene	CH_2Cl_2	Et_2O	THF	DME	DMF
$E:Z$ (**84**)	9:91	9:91	11:89	52:48	71:29	78:22

Solvent and base effects are now routinely exploited to influence the stereochemical outcome of the modified Julia olefination and a varied assortment of complex target molecules have been synthesised with the aid of the reaction. In many cases the modified Julia olefination has been used as a device for linking together highly advanced multifunctional synthetic intermediates. The most successful examples of alkene synthesis were based on a considered selection of four reaction determinants: substrate pairing (tactical bond disconnection), heteroaryl nucleus, reaction solvent and base counter-cation. The following sections survey all applications of the modified Julia olefination in target directed synthesis published to date. Examples are grouped according to the type of alkene unit prepared, whether 1,2-disubstituted and non-conjugated (Section 4.1), 1,2-disubstituted and conjugated (Section 4.2), or trisubstituted (Section 4.3). Graphical tables illustrating the alkenes synthesised accompany the text and individual entries are arranged in alphabetical order according to the ultimate natural product target molecule.

4.1 Synthesis of non-conjugated 1,2-disubstituted alkene targets

The modified Julia olefination has been used to synthesise a variety of complex non-conjugated 1,2-disubstituted alkenes (Table 3). The (E)-alkene is generally favoured and the PT variant of the reaction may be regarded as superior to the original BT based method in virtually all cases. In the absence of biasing electronic and steric factors, BT-sulfones do not furnish olefins with satisfactory levels of stereoselectivity and are therefore less generally useful than their PT-sulfone congeners for the preparation of non-conjugated alkenes.

When chain branching elements are in place to flank the newly generated non-conjugated olefin, BT-sulfones have given good *trans* selectivity. The first such example was provided during Charette's synthesis of *ent*-U-106305 and was discussed above.[28] Ley and co-workers later used the BT method in spectacular fashion to conjure up a highly advanced derivative of the protein phosphatase inhibitor okadaic acid.[61] Employing the coupling conditions developed by Charette and Lebel,[28] BT-sulfone **140** was condensed with aldehyde **141** to yield a protected form of okadaic acid **142** directly in 66% yield. Only slight traces (not quantified) of the corresponding (Z)-isomer were formed.

The Banwell[72] and Liu[73] groups both employed branched BT-sulfone **106** to generate (E)-alkenes during the course of their respective syntheses of the cytotoxic sponge metabolite bengamide E.¶¶ Use of a lithium amide base in relatively polar reaction media gave the desired alkene products **108** and **110** with excellent stereoselectivity ($E:Z > 95:5$) in each case. Pattenden and Lam prepared related alkene **102** in a similar manner towards the presumed amphidinolide A,[75] but obtained an $E:Z$ ratio of only 80 : 20 using KHMDS as base. It is noteworthy that epimerisation of the base sensitive α-silyloxy aldehyde **107** was not observed in the Banwell synthesis of **108** despite the use of Barbier conditions. Epimerisation of chiral α-substituted aldehydes has not been encountered in any applications of the modified Julia olefination. Elaboration of alkene **130** by Suzuki and co-workers, as part of their route to the oft synthesised marine natural product malyngolide, further exemplifies that chain branching can improve stereoselectivity for the synthesis of non-conjugated olefins with BT-sulfones.[76] The synthesis of **130** was low yielding (30–40%) using an analogous Wittig reaction based route.

The introduction of PT-sulfones for the modified Julia olefination has had a significant impact on the synthesis of non-conjugated 1,2-disubstituted (E)-alkenes. A combination

¶¶ Kinder and co-workers also attempted a synthesis of the bengamide natural products by a modified Julia coupling route but without success, see ref. 74.

Table 3 Synthesis of non-conjugated 1,2-disubstituted alkenes *via* the modified Julia olefination

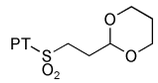
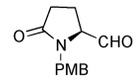
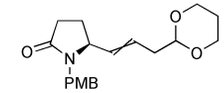
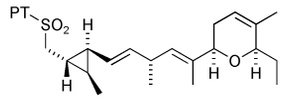
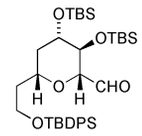
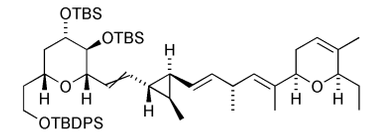
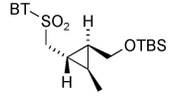
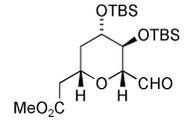
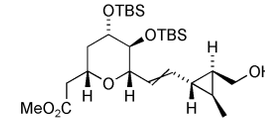
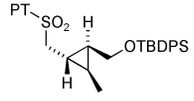
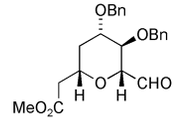
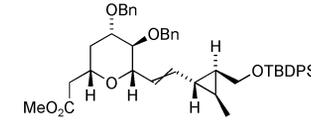
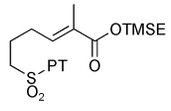
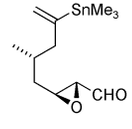
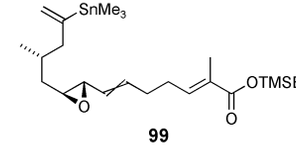
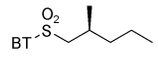
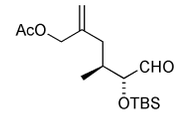
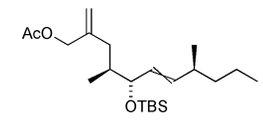
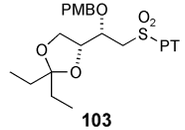
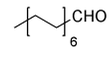
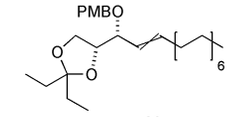
Target molecule	Heteroaryl sulfone	Carbonyl compound	Reaction conditions[a]	Alkene product[b]	Yield (%)	$E:Z$[c]	Ref.
5-Allylhexahydro-indolizidin-3-one	 **85**	 **86**	KHMDS, DME	 **87**	55	"*E* only"	84
Ambruticin	 **88**	 **89**	*premetallate* LiHMDS DMF–DMPU −35 °C	 **90**	> 90	> 97 : 3	60[d]
Ambruticin	 **91**	 **92**	(a) *premetallate* NaHMDS, DMF −50 °C⟶ r.t. (b) TFA, THF–H_2O	 **93**	51	72 : 28	83
Ambruticin	 **94**	 **95**	*premetallate* LiHMDS THF–HMPA −78 °C ⟶ r.t.	 **96**	63	90 : 10	82
Amphidinolide B	 **97**	 **98**	*premetallate* KHMDS, DME −78 °C	 **99**	65	75 : 25	85
Amphidinolide A	 **100**	 **101**	*premetallate* KHMDS, THF −78 °C ⟶ r.t.	 **102**	78	80 : 20	75
Azidosphingosine	 **103**	 **104**	*premetallate* KHMDS, DME −55 °C ⟶ r.t.	 **105**	53	80 : 20	86[d]

Table 3 (*Contd.*)

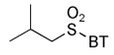
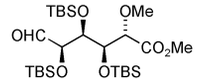
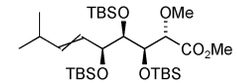
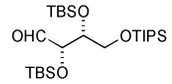
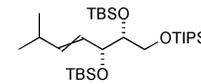
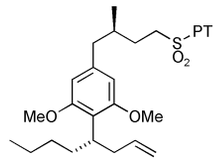
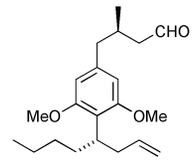
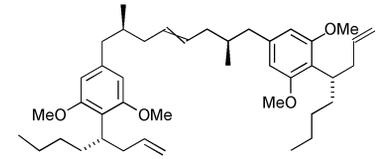
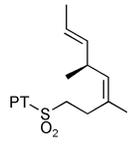
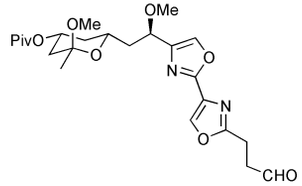
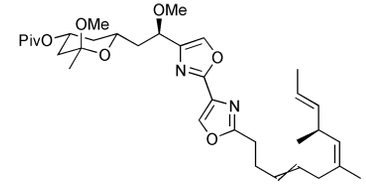
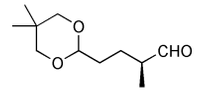
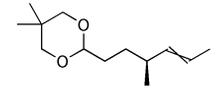
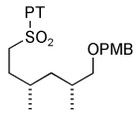
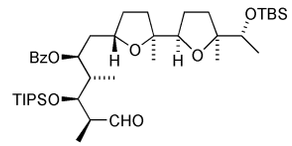
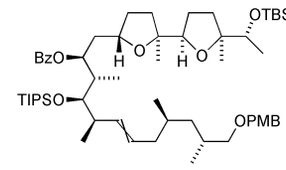
Target molecule	Heteroaryl sulfone	Carbonyl compound	Reaction conditions[a]	Alkene product[b]	Yield (%)	$E:Z$[c]	Ref.
ent-bengamide E	 **106**	 **107**	*Barbier* LiHMDS, THF–DME −78 °C ⟶ r.t.	 **108**	64	> 97 : 3	72[d]
Bengamide E	**106**	 **109**	*premetallate* LiHMDS THF −78 °C ⟶ r.t.	 **110**	92	> 95 : 5	73
Cylindrocyclophane A/F	 **111**	 **112**	*premetallate* KHMDS, THF −78 °C ⟶ r.t.	 **113**	74	> 94 : 6	47[d]
Hennoxazole	 **114**	 **115**	*premetallate* KHMDS, DME −55 °C	 **116**	85	91 : 9	79[d]
Herboxidiene	 **117**	 **118**	*Barbier* KHMDS, DME −60 °C	 **119**	93	93 : 7	46[d]
Ionomycin	 **120**	 **121**	*premetallate* KHMDS, THF −78 °C ⟶ r.t.	 **122**	85	"*E* only"	80[d]

Table 3 (*Contd.*)

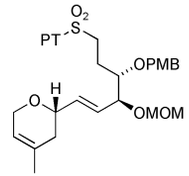
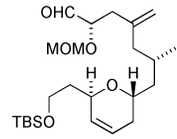
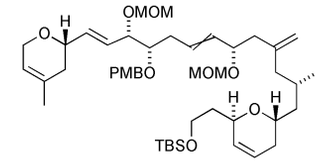
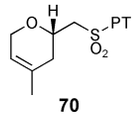
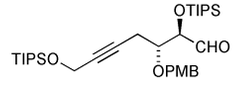
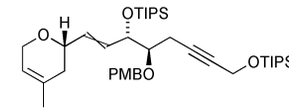
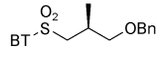
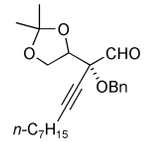
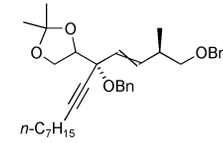
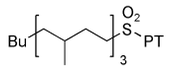
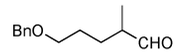
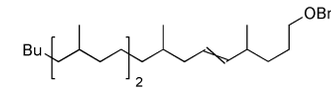
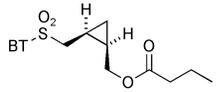
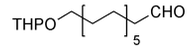
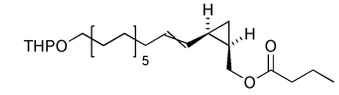
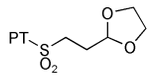
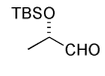
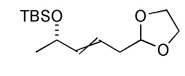
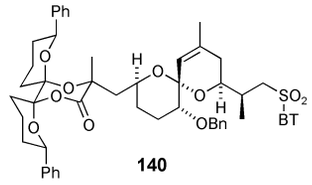
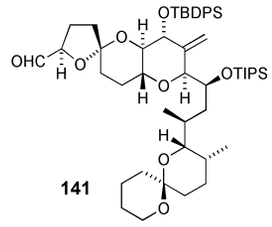
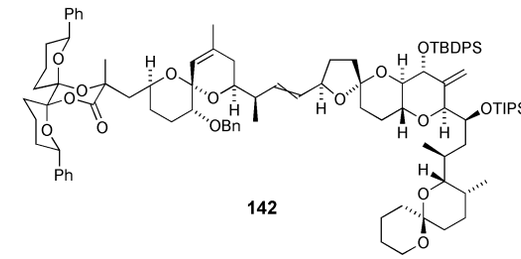
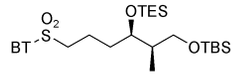
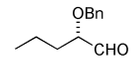
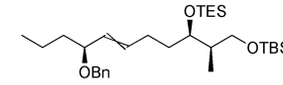
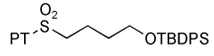
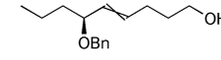
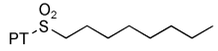
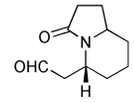
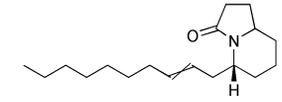
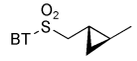
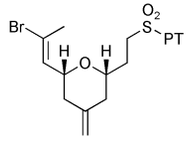
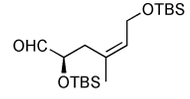
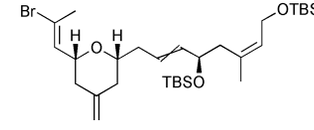
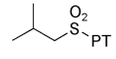
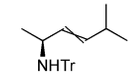
Target molecule	Heteroaryl sulfone	Carbonyl compound	Reaction conditions[a]	Alkene product[b]	Yield (%)	$E:Z$[c]	Ref.
Laulimalide	 **123**	 **124**	*premetallate* KHMDS, DME −60 °C ⟶ r.t.	 **125**	62	92 : 8	59
Laulimalide	 **70**	 **126**	*premetallate* KHMDS, DMF	 **127**	81	83 : 17	58
Malyngolide	 **128**	 **129**	*premetallate* LiHMDS, THF −78 °C ⟶ r.t.	 **130**	90	97 : 3	76
Mannosyl phosphoisoprenoid	 **131**	 **132**	*premetallate* LiHMDS, THF −78 °C ⟶ r.t.	 **133**	90	Not determined	87[d]
Meromycolic acid	 **134**	 **135**	NaHMDS, THF	 **136**	62	43 : 57	88
Mycarose/ kedarosamine	 **137**	 **138**	*premetallate* KHMDS, DME −55 °C ⟶ r.t.	 **139**	92	95 : 5	78
Okadaic acid	 **140**	 **141**	*premetallate* NaHMDS, DMF–THF −60 °C ⟵ r.t.	 **142**	66	*E* major product	61

Table 3 (*Contd.*)

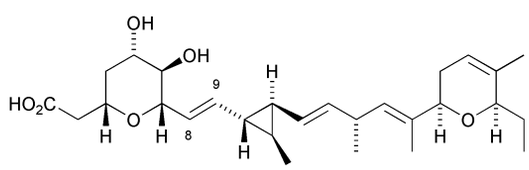
Target molecule	Heteroaryl sulfone	Carbonyl compound	Reaction conditions[a]	Alkene product[b]	Yield (%)	$E:Z$[c]	Ref.
Panamycin-607	 **143**	 **144**	*premetallate* LiHMDS, THF −78 °C ⟶ r.t.	 **145**	80	55 : 45	89
Panamycin-607	 **146**	**144**	(a) *premetallate* KHMDS, DME −78 °C ⟶ r.t. (b)TBAF, THF	 **147**	72	88 : 12	89
Piclavine A1/A2	 **148**	 **149**	KHMDS, DME	 **150**	62	72 : 25	90
ent-U-106305	 **82**	 **151**	(a) *Barbier* NaHMDS, THF–DMF −60 °C (b) TBAF, THF	 **152**	92	81 : 19	28[d]
Zampanolide	 **153**	 **154**	*premetallate* KHMDS, THF −78 °C	 **155**	88	"*E* only"	81
n/a (unnatural target)	 **156**	 **157**	*premetallate* NaHMDS, DME −55 °C	 **158**	70	"*E* only"	91[d]

[a] *premetallate* = base added to sulfone and then carbonyl added, *Barbier* = base added to a mixture of sulfone and carbonyl. [b] Crossed double bond indicates newly formed alkene. [c] Isomeric ratio about crossed double bond. [d] Detailed experimental procedure provided.

of KHMDS base and DME solvent generally provides optimum reaction conditions for the generation of simple (*E*)-alkenes from PT-sulfones.[29] The PT based method found its first application in Kocienski's synthesis of the herbicidal polyketide herboxidiene.[46] In the course of the synthesis, ethyl PT-sulfone **117** was used to prepare a relatively simple alkene **119**. The potassium metallate of **117** readily self-condensed and adoption of a Barbier protocol was essential for obtaining an acceptable yield of the olefin.|||| Epimerisation of the aldehyde substrate **118** was not observed and the (*E*)-alkene product **119** was formed highly enantioenriched (er >94 : 6) and in an excellent yield (93%, *E* : *Z* = 93 : 7). Hirama and Lear later synthesised a similar alkene (**139**) towards the kedarcidin chromophore sugar sub-units mycarose and kedarosamine with even better results and on a 40 g scale.[78]

The Williams group synthesis of the antiviral agent hennoxazole demonstrates that excellent stereoselectivity is achievable with the PT based method in the absence of chain branching.[79] Condensation of sulfone **114** with the bisoxazolyl aldehyde **115** gave skipped triene **116** in 85% yield with an *E* : *Z* ratio of 91 : 9 about the newly formed double bond. Simple hydrolysis of a pivalyl ester protecting group then yielded the completed natural product. Smith's synthetic studies of the cylindrophanes A and F provide a related example; the bisresorcinol ether **113** was generated in 74% yield and with near total stereoselectivity (*E* : *Z* > 94 : 6) despite lacking chain branching elements proximal to the double bond.[47] Table 3 contains other exemplars of the PT-sulfone–KHMDS–DME (or THF) method for the synthesis of non-conjugated 1,2-disubstituted (*E*)-alkenes. Of particular note are the complex fragment linkage reactions evident in the syntheses of ionomycin,[80] laulimalide[59] and zampanolide.[81]

Jacobsen and Liu observed unprecedented base and solvent effects for a PT-sulfone coupling reaction during a total synthesis of the antifungal agent ambruticin.[60] Addition of the potassium metallate of cyclopropyl PT-sulfone **88** with aldehyde **89** in DME (provided with 18-crown-6) furnished **90** with an *E* : *Z* ratio of 25 : 75 about the newly formed alkene (> 90% yield). Similar conditions are more commonly associated with stereoselective generation of the (*E*)-alkene product as discussed above. Conducting the same reaction in THF solvent and with NaHMDS base gave **90** with higher *cis* selectivity (*E* : *Z* = 11 : 89). Further experimentation revealed that the desired *trans* isomer of **90** could be generated with exceptional stereocontrol (*E* : *Z* > 97 : 3) from **88** and **89** using a lithium base (LiHMDS) in highly co-ordinating dipolar solvent mixtures (DMF–HMPA or DMF–DMPU). Determination of the generality of Jacobsen's conditions for the synthesis of a broader range of olefin targets awaits further study; however, Lee and co-workers have already applied very similar conditions for the production of an analogous alkene target **96** also *en route* to ambruticin.[82] In related work, Martin and co-workers used BT-sulfone **91** to access **93** *via* Charette-type conditions with decidedly mediocre results.[83]



ambruticin

4.2 Synthesis of conjugated 1,2-disubstituted alkene targets

The modified Julia olefination has been particularly useful for the synthesis of conjugated 1,2-disubstituted alkenes contained within complex natural product molecules (Table 4). The olefin products are generally formed in excellent yield and with high stereoselectivity by both BT and PT based variants of the reaction. Three distinct synthetic strategies may be identified for the construction of a generalised conjugated segment *via* the modified Julia reaction (Fig. 4). A 1,2-disubstituted alkene

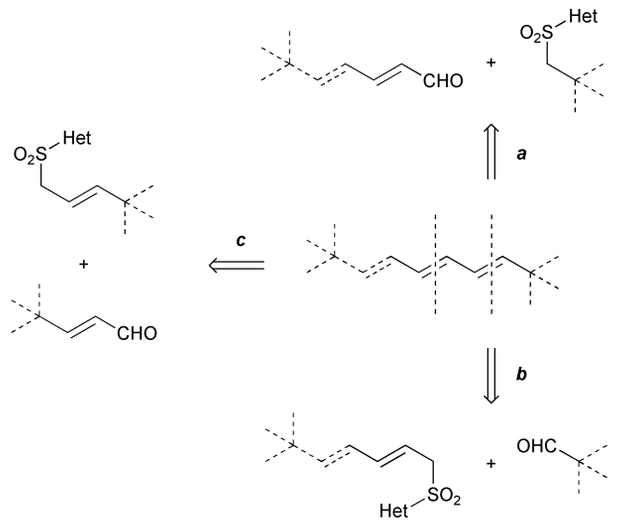


Fig. 4 Retrosynthetic disconnections for conjugated segments.

within a conjugated system may be synthesised from: (a) an α,β-unsaturated aldehyde and a ″simple″ heteroarylsulfone, (b) a non-conjugated aldehyde and a β,γ-unsaturated heteroarylsulfone, or (c) an α,β-unsaturated aldehyde and a β,γ-unsaturated heteroarylsulfone.

Strategies (a) and (b) are available for the synthesis of all types of conjugated systems and have potentially stereodivergent outcomes. Both strategies have been extensively explored in the course of numerous total synthesis efforts (*vide infra*). While the former strategy has led predominantly to the (*E*)-alkene in all cases (with the exception of a limited number of PYR-sulfones[32]), the stereochemical outcome of the latter approach is less certain. In cases where chain branching elements exist about the newly formed olefin, strategy (b) is also likely to proffer the (*E*)-alkene. However, when such elements are absent, (*Z*)-alkenes are typically formed (see also Section 2.1). Strategy (c) offers a more convergent route to conjugated trienes and higher homologues but has been much less studied. Applications of strategies (a), (b) and (c) in target directed synthesis are now surveyed in turn.

The efficacy of strategy (a), as applied to target directed synthesis, was first demonstrated by Kocienski *et al* in the course of work directed at the immunosuppressant rapamycin and resulted in the preparation of (*E,E,E*)-triene **79** as discussed above.[26] The same approach and reaction conditions (*i.e.* BT-sulfone, lithium amide base, THF solvent) have proven equally effective in the synthesis of other all *trans* conjugated dienes and trienes.

Kocienski and co-workers synthesised the conjugated (*E,E*)-diene segment of notional target herboxidiene A from lithiated BT-sulfone **174** and enal **175** in good yield (71%) and with excellent stereoselectivity (*E* : *Z* = 92 : 8).[27] The work was later extended to the synthesis of the natural diastereoisomer of herboxidiene.[46] Sulfone **177**, replete with the C14–C15 epoxide moiety of herboxidiene, was deprotonated with LDA and treated with **175** in THF solvent at −78 °C to yield a protected form of herboxidiene **178** directly. Protonolysis of the reaction mixture at −78 °C gave **178** in only 60% yield with an *E* : *Z* ratio of 80 : 20 about the newly formed C10–C11 alkene.[31] Allowing the reaction mixture to warm to −20 °C prior to quenching improved both the yield (60% ⟶ 81%) and stereoselectivity

|||| The failure of a methylenation reaction using $PTSO_2Me$ during a recent synthesis of epothilones B and D was no doubt also due to instability of the sterically unencumbered sulfone metallate, see ref. 77.

Table 4 Synthesis of conjugated 1,2-disubstituted alkenes *via* the modified Julia olefination

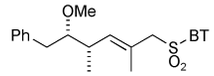
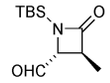
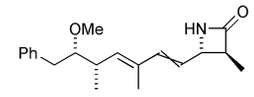
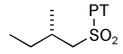
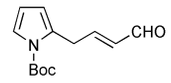
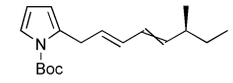
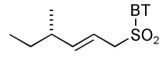
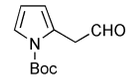
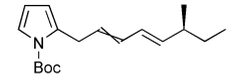
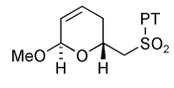
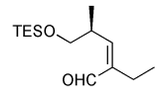
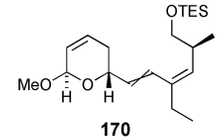
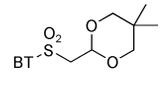
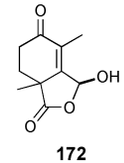
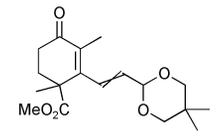
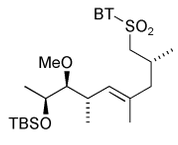
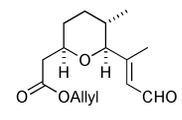
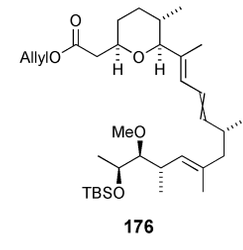
Target molecule	Heteroaryl sulfone	Carbonyl compound	Reaction conditions[a]	Alkene product[b]	Yield (%)	$E:Z$[c]	Ref.
ADDA conjugates	 **159**	 **160**	(a) *premetallate* KHMDS, THF −78 °C ⟶ r.t. (b) KF, MeOH	 **161**	45	75 : 25	53[d]
Axinellamine A	 **162**	 **163**	*premetallate* LDA, THF	 **164**	58	90 : 10	52[d]
Axinellamine A	 **165**	 **166**	Not given	 **164**	—	40 : 60	52
Callystatin A	 **168**	 **169**	*premetallate* NaHMDS, DME–HMPA −78 °C	 **170**	35	"*E* only"	99[d]
Cassiol	 **171**	 **172**	(a) *premetallate* LDA, THF −80 °C (add sodium alkoxide of lactol **172** to sulfone metallate) (b) CH_2N_2	 **173**	75	"*E* only"	94
Herboxidiene A	 **174**	 **175**	*premetallate* LDA, THF −78 °C ⟶ r.t.	 **176**	71	92 : 8	27[d]

Table 4 (*Contd.*)

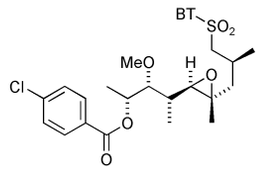
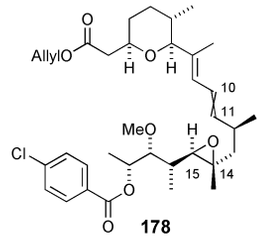
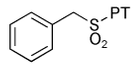
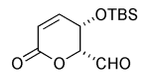
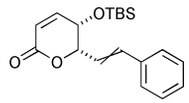
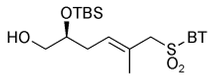
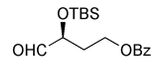
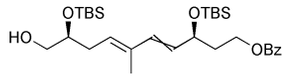
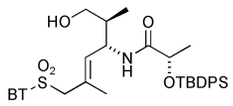
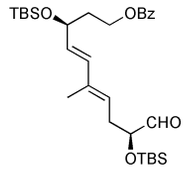
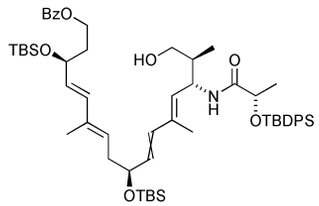
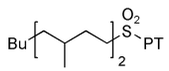
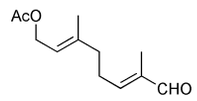
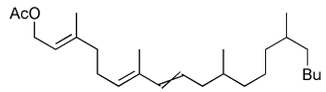
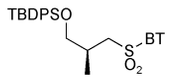
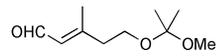
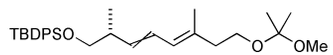
Target molecule	Heteroaryl sulfone	Carbonyl compound	Reaction conditions[a]	Alkene product[b]	Yield (%)	$E:Z$[c]	Ref.
Herboxidiene	 **177**	**175**	*premetallate* LDA, THF −78 °C ⟶ −20 °C	 **178**	81	91 : 9	46[d]
Isoaltholactone	 **179**	 **180**	*premetallate* KHMDS, THF −78 °C	 **181**	40	>93 : 7	104[d]
Lankacyclinol	 **182**	 **183**	*premetallate* LDA, THF −78 °C ⟶ r.t.	 **184**	57	"*E* only"	45
Lankacyclinol	 **64**	 **185**	*premetallate* LDA, THF −78 °C ⟶ r.t.	 **186**	72	"*E* only"	45
Mannosyl phosphoisoprenoid	 **187**	 **188**	*premetallate* LiHMDS, THF −78 °C ⟶ r.t.	 **189**	90	Not determined	87[d]
Mycaperoxide B	 **190**	 **191**	*Barbier* LiHMDS, THF −78 °C ⟶ r.t.	 **192**	95	"*E* only"	93[d]

Table 4 (*Contd.*)

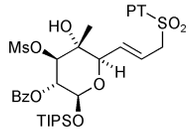
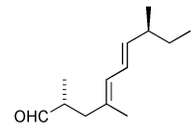
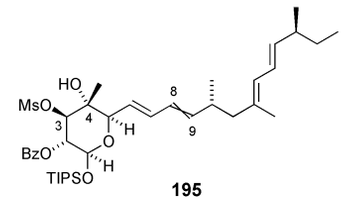
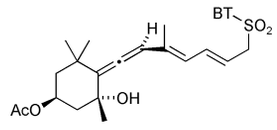
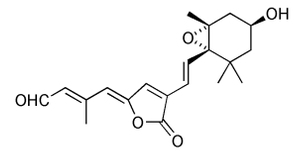
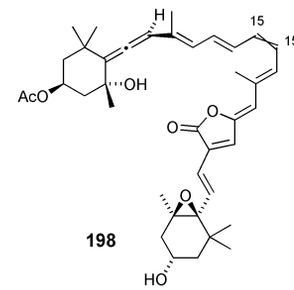
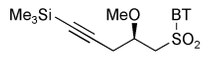
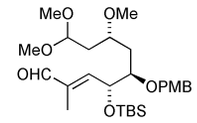
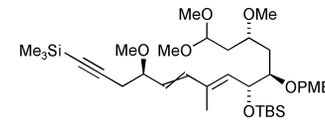
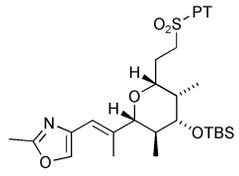
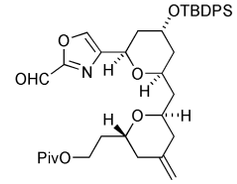
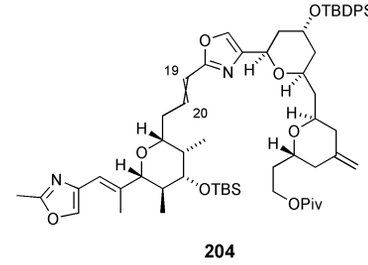
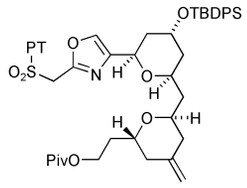
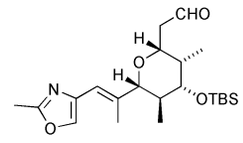
Target molecule	Heteroaryl sulfone	Carbonyl compound	Reaction conditions[a]	Alkene product[b]	Yield (%)	$E : Z$[c]	Ref.
Nafuredin	 **193**	 **194**	*premetallate* KHMDS, THF	 **195**	79	"*E* only"	97[d]
Peridinin	 **196**	 **197**	*Barbier* NaHMDS THF, −78 °C	 **198**	50	25 : 75	105
Phorboxazole A	 **199**	 **200**	*Barbier* NaHMDS THF, −78 °C	 **201**	74	"*E* only"	95
Phorboxazole A	 **202**	 **203**	*premetallate* KHMDS, DME −65 °C ⟶ r.t.	 **204**	42	67 : 33	39
Phorboxazole A	 **205**	 **206**	*premetallate* KHMDS, DME −65 °C ⟶ r.t.	**204**	46	9 : 91	39

Table 4 (*Contd.*)

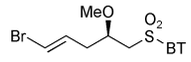
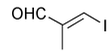
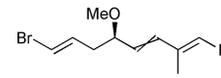
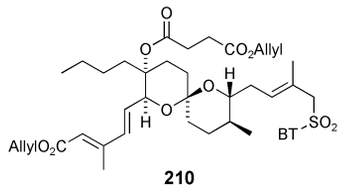
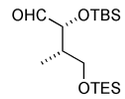
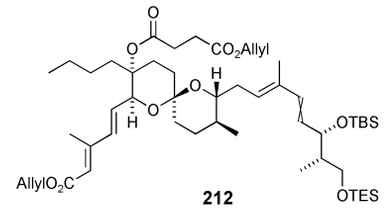
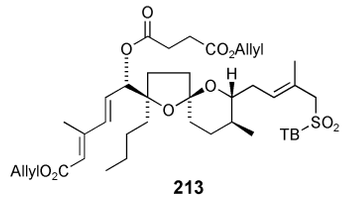
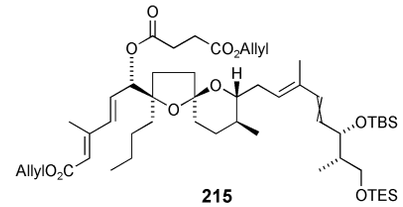
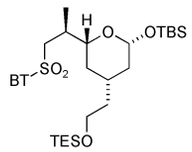
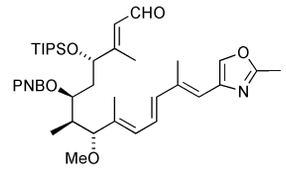
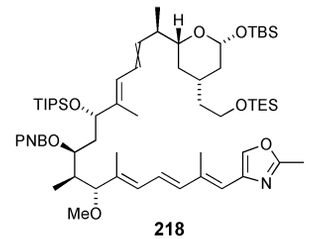
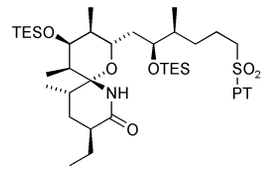
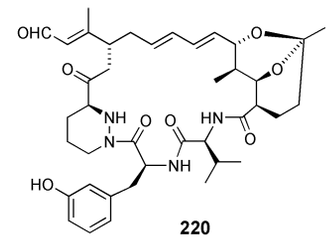
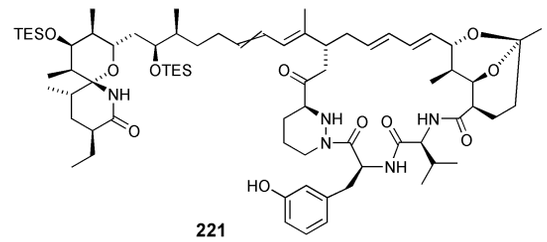
Target molecule	Heteroaryl sulfone	Carbonyl compound	Reaction conditions[a]	Alkene product[b]	Yield (%)	$E:Z$[c]	Ref.
Phorboxazole B	 **207**	 **208**	*Barbier* NaHMDS, THF −78 °C ⟶ r.t.	 **209**	75	>95 : 5	96
Reveromycin A	 **210**	 **211**	*premetallate* LiHMDS, THF −78 °C ⟶ r.t.	 **212**	90	"*E* only"	102
Reveromycin B	 **213**	**211**	*premetallate* LiHMDS, THF −78 °C ⟶ 0 °C	 **215**	56	"*E* only"	101
Rhizoxin D	 **216**	 **217**	*Barbier* LiHMDS, THF −78 °C ⟶ r.t.	 **218**	79	"*E* only"	92
Sanglifehrin	 **219**	 **220**	*Barbier* KHMDS, DME −78 °C	 **221**	49	"*E* only"	50[d]

Table 4 (*Contd.*)

Target molecule	Heteroaryl sulfone	Carbonyl compound	Reaction conditions[a]	Alkene product[b]	Yield (%)	$E:Z$[c]	Ref.
Thiazino-trienomycin	**222**	**223**	*premetallate* KHMDS, THF −78 °C ⟶ r.t.	**224**	85	91 : 9	98[d]

[a] *premetallate* = base added to sulfone and then carbonyl added, *Barbier* = base added to a mixture of sulfone and carbonyl. [b] Crossed double bond indicates newly formed alkene. [c] Isomeric ratio about crossed double bond. [d] Detailed experimental procedure provided.

($E:Z = 80:20 \longrightarrow E:Z = 91:9$) of the bond forming process. Trapping of a moderately stable *anti*-β-alkoxy-BT-sulfone intermediate at low temperature *via* protonolysis presumably accounts for the above findings.

The Leahy group used the Kocienski conditions to prepare a single isomer of a late stage rhizoxin D intermediate (**218**) which contained all but two of the requisite skeletal carbon atoms necessary to complete the natural product.[92] Harwood and associates used identical conditions with excellent results to prepare diene **192** in near quantitative yield *en route* to the putative biogenetic precursor of mycaperoxide B.[93] Rúveda and co-workers employed lactol **172** in a modified Julia olefination to facilitate a synthesis of the anti-ulcerogenic cyclohexenone cassiol.[94] Under standard conditions the alkene product **173** was isolated in only 18% yield accompanied by substantial quantities of adducts derived from Cannizzaro-type reactions of lactol **172**. The unwanted side-reactions were ultimately obviated by preforming the sodium alkoxide of **172** immediately prior to its addition to the lithium metallate of BT-sulfone **171**. Diene **173** was formed as a single detectable isomer and in 75% yield by the modified conditions.[94] Use of lithium bases in THF solvent is not necessarily optimum for the stereoselective formation of conjugated 1,2-disubstituted (*E*)-alkenes. Pattenden and co-workers applied NaHMDS and Barbier conditions in THF solvent to prepare (*E,E*)-diene **201**, a fragment in a projected synthesis of the potent cytostatic agent phorboxazole A.[95] Elimination of sodium methoxide from BT-sulfone **199** was not observed and **201** was formed in 74% yield as a single isomer as adjudged by ^{1}H NMR analysis. Other heteroaryl sulfones containing β-alkoxy groups have been successfully utilised in the modified Julia olefination without the manifestation of E1cb side-reactions.[86,96]

The synthesis of conjugated alkenes *via* strategy (a) has also been successfully demonstrated with PT-sulfones. In an impressive example of complex fragment linkage, Metternich and co-workers directly prepared a protected form of the immunosuppressant sanglifehrin by Julia coupling of PT-sulfone **219** with enal **220**.[50] The reaction is all the more remarkable when one considers the comparative lack of protecting groups adorning the coupling partners. Using Barbier conditions and only two equivalents of KHMDS in DME solvent the desired olefination reaction occurred in the presence of a phenolic hydroxy group, three amido NH groups and a free secondary amine! The modestly protected sanglifehrin product **221** was formed as a single stereoisomer and in reasonable yield (49%). If the reaction mixture was allowed to warm to ambient temperature prior to quenching then by-products resulting from S ⟶ O transfer of the heterocyclic moiety from sulfone **219** to the phenoxide anion were observed. Other examples of one-pot Julia olefination in the presence of free hydroxy groups have been reported.[45,97] Smith and Wan used the PT variant of the modified Julia olefination to synthesise a triene fragment of the novel ansamycin antibiotic thiazinotrienomycin E.[98] In an example reminiscent of Kocienski's rapamycin studies, (*E,E,E*)-triene **224** was prepared in excellent yield (85%) and with high stereoselectivity ($E:Z = 91:9$) by the addition of (*E,E*)-dienal **223** to the potassium metallate of PT-sulfone **222**. In a more recent effort from the same group, facile β-elimination and subsequent decomposition of metallated PT-sulfone **168** severely compromised a route to cytotoxic agent callystatin A.[99] The desired alkene product **170** was formed in only 35% yield albeit with complete stereocontrol. Addition of a single equivalent of HMPA to the reaction mixture was critical for minimising decomposition pathways.

In a concise synthesis of the unnatural enantiomer of the pyrrole alkaloid axinellamine, Mori and Seki condensed lithiated PT-sulfone **162** with enal **163** in THF solvent to yield diene intermediate **164** in moderate yield and with good stereoselectivity ($E:Z = 90:10$).[52] Repetition of the reaction with a BT-sulfone analogous to **162** under otherwise identical reaction

conditions gave **164** with slightly reduced stereoselectivity (E : Z = 87 : 13). Preparation of diene **164** *via* strategy (b) was also examined. Under unspecified reaction conditions, β,γ-unsaturated BT-sulfone **165** and non-conjugated aldehyde **166** gave **164** with predominantly *cis* stereochemistry about the newly formed alkene (E : Z = 40 : 60).[52] As noted above, the preparation of a conjugated alkene using strategy (b) is likely to yield the *cis* olefin if the aldehyde lacks an α-substituent. Williams and Clark also explored both strategies (a) and (b) to prepare the C19–C20 (*E*)-alkene of **204** towards phorboxazole A.[39] Treatment of the potassium metallate of PT-sulfone **202** with conjugated aldehyde **203** in DME solvent gave **204** in low yield (42%) and with disappointing stereoselectivity about the newly formed double bond (E : Z = 67 : 33). It should be emphasised that while a combination of KHMDS base–DME solvent is often optimum for the stereoselective formation of *non-conjugated* 1,2-disubstituted (*E*)-alkenes *via* PT-sulfones, the same reaction conditions are not necessarily the best for formation of *conjugated* 1,2-disubstituted (*E*)-alkenes *via* PT-sulfones. In any event, reversal of the coupling partners did not lead to an improved result. Reaction of the stabilised metallated sulfone **205** with non-conjugated aldehyde **206** produced the C19–C20 alkene of **204** with a strong bias towards the unwanted *cis* isomer (E : Z = 9 : 91) as might be predicted from the above. The Kende variant[36] of the classical Julia olefination employing an imidazolyl sulfone analogous to **202** was also examined and gave a 50% yield of **204** with an E : Z ratio of 82 : 18 about the C19–C20 alkene. The best result was finally obtained by Horner–Wadsworth–Emmons reaction between aldehyde **206** and an appropriate C19-phosphonate which gave 85% of **204** with E : Z = 80 : 20 about the C19–C20 alkene.[39]

Strategy (b) has been implemented to access conjugated 1,2-disubstituted (*E*)-alkenes from α-substituted aldehydes and β,γ-unsaturated heteroaryl sulfones with a high level of stereocontrol. McCarthy and co-workers prepared β-lactam **161**, a donor of the unusual amino acid ADDA, from β,γ-unsaturated BT-sulfone **159** and azetidinone aldehyde **160**.[53,100] The potassium metallate of **159** gave an optimum yield of diene **161** but the analogous sodium metallate gave higher stereoselectivity (E : Z = 80 : 20) albeit with a much reduced yield (*ca* 25%). Nakata's syntheses of the polyketide antibiotics reveromycins A and B provide more convincing examples.[101,102] Lithiated [5,6]-spirocyclic BT-sulfone **213** gave a single isomer of the reveromycin B intermediate **215** in 56% yield after treatment with α-silyloxyaldehyde **214** (76% yield based on the amount of recovered sulfone **213**).[101] Even better results were subsequently obtained when a related [6,6]-spirocyclic BT-sulfone **210** was reacted with the same aldehyde under near identical conditions to yield isomerically pure **212** in 90% yield *en route* to reveromycin A.[102] Williams and co-workers synthesised the unusual carbocyclic antibiotic lankacyclinol by a highly convergent and concise route which incorporated two modified Julia olefination reactions.[45] The first Julia reaction was used to conjoin β,γ-unsaturated BT-sulfone **182** with α-branched aldehyde **183** and gave (*E,E*)-diene **184** as a single isomer in moderate yield. The absence of a protective group on the primary hydroxy of sulfone **182** was not detrimental to the coupling reaction and allowed product **184** to be directly converted to aldehyde **185** in preparation for the second olefination reaction. Low temperature lithiation of the minimally protecting β,γ-unsaturated BT-sulfone **64** followed by addition of **185** in THF solvent gave 72% yield of the advanced lankacyclinol intermediate **186** again as a single isomer. Potential fragmentation of metallated **64** by loss of the allylic amido residue was not encountered and undesired adducts resulting from N ⟶ O acyl migration were also not produced. The skipped all *trans* tetraene **186** was subsequently elaborated to lankacyclinol in a further five steps.[45]

O'Doherty and Harris used benzyl PT-sulfone **179** in the synthesis of several biologically active styryllactone derived natural products including isoaltholactone.[103,104] Styrene **181** was prepared in low yield (40%) but with excellent stereoselectivity (E : Z > 93 : 7) by reaction of the potassium metallate of **179** with aldehyde **180** in THF solvent. In contrast, a Wittig reaction between **180** and benzylidene triphenylphosphorane gave styrene **181** (60% yield) in predominantly *cis* form (E : Z = 12 : 88).[104] Omura and co-workers synthesised the C8–C9 conjugated 1,2-disubstituted (*E*)-alkene of fungal metabolite nafuredin from β,γ-unsaturated PT-sulfone **193** and α-methyl aldehyde **194**.[97] Treatment of **193** with two equivalents of KHMDS in THF solvent followed by addition of aldehyde **194** gave the all *trans* isomer of **195** (79% yield) as the only detectable isomer. Allowing the reaction mixture to warm before quenching did not result in the desired formation of the C3–C4 epoxide moiety characteristic of nafuredin.

Strategy (c) was first explored by Kocienski and co-workers as a potential route to the rapamycin triene fragment **79** as discussed above.[26] Only one other example of this approach to polyene synthesis has been reported. Katsumura and co-workers conjoined polyunsaturated BT-sulfone **196** and polyunsaturated aldehyde **197** to yield a mixture of stereoisomers of the polyfunctional carotenoid peridinin **198**.[105] The C15–C15′ double bond of **198** was formed in 50% yield and with an E : Z ratio of 25 : 75 by the action of NaHMDS on a mixture of **196** and **197** in THF solvent at −78 °C. After standing at ambient temperature in a darkened benzene solution for three days, the polyolefinic system of **198** spontaneously isomerised to the natural all *trans* configuration.[105]

4.3 Synthesis of trisubstituted alkene targets

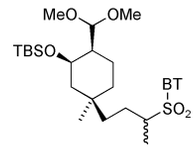
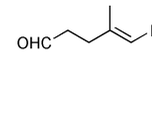
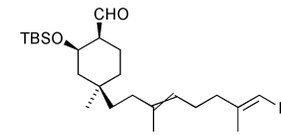
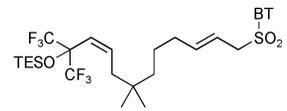
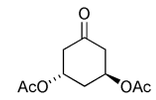
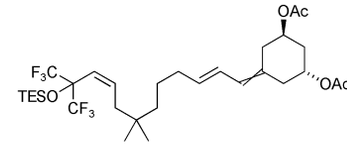
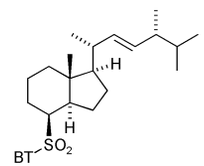
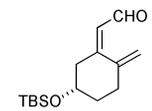
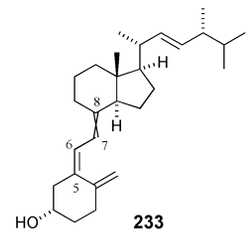
Very few trisubstituted alkenes *en route* to complex target molecules have been prepared with the modified Julia olefination (Table 5). Direct carbonyl olefination methods do not generally provide a satisfactory means for the stereocontrolled elaboration of trisubstituted alkenes and the modified Julia olefination proves no exception. Trisubstituted alkenes have been synthesised both from primary alkyl heteroarylsulfones and ketones, and secondary alkyl heteroarylsulfones and aldehydes.

The classical Julia olefination was first developed as an alternative to the Horner–Wittig reaction to construct the C7–C8 trisubstituted (*E*)-alkene of vitamin D_4.[17] Kocienski and co-workers recently prepared the closely related vitamin D_2 (**233**) using BT-sulfone based methodology.[49] A comparison of classical and modified Julia olefination routes to these biologically significant targets can now be made. Union of BT-sulfone **231** and dienal **232****** under highly optimised reaction conditions gave a 70% yield of a pair of vitamin D_2 isomers **233** following silyl ether deprotection. The C7–C8 trisubstituted double bond of vitamin D_2 was formed with modest stereoselectivity in favour of the natural (*E*)-configuration (E : Z = 72 : 38) and isomerisation about C5–C6 was not observed.[49] An analogous classical Julia olefination gave a 65% yield of four vitamin D_4 isomers, only 75% of the product mixture comprised the natural (5*Z*,7*E*)-isomer.[106]

Hilpert and Wirz prepared a structurally simplified vitamin D_3 analogue using C_2-symmetric ketone **229**. Coupling of lithiated β,γ-unsaturated BT-sulfone **228** and **229** under standard reaction conditions gave an excellent yield of triene **230** which was deprotected to yield Ro 65-2299, a potential antipsoriatic.[51] Trivial symmetrical ketones had previously been briefly examined as substrates in the modified Julia olefination.[13,25] Lastly, Maleczka and Mi have synthesised analogues of the platelet activating factor (PAF) antagonists phomactins A, C and D from a trisubstituted alkene (**227**) prepared with the modified Julia olefination.[107] The sodium metallate of BT-sulfone **225** was treated with aldehyde **226** in DME solvent

**** Dienal **232** exists in dynamic equilibrium with a 2*H*-pyran tautomer resulting from 6π-electron electrocyclisation.

Table 5 Synthesis of trisubstituted alkenes *via* the modified Julia olefination

Target molecule	Heteroaryl sulfone	Carbonyl compound	Reaction conditions[a]	Alkene product[b]	Yield (%)	$E:Z$[c]	Ref.
Phomactin	 **225**	 **226**	(a) *premetallate* NaHMDS, DME −78 °C ⟶ r.t. (b) AcOH, THF–H_2O	 **227**	66	57 : 43	107[d]
Ro 65-2299	 **228**	 **229**	*premetallate* LiHMDS, THF −78 °C ⟶ r.t.	 **230**	85	*n/a*	51[d]
Vitamin D_2	 **231**	 **232**	(a) *premetallate* NaHMDS, Et_2O −100 °C ⟶ r.t. (b) TBAF, THF	 **233**	70	72 : 38	49[d]

[a] *premetallate* = base added to sulfone and then carbonyl added, *Barbier* = base added to a mixture of sulfone and carbonyl. [b] Crossed double bond indicates newly formed alkene. [c] Isomeric ratio about crossed double bond. [d] Detailed experimental procedure provided.

and gave a 66% yield of **227** following acetal hydrolysis. A slight preference for the desired (*E*)-isomer of **227** was observed when the reaction was conducted in DME solvent (*E* : *Z* = 57 : 43), whereas in DMF solvent the (*Z*)-isomer was the major product (*E* : *Z* = 33 : 67). Alternative reaction conditions gave inferior

5 Conclusions and outlook

The modified Julia olefination is rapidly becoming one of the premier methods for advanced fragment linkage and many further applications of this new technology are likely to be reported in the near future. Excellent functional group compatibility together with the ability to alter stereoselectivity through a combination of solvent, base, and heterocycle effects add greatly to the versatility of the operationally simple one-pot method. BT- and PT-sulfone based variants of the modified Julia olefination have already had a significant impact on target directed synthesis and it remains to be seen whether other heteroarylsulfones, such as TBT- and PYR-sulfones, will also be adopted as standard synthetic tools. Further study of the mechanistic underpinnings of the reaction will no doubt lead to additional enhancements in stereoselectivity and efficiency.

To summarise the current state of the art regarding the modified Julia olefination, we conclude with an overview of a recent synthesis of *ent*-lasonolide A, the unnatural enantiomer of a cytotoxic macrolide isolated from a shallow water Caribbean sponge. Lee and co-workers deftly combined a variety of alkene forming methods to construct the different carbon–carbon double bond types present in *ent*-lasonolide A (Fig. 5).[108]

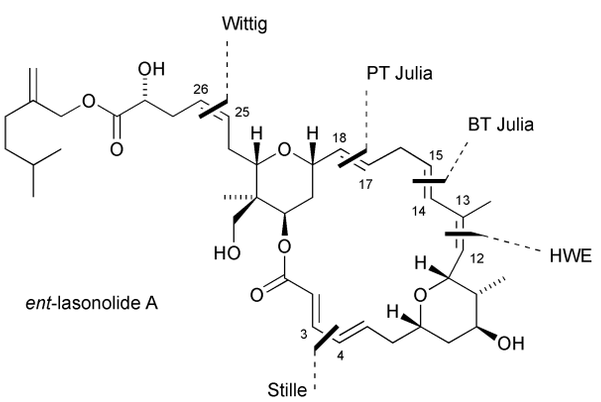
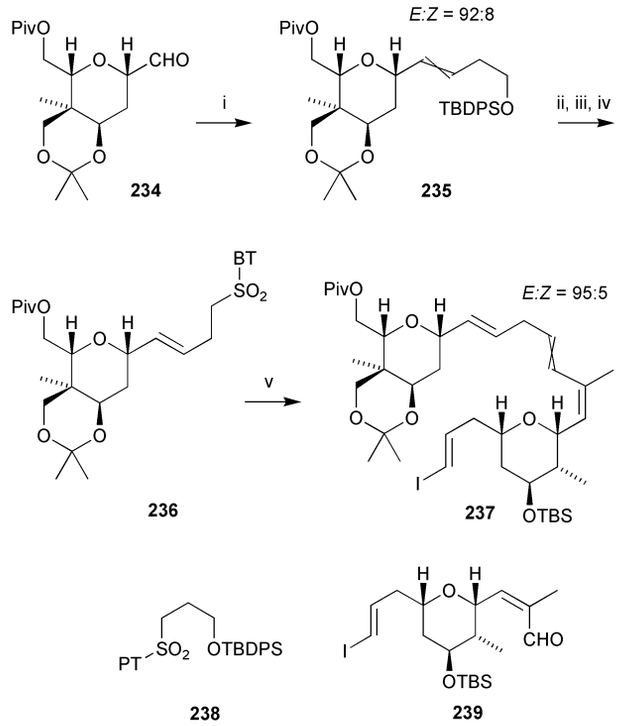


Fig. 5 Lee's strategy for the synthesis of *ent*-lasonolide A.[108]

BT and PT variants of the modified Julia olefination were directed at the respective syntheses of conjugated, and non-conjugated (*E*)-alkenes, while variants of the Wittig reaction were used to access (*Z*)-alkenes. Lithiated PT-sulfone **238** condensed with aldehyde **234** in a mixture of THF and HMPA to give a 67% yield of **235** and set the C17–C18 non-conjugated 1,2-disubstituted (*E*)-alkene of *ent*-lasonolide with excellent stereoselectivity (*E* : *Z* = 92 : 8) (Scheme 6). Following high yielding conversion of the silyl ether group of **235** into a BT-sulfone moiety, a second modified Julia reaction between sulfone **236** and α,β-unsaturated aldehyde **239** resulted in formation of the C14–C15 conjugated 1,2-disubstituted (*E*)-alkene of *ent*-lasonolide A with equally impressive stereoselectivity (*E* : *Z* (**237**) = 95 : 5). The Still–Gennari modification of the Horner–Wadsworth–Emmons (HWE) reaction[109] was used to prepare the C12–C13 trisubstituted (*Z*)-alkene of *ent*-lasonolide A within aldehyde fragment **239**, while a traditional Wittig reaction gave the C25–C26 non-conjugated 1,2-disubstituted (*Z*)-alkene of the target molecule during the final stages of the synthesis. Macrocyclisation was achieved with a Stille reaction[110] which forged the C3–C4 bond from appropriately tethered vinyl iodide and vinyl stannane moieties.



Scheme 6 *Reagents and conditions*: i, **238**, LiHMDS, THF–HMPA (5 : 1), −78 °C, then **234**, −78 °C ⟵ r.t., 12 h, 67%; ii, TBAF, THF, r.t., 3 h; iii, Ph_3P, DIAD, BTSH, THF, 0 °C, 1 h; iv, $(NH_4)_6Mo_7O_{24}$, H_2O_2, EtOH, 0 °C, 2 h, 89% from **235**; v, LDA, THF, −78 °C, then **239**, −78 °C ⟶ r.t., 10 h, 70%.

6 Acknowledgements

The Author thanks the Royal Society for a University Research Fellowship (RS URF).

7 References

1 K. C. Nicolaou, D. Vourloumis, N. Winssinger and P. S. Baran, *Angew. Chem., Int. Ed.*, 2000, **39**, 44.
2 *Preparation of Alkenes: A Practical Approach*, ed. J. M. J. Williams, Oxford University Press, Oxford, 1996.
3 S. E. Kelly, Alkene Synthesis, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, Oxford, 1991, Vol. 1, pp. 729–817.
4 (*a*) G. Wittig and G. Geissler, *Liebigs Ann. Chem.*, 1953, **580**, 44; (*b*) G. Wittig and U. Schöllkopf, *Chem. Ber.*, 1954, **87**, 1318.
5 Reviews: (*a*) E. Vedejs and M. J. Peterson, *Top. Stereochem.*, 1994, **21**, 1; (*b*) A. W. Johnson, *Ylides and Imines of Phosphorus*, Wiley, New York, 1993; (*c*) B. E. Maryanoff and A. B. Reitz, *Chem. Rev.*, 1989, **89**, 863.
6 (*a*) L. Horner, H. Hoffmann and H. G. Wippel, *Chem. Ber.*, 1958, **91**, 61; (*b*) L. Horner, H. Hoffmann, H. G. Wippel and G. Klahre, *Chem. Ber.*, 1959, **92**, 2499.
7 (*a*) W. S. Wadsworth and W. D. Emmons, *J. Am. Chem. Soc.*, 1961, **83**, 1733; (*b*) W. S. Wadsworth, *Org. React.*, 1977, **25**, 73.
8 D. J. Peterson, *J. Org. Chem.*, 1968, **33**, 780.
9 Reviews: (*a*) L. F. van Staden, D. Gravestock and D. J. Ager, *Chem. Soc. Rev.*, 2002, **31**, 195; (*b*) D. J. Ager, *Org. React.*, 1990, **38**, 1.
10 C. R. Johnson, J. R. Shanklin and R. A. Kirchhoff, *J. Am. Chem. Soc.*, 1973, **95**, 6462.
11 M. Julia and J.-M. Paris, *Tetrahedron Lett.*, 1973, 4833.
12 P. J. Kocienski, Reductive Elimination, Vicinal Deoxygenation and Vicinal Desilylation, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, Oxford, 1991, Vol. 6, pp. 975–1010.
13 J. B. Baudin, G. Hareau, S. A. Julia and O. Ruel, *Tetrahedron Lett.*, 1991, **32**, 1175.
14 P. J. Kocienski, B. Lythgoe and S. Ruston, *J. Chem. Soc., Perkin Trans. 1*, 1978, 829.
15 P. J. Kocienski, B. Lythgoe and D. A. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1978, 834.
16 P. J. Kocienski, B. Lythgoe and I. Waterhouse, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1045.
17 P. J. Kocienski, B. Lythgoe and S. Ruston, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1290.

18 Selected recent examples: (*a*) G. Zanoni, A. Porta and G. Vidari, *J. Org. Chem.*, 2002, **67**, 4346; (*b*) J. P. Marino, M. S. McClure, D. P. Holub, J. V. Comasseto and F. C. Tucci, *J. Am. Chem. Soc.*, 2002, **124**, 1664; (*c*) A. K. Ghosh, Y. Wang and J. T. Kim, *J. Org. Chem.*, 2001, **66**, 8973; (*d*) M. Horigone, H. Motoyoshi, H. Watanabe and T. Kitahara, *Tetrahedron Lett.*, 2001, **42**, 8207.
19 G. E. Keck, K. A. Savin and M. A. Weglarz, *J. Org. Chem.*, 1995, **60**, 3194.
20 P. Kocienski, *Phosphorus, Sulfur Relat. Elem.*, 1985, **24**, 97.
21 I. E. Markó, F. Murphy and S. Dolan, *Tetrahedron Lett.*, 1996, **37**, 2089.
22 A. R. Katritzky, X. Lan, J. Z. Yang and O. V. Denisko, *Chem. Rev.*, 1998, **98**, 409.
23 W. E. Truce, E. M. Kreider and W. W. Brand, *Org. React.*, 1970, **18**, 99.
24 (*a*) E. Hoggarth, *J. Chem. Soc.*, 1949, 3311; (*b*) T. P. Johnston and A. Gallagher, *J. Org. Chem.*, 1963, **28**, 1305; (*c*) J. Bourdais, D. Abenhaim, B. Sabourault and A. Lorre, *J. Heterocycl. Chem.*, 1976, **13**, 491; (*d*) P. Gayral, J. Bourdais, A. Lorre, D. Abenhaim, F. Dusset, M. Pommies and G. Fouret, *Eur. J. Med. Chem. Chim. Ther.*, 1978, **13**, 171; (*e*) Y. Nomoto, H. Takaj, T. Ohno and K. Kubo, *Chem. Pharm. Bull.*, 1991, **39**, 352; (*f*) C. Lorin and P. Rollin, *Synthesis*, 1998, 1506; (*g*) D. Gueyrard, C. Lorin, J. Moravcova and P. Rollin, *J. Carbohydr. Chem.*, 1999, **18**, 317.
25 J. B. Baudin, G. Hareau, S. A. Julia, R. Lorne and O. Ruel, *Bull. Soc. Chim. Fr.*, 1993, **130**, 856.
26 R. Bellingham, K. Jarowicki, P. Kocienski and V. Martin, *Synthesis*, 1996, 285.
27 N. D. Smith, P. J. Kocienski and S. D. A. Street, *Synthesis*, 1996, 652.
28 A. B. Charette and H. Lebel, *J. Am. Chem. Soc.*, 1996, **118**, 10327.
29 P. R. Blakemore, W. J. Cole, P. J. Kocienski and A. Morley, *Synlett*, 1998, 26.
30 J. B. Baudin, G. Hareau, S. A. Julia and O. Ruel, *Bull. Soc. Chim. Fr.*, 1993, **130**, 336.
31 P. R. Blakemore, Development and application of the one-pot Julia olefination, PhD Thesis, University of Glasgow, Glasgow, 1999.
32 A. B. Charette, C. Berthelette and D. St-Martin, *Tetrahedron Lett.*, 2001, **42**, 5149.
33 A. B. Charette, C. Berthelette and D. St-Martin, *Tetrahedron Lett.*, 2001, **42**, 6619.
34 P. J. Kocienski, A. Bell and P. R. Blakemore, *Synlett*, 2000, 365.
35 P. J. Kocienski, A. G. Bell and P. R. Blakemore, unpublished results.
36 A. S. Kende and J. S. Mendoza, *Tetrahedron Lett.*, 1990, **31**, 7105.
37 D. A. Evans, P. H. Carter, E. M. Carreira, A. B. Charette, J. A. Prunet and M. Lautens, *J. Am. Chem. Soc.*, 1999, **121**, 7540.
38 S. Hanessian, L. D. Cantin and D. Andreotti, *J. Org. Chem.*, 1999, **64**, 4893.
39 D. R. Williams and M. P. Clark, *Tetrahedron Lett.*, 1999, **40**, 2291.
40 S. C. Yoon and K. Kim, *Heterocycles*, 1995, **41**, 103.
41 H. Quast and L. Bieber, *Chem. Ber.*, 1981, **114**, 3253.
42 M. E. Peach, Thiols as Nucleophiles, in *The Chemistry of the Thiol Group*, ed. S. Patai, Wiley, New York, 1974, Pt. 2, pp. 721–784.
43 Reviews: (*a*) D. L. Hughes, *Org. React.*, 1992, **42**, 335; (*b*) O. Mitsunobu, *Synthesis*, 1981, 1.
44 C. Ahn, R. Correia and P. DeShong, *J. Org. Chem.*, 2002, **67**, 1751.
45 D. R. Williams, G. S. Cortez, S. L. Bogen and C. M. Rojas, *Angew. Chem., Int. Ed.*, 2000, **39**, 4612.
46 P. R. Blakemore, P. J. Kocienski, A. Morley and K. Muir, *J. Chem. Soc., Perkin Trans. 1*, 1999, 955.
47 A. B. Smith, III, C. M. Adams, S. A. Kozmin and D. V. Paone, *J. Am. Chem. Soc.*, 2001, **123**, 5925.
48 A. B. Smith, III, T. J. Beauchamp, M. J. LaMarche, M. D. Kaufman, Y. Qiu, H. Arimoto, D. R. Jones and K. Kobayashi, *J. Am. Chem. Soc.*, 2000, **122**, 8654.
49 P. R. Blakemore, P. J. Kocienski, S. Marzcak and J. Wicha, *Synthesis*, 1999, 1209.
50 R. Metternich, D. Denni, B. Thai and R. Sedrani, *J. Org. Chem.*, 1999, **64**, 9632.
51 H. Hilpert and B. Wirz, *Tetrahedron*, 2001, **57**, 681.
52 M. Seki and K. Mori, *Eur. J. Org. Chem.*, 2001, 503.
53 D. J. Cundy, A. C. Donohue and T. D. McCarthy, *J. Chem. Soc., Perkin Trans. 1*, 1999, 559.
54 S. Uemura, Oxidation of Sulfur, Selenium and Tellurium, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, Oxford, 1991, Vol. 7, pp. 757–787.
55 D. J. Procter, *J. Chem. Soc., Perkin Trans. 1*, 2001, 335 and earlier reviews in the series.
56 A. S. Rao and H. R. Mohan, in *Encyclopedia of Reagents for Organic Synthesis*, ed. L. A. Paquette, Wiley, Chichester, 1995, Vol. 2, pp. 1192–1198.
57 H. S. Schultz, H. B. Freyermuth and S. R. Buc, *J. Org. Chem.*, 1963, **28**, 1140.
58 A. Sivaramakrishnan, G. T. Nadolski, I. A. McAlexander and B. S. Davidson, *Tetrahedron Lett.*, 2002, **43**, 213.
59 J. Mulzer and E. Öhler, *Angew. Chem., Int. Ed.*, 2001, **40**, 3842.
60 P. Liu and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2001, **123**, 10772.
61 S. V. Ley, A. C. Humphries, H. Eick, R. Downham, A. R. Ross, R. J. Boyce, J. B. J. Pavey and J. Pietruszka, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3907.
62 Y. Nezu, M. Miyazaki, K. Sugiyama, N. Wada, I. Kajiwara and T. Miyazawa, *Pestic. Sci.*, 1996, **47**, 115.
63 P. T. Gallagher, B. Iddon and H. Suschitzky, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2362.
64 P. A. Ramazanova, M. V. Vagabov, A. V. Tarakanova, N. G. Akhmedov and A. V. Anisimov, *Vestn. Mosk. Univ., Ser. 2: Khim.*, 2000, **41**, 119.
65 S. R. El-Ezbawy and M. A. Alshaikh, *J. Chem. Technol. Biotechnol.*, 1990, **47**, 209.
66 K. Nagarajan, V. P. Arya, T. George, V. Sudarsanam, R. K. Shah, A. N. Goud, S. J. Shenoy, V. Honkan, Y. S. Kulkami and M. K. Rao, *Indian J. Chem., Sect. B*, 1982, **21**, 928.
67 Y. Ueno, A. Kojima and M. Okawara, *Chem. Lett.*, 1984, 2125.
68 L. V. Alam, R. V. Kharbash and G. I. Koldobskii, *Russ. J. Org. Chem.*, 2000, **36**, 916.
69 K. Ohta, E. Kawachi, N. Inoue, H. Fukasawa, Y. Hashimoto, A. Itai and H. Kagechika, *Chem. Pharm. Bull.*, 2000, **48**, 1504.
70 V. Khanna, G. C. Maikap and J. Iqbal, *Tetrahedron Lett.*, 1996, **37**, 3367.
71 D. A. Evans and G. C. Andrews, *Acc. Chem. Res.*, 1974, **7**, 147.
72 M. G. Banwell and K. J. McRae, *J. Org. Chem.*, 2001, **66**, 6768.
73 W. Liu, J. M. Szewczyk, L. Waykole, O. Repic and T. J. Blacklock, *Tetrahedron Lett.*, 2002, **43**, 1373.
74 F. R. Kinder, S. Wattanasin, R. W. Versace, K. W. Bair, J. Bontempo, M. A. Green, Y. J. Lu, H. R. Marepalli, P. E. Phillips, D. Roche, L. D. Tran, R. M. Wang, L. Waykole, D. D. Xu and S. Zabludoff, *J. Org. Chem.*, 2001, **66**, 2118.
75 H. W. Lam and G. Pattenden, *Angew. Chem., Int. Ed.*, 2002, **41**, 508.
76 T. Suzuki, K. Ohmori and K. Suzuki, *Org. Lett.*, 2001, **3**, 1741.
77 M. S. Ermolenko and P. Potier, *Tetrahedron Lett.*, 2002, **43**, 2895.
78 M. J. Lear and M. Hirama, *Tetrahedron Lett.*, 1999, **40**, 4897.
79 D. R. Williams, D. A. Brooks and M. A. Berliner, *J. Am. Chem. Soc.*, 1999, **121**, 4924.
80 M. Lautens, J. T. Colucci, S. Hiebert, N. D. Smith and G. Bouchain, *Org. Lett.*, 2002, **4**, 1879.
81 A. B. Smith, III, I. G. Safonov and R. M. Corbett, *J. Am. Chem. Soc.*, 2001, **123**, 12426.
82 E. Lee, S. J. Choi, H. Kim, H. O. Han, Y. K. Kim, S. J. Min, S. H. Son, S. M. Lim and W. S. Jang, *Angew. Chem., Int. Ed.*, 2002, **41**, 176.
83 T. A. Kirkland, J. Colucci, L. S. Geraci, M. A. Marx, M. Schneider, D. E. Kaelin and S. F. Martin, *J. Am. Chem. Soc.*, 2001, **123**, 12432.
84 D. Potts, P. J. Stevenson and N. Thompson, *Tetrahedron Lett.*, 2000, **41**, 275.
85 M. B. Cid and G. Pattenden, *Tetrahedron Lett.*, 2000, **41**, 7373.
86 F. Compostella, L. Franchini, L. Panza, D. Prosperi and F. Ronchetti, *Tetrahedron*, 2002, **58**, 4425.
87 D. Crich and V. Dudkin, *J. Am. Chem. Soc.*, 2002, **124**, 2263.
88 J. R. Al Dulayymi, M. S. Baird and E. Roberts, *Tetrahedron Lett.*, 2000, **41**, 7107.
89 S. H. Kang, J. W. Jeong, Y. S. Hwang and S. B. Lee, *Angew. Chem., Int. Ed.*, 2002, **41**, 1392.
90 H. McAlonan, D. Potts, P. J. Stevenson and N. Thompson, *Tetrahedron Lett.*, 2000, **41**, 5411.
91 D. S. Stoianova and P. R. Hanson, *Org. Lett.*, 2000, **2**, 1769.
92 J. A. Lafontaine, D. P. Provencal, C. Gardelli and J. W. Leahy, *Tetrahedron Lett.*, 1999, **40**, 4145.
93 M. G. B. Drew, L. M. Harwood, A. Jahans, J. Robertson and S. Swallow, *Synlett*, 1999, 185.
94 M. I. Colombo, J. Zinczuk, M. P. Mischne and E. A. Rúveda, *Tetrahedron: Asymmetry*, 2001, **12**, 1251.
95 G. Pattenden, A. T. Plowright, J. A. Tornos and T. Ye, *Tetrahedron Lett.*, 1998, **39**, 6099.
96 D. A. Evans, V. J. Cee, T. E. Smith, D. M. Fitch and P. S. Cho, *Angew. Chem., Int. Ed.*, 2000, **39**, 2533.

97 D. Takano, T. Nagamitsu, H. Ui, K. Shiomi, Y. Yamaguchi, R. Masuma, I. Kuwajima and S. Omura, *Org. Lett.*, 2001, **3**, 2289.
98 A. B. Smith, III and Z. Wan, *J. Org. Chem.*, 2000, **65**, 3738.
99 A. B. Smith, III and B. M. Brandt, *Org. Lett.*, 2001, **3**, 1685.
100 D. J. Cundy, A. C. Donohue and T. D. McCarthy, *Tetrahedron Lett.*, 1998, **39**, 5125.
101 T. Masuda, K. Osako, T. Shimizu and T. Nakata, *Org. Lett.*, 1999, **1**, 941.
102 T. Shimizu, T. Masuda, K. Hiramoto and T. Nakata, *Org. Lett.*, 2000, **2**, 2153.
103 J. M. Harris and G. A. O'Doherty, *Org. Lett.*, 2000, **2**, 2983.
104 J. M. Harris and G. A. O'Doherty, *Tetrahedron*, 2001, **57**, 5161.
105 N. Furuichi, H. Hara, T. Osaki, H. Mori and S. Katsumura, *Angew. Chem., Int. Ed.*, 2002, **41**, 1023.
106 P. R. Blakemore, P. Grzywacz, P. J. Kocienski, S. Marczak and J. Wicha, *Pol. J. Chem.*, 1999, **73**, 1209.
107 B. Mi and R. E. Maleczka, *Org. Lett.*, 2001, **3**, 1491.
108 E. Lee, H. Y. Song, J. W. Kang, D. S. Kim, C. K. Jung and J. M. Joo, *J. Am. Chem. Soc.*, 2002, **124**, 384.
109 W. C. Still and C. Gennari, *Tetrahedron Lett.*, 1983, **24**, 4405.
110 Reviews: (*a*) V. Farina, V. Krishnamurthy and W. J. Scott, *Org. React.*, 1997, **50**, 1; (*b*) T. N. Mitchell, *Synthesis*, 1992, 803.