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Expanding the Potential of Heteroaryl Vinyl Sulfones

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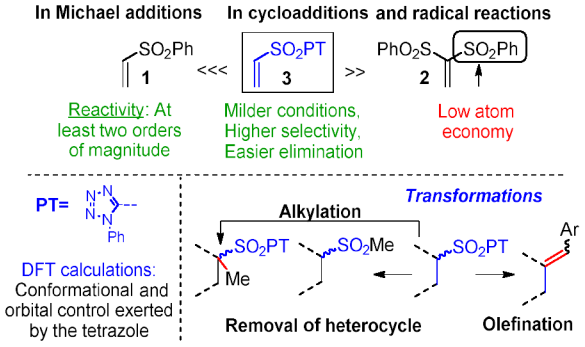
ABSTRACT



The easily available vinyl sulfone **3** showed a great potential for new applications in several fields, such as organic synthesis and bioconjugates formation. This was demonstrated by performing a systematic assessment of its reactivity in Michael, radical and cycloaddition reactions. Heteroaryl vinyl sulfone **3** presented an excellent output in terms of reactivity and selectivity, proving superior to phenyl vinyl sulfone **1** and with clear advantages over bis-sulfone **2**. This behavior might be due to the conformational and orbital control exerted by the tetrazole unit according to DFT calculations. Moreover, some alternative transformations to the Julia-Kocienski olefination on the obtained products are also described.

Introduction

Vinyl sulfones are important not only for their well established synthetic utility[1] but also they have interest in medicinal chemistry as they have proven to inhibit several enzymatic processes.[2] Moreover, they have been used in bioconjugation and immobilization of biomolecules due to the mild conditions required to react with the amine and thiol groups naturally present in biomolecules.[3] Although vinyl sulfones have demonstrated their value as synthons and building

blocks in organic chemistry in a plethora of very different reactions,[1] including asymmetric version,[4] they have been used mainly as Michael acceptors and dipolarophiles in cycloaddition reactions.[1]

Phenylsulfonylethylene **1** has been extensively employed as a model to explore new synthetic methods.[5 6 7 8 9] Nevertheless, **1** displayed a very low or null reactivity in some reactions. As a result, the presence of a second electron withdrawing group at the geminal position was necessary to increase the reactivity of the double bond. Consequently, 1,1-bis(sulfonyl)ethylene **2** became a common building block especially in organocatalytic processes,[10] being alkylation and partial or complete desulfonylation the most common transformations subsequently performed. Although vinyl sulfone **2** has been used in a wide variety of reactions, the presence of the two sulfonyl groups has some drawbacks, such as the evident low atom economy of the whole process and the difficulties of using the obtained adducts as substrates in olefination reactions.

Very recently, and conscious of this limitation, we have demonstrated that the introduction of a phenyltetrazole ring at the sulfur atom provides a highly reactive electrophile **3** (Figure 1) [11,12] with new interesting synthetic possibilities,[13] as this group has been successfully used in Julia-Kocienski olefinations.[14]

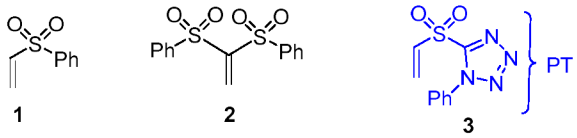
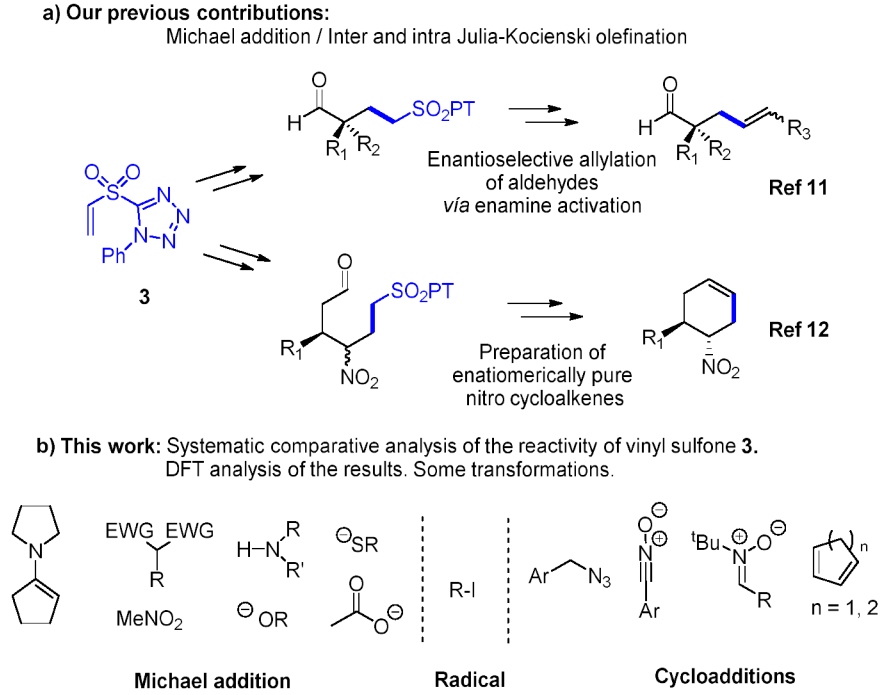


Figure 1. Traditional aryl and new heteroaryl vinyl sulfones

We have described the participation of this new inexpensive and readily available vinyl sulfone **3** in sequential Michael/Julia-Kocienski processes in both inter and intramolecular version, thus making possible the introduction of a variety of substituents through both ends of the vinyl moiety (Scheme 1, a).[11,12] This strategy has allowed us to prepare frameworks difficult to obtain by other ways such as the enantioselective allylation of aldehydes *via* enamine activation[11] and functionalized cyclohexenes in enantiomerically pure form[12] (scheme 1, a). Furthermore, using this heteroaryl vinyl sulfone **3**, new enantioselective applications have also arisen by Ooi[15] in the formal α-allylation of nitroalkanes; by Namboothiri in the enantioselective synthesis of α-amino-

γ-sulfonyl phosphonates;[16] and by Mukherjee in a catalytic asymmetric formal γ-allylation of deconjugated butenolides.[17]

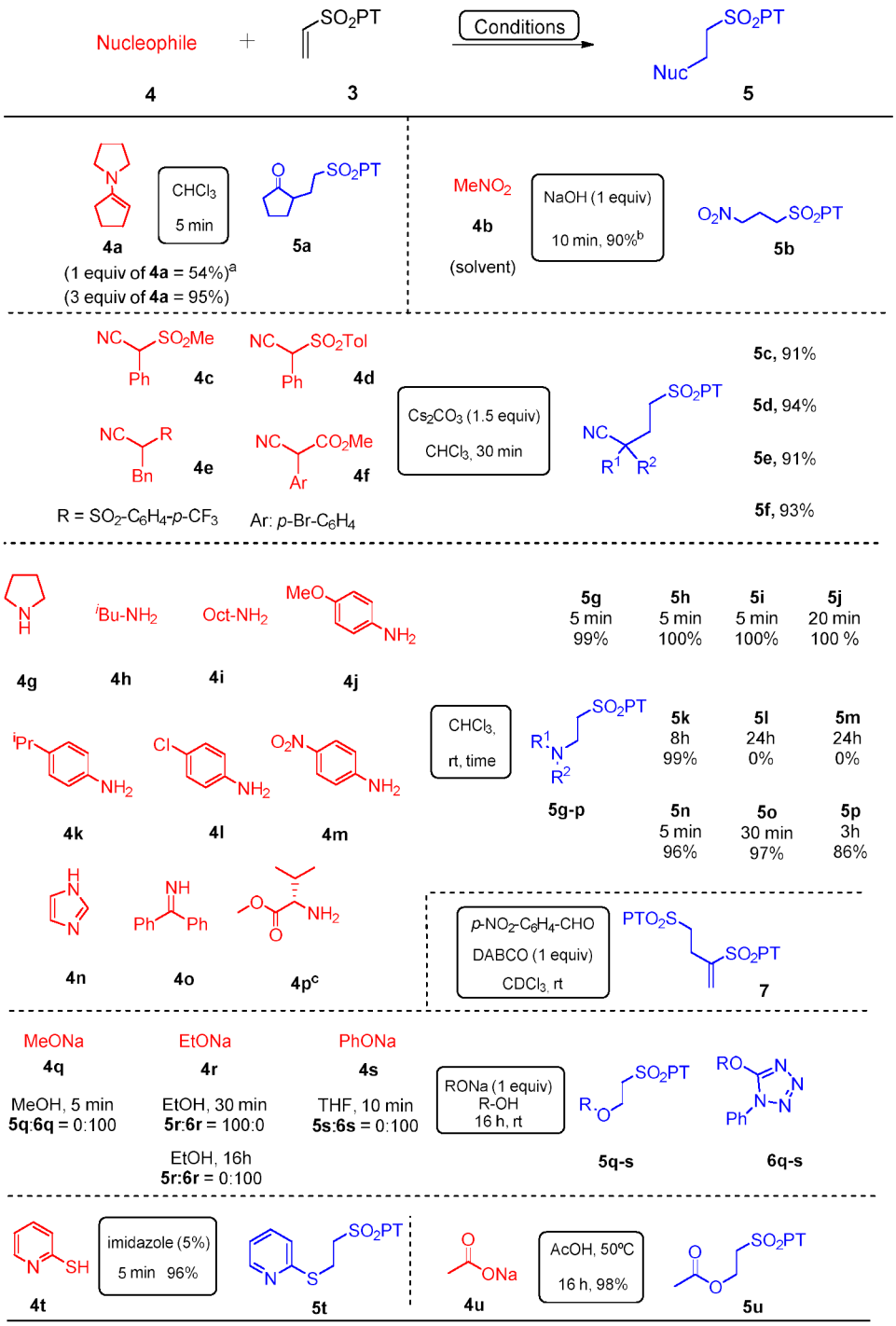
A basic and systematic analysis of the reactivity of sulfone **3** would give a good assessment to design new transformations including those that imply asymmetric catalysis. For this purpose, we have systematically analysed the Michael addition of different soft carbon nucleophiles and heteronucleophiles to vinyl sulfone **3**, as well as radical reactions and cycloadditions (Scheme 1, b) and we have compared its reactivity with **1** and **2** through different competition experiments. Moreover, the facts determining its excellent reactivity have been analysed by DFT calculations. Finally, in order to extend the applicability of sulfone **3**, we have also performed some synthetic transformations on the resulting alkyl heteroaryl sulfone.



Scheme 1. Developed transformations with vinyl sulfone **3** and description of the work presented herein.

Results and Discussion

We firstly explored the reactivity of vinyl sulfone **3** as Michael acceptor using different soft carbon nucleophiles such as enamines, nitromethane, cyanoesters and cyanosulfones; and heteronucleophiles such as amines, alkoxides, thiolates and carboxylates. All these results are depicted in Table 1.



[a] Adduct **5g** was also obtained.
[b] In lower scale than 0,5 g the reaction occurs in higher yield and shorter reaction time.
[c] A H_2O : THF = 5:1 was used as solvent

Table 1. Evaluation of the reactivity of heteroaryl vinyl sulfone **3** with different carbon nucleophiles and heteronucleophiles **4**.

As mentioned before, we have proven that vinyl sulfone **3** is able to react with enamines to generate quaternary centers in a catalytic and enantioselective manner (Scheme 1 a).[11] To assess

the reactivity of **3** with enamines in a stoichiometric manner, we carried out the reaction with commercially available **4a**. We could observe that the Michael reaction was almost instantaneous to provide the cyclopentanone **5a**. Nevertheless, the pyrrolidine liberated to the reaction media underwent Michael addition to vinyl sulfone **3** to provide **5g**, lowering the yield of **5a** to 54% when only one equivalent of enamine **4a** was used. This problem could be sorted out with the use of 3 equiv of enamine **4a**, providing **5a** in 95% yield.

Having investigated enamines, we next explored the reactivity of nitromethane. To avoid double and triple Michael additions, we used the conditions that had been previously developed for a diasteroselective aza-Henry methodology between nitromethane and sulfinyl imines in our group.[18] In this way, using nitromethane as solvent and NaOH as base, [12] the corresponding adduct **5b** was obtained in 90% yield in a scale of 0.5 g. These conditions are also recorded in Table 1. The reactivity of diactivated nucleophiles, typically employed in asymmetric catalysis using chiral bases,[19] bifunctional Takemoto-type thiourea catalysts[20] or phase transfer activation,[21] was also studied. Substituted cyanosulfones **4c-e** and cyanoester **4f** provided the corresponding Michael adducts in excellent yields (91-94%) under very mild conditions, which shows the potential of these activation modes in future strategies to form compounds with quaternary stereocenters in an enantioselective way.[22]

The introduction of amines as heteronucleophiles is not only interesting from a synthetic point of view[23] but it is also an attractive methodology for bioconjugation.[3] The use of very reactive vinyl sulfones present interest: the milder the conditions to produce the Michael addition of the amino groups present in the corresponding biomolecule are, the more compatible they will be with the biological function.

As we had observed in the experiment with the enamine **4a**, the released pyrrolidine **4g** reacted almost instantaneously with vinyl sulfone **3** (see note a, Table 1). We obtained the Michael adduct **5g** in an almost quantitative yield when mixing pyrrolidine **4g** and vinyl sulfone **3**. The reaction also worked when we used different aliphatic primary amines **4h** and **4i**. The reaction with aromatic primary amines took place when electron donating groups were present in the molecule (**4j** and **4k**) leading to adducts **5j** and **5k**, although in these cases we needed longer reaction times

in comparison with aliphatic amines. When deactivating groups such as Cl or NO_2 were bonded to the aromatic ring (anilines **4l** and **4m**), the Michael addition did not occur at room temperature, presumably due to the lower nucleophilicity of these amines. Imidazole **4n** also afforded the Michael adduct, and we obtained adduct **5o** from the addition of the corresponding imine **4o**.

Taking advantage of the excellent reactivity that the amines presented in the Michael addition with vinyl sulfone **3**, we decided to test this reaction with a protected amino acid in an aqueous medium. We utilized the methyl ester of L-valine after *in-situ* liberation of its hydrochloride salt. The reaction provided the adduct **5p** in 86% yield. All the experiments displayed above revealed that vinyl sulfone **3** could be used in bioconjugation processes.[3]

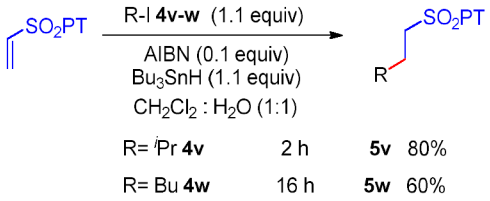
Interestingly, with the intention to obtain the corresponding Morita-Baylis-Hillman adduct,[24] we used a tertiary amine such as DABCO in the presence of *p*-nitrobenzaldehyde. However, we only detected the self-condensation product **7** in the crude mixture. This experiment demonstrated that vinyl sulfone **3** presents higher electrophilicity than *p*-nitrobenzaldehyde, which remained unaltered under the reaction conditions. Compound **7** was also formed in the absence of aldehyde.

The study of alkoxides as heteronucleophiles turned out to be more complicated. A small alkoxide, such as sodium methoxide **4q** in MeOH, showed preference towards the electrophilic carbon of the tetrazole ring to provide only compound **6q** in a fast and clean manner. When sodium ethoxide **4r** was used in EtOH as solvent, we could isolate the Michael product **5r** stopping the reaction at short times (30 minutes). However, longer reaction times led to the formation of compound **6r** in the reaction crude, due to the attack of the ethoxide to the electrophilic carbon of the tetrazole, even using only 1 equivalent of nucleophile **4r**. Sodium phenoxide **4s** in THF also showed preference for the attack to the carbon of the tetrazole affording compound **6s**. As it will be seen below, taking advantage of this reactivity, alkoxides will be used to remove the heterocycle in a more functionalized compound (Scheme 7).

Thiols are also used as functional groups for bioconjugation as they are easily deprotonated in the presence of histidine, being the imidazole ring of this amino acid the one that acts as a base.[1c] We verified that the addition of mercaptopyridine **4t** to the vinyl sulfone **3** took place smoothly after

1 h using 5 mol% of imidazole, to afford the corresponding adduct **5t** in 94% yield. It is important to note that the product of addition of imidazole **5n** was also detected when it was used in a higher loading (20 mol%). Regarding carboxylates, vinyl sulfone **3** underwent the Michael addition of sodium acetate to afford product **5u** in an almost quantitative yield (98%) when heating at 50 ºC in acetic acid as solvent.

Once analysed the relative reactivity of vinyl sulfone **3** in Michael addition reactions using nucleophilic reagents, we next evaluated the analogous processes in radical reactions (Scheme 2). Radical addition to vinyl sulfones is another well-described reaction.[25] Using classical conditions for the formation of radicals, alkyl iodide **4v** reacted successfully with vinyl sulfone **3**, affording product **5v** in an 80% yield. Even a primary iodide such as **4w** reacted with vinyl sulfone **3**, giving the corresponding aliphatic sulfone **5w** (60% yield).



Scheme 2. Radical addition of alkyl iodides **4w** and **4x** to vinyl sulfone **3.**

Once the performance of vinyl sulfone **3** in Michael additions and in radical reactions was established, we proceeded to compare its reactivity with the corresponding one of vinyl sulfones **1** and **2** (Tables 2 and 3, respectively). To this end, we carried out competition experiments with a series of representative selected nucleophiles previously used. For these competition experiments, we combined 0.1 mmol of vinyl sulfone **3** with 0.1 mmol of either **1** or **2**, adding subsequently one equivalent of the nucleophile (in Michael additions) or the corresponding alkyl iodide (in radical reaction).

The results of the competition experiments between vinyl sulfones **1** and **3** turned out to be quite conclusive (Table 2).

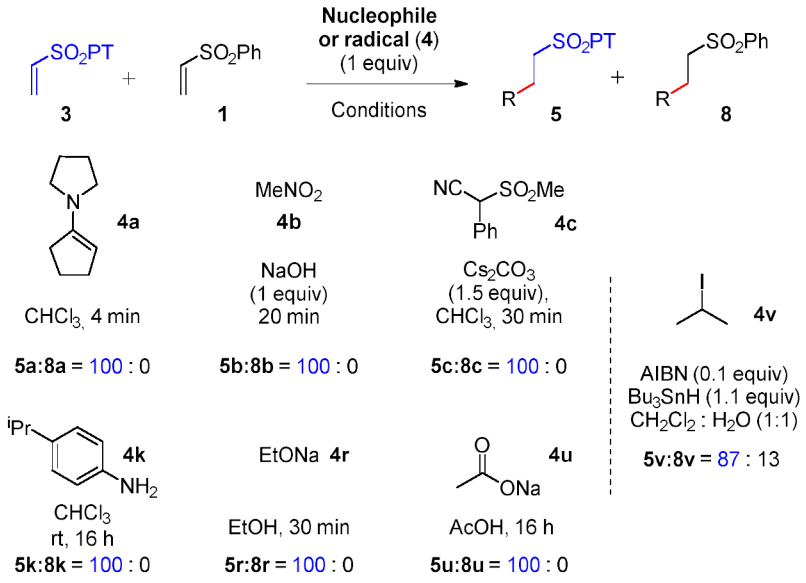


Table 2. Competition experiments between vinyl sulfones **1** and **3** in Michael and radical addition.

With both carbonucleophiles and heteronucleophiles **4**, vinyl sulfone **3** proved to be, in all the cases, at least two orders of magnitude more reactive than the monosubstituted phenyl vinyl sulfone **1**, since the corresponding adducts **8** were not detected in any of the competition experiments. Only in the case of the radical reaction, using 2-iodopropane **4v** as alkyl iodide, we observed an 87:13 mixture of adducts **5v** and **8v** in the reaction crude.

On the contrary, the competition experiments between vinyl sulfones **2** and **3** were more complicated (Table 3). In some cases, when both vinyl sulfones were present in the same reaction vial, they provided complex reaction mixtures. Therefore, in those cases we followed a different strategy, namely monitoring the reactions separately on different flasks and stopping the reactions after the same times in order to get comparable data. Such was the case of enamine **4a**, that underwent almost instantaneous reaction in separated flasks with both vinyl sulfones.[26] The competition experiment using nitromethane **4b** as solvent, suggested a similar reactivity for both sulfones since after 20 minutes we observed a mixture **5b**:**9b** = 50:50, with the total disappearance of the starting sulfones.

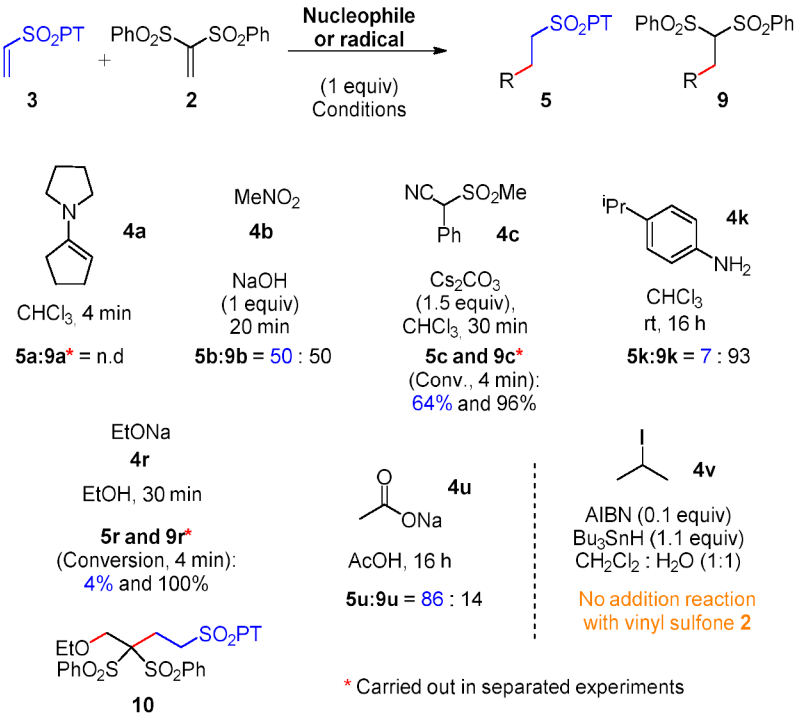


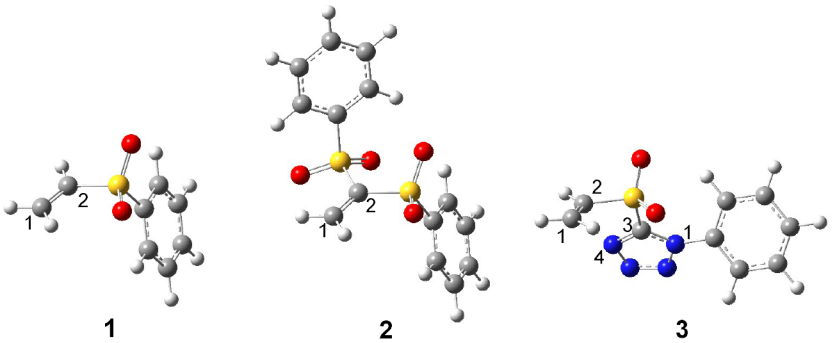
Table 3. Competition experiments between vinyl sulfones **2** and **3** in Michael and radical addition.

The reactivity of vinyl sulfone **2** was slightly higher than the one observed for vinyl sulfone **3** with cyanosulfone **4c**, but much higher in the case of the aromatic amine **4k**, (**5k**:**9k** = 7:93) and sodium ethoxide **4r** (4% conversion versus 100% in separated flasks). Interestingly, we could isolate product **10** in a very high yield (94%) when sodium ethoxide was mixed with both vinyl sulfones. A Michael addition between **4r** and vinyl sulfone **2** followed by an attack of the anion formed at the α-position of the sulfonyl groups to vinyl sulfone **3,** would explain the formation of compound **10**. Surprisingly, the competition reaction with sodium acetate **4u** in acetic acid showed a mixture of products in favour of the corresponding adduct from vinyl sulfone **3** (84:16).

We could not carry out the competition experiment in the radical addition reaction, as vinyl sulfone **2** did not react with alkyl iodide **4v**, but the reduction of the double bond took place instead. Therefore, these results confirmed again that vinyl sulfone **3** could be a very interesting electrophile for this type of processes.

In order to understand the origin of the different reactivity of sulfones **1-3,** we carried out a theoretical analysis of their structures by DFT calculations (Figure 2, see Supporting Information

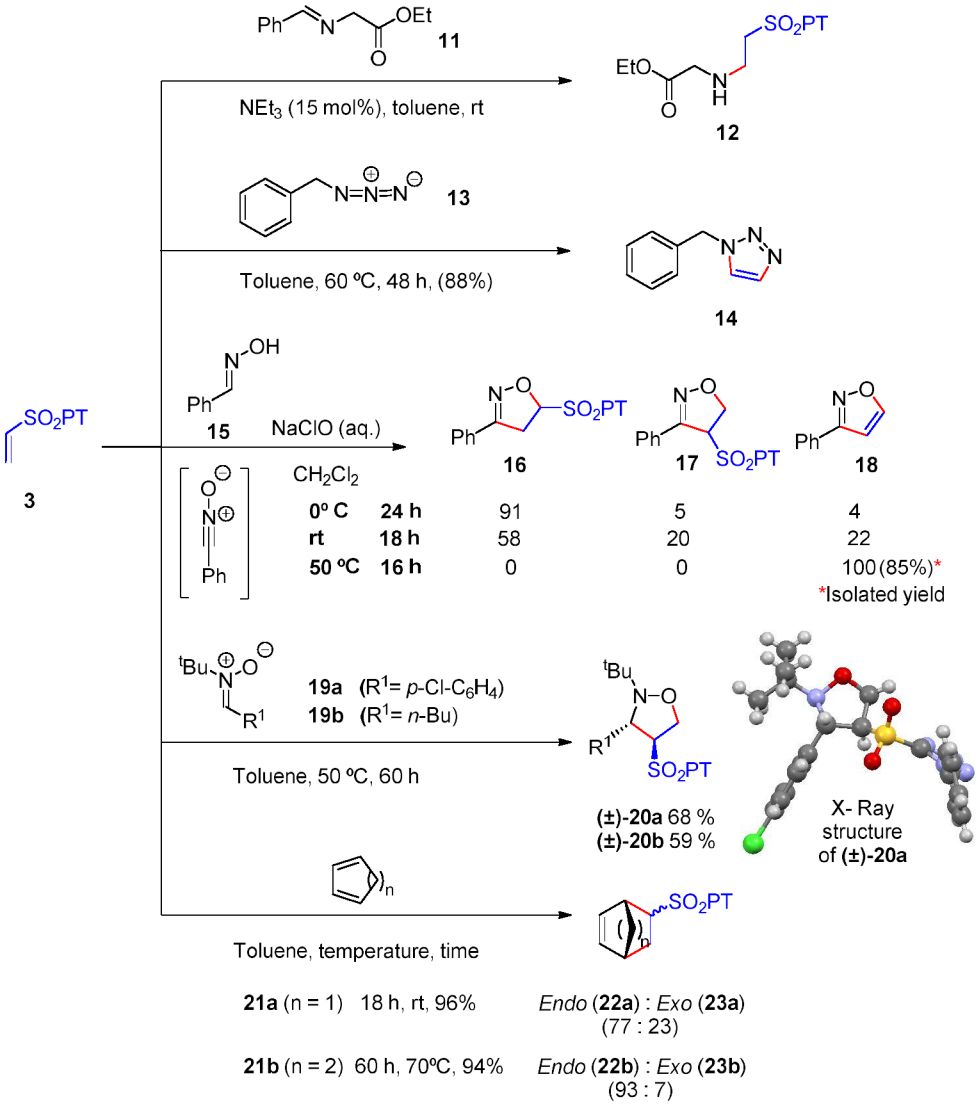
for details). The differences between the natural charge of the carbons that form the reactive double bond suggest a higher polarization of this bond in the case of compound **2** (Δq= 0.27), carrying two electron-withdrawing groups, than in the case of compounds **3** (Δq= 0.17) and **1** (Δq= 0.14). Thus, a higher reactivity against a nucleophile could be expected for **2** followed by **3** and **1** which is in agreement with many of the experimental results summarized in tables 2 and 3. Interestingly, the reactivity of sulfone **3** could be enhanced in acid media by protonation of the tetrazole unit which could explain the reverse selectivity found in the case of the reaction of sulfones **3** and **2** with sodium acetate (**5u:9u** = 86:14, table 3). Thus, the structure of sulfone **3** protonated at N(4) showed a stronger polarized double bond (Δq= 0.32, see SI). Another feature that strongly varies for these compounds is the dipole moment value. Sulfone **2**, due to the *anti* arrangement of both sulfonyl groups, showed, as expected, the lowest value. In the case of structures **3** and **1**, the presence of the tetrazole ring in the former one also determines an important variation due to the nitrogen atoms as well as a control of the conformation of the aryl moiety (torsion angle C2-S-C3-N1 = -164.5°). Changes in these values between starting materials and transition states are usually responsible for important variations in reactivity, depending on the reaction conditions.



Comp.	qC_1	qC_2	Δq	μ
1	-0.31	-0.45	0.14	5.383
2	-0.27	-0.54	0.27	0.661
3	-0.28	-0.45	0.17	2.833

Figure 2. Optimized structures of sulfones **1-3** [M062X/6-311+g(d,p)]. Natural charges (q_i) from the NBO analysis and dipole moment (Debye) are indicated.

Then, we studied the behavior of **3** in cycloaddition reactions. Vinyl sulfones have been widely employed in 1,3-dipolar processes and in Diels–Alder reactions. For this study, we used an azomethine ylide, benzyl azide, phenyl nitrile oxide and several nitrones as dipoles; and cyclopentadiene and cyclohexadiene for Diels–Alder reaction. All the results are summarized in Scheme 3.



Scheme 3. Evaluation of the reactivity of heteroaryl vinyl sulfone **3** with different dipoles and dienes.

Azomethine yilde **11** is a commonly used dipole with aryl[4a] and even heteroaryl vinyl sulfones.[13a, 27] However, in the reaction of **11** with vinyl sulfone **3** using triethylamine as base, we did not observe the expected functionalized pyrrolidine, but traces of product **12**. We also obtained this

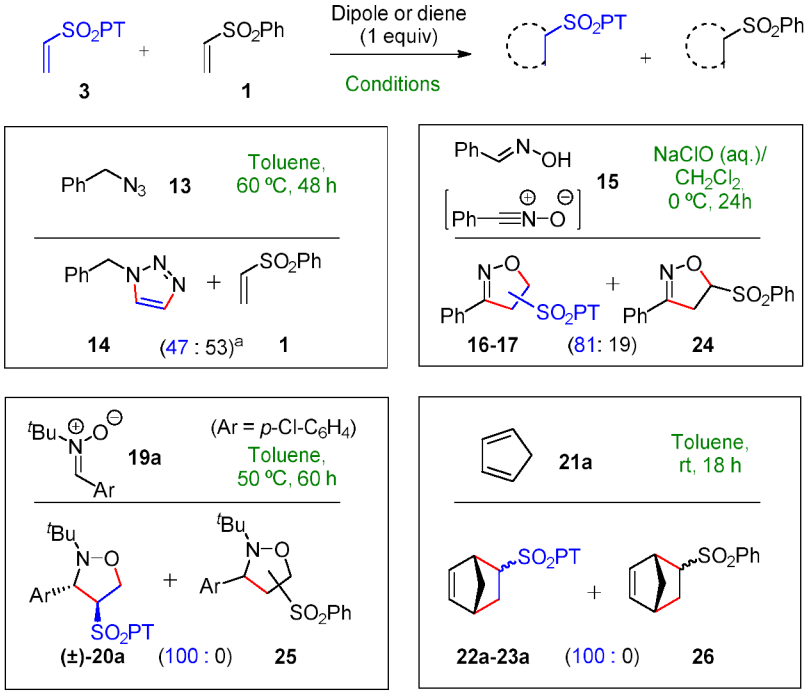
product when we preformed the anion and added right after vinyl sulfone **3** to the reaction mixture. Azides are also commonly used dipoles in reactions with different vinyl sulfones,[28] even with other heteroaryl vinyl sulfones.[29] They lead to the synthesis of triazoles through an *in situ* elimination of the sulfonyl group. The reaction of vinyl sulfone **3** with benzyl azide **13**, used as a model dipole, afforded directly the triazole **14** in 88% yield. The reaction between nitrile oxides and vinyl sulfones is also a well-known process[30-31]. Phenyl nitrile oxide **15**, generated from the corresponding phenyl oxime using commercial bleach as oxidant, was used as a dipole model. In this case, depending on the reaction conditions, different mixtures of the regioisomers **16** and **17** were observed along with the aromatic isoxazole **18**. A control of the regioselectivity, in favour of the regioisomer **16**, is possible by lowering the temperature (compare ratios of **16-18** at different temperatures, Scheme 3). The observed regioselectivity is the expected one according to the literature.[30 31] When heating the mixture, the aromatic isoxazole **18** is the only product observed and isolated in an 85% yield.

The reaction with nitrones[32] is a very interesting process, as the formed cycloadducts have found numerous applications in synthesis through reductive cleavage of the N-O bond to give γ-amino alcohols.[32] Remarkably, and differently from other dipoles, relatively few examples of vinyl sulfones reacting with open chain nitrones have been described in the literature.[33] Nitrone **19a**, prepared following the organocatalytic method recently described by us,[34] provided exclusively regioisomer **20a** in 68% yield. Surprisingly, in the literature there are no examples of reactions between *tert*-butyl nitrones and vinyl sulfones. As vinyl sulfone **3** reacted very smoothly, the process was extended to an aliphatic substituent in the nitrone, such as *n*-butyl (**19b**) to obtain the corresponding product **20b** in 59% yield. The reaction proved to be not only regioselective, but also diastereoselective. The relative stereochemistry was unequivocally assigned as *trans* (*endo* adduct) on the basis of its X-Ray diffraction analysis.

To conclude with cycloadditions, we also explored the Diels-Alder reaction, a process in which vinyl sulfones have been used as synthetic equivalents of ethylene, after a later elimination of the sulfonyl moiety.[35] The reaction with cyclopentadiene **21a** as diene proceeded smoothly at room

temperature in 96% yield, affording a mixture of *endo* and *exo* adducts **22a** and **23a** in a 77:23 ratio, after 18 hours. The much less reactive 1,3-cyclohexadiene **21b** also provided the corresponding adducts **22b** and **23b** in 94% yield as a 93:7 *endo*/*exo* mixture (Scheme 2.23). It is interesting to point out that the *endo*/*exo* selectivity using vinyl sulfone **3** (93:7) was higher than the one described for vinyl sulfone **1** (80:20).[35]

Once we had analyzed the possibilities of vinyl sulfone **3** in cycloaddition reactions, we proceeded, as in the case of Michael and radical additions, to compare its reactivity with that of vinyl sulfones **1** and **2**. For these competition experiments, we also combined 0.1 mmol of vinyl sulfone **3** with 0.1 mmol of vinyl sulfones **1** or **2**, subsequently adding one equivalent of the dipole or the diene. We used benzyl azide **13**, phenyl oxime **15**, *tert*-butyl nitrone **19a** as dipoles and cyclopentadiene **21a** as diene. The results for the competition experiments between **1** and **3** are summarized in Scheme 4**.**

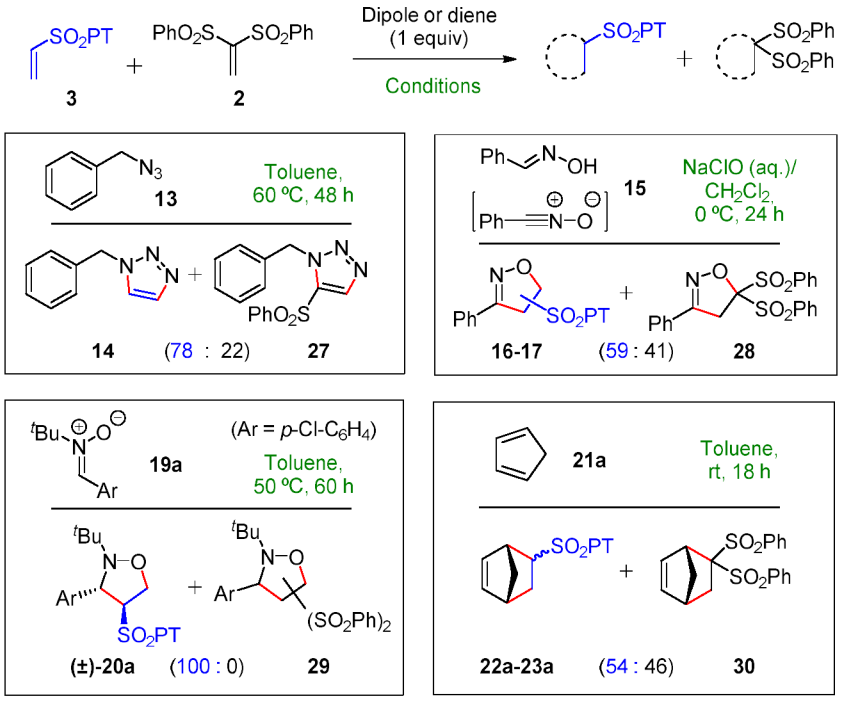


a. Since the adduct of both vinyl sulfones **1** and **3** is the same, the comparison was made with the remaining vinyl sulfone **1** and triazole **14.** No vinyl sulfone **3** was observed in the reaction crude.

Scheme 4. Competition experiments between vinyl sulfones **1** and **3** in cycloadditions.

In all the examples, vinyl sulfone **3** showed higher reactivity than vinyl sulfone **1**. Reaction of benzyl azide **13** with both vinyl sulfones **1** and **3** provides the same triazole **14**. Therefore, we evaluated the relative reactivity by determining the ratio of the remaining vinyl sulfone **1** and the formed triazole **14**. After 48 h, we only observed the final expected triazole **14** and vinyl sulfone **1** in the reaction crude, with no evidence of traces of vinyl sulfone **3** or starting azide **13**. Nitrile oxide derived from oxime **15** also offered a significant advantage in terms of elimination against vinyl sulfone **1** as the elimination of the heteroaryl sulfonyl moiety in the mixture of regioisomers was possible under just mild heating (50 ºC). Remarkably, the elimination of the phenyl sulfone in adduct **24** to provide the corresponding isoxazole **18**, would presumably require the use of a strong base.[31] With both *tert*-butyl nitrone **19a** and cyclopentadiene **21a**, we only observed the derived adduct from vinyl sulfone **3**, not detecting neither adduct **25** nor **26** in the reaction crude.

The results of the competition experiments of sulfones **2** and **3** are summarized in Scheme 5.



Scheme 5. Competition experiments between vinyl sulfones **2** and **3** in cycloadditions.

Interestingly, vinyl sulfone **3** proved to be more reactive than vinyl sulfone **2** in cycloaddition reactions, although the reactivity was similar in some examples. The results using *tert*-butyl nitrone **19a** were especially noteworthy. We observed that only isoxazoline **20a** was formed after

60 h, without detecting product **29**. In fact, the cycloaddition with vinyl sulfone **2** and nitrone **19a** did not take place even at longer reaction times (72 h) under the same reaction conditions.

To understand the origin of the higher reactivity of sulfone **3** in the reaction with nitrone **19a**, that takes place under neutral conditions in toluene as a solvent, we carried out a theoretical study of the transition states arising from the *endo*[36] approach of nitrone **19a** to sulfones **1-3** (Figure 3).

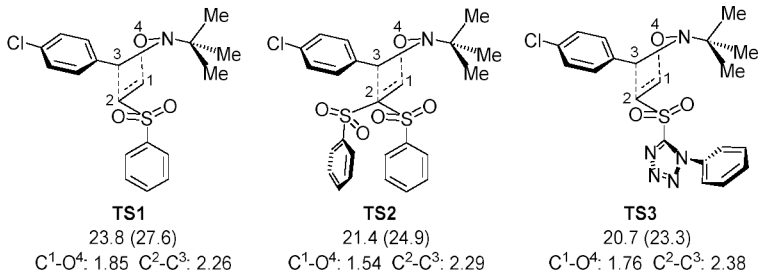
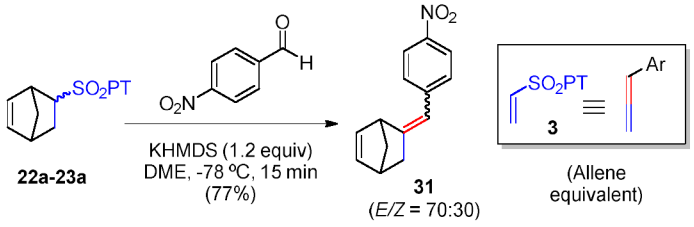


Figure 3. Optimized geometries of the possible *endo* transition states involved in the reaction of sulfones **1-3** with nitrone **19a**. Calculated relative free energy with respect to the starting materials (nitrone and the corresponding sulfone in each case) in the gas phase [M062X/6-311+G(2df,2p)//B3LYP/6-31G(d)] are reported at 298 K (kcal·mol^{-1}). Single point solvation energy corrections (toluene, SMD model) are indicated in parentheses. Distances are given in Å.

The structures of these transitions states are quite similar and asynchronous, especially in the case of **TS2,** in which C1-O4 bond is almost completely formed. Free energy barriers predict a faster reaction for sulfone **3** followed by **2** and **1** that is in good agreement with the experimental results. However, the difference between **3** and **2** is not too high but increases when solvent effects are considered ($\Delta\Delta G^{\ddagger}$ = 0.7 kcal·mol^{-1}in the gas phase but 1.6 kcal·mol^{-1} in toluene). According to the NBO analysis, the origin of the higher stabilization of **TS3** could be related to a higher ability to stabilize the charge that is being developed in C2 as the reaction proceeds due to the presence of the tetrazole unit.[37]

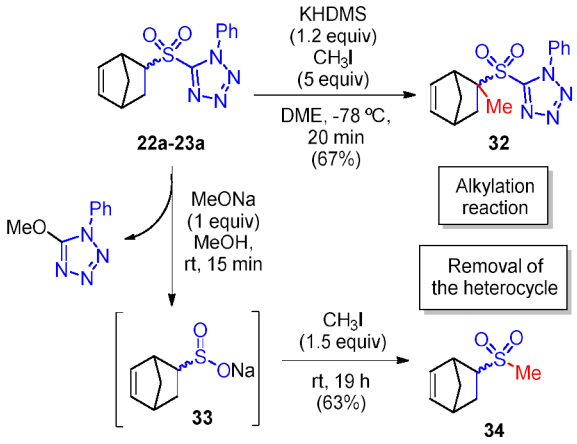
Finally, in order to prove that the monoactivated vinyl sulfone **3** is a very versatile synthon, we carried out some transformations on the Diels-Alder adducts **22a-23a** (Schemes 6 and 7). Firstly,

we submitted the *endo/exo* mixture to a Julia-Kocienski olefination under classical conditions: KHMDS as base in DME at −78 °C and *p*-nitrobenzaldehyde as electrophile to provide **31** as a mixture of *E/Z* alkenes in a 70:30 ratio and 77% yield (Scheme 6). This moderate *E/Z* selectivity was expected according to the similar nature of the substituents linked to the double bond.[38] This reaction demonstrated that vinyl sulfone **3** can be used as synthetic equivalent of an allene in Diels-Alder reactions.



Scheme 6. Julia–Kocienski olefination on the Diels-Alder adducts **22-23a**.

α-Alkylation is a typical reaction for alkyl aryl sulfones. Nevertheless, although an acylation reaction has been published with an alkyl phenyltetrazole-substituted sulfone,[39] to our knowledge no alkylation reactions have been described with this type of substrates. We could perform the alkylation at the α-position of the PT sulfone using KHMDS as base and methyl iodide as alkylating reagent to afford product **32** (Scheme 7, upper part). Finally, as small alkoxides have shown to attack the tetrazole ring easily (see table 1, **4q**), the use of NaOMe allowed the elimination of the heterocycle to evolve towards the sodium sulfinate intermediate **33**. This intermediate could be trapped using methyl iodide to afford methyl sulfone **34** in 63% yield (Scheme 7, lower part). To our knowledge this transformation is described for pyridyl[40] and benzothiazolyl[41] sulfonyl derivatives but not for the tetrazolyl ones.



Scheme 7. α-Alkylation and removal of PT heterocycle over the Diels–Alder adducts **22-23a**.

In summary, the reactivity of heteroaryl vinyl sulfone **3** has been systematically evaluated in Michael, radical additions and cycloadditions with a wide variety of substrates. Heteroaryl vinyl sulfone **3** has proven to be, at least, two orders of magnitude more reactive than phenyl vinyl sulfone **1,** traditionally used in a vast number of processes. When comparing the reactivity of vinyl sulfones **2** and **3**, vinyl sulfone **3** proved to be superior in radical additions and most cycloaddition reactions. Especially remarkable was the case of *tert*-butyl nitrones, where **2** turned out to be unreactive. Several DFT studies point to the electron withdrawing ability of the phenyltetrazole ring as the origin of the higher reactivity observed for vinyl sulfone **3**, which could be increased by simple protonation. Moreover, the phenyltetrazole moiety seems to be involved in some orbital interactions stabilizing the transition state of the 1,3-dipolar cycloaddition with nitrones. This type of interactions could also favor some otherwise disfavored processes. Furthermore, the heteroaryl sulfone moiety can be more easily eliminated than the corresponding aryl sulfones and allows mild olefination conditions through a Julia-Kocienski protocol. In addition, the phenyltetrazole moiety can be easily eliminated by treatment with small alkoxides, which allows the transformation into the corresponding dialkylsulfone. We also performed an unprecedented α-alkylation reaction on an alkyl heteroaryl sulfone. The easy manipulation, the simple and inexpensive preparation of heteroaryl vinyl sulfone **3**, its high performance under very mild conditions in many types of bond-forming reactions, the control of the regio- and stereoselectivity in some cycloadditions as well as the variety of possible

transformations, allow us to envision a wide range of future applications in synthetic organic chemistry and bioconjugate formation.

Experimental section

General methods and materials:

NMR spectra were acquired at 25 ºC using $CDCl_3$ as the solvent, running at 300 and 75 MHz for ^1H and ^{13}C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CDCl_3$, 7.26 ppm for ^1H NMR, and 77.0 ppm for ^{13}C NMR). In all ^1H NMR spectra, multiplicity is indicated as follows: bs (broad signal), s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sex (sextet), sep (septet), non (nonet) or m (multiplet). Coupling constant values (in Hertz) and number of protons for each signal are also indicated. The substitution of the carbon atoms (C, CH, CH_2, CH_3) has been determined using ^{13}C NMR DEPT 90 and DEPT 135 experiments. Melting points were measured using open capillary tubes. For thin layer chromatography (TLC) silica gel plates with fluorescence indicator 254 nm were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of $KMnO_4$ (1.5 g), K_2CO_3 (10 g), and 10% NaOH (1.25 mL) in H_2O (200 mL) or a solution of phosphomolybdic acid (12 g), in EtOH (250 mL) followed by heating. Flash column chromatography (FCC) was performed using silica gel and compressed air. Mass spectra (MS) and High Resolution Mass Spectra (HRMS) were obtained in positive electrospray ionisation (ESI) or electron impact ionisation (EI) using TOF as analyser. Obtained data are expressed in mass/charge (m/z) units. Values between parentheses indicate relative intensities with regard to the base peak. All the reactants and solvents were used from commercial sources without any previous treatment.

Michael additions with nucleophiles 4a-u

Enamine 4a: Vinyl sulfone **3** (23.6 mg, 0.1 mmol) was dissolved in 0.6 mL of $CHCl_3$, whereupon enamine **4a** (44 μL, 0.3 mmol) was added to the solution. The mixture was stirred for 5 min at room temperature. The solvent was evaporated under reduced pressure and the crude was purified

by flash column chromatography (cyclohexane/EtOAc = 3:1) to afford compound **5a**. **2-(2-((1-Phenyl-1*H*-tetrazol-5-yl)sulfonyl)ethyl)cyclopentan-1-one (5a).** White solid. Melting point: 100-102 ºC. Yield: 95% (30.3 mg). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.74-7.56 (m, 5H), 4.07-3.96 (m, 1H), 3.94-3.80 (m, 1H), 2.44-1.97 (m, 7H), 1.92-1.75 (m, 1H), 1.69-1.52 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): 218.9 (C=O), 153.3 (C), 133.0 (C), 131.5 (CH), 129.7 (2 CH), 125.1 (2 CH), 54.1 (CH_2), 46.9 (CH), 37.7 (CH_2), 29.6 (CH_2), 22.6 (CH_2), 20.5 (CH_2). MS (ESI): m/z 321 (M^+ + H, 100), 175 (4), 111 (3). HRMS (ESI): calculated for $C_{14}H_{17}N_4O_3S$ (M^+ + H): 321.1015; found: 321.1016.

Nitromethane 4b[12]**:** Vinyl sulfone **3** (1.41 g, 6 mmol) was added to a solution of sodium hydroxide in pearls (240 mg, 6 mmol) in nitromethane **4b** (15 mL). The mixture was stirred for 3 h, whereupon water (20 mL) was added. The mixture was transferred to a separatory funnel and was extracted with EtOAc (2 × 25 mL). The organic layers were combined and were washed with brine (25 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure to afford **5b** as a white solid (1.60 g, yield: 90%). **5-(3-Nitropropylsulfonyl)-1-phenyl-1*H*-tetrazole (5b)**[12] White solid. Melting point: 81-83 ºC. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.71-7.54 (m, 5H), 4.62 (t, *J* = 6.5 Hz, 2H), 3.92 (t, *J* = 7.1 Hz, 2H), 2.71 (quint, *J* = 6.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.1 (C), 132.8 (C), 131.6 (CH), 128.8 (2 CH), 124.9 (2 CH), 72.3 (CH_2), 52.9 (CH_2), 20.4 (CH_2). MS (ESI): m/z 298 (M^+ + H, 46), 149 (67), 119 (26), 113 (100). HRMS (ESI): calculated for $C_{10}H_{12}N_5O_4S$ (M^+ + H): 298.0604; found: 298.0615.

Cyanosulfones and cyanoesters 4c-f: The corresponding nucleophile **4c-f** (0.1 mmol) was dissolved in $CHCl_3$ (1 mL), and Cs_2CO_3 (49 mg, 0.15 mmol) was added to the solution. The mixture was stirred for 1 min, whereupon vinyl sulfone **3** (23.6 mg, 0.1 mmol) was added to the suspension. After that time, the mixture was filtered through a short pad of silica, and the solvent was eliminated under reduced pressure, to afford the corresponding Michael adducts **5c-f**. **2-(Methylsulfonyl)-2-phenyl-4-((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)butanenitrile (5c).** Colourless oil. Yield: 91% (39.3 mg). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.81-7.74 (m, 2H), 7.70-7.56 (m, 8H), 3.99-3.85 (m, 1H), 3.73-3.60 (m, 1H), 3.36-3.22 (m, 2H), 2.87 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.0 (C), 132.7 (C), 131.7 (CH), 131.4 (CH), 130.1 (2 CH), 129.9 (2 CH),

128.0 (2 CH), 127.1 (CH), 124.9 (2 CH), 115.0 (CN), 68.8 (C), 52.1 (CH_2), 36.9 (CH_3), 25.8 (CH_2). MS (ESI): m/z 432 (M^+ + H, 100), 338 (10), 150 (25), 133 (49), 114 (41). HRMS (ESI): calculated for $C_{18}H_{18}N_5O_4S_2$ (M^+ + H): 432.0794; found: 432.0788. **2-Phenyl-4-((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)-2-tosylbutanenitrile (5d).** Colourless oil. Yield: 94% (47.7 mg). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.74-7.59 (m, 5H), 7.52-7.37 (m, 7H), 7.22 (d, *J* = 8.0 Hz, 2H), 3.97-3.84 (m, 1H), 3.78-3.65 (m, 1H), 3.47-3.30 (m, 2H), 2.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.0 (C), 146.9 (C), 132.8 (C), 131.6 (CH), 130.9 (CH), 130.7 (2 CH), 129.9 (C), 129.8 (2 CH), 129.6 (2 CH), 129.3 (2 CH), 128.4 (2 CH), 127.2 (C), 125.0 (2 CH), 115.4 (CN), 70.1 (C), 52.4 (CH_2), 25.8 (CH_2), 21.8 (CH_3). MS (ESI): m/z 508 (M^+ + H, 100), 338 (13), 150 (30), 133 (97), 114 (48). HRMS (ESI): calculated for $C_{24}H_{22}N_5O_4S_2$ (M^+ + H): 508.1107; found: 508.1115. **2-Benzyl-4-((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)-2-((4-(trifluoromethyl)phenyl)sulfonyl) butanenitrile (5e).** Colourless oil. Yield: 91% (52.4 mg). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.27 (d, *J* = 8.2 Hz, 2H), 7.99 (d, *J* = 8.2 Hz, 2H), 7.66-7.58 (m, 5H), 7.41-7.34 (m, 3H), 7.33-7.25 (m, 2H), 4.09-3.94 (m, 1H), 3.68-3.54 (m, 1H), 3.36-3.16 (m, 2H), 2.93-2.79 (m, 1H), 2.71-2.57 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 152.8 (C), 137.3 (d, *J* = 34 Hz, C), 136.8 (C), 132.7 (C), 131.8 (2 CH), 131.7 (CH), 130.6 (C), 130.3 (2 CH), 129.9 (2 CH), 129.5 (2 CH), 129.1 (CH), 126.9 (q, *J* = 4 Hz, 2 CH), 125.0 (2 CH), 124.4 (q, *J* = 274 Hz, CF_3), 115.1 (CN), 65.4 (C), 52.3 (CH_2), 38.6 (CH_2), 24.8 (CH_2). MS (ESI): m/z 576 (M^+ + H, 100), 338 (14), 182 (12), 150 (34), 133 (56), 114 (59). HRMS (ESI): calculated for $C_{25}H_{21}N_5O_4F_3S_2$ (M^+ + H): 576.0981; found: 576.0981. **Methyl-2-(4-bromophenyl)-2-cyano-4-((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)butanoate (5f).** Colourless oil. Yield: 93% (45.6 mg). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.72-7.56 (m, 7H), 7.44 (d, *J* = 8.6 Hz, 2H), 3.95-3.78 (m, 4H), 3.73-3.63 (m, 1H), 3.09-2.86 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.3 (C), 153.0 (C), 132.9 (CH_2), 132.8 (C), 131.6 (CH), 131.2 (C), 129.8 (2 CH), 129.6, 127.7 (2 CH), 125.0 (2 CH), 124.3 (C), 116.3 (CN), 54.7 (CH_3), 52.4 (CH_2), 51.8 (C), 30.7 (CH_2). MS (ESI): m/z 490 (M^+ + H, 98), 492 (100), 338 (21), 191 (41), 163 (67), 147 (30), 133 (28), 119 (35). HRMS (ESI): calculated for $C_{19}H_{17}BrN_5O_4S_2$ (M^+ + H): 490.0179; found: 490.0175.

Amines 4g-n and imine 4o: The corresponding amine or imine **4g-o** (0.1 mmol) was dissolved

in $CHCl_3$ (1 mL), and vinyl sulfone **3** (23.6 mg, 0.1 mmol) was added to the solution. After the corresponding time (see Table 1), the solvent was eliminated under reduced pressure, to afford the corresponding Michael adducts **5g-o**. **1-Phenyl-5-((2-(pyrrolidin-1-yl)ethyl)sulfonyl)-1*H*-tetrazole (5g).** Colourless oil. Yield: 99% (30.5 mg). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.70-7.58 (m, 5H), 3.87 (t, *J* = 6.5 Hz, 2H), 3.06 (t, *J* = 6.5 Hz, 2H), 2.52-2.43 (m, 4H), 1.69-1.60 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.8 (C), 133.2 (C), 131.3 (CH), 129.4 (2 CH), 125.3 (2 CH), 55.2 (CH_2), 53.6 (2 CH_2), 48.9 (CH_2), 23.4 (2 CH_2). MS (ESI): m/z 308 (M^+ + H, 100), 146 (36), 114 (15). HRMS (ESI): calculated for $C_{13}H_{18}N_5O_2S$ (M^+ + H): 308.1175; found: 308.1179.

2-Methyl-*N*-(2-((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)ethyl)propan-1-amine (5h) Colourless oil. Quantitative yield (30.9 mg). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.70-7.55 (m, 5H), 3.89 (t, *J* = 6.2 Hz, 2H), 3.23 (t, *J* = 6.2 Hz, 2H), 2.37 (d, *J* = 6.7 Hz, 2H), 1.60 (Non, *J* = 6.7 Hz, 1H), 0.84 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.9 (C), 133.1 (C), 131.4 (CH), 129.6 (2 CH), 125.2 (2 CH), 57.3 (CH_2), 56.1 (CH_2), 43.1 (CH_2), 28.2 (CH), 20.4 (2 CH_3). MS (ESI): m/z 310 (M^+ + H, 38), 218 (100), 147 (17), 133 (30), 119 (13). HRMS (ESI): calculated for $C_{13}H_{20}N_5O_2S$ (M^+ + H): 310.1332; found: 310.1345. ***N*-(2-((1-Phenyl-1*H*-tetrazol-5-yl)sulfonyl)ethyl)octan-1-amine (5i).** Colourless oil. Quantitative yield (36.3 mg). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.69-7.55 (m, 5H), 3.88 (t, *J* = 6.2 Hz, 2H), 3.23 (t, *J* = 6.2 Hz, 2H), 2.54 (t, *J* = 7.0 Hz, 2H), 1.40-1.18 (m, 12H), 0.87 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.8 (C), 133.0 (C), 131.4 (CH), 129.6 (2 CH), 125.2 (2 CH), 56.0 (CH_2), 49.3(CH_2), 42.9 (CH_2), 31.7 (CH_2), 29.8 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 27.1 (CH_2), 22.6 (CH_2), 14.1 (CH_3). MS (ESI): m/z 274 (M^+ + H, 100), 248 (33), 147 (10), 130 (39). HRMS (ESI): calculated for $C_{15}H_{24}N_5$ (M^+ + H): 274.2026; found: 274.2041.[42] **4-Methoxy-*N*-(2-((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)ethyl)aniline (5j).** Colourless oil. Yield: 99% (35.6 mg). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.70-7.53 (m, 5H), 6.79 (d, *J* = 8.7 Hz, 2H), 6.57 (d, *J* = 8.7 Hz, 2H), 3.92 (t, *J* = 5.9 Hz, 2H), 3.83 (t, *J* = 5.9 Hz, 2H), 3.76 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.7 (C), 153.5 (C), 132.9 (C), 131.6 (CH), 129.7 (2 CH), 125.2 (2 CH), 115.2 (2 CH), 114.8 (2 CH), 55.8 (CH_3), 55.0 (CH_2), 38.7 (CH_2). MS (ESI): m/z 360 (M^+ + H, 100), 150 (59), 136 (55), 114 (13). HRMS (ESI): calculated for $C_{16}H_{18}N_5O_3S$ (M^+ + H): 360.1124; found: 360.1140. **4-Isopropyl-*N*-(2-((1-phenyl-**

1*H*-tetrazol-5-yl)sulfonyl)ethyl)aniline (5k). Colourless oil. Yield: 99% (36.8 mg). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.71-7.53 (m, 5H), 7.09 (d, *J* = 8.6 Hz, 2H), 6.54 (d, *J* = 8.6 Hz, 2H), 3.98-3.82 (m, 4H), 2.84 (sep, *J* = 7.0 Hz, 1H), 1.23 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.7 (C), 143.7 (C), 139.6 (C), 132.8 (C), 131.6 (CH), 129.7 (2 CH), 127.5 (2 CH), 125.3 (2 CH), 113.3 (2 CH), 55.0 (CH_2), 38.0 (CH_2), 33.2 (CH), 24.3 (2 CH_3). MS (ESI): m/z 372 (M^+ + H, 100), 148 (21), 136 (15), 114 (15). HRMS (ESI): calculated for $C_{18}H_{22}N_5O_2S$ (M^+ + H): 372.1488; found: 372.1500. **5-((2-(1*H*-Imidazol-1-yl)ethyl)sulfonyl)1-phenyl-1*H*-tetrazole (5n).** White solid. Melting point: 99-101 ºC. Yield: 99% (30.5 mg). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.71-7.55 (m, 5H), 7.51 (s, 1H), 7.05 (s, 1H), 6.99 (s, 1H), 4.64, (t, *J* = 6.7 Hz, 2H), 4.19 (t, *J* = 6.7 Hz 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.1 (C), 137.3 (CH), 132.7 (C), 131.8 (CH), 130.5 (CH), 129.9 (2 CH), 124.9 (2 CH), 118.7 (CH), 56.4 (CH_2), 40.4 (CH_2). MS (ESI): m/z 305 (M^+ + H, 100), 213 (14), 185 (6), 145 (8). HRMS (ESI): calculated for $C_{12}H_{13}N_6O_2S$ (M^+ + H): 305.0815; found: 305.0809. **1,1-Diphenyl-*N*-(2-((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)ethyl)methanimine (5o).** White solid. Melting point: 140-141 ºC. Yield: 95% ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.62-7.36 (m, 9H), 7.32-7.28 (m, 4H), 7.11-7.05 (m, 2H), 4.04 (t, *J* = 6.5 Hz, 2H), 3.85 (t, *J* = 6.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): 171.1 (C), 154.3 (C), 138.7 (C), 135.8 (C), 133.2 (C), 131.3 (CH), 130.7 (CH), 129.5 (2 CH), 128.9 (CH), 128.8 (2 CH), 128.4 (2 CH), 128.2 (2 CH), 127.3 (2 CH), 125.5 (2 CH), 57.4 (CH_2), 47.4 (CH_2). MS (ESI): m/z 418 (M^+ + H, 100), 326 (3), 256 (3), 208 (7). HRMS (ESI): calculated for $C_{22}H_{20}N_5O_2S$ (M^+ + H): 418.1332; found: 418.1318.

Aminoacid 4p: L-Valine methyl ester hydrochloride **4p** (17.5 mg, 0.1 mmol) was dissolved in a 5:1 H_2O:THF mixture (1 mL), whereupon $NaHCO_3$ (9.2 mg, 0.11 mmol) was added to the solution. After 10 min, vinyl sulfone **3** (23.6 mg, 0.1 mmol) was added to the mixture, which was stirred at room temperature for 3 h. The solution was transferred to a separatory funnel and extracted with EtOAc (3 x 5 mL). The organic layers were combined and were washed with brine (10 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (cyclohexane/EtOAc = 3:1) to afford product **5p. Methyl-(2-((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)ethyl)-*L*-valinate (5p).** Colorless oil. Yield:

86% (31.4 mg). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.73-7.56 (m, 5H), 4.09-3.97 (m, 1H), 3.78 (dt, *J* = 15.0 and 6.0 Hz, 1H), 3.70 (s, 3H), 3.31 (dt, *J* = 13.1 and 6.0 Hz 1H), 3.06-2.94 (m, 2H), 1.90-1.76 (m, 1H), 0.85 (d, *J* = 6.9 Hz, 3H), 0.81 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 174.8 (C), 154.0 (C), 133.1 (C), 131.5 (CH), 129.7 (2 CH), 125.2 (2 CH), 67.1 (CH), 56.4 (CH_2), 51.7 (CH), 42.2 (CH_2), 31.4 (CH), 19.2 (CH_3), 18.2 (CH_3). MS (ESI): m/z 368 (M^+ + H, 100), 206 (6), 144 (7), 116 (7). HRMS (ESI): calculated for $C_{15}H_{22}N_5O_4S$ (M^+ + H): 368.1387; found: 368.1384.

Alkoxides 4q-s: Vinyl sulfone **3** (23.6 mg, 0.01 mmol) was dissolved in the corresponding solvent (1 mL, see Scheme 2.12) and alkoxide **4q-s** (0.1 mmol) was added to the solution. The mixture was stirred for the corresponding time (see Table 1) and was quenched with sat. aq. NH_4Cl (5 mL). The solution was transferred to a separatory funnel and extracted with EtOAc (2 x 5 mL). The organic layers were combined and were washed with brine (5 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure to afford the corresponding products **5r** or **6q-s. 5-Methoxy-1-phenyl-1*H*-tetrazole (6q).** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.75-7.68 (m, 2H), 7.57-7.41 (m, 3H), 4.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 160.7 (C), 133.3 (C), 129.6 (2 CH), 129.0 (CH), 121.7 (2 CH), 60.3 (CH_3). MS (ESI): m/z 177 (M^+ + H, 100), 163 (2), 134 (6). HRMS (ESI): calculated for $C_8H_9N_4O$ (M^+ + H): 177.0770; found: 177.0775. **5-((2-Ethoxyethyl)sulfonyl)1-phenyl-1*H*-tetrazole (5r).** White oil. Yield: 95% (26.7 mg). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.72-7.55 (m, 5H), 3.91 (t, *J* = 5.5 Hz, 2H), 3.75 (t, *J* = 5.5 Hz, 2H), 3.37 (q, *J* = 7.1 Hz, 2H), 0.99 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 154.1 (C), 133.1 (C), 131.5 (CH), 129.6 (2 CH), 125.7 (2 CH), 66.8 (CH_2), 63.2 (CH_2), 56.3 (CH_2), 14.7 (CH_3). MS (ESI): m/z 283 (M^+ + H, 100), 172 (9), 137 (10), 108 (6). HRMS (ESI): calculated for $C_{11}H_{15}N_4O_3S$ (M^+ + H): 283.0859; found: 283.0867. **5-Ethoxy-1-phenyl-1*H*-tetrazole (6r).** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.73-7.46 (m, 5H), 4.71 (q, *J* = 7.2 Hz, 2H), 1.54 (t, *J* = 7.2 Hz, 3H). Data is in agreement with the literature.[43] **5-Phenoxy-1-phenyl-1*H*-tetrazole (6s)** White solid. Melting point: 125-127 ºC. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.86-7.79 (m, 2H), 7.64-7.39 (m, 7H), 7.35-7.30 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.5 (C), 133.1 (C), 130.1 (2 CH), 129.7 (2 CH), 129.5 (CH), 126.6 (CH), 122.2 (CH), 119.4 (CH). MS (ESI): m/z 239 (M^+ + H, 100), 211

(37), 196 (3). HRMS (ESI): calculated for $C_{13}H_{11}N_4O$ (M^+ + H): 239.0927; found: 239.0933.

Thiol 4t: 2-Mercaptopyridine **4t** (23.2 mg, 0.21 mmol), and imidazole (0.7 mg, 0.01 mmol) were dissolved in $CHCl_3$. The mixture was stirred for 5 min, whereupon vinyl sulfone **3** (47.2 mg, 0.2 mmol) was added to the solution. The mixture was stirred for 1 h at room temperature and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography (cyclohexane/EtOAc = 1:1) to afford pure **5t** as a white solid. **2-((2-((1-Phenyl-1*H*-tetrazol-5-yl)sulfonyl)ethyl)thio)pyridine (5t)**. White solid. Melting point: 123-124 ºC Yield: 98% (29.1 mg). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.40 (d, *J* = 5.0 Hz, 1H), 7.72-7.48 (m, 6H), 7.16 (d, *J* = 8.1 Hz, 1H), 7.06-7.00 (m, 1H), 4.22-4.14 (m, 2H), 3.70-3.62 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.3 (C), 153.5 (C), 149.8 (CH), 136.3 (CH), 133.0 (C), 131.5 (CH), 129.7 (2 CH), 125.2 (2 CH), 122.4 (CH), 120.1 (CH), 56.3 (CH_2), 22.5 (CH_2). MS (ESI): m/z 348 (M^+ + H, 100), 221 (9), 201 (9), 186 (18), 138 (26). HRMS (ESI): calculated for $C_{14}H_{14}N_5O_2S_2$ (M^+ + H): 348.0583; found: 348.0567.

Carboxylate 4u: Vinyl sulfone **3** (23.6 mg, 0.1 mmol) was dissolved in acetic acid (1 mL) and sodium acetate (8.2 mg 0.1 mmol) was added to the solution. The mixture was stirred at 50ºC for 16 h. Acetic acid was removed under reduced pressure and the crude was dissolved in EtOAc and filtered through a short pad of silica. After removal of the solvent, **5u** was obtained as a white solid. **2-((1-Phenyl-1*H*-tetrazol-5-yl)sulfonyl)ethyl acetate (5u).** Yellow solid. Melting point: 59-60 ºC. Yield: 98% (29.1 mg). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.72-7.58 (m, 5H), 4.62 (t, *J* = 5.7 Hz, 2H), 4.07 (t, *J* = 5.7 Hz, 2H), 1.99 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.1 (C), 153.6 (C), 132.9 (C), 131.1 (CH), 129.7 (2 CH), 125.1 (2 CH), 56.7 (CH_2), 55.7 (CH_2), 20.5 (CH_3). MS (ESI): m/z 297 (M^+ + H, 45), 255 (100), 230 (23), 122 (14), 119 (48). HRMS (ESI): calculated for $C_{11}H_{13}N_4O_4S$ (M^+ + H): 297.0652; found: 297.0643.

Radical addition of 4v-w: The reaction was carried out under argon atmosphere. Vinyl sulfone **3** (23.6 mg, 0.1 mmol) and AIBN (1.6 mg, 0.01 mmol) were dissolved in a 1:1 mixture of CH_2Cl_2:H_2O (1 mL), whereupon the corresponding iodide **4v-w** (0.12 mmol) and $SnBu_3H$ (32 µL, 0.12 mmol) were added to the solution. After the corresponding time (see Scheme 2), the mixture was extracted with CH_2Cl_2 (2 x 10 mL), and the organic phases were washed with brine (10 mL),

dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (cyclohexane/EtOAc = 15:1 to 8:1). This flash column chromatography was performed twice, in order to remove all the tin residues, affording pure products **5v-w**. **5-((3-Methylbutyl)sulfonyl)-1-phenyl-1*H*-tetrazole (5v).** Colourless oil. Yield: 80% (22.5 mg). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.75-7.57 (m, 5H), 3.80-3.70 (m, 2H), 1.91-1.78 (m, 2H), 1.46-1.33 (m, 1H), 0.99 (d, *J* = 6.2 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.5 (C), 133.1 (C), 131.4 (CH), 129.7 (2 CH), 125.1 (2 CH), 54.5 (CH_2), 30.1 (CH_2), 27.3 (CH), 22.0 (2 CH_3). MS (ESI): m/z 281 (M^+ + H, 100), 149 (2), 119 (39). HRMS (ESI): calculated for $C_{12}H_{17}N_4O_2S$ (M^+ + H): 281.1066; found: 281.1069. **5-(Hexylsulfonyl)-1-phenyl-1*H*-tetrazole (5w).** Colourless oil. Yield: 60% (17.7 mg). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.75-7.56 (m, 5H), 3.74 (t, *J* = 7.9 Hz, 2H), 2.03-1.91 (m, 2H), 1.58-1.45 (m, 2H), 1.41-1.24 (m, 4H), 0.91 (t, *J* = 7.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.5 (C), 133.1 (C), 131.4 (CH), 129.7 (2 CH), 125.1 (2 CH), 56.1 (CH_2), 31.0 (CH_2), 27.8 (CH_2), 22.2 (CH_2), 21.9 (CH_2), 13.9 (CH_3). MS (ESI): m/z 295 (M^+ + H, 100), 149 (3), 119 (51). HRMS (ESI): calculated for $C_{13}H_{19}N_4O_2S$ (M^+ + H): 295.1223; found: 295.1236.

Competition experiments for Michael and radical additions: The competition experiments were carried out with 0.1 mmol of vinyl sulfone **3** (23.6 mg) and 0.1 mmol of vinyl sulfones **1** (16. 8 mg) or **2** (30.8 mg) under the same reaction conditions than the ones described for every substrate.

5-(4-Ethoxy-3,3-bis(phenylsulfonyl)butyl)sulfonyl)-1-phenyl-1*H*-tetrazole (10)

White solid. Melting point: 59-61 ºC. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.03 (d, *J* = 8.0 Hz, 4H), 7.77-7.54 (m, 11H), 4.39-4.30 (m, 2H), 3.92 (s, 2H), 3.17 (q, *J* = 7.0 Hz, 2H), 2.94-2.86 (m, 2H), 0.85 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.1 (C), 136.9 (2C), 135.0 (2 CH), 132.9 (C), 131.6 (CH), 131.1 (4 CH), 129.7 (2 CH), 128.9 (4 CH), 125.3 (2 CH), 87.9 (C), 67.1 (CH_2), 66.9 (CH_2), 52.2 (CH_2), 23.4 (CH_2), 14.2 (CH_3). MS (ESI): m/z 591 (M^+ + H, 100), 338 (7), 172 (14), 154 (5). HRMS (ESI): calculated for $C_{25}H_{27}N_4O_7S_3$ (M^+ + H): 591.1036; found: 591.1033.

Cycloadditions

Azide: Benzyl azide **13** (14 μL, 0.11 mmol) and vinyl sulfone **3** (23.6 mg, 0.1 mmol) were dissolved in toluene (1 mL). This mixture was heated at 60ºC and stirred for 48 h, whereupon the solvent was eliminated under reduced pressure. The crude was purified by flash column chromatography (cyclohexane/EtOAc = 2:1), to afford 14.0 mg (Yield: 88%) of compound **14**. **1-Benzyl-1*H*-1,2,3-triazole (14).** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.66 (s, 1H), 7.46 (s, 1H), 7.36-7.29 (m, 3H), 7.26-7.20 (m, 2H), 5.49 (s, 2H). Data is in agreement with the literature.[44]

Nitrile oxide: Vinyl sulfone **3** (23.6 mg, 0.1 mmol) and phenyl oxime **15** (12.3 mg, 0.11 mmol) were dissolved in CH_2Cl_2 (1 mL) at 0ºC, whereupon commercial bleach (4% wt of ClO^-, 1 mL) was added to the solution. The solution was stirred at 0ºC for 24 h, whereupon it was transferred to a separatory funnel. The aqueous phase was extracted twice with CH_2Cl_2 (2 x 5 mL) and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Compound **16** was obtained after flash column chromatography of the crude (cyclohexane/EtOAc = 2:1): 31.4 mg (Yield: 89%). **3-Phenyl-5-((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl-4,5-dihydroisoxazole (16).** White solid. Melting point: 172-173 ºC. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.70-7.55 (m, 7H), 7.53-7.38 (m, 3H), 6.15 (dd, *J* = 10.6 and 4.0 Hz, 1H), 4.25 (dd, *J* = 18.7 and 4.0 Hz, 1H), 3.98 (dd, *J* = 18.7 and 10.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.8 (C), 151.4 (C), 132.9 (C), 131.7 (CH), 131.6 (CH), 129.5 (2 CH), 129.1 (2 CH), 127.3 (2 CH), 126.5 (C), 125.9 (2 CH), 94.5 (CH), 37.6 (CH_2). MS and HRMS could not be obtained due to the easy elimination of the sulfone to afford the corresponding isoxazole **18**. To obtain compound **18**, the crude was dissolved in $CHCl_3$ and heated at 50ºC for 16 h. The solvent was evaporated under reduced pressure and the crude was purified by flash column chromatography (cyclohexane/EtOAc = 5:1): 12.3 mg (Yield: 85%). **3-Phenylisoxazole (18).** ^{1}H NMR (300 MHz): δ 8.46 (d, *J* = 1.7 Hz, 1H), 7.85-7.81 (m, 2H), 7.49-7.44 (m, 3H), 6.67 (d, *J* = 1.7 Hz, 1H). Data is in agreement with the literature.[45]

Nitrones: The corresponding nitrone **19a-b** (0.11 mmol) and vinyl sulfone **3** (23.6 mg, 0.1 mmol) were dissolved in toluene (1 mL). The mixture was heated at 50 ºC for 60 h, whereupon the solvent was eliminated under reduced pressure. The crude was purified by flash column chromatography (hexane/EtOAc = 10:1) to afford the corresponding isoxazolines **20a-b**. **2-*tert*-**

Butyl-3-(4-chlorophenyl)-4-((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)isoxazolidine (20a). White solid. Melting point: 171-172 ºC Yield: 68% (30.3 mg).^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.70-7.59 (m, 5H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 4.64 (d, *J* = 5.0 Hz, 1H), 4.54-4.40 (m, 3H), 1.03 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.2 (C), 139.8 (C), 134.1(C), 132.8 (C), 131.7 (CH), 129.8 (2 CH), 129.1 (2 CH), 128.8 (2 CH), 125.1 (2 CH), 77.6 (CH), 65.8 (CH_2), 60.9 (CH), 59.2 (C), 26.2 (CH_3). MS (ESI): m/z 448 (M^+ + H, 100), 392 (11), 230 (4). HRMS (ESI): calculated for $C_{20}H_{23}N_5O_3SCl$ (M^+ + H): 448.1204; found: 448.1203. **2-*tert*-Butyl-3-butyl-4-((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)isoxazolidine (20b).** White oil. Yield: 59% (23.4 mg). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.75-7.58 (m, 5H), 4.55-4.48 (m, 1H), 4.43 (d, *J* = 11.1 Hz, 1H), 4.23 (dd, *J* = 11.1 and 6.1 Hz, 1H), 3.75-3.68 (m, 1H), 1.85-1.56 (m, 2H), 1.52-1.29 (m, 4H), 1.16 (s, 9H), 0.91 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.3 (C), 133.0 (C), 131.6 (CH), 129.8 (2 CH), 125.1 (2 CH), 74.1 (CH), 66.0 (CH_2), 59.0 (C), 57.3 (CH), 36.9 (CH_2), 27.5 (CH_2), 26.2 (3 CH_3), 22.5 (CH_2), 14.0 (CH_3). MS (ESI): m/z 394 (M^+ + H, 100), 338 (5), 128 (4). HRMS (ESI): calculated for $C_{18}H_{28}N_5O_3S$ (M^+ + H): 394.1907; found: 394.1917.

Diels-Alder: Vinyl sulfone **3** (236 mg, 1 mmol) was dissolved in toluene (10 mL), whereupon freshly distillated cyclopentadiene **21a** (336 µL, 4 mmol) or 1,3-cyclohexadiene (381 µL, 4 mmol) was added to the solution. The mixture was stirred at the corresponding temperature the corresponding time whereupon the solvent was eliminated under reduced pressure.

Cyclopentadiene 21a: 18h at room temperature. The *endo:exo* adducts were separated by flash column chromatography (hexane/EtOAc = 10:1), to afford 224 mg of the *endo* adduct **22a** and 67 mg of the *exo* adduct **23a** (291 mg for both diastereomers, 96% yield). **5-(1*R**,2*R**,4*R**)-(Bicyclo[2.2.1]hept-5-en-2-ylsulfonyl)-1-phenyl-1*H*-tetrazole and 5-(1*R**,2*S**,4*R**)-(bicyclo[2.2.1]hept-5-en-2-ylsulfonyl)-1-phenyl-1*H*-tetrazole (22 and 23a).** *Endo* adduct (**22a**). White solid. Melting point: 96-97 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.74-7.55 (m, 5H), 6.33 (dd, *J* = 5.5 and 3.1 Hz, 1H), 6.10 (dd, *J* = 5.6 and 2.7 Hz, 1H), 4.63 (ddd, *J* = 9.5, 4.9 and 3.2 Hz, 1H), 3.63 (bs, 1H), 3.15 (bs, 1H), 2.48-2.37 (m, 1H), 1.74-1.62 (m, 2H), 1.55-1.47 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 154.4 (C), 138.3 (CH), 133.1 (C), 131.3 (CH), 131.0 (CH), 129.6 (2 CH), 125.2 (2 CH), 65.3 (CH), 49.9 (CH_2), 45.2 (CH), 42.8 (CH), 30.1 (CH_2). MS (ESI):

m/z 303 (M^+ + H, 100), 185 (15), 128 (17), 119 (14). HRMS (ESI): calculated for $C_{14}H_{15}N_4O_2S$ (M^+ + H): 303.0910; found: 303.0924. *Exo* adduct (**23a**). White solid. Melting point: 121-122 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.74-7.54 (m, 5H), 6.29 (dd, *J* = 5.5 and 2.9 Hz, 1H), 6.17 (dd, *J* = 5.5 and 3.6 Hz, 1H), 3.67 (ddd, *J* = 8.5, 4.3 and 0.9 Hz, 1H), 3.55-3.49 (m, 1H), 3.02 (bs, 1H), 2.22-2.13 (m, 1H), 1.87-1.72 (m, 2H), 1.53-1.44 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 154.1 (C), 140.8 (CH), 134.9 (CH), 133.4 (C), 131.4 (CH), 129.9 (2 CH), 125.3 (2 CH), 64.8 (CH), 46.1 (CH_2), 44.6 (CH), 41.6 (CH), 29.0 (CH_2). MS (ESI): m/z 303 (M^+ + H, 100), 185 (37), 143 (62), 119 (20), 98 (15). HRMS (ESI): calculated for $C_{14}H_{15}N_4O_2S$ (M^+ + H): 303.0910; found: 303.0925.

1,3-cyclohexadiene 21b: 60h at 70 ºC. The crude was purified by flash column chromatography (hexane/EtOAc = 8:1), to afford 298 mg of a 93:7 *endo:exo* mixture of adducts **22b** and **23b** (Yield: 94%). **5-(1*R**,2*R**,4*R**)-(Bicyclo[2.2.2]oct-5-en-2-ylsulfonyl)-1-phenyl-1*H*-tetrazole (22b).** Data for the major diastereomer (*Endo* adduct): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.72-7.52 (m, 5H), 6.37 (t, *J* = 7.3 Hz, 1H), 6.17 (t, *J* = 7.3 Hz, 1H), 4.27 (ddd, *J* = 9.8, 6.1 and 1.8 Hz, 1H), 3.36-3.28 (m, 1H), 2.83-2.75 (m, 1H), 2.17 (ddd, *J* = 13.1, 9.8 and 2.8 Hz, 1H), 1.85-1.22 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.6 (C), 135.2 (CH), 133.1 (C), 131.3 (CH), 130.0 (CH), 129.5 (2 CH), 125.2 (2 CH), 64.3 (CH), 29.4 (CH_2), 29.2 (CH), 29.0 (CH), 25.8 (CH_2), 23.0 (CH_2). MS (ESI): m/z 317 (M^+ + H, 100), 230 (46), 225 (13), 122 (20), 107 (23). HRMS (ESI): calculated for $C_{15}H_{17}N_4O_2S$ (M^+ + H): 317.1066; found: 317.1067.

Competition experiments for cycloadditions: The competition experiments were carried out with 0.1 mmol of vinyl sulfone **3** (23.6 mg) and 0.1 mmol of vinyl sulfones **1** (16.8 mg) or **2** (30.8 mg) in the same reaction conditions that the ones described for every substrate. **(1*R**,4*R**)-5,5-(Bis(phenylsulfonyl)bicyclo[2.2.1]hept-2-ene (30).** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.05-7.97 (m, 4H), 7.75-7.49 (m, 6H), 6.35-6.28 (m, 1H), 6.21-6.14 (m, 1H), 3.49-3.43 (m, 1H), 3.12-3.05 (m, 1H), 2.81 (dd, *J* = 14.0 and 3.8 Hz, 1H), 2.36-2.23 (m, 2H), 1.49-1.41 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 141.1 (CH), 140.8 (C), 138.5 (C), 134.2 (CH), 134.1 (CH), 133.9 (CH), 130.8 (2 CH), 130.5 (2 CH), 128.7 (2 CH), 128.5 (2 CH), 98.7 (C), 52.2 (CH), 49.9 (CH_2), 42.7 (CH),

34.3 (CH_2). MS (ESI): m/z 375 (M^+ + H, 100), 309 (15), 149 (15), 125 (67), 114 (24). HRMS (ESI): calculated for $C_{19}H_{19}O_4S_2$ (M^+ + H): 375.0719; found: 375.0733.

Data is in agreement with literature.[46]

Transformations

Julia-Kocienski olefination: The Diels-Alder adducts **22-23a** (24.2 mg, 0.08 mmol) and *p*-nitrobenzaldehyde (18.1 mg, 0.12 mmol) were dissolved in DME (2 mL). The mixture was cooled in a CO_2 / acetone at - 78ºC and was stirred for 5 min, whereupon KHDMS (0.5 M in toluene, 0.2 mL, 0.1 mmol), was added to the solution. After 10 min, the reaction was quenched with sat. aq. NH_4Cl (10 mL), and the mixture was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (hexane/EtOAc = 10:1) to afford 14.0 mg (Yield: 77%) of the corresponding olefin **31** as a 70:30 mixture of diastereomers. **(*Z*) and (*E*)-5-(4-Nitrobenzylidene)bicyclo[2.2.1]hept-2-ene (31).** Brown oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) (mixture of diastereomers): δ 8.26-8.14 (m, $2H_{major}$, $2H_{minor}$), 7.51-7.40 (m, $2H_{major}$, $2H_{minor}$), 6.65-6.57 (m, $1H_{minor}$), 6.38-6.13 (m, $3H_{major}$, $2H_{minor}$), 3.80 (bs, $1H_{major}$), 3.43 (bs, $1H_{minor}$), 3.23 (bs, $1H_{minor}$), 3.08 (bs, $1H_{major}$), 2.65-2.46 (m, $1H_{major}$, $1H_{minor}$), 2.26-2.13 (m, $1H_{minor}$), 2.09-1.97 (m, $1H_{major}$), 1.82-1.70 (m, $1H_{major}$, $1H_{minor}$), 1.64-1.44 (m, $1H_{major}$, $1H_{minor}$). **^{13}C NMR** ($CDCl_3$, 75 MHz) (mixture of diastereomers): δ 151.7 (C), 150.7 (C), 145.5 (C), 138.7 (CH), 138.0 (CH), 133.9 (CH), 132.6 (CH), 128.5 (CH), 127.8 (CH), 124.0 (CH), 123.7 (CH), 118.8 (CH), 53.7 (CH), 50.7 (CH_2), 47.2 (CH), 42.9 (CH), 40.9 (CH), 35.8 (CH_2), 35.1 (CH_2), 29.8 (CH_2). MS (EI): m/z 228 (M^+ + H, 36), 181 (16), 122 (100), 115 (20), 91 (22), 77 (17). HRMS (EI): calculated for $C_{14}H_{14}NO_2$ (M^+ + H): 228.1024; found: 228.1034.

α-Alkylation: Diels-Alder adducts **22-23a** (24.2 mg, 0.08 mmol) were dissolved in dry DME (2 mL). The mixture was cooled in a CO_2 / acetone at –78ºC and was stirred for 5 min, whereupon KHDMS (0.5 M in toluene, 0.2 mL, 0.1 mmol) and MeI (0.02 mL, 0.32 mmol) were subsequently added. After 20 min the reaction was quenched with sat. aq. NH_4Cl (10 mL), and the mixture was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified

by flash column chromatography (hexane / EtOAc = 10:1) to afford 17 mg (Yield: 67%) of compound **32** as a 1:1 mixture of diastereomers. **5-(2-Methylbicyclo[2.2.1]hept-5-en-2-yl)sulfonyl)-1-phenyl-1*H*-tetrazole (32).** White solid. Melting point: 121-123 ºC. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.64-7.57 (m, 5H), 6.24 (dd, *J* = 5.5 and 2.9 Hz, 1H), 6.10 (dd, *J* = 5.3 and 2.9 Hz, 1H), 3.26 (bs, 1H), 3.06 (bs, 1H), 2.25 (d, *J* = 13.1 Hz, 1H), 1.86 (dd, *J* = 13.1 and 3.6 Hz, 1H), 1.74-1.52 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.3 (C), 137.9 (CH), 133.2 (CH), 131.4 (CH), 129.4 (2 CH), 126.0 (2 CH), 73.5 (C), 52.1 (CH), 48.8 (CH_2), 43.0 (CH), 37.4 (CH_2), 24.9 (CH_3). MS (ESI): m/z 317 (M^+ + H, 100), 173 (6), 147 (43), 107 (9). HRMS (ESI): calculated for $C_{15}H_{17}N_4O_2S$ (M^+ + H): 317.1066; found: 317.1055.

Removal of the heterocycle and methylation of the sulfinate: Diels-Alder adduct **22a** (48.9 mg, 0.16 mmol) was dissolved in MeOH (2 mL) and sodium methoxide (25.3 mg, 0.48 mmol) was added to the solution. The mixture was stirred at room temperature for 15 min, whereupon MeI (0.1 mL, 1.6 mmol), was added to the solution. After 19 h, the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (hexane/EtOAc = 4:1) to afford 17.4 mg (Yield: 63%) of **34** as a yellowish oil. **(1*R**, 4*R**, 5*R**)-5-(Methylsulfonyl)bicyclo[2.2.1]hept-2-ene (34)**

Yellowish oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.24 (dd, *J* = 5.5 and 2.9 Hz, 1H), 6.06 (dd, *J* = 5.5 and 2.9 Hz, 1H), 3.63-3.51 (m, 1H), 3.37 (bs, 1H), 3.05 (bs, 1H), 2.80 (s, 3H), 2.24-2.10 (m, 1H), 1.63-1.45 (m, 2H), 1.40-1.30 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.9 (CH), 131.4 (CH), 63.5 (CH), 50.2 (CH_2), 45.1 (CH), 42.9 (CH), 41.1 (CH_3), 29.0 (CH_2). MS (EI): m/z 172 (M^+ + H, 5), 93 (51), 91 (44), 66 (100), 63 (10). HRMS (EI): calculated for $C_8H_{12}O_2S$ (M^+ + H): 172.0558; found: 172.0559.

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Supporting Information Available.

The Supporting Information is available free of charge on the ACS Publications website at DOI: Copies of ^{1}H and ^{13}C NMR spectra, X-Ray of compound **20a** and theoretical calculations (PDF).

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