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Organocatalytic Addition on 1,2-Bis(sulfone)vinylenes Leading to an Unprecedented Rearrangement

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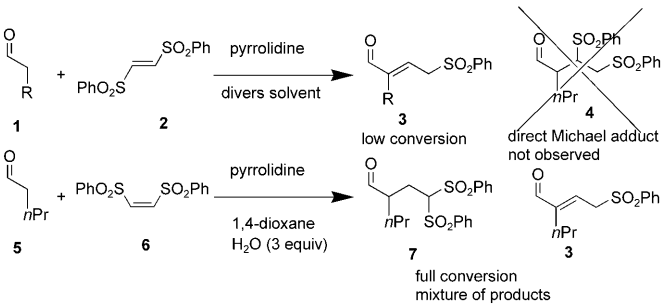
The last decade has seen a rapid and fruitful growth of organocatalysis. By allowing new modes of molecular activation, in often mild and non-anhydrous conditions, these organocatalysed reactions appear as a method of choice for its future use in industry.[1] Among the numerous catalytic activation modes, aminocatalysis, one of the most extensively studied has lead to numerous methodologies notably describing the asymmetric α-functionalization of carbonyl compounds. A large part of the research on this subject has been carried out with the aim to discover new nucleophile/electrophile combinations notably by conjugated addition that leads to the discovery of valuable synthons, and in few steps to natural products precursors.[2] Despite this impressive progress, the enantioselective direct α-alkylation of aldehydes and ketones remains a challenging task. Few reports have appeared recently on this subject and they still remain limited to specific substrates.[3] Another alternative method toward this α-alkylation has been developed in our group; this method makes use of the Michael addition on bis-activated substrates, such as 1,1-bis(sulfone)vinylenes and 1,1-bis(phosphonate)vinylenes.[4] Indeed, sulfones are highly valuable functionalities due to the great versatility of the sulfonyl group, which can undergo numerous transformations and can easily be cleaved at various synthetic stages.[5] In view of expanding the range of these highly tunable products, we wondered about using more versatile Michael adducts. Since we had previously shown that a single sulfone was not sufficient to undergo the enamine attack, we wondered if a 1,2-bis(sulfone)vinylene (IUPAC name: {[(*E*/*Z*)-2(phenylsulfonyl)ethenyl]sulfonyl}benzene) could accelerate the reaction leading to two different tunable functionalities.

Herein we report on the use of those 1,2-bis(sulfone)vinylenes in enamine catalysis. In an unexpected manner, these sulfones lead to a new rearrangement arising from a sulfone shift to the adjacent carbon atom. This quite general and impressively fast rearrangement constitutes an indirect practical α-alkylation of either aldehydes or ketones.

At the outset of our study, we focused our interest on bis(sulfone)vinylene **2**. As previously shown in our group, this compound, a powerful dienophile, did not react with *n*-valeraldehyde in the presence of pyrrolidine to give the expected Michael adduct **4**.[4a,c] However, a close scrutiny of the reaction mixture showed us that compound **3**, resulting from sulfinic acid elimination was formed (Scheme 1).[6a] Interestingly, use of the cheaper (*Z*)-1,2-bis(sulfone)vinylene **6** lead to full conversion after a short reaction time in dioxane, using H_2O as co-catalyst to accelerate the reaction.[6b] This difference between *E* and *Z* isomers seemed intriguing, since *Z* Michael acceptors are known to isomerize to the thermodynamically more favoured *E* isomer in the presence of amine catalysts.[7] More surprisingly, instead of the expected Michael adduct **4**, a new unexpected product **7** appeared, together with the elimination product **3**. A careful NMR study indicated that this new product was gem-disulfone **7**, and was corroborated by comparison with an authentic sample[4c] (Scheme 1).



Scheme 1. First trials on the Michael addition on 1,2-bis(sulfone)vinylenes.

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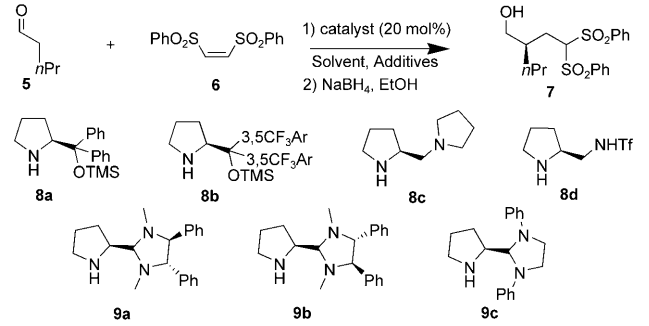
The presence of this product **7** coming from an unknown rearrangement was unexpected and it intrigued us. Indeed, to the best of our knowledge, such sulfone rearrangement had never been observed previously and could lead to interesting gem-disulfone adducts. This lead us to undergo a complete study on this reaction by starting optimising the reaction conditions in order to obtain a complete selectivity in favour of the rearranged product (Table 1).

Table 1. Catalysts and conditions screening for the addition of aldehyde to 1,2 bis sulfone **6**.[a]



	Cat	Solvent	t [h]	Conv[b] [%]	Yield[c] [%]	ee[d] [%]
1	**8a**	dioxane	7	45	traces	92
2	**8b**	dioxane	24	<10	nd	nd
3	**8c**	dioxane	3	100	32	0
4	**8d**	dioxane	9	25	nd	nd
5	**9a**	dioxane	3	100	56	70
6	**9b**	dioxane	3.5	100	26	43
7	**9c**	dioxane	3	100	36	64
8	**9a**[e]	$CHCl_3$	6	100	84	72
9	**9a**[e]	toluene	4	100	83 (71)	70
10	**9a**[e]	toluene (−10°C)	45	100	77 (49)	81

[a] Reactions were performed by using catalyst (20 mol%) and aldehyde (10 equiv) with bis(sulfone)vinylene (0.1 mmol) in solvent (0.2 mL). When using 1,4-dioxane as solvent, three equivalents of water as additive was needed to allow the reaction. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by ^{1}H NMR spectroscopy. Isolated yields are shown in brackets. nd= not determined. [d] Determined by super fluid chromatography. [e] Catalyst (10 mol%) and aldehyde (5 equiv) were used.

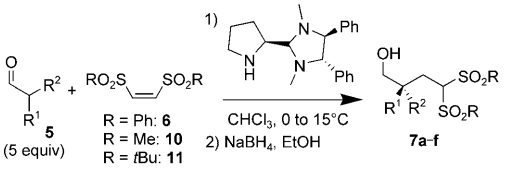
The first attempts using commercially available catalysts were rather disappointing. Indeed, only catalyst **8c** lead to complete conversion, but, unfortunately, gave a racemate (entry 3). In contrast, diphenylprolinol silyl ether **8a**, usually a powerful catalyst for Michael additions,[8] showed excellent enantiocontrol (92% *ee*), but only 45% conversion (entry 1). Furthermore, with all these catalysts, the reaction was really messy, leading to many byproducts (such as the product arising from the sulfinic acid elimination **3**). The absolute configuration of the rearranged product was ascribed by comparison with known compounds arising from the Michael addition on 1,1-bis(sulfone)vinylenes.[4]

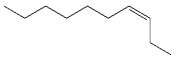
Unfortunately, all the attempts to obtain a useful reaction in terms of chemical yield failed using catalyst **8a**.[9] The use of chloroform, acidic additives in water (PhCOOH, AcOH), or 5% ethanol in water as recently used in our group,[10] lead to no, or dirty, reaction (result not presented). With this catalyst, the cleanest reaction (68% conversion, 40% NMR spectroscopic yield and 88% *ee* in 8 h) was in water. However, this reactivity was limited to this example, since no reaction at all was observed with isovaleraldehyde as donor. All these disappointing results lead us to turn our attention to the use of our recently developed aminal–pyrrolidine catalysts, which already showed excellent reactivity on 1,1-bis(sulfone)vinylenes.[11] To our delight, the three already published catalysts **9a**–**9c** lead to a cleaner reaction in an impressive short reaction time (entries 5–7). A short solvent screening using 10 mol% of the best catalyst **9a** and decreasing the amount of aldehyde to five equivalents, indicated that the reaction performed best in toluene or chloroform with less then 20% self-aldol product formed (entries 8 and 9). Full conversion was obtained and the elimination compound **3** was observed in less then 15% using these solvents (entries 8–10).[12] Finally, decreasing the temperature to −10°C considerably slowed down the reaction, while increasing the *ee* to 81%. To keep an excellent reactivity, a temperature of 15°C was then used in the reaction and other aldehydes were tested to confirm the generality of this reaction (Table 2).

Interestingly, using catalyst **9a**, this rearrangement was observed with different Michael donors. Indeed, by using different linear aldehydes, good yields and enantioselectivities could be obtained in an impressively short time. The more bulky the aldehyde, the better the yield and enantioselectivity. Indeed, using *i*Pr or *t*Bu as R^1 groups, no traces of the elimination product was observed, while *ee* up to 87% could be reached (entries 4 and 5). In contrast, when using propionaldehyde as Michael donor (R^1=Me), poor conversions were obtained, probably due to the formation of a large amount of sulfinic acid by the elimination pathway (result not shown in the table). Changing the sulfone group to SO_2Me instead of SO_2Ph also lead to an increased reactivity and excellent yield, while lower *ee* was observed. This lower enantioselectivity indicates that the more bulky SO_2Ph must interact strongly with the catalyst in the transition state, leading to the higher *ee*. In contrast, the reaction with the SO_2tBu group lead to a slow reaction rate and to a messy mixture (entry 7). Finally, this process is equally efficient, in terms of yields, when an α-disubstituted aldehyde is used, while leading to lower enantioselectivity (entry 8). Although low (*ee*=30%), the *ee* is still higher then the one already observed in the case of 1,1-bis(sulfone)vinylene.[4c] Surprisingly, when using the *E* starting material **2** in DMF (in order to increase the solubility of bis(sulfone)vinylene), 87% of the Michael adduct **7g** could be obtained (entry 9).

The Michael addition of ketones to bis(sulfone)vinylenes represents an even more challenging task in enamine catalysis. Indeed, using catalyst **9a**, the addition of cyclohexanone to 1,1-bis(sulfone)vinylene leads to a complex mixture of mono- and di-addition product and product arising from the degradation of the bis(sulfone)vinylene, with poor enantiocontrol (Scheme 2). Only recently, Lu et al. described the addition of six-membered ring ketones to this disulfone, using a primary amine cinchonidine derivative.[13]

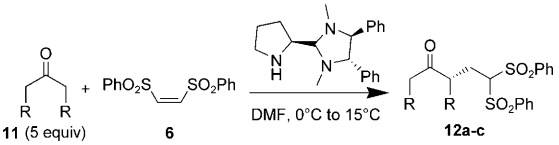
Table 2. Addition of aldehydes to 1,2-bis(sulfone)vinylenes.[a]

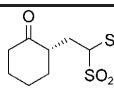
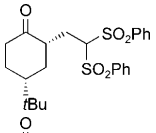
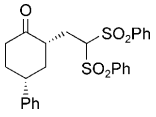


	R	R^1, R^2	Product	**9a** [mol %]	*t* [h]	Yield[b] [%]	*ee*[c] [%]
1[d]	Ph	*n*Pr, H	**7a**	10	45	49	81
2	Ph	C_7H_{15}, H	**7b**	15	3	72	78
3	Ph		**7c**	15	3	59	76
4	Ph	*i*Pr, H	**7d**	20	6	86	82
5	Ph	*t*Bu, H	**7e**	20	9	89	87
6[e]	Me	*i*Pr, H	**7f**	15	2	92	45
7[f]	*t*Bu	*n*Pr, H	–	20	24	nr	nr
8[f]	Ph	Et, Me	**7g**	20	17	76	30
9[f,g]	Ph	Et, Me	**7g**	20	14	87	28

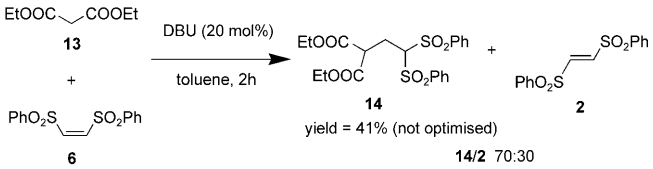
[a] Reactions were performed with bis(sulfone)vinylene (0.2 mmol) in solvent (0.4 mL). [b] Isolated yields; nr = no reaction. [c] Determined by super fluid chromatography. [d] Reaction performed at −10 °C in toluene. [e] Reaction performed with bis(sulfone)vinylene (0.3 mmol). The enantiomeric excess was determined by derivatisation to the corresponding imidazolidine (see the Supporting Information). [f] Reaction performed at room temperature (25 °C). The results are obtained without reduction to the alcohol [g] The *E* starting bis(sulfone)vinylene **2** was used in DMF as solvent.

Table 3. Addition of ketones to 1,2-bis(sulfone)vinylenes **6**.[a]



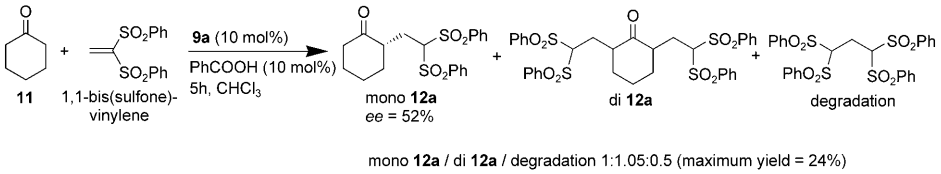
	Product	*t* [h]	d.r. (*syn*/anti)[b]	Yield [%][c]	*ee*[d] [%]
1		9	–	66	69
2		5.5	1.85:1 (1.5:1)[e]	61 (63)[e]	71 (68)[e]
3		9	3.76:1	67	73

[a] Reactions were performed with bis(sulfone)vinylene (0.2 mmol) in solvent (0.4 mL). [b] Determined by ^{1}H NMR spectroscopy. [c] Isolated yields. [d] Determined by super fluid chromatography. [e] Result obtained with catalyst **8c** are shown in brackets.



Scheme 3. Observed rearrangement using Bronsted base catalysis

We were therefore interested to know if our methodology could be a valuable alternative for this addition of ketones to bis(sulfone)vinylenes. Preliminary results are summarized in Table 3. Gratifyingly, using more polar solvents as DMF, 1,2-bis(sulfone)vinylene **6** did undergo the expected reaction

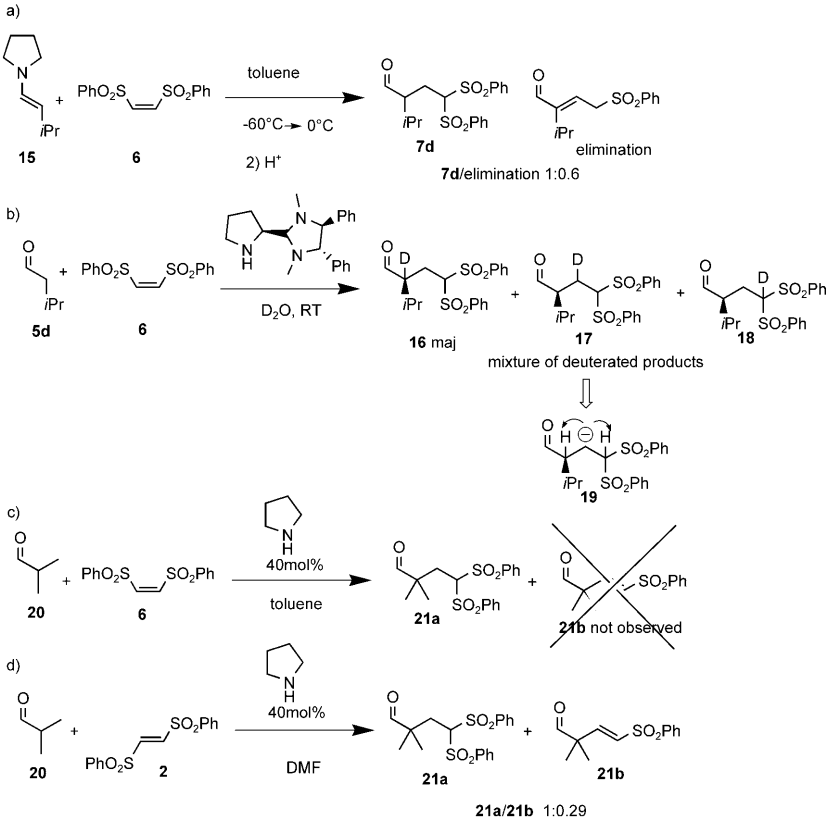


Scheme 2. Addition of cyclohexanone to 1,1-bis(sulfone)vinylene

in a fast and efficient way. The rearranged product could be obtained in good yield and moderate enantioselectivity. Commercially available catalyst **8c** also gave similar levels of yield and *ee* in this reaction (entry 2).

Finally, in a first test, the reaction of diethyl malonate with sulfone **6** confirmed that this rearrangement could be generalized to other nucleophiles (Scheme 3). Indeed, in the presence of DBU as catalytic base, compound **14** was formed in 41 % yield after 2 h. A control experiment by mixing a catalytic amount of DBU with the (*Z*)-sulfone **6** lead to the formation of the *E* isomer after 24 h, without any traces of 1,1-bis(sulfone)vinylene. Furthermore, this *E* isomer did not react under these reaction conditions.

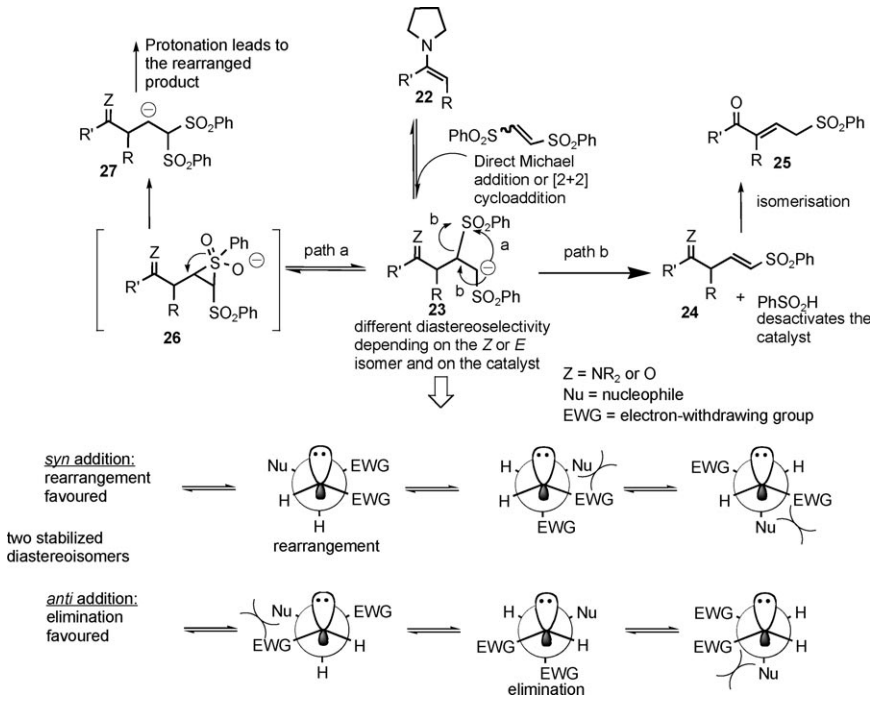
In view of the broad generality of the observed rearrangement, a short mechanistic study was undergone to better understand what was really going on in this reaction. Thus, several observations were made and are summarized in Scheme 4. The various results (both in terms of reactivity and enantioselectivity) using 1,2-bis(sulfone)vinylene and 1,1-bis(sulfone)vinylene, and the absence of any trace of the 1,1-bis(sulfone)vinylene, while monitoring the reaction by NMR spectroscopy, let us think that the rearrangement must occur after the enamine attack. This was further confirmed by the fact that mixing the catalyst and the 1,2-bis(sulfone)vinylene without aldehyde leads to an unidentifiable mixture of products that do not react with isovaleraldehyde. Furthermore, preformed enamine **15** reacted with the 1,2-bis(sulfone)vinylene, rapidly, affording a mixture of compounds **7d** and elimination product (Scheme 4a). An experience of anion trapping in deuterated water lead to a mixture of the three different deuterated compounds **16**, **17**, and **18** (Scheme 4b). We hypothesize



Scheme 4. Mechanistic observations

that these three compounds may come from the same intermediate anion **19**. A control experiment indicated that addition to the 1,1-bis-(sulfone)vinylene lead to the single deuterated compound **18** coming from the anion located on the carbon bearing the two sulfonyl groups. The formation of this anion provides good information in terms of mechanism, but should not be applied as a model in terms of stereoselection, since lower *ee* values are obtained in this solvent.

All these results clearly show that the 1,2-bis(sulfone)vinylene reacts directly with the nucleophile forming an ionic intermediate, which then undergoes the rearrangement. This lead us to postulate a plausible mechanism presented in Scheme 5. In a first part, the enamine reacts on the 1,2-bis(sulfone)vinylene by a Michael addition, or by a [2+2] cycloaddition as already described on the addition to diethyl fumarate.[14] This [2+2] cycloaddition is consistent with the observed high reactivity. Cyclobutane-opening by water would then lead to the formal Michael adducts. Depending on the substrate, two possibilities appear with this anion **23** depending on the relative conformation of the sulfone and the adjacent anion. If the anion is placed *antiperiplanar* to the adjacent sulfone, the direct sulfinic acid elimination through path b leads to the elimination product **24** and catalyst deactivation. If the anion is placed *syn* to the adjacent sulfone, we postulate that the only possible reaction is the attack of this anion on the sulfur atom leading to the unstable species **26**, which instantaneously rearranges to compound **27**. Further fast reprotonation leads to the final rearranged compound. This instantaneous reprotonation



Scheme 5. Possible mechanism and explanation of the observed selectivity between rearranged and elimination product.

should prevent the isomerisation of the product and the elimination of one of the two sulfone α to the anion.

To explain the fact that the elimination occurs or not depending on the different substrates, we postulate that the formed anion is pyramidal[15] and relatively long living. This is consistent with the different results obtained using the two starting materials *E* or *Z*. As depicted in Scheme 4c and d, by using the same Michael donor in the case of the *Z* isomer no elimination is observed, while this elimination product is formed when using the *E* isomer. This is consistent with the formation of a chiral anion as shown in Scheme 5. Indeed, if one of the two isomers is formed during the reaction, the nucleophile being bulky enough to prevent the rotation around the C–C bond, and if the interconversion between the two diastereoisomers is sufficiently slow, a perfect selectivity in favour of the rearranged product is observed. This would indicate that the rearrangement is faster then the isomerisation of the chiral anion. In the case of the *E* isomer a poor diastereocontrol leads to an increased amount of elimination product. In the case of less hindered nucleophiles (as propionaldehyde), either a lower diastereoselection or the free rotation in the C–C bond is easier. This leads to a higher amount of the form able to undergo the elimination.

In conclusion, by using cheap and easily available 1,2-bis-(sulfone)vinylene, an unprecedented rearrangement consisting in a sulfone shift leading to gem-disulfone has been observed. Our newly designed aminal–pyrrolidine catalyst gave impressively high reactivity in this transformation and up to 87% *ee* could be obtained. This unprecedented rearrangement is quite general, as long as the nucleophile used is sufficiently bulky, and as long as a good diastereocontrol is obtained on the transient anion. It constitutes an interesting alternative to the use of other more expensive bis-(sulfone)vinylenes in asymmetric synthesis notably in the case of ketones and constitutes an indirect practical α-alkylation of carbonyl compounds. Studies are currently underway in our laboratory to expand the scope of such reactions.

Experimental Section

For information of the experimental details please see the Supporting Information.

Keywords: asymmetric synthesis · enamines · organocatalysis · rearrangement · sulfones

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