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PAPER

1,2-Sulfone rearrangement in organocatalytic reactions†

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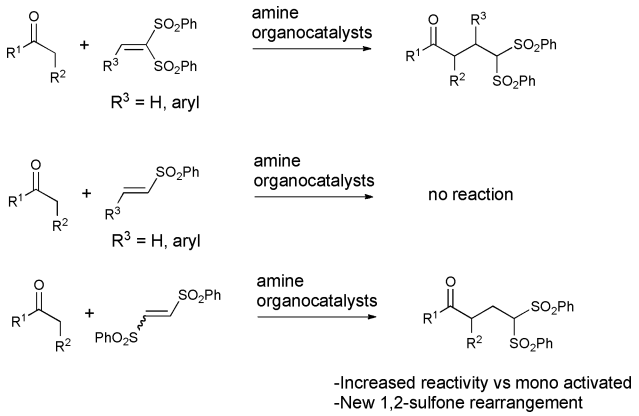
The 1,2-sulfone rearrangement resulting from nucleophilic addition to bis activated vinyl-sulfones has been studied in more detail. Various nucleophiles activated by different types of catalysts (enamine, Brönsted base, thiourea) are able to promote such rearrangement in excellent yields and moderate to excellent enantioselectivities (up to 94% *ee*). Mechanistic studies have led to a better understanding of the mechanism and allowed its application to other electrophiles such as vinyl-sulfone acrylates.

Introduction

The synthesis of enantiopure molecules remains a challenging task in organic synthesis. In the past ten years, organocatalysis has received much attention from the scientific community. This is due to the relative novelty of the area where everything had to be discovered and to its operational easiness.[1] Among the reaction modes, enamine catalysis and bifunctional Brönsted base/thiourea catalysis have proven their ability in a wide range of reactions, notably Michael additions that allowed the formation of new C–C bonds.[2] Interestingly, these new modes of reaction have led to the discovery of new reactivities and thus to new chemical rearrangements.[3]

Sulfones have recently appeared as a functionality of choice in organocatalysis.[4] Due to their strong electron withdrawing ability, they can activate either the electrophilic or the nucleophilic partner notably in conjugate addition, leading to the creation of new interesting C–C bonds. In addition, this group can easily be used in further transformation rendering it highly useful for its future application in total synthesis or in Diversity Oriented Synthesis.[5] At the end of the reaction sequences it is thus easy to remove it by either reductive elimination using Mg° or Na°/Hg or by elimination, leading to new functional groups such as carbonyls or C–C double or triple bonds. Another practical advantage: sulfones are easy to handle, often-crystalline solids making them attractive for industrial applications. All these advantages have led during the last two years to numerous applications of sulfones in organocatalytic reactions.[4]

Our group was the first to introduce 1,1-bis(phenylsulfonyl)ethene (R^3 = H) in enamine organocatalysis (Scheme 1).[6] This electrophile was found to be highly reactive, leading to impressively clean and fast reactions using either linear/α-branched aldehydes, or ketones.[7] Furthermore,



Scheme 1 Hypothesis for the application of 1,2-diactivated substrates.

alkylation/desulfonylation sequences led to a formal α-alkylation of carbonyl, a challenging reaction in enamine catalysis.[8] When a substituent is added to this electrophile, (R^3 = Ar), numerous side reactions, such as the retro–Michael reaction can occur limiting the scope of such acceptors.[7] On the contrary, singly activated vinyl-sulfone showed no reactivity at all in these reactions except in their intramolecular version.[9] 1,2-Diactivated vinyl electrophiles have mostly found applications as dienophiles in dipolar cycloadditions where the LUMO of the dienophile is strongly lowered by the two electron-withdrawing substituents.[10] This property was thus applied in the addition of preformed enamine leading to a fast [2 + 2] cycloaddition reaction.[11] Recently several research groups have applied 1,2-diactivated Michael adducts to enamine organocatalysis constructing multiple functionalized synthons.[12] These valuable synthons have found several applications notably toward the synthesis of natural product core.

Taking into account this increased reactivity of 1,2-diactivated vinyl electrophiles we thus wondered about increasing the scope of the Michael addition on vinyl sulfone by introducing a second sulfone on a Michael adduct that would accelerate the reaction (Scheme 1). These new substrates have led to the discovery of a

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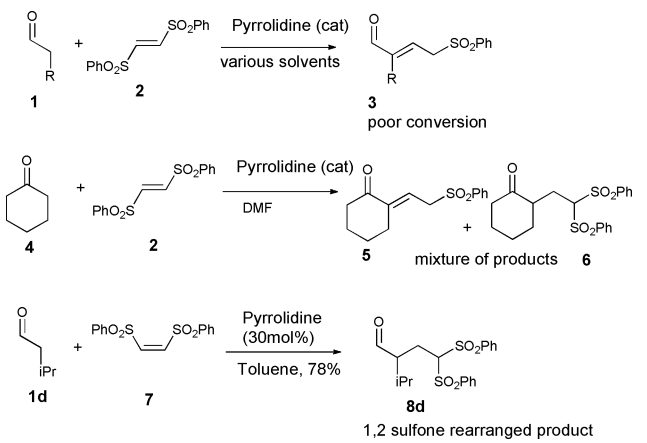
new 1,2-sulfone rearrangement using enamine organocatalysis.[13] Herein we report a full account of this new rearrangement including increased enantioselectivity using aminal–pyrrolidine organocatalysts, new applications in Brönsted base catalysis, mechanistic investigation and electrophilic scope using notably other electron-withdrawing groups. All this study demonstrates the power of the 1,2-sulfone rearrangement and its utility as a complementary method for the formal α- alkylation of carbonyls.

Results and discussion

Preliminary discovery in enamine catalysis

Cis-1,2-bis(phenylsulfonyl)ethene **7** is a molecule easily obtained in two steps from *cis* 1,2-dichloroethene.[10] In order to test the difference in reactivity between mono vinyl sulfone and 1,2-diactivated sulfones, the addition of linear aldehydes catalysed by pyrrolidine was tested in various solvents (Scheme 2). Using *trans*-1,2-bis(phenylsulfonyl)ethene **2** and linear aldehydes, almost no reaction was observed under different conditions, and only the elimination product **3** was detected in the reaction mixture. In the case of cyclohexanone **4**, a mixture of two products **5** and **6** (1 : 1 ratio) was obtained. This clearly shows an activation by the two sulfones, increasing the reactivity compared to mono-vinyl sulfone, where no reaction at all occurs. The observation of elimination product **5** was quite normal since sulfones are known also to be good leaving groups.[14] However, the product **6** was totally unexpected. NMR comparison with known compounds, arising from similar addition using 1,1-bis(phenylsulfonyl)ethene, confirmed that we were in the presence of the corresponding gem-disulfone **6**. This was, to our knowledge, the first example of such a 1,2-sulfone shift. We thus decided to further investigate the scope of this reaction.

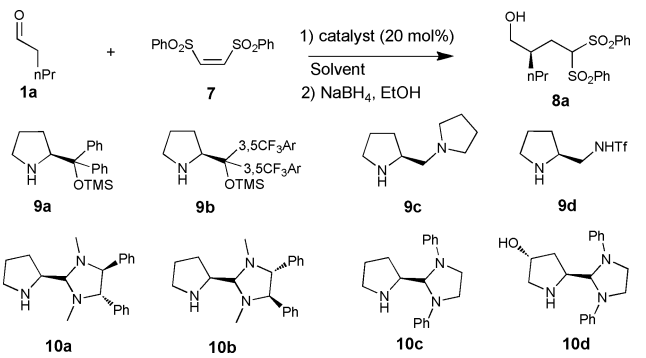


Scheme 2 Preliminary discovery of the 1,2-sulfone rearrangement.

Screening of conditions for the aldehyde addition

First, a catalyst survey was done to find a chiral catalyst that would perform well in such a reaction (Table 1). From the first trials, it was obvious that the critical point for the development of such a reaction was the control of the selectivity between elimination and rearranged product that seemed to depend directly on the catalyst. Using conventional commercially available enamine catalysts

Table 1 Catalysts and conditions screening for the addition of aldehyde to *cis*-1,2-bis(phenylsulfonyl)ethene **7**

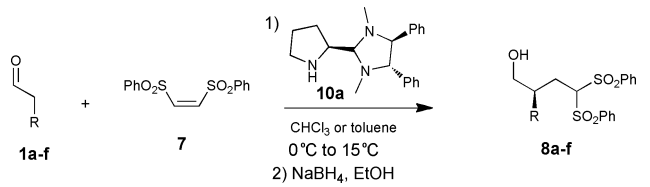


Entry[a]	Cat.	Solvent	t (h)	Conv[b] (%)	Yield[c] (%)	*ee*[d] (%)
1	9a	dioxane	7 h	45%	traces	92%
2	9b	dioxane	24 h	<10%	nd	nd
3	9c	dioxane	3 h	100%	32%	0%
4	9d	dioxane	9 h	25%	nd	nd
5	9a	toluene	24 h	<10%	nd	nd
6	9a	$CHCl_3$	24 h	<10%	nd	nd
7	9a	H_2O	20 h	68%	40%	88%
8	10a	dioxane	3 h	100%	56%	70%
9	10b	dioxane	3.5 h	100%	26%	43%
10	10c	dioxane	3 h	100%	36%	64%
11	10d	dioxane	8 h	15%	nd	nd
12	10a	CH_3CN	20 h	19%	nd	nd
13	10a	MeOH	24 h	<10%	nd	nd
14	10a	H_2O	20 h	100%	86% (64%)	20%
15	**10a**[e]	**$CHCl_3$**	**6 h**	**100%**	**84%**	**72%**
16	**10a**[e]	**toluene**	**4 h**	**100%**	**83% (71%)**	**70%**
17	**10a**[e]	**toluene (–10 °C)**	**45 h**	**100%**	**77% (49%)**	**81%**

[a] Reactions were performed using 20 mol% of catalyst and 10 equivalents of aldehyde on 0.1 mmol of vinyl sulfone in 0.2 ml of solvent. When using 1,4 dioxane as solvent, 3 equivalents of water as additive was needed to allow the reaction. [b] Determined by ^{1}H NMR. [c] Determined by ^{1}H NMR. Isolated yields are shown in parentheses. [d] Determined by super fluid chromatography. [e] 10 mol% of catalyst and 5 equivalents of aldehyde were used.

failed to give an applicable reaction (entries 1–4). Really poor rearranged product selectivity was obtained using all these catalyst in dioxane, although a good result in terms of enantioselectivity was obtained (entry 1). All attempts to obtain better reactivity and selectivity with catalyst **9a** failed (entries 5–6). Only the use of water led to an increased selectivity with 40% NMR yield. Further attempts using acidic additives totally inhibited the reaction. Gratifyingly, turning our attention to our recently developed aminal–pyrrolidine catalysts, notably **10a**, led to a promising 56% NMR yield of the rearranged product together with a good 70% *ee* (entry 8).[15] Solvent screening indicated that both rearrangement selectivity and enantioselectivity were highly solvent dependent. Yields varied from only traces using acetonitrile or methanol to 64–71% using toluene or water (entries 12–16). Quite surprisingly, when using water, only 20% *ee* was obtained, probably due to an erosion of the enantioselectivity on the final product. In contrast, in toluene, 70% *ee* was obtained at room temperature. Furthermore, this result could be increased to 81% by decreasing the temperature to –10 °C together with a slightly lower selectivity in favour of the rearranged product (entry 17).

Table 2 Addition of aldehydes to *cis*-1,2-bis(phenylsulfonyl)ethene



Entry	R	Prod.	mol% **10a**	t (h)	Yield[a]	Charton value (υ)[b]	*ee*[c] (%)
1	*n*Pr	8a	15	3 h	64%	0.68	77%
2[d]	*n*Pr	8a	10	45 h	49%	0.68	81%
3	C_7H_{15}	8b	15	3 h	72%	0.73	78%
4		8c	15	3 h	59%	—	76%
5	*i*Pr	8d	20	6 h	86%	0.76	82%
6	*t*Bu	8e	20	9 h	89%	1.24	87%
7	Me	8f	20	24 h	trace	0.52	nd

[a] Isolated yields. [b] See ref [16] for Charton values. [c] Determined by super fluid chromatography. [d] reaction performed at −10 °C in toluene.

Scope of the reaction with aldehydes

The generality of the reaction was confirmed using various aldehydes (Table 2). All the aldehydes were reduced prior to purification to avoid any epimerisation. To our delight, the rearrangement was observed in good isolated yields (49–89%) and moderate to good enantioselectivities (76–87% *ee*) from small linear aldehydes (R = *n*Pr) to bulky aldehydes (R = *t*Bu). The smaller the substituent the lower the yield, while bigger substituents, such as *t*Bu or *i*Pr lead to a total selectivity in favour of the rearranged product. The same trend is observed for the *ee* ranging from 77% in the case of *n*Pr to 87% in the case of *t*Bu. 20 mol% of catalyst was used in the case of bulkier aldehydes to ensure total conversion.

Charton analysis

To try to correlate directly these observed selectivities to the size of the R substituent a Charton analysis was performed.[16] Charton correlation has recently been applied to directly correlate the size of substituents to enantioselectivity in asymmetric catalysis.[17] Plotting the enantioselectivity as a function of the size of the R substituent of the aldehyde gave a good correlation (Fig. 1). The enantioselectivity directly depends on the size of the substituent even if the sensitivity factor is relatively small (ψ = 0.45). This indicates a direct dependence of the catalyst's activity on the substrate size, and thus the necessity of designing a better catalyst.

A direct correlation between yield and Charton value was then undertaken (Fig. 2). This was possible since the yield is directly dependant on the selectivity between the rearranged product and the elimination one. Furthermore this selectivity does not depend on the reaction time. An impressive effect of the substituent was observed on the rearrangement selectivity. Indeed, a sensitivity factor ψ of 3.54 was observed with an excellent correlation. When the maximum selectivity is observed (R = *i*Pr), the curve becomes flat, and the yield does not depend any more on the size of the substituent, but the major factors come from technical operations. Thus 100% selectivity in favour of the rearranged product is obtained for bigger substituents.

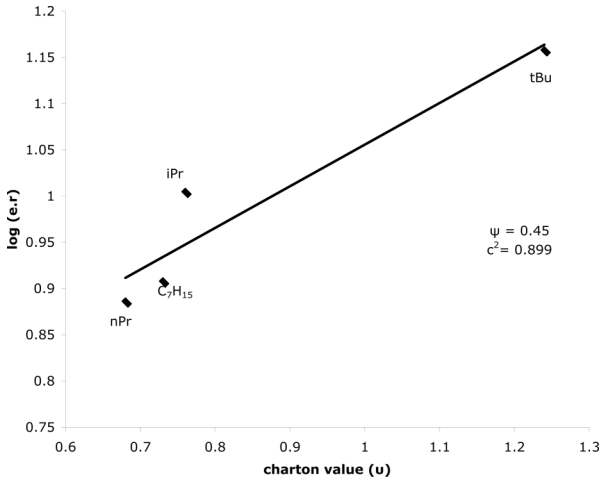


Fig. 1 Charton plot of the enantioselectivity of the sulfone rearrangement.

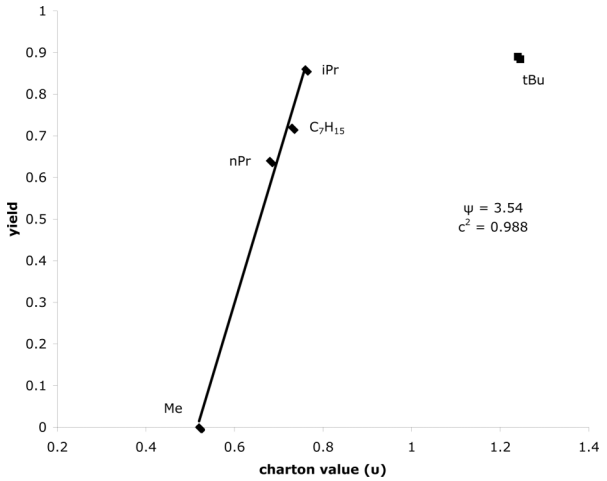


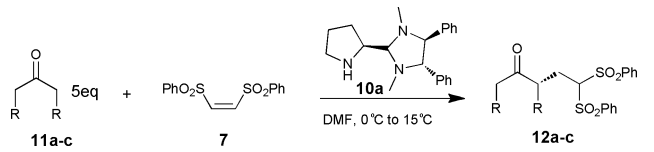
Fig. 2 Charton plot of the yield of the sulfone rearrangement.

This observation is of great importance in terms of mechanism since it clearly indicates that the selectivity of the rearrangement only depends on one parameter: the steric bulk of the substituent on the aldehyde; the larger the group was, the higher the selectivity was.

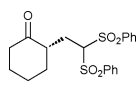
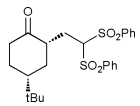
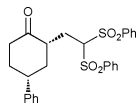
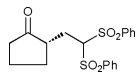
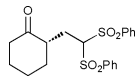
Addition of ketones and α-substituted aldehydes

In addition to simple aldehydes, we wondered if this rearrangement could be applied to other substrates. Thus, different cyclohexanones afforded the rearrangement in good yields (61–67% yield) and moderate enantioselectivities (69–73% *ee*) (Table 3). Highly polar solvents such as DMF had to be used in these transformations since toluene or chloroform only afforded partial conversions. The use of cyclopentanone only afforded traces of the product together with a mixture of starting material and elimination product (entry 4). This suggests a dependence of the rearrangement on the geometry of the enamine. This is further confirmed by the use of the *trans*-isomer of the 1,2-disulfone (entry 5). While it did not undergo any rearrangement in the case of aldehydes, cyclohexanone gave 84 : 16 selectivity in favour of the rearranged product, *versus* the elimination product.

Table 3 Addition of ketones to *cis*-1,2-bis(phenylsulfonyl)ethene

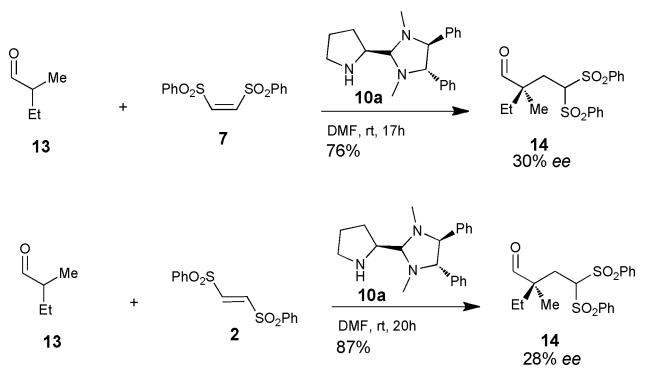


11a-c 7 12a-c

Entry	Product	t (h)	dr (*syn*/*anti*)[a]	Yield[b]	*ee*[c] (%)
1		9 h	—	66%	69%
2		5 h 30	1.85/1 (1.5/1)[d]	61% (63%)[d]	71% (68%)[d]
3		9 h	3.76/1	67%	73%
4		9 h	—	traces	—
5[e]		22 h	—	68%	64%

[a] Determined by ^{1}H NMR. [b] Isolated yields. [c] Determined by super fluid chromatography. [d] Result obtained using catalyst **9c** are shown in parentheses. [e] Using *trans*-1,2-bis(phenylsulfonyl)ethene. NMR yield.

Finally, the 1,2-sulfone rearrangement was observed using α-substituted aldehydes (Scheme 3). Again, both *cis* and *trans* isomers perform well in this reaction but, unfortunately with relatively low enantioselectivity (28–30% *ee*). This is due to the difficulty in controlling the enamine geometry when two relatively similar groups are present.



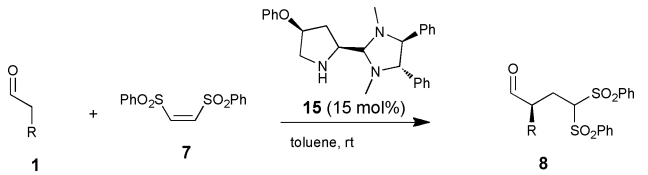
Scheme 3 1,2-Sulfone rearrangement using α-substituted aldehydes.

Improved catalyst for the enamine 1,2-sulfone rearrangement

Although good selectivities in favour of the rearranged product could be obtained using catalyst **10a**, we thought about improving the enantioselectivities of the reactions. We recently disclosed the synthesis of an improved version of the aminal–pyrrolidine catalysts by introduction of a phenoxy group in the 4-position of the pyrrolidine ring.[7e] As expected, this improved catalyst **15** did give good enantioselectivities together with excellent selectivities in favour of the rearranged product (Table 4). Up to 94% *ee* could be obtained in the case of the *i*Pr group (entry 2). Surprisingly, a lower 90% *ee* is obtained in the case of the bulkier *t*Bu group. This suggests a secondary interaction between this *t*Bu group and the catalyst, slightly changing the transition state.

Finally, in the case of cyclohexanone, just a slight improvement was observed and the resulting rearranged adduct was obtained in 76% *ee* (Scheme 4).

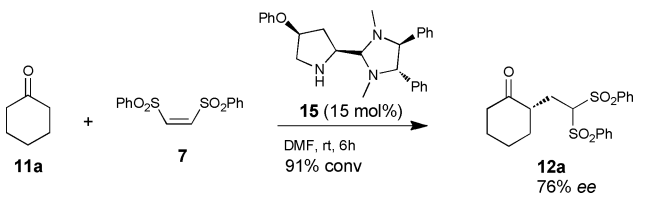
Table 4 Addition of aldehydes to *cis*-1,2-bis(phenylsulfonyl)ethene



1 7 8

Entry	R	Prod.	t (h)	Yield[a]	*ee*[b] (%)
1[c]	*n*Pr	8a	4 h	59%	84%
2	*i*Pr	ald-8d	10 h	88%	94%
3	*t*Bu	ald-8e	5 h	76%	90%

[a] Isolated yields. [b] Determined by super fluid chromatography. [c] After reduction to the corresponding alcohol.



11a 7 12a
76% *ee*

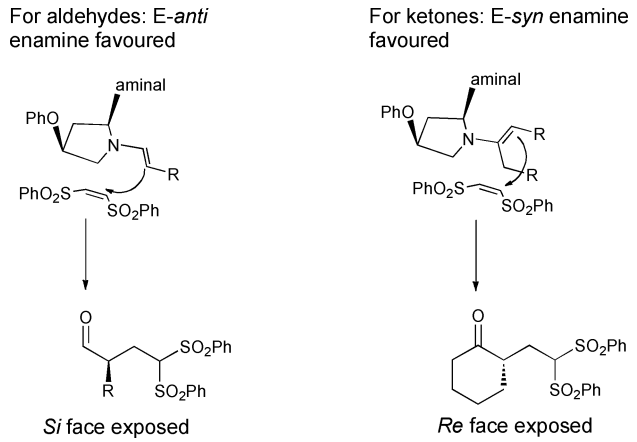
Scheme 4 1,2-Sulfone rearrangement using cyclohexanone and **15**.

Stereochemical outcome of the reaction

The absolute configuration of the rearranged product was determined by direct comparison with original samples obtained by addition of 1,1-bis(phenylsulfonyl)ethane.[6,7] The asymmetric induction is exactly the same as for 1,1-bis(phenylsulfonyl)ethene and can thus be rationalized by a transition state based on steric interactions (Scheme 5). In the case of aldehydes, the E-*anti* enamine is favoured and the two bulky groups efficiently shield the upper face of the enamine. Thus the *Si* face is the only one available for the electrophilic attack. In the ketone's case, the E-*syn* enamine is favoured since the sp^2 carbon is smaller than the sp^3 one. Consequently, the attack occurs on the less hindered *Re* face.

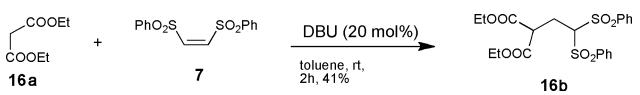
1,2-Sulfone rearrangement catalysed by chiral base/thiourea catalysts

Having shown that the 1,2-sulfone rearrangement was quite general in enamine catalysis, we thus wondered about broadening its scope to other type of nucleophiles. Bifunctional Brönsted base/acid catalysts have been widely used in the addition of various nucleophiles to vinyl sulfones.[18] Since the nucleophiles used are relatively bulky and the reactions occur in really mild conditions, with well-defined transition states, we decided to test



Scheme 5 Stereochemical outcome of the reaction.

our rearrangement using such activation. Gratifyingly, the first experiment using DBU as a base catalyst in the addition of diethyl malonate to *cis*-1,2-bis(phenylsulfonyl)ethene led to a promising 41% yield of the expected rearranged product (Scheme 6). This result was highly promising since it showed that the 1,2-sulfone rearrangement could be generalised to other types of activation and thus to other electrophiles.

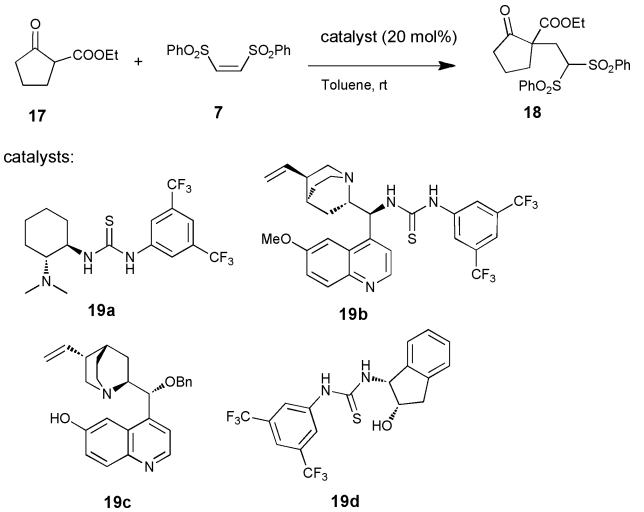


Scheme 6 First experiment using base catalysis.

We next turned our attention to the asymmetric version of this reaction by first focusing on pro-chiral keto-ester **17** (Table 5). A catalyst survey was performed using different chiral bases ((DHQD)$_2$PHAL), thiourea (**19d**), or bifunctional catalysts (**19b**, **19c**). We were pleased to see that the 1,2-sulfone rearrangement was observed in a clean manner with all the different catalysts. This indicates that different modes of activation are able to promote the addition to cis-1,2-bis(phenylsulfonyl)ethene and the subsequent rearrangement. Indeed, even catalyst **19d** that contains only a strong acidic thiourea without any strong base is able to activate the electrophile sufficiently and to promote the rearrangement. Furthermore, in all the cases the reaction was very clean, leading almost exclusively to the rearranged product in high yields (75–93% yield). Unfortunately, none of these catalysts gave good stereoselectivity in this reaction. The best result (44% *ee*) was obtained when performing the reaction at –20 °C using **19a**. Alas, this is too low to afford any valuable reaction.

We then looked at another class of donor: nitro-esters **20a** and **20b** (Table 6). In a preliminary attempt using DBU as the base, a mixture of rearranged and elimination products was obtained. Fortunately, turning to chiral base catalysts led to a total selectivity in favour of the rearranged adduct. Catalyst screening indicated that at room temperature, cinchona derivative **19b** performed the best leading to a promising 60% *ee* (entry 3). It seems that a dual activation of both the nucleophile by the basic part, and of the electrophile by the thiourea, is primordial for a good enantioselectivity since all the catalysts containing only one of the two activations only lead to low enantioselectivities. When the temperature was decreased to –20 °C, the enantioselectivity could be increased to

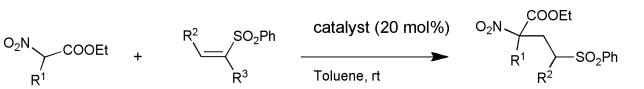
Table 5 Addition of keto-ester **17** to *cis*-1,2-bis(phenylsulfonyl)ethene



Entry	Catalyst	t (h)	Conv[a]	*ee*[b] (%)
1	quinine	20 h	100% (75%)	6%
2	quinidine	18 h	100% (84%)	6%
3	19a	1 h 30	100% (93%)	6%
4	19b	1 h 30	100% (88%)	0%
5	19c	16 h	full conv	28%
6	19d	24 h	full conv	8%
7	(DHQD)$_2$PHAL	24 h	100% (79%)	20%
8	**19a (–20 °C)**	**120 h**	**100% (91%)**	**44%**

[a] Conversion determined by ^{1}H NMR. Isolated yields are shown in parentheses. [b] Determined by super fluid chromatography.

Table 6 Addition of nitro-esters to *cis*-1,2-bis(phenylsulfonyl)ethene



R = Me, **20a**
R = Et, **20b**

$R^2 = SO_2Ph$, $R^3 = H$ **7**
$R^2 = H$, $R^3 = SO_2Ph$ **21**
$R^2 = H$, $R^3 = H$ **22**

R^1 = Me, $R^2 = SO_2Ph$ **23a**
R^1 = Et, $R^2 = SO_2Ph$ **23b**
R^1 = Me, $R^2 = H$ **24**

Entry[a]	Product	Catalyst	t (h)	Yield[b]	*ee*[c] (%)
1	23a	DBU	2 h	100%[d]	—
2	23a	19a	5 h	73%	35%
3	23a	19b	8 h	83%	60%
4	23a	19c	6 h	full conv	14%
5	23a	19q	16 h	full conv	6%
6	23a	(DHQD)$_2$PHAL	4 h	100% (75%)	14%
7[e]	**23a**	**19a**	**20 h**	**100% (78%)**	**76%**
8[e]	**23a**	**19b**	**20 h**	**100%**	**73%**
9[e]	**23b**	**19a**	**24 h**	**74%**	**74%**
10[e]	**23b**	**19b**	**24 h**	**100% (85%)**	**76%**
11[f]	23a	19b	1 h	100%	28%
12[g]	24	19b	6 h 30	100%	16%

[a] Reaction performed at 0. 5 mol L^{-1} at room temperature. [b] Conversion observed by ^{1}H NMR. Isolated yields are shown in parentheses. [c] Determined by super fluid chromatography. [d] Product consisted of a 1.5 : 1 mixture of rearranged and elimination products. [e] Reaction performed at –20 °C and 0.1 mol L^{-1} for a better solubility of the mixture. [f] Reaction using **21**. [g] Reaction using **22**.

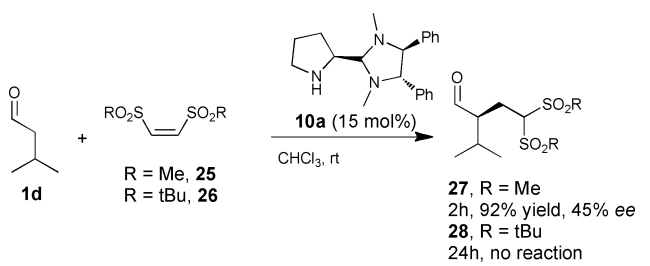
a good 73% *ee* (entry 8). Further temperature decrease led to longer reaction time with a slight loss of enantioselectivity. Other solvents

such as xylene (48% *ee*), CH_3CN (6% *ee*) or CH_2Cl_2 (40% *ee*) led to lower enantioselectivities while keeping the same reactivity. A more polar solvent such as DMF led to the formation of numerous side products.[19] Finally, dilution did not have any strong influence on the enantioselectivity. Surprisingly, when using catalyst **19a** at –20 °C, a great improvement in the enantioselectivity from 30 to 76% *ee* was observed, together with an excellent 78% yield (entry 7). Finally, substituting the methyl R group by an ethyl (compound **23b**) in the starting material, led to the same reactivity (85% yield after 24 h at –20 °C) and the same enantioselectivity (76% *ee*) using **19b** (entry 10).

For comparison, the reaction of 1,1-bis(phenylsulfonyl)ethene **21** and mono-vinyl sulfone **22** was performed using catalyst **19b** but led to much lower enantioselectivities (entries 11–12). In view of the good yields and enantioselectivities, the obtained adducts can be valuable synthons since they can potentially give in a few steps non-natural tetra-substituted amino acids.

Application to other electrophiles

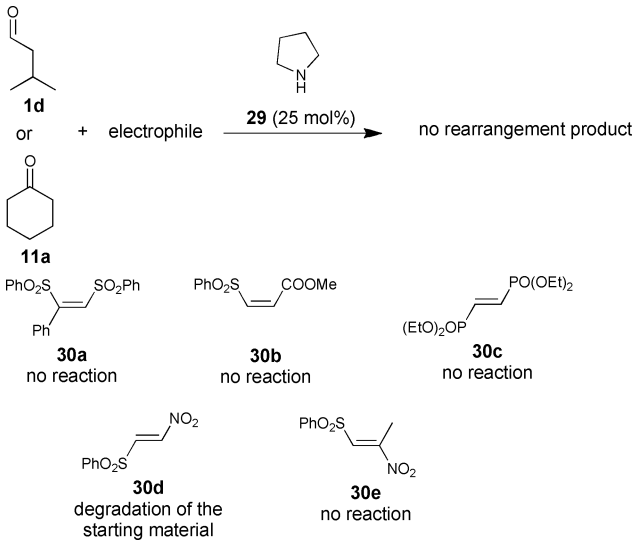
Having shown the broad generality of the rearrangement using 1,2-bis(phenylsulfonyl)ethane, we wondered if the rearrangement could also be applied to other electrophiles. Attention was first focused on other 1,2-bis-vinyl sulfones using enamine catalysis (Scheme 7). When the phenyl substituent of the sulfone is replaced by a methyl, good reactivity and excellent selectivity in favour of the rearranged product **27** are obtained. However, the poorer enantioselectivity obtained than for the phenyl substituent (45% *vs* 82% *ee* for the phenyl sulfone), indicates that the interactions between the catalyst and the substrate are weaker in the case of the methyl sulfone, thus lowering the *ee*. With the bulkier *t*Bu sulfone, no reaction at all is observed corroborating our hypothesis. Indeed, in this case, the interaction between the *t*Bu group and the catalyst are too strong to allow any reaction.



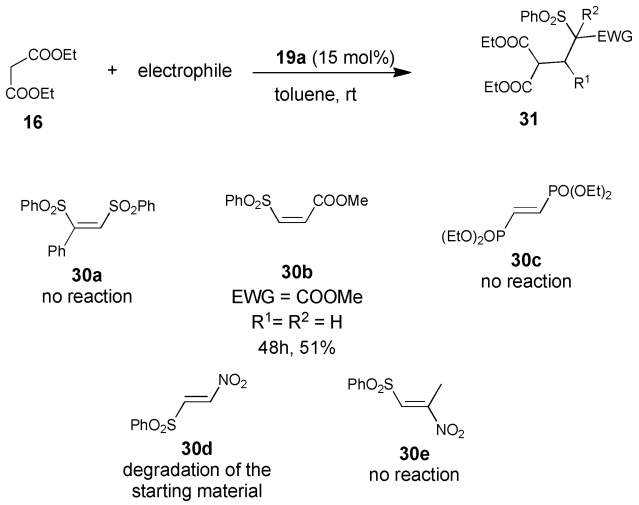
Scheme 7 Application to other 1,2-bis-vinylsulfones.

Aside from 1,2-vinyl sulfones, we were interested in knowing if other electron-withdrawing groups could promote such sulfone rearrangement (Scheme 8). Unfortunately using enamine catalysis, none of the Michael acceptors tested led to the 1,2-sulfone rearrangement. Most of the electrophiles were not reactive enough to undergo any reaction. For compounds **30a** and **30e**, the additional substituent inhibits the reaction while ester or phosphonates are not sufficiently electron-withdrawing to activate the double bond. Finally, compound **30d** is not stable enough and undergoes rapid decomposition in the presence of different amine catalysts.

With chiral base **19**, the same trend was observed except in the case of the sulfonyl-acrylate **30b** where complete conversion was obtained after 48 hours (Scheme 9). Gratifyingly, the rearranged



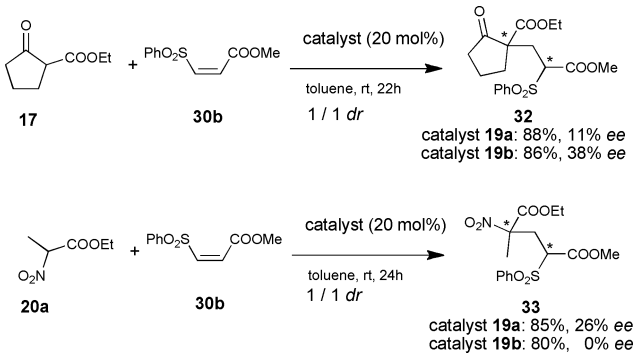
Scheme 8 Application to other electrophiles.



Scheme 9 Application to other electrophiles using chiral bases.

product is the only one using bifunctional catalyst **19a**. In this case, DBU gave an undefined mixture of products, indicating that a well-defined transition state is needed to obtain good selectivity in favour of the rearranged compound.

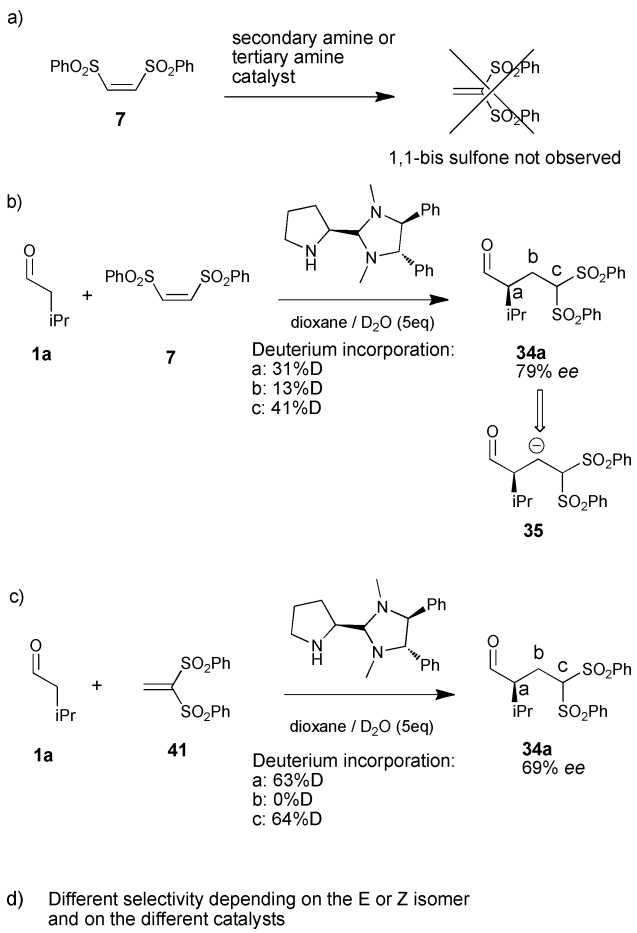
The observed rearrangement in the case of compound **31b** is of high importance since it indicates that this 1,2-sulfone shift can be generalized to other electrophiles. Furthermore, after removal of the sulfone, this reaction could be considered as a formal addition to methyl acrylate. We thus decided to study the asymmetric version of this reaction using various nucleophiles (Scheme 10). As expected, the addition of keto-esters or nitro-esters did lead to the 1,2-sulfone shift in excellent isolated yields. Unfortunately, really poor enantio-discrimination was obtained using bifunctional-catalysts **19a** or **19b** (up to 38% *ee*). Despite these low enantioselectivities, the excellent selectivity in favour of the rearranged product is promising in terms of synthetic applications.



Scheme 10 1,2-Sulfone rearrangement in the addition to phenylsulfonyl-acrylate.

Mechanistic discussion

In view of the broad generality of the 1,2-sulfone rearrangement, a more detailed mechanistic study had to be undertaken (Scheme 11).



Scheme 11 Mechanistic observations.

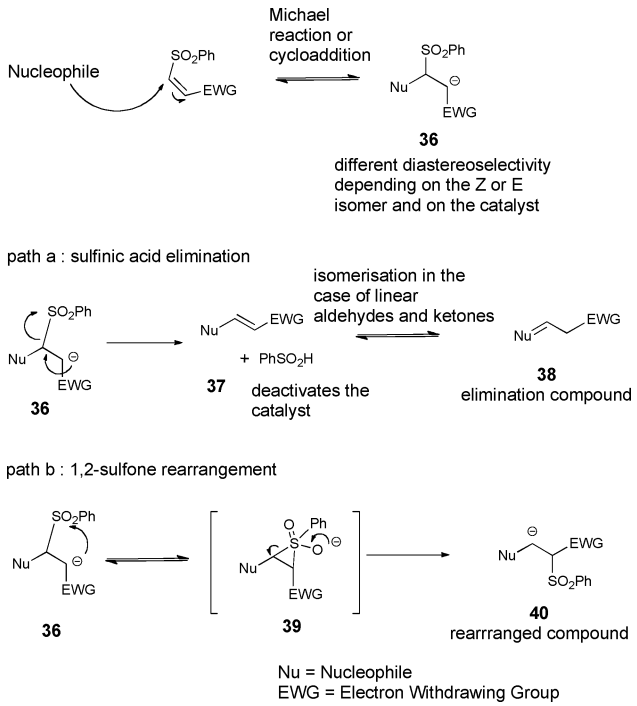
Careful NMR analysis during the reaction indicated that the selectivity of the reaction did not depend on the time and that the starting material was directly transformed into the rearranged product without any other detectable intermediate. Since the results are totally different between 1,1-bis sulfone and *cis*-1,2-bis(phenylsulfonyl)ethene and 1,1-bis(phenylsulfonyl)ethene it seemed to us that the rearrangement should occur after the first Michael addition to the electrophile. Furthermore, the fact that the reaction occurs with the non-basic strongly acidic thiourea **19d**, confirms that there is no attack of the catalyst on the electrophile before the Michael addition (eq a, Scheme 11). It is probably the anionic intermediate, formed upon Michael addition, that undergoes then, the 1,2-sulfone rearrangement.

Indeed, anion trapping by performing the reaction in a mixture of anhydrous dioxane and deuterated water confirmed this hypothesis (eq b). A mixture of compounds with deuteration at position a (31%), b (13%) and c (41%) was obtained. The deuteration at positions b and c can arise from the same intermediate **35**, since the anion **35** can migrate to the more acidic position c relatively easily. Control experiments performing the addition to 1,1-bis(phenylsulfonyl)ethene led to deuteration in positions a and c and not at all in position b (eq c). The impressive amount of deuteration at the position a (31–63%) in both cases together with good enantioselectivity (69–79% *ee*) seems to indicate that the deuteration comes from an equilibrium before the C–C bound formation. Using aminal–pyrrolidine catalyst, this iminium–enamine equilibrium is impressively fast and the C–C bound formation should be the rate-determining step. This interesting result probably accounts for the high reactivity observed in reactions using aminal–pyrrolidine catalysts, contrary to the case of catalyst **9a** which led to major deuteration in position c (62% c, 12% a deuteration) when using sulfone **41**.

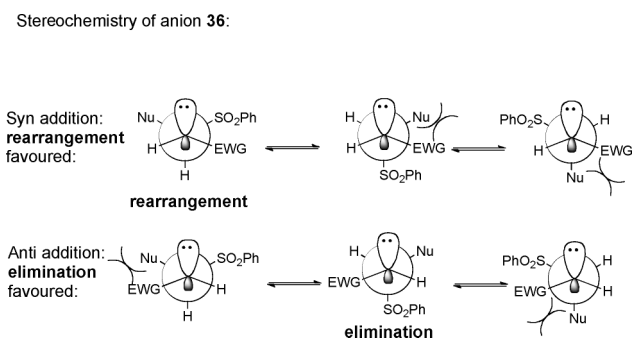
To account for the selectivity of the reaction between the two different isomers *cis* and *trans* of the starting material (eq d), or for the different selectivity observed with the various catalysts, the geometry of the anion formed after the Michael addition has to be taken in account. It is known that stabilised carbanions, notably adjacent to a sulfone, are sp^3 hybridised and can thus be considered as chiral.[20]

At this point, a mechanism can be proposed taking into account all these observations (scheme 12).

Either direct Michael addition or [2 + 2] cycloaddition leads to the anionic species **36**. The fact that the mechanism goes through a cycloaddition was not confirmed but could be in accordance with the high reactivity observed using the *cis* starting material. Then, the anionic species **36** can contain two adjacent stereogenic centers, and can thus be formed as a mixture of two diastereoisomers (Scheme 13). The pyramidal anion α- to the electron-withdrawing group can spontaneously decompose by two possible pathways. If the lone pair and the sulfone are preferentially *antiperiplanar* after an *anti* addition, the elimination pathway will be favoured. If the lone pair is at the proximity of the sulfone after a *syn* addition, the rearrangement will occur preferentially. The observation that the larger the nucleophile, the higher the selectivity in favour of the rearrangement is consistent with this mechanism. Indeed, the bulky substituent can favour the formation of one of the two diastereoisomers and can also prevent the free rotation around the C–C bond, forcing a defined transition state where the only possibility is the attack of the anion on the sulfone. This bulky group can also prevent the interconversion of the pyramidal anion, which is then slower than the spontaneous rearrangement. The different selectivity obtained with the different catalysts can also be explained by this mechanism.



Scheme 12 Proposed mechanism of the 1,2-sulfone rearrangement.



Scheme 13 Stereochemistry of the transient anion.

Conclusions

In conclusion, we have disclosed a systematic study on the application and scope of the 1,2-sulfone rearrangement and notably on its asymmetric variant. Different types of nucleophiles (aldehydes, ketones, malonates, keto-esters or nitro-esters) can be used, leading to the formation of highly functionalised substrates in moderate to excellent enantioselectivities (up to 94% *ee*).[21] Enamine as well as base or thiourea catalysis is able to promote the rearrangement with excellent selectivities in favour of the rearranged product. The mechanistic study indicates that the rearrangement is general as long as a bulky nucleophile is used and that a stereodefined transient anion is obtained. This property was further expanded to phenylsulfonyl acrylates where a total selectivity in favour of the rearranged product was obtained. This 1,2-sulfone rearrangement can be of high synthetic interest since it constitutes an alternative to the use of expensive 1,1-bis(phenylsulfonyl)ethene and leads to a formal alkylation of the nucleophile. Furthermore, the application to the addition to acrylate derivative is promising and should find further synthetic applications, notably in the case of enamine catalysis by increasing the electrophilicity of the ester group.

Experimental

^{1}H (400 MHz or 300 MHz), ^{13}C (75 MHz or 100 MHz) NMR spectra were recorded on a Bruker 400 FT or Bruker 300 FT NMR in $CDCl_3$, and chemical shifts (δ) are given in ppm relative to residual $CHCl_3$. Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), dt (doublet of triplets), brs (broad singlet). Coupling constants are reported in Hertz (Hz). Mass spectra (MS) were obtained by ESI and High resolution mass spectra HRMS by Electrospray Ionisation (ESI). Optical rotations were recorded on a Perkin–Elmer 241 polarimeter at 20 °C in a 10 cm cell in $CHCl_3$; $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1} (concentration c given as g 100 mL^{-1}). Enantiomeric excesses were determined by chiral-SFC measurement on a Berger SFC with the stated column or chiral GC analysis. Gradient programs are described as follows: initial methanol concentration (%) - initial time (min) - percent gradient of methanol (%/min) - final methanol concentration (%); retention times (R_T) are given in min. Flash chromatography was performed using silica gel 60 Å. All the organocatalysed reactions were conducted in non-dried solvents. Compounds **7**,[10] **25**,[22] **26**,[22] **30b**,[23] **30c**,[24] **30d**,[25] **30e**,[25] **30a**,[26] were prepared by known literature procedures. Aminal–pyrrolidine catalysts were prepared according to procedures developed in our group.[7e] If non-specified, products were purchased directly from commercial sources. The absolute and relative configuration of the Michael adducts were attributed by comparison with known compounds coming from the direct Michael addition to 1,1′-vinyl sulfones.[6,7]

General procedure for the enamine addition of aldehydes to *cis*-1,2-bis(phenylsulfonyl)ethene

To a solution of the aminal–pyrrolidine catalyst **15** (6.4 mg, 0.015 mmol, 15 mol%) in 0.4 ml of toluene is added successively the carbonyl compound (0.5 mmol, 5 eq) and finally the *cis*-1,2-bis(phenylsulfonyl)ethene (0.1 mmol, 1 eq). The mixture is stirred at room temperature and conversion is controlled by TLC. When the reaction is completed, the reaction is brought to 0 °C, 1.0 ml of ethanol is added followed by the slow addition of $NaBH_4$ (23 mg, 0.6 mmol, 6 eq). The mixture is stirred at 0 °C for 30 minutes. 3 ml of 1 M HCl are then added, the organic layer extracted by three times 4 ml of dichloromethane, dried on sodium sulfate and the solvent evaporated. Purification by flash chromatography using a cyclohexane/ethyl acetate mixture afforded the corresponding Michael adduct. Spectroscopic data are in agreement with literature.[6,7]

(*R*)-2-(2,2-Bis(phenylsulfonyl)ethyl)pentan-1-ol (8a)

The enantiomeric excess was determined by SFC (chiralcel OJ column, 2 ml min^{-1}, 200 bar, MeOH, 5%-2min-1%/min-25%, 30 °C). Rt: 8.07 Rt: 9.0. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (t, 3H, *J* = 7.2 Hz), 1.11–1.26 (m, 4H), 1.78–1.84 (m, 2H), 2.15–2.25 (m, 2H), 3.40–3.48 (m, 1H), 3.68–3.72 (m, 1H), 5.06 (dd, 1H, *J* = 6.7, 3.6 Hz), 7.58 (t, 4H, *J* = 7.6 Hz), 7.68–7.70 (m, 2H), 7.96 (t, 4H, *J* = 3.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7 (CH_3), 20.4 (CH_2), 29.1 (CH_2), 34.4 (CH_2), 39.3 (CH), 66.4 (CH_2), 81.5

(CH), 129.6 (CH), 130.1 (CH), 130.3 (CH), 135.1 (Cquat), 138.4 (Cquat). MS EI: m/z = 397.3 [M+H]+, 414.3.

(*R*)-2-(2,2-Bis(phenylsulfonyl)ethyl)nonan-1-ol (8b)

The enantiomeric excess was determined by SFC (chiralcel OJ column, 2 ml min^{-1}, 200 bar, MeOH, 5%-2min-1%/min-25%, 30 °C). Rt: 9.01 (R), Rt: 12.61 (S). $[\alpha]_{20}^{D}$ = −22.4 ($CHCl_3$, c = 1.2, 78% *ee*). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88–1.42 (m, 15H), 1.79–1.90 (m, 2H), 2.14–2.26 (m, 2H), 3.38–3.44 (m, 1H), 3.66–3.69 (m, 1H), 5.07 (dd, 1H, *J* = 6.9; 3.9 Hz), 7.53–7.58 (m, 4H), 7.66–7.70 (m, 2H), 7.92–7.97 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.6 (CH_2), 26.7 (CH_2), 28.5 (CH_2), 29.1 (CH_2), 29.7 (CH_2), 31.8 (CH_2), 39.0 (CH), 65.9 (CH_2), 81.5 (CH), 129.00 (CH), 129.6 (CH), 134.5 (Cquat), 137.8 (Cquat). MS ESI: m/z = 453.3 [M+H]+. HRMS calcd for $C_{23}H_{33}O_5S_2$ 453.1763, found 453.1761.

(*R*,*Z*)-2-(2,2-Bis(phenylsulfonyl)ethyl)undec-8-en-1-ol (8c)

The enantiomeric excess was determined by SFC (chiralcel IC column, 2 ml min^{-1}, 200 bar, MeOH, 10%-2min-1%/min-25%, 30 °C). R_t: 14.92 (*R*), R_t: 15.57 (*S*). $[\alpha]^{20}_{D}$ = −14.8 ($CHCl_3$, c = 0.8, 76% *ee*). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (t, 3H, *J* = 4.8 Hz), 1.21–1.30 (m, 6H), 1.79–2.25 (m, 6H), 3.39–3.46 (m, 1H), 3.67–3.73 (m, 1H), 5.05 (dd, 1H, *J* = 6.9, 3.9 Hz), 5.29–5.44 (m, 2H), 7.55–7.60 (m, 4H), 7.68–7.70 (m, 2H), 7.93–7.95 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 23.6 (CH_2), 26.6 (CH_2), 28.5 (CH_2), 29.3 (CH_2), 31.6 (CH_2), 32.5 (CH_2), 39.0 (CH), 65.8 (CH_2), 81.5 (CH), 129.00 (CH), 129.6 (CH), 134.5 (Cquat), 134.6 (CH), 137.7 (Cquat). MS ESI: *m/z* = 479.4 $[M+H]^+$. HRMS calcd for $C_{25}H_{35}O_5S_2$ 479.192, found 479.1939.

(*S*)-2-Isopropyl-4,4-bis(phenylsulfonyl)butan-1-ol (8d)

The enantiomeric excess was determined by SFC (chiralcel OJ column, 2 ml min^{-1}, 200 bar, MeOH, 5%-2min-1%/min-25%, 30 °C). R_t: 7.73 (*S*), R_t: 8.50 (*R*). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.82–0.85 (m, 4H), 1.60–1.75 (m, 3H), 2.19–2.30 (m, 2H), 3.50–3.56 (m, 1H), 3.56–3.76 (m, 1H), 5.20 (dd, 1H, *J* = 7.1, 3.3 Hz), 7.54–7.60 (m, 4H), 7.66–7.70 (m, 2H), 7.93 (t, 4H, *J* = 3.1 Hz). Spectroscopic data are in agreement with literature.[6,7]

(*S*)-2-(2,2-Bis(phenylsulfonyl)ethyl)-3,3-dimethylbutan-1-ol (8e)

The enantiomeric excess was determined by SFC (chiralcel OJ column, 2 ml min^{-1}, 200 bar, MeOH, 5%-2min-1%/min-25%, 30 °C). R_t: 6.09 (*S*), R_t: 7.29 (*R*). $[\alpha]^{20}_{D}$ = −16.2 ($CHCl_3$, c = 0.9, 87% *ee*). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (s, 9H), 1.70–1.84 (m, 2H), 2.21–2.37 (m, 2H), 3.48–3.54 (m, 1H), 3.92–3.95 (m, 1H), 5.50 (dd, 1H, *J* = 8.1, 2.4 Hz), 7.52–7.58 (m, 4H), 7.69–7.70 (m, 2H), 7.92–7.95 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.2 (CH_2), 27.7 (CH_3), 32.9 (Cquat), 31.3 (CH_2), 48.1 (CH), 40.9 (CH_3), 64.3 (CH_2), 81.5 (CH), 129.00 (CH), 129.6 (CH), 134.4 (Cquat), 138.1 (Cquat). MS ESI: *m/z* = 411.1 $[M+H]^+$. HRMS calcd for $C_{20}H_{27}O_5S_2$ 411.1294, found 411.1292.

(*S*)-2-Isopropyl-4,4-bis(phenylsulfonyl)butanal (ald-8d)

Obtained by direct acidic work-up without any $NaBH_4$ reduction. The enantiomeric excess was determined by chiral SFC (chiralcel OJ column, 2 mL min^{-1}, 200 bar, MeOH 10%-2min-1%/min-25%, 30 °C, R_T: 4.5, 6.20). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (d, 3H, *J* = 6.8 Hz), 0.99 (d, 3H, *J* = 7.1 Hz), 2.11–2.17 (m, 2H), 2.47–2.54 (m, 1H), 2.90–2.94 (m, 1H), 4.68–4.71 (dd, 1H, *J* 9.1, 3.1 Hz), 7.53–7.60 (m, 4H), 7.67–7.73 (m, 2H), 7.88–7.96 (m, 4H), 9.59 (s, 1H).

(*S*)-2-(2,2-Bis(phenylsulfonyl)ethyl)-3,3-dimethylbutanal (ald-8e)

Obtained by direct acidic work-up without any $NaBH_4$ reduction. The enantiomeric excess was determined by chiral SFC (chiralcel OB column, 2 mL min^{-1}, 200 bar, MeOH 10%-2min-1%/min-25%, 30 °C, R_T: 3.6, 3.9). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (s, 9H), 2.20–2.27 (m, 1H), 2.50–2.57 (m, 1H), 2.76 (d, 1H, *J* = 12 Hz), 4.55 (d, 1H, *J* = 7.6 Hz), 7.54–7.59 (m, 4H), 7.68–7.73 (m, 2H), 7.85–7.96 (m, 4H), 9.70 (s, 1H). Spectroscopic data are in agreement with literature.[6,7]

(*R*)-2-Ethyl-2-methyl-4,4-bis(phenylsulfonyl)butanal (14)

Obtained by direct acidic work-up without any $NaBH_4$ reduction. The enantiomeric excess was determined by SFC (chiralcel AD column, 2 mL min^{-1}, 200 bar, MeOH, 5%-2min-1%/min-25%, 30 °C). R_t: 8.03 R_t: 8.87. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 (t, 3H, 7.5 Hz), 0.94 (s, 3H), 1.43–1.48 (m, 1H), 1.74–1.78 (m, 1H), 2.32 (dd, 1H, *J* = 16.4, 3.6 Hz), 2.58 (dd, 1H, *J* = 16.4, 4.4 Hz), 4.45 (dd, 1H, *J* = 5.2, 3.6 Hz), 7.51–7.86 (m, 10H), 9.50 (s, 1H). Spectroscopic data are in agreement with literature.[6,7]

General procedure for the enamine addition of ketones to *cis*-1,2-bis(phenylsulfonyl)ethene

To a solution of the aminal–pyrrolidine catalyst **10a** (10.6 mg, 0.030 mmol, 15 mol%) in DMF (0.4 ml) at 0 °C is added successively the ketone (1.0 mmol, 5 eq) and finally the 1,2-bis(vinylsulfonyl)ethylene (0.2 mmol, 1 eq). The mixture is slowly warmed to 15 °C and stirred at this temperature. Conversion is controlled by TLC or direct ^{1}H NMR of a small sample. When conversion is completed, 2 ml of saturated NH_4Cl are then added, the organic layer extracted by three times 3 ml of dichloromethane, dried on sodium sulfate and the solvent evaporated. Purification by flash chromatography using a cyclohexane/ethyl acetate mixture affords the corresponding Michael adduct.

(*S*)-2-(2,2-Bis(phenylsulfonyl)ethyl)cyclohexanone (12a)

The enantiomeric excess was determined by SFC (chiralcel OJ column, 2 ml min^{-1}, 200 bar, MeOH, 5%-2min-2%/min-25%. 30 °C). Rt: 8.55 Rt: 12.37. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25–1.30 (m, 1H), 1.62–2.10 (m, 8H), 2.28–2.35 (m, 3H), 2.47–2.57 (m, 1H), 3.03–3.09 (m, 1H), 4.97 (dd, 1H, J = 9.3, 3.6 Hz), 7.53–7.69 (m, 6H), 7,87–7.96 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.0 (CH_2), 26.5 (CH_2), 27.8 (CH_2), 34.8 (CH_2), 42.9 (CH_2), 47.3 (CH), 80.7 (CH), 129.0 (CH), 129.3 (CH), 129.7 (CH), 134.4 (Cquat). Spectroscopic data are in agreement with literature.[7c]

(*S*)-2-(2,2-Bis(phenylsulfonyl)ethyl)-4-(tert-butyl)cyclohexanone (12b)

The enantiomeric excess was determined by SFC (chiralcel OB column, 2 ml min^{-1}, 200 bar, MeOH, 5%-2min-1%/min-25%,

30 °C). R_t: 5.2 R_t (minor dia): 7.1 R_t: 8.2. NMR (300 MHz, $CDCl_3$): δ = 0.87–0.92 (m, 9H), 1.26–1.92 (m, 6H), 1.88–1.97 (m, 2H), 2.26–2.35 (m, 3H), 2.57–2.79 (m, 2H), 4.76–4.79 (m, 1H from major dia (syn)), 5.03–5.06 (m, 1H from minor dia), 7.53–7.69 (m, 6H), 7.84–7.92 (m, 4H). Spectroscopic data are in agreement with literature.[7c]

(*S*)-2-(2,2-Bis(phenylsulfonyl)ethyl)-4-phenylcyclohexanone (12c)

The enantiomeric excess was determined by SFC (chiralcel OB column, 2 ml min^{-1}, 200 bar, MeOH, 5%-2min-1%/min-25%, 30 °C). R_t (minor dia): 14.8 R_t: 16.8 R_t: 18.5. NMR (300 MHz, $CDCl_3$): δ = 0.84–0.91 (m, 1H), 1.23–1.25 (m, 1H), 1.86–2.38 (m, 6H), 2.76–2.83 (m, 1H), 3.09–3.38 (m, 1H), 4.68–4.73 (m, 1H from major dia (syn)), 5.01–5.07 (m, 1H from minor dia), 7.23–7.41 (m, 5H), 7.52–7.68 (m, 6H), 7.85–7.94 (m, 4H). Spectroscopic data are in agreement with literature.[7c]

(*S*)-2-Isopropyl-4,4-bis(methylsulfonyl)butanal (27)

According to general procedure without reduction to the alcohol. $[\alpha]^{20}_D$ = +34.5 ($CHCl_3$, c = 1.4, 45% *ee*). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.00 (d, 3H, *J* = 6.7 Hz), 1.06 (d, 3H, *J* = 6.7 Hz), 2.08–2.26 (m, 2H), 2.56–2.66 (m, 1H), 2.97–3.02 (m, 1H), 3.21 (s, 3H), 3.23 (s, 3H), 4.25 (dd, 1H, *J* = 10.5, 4,5 Hz), 9.69 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0 (CH_3), 19.5 (CH_2), 19.7 (CH_3), 28.6 (CH), 31.3 (CH_2), 40.5 (CH_3), 40.9 (CH_3), 54.5 (CH), 79.0 (CH), 203.6 (CH). MS ESI: *m/z* = 288.1 $[M+NH_4^+]^+$. HRMS calcd for $C_9H_{22}NO_5S_2$ 288.0933, found 288.0926. *ee* was determined by derivatisation to the corresponding imidazolidine. In a small vial were mixed 0.054 mmol of the aldehyde and 2 equivalent of (1*S*,2*S*)-N^1,N^2-dimethyl-1,2-diphenylethane-1,2-diamine in 0.5 ml of anhydrous dichloromethane. Activated molecular sieves was added and the resulting mixture stirred overnight. The molecular sieves were then filtered, washed with dichloromethane and the solvent evaporated to give a diastereoisomeric mixture of imidazolidine. Diastereoisomeric proton in ^1H (400 MHz, $CDCl_3$): δ = 3.99 (d, 1H, *J* = 9.6 Hz) (*R*) enantiomer, = 3.88 (d, 1H, *J* = 9.6 Hz) (*S*) enantiomer.

General procedure for the base catalyzed addition to *cis*-1,2-bis(phenylsulfonyl)ethene

To a solution of 20 mol% of base catalyst, 0.3 mmol of Michael donor in 0.4 ml of toluene is added 0.1 mmol of 1.2 disulfone. The reaction is stirred at room temperature and monitored by TLC. After complete consumption of the starting material, the product is directly purified by silica gel chromatography using cyclohexane/ethyle acetate (8/2) as eluent affording the rearranged compound.

Diethyl-2-(2,2-bis(phenylsulfonyl)ethyl)malonate (16)

^1H NMR (300 MHz, $CDCl_3$): δ = 1.24 (t, 3H, *J* = 7.2 Hz), 2.67 (t, 2H, *J* = 7.5 Hz), 4.05–4.19 (m, 5H), 4.87 (t, 1H, *J* = 6.3 Hz), 7.55–7.60 (m, 4H), 7.60–7.67 (m, 2H), 7.94–7.97 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 24.7 (CH_2), 49.0 (CH), 62.0 (CH_2), 80.1 (CH), 129.2 (CH), 129.7 (CH), 134.8 (CH), 137.4 (Cquat), 168.1 (Cquat). MS ESI: *m/z* = 469.1 $[M+H]^+$. HRMS calcd for $C_{21}H_{25}O_8S_2$ 469.0985, found 469.0983.

Ethyl-1-(2,2-bis(phenylsulfonyl)ethyl)-2oxocyclopentanecarboxylate (18)

The enantiomeric excess was determined by SFC. (chiralcel OJ column, 2 ml min^{-1}, 200 bar, MeOH, 10%-2min-1%/min-25%, 30 °C). R_t: 4.8; R_t: 5.4. $[\alpha]_{20}^D$ = −18.5 ($CHCl_3$, c = 1.4; 44% *ee*).^1H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, 3H, *J* = 7.2 Hz), 1.93–2.04 (m, 3H), 2.39–2.83 (m, 5H), 4.09–4.14 (m, 2H), 5.41 (dd, 1H, *J* = 5.7, 3.6 Hz), 7.49–7.56 (m, 4H), 7.63–7.66 (m, 2H), 7.90–7.96 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_3), 19.3 (CH_2), 28.7 (CH_2), 35.8 (CH_2), 38.1 (CH_2), 57.5 (Cquat), 62.2 (CH_2), 78.4 (CH), 129.2 (CH), 129.6 (CH), 130.1 (CH), 134.5 (CH), 137.2 (Cquat), 138.3 (Cquat), 170.4 (Cquat,), 213.7 (Cquat). MS ESI: *m/z* = 465.3 $[M+H]^+$. HRMS calcd for $C_{19}H_{25}N_2O_8S_2$ 482.1301, found 482.1283.

Ethyl-2-methyl-2-nitro-4,4-bis(phenylsulfonyl)butanoate (23a)

The enantiomeric excess was determined by SFC. (chiralcel OB column, 2 ml min^{-1}, 200 bar, MeOH, 2%-2min-1%/min-25%, 30 °C). R_t: 10.1; R_t: 11.2. $[\alpha]_{20}^D$ = +9.5 ($CHCl_3$, c = 1.3, 76% *ee*). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.30 (t, 3H, *J* = 7.2 Hz), 1.82 (s, 3H), 3.06 (dd, 1H, *J* = 16.8, 4.2 Hz), 3.29 (dd, 1H, *J* = 16.8, 4,5 Hz), 4.30 (q, 2H, *J* = 5.4 Hz), 4.78 (dd, 1H, *J* = 9.0, 4.5 Hz), 7.55–7.60 (m, 4H), 7.68–7.74 (m, 2H), 7.90–7.93 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.6 (CH_3), 22.1 (CH_3), 30.6 (CH_2), 63.8 (CH_2), 78.7 (CH), 90.3 (Cquat), 129.2 (CH), 129.3 (CH), 129.8 (CH), 135.0 (CH), 136.8 (Cquat), 137.4 (Cquat), 166.4 (Cquat). MS ESI: *m/z* = 456.3 $[M+H]^+$. HRMS calcd for $C_{19}H_{25}N_2O_8S_2$ 473.1046, found 473.1033.

Ethyl-2-ethyl-2-nitro-4,4-bis(phenylsulfonyl)butanoate (23b)

The enantiomeric excess was determined by SFC. (chiralcel IC column, 2 ml min^{-1}, 200 bar, MeOH, 5%-2min-1%/min-25%, 30 °C). R_t: 7.5; R_t: 8.0. $[\alpha]_{20}^D$ = −5.0 ($CHCl_3$, c = 0.9, 76% *ee*). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.94 (t, 3H, *J* = 7.2 Hz), 1.30 (t, 3H, *J* = 6.9 Hz), 2.20–2.44 (m, 2H), 3.02 (AB, 1H, *J* = 12.3, 4.5 Hz), 3.22 (AB, 1H, *J* = 12.3, 4.5 Hz), 4.33 (m, 2H), 4.88 (t, 1H, *J* = 4.2 Hz), 7.54–7.71 (m, 6H), 7.88–7.95 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.8 (CH_3), 13.6 (CH_3), 27.4 (CH_2), 28.0 ($CH)_2$, 63.6 (CH_2), 78.7 (CH), 94.3 (Cquat), 129.2 (CH), 129.7 (CH), 130.1 (CH), 134.8 (CH), 134.9 (CH), 136.8 (Cquat), 137.5 (Cquat), 166.4 (Cquat). MS ESI: *m/z* = 470.1 $[M+H]^+$. HRMS calcd for $C_{20}H_{24}NO_8S_2$ 470.0937, found 470.0937.

(*E*)-Ethyl-2-methyl-2-nitro-4-(phenylsulfonyl)but-3-enoate

Elimination product isolated using DBU as catalyst in the addition of ethyl-2-nitropropionate to *cis*-1,2-bis(phenylsulfonyl)ethene. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.36 (t, 3H, *J* = 7.2 Hz),), 2.26 (s, 3H), 4.41 (m, 2H), 6.38 (d, 1H, *J* = 12.3 Hz), 6.92 (d, 1H, *J* = 12.3 Hz), 7.55–7.60 (m, 2H), 7.66–7.68 (m, 1H), 7.88–7.91 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7 (CH_3), 25.0 (CH_3), 63.7 (CH_2), 78.7 (CH), 86.4 (Cquat), 127.9 (CH), 129.5 (CH), 132.0 (CH), 134.6 (CH), 136.4 (CH), 136.9 (Cquat). MS ESI: *m/z* = 331.0 $[M+NH_4^+]^+$.HRMS calcd for $C_{13}H_{19}NO_6S$ 331.0958, found 331.0967.

Ethyl-2-methyl-2-nitro-4-(phenylsulfonyl)butanoate (24)

The enantiomeric excess was determined by SFC. (chiralcel OJ column, 2 ml min^{-1}, 200 bar, MeOH, 0%-2min-1%/min-25%, 30 °C). R_t: 5.91, R_t: 6.53. $[\alpha]_{20}^{D}$ = –2.9 ($CHCl_3$, c = 0,9, 16% *ee*). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.24 (t, 3H, *J* = 7.2 Hz), 1.76 (s, 3H), 4.49–2.59 (m, 2H), 3.19 (t, 2H, *J* = 8.4 Hz), 4.23 (q, 2H, *J* = 7.2 Hz), 7.56–7.91 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.9 (CH_3), 29.8 (CH_2), 51.2 (CH_2), 63.4 (CH_2), 78.7 (CH), 90.7 (Cquat), 128.0 (CH), 129.5 (CH), 134.2 (CH), 138.3 (Cquat), 166.1 (Cquat). MS ESI: *m/z* = 316.3 $[M+H]^+$.HRMS calcd for $C_{13}H_{18}NO_6S$ 316.0849, found 316.0840.

1,1-Diethyl 3-methyl 3-(phenylsulfonyl)propane-1,1,3-tricarboxylate (31b)

δ = 1.19–1.25 (m, 6H), 2.56 (AB, 2ddd, 2H, *J* = 9.6, 6.4, 3.2 Hz), 3.48 (dd, 1H, *J* = 8.4, 6.4 Hz), 3.65 (s, 3H), 4.14–4.20 (m, 4H), 7.55–7.59 (m, 2H), 7.67–7.68 (m, 1H), 7.86–7.90 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_3), 25.5 (CH_2), 48.8 (CH), 53.1 (CH_3), 61.9 (CH_2), 67.9 (CH), 129.2 (CH), 134.5 (CH), 136.9 (Cquat), 165.7 (Cquat), 168.0 (Cquat). MS ESI: *m/z* = 387.0 $[M+H]^+$. HRMS calcd for $C_{17}H_{23}O_{10}S$ 387.1108, found 387.1108.

Ethyl-1-(3-methoxy-3-oxo-2-(phenylsulfonyl)propyl)-2-oxocyclopentanecarboxylate (32)

The compound consisted of a 1/1 mixture of two diastereoisomers. The enantiomeric excess was determined by SFC. (chiralcel IC column, 2 ml min^{-1}, 200 bar, MeOH, 2%-2min-1%/min-25%, 30 °C). R_t dia 1: 12.2; R_t: 14.8; R_t dia 2: 12.8. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.15–1.19 (m, 6H), 1.83–2.05 (m, 6H), 2.31–2.64 (m, 10H), 3.58 (s, 3H, 1dia), 3.65 (s, 1dia), 4.05–4.11 (m, 4H), 4.29 (dd, 1H, 1dia, *J* = 4.0; 3.6 Hz), 4.44 (dd, 1H, 1dia, *J* = 6.0; 2.4 Hz), 7.54–7.58 (m, 4H), 7.65–7.68 (m, 2H), 7.83–7.86 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = (13.9 (CH_3, 1dia), 14.0 (CH_3, 1dia)), (19.5 (CH_2, 1dia), 19.6 (CH_2, 1dia)), (29.4 (CH_2, 1dia), 29.5 (CH_2, 1dia)), (33.9 (CH_2, 1dia), 35.1 (CH_2, 1dia)), (37.4 (CH_2, 1dia), 37.9 (CH_2, 1dia)), (52.8 (CH_3, 1dia), 53.1 (CH_3, 1dia)), (58.2 (Cquat, 1dia), 58.3 (Cquat, 1dia)), 61.9 (CH_2, 1dia), 62.0 (CH_2, 1dia)), (66.5 (CH, 1dia), 67.6 (CH, 1dia)), 129.1 (CH), 134.2 (CH), 137.4 (Cquat), (166.3 (COO, 1dia), 166.6 (COO, 1dia)), (170.4 (COO, 1dia), 170.9 (COO, 1dia)), (213.6 (CO, 1dia), 214.5 (CO, 1dia)). MS ESI: *m/z* = 383.0 $[M+H]^+$. HRMS calcd for $C_{18}H_{23}NO_7S$ 383.1159, found 383.1162.

1-Ethyl-5-methyl-2-methyl-2-nitro-4-(phenylsulfonyl)pentanedioate

The compound consisted of a 1/1 mixture of two diastereoisomers. The enantiomeric excess was determined by SFC. (chiralcel IC column, 2 ml min^{-1}, 200 bar, MeOH, 0%-2min-1%/min-25%, 30 °C). R_t (1dia + 1enantiomer): 14.2; R_t (other enantiomer): 14.6. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.23–1.30 (m, 6H), 1.79 (brs, 6H), 2.95–2.99 (m, 4H), 3.62 (s, 3H, 1dia), 3.63 (s, 1dia), 4.17–4.28 (m, 6H), 7.56–7.58 (m, 4H), 7.59–7.62 (m, 2H), 7.69–7.70 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = (13.6 (CH_3, 1dia), 13.7 (CH_3, 1dia)), (22.3 (CH_3, 1dia), 22.4 (CH_3, 1dia)), (32.7 (CH_2, 1dia), 32.8 (CH_2, 1dia)), 53.3 (CH_3), (63.5 (CH_2, 1dia), 63.6 (CH_2, 1dia)), (66.4 (CH, 1dia), 66.6 (CH, 1dia)), 90.6 (Cquat), 129.3 (CH), 134.7 (CH), 136.8 (Cquat), (165.6 (COO, 1dia), 165.7 (COO, 1dia)), (166.1 (COO, 1dia), 166.2 (COO, 1dia)). MS ESI: *m/z* = 374.3 $[M+H]^+$. HRMS calcd for $C_{15}H_{20}NO_8S$ 374.0904, found 374.0895.

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