DOI: 10.1002/ejoc.200600587

Direct Asymmetric α-Sulfamidation of α-Branched Aldehydes: A Novel Approach to Enamine Catalysis

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Keywords: Asymmetric synthesis / Organocatalysis / Amination / 1,3-Dipolar cycloaddition / Amino acids

Proline-catalysed reactions between α-branched aldehydes and sulfonyl azides provide scalemic configurationally stabilised α-sulfamidated products with *ee* values of up to 86%. The reactions can also be carried out in a one-pot fashion, with catalyst, aldehyde, sulfonyl chloride and sodium azide. The proposed mechanism differs fundamentally from the mechanistic model usually ascribed to enamine catalysis, containing as a key step the diastereoselective cycloaddition of the azide to an enamine formed in situ. The products obtained in the reaction can be converted into the corresponding unnatural amino acids in two additional steps.

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Introduction

Chiral amino compounds in general, and α-amino acids and their derivatives in particular, play a central role in the design of living organisms. While the importance of the twenty "natural" (proteinogenic) amino acids as building blocks in peptides is self-evident, there are also numerous examples of non-proteinogenic α-amino acid derivatives that have gained attention in biochemical research and drug discovery. They differ from their "natural" relatives in the make up of their α-carbon centres, which display opposite stereochemistry or untypical substitution patterns.

In the class of α,α-disubstituted amino acids, remarkable examples in terms of biological activity include α-methyl-α-(4-carboxyphenyl)glycine (MCPG), a highly potent metabotropic glutamate receptor antagonist,[1] (*S*)-α-methyldopa, the premier antihypertensive in the 1960s and 1970s,[2] and the fungicide (*S*)-fenamidone.[3] In contrast, L-isovaline has attracted mainly academic attention, since samples of material found on carbonaceous meteorites were shown to contain this compound in moderate enantiomeric excess, possibly revealing glimpses of the very beginning of life.[4] Some of these "unnatural" amino acids, namely α-aminoisobutyric acid (Aib) and D-isovaline (D-Iva), are actually characteristic building blocks in a naturally occurring class of microbial peptide antibiotics – the peptaibols.[5] An interesting feature of α-alkylated amino acids as building blocks in larger structures is their tendency to stabilise certain secondary structures in small peptides, such as β- and γ-turns[6] or 3_{10}- and α-helices.[7] Moreover, incorporation of α-disubstituted amino acids into peptides has been shown to result in increased resistance against chemical degradation[8] and protease enzymes.[9]

Unlike the proteinogenic species, these "unnatural" amino acids cannot usually be obtained from the natural pool but have to be made available by synthetic means.[10] A number of enzymes and microorganisms have been found to effect the kinetic resolution of racemic α,α-disubstituted amino esters,[11] amino acid amides,[12] *N*-acylated amino acids[13] and even α-nitro carboxylic acids.[14] Most strategies for the asymmetric synthesis of α,α-disubstituted amino acids that have been developed over the years involve auxiliary-controlled electrophilic alkylation of amino acid enolate equivalents such as metallated bis-lactim ethers (Schöllkopf[15]) or oxazinones (Williams[16]). Related methods for the alkylation of modified naturally occurring amino acids with self-reproduction of the stereocentre have been developed: for imidazolidinones[17] and oxazolidinones[18] (Seebach[19]), or oxazaborolidinones[20] and open-chained borane-aminoester adducts.[21] Deprotonated oxazolin-5-ones (azlactones) have for some time been used as amino acid enolate equivalents in the synthesis of racemic α-alkylated amino acids,[22,23] often followed by separation of diastereomeric dipeptides.[23] More recent developments have also seen the emergence of asymmetric catalytic variants,[24,25] of which the palladium-catalysed approach devised by Trost et al. has been successfully utilised for the total synthesis of sphingofungin F.[25c] During the past 15 years, the development of a number of phase transfer-catalytic (PTC) processes[26] has resulted in the successful alky-

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lation not only of cyclic amino acid equivalents,[27] but also of open-chain amino acid-derived Schiff's bases.[28] Further interesting strategies involving electrophilic alkylation of amino acid enolate equivalents include the use of chiral β-lactams either as chiral auxiliaries[29] or as amino acid equivalents,[29,30] palladium-catalysed allyl alkylation of open-chain α-acetamido-β-keto esters[31] and the alkylation of *N*-Boc-protected lithium enolates of phenylalanine with self-regeneration of the stereocentre.[32]

A different approach involves the stereoselective addition of carbon nucleophiles to C–N multiple bonds with formation of C–C bonds. The main efforts in this respect have been committed to the development of asymmetric Strecker syntheses, with use of cyanide as a nucleophile to attack ketimines derived from ketones and primary amines. The resulting nitriles can be hydrolysed to give the corresponding carboxylic acid in a following step. Initially, the stereoinformation was transferred by chiral amino compounds, such as a chiral 5-amino-1,3-dioxane,[33] 1-phenylethylamine,[34] sulfinylamines,[35] or valine,[36] but since the mid-nineties a number of catalytic asymmetric Strecker syntheses have emerged.[37] Until Vachal and Jacobsen developed the first asymmetric catalytic Strecker synthesis of α,α-disubstituted amino acids,[38] however, most of these methods involved only aldimines as substrates, affording α-monosubstituted amino acids. Since then, Shibasaki et al. in particular have committed extensive research efforts to the application of the catalytic Strecker reaction to ketimines.[39] The synthesis of α,α-disubstituted amino acids by addition to a C–N triple bond was accomplished by a sequential nucleophilic dialkylation of a threitol-derived nitrile.[40]

Although in the past a multitude of approaches setting out to utilise nitrogen electrophiles such as chiral and achiral nitroso compounds, oxaziridines, sulfonyloxycarbamates, sulfonyl azides, and especially azodicarboxylates[41] for the asymmetric α-amination of carbonyl compounds under "umpolung" principles have been devised, only a few have considered the possibility of the use of α-branched substrates in order to provide access to α,α-disubstituted amino acid derivatives.[42–45] Before we entered the field in 2003, the only general approach had been presented by Jørgensen, who described reactions between α-substituted β-keto esters and dibenzyl azodicarboxylate catalysed by copper(II)-bis(oxazoline) complexes.[46]

With the aid of a procedure developed by List and Jørgensen for the proline-catalysed α-amination of linear aldehydes[47] and ketones[48] with azodicarboxylates, we had been able to show that this strategy can also be transferred to α-branched aldehydes, among them a potential precursor to MCPG, giving *ee* values of up to 86%.[49] The scope of this reaction was later extended by Barbas, who used it in the synthesis of two metabotropic glutamate receptor ligands[50] and furthermore introduced a proline-derived tetrazole catalyst in the preparation of the cell adhesion inhibitor BIRT-377.[51] In the meantime, organocatalytic methods have also been devised for the α-amination of α-cyano acetates[52] as well as cyclic β-keto esters and β-keto lactones[53] by catalytic use of cinchona alkaloids, while α-substituted 1,3-diketones have been shown to undergo asymmetric amination under copper catalysis conditions.[54]

All these methods have in common the use of azodicarboxylates as "NH_2^+" synthons. The cleavage of the resulting hydrazides (after modification of the aldehyde) to obtain the desired free amino acid is laborious, however, and requires rather harsh reaction conditions, thus imposing a limit on the feasibility of the key reaction when it comes to the synthesis of structurally more complex substances. Therefore, the introduction of a nitrogen electrophile allowing a more straightforward conversion to the corresponding free amino species would be highly desirable. Here we report the utilisation of sulfonyl azides as aminating agents in α-sulfamidations of α,α-disubstituted aldehydes under enamine catalysis conditions.[55]

Results and Discussion

Reaction Conditions

When racemic 2-phenylpropionaldehyde (hydratropaldehyde, **1**) was treated in THF with 4-toluenesulfonyl azide (tosyl azide, **2a**) in the presence of L-proline (**3**, 40 mol-%), the reaction did not, to our surprise, result in azide addition or transfer but, even more conveniently, delivered the scalemic α-sulfamidation product **4a** in 21% yield and with 53% *ee*. Intrigued by this preliminary result, we sought to establish reaction conditions that would give improvements in yield and stereoselectivity. A screening of different organic solvents revealed that alcohols delivered the most promising results in terms of both yield and stereoselectivity (Table 1). Although the use of DMSO as a solvent significantly enhanced the reaction rate and delivered product **4a** in comparable enantiomeric excess (Table 1, Entry 13), the yield stayed below optimum. Among the alcoholic solvents tested, the highest yield was obtained in ethanol (Table 1, Entry 6), while a decrease in yield and stereoselectivity could be observed with increasing chain length and degree of branching (Table 1, Entries 8–12).

A second set of experiments was carried out by treatment of hydratropaldehyde with 2-nitrobenzenesulfonyl azide (2-nosyl azide, **2b**) with L-proline catalysis. The product **4b** obtained from this reaction is very interesting from a synthetic point of view, as the nosyl group is commonly used as a protective group for amines and therefore allows easy conversion to the free amino compound.[56] Again, the reaction in ethanol delivered the best results, with 46% yield and 67% *ee* (Table 2, Entry 3), followed by propan-2-ol with 38% yield and 68% *ee*.[57]

Surprisingly, the exchange of technical ethanol for absolute ethanol resulted in a significant drop in stereoselectivity, from 67% *ee* to 56% *ee* (Table 2, Entries 1–3). There are two different parameters that could be held responsible for this phenomenon: either the presence of water in the reaction, or the presence of the denaturing agent. Addition of 4% of water to absolute ethanol resulted in extremely prolonged reaction times without any major improvement in enantioselectivity in comparison with absolute ethanol

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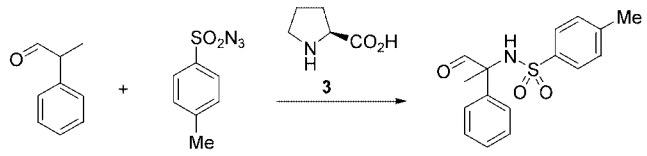
Table 1. Reaction conditions for the L-proline-catalysed reaction between hydratropaldehyde (**1**) and tosyl azide (**2a**).



1 **2a** **4a**

Entry	Solvent	**3**[a] [mol-%]	Temp.	Time	Yield[b] [%]	*ee*[c] [%]
1	THF	40	r.t.[d]	7 d[d]	21[d]	53
2	CH_3CN	40	–5 °C, r.t.[e]	2 d, 4 d[e]	14	54
3	CH_2Cl_2	40	–5 °C, r.t.[e]	2 d, 4 d[e]	–	–
4	MeOH	200	r.t.	1 d	32	59
5	abs. EtOH[f]	100	r.t.	1 d	35	59
6	tech. EtOH[g]	100	r.t.	1 d	38	56
7	tech. EtOH[g]	100	50 °C	4 h	34	59
8	*n*PrOH	100	r.t.	1 d	33	60
9	*i*PrOH	100	r.t.	1 d	21	53
10	*n*BuOH	100	r.t.	1 d	27	57
11	*t*BuOH	100	r.t.	1 d	25	54
12	1-pentanol	100	r.t.	1 d	25	52
13	DMSO	100	r.t.	2 h	28	60
14	DMSO/EtOH	100	0 °C	1 d	32	58

[a] Catalyst loading with respect to **1**. [b] Isolated yield after flash chromatography. [c] See Supporting Information for determination. Error margins are given there. [d] With DL-proline as catalyst. [e] The mixture was stirred at –5 °C for 2 d without any apparent reaction, before being warmed to room temperature. [f] Absolute ethanol, dried with potassium hydroxide and distilled from sodium and diethyl phthalate. [g] Technical ethanol, denatured with 1% petroleum ether.

(Table 2, Entry 4), so only the denaturating agent, in our case petroleum ether in a concentration of 1 vol.-%, was left as a possible cause. A test series with different alkane additives (1 vol.-% of each) in absolute ethanol was therefore performed in order to provide a better picture of the influence of nonpolar additives on the stereoselectivity of the reaction (Table 2, Entries 5–10, 16). Indeed, it turned out that the addition of alkanes to the reaction mixture provided a general increase in selectivity in relation to pure ethanol. One experiment carried out in the presence of both *n*-hexane and water verified that the latter merely produces a deceleration of the reaction without effecting any significant change in enantioselectivity (Entry 7). In order to study the influence of the additive amount, the reaction was carried out with different *n*-octane/absolute ethanol ratios (from 1% to 50% *n*-octane, Table 2, Entries 10–15). A slight maximum was determined for 5% *n*-octane, although variations of the amount of additive produced only minor changes in yield and selectivity. Interestingly, no difference between technical and absolute ethanol was observed when tosyl azide was employed instead of 2-nosyl azide (compare Table 1, Entries 5 + 6).

Apart from different alkanes and water, a variety of other additives were also tested in the L-proline-catalysed reactions between **1** and tosyl azide (**2a**) or 2-nosyl azide (**2b**). The addition of sodium dodecylbenzenesulfonate, a tenside with both polar and apolar components, did not give improved yields or enantiomeric excesses of **4b**; on the contrary, decreases in yield and stereoselectivity from 38% and 58% *ee* to 33% and 43% *ee* were observed when the amount of additive was increased from 1 equivalent (with respect to the aldehyde) to 10 wt.-% of the solvent.[56]

Bearing in mind that the rates of a number of cycloaddition reactions (see Mechanistic Considerations) experience considerable enhancement in ionic liquids,[58] *N*-butyl-*N*′-methylimidazolium tetrafluoroborate ([bmim][BF_4]) was introduced as reaction medium.[59] Although the yield of **4a** in this reaction medium remained at 38%, a remarkable enhancement in stereoselectivity could be observed, resulting in a 72% *ee* (Table 3, Entry 1). The analogous reaction with 2-nosyl azide in the same solvent delivered **4b** in higher yield, while the enantiomeric excess remained at levels similar to those obtained in technical ethanol (Table 3, Entry 2). In view of the differences in selectivity observed for reactions carried out with 2-nosyl azide in technical and in absolute ethanol (Table 2, Entries 1–3), the reaction performed in [bmim][BF_4] also represents an improvement in enantioselectivity over the reaction performed in absolute ethanol.

Other ionic liquids were also tested in the proline-catalysed reactions between **1** and either **2a** or **2b**. Although *N*-carboxypentyl-*N*′-methylimidazolium tetrafluoroborate ([capemim][BF_4], Entry 3) delivered the tosylated product **4a** in 53% yield, a pronounced loss of stereoselectivity was found. None of the other ionic liquids tested could match the initial results obtained with [bmim][BF_4], or even ethanol (Table 3, Entries 3–9).

The influence of temperature in the reaction between **1** and **2a** in technical ethanol was examined, again with L-proline as a catalyst (Table 1, Entries 6 + 7). While no reac-

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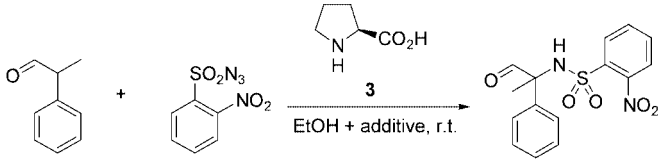
Table 2. Influence of alkane additives on the L-proline-catalysed reaction between **1** and 2-nosyl azide (**2b**).[a]



1 **2b** **4b**

Entry	Additive	[vol.-%][b]	Time	Yield[c] [%]	*ee*[d] [%]
1	none[e]	–	1 d	44	56
2	none[f]	–	1 d	44	55
3	petr. ether[g]	1	1 d	46	67
4	water	4	9 d	37	59
5	*n*-pentane	1	1 d	42	65
6	*n*-hexane	1	1 d	39	64
7	*n*-hexane + water	1, 4	11 d	41	65
8	cyclohexane	1	1 d	41	62
9	*n*-heptane	1	1 d	35	57
10	*n*-octane	1	1 d	43	60
11	*n*-octane	2	1 d	44	62
12	*n*-octane	5	1 d	45	66
13	*n*-octane	10	1 d	40	64
14	*n*-octane	25	1 d	41	61
15	*n*-octane	50	1 d	40	62
16	*n*-decane	1	1 d	38	58

[a] Unless stated otherwise, the reaction was carried out in a sealed tube with 1 equiv. of **1**, 1.1 equiv. of **2b**, and 1 equiv. of **3** in a mixture of absolute ethanol (dried with potassium hydroxide and distilled from sodium and diethyl phthalate) and the additive at room temperature. [b] Of additive with respect to ethanol. [c] Isolated yield after flash chromatography. [d] See Supporting Information for determination. Error margins are given there. [e] In absolute ethanol as purchased (>99.9% purity). [f] In absolute ethanol, dried with potassium hydroxide and distilled from sodium and diethyl phthalate. [g] In technical ethanol as purchased (denatured with 1% petroleum ether).

Table 3. L-Proline-catalysed reactions between **1** and **2a** or **2b** in ionic liquids.[a]

Entry	Ionic liquid	Azide	Product	Time	Yield[b] [%]	*ee*[c] [%]
1	[bmim][BF_4][d]	**2a**	**4a**	1 d	38	72
2	[bmim][BF_4][d]	**2b**	**4b**	1 d	55	66
3	[capemim][BF_4][e]	**2a**	**4a**	1 d	53	20
4	[C_3OHminm][BF_4][f]	**2a**	**4a**	1 d	–	–
5	ECOENG 212™ [g]	**2b**	**4b**	1 d	36	53
6	ECOENG 1111P™ [g]	**2b**	**4b**	2 d	21	59
7	AMMOENG 100™ [g]	**2b**	**4b**	3 d	38	28
8	AMMOENG 102™ [g]	**2b**	**4b**	3 d	–	–
9	AMMOENG 120™ [g]	**2b**	**4b**	3 d	–	–

[a] Reaction was carried out in a sealed tube with 1 equiv. of **1**, 1.1 equiv. of **2a** or **2b**, and 1 equiv. of **3** at room temperature. [b] Isolated yield after extraction and flash chromatography. [c] See Supporting Information for determination. Error margins are given there. [d] *N*-Butyl-*N*′-methylimidazolium tetrafluoroborate; see ref.[60] [e] *N*-ω-Carboxypentyl-*N*′-methylimidazolium tetrafluoroborate; see ref.[58] [f] *N*-(3-Hydroxypropyl)-*N*′-methylimidazolium tetrafluoroborate; see ref.[61] [g] Purchased from Solvent Innovation.

tion had taken place after 5 d at 0 °C, an acceleration could be observed at elevated temperature (50 °C), though resulting only in a minor improvement in stereoselectivity and a slightly lower yield in relation to room temperature. Treatment of **1** with tosyl azide at 0 °C in a 1:1 mixture of DMSO/THF was accomplished within 1 d according to TLC monitoring (Table 1, Entry 14), but did not deliver better results than reaction in DMSO at room temperature, either in terms of efficiency or selectivity (Table 1, Entry 13).

In many cases the outcome of a reaction may be positively influenced by application of a large excess of one of the reaction partners to force the equilibrium towards the product. As significant amounts of azide were usually detectable by TLC after complete consumption of the aldehyde, a tenfold excess of aldehyde was added to the reaction with tosyl azide, giving no improvement in yield whatsoever. Neither did the adjustment of other reaction parameters, such as a higher dilution or slow addition of either aldehyde or azide by syringe pump, seem to have any posi-

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tive influence on the outcome of the reaction, and so the following set of reaction conditions was established for further experiments: addition of one equivalent of the aldehyde to a solution of one equivalent of L-proline and a slight excess of the azide in absolute or technical ethanol (depending on the parameters to be investigated), followed by stirring at room temperature until TLC indicated complete reaction (usually within one day), and subsequent isolation of the product by removal of the solvent and flash chromatography of the residue.

Screening of Catalysts

Thanks to its popularity and impressive achievements in recent years, the constantly growing field of organocatalysis has given rise to the emergence of a whole variety of pyrrolidine-based organocatalysts, which can be employed as alternatives to their "originator" proline.[62,63] A number of secondary amines suitable for testing for their potential to catalyse the reactions between α,α-disubstituted aldehydes and sulfonyl azides were therefore at our disposal (Figure 1, Table 4). As a general remark it should be mentioned that

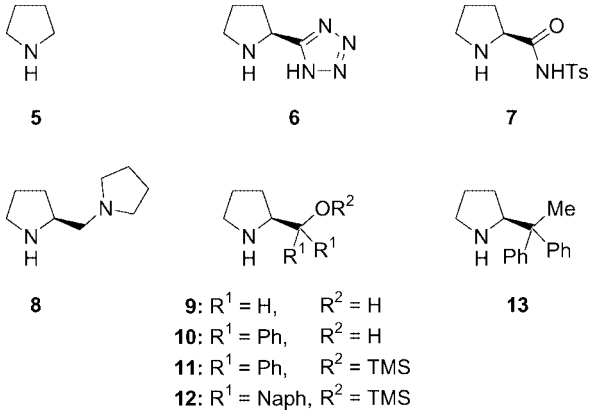

Figure 1. Pyrrolidine-based catalysts used for the α-sulfamidation of **1** (see Table 4).

the presence of an equimolar amount of catalyst is necessary to obtain maximum conversion of the aldehyde in the reaction with sulfonyl azides. Unsatisfying as this may be, it can be explained by mechanistic characteristics of the reaction, discussed in the mechanistic section.

Achiral pyrrolidine (**5**; Figure 1) delivered racemic **4a** in 36% yield, thus resembling proline in activity. Catalysts **6** (in ethanol)[51,64] and **7** (in DMSO),[64,65] on the other hand, produced deteriorations in yield, but delivered **4a** in significantly higher enantiomeric excess than L-proline (Table 4, Entries 1–3). The presence of the tosyl group in catalyst **7** seems to be essential for activity, as the free proline amide[66] was able to deliver **4b** in only 7% yield.[56] Catalyst **8**, with a pyrrolidine system in the side chain, has been reported to produce better results than L-proline in aldol reactions giving quaternary carbon centres.[67] In these reactions the presence of acid proved to be essential for the delivery of optimum results, and this was attributed to the necessity of hydrogen transfer from the conjugated acid of the side chain pyrrolidine system to the carbonyl group of the attacking aldehyde in the transition state. In the present case, the application of catalyst **8** gave poorer results than those obtained with L-proline. Although the reaction between hydratropaldehyde and 2-nosyl azide again delivered the corresponding product in higher enantiomeric excess than had been observed with tosyl azide (Table 4, Entries 4 + 5), both stereoselectivity and, especially, yield stayed below those obtained with L-proline. It should be pointed out that reduction of the amount of the acid added gave poorer results in terms both of efficiency and selectivity (Table 4, Entry 6), whereas reduction of the overall catalyst loading, while keeping a constant catalyst/acid ratio, significantly lowered the yield but not the stereochemical composition of the product (Table 4, Entry 7).

Compounds with free hydroxy groups in the catalyst side chain, such as **9** and **10**, generally displayed only very poor catalytic activity (Table 4, Entries 9 + 10); Jørgensen et al. ascribed the general low activity of prolinol derivatives in

Table 4. Screening of catalysts in the reactions between hydratropaldehyde (**1**) and tosyl azide (**2a**) or 2-nosyl azide (**2b**).[a,b] For catalysts, see Figure 1.

Entry	Catalyst	Azide	Solvent	Time	Yield[c] [%]	*ee*[d] [%]
1	**5**	**2a**	EtOH	1 d	36	*rac*
2	**6**	**2a**	EtOH	1 d	24	66
3	**7**	**2a**	DMSO	1 d	25	66
4	**8**·TFA	**2a**	DMSO	70 min	23	45
5	**8**·TFA	**2b**	DMSO	1 d[e]	26	57
6	**8**·0.6 TFA	**2b**	DMSO	1 d	22	47
7	**8**·TFA (20 mol-%)	**2b**	DMSO	1 d	22	47
8	**8**·0.6 TFA	**2b**	tech. EtOH	1 d	20	60
9	**9**	**2a**	tech. EtOH	4 d	< 10	n.d.[f]
10	**10**	**2a**	tech. EtOH	1 d	–[g]	–
11	**11**	**2b**	abs. EtOH	1 d	26[h]	n.d.[f]
12	**12**	**2b**	abs. EtOH	1 d	38[h]	64
13	**13**	**2b**	tech. EtOH	1 d	52	55

[a] Reactions were carried out in sealed tubes at room temperature with 1 equiv. of **1**, 1.1 or 1.2 equiv. of azide **2a** or **2b**, and 1 equiv. of the catalyst. [b] See Supporting Information for further experiments with different catalysts. [c] Isolated yield after flash chromatography. [d] See Supporting Information for determination. Error margins are given there. [e] TLC indicated complete consumption of aldehyde after 70 min. [f] The *ee* was not determined. [g] A different product was isolated. [h] The product was reduced with $NaBH_4$ prior to isolation.

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enamine catalysis[68] to the occurrence of unreactive hemiaminal species in the enamine-forming step.[69,70] On the other hand, the use of silyl-protected α,α-diarylprolinol catalysts, developed in his group, resulted in preparative problems, as separation of catalyst and product could only be achieved after reduction of the aldehyde, so this route was not pursued any further, once it became apparent that catalyst **12** would not provide improved stereoselectivity in relation to proline. In contrast, catalyst **13** allowed the isolation of product **4b** in 52% yield, displaying the highest reactivity of all catalysts tested in the reaction, although the selectivity remained somewhat below that achieved with L-proline.

It is very important to point out the fact that the major product possessed the same absolute configuration in *all* the reactions shown in Table 4. This contrasts with experiments carried out by Jørgensen and co-workers, who observed opposite configurations for products obtained through catalytic action of **11** (Figure 1) and related compounds in comparison to those delivered by reactions involving L-proline in a number of different enamine catalysis reactions.[68] Closer studies revealed that in these cases the opposed stereoselectivity is apparently based on shielding of the enamine face occupied by the catalyst's bulky side chain, whereas the carboxylic acid group in proline actively directs the incoming electrophile to the enamine face occupied by itself. Nothing has yet been ascertained, however, about the role of hydrogen transfer, which had been declared to be essential for reaction in earlier studies.[71] As both types of catalysts result in the preferential formation of the same enantiomer in the present case, it has to be concluded that stereoselectivity is *generally* induced through shielding of the enamine face containing the pyrrolidine substituent, thus leaving the opposite enamine face open for reaction with the incoming azide. This conclusion is further substantiated by the fact that reaction also took place with catalysts **5** and **13** (Figure 1) which carry no functional group apart from the pyrrolidine amino function, thus allowing no positive interaction such as hydrogen transfer with the attacking azide.

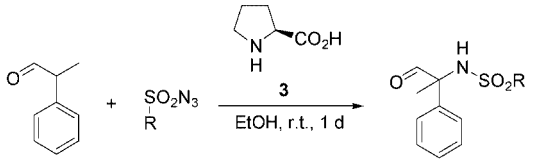
In addition to the pyrrolidine-based catalysts **3** and **5**–**13**, (2*S*,5*S*)-5-benzyl-2-*tert*-butylimidazolidinone and its (2*R*,5*S*)-diastereomer, belonging the class of imidazolidinone catalysts developed by MacMillan's group,[72] were tested for their catalytic potential in the reaction between hydratropaldehyde and tosyl azide. However, these compounds showed no catalytic activity whatsoever.[56]

From the results presented in this section, L-proline was chosen as catalyst for the subsequent experiments. Besides giving the best combination of efficiency and stereoselectivity, its better availability compared to other catalysts – which at best delivered only comparable results – backed up this decision.

Influence of the Azide Species

Different sulfonyl azides were treated with hydratropaldehyde (**1**) under L-proline catalysis conditions in absolute ethanol to establish whether electronic or steric properties of the azide species exert an influence on the efficiency of the reaction (Table 5). In terms of the electronic features of the azides employed, 4-nitrobenzenesulfonyl azide (4-nosyl azide, **2c**), which gave both the highest yield (52%) and the best enantiomeric excess (82% *ee*) in the series, appears to be a exception to the general trend that electron-rich sulfonyl azides such as **2f**, **2g** or **2h** produce higher stereoselectivities than electron-deficient species such as **2d** or **2n**. On the other hand, bulky *ortho* substituents in the case of benzenesulfonyl azides seem to result in lower enantioselectivity, as can be seen from the results delivered by 2,4,6-triisopropyl-substituted azide **2i** or by comparison between those delivered by the nitro-substituted azides **2b**, **2c** and **2d**. The same applies to the reaction between hydratropaldehyde and the thienyl-substituted species **2j**, with a chloro substituent in the position *ortho* to the sulfonyl group, which produced lower enantioselectivity than azide **2k** with a chlorine atom in the position *meta* to the sulfonyl group. Interestingly, the two nonaromatic sulfonyl azides **2m** and **2n** both produced rather low yields, while stereoselectivity was highly divergent.

Table 5. Proline-catalysed reactions between hydratropaldehyde (**1**) and different sulfonyl azides **2a**–**n**.



1 **2a–n** **4a–n**

Azide	R	Product	Yield[a,b] [%]	*ee*[a,c] [%]
2a	4-$CH_3C_6H_4$	**4a**	35/31	59/62
2b	2-$NO_2C_6H_4$	**4b**	44	56
2c	4-$NO_2C_6H_4$	**4c**	52	82
2d	2,4-$NO_2C_6H_3$	**4d**	27	45
2e	2-(CO_2CH_3)C_6H_4	**4e**	39	8
2f	3,4-(OCH_3)C_6H_3	**4f**	43	67
2g	1-naphthyl	**4g**	36	65
2h	2-naphthyl	**4h**	42	63
2i	2,4,6-*i*PrC_6H_2	**4i**	33	50
2j	C_4HSCl_2[d]	**4j**	27/38	47/47
2k	C_4H_2SCl[e]	**4k**	36/35	54/54
2l	C_5H_2NBrCl[f]	**4l**	24/31	46/60
2m	CH_3	**4m**[g]	33	71
2n	C_4F_9	**4n**[h]	24	29

[a] In the case of two values being given, the second was obtained from a one-pot fashion, with the corresponding sulfonyl chloride and sodium azide. [b] Isolated yields after flash chromatography. [c] See Supporting Information for determination. Error margins are given there. [d] 2,5-Dichlorothien-3-yl. [e] 5-Chlorothien-2-yl. [f] 6-Chloro-5-bromopyridin-2-yl. [g] The product was prepared in a one-pot fashion, with mesyl chloride and sodium azide. [h] The product was prepared in a one-pot fashion within 1 h, with perfluorobutylsulfonyl fluoride and sodium azide.

It is difficult to derive any tendency relating to the reactivity of the different sulfonyl azides employed. While both

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the most space-demanding azide **2i** and the smallest in the series, mesyl azide (**2m**), produced rather low yields, those obtained with the remaining species seem to be statistically distributed between 35% and 44%.

Electron density does not seem to be an exclusive criterion either, as the highest reactivities were observed for the electron-deficient nitro-substituted azides **2b** and **2c**, followed by the comparatively electron-rich dimethoxy-substituted **2f**, while on the other hand the most electron-deficient azide **2n** gave a yield of only 24%, although reacting at a much faster rate (the aldehyde was consumed within 1 h). In summary, there seems to be a subtle balance of different influences determining the overall reactivity and selectivity in this reaction, rather than an isolated set of features.

To make the reaction more attractive, it can be carried out in a one-pot fashion by mixing aldehyde, sulfonyl chloride, sodium azide and the catalyst without having to make the effort of preparing and isolating the sulfonyl azide beforehand. The reaction typically proceeded to give yields and enantioselectivities comparable to those obtained with the isolated sulfonyl azide (Table 5, **2a**, **2j**–**l**).

Other azides containing no sulfonyl substituent, such as electron-deficient Fmoc, 4-nitrophenyl or 4-nitrobenzyl azide, or electron-rich phenyl or benzyl azide, did not give α-sulfamidated products.

X-ray crystallographic data were collected for **4a**, **4c**, **4g** and **4j**. While the crystals obtained from **4a** and **4g** were racemic, **4c** and **4j** crystallised as enantiomerically pure substances and were assigned (*S*) configurations.

Influence of the Aldehyde

In order to determine the scope of the reaction with respect to the nature of the carbonyl compound involved, different α-branched aldehydes were employed in proline-catalysed reactions with tosyl azide (**2a**), 2-nosyl azide (**2b**) or 4-nosyl azide (**2c**).

The preparation of the commercially unavailable hydratropaldehyde derivatives **21**–**27** can be achieved through Wittig reactions between the corresponding acetophenone and methoxymethyltriphenylphosphonium chloride and subsequent acidic cleavage of the resulting acetophenone by known procedures.[73] In the case of the electron-rich aldehyde **26**, in which acidic cleavage did not provide the desired product, the corresponding alcohol was prepared by hydroboration either of the enol ether or of the analogous styrene,[74] obtained in a Wittig reaction with methyltriphenylphosphonium bromide, followed by Dess–Martin oxidation to give the desired aldehyde.[75] Alternatively, the corresponding acetophenone can be converted into an epoxide in a Corey–Chaikovsky procedure,[76] and this then can be opened by an indium(III)-catalysed rearrangement to afford the desired starting material.[77]

In the case of the achiral aldehydes **14**–**17**, yields between 36% and 52% were obtained (Table 6, Entries 1–4). While the presence of α-phenyl substituents lowered the yield to below 40%, no trend concerning the size of aliphatic α substituents could be observed. The same applies to the yields of reactions involving chiral aldehydes **18**–**20**, which carry two aliphatic substituents (Table 6, Entries 5–7). However, an increase in stereoselectivity with the difference in sizes of the α-substituents can be observed [the higher enantiomeric excess of **34** (Entry 7) is most probably due to the application of 2-nosyl azide instead of tosyl azide].

A remarkable enhancement in terms of stereoselectivity was observed when one of the α-alkyl substituents was exchanged for an aryl group. While the phenyl-substituted aldehyde **1** delivered between 56 and 82% *ee* (Table 5) – depending on the nature of the azide involved – an increase in selectivity took place when the aromatic moiety was substituted with one methoxy group (Table 6, Entries 8–13). In that case, the distance between the substituent and the reactive region seems to play an important role for the efficiency of the reaction, with a general increase with respect to both yield and stereoselectivity being observed from *ortho*- through *meta*- to *para*-substitution. A change of order was observed only in two instances: in the reactions between *ortho*- and *meta*-substituted aldehydes **21** and **22** and 2-nosyl azide in absolute ethanol the stereoselectivity was higher for the *ortho*-substituted **21** (Entries 9 + 11), whilst the *meta*-substituted **36b** was isolated in slightly higher yield than the *para*-substituted **37b** (Entries 11 + 13). While the yields of *meta*- and *para*-substituted aldehydes only varied within a certain frame, always staying well above 40%, the efficiency of the reaction dropped dramatically when *ortho*-substituted **21** was employed, resulting in mere 21–27% yields after prolonged reaction times (approx. 7 d, Entries 8 + 9). This points towards steric rather than electronic reasons for the different reactivities observed, as mesomeric effects should result in a closer resemblance of the results obtained for *ortho*- and *para*-substituted products than for *meta*- and *para*-substituted products.

When technical ethanol was exchanged for absolute ethanol as solvent, a decline in stereoselectivity could be observed in the case of **36a** (Table 6, Entry 10) in analogy to the results delivered by hydratropaldehyde, but not in that of **35a** (Entry 8). Interestingly, comparison between the results obtained with 2- and 4-nosyl azide reveals an inverse tendency for all monomethoxy-substituted aldehydes **21**–**23** relative to unsubstituted aldehyde **1**.

An improvement in the yield can be observed upon introduction of a second methoxy substituent into the aromatic system, though a reversed influence on stereoselectivity also has to be noted. In contrast, the 3,5-dibenzyloxy-substituted aldehyde **40** was obtained in higher enantiomeric excess but lower yield than the *meta*-monomethoxy-substituted aldehyde **36a**. Any interpretation based on the comparison between these two compounds might be misleading, however, as – because of the different natures of the substituents – both electronic and steric reasons could be responsible for the differences in reactivity and selectivity.

The argument that increased electron density of the aromatic moiety causes higher reactivity is substantiated by the result obtained with the 4-*tert*-butyl-substituted aldehyde **27**. If the use of absolute ethanol as solvent in this reaction

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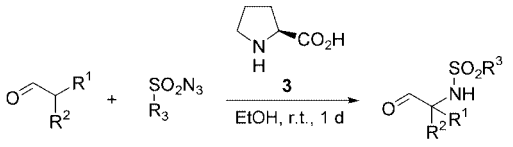
Table 6. Reactions between different aldehydes **14**–**27** and tosyl azide (**2a**, R^3 = Ts = 4-MeC_6H_4), 2-nosyl azide (**2b**, R^3 = 2-Ns = 2-$NO_2C_6H_4$) or 4-nosyl azide (**2c**, R^3 = 4-Ns = 4-$NO_2C_6H_4$).[a]



14–27 **2a–c** **28–41**

Entry	Aldehyde	R^1	R^2	R^3	Product	Yield[b,c] [%]	*ee*[c,d] [%]
1	**14**	Me	Me	Ts	**28**[c]	42	–[f]
2	**15**	Et	Et	Ts	**29**[c]	47	–[f]
3	**16**	$-(CH_2)_5-$		Ts	**30**[c]	52	–[f]
4	**17**	Ph	Ph	Ts	**31**[c]	36	–[f]
5	**18**	Me	Et	Ts	**32**[c]	49	5
6	**19**	Me	Pr	Ts	**33**[e]	51	12
7	**20**	Et	Bu	2-Ns	**34**	54	28
8	**21**	Me	2-$OMeC_6H_4$	2-Ns	**35a**[g]	21/27	72/72
9	**21**	Me	2-$OMeC_6H_4$	4-Ns	**35b**[g]	21	59
10	**22**	Me	3-$OMeC_6H_4$	2-Ns	**36a**	47/45	84/66
11	**22**	Me	3-$OMeC_6H_4$	4-Ns	**36b**[h]	49	69
12	**23**	Me	4-$OMeC_6H_4$	2-Ns	**37a**	53	86
13	**23**	Me	4-$OMeC_6H_4$	4-Ns	**37b**	44	76
14	**24**	Me	2,4-$OMeC_6H_3$	2-Ns	**38**[e,i]	34	45
15	**25**	Me	2,5-$OMeC_6H_3$	2-Ns	**39**[e,i]	32	54
16	**26**	Me	3,5-$OBnC_6H_3$	2-Ns	**40**	31	72
17	**27**	Me	4-*t*BuC_6H_4	2-Ns	**41**[e]	55	61

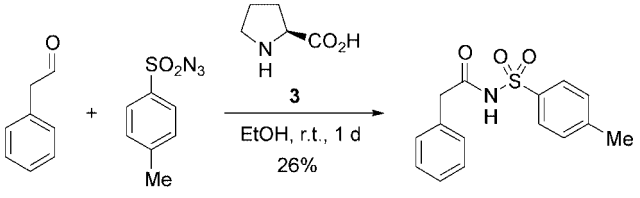
[a] Unless stated otherwise, reactions were carried out in sealed tubes with 1 equiv. of aldehyde, 1.1–1.2 equiv. of sulfonyl azide, and 1 equiv. of L-proline in technical ethanol (denatured with 1% petroleum ether) within 1 d. [b] Isolated yields after flash chromatography. [c] In the case of two values being given, the second applies to reaction in absolute ethanol. [d] See Supporting Information for determination. Error margins are given there. [e] The reaction was carried out in absolute ethanol. [f] Achiral product. [g] Workup after 7 d. Aldehyde still detectable by TLC. [h] Workup after 4 d. TLC indicated complete consumption of the aldehyde after 2 d. [i] Reaction time was 4 d.

is taken into account, a slight increase in stereoselectivity in relation to the analogous reaction with hydratropaldehyde can be observed.

In conclusion, increased electron density of the aromatic substituents seems to be a criterion for higher reactivity, as long as the presence of a substituent in the *ortho*-position does not exert an adverse influence due to steric hindrance. The latter effect can, however, be partly compensated by further increase in electron density, through the introduction of, for example, further donor substituents. Although in general the presence of electron-donating substituents also seems to enhance stereoselectivity, the results obtained with the very electron-rich dimethoxy-substituted species indicate that this cannot be an exclusive criterion.

Crystal structures of **31**, **35a** and **39** could be obtained by X-ray analysis. The chiral products **35a** and **39** crystallised in an enantiopure state. For these products, (*S*) configurations were determined in analogy to the crystal structures obtained for **4c** and **4j**.

It would unquestionably be desirable to extend this concept to the sulfamidation of α-unbranched aldehydes or ketones. Unfortunately, though, phenylacetaldehyde (**42**), the linear homologue of hydratropaldehyde, underwent an entirely different reaction, to afford the achiral tosyl benzacetamide **43** (Scheme 1), while no product could be isolated from reactions involving linear aliphatic aldehydes or ketones such as propiophenone, hexanal, cyclohexanone or 1,3-diphenylacetone.



42 **2a** **43**

Scheme 1. Proline-mediated reaction between phenylacetaldehyde (**42**) and **2a**.

Mechanistic Considerations

The findings described above cannot be satisfactorily explained by the pathway usually associated with enamine catalysis: the attack on an enamine formed between a carbonyl compound and a secondary amine catalyst by an electrophile in the α-position.[62,70,78] In the present case, this would result in the formation of triazenes or azide transfer,

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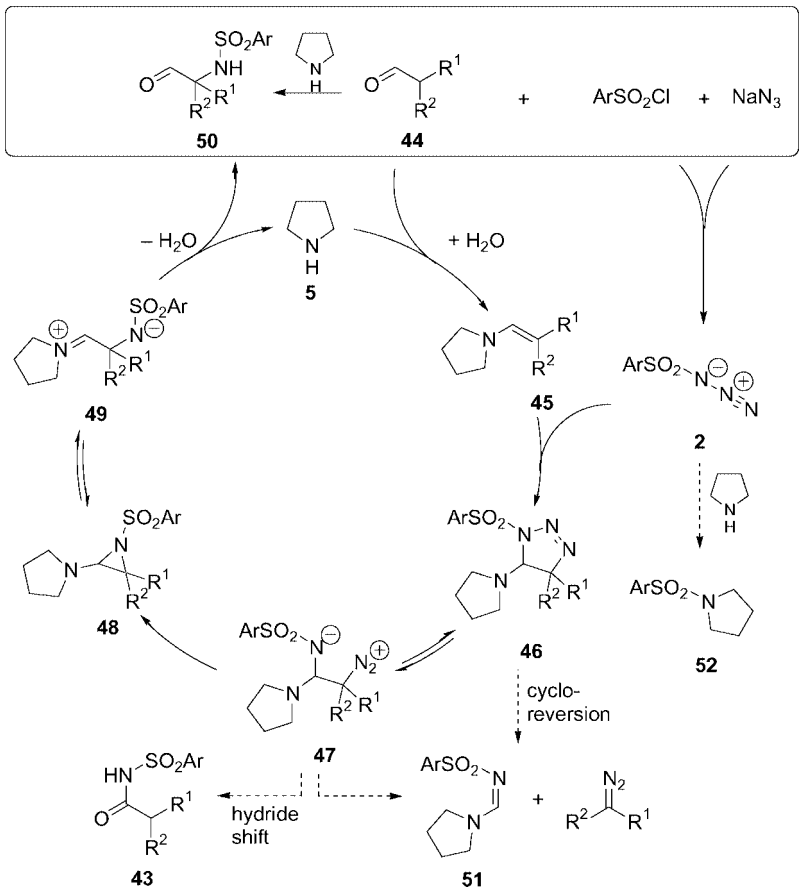

Scheme 2. Proposed mechanism for the pyrrolidine-catalysed α-sulfamidation of α-branched aldehydes.

but not α-sulfamidation, since electron-deficient azides are known to exhibit electrophilicity at the terminal nitrogen atom.[79] From the nature of the main product, and also from the byproducts isolated in the reaction between hydratropaldehyde and tosyl azide in the presence of the achiral pyrrolidine (Scheme 2), and in accordance with literature published earlier in this field,[80–83] we therefore propose a mechanism featuring as a central step a regioselective 1,3-dipolar cycloaddition between sulfonyl azide **2** and enamine **45**,[84,85] formed in situ between the aldehyde and the amine catalyst, followed by a number of rearrangement steps as depicted in Scheme 2.

Earlier publications dealing with reactions between sulfonyl azides and heterosubstituted double bonds have already pointed out the occurrence of sulfamidation reactions featuring regioselectivity analogous to that encountered in the present reaction (i.e., sulfamidation of the carbon centre next to the one carrying the electron-donating substituent). Treatment of benzocyclic β-keto esters with arenesulfonyl azides thus resulted in the formation of α-sulfamidated side products,[79b] while treatment with trifluoromethylsulfonyl azide (trisyl azide) even delivered the corresponding α-sulfonamido compound as the main product.[79c] Similar observations have been made for reactions of silyl enol ethers[80a] and disilyl ketene acetals,[80b] as well as for electron-rich carbazole derivatives[81] and enamines formed in situ from α-keto esters[82] with perfluorinated alkanesulfonyl azides. To the best of our knowledge, however, this is the first account of an asymmetric organocatalytic α-sulfamidation reaction.

The reaction can take place either in a concerted or in a stepwise manner. In either case it can be characterised as a Sustmann type-III cycloaddition with predominant $LUMO_{dipole}$–$HOMO_{dipolarophile}$ interactions. This specific reaction type produces the regioselectivity specified for triazoline **46** in Scheme 2.[86] At this point, the ratio of (*E*) and (*Z*) isomers in the formation of enamine **45** should be decisive for the relative configuration of the diastereomeric cycloaddition products: while (*E*)-**45** would give rise to a *trans* configuration in **46**, (*Z*)-**45** has to result in a *cis*-triazoline (Scheme 3). At least in the case of α-aryl-substituted enamines, it is very likely that the preferential form should be (*E*)-**45**. The formation of (*Z*)-**45** should be strongly disfavoured, as the proximity of both pyrrolidine system and aryl group would force both of them to rotate out of the enamine plane, resulting in a loss of conjugation energy. Moreover, cycloaddition to the enamine double bond by any spatially demanding dipole would be hampered, as the substituents protruding out of the enamine plane would shield the double bond from attack. At the same time, an equilibrium between the energetically less divergent (*E*)- and (*Z*)-enamines formed with all-aliphatic aldehydes **18**–**20** might be responsible for the lower enantioselectivity obtained in these cases.

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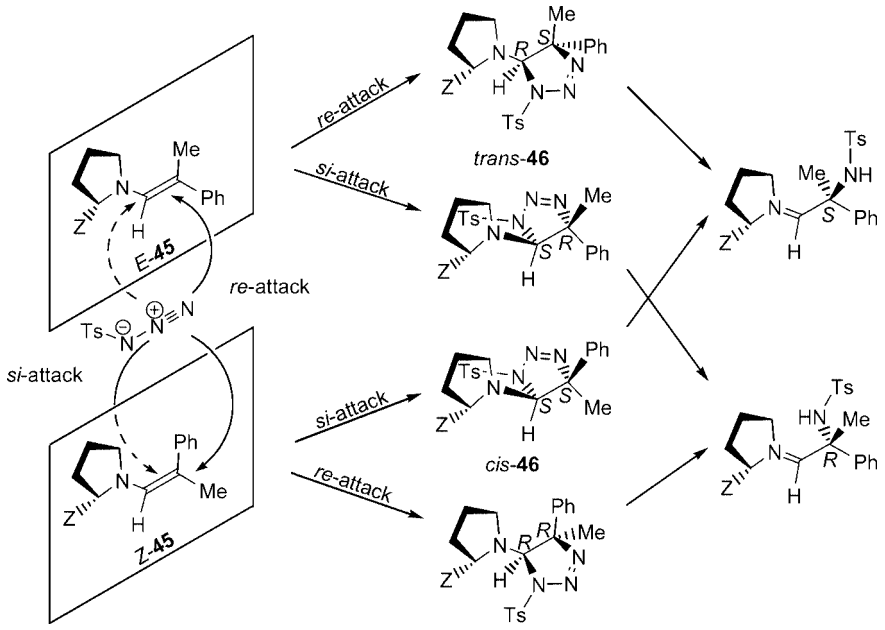

Scheme 3. Influence of (*E*)/(*Z*) configurations on product distribution.

If a chiral amino compound such as L-proline is involved in the enamine formation, the stereoinformation inherent in the molecule can result in an energetic differentiation of the transition states involved in addition at either of the two enamine faces. If total discrimination of one face is assumed, the product's enantiomeric excess would then reflect the (*E*)/(*Z*) ratio of the enamine formation. Preference for one of the faces can be achieved either by passive shielding of the opposite face, or by active interaction of the catalyst's side chain with the incoming sulfonyl azide (e.g., by hydrogen bonding between the carboxylate group and the sulfonyl group, possibly also involving one or several solvent molecules). The fact that the same stereochemical preference was observed for catalysts with potentially active functional side chains as for catalysts in which no positive directing ability is conceivable suggests that transfer of the chiral information is accomplished in the present case by successful shielding of one of the enamine faces from attack. At first, this seems to be contradictory to the observation that very bulky catalytic systems, such as the diaryl-substituted catalysts **12** and **13**, exerted less stereocontrol than proline, with a comparatively small carboxylate group. On the other hand, if the influence of the solvent is taken into account, self-organisation of solvent molecules around the more polar carboxylate group in proline might add to its bulkiness to result in more efficient shielding of one enamine face than by the more or less unsolvated apolar side groups in the former catalysts. This would also explain the decline in selectivity caused by increasing chain size of the alcohol, since this should result in the formation of more labile solvates.

In this context, a third parameter has to be discussed, in addition to the influence of the (*E*)/(*Z*) ratio and the mode of chiral transfer from the catalyst to the product. Although the rotation of the C–N bond in the enamine should be restricted, due to conjugation between the lone electron pair of the nitrogen atom and the C–C double bond, there are still two conceivable conformations the catalyst can assume relative to the double bond: *syn* and *anti* (Figure 2). As a result, axial chirality is introduced in addition to the central chirality inherent in the catalyst. The formation of a diastereomeric pair of enamines consequently results in opposed preferences for the attack on the double bond by a dipole – the *syn* conformation resulting in *si* attack and the *anti* conformation promoting reaction on the *re*-face. Because of steric interactions between the side chain of the catalyst and the vicinal methyl group in (*E*)-enamines the formation of *anti*-**45** should be favoured. Consequently, cycloaddition between a sulfonyl azide and an *anti*-(*Z*)-enamine should result in a (4*S*,5*R*)-triazoline, in which the stereocentre in the resulting product has an (*S*) configuration, which is in accordance with the absolute configurations encountered in all nonracemic crystal structures. At the same time, the formation and subsequent reaction of *syn*-**45** cannot be completely ruled out and might be partly responsible for loss of stereoselectivity.

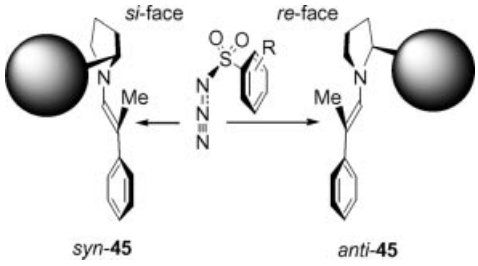

Figure 2. Influence of *syn* and *anti* conformations on steric differentiation of enamine faces.

In aryl-substituted enamines, conjugation with an aromatic system should result in a reduction in the HOMO

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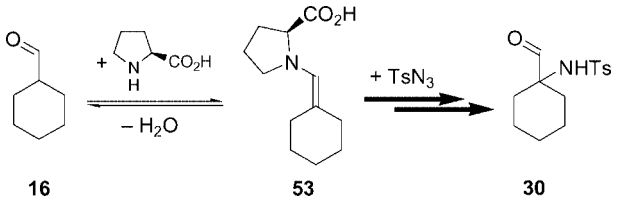
energy. Since the predominant interaction in a Sustmann type III cycloaddition is between the dipolarophile's HOMO and the dipole's LUMO, this should result in higher activation energies for aryl-substituted enamines than for dialkyl-substituted species. The presence of electron-donating aryl substituents such as methoxy groups should, on the other hand, raise the HOMO energy again, giving rise to an increase in reactivity relative to unsubstituted aryl-enamines. These assumptions correspond to the experimental findings. Thus, the yields obtained with all-aliphatic species (see Table 6, Entries 1–3, 5–7) were typically higher than those delivered by aryl-substituted aldehydes (see Table 6, Entries 4, 8–17), while electron-rich aryl-substituted aldehydes (other than *ortho*-methoxy species) displayed higher reactivity than hydratropaldehyde (see Table 6, Entries 10–13).

In the case of enamines derived from *ortho*-substituted arylpropionaldehydes, steric interactions might force the aromatic ring to rotate out of the enamine plane (Figure 3). This constriction facilitates the interpretation of a number of observations. The shielding of the double bond, caused by the *ortho* substituent protruding from the enamine plane, would lower the reactivity. A rotational barrier, preventing the free rotation of the aromatic system, would result in two different atropisomers, (R_a)-**45** and (S_a)-**45**, with the methoxy group protruding at different sides of the enamine double bond (Figure 3). It is likely that the preference for either of the two diastereomers is rather small, if the possibility of hydrogen bonding between the catalyst's functional group (e.g., the carboxylic group in proline) and the substituent's oxygen atom (which would freeze the methoxy group in a *syn* conformation) is not considered. If the obstruction caused by the methoxy group is distinct enough to prevent attack by the dipole on the same enamine face, then the participation of (S_a)-**45** might result in an increased number of "mismatch" cases (i.e., cases in which attack takes place on the enamine face shielded by the catalyst's side group), resulting in opposite stereochemistry. This would explain both the lower reactivity and stereoselectivity encountered with *ortho*-methoxyaryl-substituted aldehydes than with *meta*- and *para*-substituted species.

A slightly different, but no less interesting, case is the reaction between cyclohexanecarbaldehyde (**16**) and tosyl azide, in which the formation of enamine **53** results in a strained cyclic system with an *exo*-double bond (Scheme 4). This should produce an enhancement in the reactivity, and indeed this reaction delivered the highest yield of all aldehydes employed (in reactions involving tosyl azide as dipole).



Scheme 4. Explanation for higher reactivity of cyclohexanecarbaldehyde (**16**).

After cycloaddition the resulting triazoline **46** opens spontaneously to form betaine **47** (Scheme 2). To the best of our knowledge there is no hard evidence for the existence of betaines resembling **47**, but it seems to be widely accepted that a variety of fragmentation and decomposition reactions of triazolines derived from azides and electron-rich olefins do in fact involve the formation of this type of intermediate.[87,88] The emergence of symmetrically substituted *N*,*N*′-disulfonyl-2,5-dimethoxypiperazines as side products in reactions between enol ethers and sulfonyl azides as a result of dimerisation seems to be a clear indication of the ring-opening of the cycloaddition product in an analogous manner.[87,89] On the other hand, ab initio calculations indicate that benzyl diazonium cations do not exist in the classical sense, but rather as electrostatically bound complexes between benzyl cation and dinitrogen.[90] As a consequence, betaine **47** might not exist in the precise form displayed in Scheme 2, but rather as a carbenium cation more or less loosely bound to a dinitrogen molecule. This is of some importance for the stereochemical outcome of the reaction. If we are dealing with a carbenium species rather than a covalently bound diazonium cation, the subsequent formation of aziridine **48a** can take place in an S_N1-like reaction (i.e., with retention), whereas in the opposite case the diazonium cation would have to be substituted by a rear-attack in an S_N2-like manner, involving inversion of the participating carbon centre (Scheme 5). This means that the intermediate **47** would require a lifetime sufficient to carry out a 180° rotation around the α-carbon-aminal

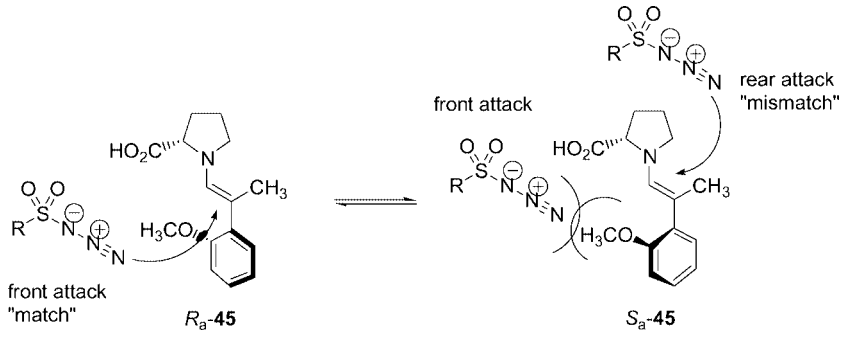


Figure 3. Possible explanation for lower reactivity and stereoselectivity of *ortho*-substituted aldehyde **21**.

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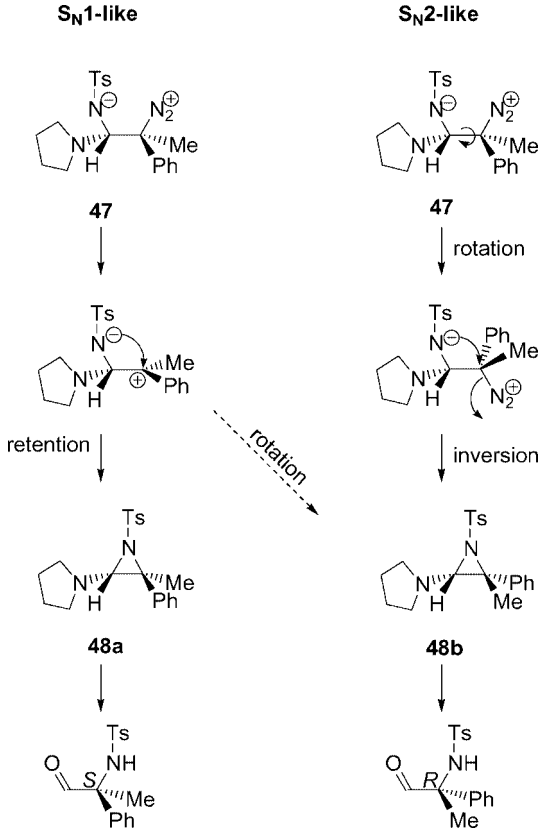
bond. Moreover, this process would result in the opposite stereochemistry for aziridine **48b** and, consequently, the product. Taking into account again that the absolute configurations of a number of products were determined to be (*S*) by X-ray crystallography – and still assuming azide attack to the *trans*-(*E*)-enamine **45** – the former case seems to be more likely. Rotation of either the diazonium species or the carbenium cation as described above might still take place, however, and thus be a further cause of loss of stereoinformation.



Scheme 5. Influence of diazonium stability on stereochemistry.

The emergence of the isolated side product **51** can be explained either by cycloreversion of triazoline **46**, or by rearrangement of betaine **47** to stabilise positive charges. In either case, it supports the involvement of a triazoline intermediate and thus a cycloaddition step. The formation of the sulfonamide **52** may also be considered as a possible side reaction, although the fact that significant amounts of azide can usually be detected after complete consumption of the aldehyde indicates that the rate of this reaction is negligible in comparison to that of the main reaction.

At this stage, a closer look at the competition between triazene formation and fragmentation might help resolve an apparent contradiction in attempting to connect the sulfonyl azides' steric and electronic properties to their reactivities. Although the most electron-deficient – and in addition least space-demanding – azides, nonaflyl azide (**2m**) and mesyl azide (**2n**, see Table 5), should engage in cycloaddition with enamine **45** more readily than the bulkier aryl-substituted analogues, and although a remarkable acceleration for the reaction of perfluorobutyl-substituted **2n** was observed, the yields finally obtained from these azides were significantly lower. A possible cause of deterioration in yield might be a preference of triazoline **46** for fragmentation to give the side product **51** over-ring closure to form the aziridine **48**. If the space demand of the catalytic side group is taken into account, steric pressure should result in an increased tendency for bulky sulfonamido groups to evade close proximity to the catalytic system attached at the same carbon centre. As a result, formation of aziridine **48** and subsequent ring-opening to form the α-sulfamidated product would be favoured over fragmentation, which would afford **51**, in which the same carbon centre carries both the pyrrolidine system and sulfonamide. In contrast, smaller sulfonyl substituents, such as the methyl group in **2m** or the perfluorobutyl group in **2n**, are better tolerated in the vicinity of the catalytic system, therefore resulting in a larger proportion of fragmentation reactions and reducing the final yield. This cannot be an exclusive criterion for determining the influence of the azide on the reaction's efficiency, however, as the most space-demanding azide **2i**, containing three isopropyl groups, delivered only slightly better yields than **2m** and **2n**. On the other hand, this can again be explained by a reduced readiness to engage in cycloaddition as a result of steric interactions. These divergent influences of steric properties on the overall reactivity make any prediction based on the nature of the azide species and concerning the outcome of the reaction exceedingly difficult. Moreover, this model, although helpful in interpreting a number of results connected to reactivity, does not provide an explanation for the differences in stereoselectivity encountered in connection with electronic features of the aldehyde or the nature of the azide. Neither does it provide an understanding of the role of alkane additives to the solvent in reactions involving 2-nosyl azide as a dipole.

Regardless of these considerations, the intramolecular substitution of dinitrogen (the release of which can be observed in the reaction) results in the formation of aziridine **48**. A similar process has been reported for reactions of 1,2-dihydropyridines with cyanogen and sulfonyl azides to form aziridines via triazoline intermediates.[86,91] Aziridine **48** then opens in the opposite direction to form the α-sulfamidated iminium species **49**, stabilising arising positive charges by delocalisation. Hydrolysis of the enamine finally releases the product **50** and the amine catalyst, which can enter a new reaction cycle.

The emergence of benzacetamide **43** in the reaction between phenylacetaldehyde (where R^1 = H, R^2 = Ph) and tosyl azide (**2a**) fits closely in the mechanism suggested above, if it is assumed that the aldehyde does indeed form an enamine with the catalyst to undergo cycloaddition with the azide as described in Scheme 6. However, it then adopts a different way to stabilise betaine **47** (or again the corresponding carbenium cation) by initialising a hydride shift from the aminal carbon to the adjacent α-carbon, enabling the amino group to stabilise the positive charge. The analogous decomposition of 5-aminotriazolines with hydride or alkyl shifts is well known[86] and has been used in the asym-

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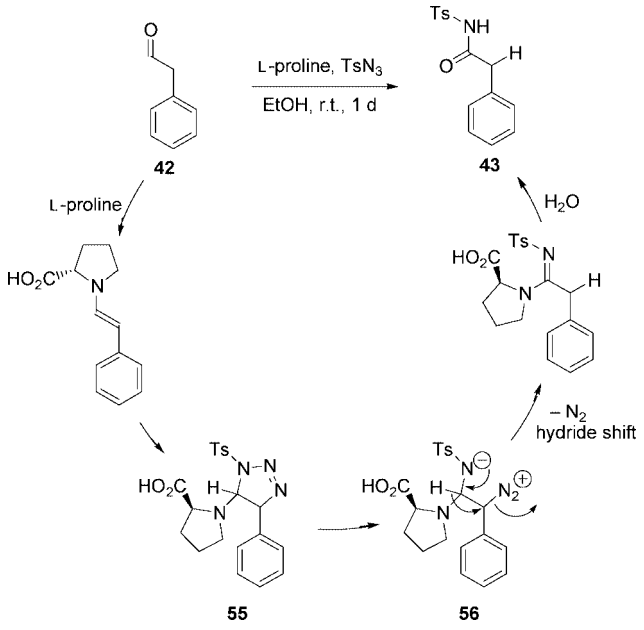
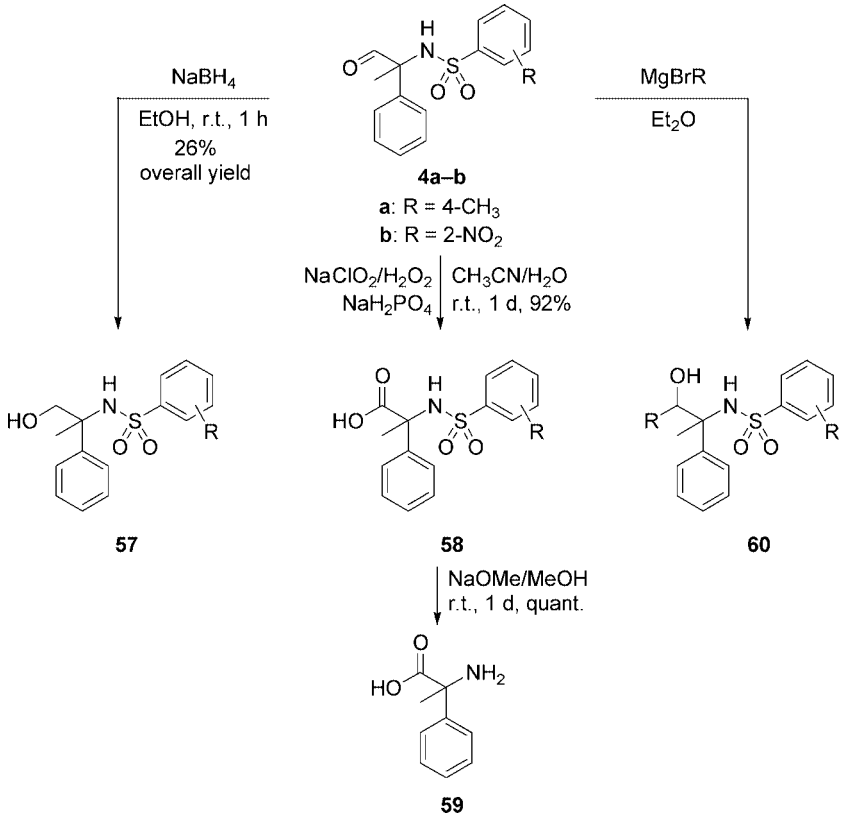
metric synthesis of chiral amidines with employment of proline as secondary amine.[92] In the case of α-branched aldehydes, the presence of a second substituent in the α-position seems to stabilise the zwitterionic intermediate sufficiently to prevent an analogous hydride shift, thus enabling the formation of the aziridine **48** as shown in Scheme 2.



Scheme 6. Reaction of linear aldehyde **42** towards benzacetamide **43**.

The fact that equimolar amounts of the amine catalyst are required to obtain maximum conversion of the aldehyde into the α-sulfamidated product may infer that the reaction should be denied status as a catalytic process. On closer inspection of the mechanistic details, however, it becomes evident that the amine species denominated as the catalyst is consumed only as a result of the side reaction(s). In contrast, the main reaction follows a catalytic cycle to release the amine at the end to enter a new cycle. Treatment of **1** with **2b** in the presence of only 10 mol-% of L-proline gave a yield of 18% of **4b** in 51% *ee*. Since no reaction could be observed in the absence of secondary amines, a noncatalytic pathway involving cycloaddition of the azide to the enolised form of **1** can be ruled out. This means that the presence of 10 mol-% of the catalyst produces the formation of 18% of product, thus giving a turnover number larger than one, so the actual sulfamidation reaction can indeed be regarded as a catalytic reaction, although the ratio of reaction rates of the catalytic formation of the desired product and the noncatalytic side reaction is difficult to control, since both reactions follow first-order kinetics after formation of the triazoline.

Kinetic resolution, which on account of the maximal yields being around 50% does not seem completely improbable, can be ruled out by several arguments. Kinetic resolution would apply if only one enantiomer of the racemic starting material were able to form enamines with the enantiopure catalyst to enter the reaction cycle, while the other enantiomer remained unreactive. As a consequence,



Scheme 7. Manipulations of the α-sulfamidation products **4a** and **4b**.

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at least 50% of unreacted starting material should remain in the reaction mixture to be reisolated. TLC analysis, however, indicated that this is not the case in practically all the reactions carried out in this study. Moreover, other reactions involving the formation of enamines from L-proline and racemic α-branched aldehydes delivered more than 80% yields in more than 80% *ee*s. These results are absolutely impossible to obtain by kinetic resolution and thus establish that both enantiomers of the starting material engage in enamine formation.

Since unprotected α-amino aldehydes are not usually chemically stable,[93] the carbonyl group in the sulfamidated product has to be transformed prior to deprotection of the amino group. This can be achieved either by treatment of the ethanolic reaction mixture with sodium borohydride after the reaction is complete – to produce the corresponding amino alcohol **57** – or by oxidation of the isolated product **4b** with sodium chlorite and hydrogen peroxide to yield the corresponding acid **58** (Scheme 7).[94] The removal of the 2-nosyl group can be accomplished by treatment of the protected amino acid **58** with sodium methoxide in dioxane.[95]

Conclusions

In summary, we present the first asymmetric organocatalytic α-sulfamidation of α,α-disubstituted aldehydes. The reaction can be conveniently carried out in a one-pot fashion, starting from an aldehyde, sulfonyl chloride and sodium azide without any prior isolation of the sulfonyl azide. A wide range of α,α-disubstituted aldehydes is tolerated, although the yields and stereoselectivities obtained in this study require further optimisation to render the reaction attractive for preparative purposes. However, the mechanistic model proposed for the organocatalytic key step represents an extension for existing concepts in enamine catalysis to include an interesting set of cycloaddition/rearrangement reactions as described here. Further studies will have to be performed to establish a more profound understanding of the mechanistic details. The configurationally stable products obtained from the sulfamidation reaction can easily be converted into the corresponding unnatural amino acids, thus making this reaction one of the most straightforward approaches to α-branched amino acid synthesis.

Experimental Section

General Methods: Flash chromatography (FC) was carried out with Merck silica gel 60 (230–400 mesh). TLC was carried out on Merck silica gel-coated aluminium sheets with fluorescence indicator (silica gel 60 F_{254}). ^{1}H NMR spectra were recorded at 250 MHz on a Bruker AC 300 instrument, at 300 MHz on a Bruker DP 300 and at 400 MHz on a Bruker DP 400 and a Bruker AM 400. The ^{13}C NMR spectra were recorded at 75 MHz and 100 MHz. The chemical shifts are reported in ppm relative to the residual solvent peak.[96] Mass spectra were recorded on a Kratos MS50 spectrometer, a Finnigan MAT 90 (EI-MS, HRMS), a Thermo Quest Finnigan MAT 95 XL (EI-MS) or a Kratos Concept 1H (FAB). Elemental analysis was carried out on Elementar Vario EL and Heraeus CHN-O-Rapid instruments. HPLC was performed on an Agilent 1100 Series instrument with Diacel Chiralpak AS (250 × 4.6 mm) or Diacel Chiracel OD (250 × 4.00 mm, 10 μm). Rotational values were determined on a Perkin–Elmer 241 Polarimeter at λ = 589 nm (sodium D-line). The concentration c is given in [g/100 mL]. *Ee*s were determined by comparison with the racemic products obtained by application of DL-proline as catalyst by HPLC or by determination of the *de* of the corresponding Mosher's ester (see Supporting Information).[97]

Materials: All reagents available from commercial sources (Acros, Aldrich, Fluka, Lancaster, Merck) were used without further purification. Sulfonyl azides were synthesised by known procedures.[98] The ionic liquids [bmim][BF_4],[60] [capemim][BF_4][58] and [C_3OHmim][BF_4][61] were synthesised by known procedures, whilst the ionic liquids ECOENG 212™, ECOENG 1111P™, AMMOENG 100™, AMMOENG 102™ and AMMOENG 120™ were purchased from Solvent Innovations. Commercially unavailable aldehydes **21**–**27** were synthesised by known procedures.[99–103] Solvents were dried and distilled under argon by general laboratory methods.

General Procedure for the Sulfamidation of α,α-Disubstituted Aldehydes

Method A: In a sealed tube, a solution or suspension of the catalyst (1 equiv.) in the solvent (10 to 20 mL per mmol aldehyde) was treated successively with the sulfonyl azide (1 to 1.2 equiv.) and the aldehyde (1 equiv.) at room temperature until TLC monitoring indicated complete consumption of the aldehyde. The solvent was then removed by evaporation under reduced pressure and the product was isolated by flash chromatography. When ionic liquids were used as solvent, the ionic liquid phase was extracted exhaustively with ethyl acetate and THF after completion of the reaction, until TLC monitoring of the separated non-ionic phase indicated there was no more product (about five times). The non-ionic phases were collected, the solvent was removed by evaporation, and the product was then isolated by flash chromatography of the residue.

Method B: In a sealed tube, a solution of 1 equiv. of the catalyst in ethanol (20–30 mL of ethanol per mmol aldehyde) was treated successively at room temperature with sodium azide (1.4 equiv.), aldehyde (1 equiv.), and sulfonyl chloride (1.2 equiv.). After TLC monitoring indicated complete consumption of the aldehyde, the solvent was removed under reduced pressure and the product was isolated by flash chromatography.

(+)-2-Phenyl-2-(tolyl-4-sulfonylamino)propionaldehyde (4a): This compound was obtained by Method A, in technical ethanol (denatured with 1% petroleum ether): 56.6 mg, 38% yield. For further reaction conditions, yields and *ee*s, see Table 1, Table 2, and Table 4, as well as the Supporting Information; m.p. 113 °C. $[\alpha]_D^{20}$ = +59.7 (*c* = 0.330, $CHCl_3$; for 56% *ee*). R_f = 0.15 (*n*-pentane/Et_2O 2:1). HPLC (Chiralpak AS, 0.8% diethylamine in *n*-heptane/propan-2-ol 64:36, 0.8 mL min^{-1}): R_t(min) = 15.4 min, R_t(maj) = 27.7 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.82 (s, 3 H), 2.28 (s, 3 H), 5.85 (br s, 1 H), 6.99 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H), 7.03–7.09 (m, 2 H), 7.09–7.21 (m, 3 H), 7.29 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H), 9.06 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.1 (+), 21.5 (+), 66.9 (q), 126.8 (+), 127.6 (+), 128.7 (+), 129.0 (+), 129.3 (+), 134.3 (q), 139.3 (q), 142.9 (q), 194.4 (+) ppm. IR (KBr): $\tilde{\nu}$ = 3252.1 (m, υ[NH]), 1743.9 (m, δ[NH]), 1733.0 [m, υ(C=O)], 1327.4 (m, $\upsilon_{as}[SO_2]$), 1156.2 (m, $\upsilon_{sy}[SO_2]$) cm^{-1}. MS (FAB): *m*/*z* = 304 [M + 1]$^+$. HRMS: *m*/*z*: calcd. for [M – CHO]$^+$: 274.0902; found:

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274.0900. $C_{16}H_{17}NO_3S$ (303.38 g mol^{-1}): calcd. C 63.35, H 5.65, N 4.62, S 10.57; found: C 63.71, H 5.68, N 4.64, S 10.60.

(+)-2-(2-Nitrophenylsulfonylamino)-2-phenylpropionaldehyde (4b): This compound was obtained by Method A, in technical ethanol (denatured with 1% petroleum ether): 77.3 mg, 46% yield. For further reaction conditions, yields and *ee*s, see Table 2, Table 3 and Table 4, as well as the Supporting Information; m.p. 173 °C. $[\alpha]_D^{20}$ = +226.3 (*c* = 0.175, $CHCl_3$; for 61% *ee*). R_f = 0.15 (*n*-pentane/Et_2O 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.96 (s, 3 H), 6.99–7.22 (m, 9 H), 7.44 (ddd, $^3J_{H,H}$ = 7.7, 7.6 Hz, $^4J_{H,H}$ = 1.7 Hz, 1 H), 7.68 (dd, $^3J_{H,H}$ = 7.9 Hz, $^4J_{H,H}$ = 1.1 Hz, 1 H), 9.07 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.3 (+), 67.3 (q), 124.9 (+), 127.9 (+), 128.9 (+), 129.2 (+), 130.2 (+), 132.4 (+), 132.7 (+), 133.6 (q), 135.4 (q), 147.4 (q), 193.4 (+) ppm. IR (KBr): $\tilde{\nu}$ = 3321.8 (m, υ[NH]), 1717.1 (m, υ[C=O]), 1541.4 (m, υ_{as}[NO_2]), 1367.0 (m, υ_{as}[SO_2]), 1337.0 (m, υ_{sy}[NO_2]), 1157.4 (m, υ_{sy}[SO_2]) cm^{-1}. MS (FAB): *m*/*z*: 335 [M + 1]$^+$. HRMS: *m*/*z*: calcd. for [M – CHO]$^+$: 305.0596; found: 305.0596. $C_{15}H_{14}N_2O_5S$ (334.35 g mol^{-1}): calcd. C 53.88, H 4.22, N 8.38, S 9.59; found: C 54.12, H 4.40, N 8.12, S 9.85.

(*S*)-(+)-2-(4-Nitrophenylsulfonylamino)-2-phenylpropionaldehyde (4c): This compound was obtained by Method A, in absolute ethanol: 86.6 mg, 52% yield; 82% *ee* (determined as the *de* of the corresponding Mosher's ester, see Supporting Information). This compound was also obtained by Method A, in technical ethanol: 76.3 mg, 46% yield; 83% *ee* (determined as the *de* of the corresponding Mosher's ester, see Supporting Information). m.p. 183–187 °C. $[\alpha]_D^{20}$ = +18.6 (*c* = 0.370, $CHCl_3$). R_f = 0.17 (cyclohexane/ethyl acetate 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.01 (s, 3 H), 6.28 (br s, 1 H), 6.99–7.05 (m, 2 H), 7.10–7.17 (m, 2 H), 7.23 (dddd, $^3J_{H,H}$ = 8.0, 6.7 Hz, $^4J_{H,H}$ = 1.1, 1.1 Hz, 1 H), 7.48 (ddd, $^3J_{H,H}$ = 9.2 Hz, $^4J_{H,H}$ = 2.2, 2.2 Hz, 2 H), 8.01 (ddd, $^3J_{H,H}$ = 9.2 Hz, $^4J_{H,H}$ = 2.2, 2.2 Hz, 2 H), 9.07 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.1 (+), 66.8 (q), 123.8 (+), 127.9 (+), 128.1 (+), 129.0 (+), 129.3 (+), 132.8 (q), 147.4 (q), 149.4 (q), 193.6 (+) ppm. IR (KBr): $\tilde{\nu}$ = 3295.2 (m, ν[NH]), 1722.0 (m, ν[C=O]), 1524.4 (m, ν_{as}[NO_2]), 1350.6 (m, ν_{as}[SO_2]), 1314.6 (m, ν_{sy}[NO_2]), 1170.9 (m, ν_{sy}[SO_2]) cm^{-1}. MS (EI = 70 eV): *m*/*z*: 305 [M – CHO]$^+$. HRMS: *m*/*z*: calcd. for [M – CHO]$^+$: 305.0596; found: 305.0598.

(+)-2-(2,4-Dinitrophenylsulfonylamino)-2-phenylpropionaldehyde (4d): This compound was obtained by Method A: 51.1 mg, 27% yield; 45% *ee*; m.p. 128 °C (decomp.). $[\alpha]_D^{20}$ = +14.4 (*c* = 0.655, $CHCl_3$). R_f = 0.48 (cyclohexane/ethyl acetate 3:2). HPLC (Chiralpak AS, *n*-heptane/propan-2-ol 50:50, 0.5 mL min^{-1}): R_t(maj) = 22.2 min, R_t(min) = 46.1 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.02 (s, 3 H), 6.44 (d, $^3J_{H,H}$ = 9.6 Hz, 1 H), 7.37–7.51 (m, 5 H), 7.97 (dd, $^3J_{H,H}$ = 9.5 Hz, $^4J_{H,H}$ = 2.4 Hz, 1 H), 9.15 (d, $^4J_{H,H}$ = 2.8 Hz, 1 H), 9.22 (s, 1 H), 10.12 (br s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.8 (+), 67.4 (q), 116.8 (+), 124.3 (+), 126.9 (+), 129.4 (+), 129.6 (+), 130.3 (+), 132.1 (q), 134.5 (q), 136.7 (q), 145.8 (q), 192.7 (+) ppm. IR (KBr): $\tilde{\nu}$ = 3295.7 (m, ν[NH]), 1725.4 (m, ν[C=O]), 1523.2 (m, ν_{as}[NO_2]), 1334.8 (m, ν_{as}[NO_2]), 1157.2 (m, ν_{sy}[SO_2]) cm^{-1}. Because of fast decomposition (within days) no further analytical data could be obtained.

(+)-2-(2-Methoxycarbonylphenylsulfonylamino)-2-phenylpropionaldehyde (4e): This compound was obtained by Method A, in absolute ethanol: 67.1 mg, 39% yield; 8% *ee*; m.p. 134–137 °C. $[\alpha]_D^{20}$ = +78.7 (*c* = 0.385, $CHCl_3$). R_f = 0.16 (*n*-pentane/Et_2O 2:1). HPLC (Chiralpak AS, *n*-heptane/propan-2-ol 80:20, 0.7 mL min^{-1}): R_t(maj) = 24.0 min, R_t(min) = 31.4 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.76 (s, 3 H), 4.04 (s, 3 H), 7.08–7.20 (m, 5 H), 7.22 (ddd, $^3J_{H,H}$ = 7.7, 7.7 Hz, $^4J_{H,H}$ = 1.3 Hz, 1 H), 7.31 (dd, $^3J_{H,H}$ = 8.0 Hz, $^4J_{H,H}$ = 1.1 Hz, 1 H), 7.44 (ddd, $^3J_{H,H}$ = 7.6, 7.6 Hz, $^4J_{H,H}$ = 1.4 Hz, 1 H), 7.57 (br s, 1 H), 7.72 (dd, $^3J_{H,H}$ = 7.7 Hz, $^4J_{H,H}$ = 1.1 Hz, 1 H), 9.21 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.4 (+), 53.5 (+), 67.4 (q), 127.6 (+), 128.5 (+), 128.7 (+), 128.7 (+), 129.7 (q), 130.4 (+), 131.5 (+), 131.6 (+), 134.2 (q), 141.3 (q), 168.1 (q), 194.2 (+) ppm. IR (KBr): $\tilde{\nu}$ = 3256.9 (m, ν[NH]), 1716.0 (m, ν[C=O]), 1334.0 (m, ν_{as}[SO_2]), 1161.0 (m, ν_{sy}[SO_2]) cm^{-1}. MS (FAB), *m*/*z*: 348 [M + 1]$^+$. HRMS: *m*/*z*: calcd. for [M – CHO]$^+$: 318.0800; found: 318.0807. $C_{17}H_{17}NO_5S$ (347.39 g mol^{-1}): calcd. C 58.78, H 4.93, N 4.03, S 9.23; found: C 58.82, H 4.86, 3.93, S 8.74.

(+)-2-(3,4-Dimethoxyphenylsulfonylamino)-2-phenylpropionaldehyde (4f): This compound was obtained by Method A, in absolute ethanol: 75.1 mg, 43% yield; 67% *ee*. $[\alpha]_D^{20}$ = +269.2 (*c* = 0.189, $CHCl_3$). R_f = 0.29 (cyclohexane/ethyl acetate 3:1). HPLC (Chiracel OD, *n*-heptane/propan-2-ol 92:8, 1.0 mL min^{-1}): R_t(maj) = 34.4 min, R_t(min) = 37.7 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.92 (s, 3 H), 3.76 (s, 3 H), 3.88 (s, 3 H), 5.99 (br s, 1 H), 6.70 (d, $^3J_{H,H}$ = 8.7 Hz, 1 H), 6.85 (d, $^4J_{H,H}$ = 2.1 Hz, 1 H), 7.06–7.14 (m, 3 H), 7.15–7.25 (m, 3 H), 9.11 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.1 (+), 56.1 (+), 56.1 (+), 66.8 (q), 109.4 (+), 110.4 (+), 120.6 (+), 127.8 (+), 128.8 (+), 128.8 (+), 133.9 (q), 134.0 (q), 148.6 (q), 152.2 (q), 194.3 (+) ppm. IR (KBr): $\tilde{\nu}$ = 3274.3 (m, ν[NH]), 1731.2 (m, ν[C=O]), 1324.6 (m, ν_{as}[SO_2]), 1182.2 (m, ν_{sy}[SO_2]) cm^{-1}. MS (FAB), *m*/*z*: 350 [M + 1]$^+$. HRMS[1]: calcd. for [M]$^+$: 349.0984; found: 349.0983.

(–)-2-(Naphthalene-1-sulfonylamino)-2-phenylpropionaldehyde (4g): This compound was obtained by Method A, in absolute ethanol: 61.2 mg, 36% yield; 65% *ee* (determined as the *de* of the corresponding Mosher's ester, see Supporting Information). m.p. 168–170 °C. $[\alpha]_D^{20}$ = –14.2° (*c* = 0.120, $CHCl_3$). R_f = 0.34 (*n*-pentane/Et_2O 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.88 (s, 3 H), 6.28 (br s, 1 H), 6.82 (dd, $^3J_{H,H}$ = 8.4 Hz, $^4J_{H,H}$ = 1.2 Hz, 2 H), 6.90 (dd, $^3J_{H,H}$ = 8.1, 7.6 Hz, 2 H), 7.04 (dddd, $^3J_{H,H}$ = 7.3, 7.3 Hz, $^4J_{H,H}$ = 1.0, 1.0 Hz, 1 H), 7.13 (dd, $^3J_{H,H}$ = 7.8, 7.8 Hz, 1 H), 7.58 (ddd, $^3J_{H,H}$ = 8.1, 7.0 Hz, $^4J_{H,H}$ = 1.0 Hz, 1 H), 7.62 (dd, $^3J_{H,H}$ = 7.5 Hz, $^4J_{H,H}$ = 1.1 Hz, 1 H), 7.69 (ddd, $^3J_{H,H}$ = 8.5, 7.0 Hz, $^4J_{H,H}$ = 1.5 Hz, 1 H), 7.85 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H), 7.86 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H), 8.56 (d, $^3J_{H,H}$ = 8.6 Hz, 1 H), 9.04 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.1 (+), 66.9 (q), 124.1 (+), 124.2 (+), 126.7 (+), 127.4 (+), 127.7 (q), 128.5 (+), 128.5 (+), 128.7 (+), 129.1 (+), 129.1 (+), 133.1 (q), 133.7 (+), 134.0 (q), 136.5 (q), 194.2 (+) ppm. IR (KBr): $\tilde{\nu}$ = 3330.0 (m, ν[NH]), 1716.6 (m, ν[C=O]), 1360.0 (m, ν_{as}[SO_2]), 1128.0 (m, ν_{sy}[SO_2]) cm^{-1}. MS (EI = 70 eV), *m*/*z*: 310 [M – CHO]$^+$]. HRMS: *m*/*z*: calcd. for [M – CHO]$^+$: 310.0902; found: 310.0902.

(+)-2-(Naphthalene-2-sulfonylamino)-2-phenylpropionaldehyde (4h): This compound was obtained by Method A, in absolute ethanol: 69.7 mg, 42% yield; 64% *ee* (determined as the *de* of the corresponding Mosher's ester, see Supporting Information). $[\alpha]_D^{20}$ = +68.5 (*c* = 0.305, $CHCl_3$). R_f = 0.29 (*n*-pentane/Et_2O 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.93 (s, 3 H), 6.16 (br s, 1 H), 6.95–7.02 (m, 3 H), 7.04–7.10 (m, 2 H), 7.52 (ddd, $^3J_{H,H}$ = 7.9, 7.0 Hz, $^4J_{H,H}$ = 1.0 Hz, 1 H), 7.55–7.61 (m, 2 H), 7.68 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H), 7.76 (d, $^3J_{H,H}$ = 8.7 Hz, 1 H), 7.81 (d, $^3J_{H,H}$ = 9.9 Hz, 1 H), 7.83 (s, 1 H), 9.13 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.2 (+), 66.9 (q), 122.0 (+), 127.3 (+), 127.6 (+), 127.8 (+), 128.1 (+), 128.6 (+), 128.7 (+), 128.8 (+), 129.0 (+), 129.3 (+), 131.9 (q), 133.4 (q), 134.5 (q), 138.6 (q), 194.3 (+) ppm. IR (KBr): $\tilde{\nu}$ = 3259.8 (m, ν[NH]), 1733.7 (m, ν[C=O]), 1334.9 (m, ν_{as}[SO_2]), 1152.7 (m, ν_{sy}[SO_2]) cm^{-1}. MS (FAB), *m*/*z*: 340 [M + 1]$^+$.

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(+)-2-Phenyl-2-(2,4,6-triisopropylphenylsulfonylamino)propionaldehyde (4i): This compound was obtained by Method A, in absolute ethanol: 68.0 mg, 33% yield; 49% *ee* (determined as the *de* of the corresponding Mosher's ester, see Supporting Information). $[\alpha]_D^{20}$ = +22.1 (*c* = 1.510, $CHCl_3$). R_f = 0.22 (*n*-pentane/Et_2O 4:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.05 (d, $^3J_{H,H}$ = 6.7 Hz, 6 H), 1.16 (d, $^3J_{H,H}$ = 6.7 Hz, 12 H), 1.76 (s, 3 H), 2.79 (sept, $^3J_{H,H}$ = 6.9 Hz, 1 H), 3.85 (sept, $^3J_{H,H}$ = 6.7 Hz, 2 H), 5.89 (brs, 1 H), 6.97 (s, 2 H), 7.03–7.36 (m, 5 H), 9.06 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3 (+), 23.7, 23.8 (+), 24.7, 24.9 (+), 29.8 (+), 34.3 (+), 67.7 (q), 123.6 (+), 127.3 (+), 128.7 (+), 128.9 (+), 135.2 (q), 136.1 (q), 148.9 (q), 152.6 (q), 194.7 (+) ppm. IR (KBr): $\tilde{\nu}$ = 3295.7 (m, ν[NH]), 1726.1 (m, ν[C=O]), 1322.7 (m, $\nu_{as}[SO_2]$), 1150.9 (m, $\nu_{sy}[SO_2]$) cm^{-1}. MS (FAB), *m*/*z*: 416 $[M + 1]^+$. HRMS: *m*/*z*: calcd. for $[M - CHO]^+$: 386.2154; found: 386.2148. $C_{24}H_{33}NO_3S$ (415.59 gmol^{-1}): calcd. C 69.36, H 8.00, N 3.37, S 7.72; found: C 69.14, H 7.81, N 3.13, S 7.03.

(S)-(+)-2-(2,5-Dichlorothien-3-ylsulfonylamino)-2-phenylpropionaldehyde (4j): This compound was obtained by Method A: 98.3 mg, 27% yield; 47% *ee*; This compound was also obtained by Method B: 138.4 mg, 38% yield; 47% *ee*. $[\alpha]_D^{20}$ = +12.0 (*c* = 0.510, $CHCl_3$). m.p. 134 °C. R_f = 0.57 (*n*-pentane/Et_2O 2:1). HPLC (Chiralpak AS, 0.8% diethylamine in *n*-heptane/propan-2-ol 64:36, 0.85 mLmin^{-1}): R_t(min) = 10.2 min, R_t(maj) = 12.1 min. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.00 (s, 3 H), 6.25 (s, 1 H), 6.50 (brs, 1 H), 7.13 (d, $^3J_{H,H}$ = 7.9 Hz, 2 H), 7.25–7.33 (m, $^3J_{H,H}$ = 7.9 Hz, 3 H), 9.13 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.1 (+), 66.5 (q), 126.2 (+), 126.4 (+), 127.6 (+), 128.4 (+), 128.8 (+), 129.3 (q), 132.1 (q), 138.1 (q), 193.5 (+) ppm. IR (KBr): $\tilde{\nu}$ = 3267.5 (m, υ[NH]), 1722.4 (m, δ[NH]), 1720.3 [m, υ(C=O)], 1599.3 (w, υ[C–C_{ar}]), 1337.5 (m, $\upsilon_{as}[SO_2]$), 1173.6 (m, $\upsilon_{sy}[SO_2]$) cm^{-1}. MS (EI = 70 eV), *m*/*z*: 334/336/338 (16) $[M - CHO]^+$. HRMS: *m*/*z*: calcd. for $[M]^+$: 362.9557; found: 362.9561. $C_{13}H_{11}NCl_2O_3S_2$ (364.26 gmol^{-1}): calcd. C 42.87, H 3.04, N 3.85, S 17.60; found: C 43.15, H 3.46, N 3.94, S 17.43.

(+)-2-(5-Chlorothien-2-ylsulfonylamino)-2-phenylpropionaldehyde (4k): This compound was obtained by Method A: 119.0 mg, 36% yield; 54% *ee*. This compound was also obtained by Method B: 115.3 mg, 35% yield; 54±2% *ee*. $[\alpha]_D^{20}$ = +26.3 (*c* = 0.505, $CHCl_3$). m.p. 123 °C. R_f = 0.44 (*n*-pentane/Et_2O 2:1). HPLC (Chiralpak AS, 0.8% diethylamine in *n*-heptane/propan-2-ol 64:36, 0.85 mLmin^{-1}): R_t(min) = 11.0 min, R_t(maj) = 14.0 min. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.90 (s, 3 H), 6.19 (brs, 1 H), 6.50 (d, $^3J_{H,H}$ = 4.0 Hz, 1 H), 6.66 (d, $^3J_{H,H}$ = 4.0 Hz, 1 H), 7.08 (dd, $^3J_{H,H}$ = 8.2 Hz, $^4J_{H,H}$ = 1.5 Hz, 2 H), 7.17–7.23 (m, $^3J_{H,H}$ = 8.2 Hz, 3 H), 9.03 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.8 (+), 66.9 (q), 126.1 (+), 127.7 (+), 128.9 (+), 129.0 (+), 131.2 (+), 133.2 (q), 136.9 (q), 140.9 (q), 193.8 (+) ppm. IR (KBr): $\tilde{\nu}$ = 3255.8 (m, υ[NH]), 1738.5 (m, δ[NH]), 1729.3 [m, υ(C=O)], 1333.5 (m, $\upsilon_{as}[SO_2]$), 1154.5 (m, $\upsilon_{sy}[SO_2]$) cm^{-1}. MS (EI = 70 eV), *m*/*z*: 300/302 $[M - CHO]^+$. HRMS: *m*/*z*: calcd. for $[M]^+$: 328.9947; found: 328.9940. $C_{13}H_{12}NClO_3S_2$ (329.82 gmol^{-1}): calcd. C 47.34, H 3.67, N 4.25, S 19.44; found: C 47.55, H 3.79, N 4.16, S 19.64.

(+)-2-(5-Bromo-6-chloropyridin-3-ylsulfonylamino)-2-phenylpropionaldehyde (4l): This compound was obtained by Method A: 97.1 mg, 24% yield; 46% *ee*. This compound was also obtained by Method B: 125.0 mg, 31% yield; 60±7% *ee*. m.p. 148 °C. $[\alpha]_D^{20}$ = +28.4 (*c* = 0.575, $CHCl_3$). R_f = 0.28 (*n*-pentane/Et_2O 2:1). HPLC (Chiralpak AS, 0.8% diethylamine in *n*-heptane/propan-2-ol 64:36, 0.85 mLmin^{-1}): R_t(min) = 10.5 min, R_t(maj) = 12.8 min. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.01 (s, 3 H), 6.43 (brs, 1 H), 7.08 (d, $^3J_{H,H}$ = 7.5 Hz, 2 H), 7.24–7.38 (m, 3 H), 7.57 (s, 1 H), 8.35 (s, 1 H), 9.14 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.0 (+), 66.7 (q), 120.1 (q), 128.2 (+), 129.1 (+), 130.0 (+), 131.8 (q), 137.8 (q), 140.0 (+), 145.8 (+), 153.9 (q), 193.5 (+) ppm. IR (KBr): $\tilde{\nu}$ = 3252.7 (m, υ[NH]), 1737.5 (m, δ[NH]), 1732.0 [m, υ(C=O)], 1343.1 (m, $\upsilon_{as}[SO_2]$), 1147.1 (m, $\upsilon_{sy}[SO_2]$) cm^{-1}. MS (EI = 70 eV), *m*/*z*: 372/374/376 $[M - CHO]^+$. HRMS: *m*/*z*: calcd. for $[M]^+$: 401.9441; found: 401.9470.

(+)-2-Methanesulfonylamino-2-phenylpropionaldehyde (4m): This compound was obtained by Method B: 74.4 mg, 33% yield; 71% *ee* (determined as the *de* of the corresponding Mosher's ester, see Supporting Information). m.p. 85–88 °C. $[\alpha]_D^{20}$ = +45.6 (*c* = 0.620, $CHCl_3$). R_f = 0.12 (*n*-pentane/Et_2O 1:2). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.00 (s, 3 H), 2.51 (s, 3 H), 5.76 (brs, 1 H), 7.28–7.53 (m, 5 H), 9.22 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.2, 47.9, 66.9, 126.9, 127.8, 129.5, 135.0, 194.4 ppm. IR (KBr): $\tilde{\nu}$ = 3259.6 (m, ν[NH]), 1731.7 (m, ν[C=O]), 1317.5 (m, $\nu_{as}[SO_2]$), 1076.7 (m, $\nu_{sy}[SO_2]$) cm^{-1}. MS (EI = 70 eV), *m*/*z*: 198 $[M - CHO]^+$. HRMS: *m*/*z*: calcd. for $[M - CHO]^+$: 198.0589; found: 198.0587.

(+)-2-Perfluorobutylsulfonylamino-2-phenylpropionaldehyde (4n): This compound was obtained by Method B, room temp.: 104.9 mg, 24% yield; 29% *ee*; Method B, 0 °C: 61.1 mg, 14% yield; 32% *ee*; m.p. 68–74 °C. $[\alpha]_D^{20}$ = +58.6° (*c* = 0.370, $CHCl_3$). R_f = 0.21 (cyclohexane/ethyl acetate 5:1). HPLC (Chiralpak AS, *n*-heptane/propan-2-ol 90:10, 0.7 mLmin^{-1}): R_t(min) = 8.1 min, R_t(maj) = 10.5 min. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.03 (s, 3 H), 6.58 (brs), 7.35–7.50 (m, 5 H), 9.14 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.5, 68.7, 127.2, 129.6, 129.7, 135.0, 192.8 ppm. ^{19}F NMR (300 MHz, $CDCl_3$): δ = –126.5 to –126.3 (m, 2 F), –121.6 to 121.3 (m, 2 F), –112.4 (t, ^3J(F,F) = 13.5 Hz, 2 F), –81.3 (t, ^3J(F,F) = 9.5 Hz, 3 F) ppm. IR (KBr): $\tilde{\nu}$ = 3252.3 (m, ν[NH]), 1735.9 (m, ν[C=O]), 1358.5 (m, $\nu_{as}[SO_2]$), 1139.5 (m, $\nu_{sy}[SO_2]$) cm^{-1}. MS (EI = 70 eV): *m*/*z*: 402 $[M - CHO]^+$. HRMS: *m*/*z*: calcd. for $[M - CHO]^+$: 402.0210; found: 402.0217. $C_{13}H_{10}F_9NO_3S$ (431.28 gmol^{-1}): calcd. C 36.20, H 2.34, N 3.25; found: C 36.70, H 2.85, N 3.02.

2-Methyl-2-(tolyl-4-sulfonylamino)propionaldehyde (28): This compound was obtained by Method A: 101.2 mg, 42% yield; R_f = 0.27 (*n*-pentane/Et_2O 1:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.22 (s, 6 H), 2.35 (s, 3 H), 5.44 (brs, 1 H), 7.22 (d, *J* = 8.3 Hz, 2 H), 7.70 (d, *J* = 8.3 Hz, 2 H), 9.37 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5 (+), 22.5 (+), 62.4 (q), 126.8 (+), 129.7 (+), 139.6 (q), 143.5 (q), 199.5 (+) ppm. IR (KBr): $\tilde{\nu}$ = 3246.4 (m, υ[NH]), 1740.0 [m, υ(C=O)], 1738.9 (m, δ[NH]), 1324.0 (m, $\upsilon_{as}[SO_2]$), 1146.1 (m, $\upsilon_{sy}[SO_2]$) cm^{-1}. MS (EI = 70 eV), *m*/*z*: 212 $[M - CHO]^+$. HRMS (FAB): calcd. for $[M + 1]^+$: 242.0850; found: 242.0857. $C_{11}H_{16}NO_3S$ (241.30 gmol^{-1}): calcd. C 54.75, H 6.27, N 5.80, S 13.29; found: C 54.65, H 6.42, N 5.63, S 13.41.

2-Ethyl-2-(tolyl-4-sulfonylamino)butyraldehyde (29): This compound was obtained by Method A: 126.6 mg, 47% yield; R_f = 0.63 (*n*-pentane/Et_2O 1:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.51 (t, $^3J_{H,H}$ = 7.5 Hz, 6 H), 1.62 (qd, $^2J_{H,H}$ = 14.9 Hz, $^3J_{H,H}$ = 7.5 Hz, 2 H), 1.96 (qd, $^2J_{H,H}$ = 14.9 Hz, $^3J_{H,H}$ = 7.5 Hz, 2 H), 2.35 (s, 3 H), 5.26 (brs, 1 H), 7.21 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H), 7.71 (d, *J* = 8.3 Hz, 2 H), 9.14 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.5 (+), 21.5 (+), 26.2 (–), 65.9 (q), 126.8 (+), 129.6 (+), 139.7 (q), 143.3 (q), 199.6 (+) ppm. IR (KBr): $\tilde{\nu}$ = 3308.0 (m, υ[NH]), 1728.3 (m, δ[NH]), 1724.7 (m, υ[C=O]), 1334.2 (m, $\upsilon_{as}[SO_2]$), 1157.2 (m, $\upsilon_{sy}[SO_2]$) cm^{-1}. MS (EI = 70 eV), *m*/*z* (%) = 240 (100) $[M - CHO]^+$. HRMS: *m*/*z*: calcd. for $[M - CHO]^+$: 240.1058; found: 240.1054. $C_{13}H_{19}NO_3S$ (269.36 gmol^{-1}): calcd. C 57.97, H 7.11, N 5.20, S 11.90; found: C 57.99, H 7.15, N 5.18, S 11.99.

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2-(Tolyl-4-sulfonylamino)cyclohexanecarbaldehyde (30): This compound was obtained by Method A: 146.2 mg, 52% yield; m.p. 93 °C. R_f = 0.34 (*n*-pentane/Et_2O 1:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.15 (m, 3 H), 1.36 (m, 3 H), 1.58 (m, 4 H), 2.36 (s, 3 H), 5.22 (brs, 1 H), 7.23 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H), 7.72 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H), 9.53 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.6 (–), 21.6 (+), 24.7 (–), 30.2 (–), 65.2 (q), 127.0 (+), 129.7 (+), 139.1 (q), 143.7 (q), 201.0 (+) ppm. IR (KBr): $\tilde{\nu}$ = 3297.0 (m, υ[NH]), 1724.4 (m, δ[NH], υ[C=O]), 1328.2 (m, $\upsilon_{as}[SO_2]$), 1154.4 (m, $\upsilon_{sy}[SO_2]$) cm^{-1}. MS (EI = 70 eV), *m*/*z*: 252 $[M - CHO]^+$. HRMS: *m*/*z*: calcd. for $[M - CHO]^+$: 252.1058; found: 252.1054. $C_{14}H_{19}NO_3S$ (281.37 $g\,mol^{-1}$): calcd. C 59.76, H 6.81, N 4.98, S 11.40; found: C 59.80, H 6.76, N 5.01, S 11.45.

2,2-Diphenyl-2-(tolyl-4-sulfonylamino)acetaldehyde (31): This compound was obtained by Method A: 131.4 mg, 36% yield; m.p. 118 °C. R_f = 0.48 (*n*-pentane/Et_2O 2:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.22 (s, 3 H), 6.32 (brs, 1 H), 6.82 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H), 6.92 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H), 7.19–7.24 (m, 10 H), 9.29 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4 (+), 74.2 (q), 126.2 (+), 128.6 (+), 128.7 (+), 128.9 (+), 129.7 (+), 134.3 (q), 139.0 (q), 142.1 (q), 190.7 (+) ppm. IR (KBr): $\tilde{\nu}$ = 3299.1 (m, υ[NH]), 1733.9 (m, δ[NH]), 1725.7 (m, υ[C=O]), 1333.6 (m, $\upsilon_{as}[SO_2]$), 1164.2 (m, $\upsilon_{sy}[SO_2]$) cm^{-1}. MS (EI = 70 eV), *m*/*z*: 336 $[M - CHO]^+$. HRMS: *m*/*z*: calcd. for $[M - CHO]^+$: 336.1058; found: 336.1056. $C_{21}H_{19}NO_3S$ (365.45 $g\,mol^{-1}$): calcd. C 69.02, H 5.24, N 3.83, S 8.77; found: C 69.08, H 5.19, N 3.88, S 8.81.

2-Methyl-2-(tolyl-4-sulfonylamino)butyraldehyde (32): This compound was obtained by Method A: 125.2 mg, 49% yield; 5% *ee*; R_f = 0.47 (*n*-pentane/Et_2O 1:1). HPLC (Chiralpak AS, *n*-heptane/propan-2-ol 98:2, 1.0 mL min^{-1}): R_t(min) = 42.9 min, R_t(maj) = 47.9 min. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.69 (t, $^3J_{H,H}$ = 7.5 Hz, 3 H), 1.18 (s, 3 H), 1.61 (q, $^3J_{H,H}$ = 7.4 Hz, 1 H), 1.83 (q, $^3J_{H,H}$ = 7.4 Hz, 1 H), 2.35 (s, 3 H), 5.37 (brs, 1 H), 7.22 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H), 7.70 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H), 9.26 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.5 (+), 19.6 (+), 21.5 (+), 28.8 (–), 65.9 (q), 126.8 (+), 129.7 (+), 139.7 (q), 143.4 (q), 199.7 (+) ppm. IR (KBr): $\tilde{\nu}$ = 3242.0 (s, υ[NH]), 1715.6 (s, υ[C=O]), 1704.9 (w, δ[NH]), 1336.1 (m, $\upsilon_{as}[SO_2]$), 1165.9 (m, $\upsilon_{sy}[SO_2]$) cm^{-1}. MS (EI = 70 eV), *m*/*z*: 226 $[M - CHO]^+$. HRMS: *m*/*z*: calcd. for $[M - CHO]^+$: 226.0902; found: 226.0899. $C_{12}H_{17}NO_3S$ (255.33 $g\,mol^{-1}$): calcd. C 56.45, H 6.71, N 5.49, S 12.56; found: C 56.54, H 6.83, N 5.37, S 12.68.

2-Methyl-2-(tolyl-4-sulfonylamino)pentanal (33): This compound was obtained by Method A: 137.1 mg, 51% yield; 12% *ee*; R_f = 0.55 (*n*-pentane/Et_2O 1:1). HPLC (Chiralpak AS, *n*-heptane/propan-2-ol 98:2, 1.0 mL min^{-1}): R_t(min) = 32.5 min, R_t(maj) = 37.3 min. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.70 (t, $^3J_{H,H}$ = 7.3 Hz, 3 H), 0.94 (m, 1 H), 1.17 (m, 1 H), 1.18 (s, 3 H), 1.50 (ddd, $^2J_{H,H}$ = 14.3 Hz, $^3J_{H,H}$ = 12.3, 4.6 Hz, 1 H), 1.74 (ddd, $^2J_{H,H}$ = 14.3, $^3J_{H,H}$ = 12.3, 4.6 Hz, 1 H), 2.35 (s, 3 H), 5.43 (brs, 1 H), 7.22 (d, $^3J_{H,H}$ = 7.9 Hz, 2 H), 7.69 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H), 9.28 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (+), 16.6 (–), 20.1 (+), 21.5 (+), 37.8 (–), 65.6 (q), 126.8 (+), 129.6 (+), 139.7 (q), 143.1 (q), 199.6 (+) ppm. IR (KBr): $\tilde{\nu}$ = 3263.2 (s, υ[NH]), 1727.4 (s, υ[C=O]), 1721.9 (w, δ[NH]), 1325.5 (m, $\upsilon_{as}[SO_2]$), 1157.3 (m, $\upsilon_{sy}[SO_2]$) cm^{-1}. MS (EI = 70 eV), *m*/*z*: 240 $[M - CHO]^+$. HRMS: *m*/*z*: calcd. for $[M - CHO]^+$: 240.1058; found: 240.1053. $C_{13}H_{19}NO_3S$ (269.36 $g\,mol^{-1}$): calcd. C 57.97, H 7.11, N 5.20, S 11.90; found: C 58.02, H 7.13, N 5.15, S 11.97.

(+)-2-Ethyl-2-(2-nitrophenylsulfonylamino)hexanal (34): This compound was obtained by Method A: 89.9 mg, 54% yield; 28% *ee*. $[\alpha]_D^{20}$ = +0.9 (*c* = 0.325, $CHCl_3$). m.p. 86 °C. R_f = 0.12 (*n*-pentane/Et_2O 3:2). HPLC (Chiralpak AS, *n*-heptane/propan-2-ol 98:2, 1.0 mL min^{-1}): R_t(min) = 52.0 min, R_t(maj) = 57.7 min. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.67 (dd, $^3J_{H,H}$ = 7.5, 7.5 Hz, 3 H), 0.70 (t, $^3J_{H,H}$ = 7.4 Hz, 3 H), 0.81–0.96 (m, 1 H), 0.98–1.12 (m, 3 H), 1.69 (ddd, $^2J_{H,H}$ = 14.7 Hz, $^3J_{H,H}$ = 11.7, 4.5 Hz, 1 H), 1.77 (dq, $^2J_{H,H}$ = 14.7 Hz, $^3J_{H,H}$ = 7.3 Hz, 1 H), 2.02 (ddd, $^2J_{H,H}$ = 14.6 Hz, $^3J_{H,H}$ = 12.7, 3.8 Hz, 1 H), 2.10 (dq, $^2J_{H,H}$ = 15.0 Hz, $^3J_{H,H}$ = 7.6 Hz, 1 H), 6.18 (s, 1 H), 7.69–7.77 (m, 2 H), 7.87–7.94 (m, 1 H), 8.10–8.17 (m, 1 H), 9.29 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.6 (+), 13.8 (+), 22.6 (–), 25.4 (–), 26.9 (–), 33.3 (–), 71.0 (q), 125.6 (+), 129.9 (+), 133.2 (+), 133.6 (+), 136.6 (q), 147.8 (q), 198.7 (q) ppm. IR (KBr): $\tilde{\nu}$ = 3331.1 (m, υ[NH]), 1742.3 (m, υ[C=O]), 1539.8 (m, $\upsilon_{as}[NO_2]$), 1364.1 (m, $\upsilon_{as}[SO_2]$), 1339.6 (m, $\upsilon_{sy}[NO_2]$), 1166.9 (m, $\upsilon_{sy}[SO_2]$) cm^{-1}. MS (FAB): *m*/*z*: 329 $[M + 1]^+$. HRMS: *m*/*z*: calcd. for $[M - CHO]^+$: 299.1066; found: 299.1071. $C_{14}H_{20}N_2O_5S$ (328.39 $g\,mol^{-1}$): calcd. C 51.21, H 6.14, N 8.53, S 9.76; found: C 51.14, H 6.02, N 8.55, S 9.69.

(*S*)-(+)-2-(2-Methoxyphenyl)-2-(2-nitrophenylsulfonylamino)propionaldehyde (35a): This compound was obtained by Method A, in technical ethanol: 37.7 mg, 21% yield; 72% *ee*. This compound was also obtained by Method B, in absolute ethanol: 48.5 mg, 27% yield; 72% *ee*. $[\alpha]_D^{20}$ = +128.0 (*c* = 0.210, $CHCl_3$, for 72% *ee*). m.p. 185 °C. R_f = 0.18 (cyclohexane/ethyl acetate 5:2). HPLC (Chiralpak AS, *n*-heptane/propan-2-ol 80:20, 0.7 mL min^{-1}): R_t(min) = 18.9 min, R_t(maj) = 21.4 min. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.94 (s, 3 H), 3.22 (s, 3 H), 6.21 (dd, $^3J_{H,H}$ = 8.2 Hz, $^4J_{H,H}$ = 0.8 Hz, 1 H), 6.95 (dd, $^3J_{H,H}$ = 7.9 Hz, $^4J_{H,H}$ = 1.3 Hz, 1 H), 7.03 (ddd, $^3J_{H,H}$ = 7.6, 7.6 Hz, $^4J_{H,H}$ = 1.0 Hz, 1 H), 7.22–7.26 (m, 2 H), 7.48 (ddd, $^3J_{H,H}$ = 7.7, 7.7 Hz, $^3J_{H,H}$ = 1.4 Hz, 1 H), 7.56 (dd, $^3J_{H,H}$ = 7.7 Hz, $^4J_{H,H}$ = 1.6 Hz, 1 H), 7.76 (dd, $^3J_{H,H}$ = 8.1 Hz, $^3J_{H,H}$ = 1.1 Hz, 1 H), 9.08 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5 (+), 54.5 (+), 65.2 (q), 110.0 (+), 120.9 (+), 122.7 (q), 124.6 (+), 129.9 (+), 130.2 (+), 131.0 (+), 132.3 (+), 134.9 (q), 147.2 (q), 156.5 (q), 194.2 (q) ppm. IR (KBr): $\tilde{\nu}$ = 3338.8 (w, ν[NH]), 1727.8 (w, ν[C=O]), 1335.6 (w, $\nu_{as}[SO_2]$), 1254.0 (w, ν_{as}[C–O–C]), 1172.7 (w, $\nu_{sy}[SO_2]$) cm^{-1}. MS (FAB): *m*/*z*: 365 $[M + 1]^+$. HRMS: *m*/*z*: calcd. for $[M - CHO]^+$: 335.0702; found: 335.0702.

(+)-2-(2-Methoxyphenyl)-2-(4-nitrophenylsulfonylamino)propionaldehyde (35b): This compound was obtained by Method A: 37.8 mg, 21% yield; 59% *ee*. m.p. 158 °C. $[\alpha]_D^{20}$ = +39.7 (*c* = 0.300, $CHCl_3$). R_f = 0.22 (cyclohexane/ethyl acetate 5:2). HPLC (Chiracel OD, *n*-heptane/propan-2-ol 80:20, 0.7 mL min^{-1}): R_t(min) = 21.6 min, R_t(maj) = 24.3 min. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.90 (s, 3 H), 3.35 (s, 3 H), 6.20 (dd, $^3J_{H,H}$ = 8.3 Hz, $^4J_{H,H}$ = 0.9 Hz, 1 H), 6.37 (brs, 1 H), 7.01 (ddd, $^3J_{H,H}$ = 7.6, 7.6 Hz, $^4J_{H,H}$ = 1.1 Hz, 1 H), 7.18 (ddd, $^3J_{H,H}$ = 8.3, 7.5 Hz, $^4J_{H,H}$ = 1.6 Hz, 1 H), 7.39 (ddd, $^3J_{H,H}$ = 9.2 Hz, $^4J_{H,H}$ = 2.2, 2.2 Hz, 2 H), 7.50 (dd, $^3J_{H,H}$ = 7.7 Hz, $^4J_{H,H}$ = 1.6 Hz, 1 H), 7.93 (dd, $^3J_{H,H}$ = 9.1 Hz, $^4J_{H,H}$ = 2.2, 2.2 Hz, 2 H), 9.03 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2 (+), 54.8 (+), 64.3 (q), 110.6 (+), 121.0 (+), 122.1 (q), 123.0 (+), 127.9 (+), 129.8 (+), 131.4 (+), 146.6 (q), 149.1 (q), 156.1 (q), 194.5 (q) ppm. IR (KBr): $\tilde{\nu}$ = 3301.7 (m, ν[NH]), 1726.5 (m, ν[C=O]), 1533.1 (m, $\nu_{as}[NO_2]$), 1349.8 (m, $\nu_{as}[SO_2]/\nu_{sy}[NO_2]$), 1173.0 (m, $\nu_{sy}[SO_2]$) cm^{-1}. MS (FAB): *m*/*z*: 365 $[M + 1]^+$. HRMS: *m*/*z*: calcd. for $[M - CHO]^+$: 335.0702; found: 335.0705.

(+)-2-(3-Methoxyphenyl)-2-(2-nitrophenylsulfonylamino)propionaldehyde (36a): This compound was obtained by Method A, in technical ethanol: 84.9 mg, 47% yield; 84% *ee*. This compound was also obtained by Method A, in absolute ethanol: 82.5 mg, 45% yield; 66% *ee*. m.p. 148 °C. $[\alpha]_D^{20}$ = +250.7 (*c* = 0.300, $CHCl_3$, for 66% *ee*). R_f = 0.33 (cyclohexane/ethyl acetate 5:2). HPLC (Chiracel OD, *n*-heptane/propan-2-ol 90:10, 0.7 mL min^{-1}): R_t(maj) =

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18.2 min, R_t(min) = 22.8 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.18 (s, 3 H), 3.77 (s, 3 H), 6.78 (dd, $^4J_{H,H}$ = 2.1, 2.1 Hz, 1 H), 6.86 (ddd, $^3J_{H,H}$ = 8.2 Hz, $^4J_{H,H}$ = 2.5, 0.6 Hz, 1 H), 6.97 (ddd, $^3J_{H,H}$ = 7.8 Hz, $^4J_{H,H}$ = 1.6, 0.7 Hz, 1 H), 7.24 (dd, $^3J_{H,H}$ = 8.1, 8.1 Hz, 1 H), 7.39–7.48 (m, 2 H), 7.70 (ddd, $^3J_{H,H}$ = 7.8, 7.4 Hz, $^4J_{H,H}$ = 1.6 Hz, 1 H), 7.92 (dd, $^3J_{H,H}$ = 7.9 Hz, $^4J_{H,H}$ = 1.0 Hz, 1 H), 9.29 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.2 (+), 55.2 (+), 67.2 (q), 113.7 (+), 114.6 (+), 120.0 (+), 124.8 (+), 129.9 (+), 130.1 (+), 132.3 (+), 132.7 (+), 134.8 (q), 135.2 (q), 147.3 (q), 160.0 (q), 193.2 (q) ppm. IR (KBr): $\tilde{\nu}$ = 3319.8 (m, ν[NH]), 1720.3 (m, ν[C=O]), 1539.1 (m, ν_s[NO_2]), 1364.2 (m, ν_{sy}[SO_2]), 1335.1 (m, ν_{sy}[NO_2]), 1173.3 (m, ν_{sy}[SO_2]) cm^{-1}. MS (FAB): *m*/*z*: 365 (10) [M + 1]$^+$. HRMS: *m*/*z*: calcd. for [M]$^+$: 364.0729; found: 364.0725. $C_{16}H_{16}N_2O_6S$ (364.37 g mol^{-1}): calcd. C 52.74, H 4.43, N 7.69, S 8.80; found: C 53.01, H 4.56, N 7.62, S 8.46.

(+)-2-(3-Methoxyphenyl)-2-(4-nitrophenylsulfonylamino)propionaldehyde (36b): This compound was obtained by Method A: 89.0 mg, 49% yield; 69% *ee*. m.p. 138 °C. $[\alpha]_D^{20}$ = +42.7 (*c* = 0.295, $CHCl_3$). R_f = 0.27 (cyclohexane/ethyl acetate 5:2). HPLC (Chiracel OD, *n*-heptane/propan-2-ol 40:60, 0.5 mL min^{-1}): R_t(min) = 28.0 min, R_t(maj) = 36.0 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.98 (s, 3 H), 3.59 (s, 3 H), 6.27 (brs, 1 H), 6.32 (dd, $^4J_{H,H}$ = 2.2, 2.2 Hz, 1 H), 6.67–6.77 (m, 2 H), 7.11 (dd, $^3J_{H,H}$ = 8.0, 8.0 Hz, 1 H), 7.52 (ddd, $^3J_{H,H}$ = 9.2 Hz, $^4J_{H,H}$ = 2.2, 2.2 Hz, 2 H), 8.02 (ddd, $^3J_{H,H}$ = 9.2 Hz, $^4J_{H,H}$ = 2.2, 2.2 Hz, 2 H), 9.04 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.1 (+), 55.2 (+), 66.7 (q), 113.8 (+), 114.8 (+), 120.2 (+), 123.6 (+), 127.9 (+), 130.2 (+), 134.1 (q), 147.3 (q), 149.4 (q), 159.9 (q), 193.4 (+) ppm. IR (KBr): $\tilde{\nu}$ = 3234.2 (s, ν[NH]), 1732.9 (s, ν[C=O]), 1528.0 (s, ν_{as}[NO_2]), 1488.8 (s, ν[C–C_{ar}]), 1348.5 (s, ν_{as}[NO_2]/ν_{sy}[SO_2]), 1174.8 (s, ν_{sy}[SO_2] cm^{-1}. MS (EI = 70 eV): *m*/*z*: 364 [M]$^+$. HRMS: *m*/*z*: calcd. for [M – CHO]$^+$: 335.0702; found: 335.0700. $C_{16}H_{16}N_2O_6S$ (364.37 g mol^{-1}): calcd. C 52.74, H 4.43, N 7.69, S 8.80; found: C 52.41, H 4.38, N 7.67, S 8.29.

(+)-2-(4-Methoxyphenyl)-2-(2-nitrophenylsulfonylamino)propionaldehyde (37a): This compound was obtained by Method A: 95.9 mg, 53% yield; 86±1% *ee*. m.p. 145 °C. $[\alpha]_D^{20}$ = +142.6 (*c* = 0.620, $CHCl_3$). R_f = 0.27 (cyclohexane/ethyl acetate 2:1). HPLC (Chiralpak AS, *n*-heptane/propan-2-ol 50:50, 0.5 mL min^{-1}): R_t(maj) = 30.6 min, R_t(min) = 34.1 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.93 (s, 3 H), 3.65 (s, 3 H), 6.53 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H), 6.99 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H), 7.13–7.22 (m, 2 H), 7.45 (ddd, $^3J_{H,H}$ = 7.7, 7.7 Hz, $^4J_{H,H}$ = 1.7 Hz, 1 H), 7.67 (dd, $^3J_{H,H}$ = 8.0 Hz, $^3J_{H,H}$ = 1.1 Hz, 1 H), 9.02 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3 (+), 55.5 (+), 66.8 (q), 114.2 (+), 124.9 (+), 125.4 (q), 129.3 (+), 130.4 (+), 132.3 (+), 132.6 (+), 135.5 (q), 147.5 (q), 160.3 (q), 193.3 (q) ppm. MS (FAB): *m*/*z*: 365 [M + 1]$^+$. $C_{16}H_{16}N_2O_6S$ (364.37 g mol^{-1}): calcd. C 52.74, H 4.43, N 7.69, S 8.80; found: C 52.73, H 4.44, N 7.61, S 8.60. IR (KBr): $\tilde{\nu}$ = 3296.6 (m, ν[NH]), 1720.6 (m, ν[C=O]), 1534.1 (s, ν_{as}[NO_2]), 1361.7 (m, ν_{as}[SO_2]), 1335.3 (m, ν_{sy}[NO_2]), 1170.3 (m, ν_{sy}[SO_2]) cm^{-1}.

(+)-2-(4-Methoxyphenyl)-2-(4-nitrophenylsulfonylamino)propionaldehyde (37b): This compound was obtained by Method A: 80.7 mg, 44% yield; 76% *ee*. m.p. 181 °C. $[\alpha]_D^{20}$ = +51.7 (*c* = 0.41, $CHCl_3$). R_f = 0.17 (cyclohexane/ethyl acetate 5:1). HPLC (Chiracel OD, *n*-heptane/propan-2-ol 90:10, 1.0 mL min^{-1}): R_t(maj) = 50.1 min, R_t(min) = 60.5 min. ^{1}H NMR (400 MHz, [D_7]DMF): δ = 1.69 (s, 3 H), 3.76 (s, 3 H), 6.83 (d, $^3J_{H,H}$ = 9.1 Hz, 2 H), 7.27 (d, $^3J_{H,H}$ = 9.1 Hz, 2 H), 7.99 (d, $^3J_{H,H}$ = 8.9 Hz, 2 H), 8.34 (d, $^3J_{H,H}$ = 9.1 Hz, 2 H), 9.62 (s, 1 H) ppm. ^{13}C NMR (100 MHz, [D_7]DMF): δ = 20.8 (+), 55.6 (+), 67.5 (q), 114.6 (+), 124.8 (+), 128.6 (q), 128.8 (+), 129.4 (+), 149.2 (q), 150.2 (q), 160.4 (q), 197.2 (q) ppm. IR (KBr): $\tilde{\nu}$ = 3298.6 (m, ν[NH]), 1734.9 (m, ν[C=O]), 1528.8 (m, ν_{as}[NO_2]), 1349.7 (m, ν_{as}[SO_2]), 1327.9 (m, ν_{sy}[NO_2]), 1313.3 (m, ν_{sy}[NO_2]), 1151.5 (m, ν_{sy}[SO_2]) cm^{-1}. MS (EI = 70 eV): *m*/*z*: 335 [M – CHO]$^+$. HRMS: *m*/*z*: calcd. for [M – CHO]$^+$: 335.0702; found: 335.0697. $C_{16}H_{16}N_2O_6S$ (364.37 g mol^{-1}): calcd. C 52.74, H 4.43, N 7.69, S 8.80; found: C 52.92, H 4.56, N 7.41, S 8.55.

(+)-2-(2,4-Dimethoxyphenyl)-2-(2-nitrophenylsulfonylamino)propionaldehyde (38): This compound was obtained by Method A: 67.3 mg, 34% yield; 45% *ee* (determined as the *de* of the corresponding Mosher's ester, see Supporting Information). m.p. 177–179 °C. $[\alpha]_D^{20}$ = +129.5 (*c* = 0.390, $CHCl_3$). R_f = 0.18 (cyclohexane/ethyl acetate 2:1). ^{1}H NMR (400 MHz, [D_7]DMF): δ = 1.82 (s, 3 H), 3.24 (s, 3 H), 3.78 (s, 3 H), 5.93 (d, $^4J_{H,H}$ = 2.4 Hz, 1 H), 6.62 (dd, $^3J_{H,H}$ = 8.6 Hz, $^4J_{H,H}$ = 2.5 Hz, 1 H), 6.99 (dd, $^3J_{H,H}$ = 7.9 Hz, $^4J_{H,H}$ = 1.3 Hz, 1 H), 7.22 (brs, 1 H), 7.43 (ddd, $^3J_{H,H}$ = 7.7, 7.7 Hz, $^4J_{H,H}$ = 1.2 Hz, 1 H), 7.45 (d, $^3J_{H,H}$ = 8.7 Hz, 1 H), 7.75 (ddd, $^3J_{H,H}$ = 7.8, 7.8 Hz, $^4J_{H,H}$ = 1.3 Hz, 1 H), 7.99 (dd, $^3J_{H,H}$ = 8.1 Hz, $^4J_{H,H}$ = 1.0 Hz, 1 H), 9.24 (s, 1 H) ppm. ^{13}C NMR (100 MHz, [D_7]DMF): δ = 21.7 (+), 55.1 (+), 55.9 (+), 66.6 (q), 98.1 (+), 105.8 (+), 115.8 (q), 125.7 (+), 130.4 (+), 130.9 (+), 133.3 (+), 134.1 (+), 134.4 (q), 147.9 (q), 158.3 (q), 197.0 (+) ppm. IR (KBr): $\tilde{\nu}$ = 3264.6 (m, ν[NH]), 1727.6 (m, ν[C=O]), 1536.3 (m, ν_{as}[NO_2]), 1362.7 (m, ν_{as}[SO_2]), 1336.3 (m, ν_{sy}[NO_2]), 1163.0 (m, ν_{sy}[SO_2]) (cm^{-1}). MS (FAB): *m*/*z*: 395 [M + 1]$^+$. HRMS: *m*/*z*: calcd. for [M – CHO]$^+$: 365.0807; found: 365.0808. $C_{17}H_{18}N_2O_7S$ (394.40 g mol^{-1}): calcd. C 51.77, H 4.60, N 7.10, S 8.13; found: C 51.40, H 4.86, N 7.39, S 8.42.

(S)-(+)-2-(2,5-Dimethoxyphenyl)-2-(2-nitrophenylsulfonylamino)propionaldehyde (39): This compound was obtained by Method A: 62.9 mg, 32% yield; 54% *ee* (determined as the *de* of the corresponding Mosher's ester, see Supporting Information). m.p. 157–167 °C. $[\alpha]_D^{20}$ = +131.0 (*c* = 0.300, $CHCl_3$). R_f = 0.15 (cyclohexane/ethyl acetate 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.91 (s, 3 H), 3.21 (s, 3 H), 3.82 (s, 3 H), 6.15 (d, $^3J_{H,H}$ = 8.9 Hz, 1 H), 6.69 (dd, $^3J_{H,H}$ = 8.9 Hz, $^4J_{H,H}$ = 3.0 Hz, 1 H), 7.10 (d, $^4J_{H,H}$ = 3.0 Hz, 1 H), 7.12 (dd, $^3J_{H,H}$ = 8.1 Hz, $^4J_{H,H}$ = 1.5 Hz), 7.14 (brs, 1 H), 7.23 (ddd, $^3J_{H,H}$ = 7.8, 7.7 Hz, $^4J_{H,H}$ = 1.3 Hz, 1 H), 7.49 (ddd, $^3J_{H,H}$ = 7.7, 7.7 Hz, $^3J_{H,H}$ = 1.4 Hz, 1 H), 7.78 (dd, $^3J_{H,H}$ = 7.9 Hz, $^4J_{H,H}$ = 1.1 Hz, 1 H), 9.09 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4 (+), 54.8 (+), 56.1 (+), 65.2 (q), 110.6 (+), 114.9 (+), 116.4 (+), 123.7 (q), 124.7 (+), 130.4 (+), 132.2 (+), 132.4 (+), 135.0 (q), 147.2 (q), 150.6 (q), 153.8 (q), 194.0 (+) ppm. IR (KBr): $\tilde{\nu}$ = 3268.4 (w, ν[NH]), 1731.3 (m, ν[C=O]), 1532.5 (m, ν_{as}[NO_2]), 1362.6 (m, ν_{as}[SO_2]), 1332.0 (m, ν_{sy}[NO_2]), 1168.1 (m, ν_{sy}[SO_2]) cm^{-1}. MS (EI = 70 eV): *m*/*z*: 394 [M]$^+$. HRMS: *m*/*z*: calcd. for [M]$^+$: 394.0835; found: 394.0835. $C_{17}H_{18}N_2O_7S$ (394.40 g mol^{-1}): calcd. C 51.77, H 4.60, N 7.10, S 8.13; found: C 52.18, H 4.81, N 7.14, S 8.51.

(+)-2-(3,5-Dibenzyloxyphenyl)-2-(2-nitrophenylsulfonylamino)propionaldehyde (40): This compound was obtained by Method A: 72.7 mg, 31% yield; 72% *ee* (determined as the *de* of the corresponding Mosher's ester, see Supporting Information). $[\alpha]_D^{20}$ = +136.3 (*c* = 0.27, $CHCl_3$). R_f = 0.34 (cyclohexane/ethyl acetate 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.97 (s, 3 H), 4.68 (d, $^2J_{H,H}$ = 11.7 Hz, 2 H), 4.76 (d, $^2J_{H,H}$ = 11.7 Hz, 2 H), 6.38 (s, 3 H), 7.04 (brs, 1 H), 7.12 (ddd, $^3J_{H,H}$ = 7.7, 7.7 Hz, $^4J_{H,H}$ = 1.1 Hz, 1 H), 7.21 (dd, $^3J_{H,H}$ = 7.9 Hz, $^4J_{H,H}$ = 1.5 Hz, 1 H), 7.31–7.47 (m, 11 H), 7.66 (dd, $^3J_{H,H}$ = 8.0 Hz, $^4J_{H,H}$ = 1.0 Hz, 1 H), 9.08 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.2 (+), 67.1 (q), 70.1 (–), 102.6

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(+), 107.4 (+), 124.6 (+), 127.6 (+), 128.4 (+), 128.8 (+), 130.2 (+), 132.1 (+), 132.7 (+), 135.2 (q), 135.6 (q), 136.3 (q), 147.3 (q), 160.2 (q), 193.0 (+) ppm. MS (EI = 70 eV): *m*/*z*: 517 $[M - CHO]^+$. HRMS: *m*/*z*: calcd. for $[M - CHO]^+$: 517.1433; found: 517.1427.

(+)-2-(4-*tert*-Butylphenyl)-2-(2-nitrophenylsulfonylamino)propionaldehyde (41): This compound was obtained by Method A: 107.5 mg, 55% yield; 61% *ee*. m.p. 138–140 °C. $[\alpha]_D^{20}$ = +198.3 (*c* = 0.300, $CHCl_3$). R_f = 0.37 (cyclohexane/ethyl acetate 5:1). HPLC (Chiralpak AS, *n*-heptane/propan-2-ol 80:20, 0.5 mL min^{-1}): R_t(maj) = 31.5 min, R_t(min) = 43.5 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 (s, 9 H), 2.02 (s, 3 H), 7.06 (d, $^3J_{H,H}$ = 8.7 Hz, 2 H), 7.11 (d, $^3J_{H,H}$ = 8.8 Hz, 2 H), 7.15–7.22 (m, 2 H), 7.49 (ddd, $^3J_{H,H}$ = 8.0, 6.5 Hz, $^4J_{H,H}$ = 2.5 Hz, 1 H), 7.74 (dd, $^3J_{H,H}$ = 7.9 Hz, $^4J_{H,H}$ = 0.6 Hz, 1 H), 9.10 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.1 (+), 31.3 (+), 34.6 (q), 66.9 (q), 124.9 (+), 125.8 (+), 127.6 (+), 130.1 (q), 130.3 (+), 132.3 (+), 132.6 (+), 135.4 (q), 147.4 (q), 152.4 (q), 193.4 (+) ppm. IR (KBr): $\tilde{\nu}$ = 3326.5 (m, ν[NH]), 1718.5 (m, ν[C=O]), 1540.1 (m, $\nu_{as}[NO_2]$), 1365.3 (m, $\nu_{as}[SO_2]$), 1340.1 (m, $\nu_{sy}[NO_2]$), 1119.6 (m, $\nu_{sy}[SO_2]$) cm^{-1}. MS (FAB): *m*/*z*: 391 $[M + 1]^+$. $C_{19}H_{22}N_2O_5S$ (390.45 g mol^{-1}): calcd. C 58.45, H 5.68, N 7.17, S 8.21; found: C 58.42, H 5.66, N 6.96, S 8.22.

***N*-(Phenylacetyl)tolyl-4-sulfonamide (43):**[104] This compound was obtained by Method A: 38.3 mg, 26% yield; R_f = 0.24 (*n*-pentane/Et_2O 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39 (s, 3 H, CH_3), 4.46 (d, $^4J_{H,H}$ = 4.5 Hz, 2 H), 5.65 (brs, 1 H), 7.28 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H), 7.46 (ddd, $^3J_{H,H}$ = 7.9, 7.3 Hz, $^4J_{H,H}$ = 1.1 Hz, 2 H), 7.60 (ddd, $^3J_{H,H}$ = 7.6, 7.3, $^4J_{H,H}$ = 1.3 Hz, 1 H), 7.78 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H), 7.85 (d, $^3J_{H,H}$ = 7.5 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6 (+), 48.8 (–), 127.3 (+), 128.0 (+), 129.1 (+), 130.0 (+), 134.0 (q), 134.5 (+), 136.3 (q), 143.8 (q), 192.7 (q).

4-Methyl-*N*-(1-pyrrolidinylmethylene)phenylsulfonamide (51): This compound was obtained by Method A, by use of **1** (134.2 mg, 1.00 mmol), toluene-4-sulfonyl azide (**2a**, 236.7 mg, 1.20 mmol) and pyrrolidine (**5**, 71.1 mg, 1.00 mmol) in ethanol (10 mL). Flash chromatography on silica with ethyl acetate delivered **51** (106 mg, 0.42 mmol) as a colourless solid in 42% yield (**4a** was obtained in 36% yield). m.p. 140 °C. R_f = 0.29 (ethyl acetate). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.87 (m, 4 H), 2.32 (s, 3 H), 3.39 (bt, $^3J_{H,H}$ = 6.5 Hz, 2 H), 3.51 (bt, $^3J_{H,H}$ = 6.5 Hz, 2 H), 7.18 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H), 7.71 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H), 8.25 (s, 1 H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 21.4 (+), 24.2 (–), 24.9 (–), 46.3 (–), 49.8 (–), 126.4 (+), 129.2 (+), 139.5 (q), 142.2 (q), 155.7 (+) ppm. IR (KBr): $\tilde{\nu}$ = 1615.9 (m, υ[C=NR]), 1315.9 (m, $\upsilon_{as}[SO_2]$), 1187.6 (w, $\upsilon_{sy}[SO_2]$) cm^{-1}. MS (EI, =70 eV), *m*/*z*: 252 $[M]^+$. HRMS: *m*/*z*: calcd. for $[M]^+$: 252.0932; found: 252.0928. $C_{12}H_{16}N_2O_2S$ (252.33 g mol^{-1}): calcd. C 57.12, H 6.39, N 11.10, S 12.71; found: C 57.36, H 6.28, N 10.93, S 12.88.

2-(2-Nitrophenylsulfonylamino)-2-phenylpropanol (57): This compound was obtained by Method A. After the reaction was complete, the reaction mixture was treated with sodium borohydride (26.5 mg, 0.7 mmol) and stirred for 2 h. The solvent was then removed by evaporation under reduced pressure, and flash chromatography on silica with ethyl acetate/cyclohexane 2:3 delivered a colourless solid (45.5 mg, 0.135 mmol) in 27% yield. m.p. 123 °C. R_f = 0.21 (ethyl acetate/cyclohexane 2:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.76 (s, 3 H), 2.20 (brs, 1 H), 3.76 (d, $^2J_{H,H}$ = 11.3 Hz, 1 H), 3.94 (d, $^2J_{H,H}$ = 11.3 Hz, 1 H), 6.24 (s, 1 H), 7.10–7.17 (m, 3 H), 7.29–7.36 (m, 2 H), 7.40 (ddd, $^3J_{H,H}$ = 7.6, 7.6 Hz, $^4J_{H,H}$ = 1.1 Hz, 1 H), 7.50 (ddd, $^3J_{H,H}$ = 7.7, 7.7 Hz, $^4J_{H,H}$ = 1.4 Hz, 1 H), 7.52 (dd, $^3J_{H,H}$ = 8.0, $^4J_{H,H}$ = 1.4 Hz, 1 H), 7.78 (dd, $^3J_{H,H}$ = 8.0 Hz, $^4J_{H,H}$ = 1.2 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.9 (+), 62.8 (q), 70.6 (–), 125.0 (+), 126.4 (+), 127.9 (+), 128.4 (+), 130.5 (+), 132.6 (+), 132.9 (+), 136.0 (q), 140.9 (q), 147.6 (q) ppm. MS (FAB): *m*/*z*: 337 (33) $[M + 1]^+$. HRMS: *m*/*z*: calcd. for $[M - CH_2OH]^+$: 305.0596; found: 305.0603.

2-(2-Nitrophenylsulfonylamino)-2-phenylpropionic Acid (58):[105] A solution of potassium dihydrogen phosphate (115.7 mg, 0.85 mmol) in water (1.4 mL) was added to a solution of **4b** (114.2 mg, 0.34 mmol) in acetonitrile (5 mL). Addition of an aqueous hydrogen peroxide solution (35%, 32.5 μL, 0.38 mmol) to the mixture at 0 °C was followed by dropwise addition of a solution of sodium chlorite (43.4 mg, 0.48 mmol) in water (2 mL). After 1 h of stirring at 0 °C, further hydrogen peroxide solution (16 μL, 0.19 mmol) was added and the mixture was stirred in a melting ice bath for 16 h. The reaction mixture was then quenched by addition of sodium sulfite, stirred for 30 min and treated with hydrochloric acid (0.5 N, 10 mL). The mixture was extracted three times with dichloromethane (15 mL, 5 mL, and 5 mL) and the combined organic phases were washed with brine and dried with sodium sulfate. Removal of the solvent by evaporation delivered a colourless solid (109.7 mg, 0.313 mmol) in 92% yield; m.p. 188 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.10 (s, 3 H), 7.00–7.15 (m, 4 H), 7.24–7.35 (m, 3 H), 7.60 (ddd, $^3J_{H,H}$ = 7.8, 7.8 Hz, $^4J_{H,H}$ = 1.4 Hz, 1 H), 7.80 (dd, $^3J_{H,H}$ = 8.1 Hz, $^4J_{H,H}$ = 1.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.9 (+), 65.3 (q), 125.9 (+), 127.7 (+), 129.2 (+), 129.4 (+), 130.9 (+), 133.6 (+), 134.1 (+), 136.2 (q), 139.3 (q), 148.7 (q), 175.5 (q) ppm. MS (FAB): *m*/*z*: 351 $[M + 1]^+$. HRMS: *m*/*z*: calcd. for $[M - CO_2H]^+$: 305.0596 $[M - CO_2H]^+$; found: 305.0596.

α-Methylphenylglycine (59):[106,107] A solution of **58** (104.0 mg, 0.30 mmol) in 1,4-dioxane (5 mL) was treated with a methanolic solution of sodium methoxide (25–30%, 0.1 mL) and stirred for 2 h. Addition of sodium methoxide solution (0.1 mL) was repeated and the reaction mixture was stirred for 18 h. The solvent was then removed by evaporation, the residue was dissolved in hydrochloric acid (1 M), and the acidic solution was washed three times with dichloromethane. The aqueous phase was dried, the residue was taken up in methanol, and, after filtration, the solvent was removed by evaporation. Purification by ion-exchange chromatography on Dowex 50WX8–100 with aqueous ammonia solution (1.4 M) delivered **59** as a colourless solid in quantitative yield. ^{1}H NMR (400 MHz, CD_3OD): δ = 1.85 (s, 3 H), 7.25–7.55 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.3, 62.7, 126.9, 130.4, 130.7, 137.5, 173.1 ppm.

Crystal Structure Determinations: The data were collected on a Nonius KappaCCD diffractometer at –150 °C with use of Mo-K_α radiation (λ = 0.71073 Å). The structures were solved by direct methods (SHELXS-97),[108] the non-hydrogen atoms were refined anisotropically, and H atoms were refined with a riding model, H(N,O) free (full-matrix least-squares refinement on F^2, SHELXL-97).[109] The absolute structure was determined by refinement of Flack's *x* parameter[110] for **4c** (SB042), **4j** (SB026), **35a** (SB044), and **39** (SB045). Details of data collection and refinement are given in Table 7 and Table 8. Crystal structures are shown in Figures 4, 5, 6, 7, 8, 9and 10. In **4a** the aldehyde and methyl group are disordered about two positions (55:45).

CCDC-605974 to -605980 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Table 7. Crystallographic data, structure solution and refinement of **4a**–**4j**.

Compound	**4a** SB034	**4c** SB042	**4 g** SB043	**4j** SB026
Formula	$C_{16}H_{17}NO_3S$	$C_{15}H_{14}N_2O_5S$	$C_{19}H_{17}NO_3S$	$C_{13}H_{11}Cl_2NO_3S_2$
M_r	303.37	334.34	339.40	364.25
Dimensions [mm]	0.10×0.15×0.30	0.35×0.45×0.55	0.08×0.12×0.24	0.20×0.30×0.50
Crystal system	monoclinic	monoclinic	monoclinic	orthorhombic
Space group	*P*21/*c* (No. 14)	$P2_1$ (No. 4)	$P2_1/c$ (No. 14)	$P2_12_12_1$ (No. 19)
a [Å]	8.6522(5)	6.5337(1)	8.764(1)	8.7059(1)
b [Å]	10.1202(6)	16.2503(3)	7.341(1)	12.7662(2)
c [Å]	16.9210(13)	7.5432(2)	25.377(3)	13.5242(2)
a [°]	90	90	90	90
β [°]	94.696(2)	94.834(1)	97.56(1)	90
γ [°]	90	90	90	90
V [Å^3]	1476.66(17)	748.94(3)	1618.5(3)	1503.10(4)
Z	4	2	4	4
ρ [g cm^{-3}]	1.365	1.483	1.393	1.610
μ [mm^{-1}]	0.229	0.244	0.217	0.717
F(000)	640	348	712	744
2*θ*max. [°]	50	55	50	55
	$-7 \le h \le 10$	$-8 \le h \le 8$	$-10 \le h \le 10$	$-11 \le h \le 11$
	$-11 \le k \le 10$	$-19 \le k \le 19$	$-6 \le k \le 8$	$-16 \le k \le 16$
	$-17 \le l \le 20$	$-9 \le l \le 9$	$-29 \le l \le 29$	$-17 \le l \le 14$
No. of meas. Data	6997	10901	3805	15903
No. of unique data	2539	3377	2606	3411
R_{int}	0.0813	0.0293	0.0593	0.0304
Refinement on	F^2	F^2	F^2	F^2
No. of parameters/restraints	189/9	211/2	220/1	193/1
x		0.04(4)		–0.01(4)
R [for $I > 2\sigma(I)$]	0.0659	0.0243	0.0937	0.0215
wR_2 (all data)	0.1569	0.0647	0.2510	0.0593
Max./min. difference peak [e·Å^{-3}]	0.280/–0.506	0.300/–0.319	0.422/–0.286	0.298/–0.343
CCDC-No.	605974	605975	605976	605977

Table 8. Crystallographic data, structure solution and refinement of **31**, **35a** and **39**.

Compound	**31** SB027	**35a** SB044	**39** SB045
Formula	$C_{21}H_{19}NO_3S$	$C_{16}H_{16}N_2O_6S$	$C_{17}H_{18}N_2O_7S$
M_r	365.43	364.37	394.39
Dimensions [mm]	0.04×0.20×0.40	0.04×0.12×0.24	0.05×0.10×0.30
Crystal system	monoclinic	monoclinic	orthorhombic
Space group	$P2_1/c$ (No. 14)	$P2_1$ (No. 4)	$P2_12_12_1$ (No. 19)
a [Å]	8.0045(3)	7.609(1)	7.5531(1)
b [Å]	26.1096(11)	8.315(1)	13.4410(2)
c [Å]	8.8573(5)	12.857(3)	17.8276(3)
a [°]	90	90	90
β [°]	104.945(2)	95.43(1)	90
γ [°]	90	90	90
V [Å^3]	1788.51(14)	809.8(2)	1809.88(5)
Z	4	2	4
ρ [g cm^{-3}]	1.357	1.494	1.447
μ [mm^{-1}]	0.202	0.237	0.222
F(000)	768	380	824
$2\theta_{max.}$ [°]	55	50	55
	$-8 \le h \le 10$	$-7 \le h \le 9$	$-9 \le h \le 9$
	$-33 \le k \le 26$	$-7 \le k \le 9$	$-17 \le k \le 17$
	$-11 \le l \le 10$	$-13 \le l \le 15$	$-23 \le l \le 23$
No. of measured data	10991	2396	26440
No. of unique data	3959	1760	4124
R_{int}	0.0676	0.0548	0.0426
Refinement on	F^2	F^2	F^2
No. of parameters/restraints	239/1	230/2	249/1
x		0.1(2)	–0.04(5)
R [for $I > 2\sigma(I)$]	0.0442	0.0560	0.0300
wR_2 (all data)	0.0778	0.1212	0.0701
Max./min. difference peak [e·Å^{-3}]	0.237/–0.355	0.268/–0.248	0.208/–0.279
CCDC-No.	605978	605979	605980

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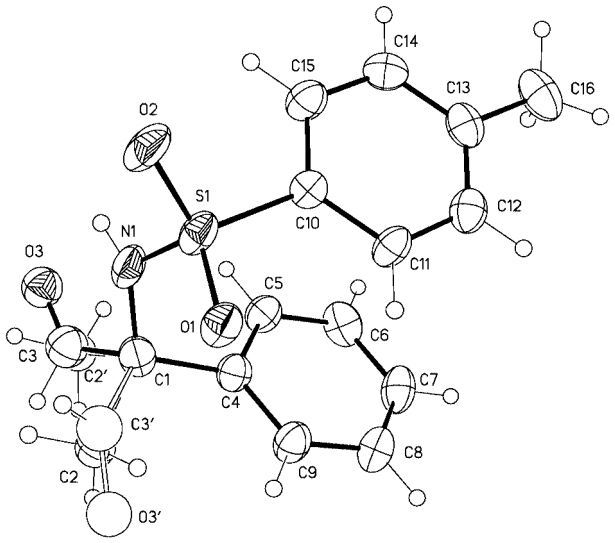
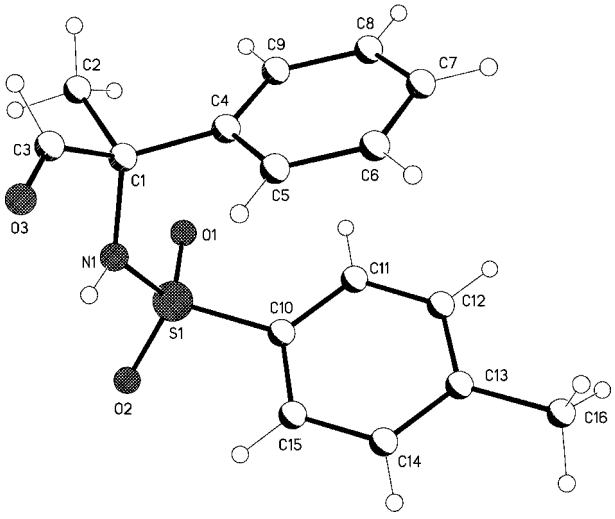


Figure 4. Crystal structure of **4a** (SB034) (50% probability, top); major disordered part (55% bottom).



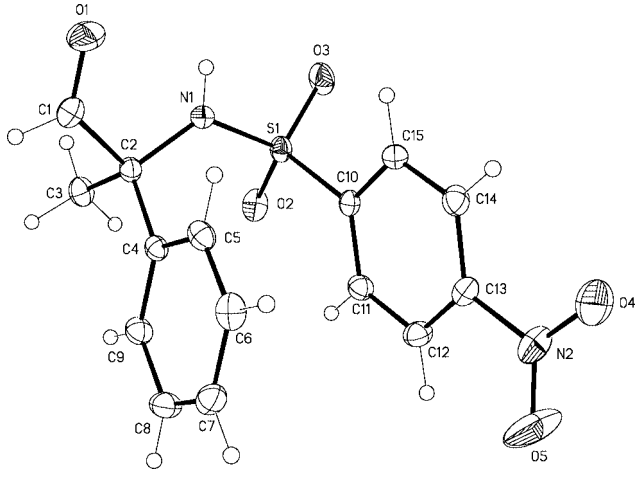


Figure 5. Crystal structure of **4c** (SB042) (50% probability).

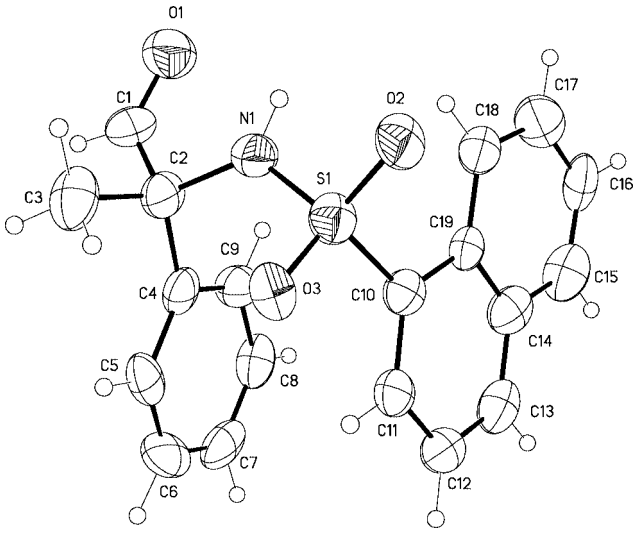


Figure 6. Crystal structure of **4g** (SB043) (50% probability).

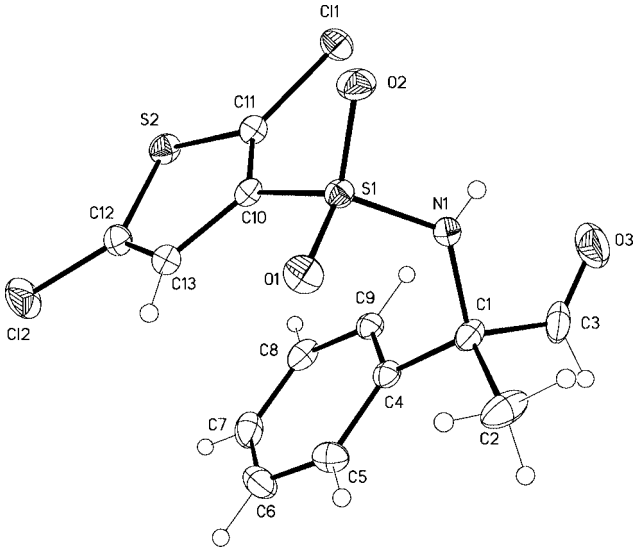


Figure 7. Crystal structure of **4j** (SB026) (50% probability).

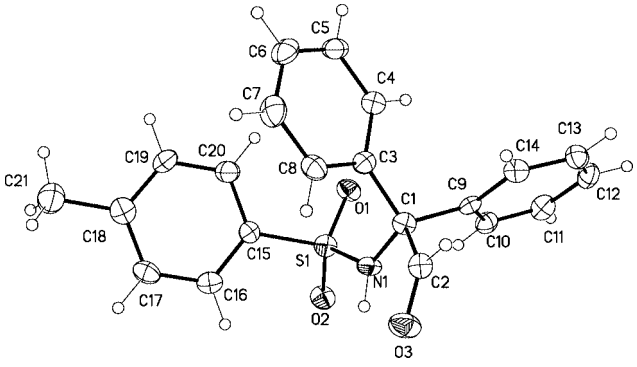


Figure 8. Crystal structure of **31** (SB027) (50% probability).

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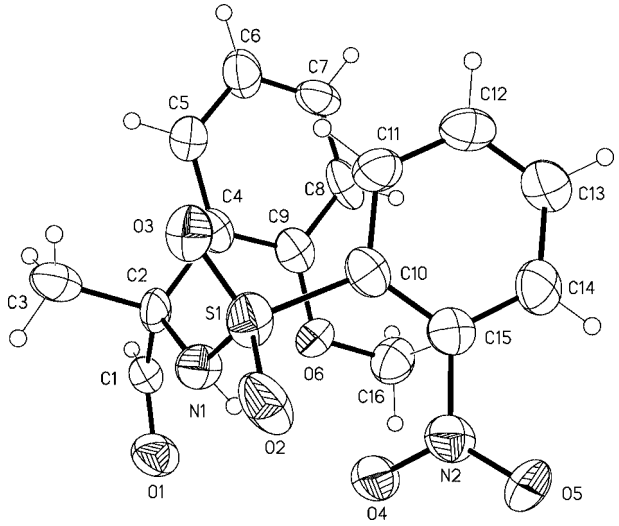

Figure 9. Crystal structure of **35a** (SB044) (50% probability).

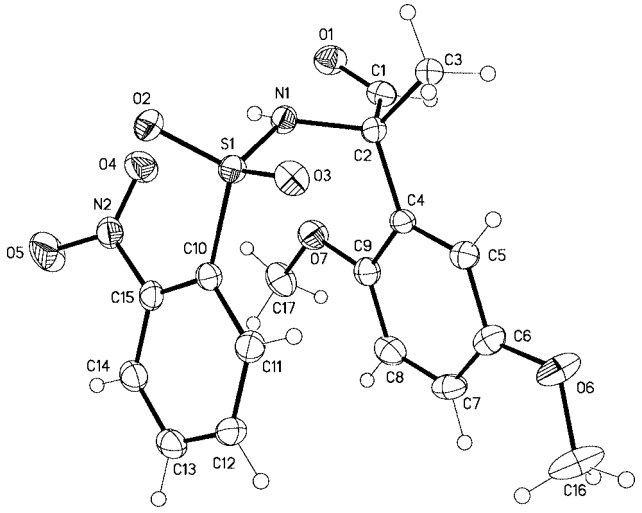

Figure 10. Crystal structure of **39** (SB045) (50% probability).

Supporting Information (see footnote on the first page of this article) containing detailed experimental procedures, additional screening conditions, and analytical data for all compounds, including determination of *ee*s, is available from the WWW under http://www.eurjoc.org or from the corresponding author.

Acknowledgments

Financial support from the DFG (SPP 1179, CFN) is gratefully acknowledged. We thank Prof. A. Berkessel (Cologne) and Prof. S. Tsogoeva (Göttingen) for sharing some organo-catalysts.

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Received: July 11, 2006
Published Online: October 5, 2006

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