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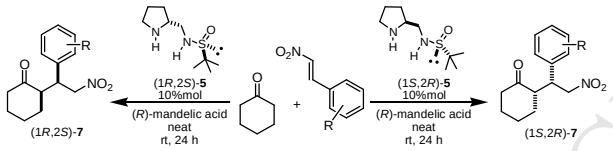

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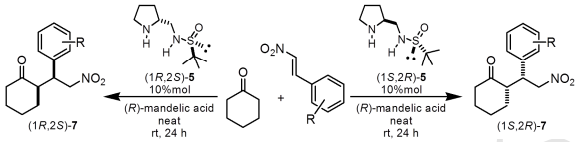

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Asymmetric Michael addition reaction organocatalyzed by stereoisomeric pyrrolidine sulfinamides under neat conditions. A brief study of self-disproportionation of enantiomers

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We dedicate this manuscript to Prof. Marian Mikołajczyk, a distinguished researcher in organosulfur chemistry, on the occasion of his 80th birthday.

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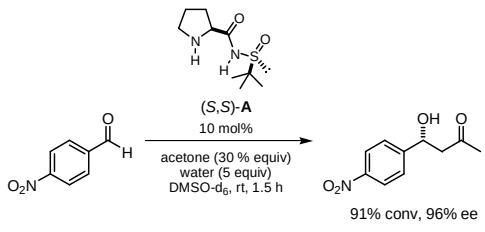
ABSTRACT

This paper describes the synthesis of all four possible stereoisomers of the pyrrolidine sulfinamides derived from (*S*)-proline or (*R*)-proline and either enantiomer of *t*-butylsulfinamide. These bifunctional derivatives were examined as organocatalysts in the asymmetric Michael addition reaction, finding that the pyrrolidine stereocenter, rather than the stereogenic sulfur, is responsible for the observed stereocontrol in the asymmetric reaction. This result is in accordance with previous reports in the literature (aldol reactions: W. Wan, J. Hao, and coworkers, *RSC Adv.* **2014**, *4*, 26563-26568; J. A. Ellman, et al., *Tetrahedron* **2011**, *67*, 4412-4416). Consequently, no evidence for double stereoinduction is found. The desired Michael adducts were obtained with good yields, high diastereoselectivities, and moderate to good enantioselectivities. Some tests designed to examine the potential manifestation of self-disproportionation of enantiomers (SDE) were carried out by means of chromatographic purification and subsequent evaluation of the enantiopurity of the corresponding Michael adducts.

1. Introduction

N-*t*-Butylsulfinamide has proved to be an efficient scaffold in asymmetric synthesis, either as chiral auxiliary or chiral reagent. In particular, the *N*-*t*-butylsulfinamide moiety is extremely useful in the preparation of chiral imines, that activate the electrophilic C=N function in addition reactions, simultaneously rendering diastereotopic faces of the double bond.[1] Lately, various organocatalytic applications of *N*-*t*-butyl sulfinamide derivatives have been reported.[2] For instance, Sun and coworkers, developed a series of chiral ligands containing the sulfinamide fragment that, by using $HSiCl_3$ as reducing agent, were evaluated as organocatalysts in the enantioselective reduction of aromatic *N*-alkyl ketimines and β-enamino esters via hydrogen transfer.[3]

In this context, asymmetric organocatalysis *via* chiral enamine intermediates derived from pyrrolidine bifunctional compounds[4] has proven to be one of the most effective methods to carry out enantioselective α-functionalizations of aldehydes and ketones.[5] In this regard, the ability of the *N*-sulfinyl functionality both as a chiral directing group and Brønsted acid moiety suitable for hydrogen-bonding has been amply studied by Ellman and coworkers.[6] These researchers evaluated various diastereomeric derivatives of *N*-aminoacyl sulfinamides as organocatalysts in the enantioselective aldol reaction between acetone and *p*-nitrobenzaldehyde, corroborating that the best combination of stereoisomeric fragments resulted from the combination of (*S*)-proline and (*S*)-2-methylpropane-2-sulfinamide (Scheme 1). Ellman, et al. concluded that "the inductive effect of the electron-withdrawing sulfinyl group acidifies the N-H bond, which serves to modulate hydrogen bonding interactions and at the same time, the close proximity between the stereogenic sulfur and the active site of the catalyst, contributes to the high level of stereocontrol in this reaction".[6]



Scheme 1. Asymmetric aldol reaction catalyzed by *N*-sulfinyl prolinamide (*S*,*S*)-**A**.

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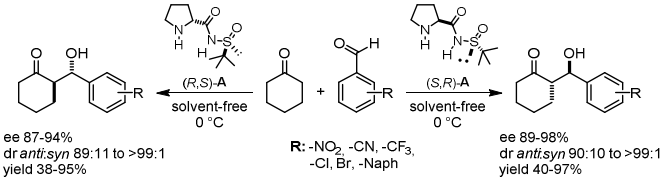
More recently, Wan, Hao, and coworkers[7] reported the asymmetric aldol reaction between cyclohexanone and diverse aryl-substituted aldehydes organocatalyzed by stereoisomers of **A** (Scheme 2). These researchers found that the most effective organocatalysts for these reactions are the *unlike* enantiomeric pair (*S*,*R*)-**A** and (*R*,*S*)-**A**, which affords the corresponding enantiomeric aldol adducts, (2*S*,1'*R*) and (2*R*,1'*S*), respectively, with high stereoselectivity.



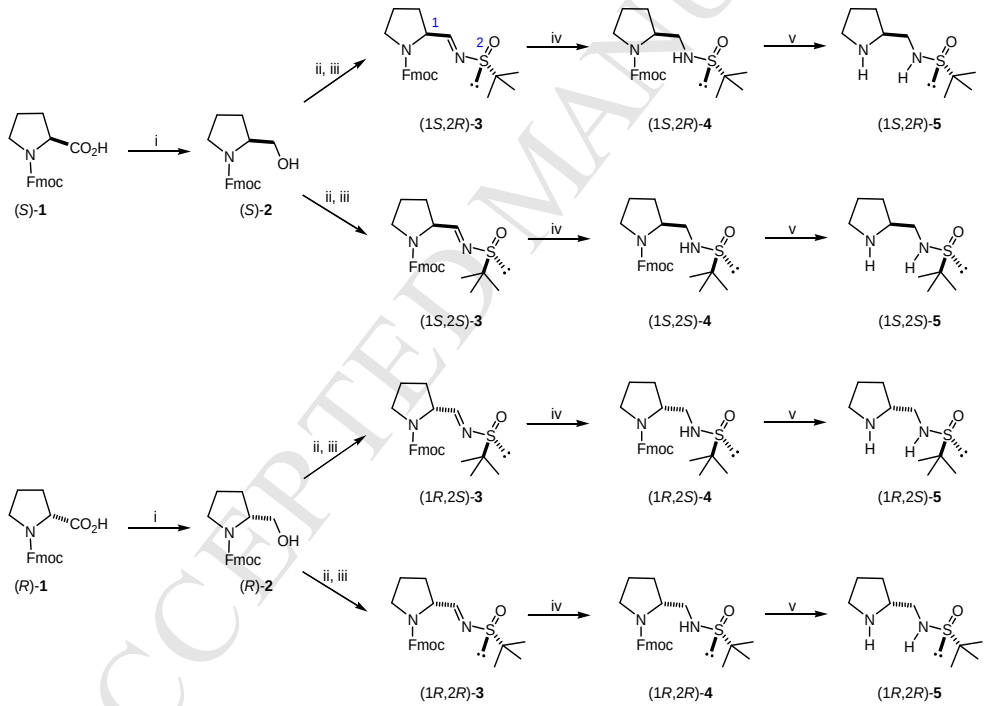
Scheme 2. Aldol reaction of cyclohexanone with substituted benzaldehyde under solvent-free conditions.

The Michael addition reaction constitutes a prototypical application of proline-derived organocatalysts,[5e-g] but as far as we are aware there are no examples reported in the literature describing applications of proline sulfinamides as organocatalysts in asymmetric Michael reactions. Here, we report the synthesis of the four possible stereoisomers prepared from the coupling of (*S*)-proline or (*R*)-proline with (*S*)- or (*R*)-*t*-butylsulfinamide. Furthermore, these diastereomeric proline sulfinamides were evaluated as organocatalysts in the asymmetric Michael addition reaction.

2. Results and discussion

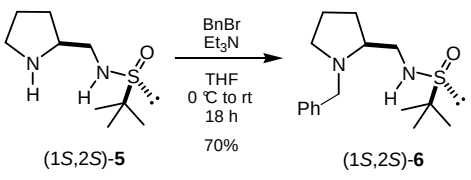
2.1. Synthesis of stereoisomeric pyrrolidine-2-ylmethyl-*N*-*t*-butyl-sulfinamides, 5

Based on a previous report by Sun and coworkers,[8] the derivatives of interest were prepared from *N*-Fmoc protected (*S*)- or (*R*)-proline **1**, by reduction of the carboxyl moiety employing $NaBH_4$ combined with $Et_2O{:}BF_3$, to give the Fmoc prolinols (*S*)-**2** or (*R*)-**2** (Scheme 3). Reoxidation of the carbinol functionality under Swern conditions using oxalyl chloride, generated the corresponding prolinals, which in turn were condensed with the appropriate enantiomer of *t*-butylsulfinamide to afford the expected imines (1*S*,2*R*)-**3**, (1*S*,2*S*)-**3**, (1*R*,2*S*)-**3**, or (1*R*,2*R*)-**3**. This reaction was achieved by means of Lewis acid catalysis with anhydrous $CuSO_4$. Each of the resulting stereoisomeric sulfinimides was reduced with $NaBH_4$, and final *N*-deprotection of the pyrrolidine derivatives **4** was accomplished by using Et_2NH as the required base to provide (1*S*,2*R*)-**5**, (1*S*,2*S*)-**5**, (1*R*,2*S*)-**5**, or (1*R*,2*R*)-**5** (Scheme 3).



[a]Reagents and conditions: (i) $NaBH_4$, $Et_2O{:}BF_3$, anhydrous THF, 0 °C, 18 h. (ii) CH_2Cl_2, $(CO)Cl_2$, dry DMSO, Et_3N. (iii) $CuSO_4$ anhydrous, dry CH_2Cl_2, (*S*)- or (*R*)-*t*-butylsulfinamide, 25 °C, 24 h. (iv) $NaBH_4$, MeOH, THF. (v) Et_2NH, THF, 25 °C, 5 h.

Scheme 3. Synthesis of the four stereoisomers of pyrrolidine *t*-butylsulfinamide, **5**.



Scheme 4. *N*-Benzylation of pyrrolidine-sulfinamide (1*S*,2*S*)-**5**.

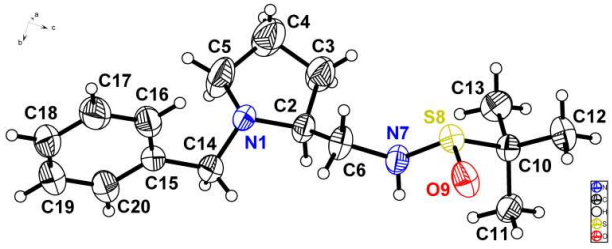


Fig. 1. X-ray crystallographic structure of the resulting *N*-benzyl pyrrolidine-sulfinamide (1*S*,2*S*)-**6** (thermal ellipsoids at 30 % probability).

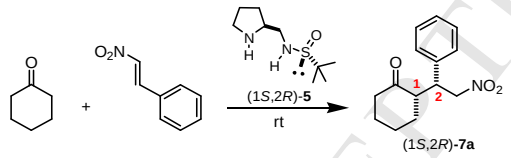
Derivative (1*S*,2*S*)-**6** obtained by *N*-benzylation of (1*S*,2*S*)-**5** (Scheme 4) afforded a suitable crystal for analysis by means of X-ray diffraction, corroborating the expected absolute configuration for both stereogenic centers (Flack *x* parameter –0.0336 with su 0.1470) (Fig. 1). In the crystallographic structure it can be appreciated that both pyrrolidine substituents are oriented *trans* to each other. Additionally, the N-H bond is oriented far away to the pyrrolidine fragment (N1-C2-C6-N7 torsion angle = 173.1°), which indicates that no intramolecular hydrogen bond is formed between both fragments. The stereogenic sulfur in the anticipated pyramidal molecular geometry is defined by the following angles: N7-S8-O9 = 111.73°, N7-S8-C10 = 98.15°, O9-S8-C10 = 105.52°.

With isomeric pyrrolidine sulfinamides (1*S*,2*R*)-**5**, (1*S*,2*S*)-**5**, (1*R*,2*S*)-**5**, and (1*R*,2*R*)-**5** at hand, we proceeded to their evaluation as organocatalysts in the Michael addition reaction between cyclohexanone and various β-nitrostyrenes.

2.2 Evaluation of stereoisomeric pyrrolidine *t*-butylsulfinamides, 5, as organocatalysts.

We first evaluated derivative (1*S*,2*R*)-**5** as organocatalyst, screening several variables in order to optimize the reaction conditions (Table 1). While (1*S*,2*R*)-**5** (20 mol-%) in the presence of $PhCO_2H$ as additive in combination with common solvents such as toluene, IPA and DMSO (entries 1-3 in Table 1) did not afford the Michael adduct **7a**; water and brine as reaction media afforded the expected product with good diastereo- and high enantioselectivity, although in moderate yields (entries 4-5 in Table 1). Importantly, the reaction proceeded efficiently *under solvent-free conditions*, observing that not only the yield increased significantly to 80%, but also good diastereo- and enantioselectivities were maintained (entry 6 in Table 1). That an organocatalytic reaction can be carried out in the absence of solvent, that is under more sustainable conditions, is a rather attractive feature of the present system.[9]

Table 1. Asymmetric Michael reaction organocatalyzed by pyrrolidine *t*-butylsulfinamide (1*S*,2*R*)-**5**.[a]



Entry	(1*S*,2*R*)-**5** mol-%	$PhCO_2H$ mol-%	Solvent	Yield[d] (%)	dr[e] *syn*:*anti*	er[f] (1*S*,2*R*):(1*R*,2*S*)
1	20	20	Toluene	—	—	—
2	20	20	IPA	—	—	—
3	20	20	DMSO	—	—	—
4[**]	20	20	H_2O	56	94:6	86:14
5[**]	20	20	Brine	54	94:6	89:11
6[*]	20	20	Neat	80	90:10	89:11
7[*]	10	10	Neat	76	93:7	85:15
8[*]	5	5	Neat	20	93:7	85:15
9[*]	2	2	Neat	—	—	—
10[*]	10	—	Neat	—	—	—
11[b,*]	10	10	Neat	—	—	—
12[c,*]	10	10	Neat	89	94:6	85:15
13[g]	10	10	Neat	87	93:7	89:11

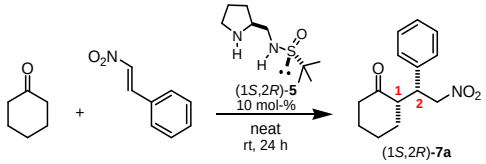
[a] Unless otherwise specified, reaction conditions were as follows: cyclohexanone (0.2 mL), β-nitrostyrene (0.5 mmol), stirring during 24 h* or 72 h**, and using the indicated solvent. [b] Reaction at –15 °C. [c] Reaction at 2 °C. [d] Isolated yield [gravity-driven chromatography, employing silica-gel (14g, 230-400 mesh) packed in glass columns (ø 1.8-2 cm, stationary phase @ 45 cm length)] and Hexane:EtOAc (8:2) as eluent. [e] Determined by ^{1}H NMR of crude products. [f] HPLC analysis with chiral columns for the *syn* isomer. (g) Reaction conducted with catalyst (1*S*,2*S*)-**5**.

Additionally, under neat conditions the reaction time diminished from three days to 24 h (compare entries 4 and 5 with entries 6-8 in Table 1). On the other hand, at 2 °C (entry 12 in Table 1), the reaction yield and the diastereomeric ratio of the Michael product remained high while the enantiomeric ratio decreased slightly. When lowering the amount of catalyst from 20 mol-% to 10 mol-%, no significant change in yield and enantioselectivity was observed (compare entries 6 and 7 in Table 1). Nevertheless, with 5 mol-% of catalyst the yield decreased dramatically (compare entry 8 in Table 1), and actually no product was observed when 2 mol-% of catalyst was used (entry 9 in Table 1). Product formation was also inhibited in the absence of the acidic additive or at temperatures below –15 °C (entries 10 and 11 in Table 1).

In order to confirm whether double stereoinduction is operative in the system, the results achieved with organocatalyst (1*S*,2*R*)-**5** (Table 1) were compared with those obtained with diastereomeric (1*S*,2*S*)-**5**, with opposite configuration at sulfur. In the event, the stereoselectivities were similar, and thus it is concluded that there is no significant contribution on stereocontrol from the stereogenic sulfur moiety.

Comparison of entries 7 and 10 in Table 1 gives evidence of the prominent role of benzoic acid as activating additive in the reaction. At this point it was decided to examine alternative Brønsted acids as additives; no drastic differences were observed (Table 2), so it is apparent that the acid catalysis is of the general type and independent of the particular structural features of the proton source, as long as the pK_a is constrained within an appropriate range (pK_a = 4-5).[10] Furthermore, the use of either enantiomer of mandelic acid as Brønsted acid additive afforded the same configuration of the product (compare entries 5 and 6 in Table 2), which argues against the possible existence of a double stereoinducing effect by the chiral acid additive.[11]

Table 2. Evaluation of diverse Brønsted acids additives.

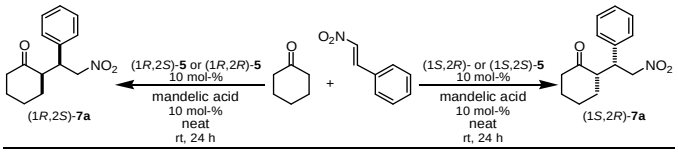


Entry	Additive 10 mol-%	Yield[a] (%)	dr[b] *syn*:*anti*	er[c] (1*S*,2*R*):(1*R*,2*S*)
1	*p*-nitrobenzoic acid	83	89:11	74:26
2	*p*-chlorobenzoic acid	93	93:7	84:16
3	*p*-methoxybenzoic acid	63	92:8	79:21
4	benzoic acid	76	93:7	85:15
5	(*S*)-mandelic acid	83	93:7	79:21
6	(*R*)-mandelic acid	83	95:5	84:16

[a] Isolated yield. [b] Determined by ^{1}H NMR of crude product. [c] HPLC analysis with chiral columns for the *syn* isomer.

Each stereoisomer of pyrrolidine sulfinamide **5** was evaluated in combination with either enantiomer of mandelic acid, and therefore each chiral organocatalyst generated a pair of diastereomeric salts. The yields and diastereomeric ratios of the Michael products obtained with these diastereomeric salts were good in all cases, reaching up to 80% ee (Table 3). Importantly, enantioenriched Michael adducts (1*S*,2*R*)-**7a** and (1*R*,2*S*)-**7a** were obtained with (*S*)-pyrrolidine [(1*S*,2*R*)-**5** and (1*S*,2*S*)-**5**] or (*R*)-pyrrolidine [(1*R*,2*S*)-**5** and (1*R*,2*R*)-**5**] derivatives, respectively, regardless the configuration of the *t*-butylsulfinamide moiety or the mandelate counterion.[12]

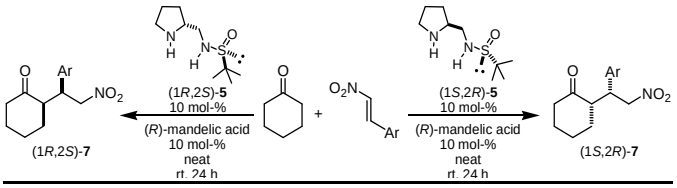
Table 3. Asymmetric Michael reaction organocatalyzed by pyrrolidine *t*-butylsulfinamides **5** in combination with mandelic acid.[a]



Entry	Organocatalyst	Mandelic acid 10 mol-%	Major Stereoisomer	Yield[b] (%)	dr[c] *syn*:*anti*	er[d] (1*S*,2*R*):(1*R*,2*S*)
1	(1*S*,2*R*)-**5**	(*R*)	(1*S*,2*R*)-**7a**	83	93:7	85:15
2		(*S*)	(1*S*,2*R*)-**7a**	83	93:7	79:21
3	(1*S*,2*S*)-**5**	(*R*)	(1*S*,2*R*)-**7a**	71	94:6	85:15
4		(*S*)	(1*S*,2*R*)-**7a**	89	92:8	86:14
5	(1*R*,2*S*)-**5**	(*R*)	(1*R*,2*S*)-**7a**	74	92:8	11:89
6		(*S*)	(1*R*,2*S*)-**7a**	77	90:10	12:88
7	(1*R*,2*R*)-**5**	(*R*)	(1*R*,2*S*)-**7a**	75	84:16	16:84
8		(*S*)	(1*R*,2*S*)-**7a**	75	83:17	10:90

[a] Reactions were performed with cyclohexanone (0.2 mL), β-nitrostyrene (0.5 mmol), 10 mol-% of organocatalyst stirring at rt during 24 h. [b] Isolated yield. [c] Determined by ^{1}H NMR of crude product. [d] HPLC analysis with chiral columns for the *syn* isomer.

Table 4. Asymmetric Michael reaction with substituted β-nitrostyrene under solvent free conditions.[a]



Entry	Ar	Product	Yield[b] (%)	dr[c] *syn*:*anti*	er[d] (*S*,*R*):(*R*,*S*)	ee (%)
1	C_6H_5	(1*S*,2*R*)-**7a**	97	96:4	85:15	70
2		(1*R*,2*S*)-**7a**	74	92:8	11:89	78
3	*o*-Cl-C_6H_4-	(1*S*,2*R*)-**7b**	83	94:6	85:15	70
4		(1*R*,2*S*)-**7b**	88	95:5	12:88	76
5	*o*-MeO-C_6H_4-	(1*S*,2*R*)-**7c**	93	96:4	83:17	66
6		(1*R*,2*S*)-**7c**	82	96:4	10:90	80
7	*o*-Br-C_6H_4-	(1*S*,2*R*)-**7d**	95	95:5	84:16	68
8		(1*R*,2*S*)-**7d**	91	94:6	9:91	82
9	*p*-MeO-C_6H_4-	(1*S*,2*R*)-**7e**	61	87:13	70:30	40
10		(1*R*,2*S*)-**7e**	64	87:13	22:78	56
11	*p*-Me-C_6H_4-	(1*S*,2*R*)-**7f**	84	96:4	73:27	46
12		(1*R*,2*S*)-**7f**	62	91:9	11:89	78
13	*p*-Cl-C_6H_4-	(1*S*,2*R*)-**7g**	89	91:9	76:24	52
14		(1*R*,2*S*)-**7g**	65	91:9	10:90	80
15	*p*-F-C_6H_4-	(1*S*,2*R*)-**7h**	86	90:10	84:16	70
16		(1*R*,2*S*)-**7h**	84	91:9	9:91	82

[a] Reactions were performed with cyclohexanone (0.2 mL, 0.19 g, 1.93 mmol), β-nitrostyrene (0.5 mmol), 10 mol-% of organocatalyst and 10 mol-% of mandelic acid, stirring at rt during 24 h. [b] Isolated yield by means of gravity-driven chromatography, employing silica-gel (14 g, 230-400 mesh) packed in glass columns (ø 2 cm, stationary phase @ 45 cm length) and Hexane:EtOAc (8:2) as eluent. [c] Determined by ^{1}H NMR of crude product. [d] HPLC analysis with chiral columns for the *syn* isomer.

To study the scope of the reaction, we chose enantiomeric organocatalysts (1*S*,2*R*)-**5** and (1*R*,2*S*)-**5**, both in combination with (*R*)-mandelic acid (Table 4). Notably, enhanced stereoinduction was observed when electron-withdrawing substituents are present in the aryl fragment of the nitrostyrene, achieving for example 82% ee for products *o*-Br (**7d**, entry 8 in Table 4) and *p*-F (**7h**, entry 16 in Table 4). By contrast, electron-donating substituents led to diminished stereoselectivity (entries 5, 9, 10 and 11 in Table 4). An exception was *o*-methoxy, which gave rise to the corresponding product (1*R*,2*S*)-**7c** in 80% ee (**7c**, entry 6 in Table 4). Stereoselectivities induced by the salt formed between (1*S*,2*R*)-**5** and (*R*)-mandelic acid remained practically constant for all aryl-nitrostyrenes with electron-withdrawing substituents, with ee values around 70%. As already noticed above, electron-donating substituents in these electrophiles provoked a marked decrease in enantioinduction.

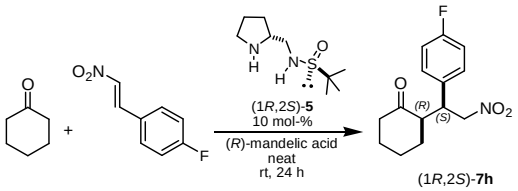
2.3 Evaluation of self-disproportionation of enantiomers *via* achiral chromatography.

The self-disproportionation of enantiomers (SDE) refers to any manipulation process under achiral conditions in which a non-racemic (scalemic) chiral compound leads to fractions containing variable proportions –either enriched and depleted, in comparison to the enantiomeric composition of the starting sample– of the enantiomers.[13] Specifically, SDE has been observed after fractional crystallization,[14] sublimation,[15] distillation[16] and achiral chromatography.[17]

Diverse factors influence the magnitude in which chiral compounds may exhibit SDE when being purified by means of gravity-driven column chromatography, such as the polarity of the solvent employed as eluent, the nature of stationary phase (e.g. alumina, silica gel), as well as particle and pore size.[13] Chiral compounds, such as β-amino acid esters,[18] acylated amines,[19] thioamides and sulfoxides[20] have exhibited SDE.

With the aim of examining whether the Michael adducts obtained in the present work might exhibit SDE, we considered two of the products described above: one obtained in high ee [(1*R*,2*S*)-**7h**] and the other obtained with the lowest ee [(1*S*,2*R*)-**7e**]. For this study, we focused on gravity driven column chromatography since it is the most common method to purify this class of compounds. In particular, the nature of the mobile phase was the variable to evaluate, considering a mixture of hexane-ethyl acetate 8:2, and pure methylene chloride as eluents.

Table 5. Effect of a low-polarity eluent [Hexane:EtOAc (8:2)] on the SDE of Michael adduct (1*R*,2*S*)-**7h** obtained from the reaction catalyzed by (1*R*,2*S*)-**5**.[a]



Fraction [b]	Mass/fraction (mg) [c]	Weight %	er [d] (*S*,*R*):(*R*,*S*)	ee (%)
1	4.0	5.66	7:93	86
2	8.3	11.74	7:93	86
3	7.0	9.90	8:92	84
4	13.3	18.81	8:92	84
5	11.0	15.56	9:91	82
6	7.3	10.32	9:91	82
7	6.5	9.19	9:91	82
8	5.1	7.21	9:91	82
9	3.3	4.67	10:90	80
10	2.8	3.96	10:90	80
11	2.1	2.97	10:90	80

[a] The reaction was carried out under the previously described conditions [*Cf.* Table 4 (a)]. [b] Product eluted in fractions of 10 mL each. [c] Isolated weight per corresponding fraction by means of gravity-driven chromatography, employing silica-gel (14 g, 230-400 mesh) packed in a glass column (ø 2 cm, stationary phase @ 45 cm length). [d] HPLC conditions: Chiralpak AS-H column, 210 nm, *n*-Hexane/*i*PrOH 95:5, *U* = 0.5 mL/min [t_R(minor *syn*) = 55.4 min, t_R(major *syn*) = 81.2 min].

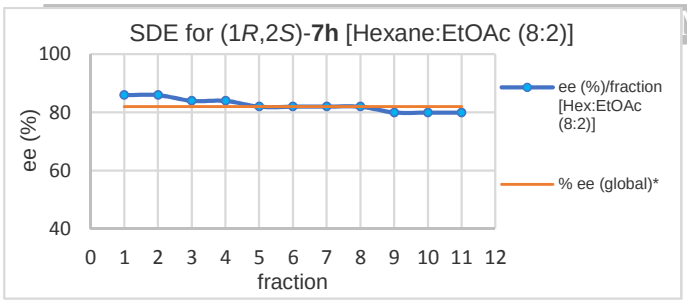
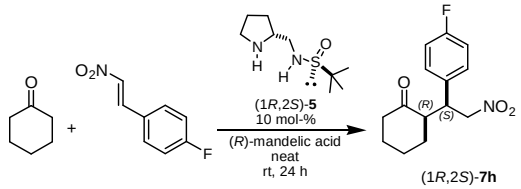


Fig. 2. Graphical representation of chromatographic behavior for Michael reaction test to obtain adduct (1*R*,2*S*)-**7h** after purification using a non-polar eluent [Hexane:EtOAc (8:2)] showing the % ee of the corresponding eluted fraction (*Cf.* Table 5). The global value 82% ee corresponds to the originally determined value (see entry 16, Table 4).

It can be appreciated that Michael product (1*R*,2*S*)-**7h**, obtained with 82% of global ee, exhibited a rather small difference of enantiomeric excess (Δee) of 4% between fractions when employing a low-polarity mobile phase (see Table 5 and Fig. 2). Furthermore, in the case of polar methylene chloride as eluent, the SDE (Δee = 2%) is almost negligible (*Cf.* Table 6 and Fig. 3). It is worth mentioning that this behavior is in line with the anticipated performance for samples of high enantiopurity.[13]

Table 6. Effect of a polar eluent [100% CH_2Cl_2] on the SDE of Michael adduct (1*R*,2*S*)-**7h** obtained from reaction catalyzed by (1*R*,2*S*)-**5**.[a]



Fraction [b]	Mass/fraction (mg) [c]	Weight %	er [d] (*S*,*R*):(*R*,*S*)	ee (%)
1	16.8	22.76	92:8	84
2	21.9	29.71	91:9	82
3	13.1	17.77	91:9	82
4	10.6	14.38	91:9	82
5	7.4	10.04	91:9	82
6	3.9	5.29	91:9	82

[a] The reaction was carried out under the previously described conditions [*Cf.* Table 4, (a)]. [b] Product eluted in fractions of 10 mL each. [c] Isolated weight per corresponding fraction by means of gravity-driven chromatography, employing silica-gel (14 g, 230-400 mesh) packed in a glass column (ø 2 cm, stationary phase @ 45 cm length). [d] HPLC conditions: Chiralpak AS-H column, 210 nm, *n*-Hexane/*i*PrOH 95:5, *U* = 0.5 mL/min [t_R(minor *syn*) = 55.4 min, t_R(major *syn*) = 81.2 min].

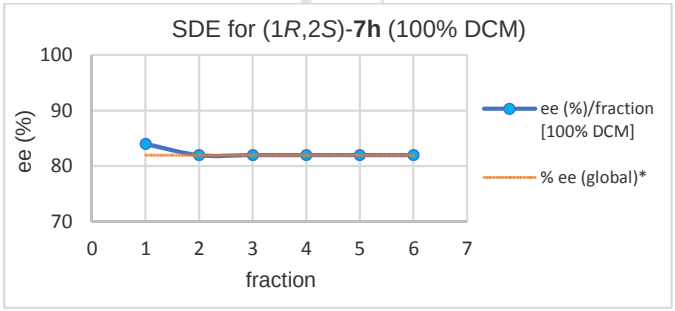
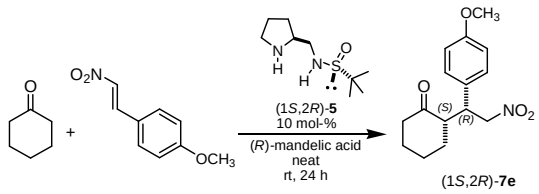


Fig. 3. Graphical representation of chromatographic behavior for Michael reaction test to obtain adduct (1*R*,2*S*)-**7h** after purification using polar 100% CH_2Cl_2, showing the % ee of the corresponding eluted fraction (*Cf.* Table 6). The global value 82% ee corresponds to the originally determined value (see entry 16, Table 4).

Table 7. Effect of a low-polarity eluent [Hexane:EtOAc (8:2)] on the SDE of Michael adduct (1*S*,2*R*)-**7e** obtained from reaction catalyzed by (1*S*,2*R*)-**5**.[a]



Fraction [b]	Mass/fraction (mg) [c]	Weight %	er [d] (*S*,*R*):(*R*,*S*)	ee (%)
1	5.2	5.08	70:30	40
2	7.5	7.32	63:37	26
3	14.4	14.06	66:34	32
4	12.4	12.11	70:30	40
5	12.7	12.40	75:25	50
6	15.4	15.04	77:23	54
7	13.9	13.57	77:23	54
8	12.5	12.20	81:19	62
9	8.4	8.20	93:7	86

[a] The reaction was carried out under the previously described conditions [*Cf.* Table 4, (a)]. [b] Product eluted in fractions of 10 mL each [c] Isolated weight per corresponding fraction by means of gravity-driven chromatography, employing silica-gel (14 g, 230-400 mesh) packed in a glass column (ø 2 cm, stationary phase @ 45 cm length). [d] HPLC conditions: Chiralpak AD-H column, λ = 210 nm, *n*-Hexane/*i*PrOH 90:10, *U* = 0.5 mL/min [t_R(minor *syn*) = 22.9 min, t_R(major *syn*) = 28.9 min].

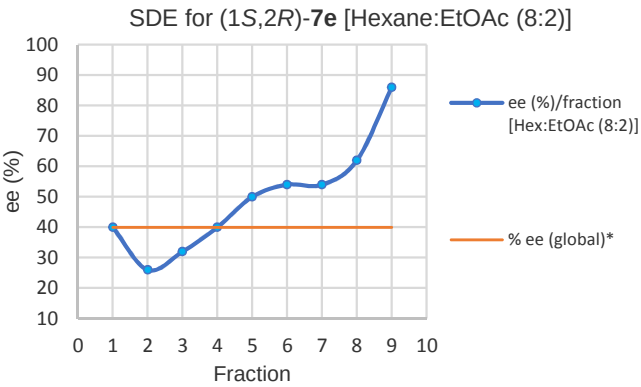


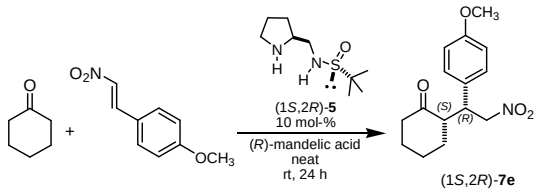
Fig. 4. Graphical representation of chromatographic behavior for Michael reaction test to obtain adduct (1*S*,2*R*)-**7e** after purification using non-polar [Hexane:EtOAc (8:2)] as eluent, showing the % ee of the corresponding eluted fraction (*Cf.* Table 7). The global % ee of 40% corresponds to the originally determines value (see entry 9, Table 4).

By contrast, compound (1*S*,2*R*)-**7h**, that had been obtained with 40% of global ee, exhibited 60% of Δee which is significantly high (see Table 7 and Fig. 4). Also remarkable is the fact that methylene chloride leads to almost complete depletion of the major enantiomer by self-disproportionation of enantiomers for this Michael adduct (*Cf.* Table 8 and Fig. 5).

Given that polar methylene chloride diminishes the SDE effect, we deemed this solvent as a more suitable mobile phase in order to unambiguously determine the enantioselectivity induced by our organocatalysts, (1*R*,2*S*)-**5** and (1*S*,2*R*)-**5**. Therefore, we repeated the tests described in Table 4 (to obtain *syn* Michael adducts **7a-h**). To our surprise, the great majority of (1*S*,2*R*)-**7** products exhibited higher enantiopurity (compare for example entry 13 in Table 4 with entry 13 in Table 9), whereas stereoisomers (1*R*,2*S*)-**7** exhibited essentially unchanged enantiomeric excesses. This contrasting behavior might be explained in terms of the possible formation of homochiral dimers and/or conglomerates in the case of (1*S*,2*R*)-**7**.[21] Though

additional studies would be necessary to confirm this point, a more detailed approach is beyond the scope of the present work.

Table 8. Effect of a more polar eluent [100% CH_2Cl_2] on the SDE of Michael adduct (1*S*,2*R*)-**7e** obtained from reaction catalyzed by (1*S*,2*R*)-**5**.[a]



Fraction [b]	Mass/fraction (mg) [c]	Weight %	er [d] (*S*,*R*):(*R*,*S*)	ee (%)
1	40.2	41.53	71:29	42
2	35.8	36.98	72:28	44
3	13.4	13.84	75:25	50
4	5.5	5.68	73:27	46
5	1.9	1.96	77:23	54

[a] The reaction was carried out under the previously described conditions [*Cf.* Table 4, (a)]. [b] Product eluted in fractions of 10 mL each. [c] Isolated weight per corresponding fraction by means of gravity-driven chromatography, employing silica-gel (14 g, 230-400 mesh) packed in a glass column (ø 2 cm, stationary phase @ 45 cm length). [d] HPLC conditions: Chiralpak AD-H column, λ = 210 nm, *n*-Hexane/*i*PrOH 90:10, *U* = 0.5 mL/min [t_R(minor *syn*) = 22.9 min, t_R(major *syn*) = 28.9 min].

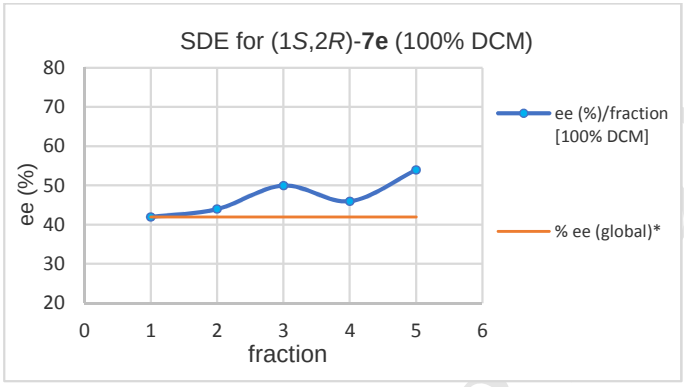
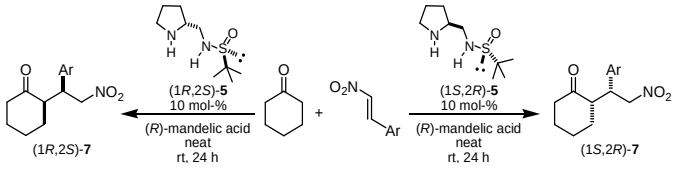


Fig. 5. Graphical representation of chromatography for Michael reaction test to obtain adduct (1*S*,2*R*)-**7e** after purification using 100% CH_2Cl_2 showing the % ee of the corresponding eluted fraction (*Cf.* Table 8). The global value 40% ee corresponds to the originally determined value (see entry 9, Table 4).

Table 9. Asymmetric Michael reaction with substituted β-nitrostyrene under solvent free reaction conditions.[a] Isolation of products, followed by quantification of ee values was carried out with methylene chloride solvent.



Entry	Ar	Product	Yield[b] (%)	dr[c] *syn*:*anti*	er[d] (*S*,*R*):(*R*,*S*)	ee (%)
1	C_6H_6	(1*S*,2*R*)-**7a**	86	97:3	86:14	72
2		(1*R*,2*S*)-**7a**	76	94:6	13:87	74
3	*o*-Cl-C_6H_5-	(1*S*,2*R*)-**7b**	99	97:3	93:7	86
4		(1*R*,2*S*)-**7b**	90	94:6	12:88	76
5	*o*-MeO-C_6H_5-	(1*S*,2*R*)-**7c**	65	97:3	92:8	84
6		(1*R*,2*S*)-**7c**	70	94:6	9:91	82
7	*o*-Br-C_6H_5-	(1*S*,2*R*)-**7d**	99	97:3	94:6	88
8		(1*R*,2*S*)-**7d**	92	94:6	9:91	82
9	*p*-MeO-C_6H_5-	(1*S*,2*R*)-**7e**	75	89:11	80:20	60
10		(1*R*,2*S*)-**7e**	65	83:17	27:73	46
11	*p*-Me-C_6H_5-	(1*S*,2*R*)-**7f**	80	92:8	91:9	82
12		(1*R*,2*S*)-**7f**	68	92:8	13:87	74
13	*p*-Cl-C_6H_5-	(1*S*,2*R*)-**7g**	81	97:3	95:5	90
14		(1*R*,2*S*)-**7g**	70	97:3	11:89	78
15	*p*-F-C_6H_5-	(1*S*,2*R*)-**7h**	81	97:3	93:7	86
16		(1*R*,2*S*)-**7h**	80	91:8	9:91	82

[a] Reactions were performed with cyclohexanone (0.2 mL), β-nitrostyrene (0.5 mmol), 10 mol-% of organocatalyst and 10 mol-% of mandelic acid, stirring at rt. [b] Isolated yield by means of gravity-driven chromatography, employing silica-gel (230-400 mesh) packed in glass columns (1.8 cm ø, stationary phase @ 23 cm length) and CH_2Cl_2 as eluent. [c] Determined by ^{1}H NMR of crude product. [d] HPLC analysis with chiral columns for the *syn* isomer.

3. Conclusions

We report synthetic routes for the preparation of all possible stereoisomers of pyrrolidine sulfinamides obtained from proline and *t*-butylsulfinamide. The four stereoisomers were tested in the asymmetric Michael reaction between cyclohexanone and β-nitrostyrene, in the presence of either enantiomer of mandelic acid as additive. No significant match/mismatch double stereoinduction was observed. It was found that the best catalytic system corresponds to the (*R*)-pyrrolidine-(*S*)-*t*-butylsulfinamide (1*R*,2*S*)-**5** combination, in the presence of (*R*)-mandelic acid. This catalytic system was evaluated in the Michael addition reaction of cyclohexanone with a series of aryl-substituted β-nitrostyrenes, obtaining the anticipated products in good yields and high diastereoselectivities, as well as good enantioselectivity.

A preliminary study on potential self-disproportionation of enantiomers (SDE) of the Michael adducts is reported. It was found that non-polar mixtures of hexane-ethyl acetate as eluent do give rise to this effect, especially when the enantiopurity of the sample is moderate. By contrast, polar methylene chloride seems to inhibit the disproportionation of enantiomers.

Most outstanding is the fact that the enantiopurity of the isolated product from organocatalyzed asymmetric reactions might be modulated by simply changing the polarity of the mobile phase during chromatographic purification. On the other hand, SDE represents a potentially ubiquitous phenomenon that must be considered before unambiguous evaluation of the stereoinduction by a given chiral catalyst or reagent.

4. Experimental section

4.1. General information

The material employed to carry out reactions in anhydrous conditions was dried at 120 °C, and conserved under inert atmosphere. Tetrahydrofuran (THF) employed anhydrous was dried by means of distillation with metallic Na under inert atmosphere. CH_2Cl_2 was dried by stirring with P_2O_5 and distilling under inert atmosphere. The reactions were monitored by TLC, employing precoated aluminum sheets (silica gel Merck 60 F_{254}) plates and visualizing by UV lamp (254 nm), staining with iodine chamber, ninhydrin or ammonium ceric sulfate. Purification was mainly carried out by flash CC, utilizing silica gel Merck (230-400 mesh) and bidistilled technical grade solvent. Optical rotations were determined in a Perkin-Elmer Model 241 polarimeter, using a 0.1 dm length cell; and for measurement, it was employed sodium D line (589 nm), at the temperature of sample compartment of the apparatus (20-25 °C). Specific rotations were reported with the sample concentration in g/100 mL, together with the solvent employed. Uncorrected melting points were determined in a Melt-Temp Electrothermal apparatus.

^{1}H, ^{13}C and two dimensions NMR spectra were obtained in the spectrometers JEOL GSX-270 (270 MHz), Bruker Advance 300 (300 MHz), JEOL Eclipse 400 (400 MHz) and JEOL ECA-500 (500 MHz). Tetramethylsilane (TMS) was usually employed as internal reference and the chemical shifts (δ) were reported in parts per million (ppm). Coupling constants (*J*) are reported in hertz (Hz). Multiplicity of the signals in ^{1}H NMR are indicated according to the following abbreviations: (s) single, (d) double, (t) triple, (q) quartet, (m) multiple and (br) broad; reporting in the last two cases, the interval where these appears.

Infrared spectra were performed in a Varian model 640 (ATR) spectrometer or in a Perkin-Elmer FTIR spectrum-GX apparatus. High resolution mass spectra were obtained in one HPLC 1100 equipment coupled to MSDTOF Agilent Series HR-MSTOF model 1069 A.

X-ray crystallographic analysis was carried out in an Enraf-Nonius Kappa CCD diffractometer. Programs SHELX-97,[22] and WinGX,[23] were used for solving and refining, while graphics were obtained with the Diamond 2.1 software. The collected structures (atomic coordinates) were deposited in the database of the Cambridge Crystallographic Data Centre (http://www.ccdc.cam.ac.uk/).

4.2 General procedure for the preparation of prolinols 2

(*S*)- or (*R*)-Fmoc proline (4.58 g, 13.6 mmol) in anhydrous THF (125 mL) was placed in a round-bottomed flask with magnetic stirrer and under inert atmosphere (N_2). The resulting solution was cooled to 0 °C, before the slow addition of $NaBH_4$ (0.82 g, 21.7 mmol). The reaction mixture was stirred during 60 minutes at 0 °C, and then 3.4 mL (3.85 g, 27.1 mmol) of boron trifluoride diethyl etherate were added dropwise, and stirring was continued for 18 hours at 0 °C. The reaction progress was monitored by TLC (CH_2Cl_2/EtOAc 70:30). Thirty milliliters of water were added at 0 °C and the resulting mixture was stirred for 30 minutes. THF was evaporated *in vacuo*, the remaining aqueous layer was extracted with EtOAc (3 x 100 mL) and the combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography, using gradient CH_2Cl_2:EtOAc (95:5)→(85:15) as eluent. The product (hard gum) was precipitated with cold hexane to obtain a white powder, which was stored at –15 °C.

4.2.1 (S)-(9H-Fluoren-9-yl)methyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate. (S)-Fmoc-prolinol. (*S*)-**2**. The general procedure was followed to obtain 6.3 g (95 % yield) of (*S*)-**2**, mp 86-88 °C. $[\alpha]_D^{25} = -29.4$ (*c* 1.0, $CHCl_3$). IR (cm^{-1}): ν_{max} 3421, 3330, 2947, 2879, 1730, 1672, 1434, 1359, 1130, 1100, 758. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.77 (d, 2H, *J* = 7.5 Hz), 7.60 (d, 2H, *J* = 7.2 Hz), 7.34 (m, 4H), 4.44 (s, 2H), 4.25 (t, 1H, *J* = 6.6 Hz), 3.99 (s, 1H), 3.10-3.80 (m, 5H), 1.50-2.10 (m, 4H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 24.05, 28.28, 47.3, 60.69, 67.50, 120.0, 125.0, 127.10, 127.76, 141.37, 143.9. HR-ESI-TOF Calcd. for $C_{20}H_{22}NO_3$ $[M + H]^+$: 324.1594; found: 324.1593.

4.2.2 (R)-(9H-Fluoren-9-yl)methyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate. (R)-Fmoc-prolinol. (*R*)-**2**. The general procedure was followed with 2.73 g (8.1 mmol) (*R*)-Fmoc proline (50 mL THF), 0.49 g (12.9 mmol) of $NaBH_4$, 2.3 g (16.2 mmol, 2 mL) of boron trifluoride diethyl etherate to obtain 2.39 g (93 % yield) of (*R*)-**2**, mp 86-87 °C. $[\alpha]_D^{25} = +26.3$ (*c* 1, $CHCl_3$). IR (cm^{-1}): ν_{max} 3421, 3328, 2948, 2879, 1703, 1671, 1434, 1359, 1130, 1100, 758,738. NMR data were identical to those recorded for enantiomer (*S*)-**2**. HR-ESI-TOF Calcd. for $C_{20}H_{22}NO_3$ $[M + H]^+$: 324.1594; found: 324.1595.

4.3 General Procedure for the preparation 3

Part 1. Swern oxidation.[24] A solution of 0.3 mL (0.32 g, 4.1 mmol) of anhydrous dimethyl sulfoxide in anhyd. CH_2Cl_2 (15 mL) was placed in a round-bottom flask with magnetic stirrer and under inert atmosphere (N_2). The mixture was cooled at –78 °C, 0.32 mL (0.48 g, 3.7 mmol) of oxalyl chloride was added dropwise and the reaction mixture was stirred during thirty additional minutes at –78 °C. (*S*)- or (*R*)-Fmoc prolinol (0.56 g, 1.7 mmol) of **2** dissolved in anhydrous CH_2Cl_2 (10 mL) was added dropwise and the resulting mixture was stirred for 60 minutes at –78 °C. Triethylamine (1.44 mL, 1.04 g, 10.28 mmol) was added dropwise and the resulting reaction mixture was stirred during 60 minutes at –78 °C and 30 minutes at 0 °C. The organic layer was washed with brine (3 x 25 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to obtain the crude product as an oil. The crude was used immediately in the next step without further purification.

Part 2. Formation of the sulfinimide: In a round bottom flask (50 mL) provided with magnetic stirrer and inert atmosphere was placed 208 mg (1.7 mmol) of (*S*)- or (*R*)-2-methylpropane-2-sulfinamide dissolved in 3 mL of anhydrous dichloromethane. To this solution was added 605 mg (3.8 mmol) of anhydrous $CuSO_4$, followed by the aldehyde previously prepared (part 1) dissolved in 2 mL of dichloromethane. The mixture was stirred at room temperature during 48 hours. TLC CH_2Cl_2:EtOAc 95:5. The reaction mixture was filtered through a celite pad, and the filter cake was washed with dichloromethane. The filtrate was evaporated *in vacuo* and the residue was purified by flash chromatography using CH_2Cl_2:EtOAc 95:5 as eluent. The product (hard gum) was precipitated with cold hexane to obtain a powdery product that was stored at –15 °C.

4.3.1 (S)-(9H-Fluoren-9-yl)methyl 2-{(E)-[((R)-tert-butylsulfinyl)imino]methyl}pyrrolidine-1-carboxylate. (1*S*,2*R*)-**3**. The general procedure describe above was followed with (*S*)-**2** and (*R*)-2-methylpropane-2-sulfinamide, to obtain 617 mg (84% yield) of (1*S*,2*R*)-**3**, mp 126-127 °C. $[\alpha]_D^{25} = -206.4$ (*c* = 1.0, $CHCl_3$). IR (cm^{-1}) ν_{max} 2958, 2889, 2160, 1702, 1451, 1408, 1332, 1113, 1268, 1080, 760. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.9 (t, 1H, *J* = 3.2 Hz), 7.76 (t, 2H, *J* = 7.7 Hz), 7.66-7.50

(m, 2H), 7.48-7.36-7.28 (m, 2H), 4.80-4.70 (m, 0.5H), 4.70-4.60 (m, 0.5H), 4.50-4.38 (m, 1H), 4.36-4.12 (m, 2H), 3.69-3.43 (m, 2H), 2.38-1.77(m, 4H), 1.17 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 168.64, 167.69, 154.84, 154.74, 144.15, 144.03, 143.80, 141.40, 141.29, 127.81, 127.22, 127.16, 125.27, 125.17, 120.07, 67.74, 67.47, 61.18, 60.79, 57.33, 57.11, 47.34, 47.15, 46.53, 30.72, 39.07, 23.99, 23.34, 22.44. HR-ESI-TOF Calcd. for $C_{24}H_{28}N_2O_3S$ [M + H] $^+$: 425.1893; found: 425.1898.

4.3.2 (S)-(9H-Fluoren-9-yl)methyl 2-{(E)-[((S)-tert-butylsulfinyl)imino]methyl}pyrrolidine-1-carboxylate. (1*S*,2*S*)-**3**. The general procedure was followed with 2 g (6.2 mmol) of prolinol (*S*)-**2**, 1.06 mL (1.16 g, 14.8 mmol) DMSO, 1.17 mL (1.73 g, 13.6 mmol) of oxalyl chloride, 5.18 mL (3.73 g, 36.9 mmol) of triethylamine, 0.75 g (6.18 mmol) of (*S*)-2-methylpropane-2-sulfinamide, and 2.17 g (13.6 mmol) of anhyd. $CuSO_4$ to obtain 2.26 g (86% yield) of (1*S*,2*S*)-**3**, mp 99-100 °C. $[\alpha]_D^{25}$ = +42.5 (*c* = 1.0, $CHCl_3$). IR (cm $^{-1}$) ν_{max} 2966, 2879, 2162, 1697, 1450, 1401, 1352, 1326, 1106, 1088, 760. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.94 (t, *J* = 5.2 Hz, 1H), 7.76 (t, *J* = 7.2 Hz, 2H), 7.64-7.50 (m, 2H), 7.45-7.36 (m, 2H), 7.35-7.26 (m, 2H), 4.78-4.60 (m, 1H), 4.52-4.38 (m, 1H), 4.38-4.12 (m, 2H), 3.64-3.44 (m, 2H), 2.26-1.80 (m, 4H), 1.22 (s, 5H), 1.14 (s, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 168.58, 168.41, 154.93, 154.79, 144.11, 144.03, 143.95, 141.41, 141.29, 127.80, 127.25, 123.16, 125.21, 125.15, 120.07, 67.59, 67.46, 60.95, 60.62, 57.35, 57.02, 47.34, 47.02, 46.72, 30.33, 29.56, 24.45, 23.2, 22.60, 22.50. HR-ESI-TOF Calcd. for $C_{24}H_{28}N_2O_3$ S [M + H] $^+$: 425.1893; found: 425.1893.

4.3.3 (R)-(9H-Fluoren-9-yl)methyl 2-{(E)-[((S)-tert-butylsulfinyl)imino]methyl}pyrrolidine-1-carboxylate. (1*R*,2*S*)-**3**. The general procedure describe above was followed with 2.93 g (9.06 mmol) of prolinol (*R*)-2, 1.54 mL (1.7g, 21.7 mmol) of DMSO, 1.71 mL (2.53g, 19.9 mmol) of oxalyl chloride, 7.6 mL (5.46 g, 54 mmol) of triethylamine, 1.01g (8. mmol) of (*S*)-2-methylpropane-2-sulfinamide, and 2.92g (18.3 mmol) of anhyd. $CuSO_4$ to obtain 3.43g (89% yield) of (1*R*,2*S*)-**3**, mp 128-130 °C. $[\alpha]_D^{25}$ = +214.0 (*c* = 1.0, $CHCl_3$). IR (cm^{-1}) ν_{max} 2958, 2889, 2159, 1702, 1408, 1451, 1408, 1333, 1114, 1080, 760. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.94 (t, *J* = 5.0 Hz, 1H), 7.76 (t, *J* = 7.2 Hz, 2H), 7.66-7.50 (m, 2H), 7.44-7.35 (m, 2H), 7.35-7.26 (m, 2H), 4.79-4.61 (m, 1H), 4.55-4.39 (m, 1H), 4.39-4.14 (m, 2H), 3.60-3.45 (m, 2H), 2.30-1.70 (m, 4H), 1.22 (s, 4.75H), 1.13 (s, 4.25H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 168.60, 168.41, 154.93, 154.79, 144.11, 144.03, 141.40, 141.28, 127.80, 127.25, 127.15, 125.20, 125.14, 120.06, 67.59, 67.46, 60.95, 60.61, 57.34, 57.02, 47.35, 47.02, 46.71, 30.32, 29.56, 24.45, 23.21, 22.59, 22.50. HR-ESI-TOF Calcd. for $C_{24}H_{28}N_2O_3$ S [M + H] $^+$: 425.1893; found: 425.1889.

4.3.4 (R)-(9H-Fluoren-9-yl)methyl 2-{(E)-[((R)-tert-butylsulfinyl)imino]methyl}pyrrolidine-1-carboxylate. (1*R*,2*R*)-**3**. The general procedure was followed with 1.91 g (5.9 mmol) of prolinol (*R*)-**2**, 1.0 mL (1.1 g, 14.2 mmol) of DMSO, 1.11 mL (1.65 g, 13 mmol) of oxalyl chloride, 4.95 mL (3.6 g, 35.2 mmol) of triethylamine, 0.72 g (5.9 mmol) (*R*)-2-methylpropane-2-sulfinamide, and 2.1g (13 mmol) of anhyd. $CuSO_4$ to obtain 2.1 g (85% yield) of (1*R*,2*R*)-**3**, mp 126-128 °C. $[\alpha]_D^{25}$ = –42.0 (*c* = 1.0, $CHCl_3$). IR (cm^{-1}) ν_{max} 2957, 2889, 2160, 1701, 1450, 1332, 1113, 1080, 760. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.94 (t, *J* = 5.4 Hz, 1H), 7.76 (t, *J* = 7.2 Hz, 2H), 7.65-7.50 (m, 2H), 7.45-7.36, (m, 2H), 7.36-7.28 (m, 2H), 4.80-4.58 (m, 1H), 4.58-4.40 (m, 1H), 4.40-4.10 (m, 2H), 3.66-3.46 (m, 2H), 2.28-1.80 (m, 4H), 1.22 (s, 5H), 1.14(s, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 168.58, 168.42, 154.93, 154.80, 144.11, 144.03, 143.94, 141.41, 141.28, 127.80, 127.25, 127.16, 125.21, 125.15, 120.0, 67.60, 67.47, 60.95, 60.62, 57.35, 57.02, 47.35, 47.02, 46.71, 30.32, 29.56, 24.44, 23.21, 22.59, 22.50. HR-ESI-TOF Calcd. for $C_{24}H_{28}N_2O_3$S [M + H] $^+$: 425.1893; found: 425.1895.

4.4. General Procedure for the preparation of 4

In a round bottom flask (50 mL) provided with magnetic stirrer, and inert atmosphere, were placed 497 mg (1.17 mmol) of **3** in 15 mL of anhydrous THF. The resulting solution was stirred at 0 °C, then 44.28 mg (1.17 mmol) of $NaBH_4$ was added and 3 mL of methanol were introduced dropwise with stirring at 0 °C during 60 min. TLC ethyl acetate-hexane 80:20. The reaction was quenched with acetone (2 mL), and then 20 mL of saturated aqueous ammonia chloride were added. The organic solvents were evaporated under vacuum at rt, the remaining aqueous phase was extracted with ethyl acetate (3 x 25 mL) and the combined organic fractions were dried over anhydrous Na_2SO_4 filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography using ethyl acetate-hexane 80:20 and pure ethyl acetate. The product (hard gum) was precipitated with cold hexane to obtain a powder, which was stored at –15 °C.

4.4.1 (S)-(9H-Fluoren-9-yl)methyl 2-{[(R)-1,1-dimethylethylsulfinamido]methyl}pyrrolidine-1-carboxylate. (1*S*,2*R*)-**4**. The general procedure was followed with (1*S*,2*R*)-**3** to obtain 429 mg (86% yield) of (1*S*,2*R*)-**4**, mp 102-103 °C. $[\alpha]_D^{25}$ = –63.9 (*c* = 1.0, $CHCl_3$). IR (cm^{-1}) ν_{max} 3199, 2949, 2161, 1696, 1410, 1332, 1114, 1045, 771, 738. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.76 (t, *J* = 7.7 Hz, 2H), 7.60 (d, *J* = 7.4 Hz, 2H), 7.40 (d, *J* = 7.2 Hz, 2H); 7.36-7.26 (m, 2H), 4.62-4.50 (m, 0.6H), 4.48-4.30 (m, 1.4H), 4.30-4.14 (m, 2H), 4.10-3.93 (br, 0.7H), 3.74-3.55 (broad, 0.3H), 3.55-2.80 (m, 4H), 2.10-1.60 (m, 4H), 1.18 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 155.92, 155.0, 144.12, 141.42, 127.80, 127.23, 127.14, 125.16, 124.90, 124.80, 120.09, 67.35, 66.74, 58.65, 57.73, 56.01, 49.43, 47.52, 47.38, 47.31, 46.97, 29.12, 23.96, 22.80, 22.71. HR-ESI-TOF Calcd. for $C_{24}H_{30}N_2O_3S$ [M + H]$^+$: 427.2050; found: 427.2052.

4.4.2 (S)-(9H-Fluoren-9-yl)methyl 2-{[(S)-1,1-dimethylethylsulfinamido]methyl}pyrrolidine-1-carboxylate. (1*S*,2*S*)-**4**. The general procedure was followed with 1.57 g (3.71 mmol) of (1*S*,2*S*)-**3**, 140 mg (3.71 mmol) of $NaBH_4$, 25.0 mL of THF, 5 mL of MeOH, 5 mL of acetone and 20 mL of saturated aqueous ammonium chloride, to obtain 1.45 g (92% yield) of (1*S*,2*S*)-**4**, mp 131-132 °C. $[\alpha]_D^{25}$ = –18.2 (*c* = 1.01, MeOH). IR (cm^{-1}) ν_{max} 3262, 2952, 2160, 1664, 1416, 1332, 1109, 1063, 764, 736. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.6 (d, *J* = 7 Hz, 2H), 7.65-7.53 (m, 2H); 7.45-7.27 (m, 4H), 4.72-4.55 (br, 0.6H), 4.55-4.45 (m, 0.6H), 4.45-4.28 (m, 1.4H), 4.23 (t, *J* = 6.8 Hz, 0.5H), 4.8-3.94 (br, 0.6H), 3.60-3.22 (m, 3H), 3.20-3.02 (m, 0.6H), 3.0-2.58 (m, 0.5H), 2.14-1.66 (m, 5H), 1.21 (s, 6H), 1,18 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 156.11, 154.86, 144.17, 144.05, 127.93, 127.80, 127.48, 127.15, 125.22, 125.14, 124.74, 120.07, 67.45, 66.32, 58.69, 57.93, 55.93, 49.63, 48.07, 47.56, 47.37, 47.01, 29.00. HR-ESI-TOF Calcd. for $C_{24}H_{30}N_2O_3$ S [M + H]$^+$: 427.2050; found: 427.2050.

4.4.3 (R)-(9H-Fluoren-9-yl)methyl 2-{[(S)-1,1-dimethylethylsulfinamido]methyl}pyrrolidine-1-carboxylate. (1*R*,2*S*)-**4**. The general procedure was followed with 1.79 g (4.22 mmol) of (1*R*,2*S*)-**3**, 160 mg (4.22 mmol) of $NaBH_4$, THF 25.0 mL, MeOH 5 mL, 5 mL of acetone and 20 mL of saturated

aqueous ammonium chloride, obtaining 1.48 g (82% yield) of (1*R*,2*S*)-**4**, mp 128-130 °C. $[\alpha]_D^{25}$ = +61.9 (*c* = 1.0, $CHCl_3$). IR (cm^{-1}) ν_{max} 3190, 2949, 2163, 1696, 1411, 1333, 1114, 1043, 739. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.77 (d, *J* = 7.7 Hz, 2H), 7.64-7.53 (m, 2H); 7.40 (t, *J* = 7.4 Hz, 2H), 7.36-7.28 (m, 2H), 4.62-4.32 (m, 2H), 4.28-3.96 (m, 2H), 3.78-3.38 (m, 2H), 3.38-2.86 (m, 2H), 2.10-1.70 (m, 5H), 1.2 (s, 1H), 1.18 (s, 8H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 155.94, 155.06, 144.12, 141.42, 127.80, 127.24, 127.13, 125.16, 124.91, 124.80, 120.09, 67.35, 66.74, 58.65, 57.72, 56.03, 49.45, 47.52, 47.37, 46.97, 29.13, 23.96, 23.06, 22.80, 22.22. HR-ESI-TOF Calcd. for $C_{24}H_{30}N_2O_3S$ $[M+H]^+$: 427.2050; found: 427.2044.

4.4.4 (R)-(9H-Fluoren-9-yl)methyl 2-{[(R)-1,1-dimethylethylsulfinamido]methyl}pyrrolidine-1-carboxylate. (1*R*,2*R*)-**4**. The general procedure was followed with 0.77 g (1.81 mmol) of (1*R*,2*R*)-**3**, 68.6 mg (1.81 mmol) of $NaBH_4$, 20 mL of THF, 4 mL of MeOH, 4 mL of acetone and 20 mL of saturated aqueous ammonium chloride, to obtain 634 mg (82% yield) of (1*R*,2*R*)-**4**, mp 128- 130 °C. $[\alpha]_D^{25}$ = +17.4 (*c* = 1.0, MeOH). IR (cm^{-1}) ν_{max} 3263, 2953, 2159, 1684, 1416, 1332, 1110, 1063, 736. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.87-7.70 (m, 2H), 7.66-7.52 (m, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.37-7.30 (m, 2H), 4.70-4.56 (br, 0.6 H), 4.55-4.28 (m, 2H), 4.23 (t, *J* = 7 Hz, 1H), 4.08-3.94 (br, 0.6H), 3.57-3.21 (m, 3H), 3.13-3.10 (m, 0.6H), 3.10-2.90 (m, 0.3H), 2.88-2.78 (m, 0.3H), 2.72-2.56 (m, 0.3H), 2.10-1.65 (m, 4.7H), 1.21 (s, 6H), 1.18 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 156.12, 154.85, 144.16, 144.04, 141.58, 141.42, 127.80, 127.49, 127.15, 125.22, 125.14, 124.75, 120.07, 67.45, 66.31, 58.69, 57.92, 55.94, 49.65, 48.06, 47.55, 47.36, 47.01, 29.60, 29.05, 24.00, 22.86, 22.76. HR-ESI-TOF Calcd. for $C_{24}H_{30}N_2O_3S$ $[M+H]^+$: 427.2050; found: 427.2050.

4.5 General procedure for the preparation of organocatalysts 5

1.8 g (4.2 mmol) of **4** dissolved in 20 mL of anhydrous THF were placed in a round bottom flask (100 mL) provided with magnetic stirrer and inert atmosphere. The solution was stirred at rt before the addition of 4.4 mL (3.1g, 42.2 mmol) of Et_2NH, and stirring was continued during 2 h. The reaction was monitored by TLC with ethyl acetate as eluent. If the starting material was not consumed after 2 h, additional 10 equiv. of Et_2NH was added; however, the reaction time should not exceed 5 h because of product decomposition. The mixture was concentrated under vacuum and the residue was purified by flash chromatography using pure methylene chloride, then methylene chloride-methanol 95:5, 100% methanol and finally methanol-NH_4OH_{aq} 95:5.

4.5.1 (R)-2-Methyl-N-[(S)-pyrrolidin-2-ylmethyl]propane-2-sulfinamide. (1*S*,2*R*)-**5**. The general procedure was followed with (1*S*,2*R*)-**4** to obtain 450 mg (52% yield) of (1*S*,2*R*)-**5** as an oil. $[\alpha]_D^{25}$ = –37.8 (*c* = 1.0, $CHCl_3$). IR (cm^{-1}) ν_{max} 3422, 3214, 2954, 2868, 1457, 1405, 1364, 1044, 795. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.14-4.2 (br, 1H), 3.45-3.34 (m, 1H), 3.29,-3.16 (m, 1H), 3.12-3.10 (br, 1H), 2.99-2.85 (m, 3H), 1.98-1.63 (m, 3H), 1.44-1.31 (m, 1H), 1.19 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 58.87, 55.98, 50.62, 46.39, 28.90, 25.79, 22.80. HR-ESI-TOF Calcd. for $C_9H_{20}N_2OS$ $[M + H]^+$: 205.1369; found: 205.1369.

4.5.2 (S)-2-Methyl-N-[(S)-pyrrolidin-2-ylmethyl]propane-2-sulfinamide. (1*S*,2*S*)-**5**. The general procedure was followed with 1.2 g (2.8 mmol) of (1*S*,2*S*)-**4**, 2.90 mL (2.05g, 28 mmol) of Et_2NH, and 20 mL of THF, to obtain 402 mg (70% yield) of (1*S*,2*S*)-**5** as an oil. $[\alpha]_D^{25}$ = +89.8 (*c* = 1.0, $CHCl_3$). IR (cm^{-1}) ν_{max} 3438, 3193, 2955, 2867, 1456, 1407, 1363, 1048, 731. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.30-4.21 (br, 1H), 4.11 (s, 1H), 3.44-3.32 (m, 1H), 3.22-3.06 (m, 2H), 3.04-2.09 (m, 2H), 1.97-1.65 (m, 3H), 1.51-1.38 (m, 1H), 1.19 (s, 8H), 1.66 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 59.22, 55.97, 49.72, 46.04, 29.03, 25.31, 22.83. HR-ESI-TOF Calcd. for $C_9H_{20}N_2OS$ $[M + H]^+$: 205.1369; found: 205.1370.

4.5.3 (S)-2-Methyl-N-[(R)-pyrrolidin-2-ylmethyl]propane-2-sulfinamide. (1*R*,2*S*)-**5**. The general procedure described above was followed with 1.48 g (3.5 mmol) of (1*R*,2*S*)-**4**, 3.6 mL (2.6 g, 35 mmol) of Et_2NH, and 20 mL of THF to obtain 481 mg (68% yield) of (1*R*,2*S*)-**5** as an oil. $[\alpha]_D^{25}$ = +38.5 (*c* = 1.0, $CHCl_3$). IR (cm^{-1}) ν_{max} 3420, 3210, 2954, 2867, 1457, 1399, 1363, 1046, 731. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.33-4.14 (br, 1H), 3.77-3.50 (br, 1H), 3.47-3.35 (m, 1H), 3.32-3.15 (m, 1H), 3.03-2.85 (m, 3H), 1.90-1.64 (m, 3H), 1.45-1.32 (m, 1H), 1.19 (s, 7.5H), 1.17 (s, 1.5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 58.94, 56.01, 50.39, 46.24, 28.84, 25.70, 22.79. HR-ESI-TOF Calcd. for $C_9H_{20}N_2OS$ $[M + H]^+$: 205.1369; found: 205.1371.

4.5.4 (R)-2-Methyl-N-[(R)-pyrrolidin-2-ylmethyl]propane-2-sulfinamide. (1*R*,2*R*)-**5**. The general procedure was followed with 0.634 g (1.48 mmol) of (1*R*,2*R*)-**4**, 1.5 mL (1.09g, 14.8 mmol) of Et_2NH, and 10 mL of THF to obtain 212 mg (70% yield) of (1*R*,2*R*)-**5** as an oil. $[\alpha]_D^{25}$ = +87.7 (*c* = 1.0, $CHCl_3$). IR (cm^{-1}) ν_{max} 3426, 3204, 2954, 2868, 1458, 1406, 1363, 1045, 795. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.13-3.98 (br, 1H), 3.72-3.48 (br, 1H), 3.36-3.20 (m, 1H), 3.17-3.02 (m, 2H), 2.98-2.86 (m, 2H), 1.97-1.63 (m, 3H), 1.47-1.33 (m, 1H), 1.19 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 59.04, 55.83, 50.02, 46.17, 29.21, 25.53, 22.80. HR-ESI-TOF Calcd. for $C_9H_{20}N_2OS$ $[M + H]^+$: 205.1369; found: 205.1373.

4.6 Procedure for the *N*-benzylation of (1*S*,2*S*)-5 to obtain its crystalline derivative (1*S*,2*S*)-6

In a round bottom flask (25 mL) provided with magnetic stirrer, and argon atmosphere, were placed 163 mg (0.8 mmol) of (1*S*,2*S*)-**5** and the content was dissolved with 10 mL of anhydrous THF. The solution was cooled at 0 °C and 0.123 mL (88.8 mg, 1.1 equiv.) of triethylamine were added, later stirring during 10 min and subsequently adding 0.094 mL (135 mg, 1 equiv.) of benzyl bromide. The reaction mixture was left at room temperature during 18 h, and after this lapse, 20 mL of saturated solution of ammonium chloride were added to quench the reaction. The resulting biphasic mixture was extracted twice with 15 mL of EtOAc, the combined organic phases were dried with Na_2SO_4, filtrated and concentrated under reduced pressure. The crude was purified by column chromatography using a gradient starting from 100% ethyl acetate to EtOAc:MeOH (90:10). The expected product was recrystallized from ethyl acetate-heptane, so it was obtained 164 mg of (1*S*,2*S*)-**6**, corresponding to 70% isolated yield, mp 71-73 °C. $[\alpha]_D^{25}$ = –20.2 (*c* = 1.0, MeOH). IR (cm^{-1}) ν_{max} 3204, 2921, 2866, 2774, 1453, 1362, 1052, 919, 823, 738, 697, 597. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.23-7.34 (m, 5H), 3.98 (d, *J* = 13.2 Hz, 1H), 3.88-3.80 (m, 1H), 3.39 (d, *J* = 13.2 Hz, 1H), 3.26-3.10 (m, 2H), 3.00-2.93 (m, 1H), 2.81-2.74 (m, 1H), 2.32-2.24 (m, 1H), 2.02-1.90 (m, 1H), 1.82-1.68 (m, 3H), 1.27 (s, 1H), 1.21 (s, 9H). ^3C NMR ($CDCl_3$, 100 MHz) δ (ppm): 128.62, 128.34, 126.99, 63.74, 59.12, 55.85, 54.33, 47.75, 28.54, 22.98, 22.78. HR-ESI-TOF Calcd. For $C_{16}H_{27}N_2OS$ $[M + H]^+$: 295.1839; found: 295.1842. Crystal data for (1*S*,2*S*)-**6**:

$C_{16}H_{26}N_2OS$, orthorhombic, space group $P2_12_12_1$, Z = 4, a = 5.6850(0) Å, b = 14.7770(0) Å, c = 20.7670(0) Å, α = β = γ = 90°, V = 1744.58(0) Å^3, crystal size: 0.35 x 0.2 x 0.08 mm^3, R_1 = 0.0498 (wR_2 = 0.1517). CCDC 000000 contains de supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

4.7 General procedure for the Michael addition reaction.

The organocatalyst (10.2 mg, 10 mol-%) was mixed with 0.2 mL (0.197 g, 2 mmol) of cyclohexanone. The mixture was stirred for 15 min, before the addition of *trans*-*β*-nitrostyrene (0.5 mmol) and the additive (acid, 10 mol %). Stirring was continued for 24 h and the crude product was purified by flash chromatography using hexane-EtOAc (8:2) or CH_2Cl_2.

4.7.1 (R)-2-[(S)-2-Nitro-1-phenylethyl]cyclohexanone. (1*R*,2*S*)-**7a**. mp 128-130 °C. $[\alpha]_D^{25}$ = +19.1 (*c* = 1.0, $CHCl_3$). IR (cm^{-1}) ν_{max} 2955, 1704, 1548, 1477, 1434, 1378, 1293, 1129, 1037, 887, 753, 688. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.34-7.24 (m, 3H), 7.2-7.4 (m, 2H), 3.76 (ddd, *J* = 10.2, 10.0, 4.5 Hz, 1H), 2.68 (ddd, *J* = 10.9. 11.2, 5.2 Hz, 1H), 2.52-2.34 (m, 2H), 2.15-2.01 (m, 1H), 1.82-1.15 (m, 4H), 1.30-1.15 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 212.11, 137.84, 128.45, 128.27, 127.87, 79.0, 52.61, 44.03, 42.87, 33.34, 28.65, 25.14. HPLC: [Chiralpak AD-H column, 210 nm, *n*-Hexane/*i*PrOH 90:10, *U* = 0.5 mL/min]: t_R(major *syn*) = 17.1 min, t_R(minor *syn*) = 20.5 min. Optical rotation, melting point and spectroscopic data are consistent with those reported in the literature.[25]

4.7.2 (R)-2-[(S)-1-(2-Chlorophenyl)-2-nitroethyl]cyclohexanone. (1*R*,2*S*)-**7b**. mp 64-66 °C. $[\alpha]_D^{25}$ = +45.3 (*c* = 1.0, $CHCl_3$). IR (cm^{-1}) ν_{max} 2941, 1704, 1548, 1477, 1434, 1378, 1293, 1129, 1037, 883, 753, 688. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.41-7.35 (m, 1H), 7.28-7.18 (m, 3H), 4.90 (m, 3H), 4.90 (m, 2H), 4.36-4.23 (m, 1H), 3.01-2.82 (m, 1H), 2.51-2.31 (m, 2H), 2.13,-2.2 (m, 1H), 1.86-1.53 (m, 4H), 1.42-1.26 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 211.80, 135.51, 134.63, 130.46, 129.56, 128.00, 127.49, 77.30, 51.80, 42.93, 41.07, 33.15, 28.64, 24.37. HPLC: [Chiralpak AD-H column, 210 nm, *n*-Hexane/*i*PrOH = 95:5, *U* = 0.5 mL/min]: t_R(major *syn*) = 22.5 min, t_R(minor *syn*) = 36.0 min. Optical rotation, melting point and spectroscopic data are in accordance with those values reported in the literature.[25]

4.7.3 (R)-2-[(S)-1-(2-Methoxyphenyl)-2-nitroethyl]cyclo-hexanone. (1*R*,2*S*)-**7c**. mp 118-120 °C. $[\alpha]_D^{25}$ = +32.1 (*c* = 1.0, $CHCl_3$). IR (cm^{-1}) ν_{max} 2939, 1702, 1544, 1493, 1432, 1379, 1297, 1244, 1123, 1023, 755, 641. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.31-7.14 (m, 1H), 7.08 (d, *J* = 7.2 Hz, 1H), 6.87 (t, *J* = 8.1, 2H), 4.88-4.76 (m, 2H), 3.95 (ddd, *J* = 10.0, 9.0, 5.0 Hz, 1H), 3.88 (s, 3H), 2.97 (ddd, *J* = 11.5, 11.0, 5.0 Hz, 1H), 2.54-2.22 (m, 2H), 2.12-1.98 (m, 1H), 1.86-1.38 (m, 4H), 1.28-1.08 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 210.0, 157.72, 131.16, 129.06, 125.45, 121.0, 111.12, 77.60, 55.49, 50.70, 42.85, 41.45, 33.43, 28.68, 25.29. HPLC: [Chiralpak AS-H column, 210 nm, *n*-Hexane/*i*PrOH 90:10, *U* = 0.5 mL/min]: t_R(major *syn*) = 24.3 min, t_R(minor *syn*) = 24.6 min. Optical rotation, melting point and spectroscopic data are congruent with values reported in the literature.[26]

4.7.4 (R)-2-[(S)-1-(2-Bromophenyl)-2-nitroethyl]cyclohexanone. (1*R*,2*S*)-**7d**. mp 68-70 °C. $[\alpha]_D^{25}$ = +40.8 (*c* = 1.0, $CHCl_3$). IR (cm^{-1}) ν_{max} 2937, 1699, 1547, 1471, 1434, 1378, 1132, 1059, 1024, 885, 771, 753, 662. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.57 (m, 1H), 7.33-7.02 (m, 3H), 5.02-4.72 (m, 2H), 4.30 (br, 1H), 2.89 (br, 1H), 2.54-2.26 (m, 2H), 2.18-2.00 (m, 1H), 1.94-1.50 (m, 4H), 1.48-1.30 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 210.0, 137.32, 133.79, 129.23, 129.05, 77.46, 52.48, 42.95, 33.14, 28.64, 25.41. HPLC: [Chiralpak AD-H column, 210 nm, *n*-Hexane/*i*PrOH 98:2, *U* = 0.5 mL/min]: t_R(major *syn*) = 37.9 min, t_R(minor *syn*) = 63.3 min. Optical rotation, melting point and spectroscopic data are consistent with those reported in the literature.[25]

4.7.5 (R)-2-[(S)-1-(4-Methoxyphenyl)-2-nitroethyl] cyclohexanone. (1*R*,2*S*)-**7e**. mp 152-154 °C. $[\alpha]_D^{25}$ = +17.0 (*c* = 1.0, $CHCl_3$). IR (cm^{-1}) ν_{max} 2931, 1699, 1551, 1514, 1390, 1292, 1255, 1181, 1130, 1026, 830, 728, 649. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.12-7.07 (m, 2H), 6.88-6.82 (m, 2H), 4.91 (dd *J* = 12.4, 4.5 Hz, 1H), 4.57 (dd, *J* = 12.3, 10 Hz, 1H), 3.77 (s, 3H), 3.71 (ddd, *J* = 9.9, 10.1, 4.5 Hz, 1H), 2.68-2.58 (m, 1H), 2.52-2.32 (m, 2H), 2.14, 1.98 (m, 1H), 1.82-1.48 (m, 4H), 1.30-1.12 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 210.0, 160.0, 129.61, 129.27, 114.38, 80.0, 55.32, 53.90, 52.76, 43.30, 42.84, 33.26, 28.64, 25.11. HPLC: [Chiralpak AD-H column, 210 nm, *n*-Hexane/*i*PrOH 90:10, *U* = 0.5 mL/min]: t_R(major *syn*) = 22.3 min, t_R(minor *syn*) = 27.9 min. Optical rotation, melting point and spectroscopic data are congruent with the previously reported values.[4c]

4.7.6 (R)-2-[(S)-2-Nitro-1-(p-tolyl)ethyl]cyclohexanone. (1*R*,2*S*)-**7f**. mp 122-124 °C. $[\alpha]_D^{25}$ = +21.8 (*c* = 1.0, $CHCl_3$). IR (cm^{-1}) ν_{max} 2932, 1698, 1550, 1516, 1384, 1313, 1130, 1015, 884, 818, 636. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.16-6.98 (m, 4H), 4.92 (dd, *J* = 12.4, 4.5 Hz, 1H), 4.6 (dd, *J* = 12.3, 10 Hz, 1H) 3.72 (ddd, *J* = 9.9, 9.9, 4.5 Hz, 1H), 2.72-2.58 (m, 1H), 2.51-2.34 (m, 2H), 2.3 (s, 3H), 2.12-1.98 (m, 1H), 1.82-1.44 (m, 4H), 1.32-1.10 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 210.0, 137.53, 134.68, 129.72, 128.31, 79.13, 52.65, 43.67, 42.85, 33.31, 28.66, 25.11, 21.17. HPLC: [Chiralpak AD-H column, 210 nm, *n*-Hexane/*i*PrOH = 90:10, *U* = 0.5 mL/min]: t_R(major *syn*) = 15.0 min, t_R(minor *syn*) = 18.9 min. Optical rotation, melting point and spectroscopic data are consistent with those values reported in the literature.[25]

4.7.7 (R)-2-[(S)-1-(4-Chlorophenyl)-2-nitroethyl]cyclohexanone. (1*R*,2*S*)-**7g**. mp 101-103 °C. $[\alpha]_D^{25}$ = +20.4 (*c* = 1.0, $CHCl_3$). IR (cm^{-1}) ν_{max} 2947, 1697, 1552, 1491, 1385, 1311, 1198, 1130, 1099, 1013, 833, 825, 785, 666. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.32-7.25 (m, 2H), 7.14-7.08 (m, 2H), 4.94 (dd, *J* = 12.5, 10 Hz, 1H), 4.59 (dd, *J* = 12.5, 10 Hz, 1H), 3.75 (ddd, *J* = 10, 9.8, 4.5 Hz, 1H), 2.69-2.58 (m, 1H), 2.50-2.32, (m, 2H), 2.14-2.0 (m, 1H), 1.84-1.48 (m, 4H), 1.28-1.16 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 211.0, 136.38, 133.71, 129.66, 129.24, 78.67, 52.48, 43.46, 42.86, 33.28, 28.55, 25.17. HPLC: [Chiralpak AD-H column, 210 nm, *n*-Hexane/*i*PrOH 90:10, *U* = 0.5 mL/min]: t_R (major *syn*) = 20.5 min, t_R(minor *syn*) = 30.1 min. Optical rotation, melting point and spectroscopic data are in accord with those reported in the literature.[25]

4.7.8 (R)-2-[(S)-1-(4-Fluorophenyl)-2-nitroethyl]cyclohexanone. (1*R*,2*S*)-**7h**. mp 68-70 °C. $[\alpha]_D^{25}$ = +19.6 (*c* = 1.0, $CHCl_3$). IR (cm^{-1}) ν_{max} 2934, 1702, 1551, 1511, 1381, 1310, 1225, 1160, 1130, 1109, 1013, 832, 730, 648. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.18-7.12 (m, 2H), 7.4-6.96 (m, 2H), 4.94 (dd, *J* = 12.4. 4.5 Hz, 1H), 4.58 (dd, *J* = 12.6, 10.2 Hz, 1H), 3.76 (ddd, *J* = 10, 10, 4.5 Hz, 1H), 2.68-2.58 (m, 1H), 2.52-2.43 (m, 1H), 2.44-2.32 (m, 1H), 2.14-2.0 (m, 1H), 1.83-1.50 (m, 4H), 1.28-1.14 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 211.0, 162.23 (d, *J* = 245.5 Hz), 129.86 (d, *J* = 8.4 Hz), 116.0 (d, *J* = 21.4 Hz), 78.94, 52.61, 43.34, 42.85, 33.27, 28.57, 25.15. HPLC: [Chiralpak AS-H

column, 210 nm, *n*-Hexane/*i*PrOH 95:5, *U* = 0.5 mL/min]: t_R(major *syn*) = 52.8 min, t_R(minor *syn*) = 81.3 min. Optical rotation, melting point and spectroscopic data are consistent with those reported in the literature.[25]

4.7.9 (S)-2-[(R)-2-Nitro-1-phenylethyl]cyclohexanone. (1*S*,2*R*)-**7a**. mp 126-128 °C. $[\alpha]_D^{25}$ = –16.7 (*c* = 1.0, $CHCl_3$). IR (cm^{-1}) ν_{max} 2955, 1697, 1548, 1449, 1384, 1313, 1129, 1013, 791, 746, 695, 641, 559. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.35-7.23 (m, 3H), 7.20-7.14 (m, 2H), 4.94 (dd, *J* = 12.6, 4.9 Hz, 1H), 4.57 (dd, *J* = 12.5, 10 Hz, 1H), 3.76 (ddd, *J* = 10, 10, 4.5 Hz, 1H), 2.51-2.44 (m, 1H), 2.44-2.36 (m, 1H), 2.14-2.01 (m, 1H), 1.81-1.48 (m, 4H), 1.31-1.12 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 210.0, 137.8, 129.0, 128.27, 79.0, 52.61, 44.04, 42.86, 33.33, 28.65, 25.14. HPLC: [Chiralpak AD-H column, 210 nm, *n*-Hexane/iPrOH 90:10, *U* = 0.5 mL/min]: t_R(minor *syn*) = 18.3 min, t_R(major *syn*) = 22.7 min.

4.7.10 (S)-2-[(R)-1-(2-Chlorophenyl)-2-nitroethyl]cyclohexanone. (1*S*,2*R*)-**7b**. mp 65-67 °C. $[\alpha]_D^{25}$ = –36.3 (*c* = 1.0, $CHCl_3$). IR (cm^{-1}) ν_{max} 2941, 1699, 1544, 1432, 1378, 1294, 1188, 1129, 1059, 1038, 753, 688. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.41-7.34 (m, 1H), 7.28-7.13 (m, 3H), 4.89 (d, *J* = 6.7 Hz, 2H), 4.33-4.18 (br, 1H), 3.0-2.73 (br, 1H), 2.52-2.22 (m, 2H), 2.13-1.97 (m, 1H), 1.82-1.48 (m, 4H), 1.42-1.18 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 210.0, 135.5, 134.6, 130.45, 129.51, 129.0, 127.48, 76.82, 51.75, 42.93, 41.05, 33.15, 28.63, 25.37. HPLC: [Chiralpak AD-H column, 210 nm, *n*-Hexane/*i*PrOH 90:10, *U* = 0.5 mL/min]: t_R(minor *syn*) = 22.4 min, t_R(major *syn*) = 35.1 min.

4.7.11 (S)-2-[(R)-1-(2-Methoxyphenyl)-2-nitroethyl]cyclohexanone. (1*S*,2*R*)-**7c**. mp 116-118 °C. $[\alpha]_D^{25}$ = –26.8 (*c* = 1.0, $CHCl_3$). IR (cm^{-1}) ν_{max} 2938, 1701, 1542, 1494, 1432, 1378, 1245, 1123, 1023, 755, 641. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.30-7.22 (m, 1H), 7.12-7.06 (m, 1H), 6.92-6.84 (m, 2H), 4.90-4.78 (m, 2H), 4.06-3.90 (m, 1H), 3.82 (s, 3H), 3.04-2.98 (m, 1H), 2.52-2.34 (m, 2H), 2.14-2.0 (m, 1H), 1.82-1.50 (m, 4H), 1.28-1.18 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 210.0, 157.71, 131.17, 129.06, 125.44, 121.01, 111.11, 77.59, 55.50, 50.69, 42.85, 41.44, 33.42, 28.68, 25.30. HPLC: [Chiralpak AS-H column, 210 nm, *n*-Hexane/*i*PrOH 90:5, *U* = 0.5 mL/min]: t_R(minor *syn*) = 25.7 min, t_R(major *syn*) = 29.7 min.

4.7.12 (S)-2-[(R)-1-(2-Bromophenyl)-2-nitroethyl]cyclohexanone. (1*S*,2*R*)-**7d**. mp 72-74 °C. $[\alpha]_D^{25}$ = –36.6 (*c* = 1.0, $CHCl_3$). IR (cm^{-1}) ν_{max} 2939, 1701, 1547, 1471, 1434, 1378, 1132, 1024, 885, 753, 719, 661. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.57 (d, *J* = 8 Hz, 1H), 7.35-7.25 (m, 1H), 7.25-7.18 (m, 1H), 7.17-7.09 (m, 1H), 5.0-4.84 (m, 2H), 4.4-4.27 (br, 1H), 3.02-2.80 (br, 1H), 2.58-2.32 (m, 2H), 2.18-2.04 (m, 1H), 1.96-1.52 (m, 4H), 1.48-1.30 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 210.00, 137.32, 133.94, 133.80, 128.12, 77.46, 52.31, 42.96, 33.14, 28.65, 25.41. HPLC: [Chiralpak AD-H column, 210 nm, *n*-Hexane/*i*PrOH 98:2, *U* = 0.5 mL/min]: t_R(minor *syn*) = 39.0 min, t_R(major *syn*) = 65.3 min.

4.7.13 (S)-2-[(R)-1-(4-Methoxyphenyl)-2-nitroethyl]cyclohexanone. (1*S*,2*R*)-**7e**. mp 130-132 °C. $[\alpha]_D^{25}$ = –15.5 (*c* = 1.0, $CHCl_3$). IR (cm^{-1}) ν_{max} 2951, 1699, 1551, 1514, 1390, 1292, 1254, 1181, 1130, 1026, 830, 728, 560. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.12-7.04 (m, 2H), 6.88-6.78 (m, 2H), 4.91, (dd, *J* = 12.3, 4.6 Hz, 1H), 4.57 (dd, *J* = 12.3, 10 Hz, 1H), 3.71 (ddd, *J* = 9.9, 9.9, 4.5 Hz, 1H), 2.52-2.30 (m, 2H), 2.12-1.98 (m, 1H), 1.81-1.48 (m, 4H), 1.31-1.14 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 210.0, 159.09, 129.6, 129.26, 114.38, 114.18, 77.47, 55.32, 52.76, 43.30, 42.69, 33.26, 28.64, 25.11. HPLC: [Chiralpak AD-H column, 210 nm, *n*-Hexane/iPrOH 90:10, *U* = 0.5 mL/min]: t_R(minor *syn*) = 22.9 min, t_R(major *syn*) = 28.9 min.

4.7.14 (S)-2-[(R)-2-Nitro-1-(p-tolyl)ethyl]cyclohexanone. (1*S*,2*R*)-**7f**. mp 114-116 °C. $[\alpha]_D^{25}$ = –16.1 (*c* = 1.0, $CHCl_3$). IR (cm^{-1}) ν_{max} 2940, 1698, 1551, 1445, 1385, 1312, 1198, 1129, 1065, 817, 773, 636, 586. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.12 (d, *J* = 7.7 Hz, 2H), 7.05 (d, *J* = 8.1 Hz, 2H), 4.92 (dd, *J* = 12.4, 4.5 Hz, 1H), 3.72 (ddd, *J* = 10, 10, 4.5 Hz, 1H), 2.52-2.43 (m, 1H), 2.43-2.33 (m, 1H), 2.31 (s, 3H), 2.13-2.02 (m, 1H), 1.82-1.5 (m, 4H), 1.32-1.13 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 210.0, 137.54, 134.69, 129.71, 128.32, 79.13, 52.66, 43.68, 42.85, 33.30, 28.65, 25.11, 21.17. HPLC: [Chiralpak AD-H column, 210 nm, *n*-Hexane/*i*PrOH 90:10, *U* = 0.5 mL/min]: t_R(minor *syn*) = 15.2 min, t_R(major *syn*) = 19.23 min.

4.7.15 (S)-2-[(R)-1-(4-Chlorophenyl)-2-nitroethyl]cyclohexanone. (1*S*,2*R*)-**7g**. mp 96-98 °C. $[\alpha]_D^{25}$ = –13.1 (*c* = 1.0, $CHCl_3$). IR (cm^{-1}) ν_{max} 2941, 1698, 1552, 1492, 1384, 1310, 1196, 1130, 1099, 1014, 823, 785, 644. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.32-7.26 (m, 2H), 7.15-7.08 (m, 2H), 4.94 (dd, *J* = 12.5, 4.5 Hz, 1H), 4.59 (dd, *J* = 12.5, 10 Hz, 1H), 3.76 (ddd, *J* = 9.9, 9.9, 4.5 Hz, 1H), 2.75-2.60 (m, 1H), 2.52-2.44 (m, 1H), 2.44-2.30 (m, 1H), 2.15-2.02 (m, 1H), 1.84-1.5 (m, 4H), 1.28-1.14 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 211.7, 136.38, 133.7, 129.6, 129.25, 78.7, 52.49, 43.46, 42.86, 33.28, 28.5, 25.10. HPLC: [Chiralpak AD-H column, 210 nm, *n*-Hexane/*i*PrOH 90:10, *U* = 0.5 mL/min]: t_R(minor *syn*) = 20.9 min, t_R(major *syn*) = 31.2 min.

4.7.16 (S)-2-[(R)-1-(4-Fluorophenyl)-2-nitroethyl]cyclohexanone. (1*S*,2*R*)-**7h**. mp 62-64 °C. $[\alpha]_D^{25}$ = –14.2 (*c* = 1.0, $CHCl_3$). IR (cm^{-1}) ν_{max} 2928, 1699, 1549, 1511, 1383, 1237, 1160, 1129, 1014, 832, 730, 558. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.20-7.12 (m, 2H), 7.06-6.93 (m, 2H), 4.93 (dd, *J* = 12.5, 4.5 Hz, 1H), 4.59 (dd, *J* = 12.5, 10 Hz, 1H), 3.76 (ddd, *J* = 9.9, 9.9, 4.5 Hz, 1H), 2.72-2.58 (m, 1H), 2.52-2.43 (m, 1H), 2.42-2.32, (m, 1H), 2.14-2.02 (m, 1H), 1.84-1.50 (m, 1H), 1.30-1.16, (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 210.0, 162.2 (d, *J* = 245.5 Hz), 133.56, 129.86 (d, *J* = 8.4 Hz), 116.0 (*J* = 21.4 Hz), 80.0, 52.63, 43.35, 42.86, 33.27, 28.58, 25.16. HPLC: [Chiralpak AS-H column, 210 nm, *n*-Hexane/*i*PrOH 95:5, *U* = 0.5 mL/min]: t_R(minor *syn*) = 55.4 min, t_R(major *syn*) = 81.2 min.

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Supplementary Material

Supplementary data associated with this article can be found in the online version.

References and notes

1. Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600-3740.

2. See, for example: Dinér, P.; Sadhukhan, A.; Blomkvist B. *ChemCatChem* **2014**, *6*, 3063-3066.
3. (a) Wu, X.; Li, Y.; Wang, C.; Zhou, L.; Lu, X.; Sun J. *Chem. Eur. J.* **2011**, *17*, 2846-2848. (b) Wang, C.; Wu, X.; Zhou, L; Sun J. *Chem. Eur. J.* **2008**, *14*, 8789-8792.
4. (a) Holland, M. C.; Gilmour, R. *Angew. Chem., Int. Ed.* **2015**, *54*, 3862-3871. (b) Panday, S. K. *Tetrahedron: Asymmetry* **2011**, *22*, 1817-1847. (c) Wang, J.; Li, H.; Lou, B.; Zu, L.; Guo, H.; Wang, W. *Chem. Eur. J.* **2006**, *12*, 4321-4332. (d) Cao, C.-L.; Ye, M.-C.; Sun, X.-L.; Tang, Y. *Org. Lett.* **2006**, *8*, 2901-2904. (e) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold J. B.; Ley S. V. *Org. Biomol. Chem.* **2005**, *3*, 84-96. (f) Vega-Peñaloza, A.; Sánchez-Antonio, O.; Avila-Ortiz, C. G.; Escudero-Casao, M.; Juaristi. E. *Asian J. Org. Chem.* **2014**, *3*, 487-496.
5. Aldol reaction: (a) Wang, W.; Li, H.; Wang, J. *Tetrahedron Lett.* **2005**, *46*, 5077-5079. (b) Trost, B. M.; Brindle, C. S. *Chem. Soc. Rev.* **2010**, *39*, 1600-1632. Mannich reaction: (c) Wang, W.; Wang, J.; Li, H. *Tetrahedron Lett.* **2004**, *45*, 7243-7246. (d) α-Aminoxylation: Wang, W.; Wang, J.; Liao, H. L. *Tetrahedron Lett.* **2004**, *45*, 7235-7238. Michael reaction: (e) Aitken, L. S.; Arezki, N. R.; Dell'Isola, A.; Cobb, A. J. A. *Synthesis* **2013**, *45*, 2627-2648. (f) Wang, W.; Wang, J.; Li, H. *Angew. Chem. Int. Ed.* **2005**, *44*, 1369-1371. (g) Wang, J.; Li, H.; Lou, B.; Zu, L.; Guo, H.; Wang W. *Chem. Eur. J.* **2006**, *12*, 4321-4332.
6. Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Tetrahedron* **2011**, *67*, 4412-4416.
7. Wan, W.; Gao, W.; Ma, G.; Ma, L.; Wang, F.; Wang, J.; Jiang, H.; Zhu, S.; Hao, J. *RSC Advances* **2014**, *4*, 26563-26568.
8. Wang, M.; Wang, C.; Lu, X.-X., Sun, J. *Hecheng Huaxue*, **2011**, *19*, 7-10. The accessible experimental information in this paper is very limited.
9. Hernández J. G., Juaristi E. *Chem. Commun.*, **2012**, *48*, 5396-5409.
10. Patora-Komisarska, K.; Benohoud, M.; Ishikawa, H.; Seebach, D.; Hayashi, Y. *Helv. Chim. Acta* **2011**, *94*, 719-745.
11. Compare: Ávila-Ortiz, C. G.; López-Ortiz, M.; Vega-Peñaloza, A.; Regla, I.; Juaristi, E. *Asymmetric Catal.* **2015**, *2*, 37-44.
12. Neither matching effect nor double stereoinduction was observed. For salient papers on double stereoinduction in asymmetric catalysis, see: (a) Binder, C. M.; Bautista, A.; Zaidlewicz, M.; Krzemiński, M. P.; Oliver, A.; Singaram, B. *J. Org. Chem.* **2009**, *74*, 2337-2343. (b) Hirose, T.; Sugawara, K.; Kodama, K. *J. Org. Chem.* **2011**, *76*, 5413-5428.
13. Suziki, Y.; Han, J.; Kitagawa, O.; Aceña, J. L.; Klika, K. D.; Soloshonok, V. A. *RSC Adv.* **2015**, *5*, 2988-2993.
14. Faigl, F.; Fogassy, E.; Nógrádi, M.; Pálovics, E.; Schindler, J. *Org. Biomol. Chem.* **2010**, *8*, 947-959.
15. (a) Pracejus, G. *Liebigs Ann. Chem.* **1959**, *622*, 10-22. (b) Han, J.; Nelson, D. J.; Sorochinsky, A. E.; Soloshonok, V. A. *Curr. Org. Synth.* **2011**, *8*, 310-317. (c) Soloshonok, V. A.; Ueki, H.; Yasumoto, M.; Mekala, S.; Hirschi, J. S.; Singleton, D. A. *J. Am. Chem. Soc.* **2007**, *129*, 12112-12113. (d) Ueki, H.; Yasumoto, M.; Soloshonok, V. A. *Tetrahedron: Asymmetry* **2010**, *21*, 1396-1400. (e) Tarasevych, A. V.; Sorochinsky, A. E.; Kukhar, V. P.; Chollet, A.; Daniellou, R.; Guillemin, J.-C. *J. Org. Chem.* **2013**, *78*, 10530-10533. (f) Bellec, A.; Guillemin, J.-C. *Chem. Commun.* **2010**, *46*, 1482-1484.
16. (a) Koppenhoefer, B.; Trettin, U. *Fresenius' Z. Anal. Chem.* **1989**, *333*, 750. (b) Katagiri, T.; Yoda, C.; Furuhashi, K.; Ueki, K.; Kubota, T. *Chem. Lett.* **1996**, *25*, 115-116. (c) Katagiri, T.; Takahashi, S.; Tsuboi, A.; Suzaki, M.; Uneyama, K. *J. Fluorine Chem.* **2010**, *131*, 517-520.
17. (a) Cundy, K. C.; Crooks, P. A. *J. Chromatogr.* **1983**, *281*, 17-33. (b) Aceña, J. L.; Soroshinsky, A. E.; Katagiri, T.; Soloshonok, V. A. *Chem. Commun.* **2013**, *49*, 373-375. (c) Soroshinsky, A. E.; Katagiri, T.; Ono, T.; Wzorek, A.; Aceña, J. L.; Soloshonok, V. A. *Chirality* **2013**, *25*, 365-368. (d) Nakamura, T.; Tateishi, K.; Tsukagoshi, S.; Hasimoto, S.; Watanabe, S.; Soloshonok, V. A. Aceña, J. L.; Kitagawa, O. *Tetrahedron* **2012**, *68*, 4013-4017.
18. Wzorek, A.; Sato, A.; Drabowicz, J.; Soloshonok, V. A.; Klika, K. D. *Amino Acids* **2016**, *48*, 605–613.
19. (a) Wzorek, A.; Sato, A.; Drabowicz, J.; Soloshonok, V. A.; Klika, K. *Helv. Chim. Acta* **2015**, *98*, 1147–1159. (b) Wzorek, A.; Sato, A.; Drabowicz, J.; Soloshonok, V. A. *Isr. J. Chem.* **2016**, *56*, 977–989.
20. Drabowicz, J.; Jasiak, A.; Wzorek, A.; Sato, A.; Soloshonok, V. A. *Arkivoc* **2017**, *ii*, 557-578.
21. Soloshonok, V. A.; Roussel, C.; Kitagawa, O. ; Soroshinsky, A. E. *Chem. Soc. Rev.* **2012**, *41*, 4180-4188.
22. (a) SHELX-97, Sheldrick, G. M. Programs for Crystal Structure Analysis; University of Göttingen: Germany, 1997. (b) Sheldrick, G. M. *Acta Crystallographica* **2008**, A*64*, 112-122.
23. (a) WinGX and ORTEP for Windows: an update, Farrugia, L. J. *J. Appl. Cryst.* **2012**, *45*, 849-854. (b) WinGX suite for small molecule single-crystal crystallography, Farrugia, L. J. *J. Appl. Cryst*. **1999**, *32*, 837-838.
24. Sabidó, E.; Tarragó, T.; Giralt, E. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3752-3755.
25. Zeng, Z.; Luo, P.; Jiang, Y.; Liu, Y.; Tang, G.; Xu, P.; Zhao, Y.; Blackburn, G. M. *Org. Biomol. Chem.* **2011**, *9*, 6973-6978.
26. Lu, A.; Gao, P.; Wu, Y.; Wang, Y.; Zhou, Z.; Tang, C. *Org. Biomol. Chem.* **2009**, *7*, 3141-3147.