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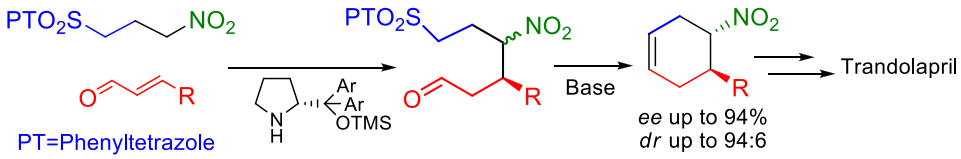
Organocatalytic Michael Addition / Intramolecular Julia – Kocienski Olefination for the Preparation of Nitrocyclohexenes

Eduardo Rodrigo, José Luis García Ruano, M. Belén Cid*

Department of Organic Chemistry. Universidad Autónoma de Madrid, Cantoblanco 28049, Madrid, Spain

belen.cid@uam.es

ABSTRACT

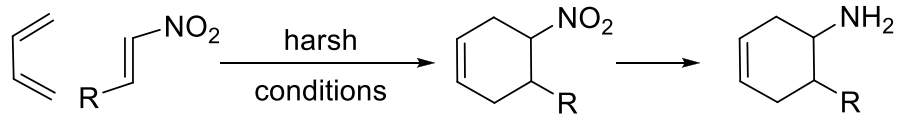


An asymmetric organocatalytic [3 + 3] annulation strategy based on a Michael addition / intramolecular Julia - Kocienski olefination sequence has been developed for the synthesis of 4-substituted-5-nitrocyclohex-1-ene compounds. The strategy is an alternative to the direct reluctant enantioselective Diels-Alder approach. The potential of the methodology has been demonstrated with a concise enantioselective formal synthesis of trandolapril.

Introduction

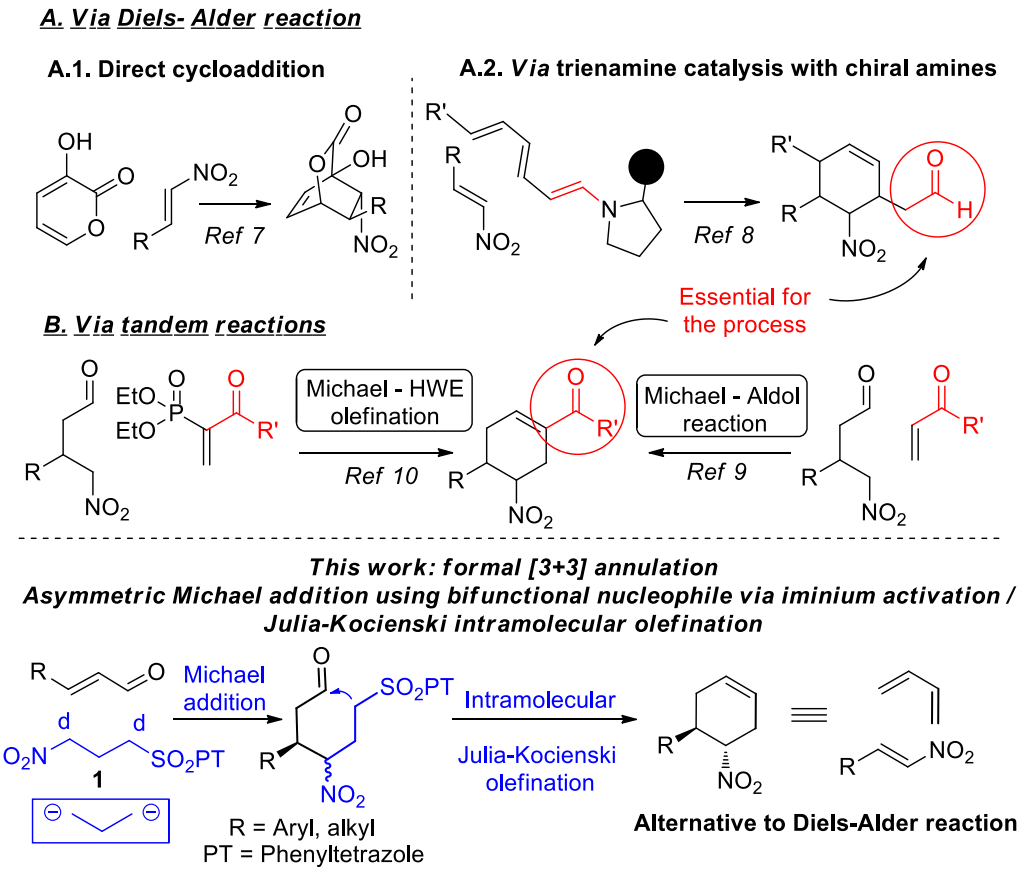
Six-membered ring structures are widespread in natural and synthetic products. As a consequence, a good deal of interest in developing novel approaches including organocatalyzed strategies for the stereoselective synthesis of cyclohexane[1] and cyclohexene[2] derivatives have emerged. Particularly, chiral cyclohexyl and cyclohexenylamine moieties are valuable building blocks present in a wide variety of natural and non-natural compounds of interest.[3] A rapid direct access to this kind of compounds would be an asymmetric [4 + 2] cycloaddition between a diene and a nitroalkene, followed by the reduction of the nitro group (Scheme 1).[4] However, the Diels-Alder reaction of non activated dienes with nitroalkenes requires the use of harsh conditions, specially with aliphatic nitroalkenes where yields are low.[4b]

Scheme 1. Diels-Alder as direct approach to amino cyclohexenes.



As a consequence of the above mentioned problem, in contrast with the plethora of organocatalyzed asymmetric Michael addition reactions,[5] there are only a few examples for the stereoselective organocatalytic Diels-Alder reactions of nitroalkenes.[6] To our knowledge, there is only one example of direct cycloaddition and it is limited exclusively to 3-hydroxy-2-pyrones and aliphatic nitroalkenes (A.1, Scheme 2).[7] Another organocatalytic enantioselective cycloaddition is based on the *in situ* generation of activated dienes from enals *via* trienamine catalysis by chiral amines (A.2, Scheme 2).[8]

Scheme 2. Organocatalytic approaches to chiral nitrocyclohexenes.



Other indirect strategies for the synthesis of these structures, such as the combination of Michael and aldol reactions,[9] as well as Michael addition-intramolecular Horner-Wadsworth-Emmons olefination,[10] have been also described (B, Scheme 2). But for all these strategies the presence of an

electronwithdrawing group at different positions is absolutely essential for the processes to occur and remains unavoidably in the molecule at the end of the process.

Although arylsulfones have been used in a wide range of organocatalytic processes,[11] that is not the case of heteroaryl sulfones despite the great advantage of the possibility to carry out Julia-Kocienski olefination reactions.[12,13] We reasoned that the deactivated nucleophile **1** bearing a heretoarylsulfonyl and nitro moieties could provide enantiopure nitrocyclohexenes through a sequential protocol of Michael addition / intramolecular Julia-Kocienski olefination (Scheme 2). The obtained compounds would be the adducts formed from the above mentioned Diels-Alder reaction (See scheme 1).

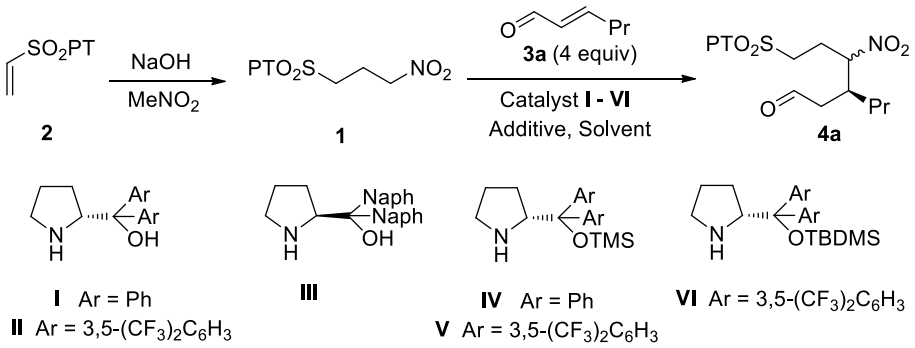
Regarding the viability of the strategy, it is important to note that both nitro and sulfone moieties will be present in both steps, but only one must react in each step. Whereas the Michael addition of nitromethane to enals *via* iminium activation has been widely employed,[14] the reaction of substituted nitroalkanes with a second nucleophilic unit has been scarcely used.[15] Moreover, since Sylvestre Julia introduced the modified Julia olefination in 1991,[16a] some adjustments have been introduced, mainly by Kocienski[16b] and many examples of intermolecular Julia-Kocienski olefination reactions have been described in the literature.[17] Nevertheless, the intramolecular version of this reaction has been hardly explored.[18] Particularly the formation of six-membered rings has only been studied on one substrate bearing *gem*-dimethyl groups,[18a] which favour the cyclation process[19] because of the Thorpe-Ingold effect.

Results and Discussion

We started our work with the synthesis of pro-bis(nucleophile) **1** bearing a phenyltetrazole moiety, which was easily accessible in a 90% yield from sulfone **2**[13] and nitromethane using NaOH as a base (See table 1).[20] Once the nitrocompound **1** had been synthezised, we began our studies to optimize the Michael addition. We tested several proline-type catalysts, using CH_2Cl_2 as solvent and *trans*-2-hexenal as model electrophile. The reaction took place only with some catalysts but exclusively through the carbon bearing the nitro moiety affording adduct **4a** as a 62:38 mixture of diastereomers. The best conversions were obtained with prolinol-type catalysts **I** and **III**, but the enantiomeric excess were poor in both cases (entries 1 and 3). Prolinol **II** and silylprolinols **IV** and **V** turned out sluggish in the absence of additive even using a 30 mol % of catalyst (entries 2, 4 and 5). TBAB, an additive recently developed

by us,[21] led to full conversion when used with catalysts **II** and **V**, improving also the enantiomeric excess up to 86% with catalyst **V** (entries 6 and 7). The more hindered catalyst **VI**, with a TBDMS group, was also tested but afforded the Michael adduct with lower conversions (entry 7). A 1:1 mixture of CH_2Cl_2/EtOH provided higher *ee* even using lower charge of catalyst (Entry 9). Finally, basic and acidic additives were also tested (entries 10 and 11). An acidic additive led to lower conversions (entry 10), while a basic additive such as LiOAc afforded very similar results to TBAB with just a slightly lower yield (entry 11). In order to optimize the later intramolecular Julia-Kocienski olefination, we scaled the reaction up to 1 gram of product using conditions of entry 9. Both yield and enantiomeric excess were maintained.

Table 1. Optimization of the Michael addition



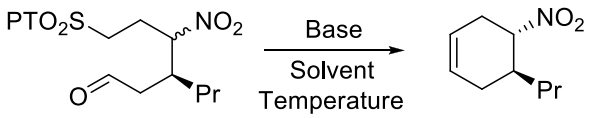
Entry	Catalyst (mol%)	Additive	Solvent	*t* (h)	Conv. (%)	Yield (%)	*ee* [a] (%)
1	**I (30)**	-----	CH_2Cl_2	24	100	69	44
2	**II (30)**	-----	CH_2Cl_2	72	23	----	----
3	**III (30)**	-----	CH_2Cl_2	24	90	----	- 41
4	**IV (30)**	-----	CH_2Cl_2	24	68	----	----
5	**V (30)**	-----	CH_2Cl_2	120	0	----	----
6	**II (30)**	TBAB [b]	CH_2Cl_2	48	100	68	80
7	**V (30)**	TBAB [b]	CH_2Cl_2	48	100	69	86
8	**VI (30)**	TBAB [b]	CH_2Cl_2	48	66	----	----
9	**V (20)**	TBAB [c]	CH_2Cl_2/EtOH	48	100	95	90
10	**V (20)**	BzOH[d]	CH_2Cl_2/EtOH	48	46	----	----
11	**V (20)**	AcOLi[d]	CH_2Cl_2/EtOH	48	100	88	89

[a] Determined by HPLC (see SI); [b](30 mol%); [c](1 equiv.), [d](20 mol%);

Since the alpha-hydrogen of the nitro moiety in **4a** is more acidic than the alpha-hydrogen to the sulfonyl group, an excess of base had to be used for the Julia- Kocienski process (Table 2). When KHMDS, the most common base for the Julia-Kocienski olefination[17a], was employed, a complex mixture was obtained (entry 1). Fortunately, we could isolate the cyclohexene **5a** using Cs_2CO_3 as a

base in a moderate yield, and a 71:29 mixture of diastereoisomers, being the *trans* isomer the major one (entry 2). According to our experience, we expected the epimerization of the carbon bearing the nitro moiety towards the most stable *trans* isomer after the cyclization process.[20b] Therefore we opted to try a stronger and more soluble base to achieve a higher *dr*. Cyclohexene **5a** could also be isolated with a moderate yield in a *dr* of 69:31 using DBU (2 equiv) and CH_3CN as solvent at room temperature (entry 3).[22] The diastereoselectivity did not increase significantly at 0 ºC, (entry 4), but at - 40 ºC the *dr* reached a satisfactory 91:9 ratio (entry 5) although lower yield was obtained. The same *dr* but better yield was obtained when the reaction was carried out at r.t., but quenched at -40 ºC (entry 6). We found optimal conditions using: a) Cs_2CO_3 at 70 ºC to carry out the olefination reaction followed by b) a treatment of the crude reaction with DBU in CH_3CN and quenched carefully at -40 ºC to increase the diastereoselectivity (entry 7).

Table 2. Intramolecular Julia-Kocienski optimization.



4a (*dr* = 62:38) **5a**

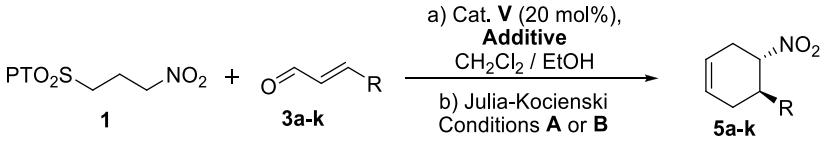
Entry	Solvent	Base	temp	*t* (min)	Yield	*dr*[a]
1	DME	KHMDS[b]	-78 ºC	15	decomp	-
2	THF/DMF[c]	Cs_2CO_3[d]	70 ºC	120	57	71:29
3	CH_3CN	DBU[b]	r.t.	30	51	69:31
4	CH_3CN	DBU[b]	0 ºC	30	51	74:26
5	CH_3CN	DBU[b]	-40 ºC	30	29	91:9
6	CH_3CN	DBU[b]	r.t. (-40 ºC)[e]	30	51	91:9
7	a)THF/DMF[a] b) CH_3CN	Cs_2CO_3[d] DBU[f]	70 ºC (-40 ºC)[e]	120 15	57	91:9

[a] Determined by ^{1}H NMR; [b] 2 equivalents; [c];THF/DMF (3:1); [d] 3 equivalents; [e] quenched at -40 ºC; [f] 1 equivalent.

Once both Michael addition and Julia-Kocienski olefination had been optimized, we checked the substrate scope of our strategy. Interestingly, a very different behavior was observed with aliphatic and aromatic enals in both Michael and Julia-Kocienski reactions. The Michael addition worked well using TBAB as additive with aliphatic enals (Table 3, entries 1-7) for a variety of chains containing different functional groups such as a double bond (**3e**) or an acetal (**3k**). The Julia-Kocienski reaction also went

on the right track under conditions of entry 7 in table 2 (conditions **A**). However, Michael addition with aromatic enals presented erratic enantioselectivity when using the same conditions utilized for the aliphatic enals owing to reversibility.[23] Nevertheless, controlling reaction times and using LiOAc as additive, Michael adducts were obtained in good yields and enantioselectivities, both with electrondonating and electronwithdrawing groups (Table 3, entries 8-11). In the case of the Julia-Kocienski olefination with the aromatic substituents we observed aromatization of the cyclohexene under conditions **A.**[24] Therefore milder conditions **B**, using DBU as base at low temperature, were employed.

Table 3. Scope of the Michael / Julia-Kocienski process.



Conditions **A** (R = Aliphatic): i) Cs_2CO_3, THF/DMF, 70 ºC, 2h; ii) DBU, CH_3CN, 15 min, -40 ºC
Conditions **B** (R = Aromatic): DBU, CH_3CN, 0 ºC, 30 min, quenching at -40 ºC

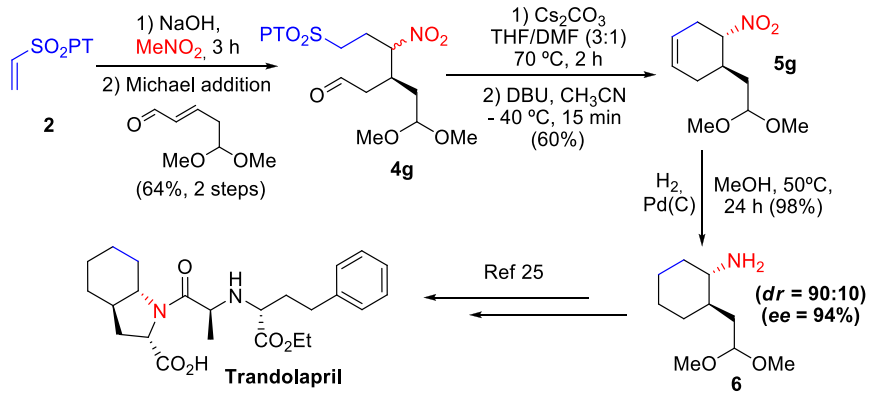
Entry	R	Michael Addition				Julia-Kocienski		
		Additive	t (h)	Prod	yield (%)	**Conditions**/ yield (%) (*dr*) [a]	Prod	*ee*[b] (%)[c]
1	**3a** Pr	TBAB[d]	48	**4a**	95	**A** / 57 (91:9)	**5a**	90
2	**3b** Me	TBAB[d]	48	**4b**	92	**B**[c] / 45 (79:21)	**5b**	86
3	**3c** Et	TBAB[d]	48	**4c**	94	**A** / 51 (92:8)	**5c**	90
4	**3d** *n*-Bu	TBAB[d]	72	**4d**	93	**A** / 60 (85:15)	**5d**	91
5	**3e**	TBAB[d]	72	**4e**	92	**A** / 63 (75:25)	**5e**	90
6	**3f** Non	TBAB[d]	72	**4f**	90	**A** / 61 (76:24)	**5f**	95
7	**3g** CH_2-CH-$(OMe)_2$	TBAB[d]	48	**4g**	71	**A** / 60 (90:10)	**5g**	94
8	**3h** Ph	LiOAc[e]	8	**4h**	77	**B** / 52 (94:6)	**5h**	92
9	**3i** *p*-NO_2-C_6H_4	LiOAc[e]	24	**4i**	83	**B** / 49 (91:9)	**5i**	75
10	**3j** *p*-Cl-C_6H_4	LiOAc[e]	24	**4j**	78	**B** / 50 (91:9)	**5j**	86
11	**3k** *p*-OMe-C_6H_4	LiOAc[e]	4	**4k**	55	**B** / 52 (85:15)	**5k**	89

[a] By ^{1}H NMR, [b] By HPLC; [c] See SI; [d] 1 equiv; [e] 20 mol%.

In order to illustrate the versatility of our pro-bis(nucleophile) **1**, we carried out a formal synthesis of trandolapril. Trandolapril is the ethyl ester prodrug of trandolaprilat, which is commonly prescribed as cardiovascular drug for controlling hypertension.[25] The preparation of trandolapril has been described from cyclohexylamine **6**, which was prepared using a low-yielding Diels-Alder reaction carried out under high temperature and pressure conditions with butadiene and the corresponding nitroalkene as key step, followed by reduction and enzymatic resolution of racemic **6**.[26] We envisioned that we could develop the first enantioselective synthesis of trandolapril by preparing enantioenriched intermediate **6**

using our methodology.[27] The combination of the optimized procedure for the Michael addition / Julia-Kocienski olefination followed by simultaneous reduction of the double bond and nitro group using H_2 / Pd(C), allowed the preparation of **6**[28] with a 94% *ee*, 90:10 *dr* and a 38% yield starting from vinylsulfone **2** (Scheme 3).

Scheme 3. Formal synthesis of trandolapril.



Conclusion

In conclusion, we have developed a sequential procedure *via* asymmetric catalytic Michael reaction involving enals and pro-bis(nucleophile) **1** followed by intramolecular Julia-Kocienski olefination to afford nitrocyclohexenes, which are versatile compounds in synthesis. The synthetic potential of this methodology for the enantio and diastereoselective preparation of nitrocyclohexenes and cyclohexylamines was illustrated with an enantioselective formal synthesis of trandolapril.

Experimental section

General Methods and Materials

NMR spectra were acquired using $CDCl_3$ as the solvent, running at 300 and 75 MHz for ^1H and ^{13}C respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals (CHCl3, 7.26 ppm for ^1H NMR, $CDCl_3$, and 77.0 ppm for ^{13}C NMR). In all ^1H NMR spectra, multiplicity is indicated as follows: bs (broad singlet), s (singlet), d (doublet), t (triplet), q (quartet), quin (quintuplet) or m (multiplet). Coupling constant values (in Hertz) and number of protons for each signal are also indicated.

Melting points were measured using *Gallenkamp melting point apparatus* in open capillary tubes. Optical rotation was recorded in cells with 10 cm path length on a Perkin-Elmer 241 MC polarimeter.

For thin layer chromatography (TLC) *Supelco* silica gel plates with fluorescence indicator 254 nm were used and compounds were visualized by irradiation with UV light and/or by treatment with a

solution of $KMnO_4$ (1.5 g), K_2CO_3 (10g), and 10% NaOH (1.25 mL) in H_2O (200 mL) or a solution of phosphomolybdic acid (12 g), in EtOH (250 mL) followed by heating. Flash column chromatography (FCC) was performed using Merck pore 60 Å, 40-63 μm silica gel and compressed air.

Mass spectra were obtained in a *VG AutoSpec Spectrometer* in positive electrospray ionisation (ESI) or electron impact ionisation (EI). Obtained data are expressed in mass/charge (m/z) units. Values between parentheses indicate relative intensities with regard to the base peak.

Enantiomeric excesses (ee) were determined by chiral-phase SFC-HPLC (HPLC in the case of **5g**) using an Agilent-1100 instrument in the indicated column and conditions in each case.

Hexane and EtOAc were supplied by *Scharlau* and were used without previous purification. All the other reactants were bought in *Aldrich*, *Fluka* or *Alfa Aesar* and were also used without any previous treatment.

Enals **3a–3f**, and **3h**, **3i** and **3k** are commercially available. Enals **3g** and **3j** and heteroaryl vinylsulfone **2**[13] were prepared following the literature procedure.

Preparation of aldehyde 3g[29]

$ZnCl_2$ (408 mg, 3 mmol) was added to a mixture of 1-trimethylsilyloxy-1,3-butadiene (4.26 g, 30 mmol) and trimethyl orthoformate (3.9 mL, 31 mmol) in CH_2Cl_2 (100 mL). The mixture was stirred vigorously at r.t. for 16 hours whereupon it was poured into water (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL) and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (Hexane:EtOAc 8:1 to 6:1) to afford 1.81 g (Yield: 42%) of aldehyde **3g** as a yellow oil. ^{1}H NMR (300 MHz): δ 9.51 (d, J = 7.9 Hz, 1H), 6.79 (dt, J = 15.7 and 7.0 Hz, 1H), 6.17 (dd, J = 15.7 and 7.9 Hz, 1H), 4.50 (t, J = 5.5 Hz, 1H), 3.35 (s, 6H), 2.64 (dd, J = 7.0 and 5.5 Hz, 2H) ^{13}C-NMR (75 MHz): 193.5 (CHO), 152.1 (CH), 134.9 (CH), 102.6 (CH), 53.2 (2 CH_3), 36.2 (CH_2)

Preparation of aldehyde 3j[30]

4-Chlorobenzaldehyde (714 mg, 5.1 mmol) was dissolved in toluene (20 mL) and (triphenylphosphoranylidene)acetaldehyde (1.50 g, 5 mmol) was added to the solution. The mixture was heated at 80 ºC and stirred for 24h. The solvent was removed under reduced pressure and the crude was

purified by flash column chromatography (Hexane 4:1 EtOAc) to afford 456 mg (Yield: 55%) of aldehyde **3j** as a yellow solid. Spectroscopic and analytical data are in agreement with the literature.

Preparation of pro-bis(nucleophile) 1

Sulfone **2** (1,41g, 6 mmol) was added to a solution of sodium hydroxide in perles (240 mg, 6 mmol) in nitromethane (15 mL). The mixture was stirred for 3 hours, whereupon water (20 mL) was added. The mixture was transferred into a separatory funnel and was extracted with EtOAc (2 × 25 mL). The organic layers were combined and were washed with brine (25 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure to afford pro-bis(nucleophile) **1** as a white solid (1.60 g, yield: 90%), which was used for the next step without further purification. White solid Mp: 81-83 ºC ^{1}H NMR (300 MHz): δ 7.71-7.54 (m, 5H), 4.62 (t, *J* = 6.5 Hz, 2H), 3.92 (t, *J* = 7.1 Hz, 2H), 2.71 (quin, *J* = 6.8 Hz, 2H) ^{13}C NMR (75 MHz): δ 153.1 (C), 132.8 (C), 131.6 (CH), 128.8 (2CH), 124.9 (2CH), 72.3 (CH_2), 52.9 (CH_2), 20.4 (CH_2) MS (*ESI*): m/z 298 (M^++1, 46), 149 (67), 119 (26), 113 (100). HRMS (ESI): calculated for $C_{10}H_{12}N_5O_4S$ (M^++1): 298.0604; found: 298.0615.

General procedure for the Michael Addition

Aliphatic enals (3a-g): Catalyst **V** (11.9 mg, 0.02 mmol) was dissolved in a 1:1 mixture of CH_2Cl_2 / EtOH (0.6 mL) and the corresponding aldehyde **3a-g** (4 mmol) was added to the solution. The mixture was stirred for 5 minutes before pro-bis(nucleophile) **1** (29.7 mg, 0.1 mmol) and TBAB (32.5 mg, 0.1 mmol) were sequentially added. The reaction mixture was stirred at room temperature the indicated time for each case (see table 3). The solvent was removed under reduced pressure and the crude was purified by flash column chromatography to afford the corresponding Michael adducts **4a-g**.

Aromatic enals (3h-k): Catalyst **V** (11.9 mg, 0.02 mmol) was dissolved in a 1:1 mixture of CH_2Cl_2 / EtOH (0.6 mL) and the corresponding aldehyde **3h-k** (4 mmol) was added to the solution. The mixture was stirred for 5 minutes before pro-bis(nucleophile) **1** (29.7 mg, 0.1 mmol) and LiOAc (1.3 mg, 0.02 mmol) were sequentially added. The reaction mixture was stirred at room temperature the indicated time for each case (see table 3). The solvent was removed under reduced pressure and the crude was purified by flash column chromatography to afford the corresponding Michael adducts **4h-k**.

General procedure for the synthesis of racemic compounds 4a-k.

The racemic compounds were obtained following the same procedure above detailed for the Michael addition, using a mixture of (*R*) and (*S*)-α-α-Diphenyl-2-pyrrolidinemethanol (15 mol% *(R)* and 15 mol% *(S)*) and TBAB (1 equiv) as additive.

Determination of enantiomeric excesses

The Michael adducts had to be derivatizated into the corresponding methyl esters or into the corresponding acetals according to methods A or B. **Method A: Acetalization** 0.05 mmol of the corresponding Michael adduct were dissolved in 1 mL of benzene. *p*-Toluenesulfonic acid (1 mg) and ethylenglicol (19 µL, 0.2 mmol) were added to the solution and the mixture was heated at 80 ºC overnight. The solution was allowed to cool to room temperature, whereupon $NaHCO_3$ (sat) (5 mL) and EtOAc (5 mL) were subsequently added. The mixture was transferred into a separatory funnel and extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated under vacuum to afford the corresponding acetal. **Method B**[31]: **Transformation into the corresponding ester**. 0.05 mmol of the corresponding Michael adduct were dissolved in a 5:1 mixture of MeOH / CH_2Cl_2 (1.2 mL) and the solution was stirred for 5 minutes at 0 ºC in an ice/water bath, whereupon NBS (13 mg, 0.075 mmol, 1.5 eq) was added to the solution. The flask was left in the bath overnight and allowed to reach r.t. The solvent was removed under reduced pressure and the crude was purified by flash column chromatography (Hexane 4:1 EtOAc) to afford the corresponding ester derivative.

(3*S*, 4*S*)-4-Nitro-6-(1-phenyl-1*H*-tetrazol-5ylsulfonyl)-3-propylhexanal and (3*S*, 4*R*)-4-Nitro-6-(1-phenyl-1*H*-tetrazol-5ylsulfonyl)-3-propylhexanal (4a)

The title compound was obtained in a 95% yield as yellowish oil after flash column chromatography (Hexane 3:1 EtOAc) according to the general procedure, using TBAB as additive (1 equiv) as a 62:38 mixture of diastereomers. The diastereomeric ratio (*dr*) was determined by HPLC. The procedure to obtain this product has been scaled up until 1 g of nitrocompound **1**. Yield: 1.23 g, 93%. ^{1}H NMR (300 MHz) (data obtain from the mixture of diastereomers): δ 9.79 (s, $1H_{major}$), 9.77 (s, $1H_{minor}$), 7.73-7.58 (m, $5H_{major}$, $5H_{minor}$), 4.91-4.77 (m, $1H_{major}$, $1H_{minor}$), 3.86-3.75 (m, $2H_{major}$, $2H_{minor}$), 2.84-2.37 (m, $5H_{major}$, $5H_{minor}$), 1.49-1.15 (m, $4H_{major}$, $4H_{minor}$), 0.93 (t, J = 6.8 Hz, $3H_{major}$,), 0.92 (t, J = 6.8 Hz, $3H_{minor}$). ^{13}C NMR (75 MHz) (Mixture of diastereomers): δ 199.6 (CHO), 199.2 (CHO), 153.1 (2C), 132.8 (2C), 131.7 (2CH), 129.9 (4CH), 125.0 (4CH), 87.8 (CH), 87.4 (CH), 52.9 ($2CH_2$), 44.2 (CH_2), 43.9 (CH_2), 35.7 (CH), 35.6 (CH), 32.9 (CH_2), 31.6 (CH_2), 23.9 (CH_2), 23.4 (CH_2), 20.2 (CH_2), 19.9

(CH_2), 13.8 ($2CH_3$). MS (*ESI*): m/z 396 (M^++1, 56), 254 (45), 236, (54), 147 (38), 80 (35). HRMS (ESI): calculated for $C_{16}H_{22}N_5O_5S$ (M^++1): 396.1336; found: 396.1353. The enantiomeric excess was determined by SFC-HPLC over the corresponding methyl ester following Method B. Chiralpak IB column [CO_2/MeOH = 98:2]; flow rate 3.0 mL/min. *ee* = 90%, τ_{major} = 7.5 and 8.4 min; τ_{minor} = 7.1 and 9.9 min.

(3*S*, 4*S*)-3-Methyl-4-nitro-6-(1-phenyl-1*H*-tetrazol-5ylsulfonyl)hexanal and (3*S*, 4*R*)-3-Methyl-4-nitro-6-(1-phenyl-1*H*-tetrazol-5ylsulfonyl)hexanal (4b)

The title compound was obtained in a 92% yield as a yellow oil after flash column chromatography (Hexane 2:1 EtOAc) according to the general procedure, using TBAB (1 equiv) as additive, as a 63:37 mixture of diastereomers. The diastereomeric ratio (*dr*) was determined by ^{1}H NMR. ^{1}H NMR (300 MHz) (Data obtain from the mixture of diastereomers): δ 9.77 (s, $1H_{major)}$, 9.74 (s, $1H_{minor}$), 7.72-7.58 (m, $5H_{major}$, $5H_{minor}$), 4.83-4.70 (m, $1H_{major}$, $1H_{minor}$), 3.86-3.74 (m, $2H_{major}$, $2H_{minor}$), 2.88-2.38 (m, $5H_{major}$, $5H_{minor}$), 1.09 (d, *J* = 6.9 Hz, $3H_{minor}$), 1.04 (d, *J* = 6.9 Hz, $3H_{major}$) ^{13}C NMR (75 MHz) (Mixture of diastereomers): δ 199.3 (CHO), 198.8 (CHO), 153.1 (2C), 132.8 (2C), 131.6 (2CH), 129.8 (4CH), 124.9 (4CH), 89.4 (CH), 88.4 (CH), 52.7 ($2CH_2$), 46.9 (CH_2), 46.2 (CH_2), 31.3 (CH), 30.9 (CH), 23.9 (CH_2), 23.4 (CH_2), 16.1 (CH_3), 14.9 (CH_3). MS (*ESI*): m/z 368 (M^++1, 100), 338 (31), 147 (19), 119 (12). HRMS (ESI): calculated for $C_{14}H_{18}N_5O_5S$ (M^++1): 368.1023; found: 368.1035. The enantiomeric excess was determined by SFC-HPLC over the corresponding methyl ester following Method B. The 4 diastereomers could not be completely separated in any of the available HPLC columns. The best conditions were the described below, which allowed to determine the *ee* in one of the diastereomers. The enantiomeric excess was determined by SFC-HPLC over the corresponding methyl ester following Method B. Chiralpak IB column [CO_2/MeOH = 98:2]; flow rate 3.0 mL/min. *ee* = 86 %, τ_{major} = 15.1 and 19.5 min; τ_{minor} = 15.1 and 16.5 min.

(3*S*, 4*S*)-3-Ethyl-4-nitro-6-(1-phenyl-1*H*-tetrazol-5ylsulfonyl)hexanal and (3*S*, 4*R*)-3-Ethyl-4-nitro-6-(1-phenyl-1*H*-tetrazol-5ylsulfonyl)hexanal (4c)

The title compound was obtained in a 94% yield as yellowish oil after flash column chromatography (Hexane 3:1 EtOAc) according to the general procedure, using TBAB as additive as a 64:36 mixture of diastereomers. The diastereomeric ratio (*dr*) was determined by HPLC. ^{1}H NMR (300 MHz) (data obtain from the mixture of diastereomers): δ 9.80 (s,$1H_{major}$) 9.78 (s, $1H_{minor}$), 7.73-7.59 (m, $5H_{major}$, $5H_{minor}$), 4.93-4.79 (m, $1H_{major}$, $1H_{minor}$), 3.86-3.77 (m, $2H_{major}$, $2H_{minor}$), 2.83-2.39 (m, $5H_{major}$, $5H_{minor}$),

1.57-1.37 (m, $2H_{major}$, $2H_{minor}$), 0.97 (t, J = 7.4 Hz, $3H_{major}$, $3H_{minor}$). ^{13}C NMR (75 MHz) (Mixture of diastereomers): δ 199.6 (CHO), 199.2 (CHO), 153.1 (2C), 132.8 (2C), 131.7 (2CH), 129.8 (4CH), 124.9 (4CH), 87.5 (CH), 87.3 (CH), 52.8 ($2CH_2$), 43.7 (CH_2), 43.5 (CH_2), 37.4 (CH), 37.2 (CH), 23.9 (CH_2), 23.7 (CH_2), 23.4 (CH_2), 22.6 (CH_2), 11.4 (CH_3), 11.0 (CH_3). MS (*ESI*): m/z 382 (M^++1, 20), 254 (30), 147 (28), 80 (100). HRMS (ESI): calculated for $C_{15}H_{20}N_5O_5S$ (M^++1): 382.1179; found: 382.1194. The enantiomeric excess was determined by SFC-HPLC over the corresponding methyl ester following Method B. Chiralpak IB column [CO_2/MeOH = 98:2]; flow rate 3.0 mL/min. *ee* = 90 %, τ_{major} = 8.5 and 8.9 min; τ_{minor} = 8.1 and 9.5 min.

(3*S*, 4*S*)-3-Butyl-4-nitro-6-(1-phenyl-1*H*-tetrazol-5ylsulfonyl)hexanal and (3*S*, 4*R*)-3-Butyl-4-nitro-6-(1-phenyl-1*H*-tetrazol-5ylsulfonyl)hexanal (4d)

The title compound was obtained as yellowish oil in a 93% yield after flash column chromatography (Hexane 3:1 EtOAc) according to the general procedure, using TBAB as additive (1 equiv) as a 64:36 mixture of diastereomers. The diastereomeric ratio (*dr*) was determined by HPLC. ^1H NMR (300 MHz) (data obtain from the mixture of diastereomers): δ 9.78 (s, $1H_{major}$), 9.76 (s, $1H_{minor}$), 7.73-7.56 (m, $5H_{major}$, $5H_{minor}$), 4.92-4.74 (m, $1H_{major}$, $1H_{minor}$), 3.87-3.71 (m, $2H_{major}$, $2H_{minor}$), 2.84-2.36 (m, $5H_{major}$, $5H_{minor}$), 1.50-1.12 (m, $6H_{major}$, $6H_{minor}$), 0.97-0.78 (m, $3H_{major,}$ $3H_{minor}$). ^{13}C NMR (75 MHz) (Mixture of diastereomers): δ 199.7 (CHO), 199.2 (CHO), 153.1 (2C), 132.8 (2C), 131.7 (2CH), 129.8 (4CH), 125.0 (4CH), 87.8 (CH), 87.5 (CH), 52.8 ($2CH_2$), 44.1 (CH_2), 43.9 (CH_2), 35.9 (CH), 35.7 (CH), 30.4 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 28.7 (CH_2), 23.8 (CH_2), 23.3 (CH_2), 22.5 ($2CH_2$), 13.8 ($2CH_3$). MS (*ESI*): m/z 410 (M^++1, 55), 149 (100), 147 (39), 119 (30), 80 (20). HRMS (ESI): calculated for $C_{17}H_{24}N_5O_5S$ (M^++1): 410.1492; found: 410.1513. The enantiomeric excess was determined by SFC-HPLC over the corresponding methyl ester following Method B. Chiralpak IB column [CO_2/MeOH = 98:2]; flow rate 3.0 mL/min. *ee* = 91%, τ_{major} = 7.8 and 8.7 min; τ_{minor} = 7.5 and 10.1 min.

(3*S*, *6Z*)-3-((1*S*)-1-Nitro-3-(1-phenyl-1*H*-tetrazol-5ylsulfonyl)propylnon-6-enal and (3*S*, *6Z*)-3-((1*R*)-1-Nitro-3-(1-phenyl-1*H*-tetrazol-5ylsulfonyl)propylnon-6-enal (4e)

The title compound was obtained in a 92% yield as yellowish oil after flash column chromatography (Hexane 3:1 EtOAc), using TBAB as additive (1 equiv) according to the general procedure. The diastereomeric ratio (*dr*) could not be properly determined. ^1H NMR (300 MHz) (data obtain from the

mixture of diastereomers): δ 9.79 (s, $1H_{major}$), 9.77 (s, $1H_{minor}$), 7.73-7.57 (m, $5H_{major}$, $5H_{minor}$), 5.52-5.38 (m, $1H_{major}$, $1H_{minor}$), 5.32-5.18 (m, $1H_{major}$, $1H_{minor}$), 4.94-4.80 (m, $1H_{major}$, $1H_{minor}$), 3.87-3.75 (m, $2H_{major}$, $2H_{minor}$), 2.86-2.38 (m, $4H_{major}$, $4H_{minor}$), 2.17-1.92 (m, $5H_{major}$, $5H_{minor}$), 1.60-1.36 (m, $2H_{major}$, $2H_{minor}$), 1.00-0.90 (m, $3H_{major}$, $3H_{minor}$). ^{13}C NMR (75 MHz) (Mixture of diastereomers): δ 199.6 (CHO), 199.1 (CHO), 153.0 (2C), 133.7 (CH), 133.5 (CH), 132.8 (2C), 131.6 (2CH), 129.9 (4CH), 126.6 (2CH), 125.0 (4CH), 87.5 (CH), 87.2 (CH), 52.8 ($2CH_2$), 44.0 (CH_2), 43.7 (CH_2), 35.3 (2CH), 30.7 (CH_2), 29.2 (CH_2), 24.3 (CH_2), 24.1 (CH_2), 23.9 (CH_2), 23.4 (CH_2), 20.6 ($2CH_2$), 14.2 ($2CH_3$)

MS (*ESI*): m/z 436 (M^++1, 23), 254 (100), 236 (64), 149 (18). HRMS (ESI): calculated for $C_{19}H_{26}N_5O_5S$ (M^++1): 436.1649; found: 436.1681. The enantiomeric excess was determined by SFC-HPLC over the corresponding acetal following Method A. The 4 diastereomers could not be completely separated in any of the available HPLC columns. The best conditions were the described below, which allowed to determine the *ee* in one of the diastereomers. The enantiomeric excess was determined by SFC-HPLC over the corresponding acetal following Method A. Chiralpak IB column [CO_2/MeOH = 98:2]; flow rate 3.0 mL/min. *ee* = 90%, τ_{major} = 15.1 and 16.2 min; τ_{minor} = 16.2 and 17.3 min.

(3*S*)-3-((*1S*)-1-Nitro-3-(1-phenyl-1*H*-tetrazol-5ylsulfonyl)propyl)dodecanal and (3*S*)-3-((*1R*)-1-Nitro-3-(1-phenyl-1*H*-tetrazol-5ylsulfonyl)propyl)dodecanal (4f)

The title compound was obtained in a 90% yield as yellowish oil after flash column chromatography (Hexane 4:1 EtOAc) according to the general procedure, using TBAB as additive (1 equiv) as a 61:39 mixture of diastereomers. The diastereomeric ratio (*dr*) was determined by HPLC. ^1H NMR (300 MHz) (data obtain from the mixture of diastereomers): δ 9.77 (s, $1H_{major}$), 9.75 (s, $1H_{minor}$), 7.72-7.56 (m, $5H_{major}$, $5H_{minor}$), 4.90-4.77 (m, $1H_{major}$, $1H_{minor}$), 3.86-3.74 (m, $2H_{major}$, $2H_{minor}$), 2.83-2.35 (m, $5H_{major}$, $5H_{minor}$), 1.48-1.17 (m, $16H_{major}$, $16H_{minor}$), 0.88 (t, *J* = 6.9 Hz, $3H_{major}$, $3H_{minor}$). ^{13}C NMR (75 MHz) (Mixture of diastereomers): δ 199.8 (CHO), 199.3 (CHO), 153.1 (2C), 132.8 (2C), 131.6 (2CH), 129.8 (4CH), 125.0 (4CH), 87.8 (CH), 87.5 (CH), 52.9 ($2CH_2$), 44.1 (CH_2), 43.9 (CH_2), 36.0 (CH), 35.8 (CH), 31.8 (CH_2), 30.7 (CH_2), 29.5-29.1 ($10CH_2$), 27.0 (CH_2), 26.6 (CH_2), 23.8 (CH_2), 23.4 (CH_2), 22.6 ($2CH_2$), 14.1 ($2CH_3$). MS (*ESI*): m/z 480 (M^++1, 22), 254 (100), 236 (69), 80 (12). HRMS (ESI): calculated for $C_{22}H_{34}N_5O_5S$ (M^++1): 480.2275; found: 480.2298. The enantiomeric excess was determined by SFC-HPLC over the corresponding acetal following Method A. Chiralpak IB column

[CO_2/MeOH = 98:2]; flow rate 3.0 mL/min. *ee* = 95%, τ_{major} = 16.9 and 19.2 min; τ_{minor} = 18.1 and 21.2 min.

(3*R*, 4*S*)-3-(2,2-Dimetoxyethyl)-4-nitro-6-(1-phenyl-1*H*-tetrazol-5-ylsulfonyl)hexanal and (3*R*, 4*R*)-3-(2,2-Dimetoxyethyl)-4-nitro-6-(1-phenyl-1H-tetrazol-5-ylsulfonyl)hexanal (4g)

The title compound was obtained in a 71% yield as yellow oil after flash column chromatography (Hexane 2:1 EtOAc) according to the general procedure, using TBAB (1 equiv) as additive as a 64:36 mixture of diastereomers. The diastereomeric ratio (*dr*) was determined by ^{1}H NMR. The enantiomeric excess was determined by HPLC over the cyclohexene derivative. The procedure to obtain this product has been scaled up until 0.9 g of nitrocompound 1. Yield: 969 mg, 71% ^{1}H NMR (300 MHz) (data obtain from the mixture of diastereomers): δ 9.72 (s, $1H_{major,}$ $1H_{minor}$), 7.73-7.56 (m, $5H_{major}$, $5H_{minor}$), 5.00-4.68 (m, $1H_{major}$, $1H_{minor}$), 4.45-4.33 (m, $1H_{major}$, $1H_{minor}$), 3.90-3.74 (m, $2H_{major}$, $2H_{minor}$), 3.35-3.27 (m, $6H_{major}$, $6H_{minor}$), 2.91-2.39 (m, $5H_{major}$, $5H_{minor}$), 1.88-1.49 (m, $2H_{major}$, $2H_{minor}$). ^{13}C NMR (75 MHz) (Mixture of diastereomers): 199.5 (CHO), 199.0 (CHO), 153.1 (2C), 132.8 (2C), 131.7 (2CH), 129.8 (4CH), 125.0 (4CH), 103.3 (CH), 102.9 (CH), 87.8 (CH), 87.3 (CH), 54.0 ($2CH_3$) 53.7 ($2CH_3$), 52.8 ($2CH_2$), 44.6 (CH_2), 44.0 (CH_2), 33.5 (CH_2), 32.5 (CH_2), 32.0 (CH), 31.8 (CH), 23.9 (CH_2), 23.1 (CH_2).MS (*ESI*): m/z 464 (M^++23, 91), 410 (20), 338 (15), 186 (25), 149 (36), 135 (17). HRMS (ESI): calculated for $C_{17}H_{23}N_5O_7SNa$ (M^++23): 464.1210; found: 464.1205.

(3*R*, 4*S*)-4-Nitro-3-phenyl-6-(1-phenyl-1*H*-tetrazol-5-ylsulfonyl)hexanal and (3*R*, 4*R*)-4-Nitro-3-phenyl-6-(1-phenyl-1*H*-tetrazol-5-ylsulfonyl)hexanal (4h)

The title compound was obtained in a 77% yield as a pale yellow solid (mp = 57-59 ºC) after flash column chromatography (Hexane 3:1 EtOAc) according to the general procedure, using LiOAc as additive (20 mol %) as a 54:46 mixture of diastereomers (33 mg, 77% yield). The diastereomeric ratio (*dr*) was determined by HPLC. ^{1}H NMR (300 MHz) (data obtain from the mixture of diastereomers): δ 9.70 (s, $1H_{minor}$), 9.56 (s, $1H_{major}$), 7.71-7.57 (m, $5H_{major}$, $5H_{minor}$), 7.41-7.10 (m, $5H_{major}$, $5H_{minor}$), 5.11-4.94 (m, $1H_{major}$, $1H_{minor}$), 3.90-3.73 (m, $2H_{major}$, $2H_{minor}$), 3.70-3.59 (m, $1H_{major}$, $1H_{minor}$) 3.25-3.11 (m, $1H_{minor}$), 3.08-2.94 (m, $1H_{major}$, $1H_{minor}$) 2.85-2.74 (m, $1H_{major}$), 2.69-2.40 (m, $1H_{major}$, $2H_{minor}$) 2.31-2.16 (m, $1H_{major}$). ^{13}C NMR (75 MHz) (Mixture of diastereomers): δ 198.7 (CHO), 197.9 (CHO), 153.1 (C), 152.8 (C), 136.5 (C), 136.1 (C), 132.7 (2C), 131.6 (2CH), 129.8 (4CH), 129.5 (2CH), 129.1 (2CH), 128.6 (2CH), 128.0 (4CH), 125.0 (2CH), 124.9 (2CH), 89.6 (CH), 89.3 (CH), 52.6 (CH_2), 52.3 (CH_2),

46.3 (CH_2), 45.3 (CH_2), 43.3 (CH), 42.4 (CH), 24.7 (CH_2), 24.2 (CH_2). MS (*ESI*): m/z 430 (M^++1, 31), 368 (19), 254 (100), 236 (64). HRMS (ESI): calculated for $C_{19}H_{20}N_5O_5S$ (M^++1): 430.1179; found: 430.1176. The enantiomeric excess was determined by SFC-HPLC over the corresponding acetal following Method A. Chiralpak IA column [CO_2/MeOH = 90:10]; flow rate 3.0 mL/min. *ee* = 92%, τ_{major} = 6.9 and 13.8 min; τ_{minor} = 10.2 and 11.7 min.

(3*R*, 4*S*)-4-Nitro-3-(4-nitrophenyl)-6-(1-phenyl-1*H*-tetrazol-5-ylsulfonyl)hexanal and (3*R*, 4*R*)-4-Nitro-3-(4-nitrophenyl)-6-(1-phenyl-1*H*-tetrazol-5-ylsulfonyl)hexanal (4i)

The title compound was obtained in a 83% yield as a yellow solid (mp = 56-61 ºC) after flash column chromatography (Hexane 2:1 EtOAc) according to the general procedure, using LiOAc as additive (20 mol %) as a 55:45 mixture of diastereomers. The diastereomeric ratio (*dr*) was determined by HPLC. ^{1}H NMR (300 MHz) (data obtain from the mixture of diastereomers): δ 9.74 (s, $1H_{minor}$), 9.53 (s, $1H_{major}$), 8.25-8.17 (m, $2H_{major}$, $2H_{minor}$) 7.72-7.58 (m, $5H_{major}$, $5H_{minor}$), 7.46-7.34 (m, $2H_{major}$, $2H_{minor}$), 5.16-5.06 (m, $1H_{major}$, $1H_{minor}$), 4.06-3.92 (m, $1H_{major}$, $1H_{minor}$), 3.90-3.73 (m, $2H_{major}$, $2H_{minor}$), 3.84-3.62 (m, $1H_{major}$, $1H_{minor}$) 3.32-3.21 (m, $1H_{minor}$), 3.15-3.01 (m, $1H_{major}$, $1H_{minor}$) 2.99-2.81 (m, $1H_{major}$), 2.72-2.47 (m, $1H_{major}$, $2H_{minor}$) 2.37-2.19 (m, $1H_{major}$). ^{13}C NMR (75 MHz) (Mixture of diastereomers): δ 197.5 (CHO), 196.8 (CHO), 153.0 (C), 152.8 (C), 147.9 (2C), 144.0 (C), 143.7 (C), 132.6 (2C), 131.7 (2CH), 129.9 (4CH), 129.5 (2CH), 129.2 (2CH), 125.0 (2CH), 124.8 (2CH), 124.6 (2CH), 124.3 (2CH), 88.8 (CH), 88.0 (CH), 52.5 (CH_2), 52.3 (CH_2), 46.0 (CH_2), 45.3 (CH_2), 42.6 (CH), 41.9 (CH), 24.8 ($2CH_2$). MS (*ESI*): m/z 475 (M^++1, 11), 242 (100), 149 (20), 147 (23). HRMS (ESI): calculated for $C_{19}H_{19}N_6O_7S$ (M^++1): 475.1030; found: 475.1053. The enantiomeric excess was determined by SFC-HPLC over the corresponding acetal following Method A. Chiralpak IB column [CO_2/MeOH = 85:15]; flow rate 3.0 mL/min. *ee* = 75%, τ_{major} = 6.8 and 12.1 min; τ_{minor} = 9.7 and 10.7 min.

(3*R*, 4*S*)-4-Nitro-3-(4-chlorophenyl)-6-(1-phenyl-1*H*-tetrazol-5-ylsulfonyl)hexanal and (3*R*, 4*R*)-4-Nitro-3-(4-chlorophenyl)-6-(1-phenyl-1*H*-tetrazol-5-ylsulfonyl)hexanal (4j)

The title compound was obtained in a 78% yield as yellowish oil after Flash column chromatography (Hexane 3:1 EtOAc) according to the general procedure, using LiOAc as additive (20 mol%) as a 55:45 mixture of diastereomers. The diastereomeric ratio (*dr*) was determined by HPLC. ^{1}H NMR (300 MHz) (data obtain from the mixture of diastereomers): δ 9.69 (s, $1H_{major}$), 9.57 (s, $1H_{minor}$), 7.69-7.55 (m,

$5H_{major}$, $5H_{minor}$), 7.34-7.25 (m, $2H_{major}$, $2H_{minor}$), 7.17-7.06 (m, $2H_{major}$, $2H_{minor}$) 5.08-4.95 (m, $1H_{major}$, $1H_{minor}$), 3.90-3.59 (m, $3H_{major}$, $3H_{minor}$), 3.24-3.11 (m, $1H_{minor}$), 3.05-2.91 (m, $1H_{major}$, $1H_{minor}$) 2.87-2.76 (m, $1H_{major}$), 2.68-2.42 (m, $1H_{major}$, $2H_{minor}$) 2.30-2.15 (m, $1H_{major}$). ^{13}C NMR (75 MHz) (Mixture of diastereomers): δ 198.3 (CHO), 197.5 (CHO), 153.0 (C), 152.8 (C), 135.1 (C), 134.7 (C), 134.5 (2C), 132.7 (2C), 131.7 (2CH), 129.8 (4CH), 129.7 (2CH), 129.4 (4CH), 129.3 (2CH), 125.0 (2CH), 124.9 (2CH), 89.3 (CH), 88.2 (CH), 52.6 (CH_2), 52.3 (CH_2), 46.2 (CH_2), 45.3 (CH_2), 42.5 (CH), 41.7 (CH), 24.6 (CH_2), 24.4 (CH_2). MS (*ESI*): m/z 464 (M^++1, 48), 149 (23), 147 (100), 119 (89). HRMS (ESI): calculated for $C_{19}H_{19}N_5O_5SCl$ (M^++1): 464.0789; found: 464.0791. The enantiomeric excess was determined by SFC-HPLC over the corresponding acetal following Method A. Chiralpak IB column [CO_2/MeOH = 90:10]; flow rate 3.0 mL/min. *ee* = 86%, τ_{major} = 6.3 and 12.1 min; τ_{minor} = 9.0 and 11.0 min.

(3*R*, 4*S*)-4-Nitro-3-(4-metoxyphenyl)-6-(1-phenyl-1*H*-tetrazol-5-ylsulfonyl)hexanal and (3*R*, 4*R*)-4-Nitro-3-(4-metoxyphenyl)-6-(1-phenyl-1*H*-tetrazol-5-ylsulfonyl)hexanal (4k)

The title compound was obtained as yellow oil after flash column chromatography (Hexane 2:1 EtOAc) according to the general procedure, using LiOAc as additive (20 mol%) as a 54:46 mixture of diastereomers (25 mg, 55% yield). The diastereomeric ratio (*dr*) was determined by HPLC. ^1H NMR (300 MHz) (data obtain from the mixture of diastereomers): δ 9.70 (s, $1H_{minor}$), 9.56 (s, $1H_{major}$), 7.71-7.57 (m, $5H_{major}$, $5H_{minor}$), 7.13-7.01 (m, $2H_{major}$, $2H_{minor}$), 6.89-6.81 (m, $2H_{major}$, $2H_{minor}$) 5.05-4.89 (m, $1H_{major}$, $1H_{minor}$), 3.82-3.57 (m, $6H_{major}$, $6H_{minor}$) 3.40-3.29 (m, $1H_{minor}$), 3.03-2.89 (m, $1H_{major}$, $1H_{minor}$) 2.81-2.70 (m, $1H_{major}$), 2.67-2.40 (m, $1H_{major}$, $2H_{minor}$) 2.36-2.17 (m, $1H_{major}$). ^{13}C NMR (75 MHz) (Mixture of diastereomers): δ 199.0 (CHO), 198.2 (CHO), 159.6 (C), 159.5 (C), 153.0 (C), 152.8 (C), 132.8 (C), 132.7 (C), 131.7 (2CH), 129.8 (4CH), 129.1 (4CH), 128.1 (C), 127.9 (C), 125.0 (2CH), 124.9 (2CH), 114.9 (2CH), 114.5 (2CH), 89.7 (CH), 88.4 (CH), 55.3 ($2CH_3$), 52.6 (CH_2), 52.4 (CH_2), 46.4 (CH_2), 45.4 (CH_2), 42.6 (CH), 41.8 (CH), 24.6 (CH_2), 24.2 (CH_2). MS (*ESI*): m/z 460 (M^++1, 100), 282 (12), 163 (41), 149 (30), 119 (22). HRMS (ESI): calculated for $C_{20}H_{22}N_5O_6S$ (M^++1): 460.1285; found: 460.1263. The enantiomeric excess was determined by SFC-HPLC over the corresponding acetal following Method A. Chiralpak IB column [CO_2/MeOH = 90:10]; flow rate 3.0 mL/min. *ee* = 80%, τ_{major} = 5.9 and 10.2 min; τ_{minor} = 7.7 and 12.0 min.

General procedure for the intramolecular Julia-Kocienski olefination

Note: Nitrocyclohexenes with short aliphatic chains (**5b** and **5c**) presented low stability working with them and the isolation was difficult.[32]

Method A: The corresponding adduct **4a-g** (0.09 mmol) was dissolved in a 3:1 mixture of THF and DMF (2 mL) and Cs_2CO_3 (3 equiv), was added to the solution in one portion under stirring at 70 ºC. The reaction was stirred for 2 hours at that temperature, whereupon it was allowed to cool to r.t. The reaction was quenched with a sat. aq. NH_4Cl solution (5 mL) and water (5 mL) and EtOAc (10 mL) were subsequently added. The mixture was transferred into a separatory funnel and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The crude was dissolved in CH_3CN (2 mL) and the flask was put in a CH_3CN / CO_2 bath at -40 ºC and DBU (16 µL, 0.1 mmol) was added dropwise. The reaction was stirred for 15 minutes at -40 ºC whereupon it was carefully quenched dropwise with a sat. aq. NH_4Cl solution (5 mL). Water (5 mL) and EtOAc (10 mL) were subsequently added and the mixture was transferred into a separatory funnel and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The crude was purified by flash column chromatography to afford the corresponding cyclohexenes **5a-g** indicated in each case.

When method A was used with Michael adduct **4i,** the biaryl by-product derived from loss of the nitro group and subsequent aromatization of the cyclohexene was observed by 1H NMR spectra. Therefore, method B was used for adducts with an aromatic substituent.

Method B: The corresponding adduct **4h-k** (0.09 mmol) was dissolved in CH_3CN (2 mL), and the mixture was stirred at 0 ºC for 1 minute and DBU (2 equiv) was added. The reaction was stirred for 30 minutes at 0 ºC whereupon it was put in a CH_3CN / CO_2 bath at -40 ºC, stirred for 15 minutes and carefully quenched dropwise with a sat. aq. NH_4Cl solution (5 mL). Water (5 mL) and EtOAc (10 mL) were subsequently added and the mixture was transferred into a separatory funnel and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The crude was purified by flash column chromatography to afford the corresponding cyclohexenes **5h-k** indicated in each case.

(4*S*, 5*S*)-5-Nitro-4-propylcyclohex-1-ene (5a)

The title compound was obtained in a 57% yield as pale yellow oil after flash column chromatography (Hexane 20:1 EtOAc) as a 91:9 mixture of diastereomers following method A. The diastereomeric ratio

(*dr*) was determined by ^{1}H NMR. ^{1}H NMR (300 MHz) (91:9 Mixture of diastereomers): δ 5.75-5-58 (m, $2H_{major}$, $2H_{minor}$), 4.72 (td, *J* = 6.1 and 3.5 Hz, $1H_{minor}$), 4.48 (td, *J* = 10.0 and 5.7 Hz $1H_{major}$), 2.77-2.09 (m, $4H_{major}$, $4H_{minor}$), 1.90-1.74 (m,$1H_{major}$, $1H_{minor}$), 1.43-1.20 ($4H_{major}$, $4H_{minor}$), 0.89 (t, *J* = 7.2 Hz, $3H_{major}$, $3H_{minor}$). ^{13}C NMR (75 MHz) (Mixture of diastereomers): Major diastereomer: δ 126.1 (CH), 122.4 (CH), 87.8 (CH), 36.6 (CH), 34.2 (CH_2), 30.3 (CH_2), 29.4 (CH_2), 19.1 (CH_2), 14.0 (CH_3). Minor diastereomer: δ 125.9 (CH), 122.1 (CH), 83.8 (CH), 36.0 (CH), 31.5 (CH_2), 28.2 (CH_2), 27.1 (CH_2), 20.2 (CH_2), 14.0 (CH_3). MS (*EI*): m/z 122 (M-NO_2^+, 3), 79 (100), 67 (11). HRMS (EI): calculated for C_9H_{14} (M-NO_2^+): 122.1097; found: 122.1096

(4*S*, 5*S*)-4-Methyl-5-nitrocyclohex-1-ene (5b)

The title compound was obtained in a 45% yield as pale yellow oil after flash column chromatography (Hexane 20:1 EtOAc) as a 79:21 mixture of diastereomers. The compound could be isolated to obtain NMR data. However, the reaction and the purification had to be performed carefully because the compound presented low stability[5]. Method B was used, but quenching the reaction at 0 ºC after 15 minutes. The diastereomeric ratio (*dr*) was determined by ^{1}H NMR. ^{1}H NMR (300 MHz) (79:21 Mixture of diastereomers): δ 5.73-5.58 (m, $2H_{major}$, $2H_{minor}$), 4.66 (ddd, *J* = 8.1, 5.8 and 3.6 Hz, $1H_{minor}$), 4.41 (td, *J* = 10.1 and 5.7 Hz, $1H_{major}$), 2.79-2.25 (m, $4H_{major}$, $4H_{minor}$), 1.95-1.79 (m, $1H_{major}$, $1H_{minor}$), 1.03 (d, *J* = 6.5 Hz, $1H_{major}$), 1.00 (d, *J* = 6.5 Hz, $1H_{minor}$). ^{13}C NMR (75 MHz) (Mixture of diastereomers): Major diastereomer: δ 126.3 (CH), 122.6 (CH), 88.9 (CH), 32.5 (CH_2), 32.4 (CH), 30.4 (CH_2), 17.8 (CH_3). Minor diastereomer: δ 125.3 (CH), 121.9 (CH), 84.4 (CH), 31.4 (CH_2), 30.8 (CH), 25.8 (CH_2), 14.5 (CH_3). MS and HRMS could not be obtained due to the instability of the compound.

(4*S*, 5*S*)-4-Ethyl-5-nitrocyclohex-1-ene (5c)

The title compound was obtained in a 51% yield as pale yellow oil after flash column chromatography (Hexane 20:1 EtOAc) as a 92:8 mixture of diastereomers following method A. The diastereomeric ratio (*dr*) was determined by ^{1}H NMR. ^{1}H NMR (300 MHz) (92:8 Mixture of diastereomers): δ 5.75-5-57 (m, $2H_{major}$, $2H_{minor}$), 4.75 (td, *J* = 6.2 and 3.2 Hz, $1H_{minor}$) 4.50 (td, *J* = 9.9 and 5.5 Hz $1H_{major}$), 2.79-2.11 (m, $4H_{major}$, $4H_{minor}$), 1.91-1.76 (m, $1H_{major}$, $1H_{minor}$), 1.57-1.32 ($2H_{major}$, $2H_{minor}$), 0.93 (t, *J* = 7.5 Hz, $3H_{major}$, $3H_{minor}$). ^{13}C NMR (75 MHz) (Mixture of diastereomers): Major diastereomer: δ 126.1 (CH), 122.4 (CH), 87.5 (CH), 38.3 (CH), 30.4 (CH_2), 29.0 (CH_2), 24.8 (CH_2), 10.3 (CH_3). Minor diastereomer: δ

125.9 (CH), 122.1 (CH), 83.2 (CH), 38.1 (CH), 27.8 (CH_2), 27.2 (CH_2), 22.4 (CH_2), 11.6 (CH_3) MS and HRMS could not be obtained due to the instability of the compound.

(4*S*, 5*S*)-4-Butyl-5-nitrocyclohex-1-ene (5d)

The title compound was obtained in a 60% yield as pale yellow oil after flash column chromatography (Hexane 20:1 EtOAc) as a 85:15 mixture of diastereomers following method A. The diastereomeric ratio (*dr*) was determined by ^{1}H NMR. ^{1}H NMR (300 MHz) (85:15 Mixture of diastereomers): δ 5.74-5-55 (m, $2H_{major}$, $2H_{minor}$), 4.73 (td, J = 6.0 and 3.3 Hz, $1H_{minor}$) 4.49 (td, J = 9.9 and 5.6 Hz $1H_{major}$), 2.78-2.09 (m, $4H_{major}$, $4H_{minor}$), 1.92-1.73 (m, $1H_{major}$, $1H_{minor}$), 1.43-1.20 ($6H_{major}$, $6H_{minor}$), 0.88 (t, J = 7.4 Hz, $3H_{major}$, $3H_{minor}$). ^{13}C NMR (75 MHz) (Mixture of diastereomers): Major diastereomer: δ 126.1 (CH), 122.4 (CH), 87.8 (CH), 36.8 (CH), 31.7 (CH_2), 30.3 (CH_2), 29.5 (CH_2), 28.1 (CH_2), 22.6 (CH_2) 13.9 (CH_3). Minor diastereomer: δ 125.9 (CH), 122.1 (CH), 83.9 (CH), 36.3 (CH), 32.0 (CH_2), 30.4 (CH_2), 29.3 (CH_2), 27.1 (CH_2), 22.7 (CH_2) 13.9 (CH_3). MS (*EI*): m/z 136 (M-NO_2^+, 2), 79 (100), 67 (14). HRMS (EI): calculated for $C_{10}H_{16}$ (M-NO_2^+): 136.1252; found: 136.1248

(4*S*, 5*S*)-4-((3*Z*)-Hex-3-enyl)-5-nitrocyclohex-1-ene (5e)

The title compound was obtained in a 63% yield as pale yellow oil after Flash column chromatography (Hexane 20:1 EtOAc) as a 75:25 mixture of diastereomers. Method A. The diastereomeric ratio (*dr*) was determined by ^{1}H NMR. ^{1}H NMR (300 MHz) (75:25 Mixture of diastereomers): δ 5.76-5-58 (m, $2H_{major}$, $2H_{minor}$), 5.45-5.32 (m, $1H_{major}$, $1H_{minor}$), 5.30-5.19 (m, $1H_{major}$, $1H_{minor}$), 4.73 (td, J = 5.9 and 3.2 Hz, $1H_{minor}$) 4.49 (td, J = 9.8 and 5.6 Hz, $1H_{major}$), 2.79-1.95 (m, $8H_{major}$, $8H_{minor}$), 1.93-1.77 (m, $1H_{major}$, $1H_{minor}$), 1.48-1.27 ($2H_{major}$, $2H_{minor}$), 0.95 (t, J = 7.5 Hz, $3H_{major}$, $3H_{minor}$). ^{13}C NMR (75 MHz) (Mixture of diastereomers): Major diastereomer: δ 132.6 (CH), 127.6 (CH), 126.0 (CH), 122.4 (CH), 87.6 (CH), 36.4 (CH), 32.0 (CH_2), 30.2 (CH_2), 29.4 (CH_2), 23.5 (CH_2), 20.5 (CH_2) 14.3 (CH_3). Minor diastereomer: δ 132.7 (CH), 127.8 (CH), 125.8 (CH), 122.2 (CH), 83.7 (CH), 35.6 (CH), 31.6 (CH_2), 28.1 (CH_2), 27.2 (CH_2), 24.5 (CH_2), 22.7 (CH_2) 14.3 (CH_3). MS (*EI*): m/z 232 (M^+ +23, 36), 179 (47), 163 (100), 149 (42). HRMS (EI): calculated for $C_{12}H_{19}NO_2Na$ (M^+ +1): 232.1308; found: 232.1314

(4*S*, 5*S*)-5-Nitro-4-nonylcyclohex-1-ene (5f)

The title compound was obtained in a 61% yield as pale yellow oil after flash column chromatography (Hexane 30:1 EtOAc) as a mixture 76:24 of diastereomers following method A. The diastereomeric ratio (*dr*) was determined by ^{1}H NMR. ^{1}H NMR (300 MHz) (76:24 Mixture of diastereomers): δ 5.74-5-

56 (m, $2H_{major}$, $2H_{minor}$), 4.73 (td, J = 3.6 and 6.1 Hz, $1H_{minor}$) 4.49 (td, J = 9.9 and 5.5 Hz $1H_{major}$), 2.78-2.11 (m, $4H_{major}$, $4H_{minor}$), 1.90-1.76 (m, $1H_{major}$, $1H_{minor}$), 1.35-1.19 (m, $16H_{major}$, $16H_{minor}$), 0.89 (t, J = 7.2 Hz, $3H_{major}$, $3H_{minor}$). ^{13}C NMR (75 MHz) (Mixture of diastereomers): Major diastereomer: δ 126.1 (CH), 122.3 (CH), 87.8 (CH), 36.8 (CH), 32.0 (CH_2), 31.8 (CH_2), 30.3 (CH_2), 29.8-29.1 ($5CH_2$), 25.9 (CH_2), 22.6 (CH_2) 14.1 (CH_3). Minor diastereomer: δ 125.9 (CH), 122.1 (CH), 83.8 (CH), 36.2 (CH), 32.0 (CH_2), 31.8 (CH_2), 30.3 (CH_2), 29.8-29.1 ($5CH_2$), 25.9 (CH_2), 22.6 (CH_2) 14.1 (CH_3). MS (*EI*): m/z 276 (M^+ +23, 40), 207 (24), 163 (55), 149 (43). HRMS (EI): calculated for $C_{15}H_{27}NO_2Na$ (M^+ +23): 276.1934; found: 276.1947

(4*R*, 5*S*)-4-(2, 2-Dimethoxyethyl)-5-nitrocyclohex-1-ene (5g)

The title compound was obtained in a 60% yield as pale yellow oil after flash column chromatography (Hexane 8:1 EtOAc) as a mixture 90:10 of diastereomers following method A. The diastereomeric ratio (*dr*) was determined by ^{1}H NMR. The procedure to obtain this product has been scaled up until 300 mg of **4g,** maintaining yield and *dr*. ^{1}H NMR (300 MHz) (90:10 Mixture of diastereomers): δ 5.73-5.55 (m, $2H_{major}$, $2H_{minor}$), 4.75-4.66 (td, J = 3.4 and 6.0 Hz, $1H_{minor}$), 4.55-4.38 (m, $2H_{major}$, $1H_{minor}$), 3.30-3.22 (m, $6H_{major}$, $6H_{minor}$), 2.78-2.07 (m, $4H_{major}$, $4H_{minor}$), 1.99-1.81 (m, $1H_{major}$, $1H_{minor}$), 1.77-1.57 (m, $1H_{major}$, $1H_{minor}$), 1.53-1.41 (m, $1H_{major}$, $1H_{minor}$). ^{13}C NMR (75 MHz) (Mixture of diastereomers): Major diastereomer: δ 125.8 (CH), 122.4 (CH), 101.9 (CH), 87.0 (CH), 53.4 (CH_3), 51.8 (CH_3), 34.8 (CH_2), 33.3 (CH), 30.0 (CH_2), 29.7 (CH_2). Minor diastereomer: δ 125.8 (CH), 122.2 (CH), 102.8 (CH), 83.4 (CH), 53.1 (CH_3), 52.7 (CH_3), 32.5 (CH_2), 32.2 (CH), 28.6 (CH_2), 27.4 (CH_2). MS (*ESI*): m/z 238 (M^++23, 81), 153 (29), 137 (61), 105 (100). HRMS (ESI): calculated for $C_{10}H_{17}NO_4Na$ (M^++23): 238.1049; found: 238.1055. The enantiomeric excess was determined by HPLC using a Chiralpak IB column [Hexane/^{i}PrOH = 99:1]; flow rate 0.5 mL/min. *ee* = 94%, τ_{major} = 40.1 and 47.4 min; τ_{minor} = 38.3 and 43.7 min. The *ee* was determined over a 74:26 diastereomers mixture.

(4*R*, 5*S*)-5-Nitro-4-phenyl-cyclohex-1-ene (5h)

The title compound was obtained in a 52% yield as colorless oil after flash column chromatography (Hexane 10:1 EtOAc) as a mixture 94:6 of diastereomers following method B. The diastereomeric ratio (*dr*) was determined by ^{1}H NMR. ^{1}H NMR (300 MHz) (94:6 Mixture of diastereomers): δ 7.36-7.18 (m, $5H_{major}$, $5H_{minor}$), 6.02-5.90 (m, $1H_{minor}$) 5.88-5.69 (m, $2H_{major}$, $1H_{minor}$), 4.99-4.82 (m, $1H_{major}$, $1H_{minor}$) 3.77-3.68 (m, $1H_{minor}$) 3.43 (td, J = 11.0 and 5.9 Hz, $1H_{major}$), 2.91-2.26 (m, $4H_{major}$, $4H_{minor}$). ^{13}C NMR (75 MHz) Major diastereomer: δ 139.9 (C), 128.9 (2 CH), 127.6 (CH), 127.4 (2 CH), 126.6 (CH), 122.7

(CH), 87.4 (CH), 44.2 (CH), 33.2 (CH_2), 31.3 (CH_2). Minor diastereomer could not be assigned due to the small proportion of this diastereomer compared with the major one. MS (*EI*): m/z 226 (M^+ +23, 28), 157 (100), 149 (19), 129 (13). HRMS (EI): calculated for $C_{12}H_{13}NO_2Na$ (M^+ +23): 226.0838; found: 226.0834

(4*R*, 5*S*)-5-Nitro-4-(4-nitro)-phenyl-cyclohex-1-ene (5i)

The title compound was obtained in a 49% yield as colorless oil after flash column chromatography (Hexane 8:1 EtOAc) as a mixture 91:9 of diastereomers following method B. The diastereomeric ratio (*dr*) was determined by ^{1}H NMR. ^{1}H NMR (300 MHz) (91:9 Mixture of diastereomers): δ 8.19 (d, J = 8.7 Hz, $2H_{major}$), 8.15 (d, J = 8.8 Hz, $2H_{minor}$), 7.42 (d, J = 8.7 Hz, $2H_{major}$) 7.38 (d, J = 8.8 Hz, $2H_{minor}$), 7.21-7.11 (m, $2H_{major}$, $2H_{minor}$), 6.01-5.94 (m, $1H_{minor}$) 5.88-5-73 (m, $2H_{major}$, $1H_{minor}$), 5.07-4.88 (m, $1H_{major}$, $1H_{minor}$) 3.91-3.81 (m, $1H_{minor}$) 3.56 (td, J = 11.2 and 6.0 Hz, $1H_{major}$), 2.92-2.26 (m, $4H_{major}$, $4H_{minor}$), ^{13}C NMR (75 MHz) (Mixture of diastereomers): Major diastereomer: δ 147.5 (C), 131.0 (C), 128.4 (2CH), 125.9 (CH), 124.2 (2CH), 123.0 (CH), 86.7 (CH), 44.1 (CH), 32.9 (CH_2), 31.1 (CH_2). Minor diastereomer could not be assigned due to the small proportion of this diastereomer compared with the major one. MS (*EI*): m/z 271 (M^+ +23, 13), 202 (16), 169 (18), 149 (61), 113 (16). HRMS (EI): calculated for $C_{12}H_{12}N_2O_4Na$ (M^+ +23): 271.0689; found: 271.0696

(4*R*, 5*S*)-5-Nitro-4-(4-chloro)-phenyl-cyclohex-1-ene (5j)

The title compound was obtained in a 50% yield as colorless oil after flash column chromatography (Hexane 10:1 EtOAc) as a mixture 91:9 of diastereomers following method B. The diastereomeric ratio (*dr*) was determined by ^{1}H NMR. ^{1}H NMR (300 MHz) (91:9 Mixture of diastereomers): δ 7.34-7.24 (m, $2H_{major}$, $2H_{minor}$), 7.21-7.11 (m, $2H_{major}$, $2H_{minor}$), 5.99-5.91 (m, $1H_{minor}$) 5.86-5-70 (m, $2H_{major}$, $1H_{minor}$), 4.99-4.82 (m, $1H_{major}$, $1H_{minor}$) 3.74 (td, J = 6.4 and 4.2 Hz $1H_{minor}$) 3.41 (td, J = 11.1 and 5.8 Hz, $1H_{major}$), 2.90-2.23 (m, $4H_{major}$, $4H_{minor}$). ^{13}C NMR (75 MHz) (Mixture of diastereomers): Major diastereomer: δ 138.5 (C), 132.4 (C), 129.1 (2CH), 128.7 (2CH), 126.3 (CH), 122.8 (CH), 87.3 (CH), 43.8 (CH), 33.1 (CH_2), 31.2 (CH_2). Minor diastereomer could not be assigned due to the small proportion of this diastereomer compared with the major one. MS (*EI*): m/z 191 (M-NO_2^+, 46), 153 (100), 149 (21), 125 (18). HRMS (EI): calculated for $C_{12}H_{12}Cl$ (M-NO_2^+): 191.0622; found: 191.06427

(4*R*, 5*S*)-5-Nitro-4-(4-methoxy)-phenyl-cyclohex-1-ene (5k)

The title compound was obtained in a 52% yield as colorless oil after Flash column chromatography (Hexane 10:1 EtOAc) as a mixture 85:15 of diastereomers following method B. The diastereomeric ratio (*dr*) was determined by ^{1}H NMR. ^{1}H NMR (300 MHz) (85:15 Mixture of diastereomers): δ 7.19-7.09 (m, $2H_{major}$, $2H_{minor}$), 6.91-6.80 (m, $2H_{major}$, $2H_{minor}$), 6.03-5.89 (m, $1H_{minor}$) 5.86-5.64 (m, $2H_{major}$, $1H_{minor}$), 4.97-4.80 (m, $1H_{major}$, $1H_{minor}$) 3.84-3.70 (m, $4H_{major}$, $4H_{minor}$) 3.36 (td, *J* = 11.0 and 5.9 Hz, $1H_{major}$), 2.96-2.25 (m, $4H_{major}$, $4H_{minor}$). ^{13}C NMR (75 MHz) (Mixture of diastereomers): Major diastereomer: δ 158.9 (C), 132.0 (C), 129.3 (2CH), 126.7 (CH), 122.6 (CH), 114.2 (2CH), 87.7 (CH), 55.2 (CH_3), 43.5 (CH), 33.2 (CH_2), 31.2 (CH_2). Minor diastereomer: δ 158.7 (C), 130.0 (C), 129.2 (2CH), 128.8 (CH), 124.5 (CH), 114.0 (2CH), 84.6 (CH), 53.7 (CH_3), 40.1 (CH), 31.9 (CH_2), 31.5 (CH_2). MS (*EI*): m/z 256 (M^+ +23, 9), 187 (100), 149 (15), 121 (66). HRMS (EI): calculated for $C_{13}H_{15}NO_3Na$ (M^+ +23): 256.0944; found: 256.0942

General procedure for the reduction of compound 5g

Nitrocyclohexene **5g** (42 mg, 0.2 mmol) was dissolved in MeOH (2 mL), and the flask was charged in open air with Pd/C catalyst (10% w/t, 30 mg). The mixture was stirred for 5 minutes, whereupon the solution was purged with a hydrogen balloon for 10 minutes and was heated at 50 ºC under hydrogen atmosphere for 24 h. After this time, the solution was filtered through a short pad of celite washing with MeOH (2 x 10 mL). The solvent was removed under reduced pressure to afford compound **6** (34 mg, yield: 98%) as a colorless oil as a 90:10 mixture of diastereomers. ^{1}H NMR (300 MHz) (Mixture of diastereomers): δ 4.55-4.41 (m, $1H_{major}$, $1H_{minor}$), 3.31 (d, *J* = 4.1 Hz, $6H_{major}$, $6H_{minor}$), 2.40-2.12 (m, $3H_{major}$, $3H_{minor}$), 2.07 – 1.94 (m, $1H_{major}$, $1H_{minor}$), 1.92-1.58 (m, $4H_{major}$, $4H_{minor}$), 1.45-1.07 (m, $6H_{major}$, $6H_{minor}$). ^{13}C NMR (75 MHz) (Mixture of diastereomers): Major diastereomer: δ 103.1 (CH), 54.8 (CH), 53.0 (CH_3), 52.1 (CH_3), 41.8 (CH), 36.5 (CH_2), 36.0 (CH_2), 31.6 (CH_2), 25.9 (CH_2), 25.3 (CH_2). Minor diastereomer: δ 103.4 (CH), 52.9 (CH_3), 52.4 (CH_3), 49.8 (CH), 41.7 (CH), 37.0 (CH_2), 36.0 (CH_2), 31.9 (CH_2), 27.1 (CH_2), 24.7 (CH_2). MS (*ESI*): m/z 188 (M^++1, 74), 121 (26), 105 (100). HRMS (ESI): calculated for $C_{10}H_{22}NO_2$ (M^++1): 187.1572; found: 187.1581

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Supporting Information Available.

Chemical correlation, spectra of compounds **1**, **3g**, **4a-k** and **5a-k** and **6**, as well as chiral SFC-HPLC conditions. This material is available free of charge via the Internet at http:/pubs.acs.org.

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