Michael addition of carbonyl compounds to nitroolefins under the catalysis of new pyrrolidine-based bifunctional organocatalysts

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Abstract

Novel bifunctional pyrrolidine-based organocatalysts for the asymmetric Michael addition of carbonyl compounds to nitroolefins have been synthesised from homoallylimines, which are easily obtained from (*R*)-glyceraldehyde as chiral precursor. Under optimal reaction conditions these bifunctional organocatalysts showed a high catalytic efficiency (almost quantitative yield in most cases) and stereoselectivity in the Michael addition reactions of a variety of aldehydes (up to 98:2 dr and 97% ee) and ketones (up to 98:2 dr and 99% ee) to nitroolefins.

Introduction

Nowadays there is no doubt about the preeminent role of organocatalysis in enantioselective synthesis. The use of simple chiral organic molecules as catalysts has provided new and convenient synthetic methodologies to obtain a wide variety of chiral building blocks and pharmaceutical products[1] and these methods have transformed the field of asymmetric catalysis.[2]

Among the different organocatalysts developed for use in enantioselective synthesis, proline and its derivatives have proven to be especially useful in reactions that take place through the formation of enamine intermediates[3] and, in combination with other functional groups, they have provided bifunctional organocatalysts that are capable of efficiently promoting a wide array of asymmetric processes.[4]

One particularly useful reaction that can be promoted by pyrrolidine-based organocatalysts is the addition of carbonyl compounds to nitroolefins. The reaction provides γ-nitrocarbonyl compounds with two contiguous stereocentres and these compounds are key precursors for the synthesis of relevant bioactive molecules.[5]

Since the pioneering reports of List[6] and Barbas[7] on this subject a number of efficient catalysts have been designed and applied to this addition reaction.[8] In spite of the progress made in this area, interest in the design and development of new and efficient chiral organocatalysts for this and other important chemical transformations still continues.

As a part of our programme aimed at developing new, easily accessible and tunable organocatalysts from the chiral pool,[9] we have now focused on the synthesis of new bifunctional organocatalysts with the privileged pyrrolidine motif from chiral imines derived from (*R*)-glyceraldehyde and their application to the enantioselective Michael addition of carbonyl compounds to nitroolefins.

Results and discussion

We have previously described that chiral pyrrolidines with a bulky tunable 2,2-disubstituted-1,3-dioxolan-4-yl moiety at C_2 are effective organocatalysts in the asymmetric Michael addition of aldehydes to nitroolefins.[9b] It has also been reported the beneficial effect on catalytic performance of the presence of the appropriate group at the 4 position of the pyrrolidine ring in pyrrolidine-based silyl ether organocatalysts.[10] Bearing these results in mind, we decided to prepare new bifunctional organocatalysts with the general structure depicted in Figure 1 with the objective of obtaining improved organocatalysts. These chiral templates combine a 2,2-disubstituted-1,3-dioxolan-4-yl moiety at the 2-position of the pyrrolidine to provide a bulky environment and a different shielding of the two faces of the intermediate enamine and a sulfonamide group at the 4 position of the ring that is capable of interacting with the reagent and directing the attack.

We presumed that these new catalysts could be prepared starting from homoallylic amine **1**, which is easily obtained on a multigram scale from *N*-benzyl imines derived from (*R*)-glyceraldehyde acetonide according to our previously described procedure.[11]

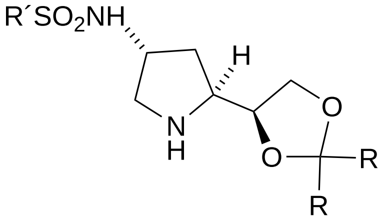
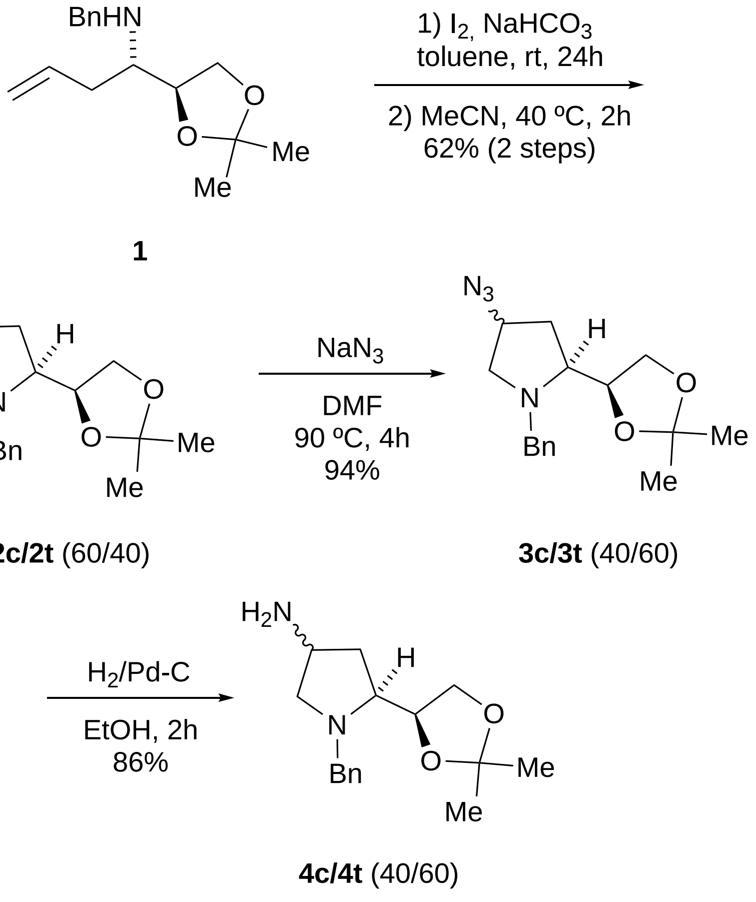


Fig. 1 General structure of new pyrrolidine-based bifunctional organocatalysts

It has been reported[12] that iodine-mediated cyclisation of homoallylamines at room temperature leads to the formation of 2,4-azetidines that are prone to isomerisation to 2,4-pyrrolidines upon heating. Iodocyclisation of homoallylamine **1** was chosen to construct the pyrrolidine ring functionalised at C_4. After some experimentation the best results were obtained by reaction of homoallylic amine **1** with iodine (4 equiv.) and sodium hydrogen carbonate (5 equiv.) in toluene at room temperature for 24 h followed by heating in acetonitrile at 40 °C for 2 h. Reaction under these conditions led to the formation of a 60/40 diastereomeric mixture of *cis*- and *trans*-pyrrolidines **2c/2t** in 62% isolated yield. Nucleophilic displacement of iodine by azide through the treatment of 4-iodopyrrolidines **2c/2t** with sodium azide in DMF at 90 °C provided 4-azidopyrrolidines **3c/3t** as a 40/60 mixture of *cis* and *trans* diastereoisomers. The diastereomeric mixture of azidopyrrolidines **3c/3t** was reduced to the corresponding *cis*- and *trans*-4-aminopyrrolidines **4c/4t** by hydrogenation over Pd/C in ethanol. The reaction sequence to prepare 4-aminopyrrolidines **4c/4t** from homoallylamine **1** is shown is Scheme 1.



1

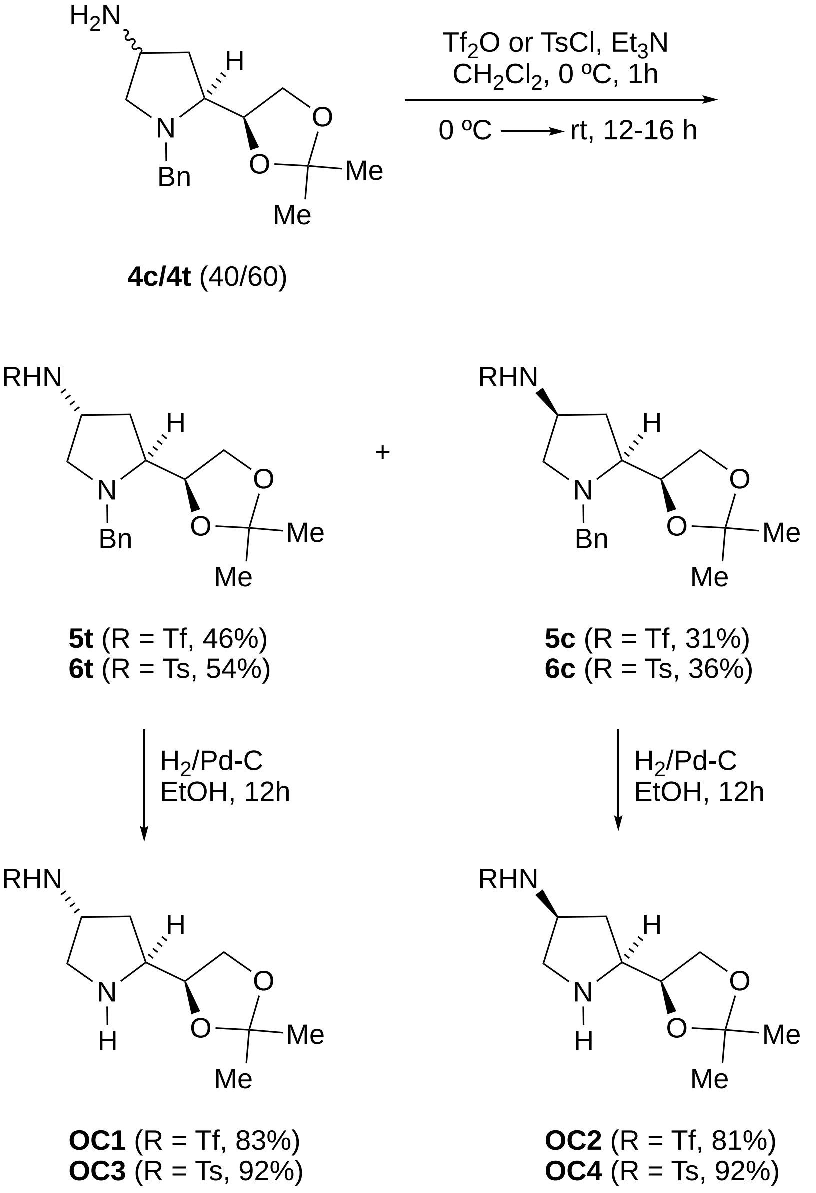
2c/2t (60/40)

3c/3t (40/60)

4c/4t (40/60)

Scheme 1 Synthesis of *cis*- and *trans*-4-aminopyrrolidines **4c/4t**

The organocatalysts **OC1** and **OC2** were prepared by treating the diastereomeric mixture of *cis*- and *trans*-4-aminopyrrolidines **4c/4t** with trifluoromethanesulfonic anhydride and triethylamine to afford the corresponding triflates **5c** and **5t**, which were easily isolated by column chromatography. Subsequent N-debenzylation was achieved by exposure of the isolated triflates to molecular hydrogen in the presence of Pd/C as a catalyst. In a similar way, tosylation of the **4c/4t** diastereomeric mixture with *p*-toluenesulfonyl chloride in the presence of triethylamine and subsequent deprotection by hydrogenolysis of isolated tosylates **6c** and **6t** provided access to organocatalysts **OC3** and **OC4** (Scheme 2).



4c/4t (40/60)

5t (R = Tf, 46%)
6t (R = Ts, 54%)

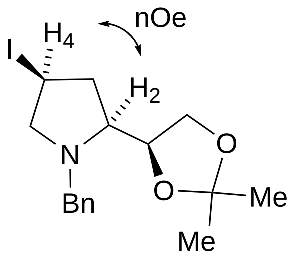
5c (R = Tf, 31%)
6c (R = Ts, 36%)

OC1 (R = Tf, 83%)
OC3 (R = Ts, 92%)

OC2 (R = Tf, 81%)
OC4 (R = Ts, 92%)

Scheme 2 Synthesis of organocatalysts **OC1–OC4**

The structure and stereochemistry of major 4-iodopyrrolidine **2c** were established on the basis of NMR data and a NOESY experiment (Figure 2). In the NOESY spectrum of compound **2c** clear cross-peaks were observed between the H_2 and H_4 resonances. These cross-peaks clearly indicate a close spatial disposition, which is only possible if these two nuclei are in a *cis* disposition. In addition, the stereochemistry of minor tosylate **6c** was determined as (2*S*,4*S*) by X-ray diffraction analysis. These results allowed the stereochemistry of the obtained compounds to be unambiguously established.

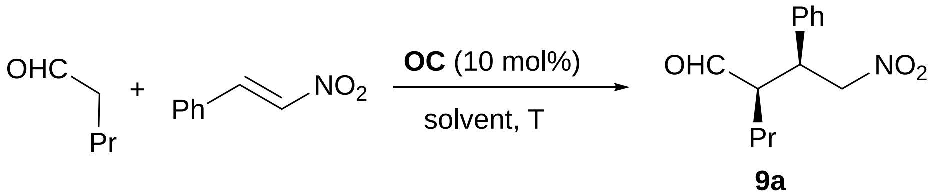


2c

Fig. 2 Diagnostic nOe for the determination of the stereochemistry of **2c**

Initial screening of the catalytic properties of the sulfonamides **OC1–OC4** for the 1,4-addition between *trans*-β-nitrostyrene and pentanal in toluene at room temperature and in the presence of 10 mol% of catalyst (Table 1) showed that a *trans* disposition of substituents was necessary for efficient catalysis. With sulfonamides **OC-2** and **OC-4**, which have a *cis* disposition between the sulfonamide and the bulky substituent, the reaction under these conditions proceeded to give a quite poor yield, whereas sulfonamides **OC-1** and **OC-3**, which have a *trans* disposition between the two substituents, promoted the reaction well, with **OC-3** being more enantioselective than **OC-1** (93% ee *vs* 87% ee). As far as the reaction medium is concerned, the best results were obtained in toluene.

Table 1 Initial screening for the Michael addition of pentanal to *trans* β-nitrostyrene.[a]



9a

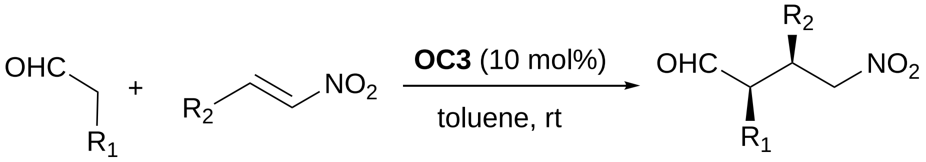
Entry	Catalyst	Solvent	T	Time	Yield[b] (%)	*syn*/*anti*[b]	ee[c] *syn* (%)
1	**OC1**	toluene	rt	24 h	100	94/6	87
2	**OC2**	toluene	rt	7 d	11	85/15	75
3	**OC3**	toluene	rt	24 h	100	94/6	93
4	**OC4**	toluene	rt	7 d	43	89/11	81
5	**OC3**	CF_3Ph	rt	24 h	100	87/13	82
6	**OC3**	$CHCl_3$	rt	24 h	99	87/13	69
7	**OC3**	THF	rt	24 h	13	72/28	49
8	**OC3**	MeCN	rt	24 h	36	68/32	44
9	**OC3**	EtOH	rt	24 h	70	61/39	33
10	**OC3**	H_2O	rt	24 h	85	93/7	86
11	**OC3**	brine	rt	24 h	100	87/13	72
12	**OC3**	toluene	0 ºC	3 d	100	95/5	91
13	**OC3**	CF_3Ph	0 ºC	5 d	100	90/10	87
14	**OC3**[d]	toluene	rt	3 d	100	95/5	92

[a] All reactions were carried out under the following conditions: aldehyde (0.33 mmol), tosylamine (0.3 mmol), $BF_3 \cdot OEt_2$ (0.33 mol), dry solvent (5 mL), room temperature, 20 h, under Ar. [b] Determined from the crude reaction mixture by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard.

It is worth mentioning that **OC-3** is an active and highly stereoselective organocatalyst that works in aqueous media, although the stereoselectivity values were lower than those observed in toluene. A decrease in the reaction temperature did not improve the results obtained on working at room temperature and extended the reaction time. The catalyst loading could be decreased and the diastereoselectivity and enantioselectivity levels were maintained, although a longer reaction time was required to achieve a similar reaction yield.

Based on the results described above, we selected *p*-toluenesulfonamide **OC3** as the organocatalyst and explored the scope of the reaction with other aldehydes and nitroolefins. The reactions were carried out at room temperature in the presence of 10 mol% of catalyst and using toluene as solvent. The results are summarised in Table 2. Under these reaction conditions most Michael adducts were obtained in almost quantitative yield with very good diastereoselectivity (*syn*/*anti* 89/11–98/2) and high enantioselectivity (75–97% ee). With 3-methylbutanal as substrate the reactions took up to 7 days to reach completion. In order to shorten reaction time *p*-toluenesulfonic acid was added to the reaction medium as Brønsted acid co-catalysts.[13] The presence of this additive improved the catalytic activity but was detrimental to the enantio- and diastereoselectivity.

Table 2 Scope of the Michael addition of aldehydes to *trans*-β-nitroolefins using catalysts **OC3**.[a]



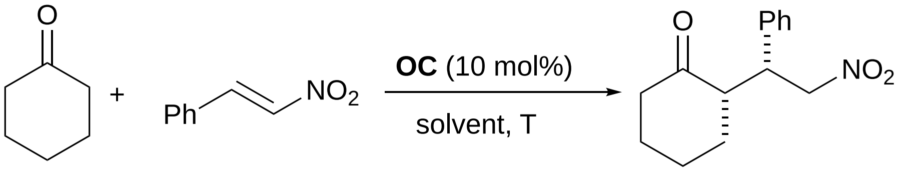
9a-9n

Entry	Product	R_1	R_2	Time	Yield[b] (%)	*syn*/*anti* [b]	ee[c] *syn* (%)
1	**9a**	*n*Pr	Ph	24 h	100	94/6	93
2	**9b**	Bn	Ph	10 h	100	95/5	88
3	**9c**	Et	Ph	24 h	100	91/9	91
4	**9d**	Me	Ph	24 h	100	95/5	91
5	**9e**	*n*Hx	Ph	24 h	100	93/7	93
6	**9f**	$CH_2=CH(CH_2)_7$	Ph	26 h	100	97/3	92
7	**9g**	^{i}Pr	Ph	7 d	100	98/2	97
8[d]	**9g**	^{i}Pr	Ph	4 d	100	85/15	95
9[e]	**9h**	*n*Pr	2-furyl	24 h	98	89/11	75
10	**9i**	*n*Pr	4-$MeOC_6H_4$	36 h	100	93/7	89
11	**9j**	*n*Pr	4-MeC_6H_4	24 h	100	93/7	92
12	**9k**	*n*Pr	4-ClC_6H_4	24 h	100	92/8	91
13	**9l**	*n*Pr	4-BrC_6H_4	24 h	99	94/6	92
14	**9m**	*n*Pr	3-BrC_6H_4	24 h	100	95/5	92
15	**9n**	*n*Pr	2-BrC_6H_4	24 h	100	95/5	92

[a] Reaction performed using 0.2 mmol of nitroolefin, 0.4 mmol of aldehyde, 10 mol% of **OC3**, in toluene (2 mL) at room temperature. [b] Determined from the crude reaction mixture by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [c] Determined by chiral HPLC. [d] Reaction performed using 0.02 mmol of *p*-nitrobenzoic acid as additive. [e] Reaction was performed in the absence of light.

A second set of experiments was conducted using new bifunctional organocatalysts **OC1** and **OC3** to promote 1,4-addition between *trans*-β-nitrostyrene and ketones (Table 3). The preliminary results obtained in the reaction of cyclohexanone and *trans*-β-nitrostyrene showed that in this case trifluoromethanesulfonamide **OC1** was the most active and enantioselective organocatalyst and that trifluoromethyl benzene was the best solvent. The use of 10 mol% of **OC1** in trifluoromethyl benzene at room temperature gave a nearly quantitative yield of the corresponding Michael adduct **10a** in 48 h. The catalyst gave high diastereoselectivity in favour of the *syn*-adduct (dr = 97/3) and an excellent enantioselectivity (ee = 99%). A decrease in the reaction temperature did not improve these results and lowering the catalyst loading to 5 mol% extended the reaction time and slightly decreased the diastereoselectivity. As before, organocatalyst **OC-1** is active and highly stereoselective in aqueous media although the stereoselectivity values were lower than those observed in trifluoromethyl benzene.

Table 3 Initial screening for the Michael addition of cyclohexanone to *trans*-β-nitrostyrene.[*a*]

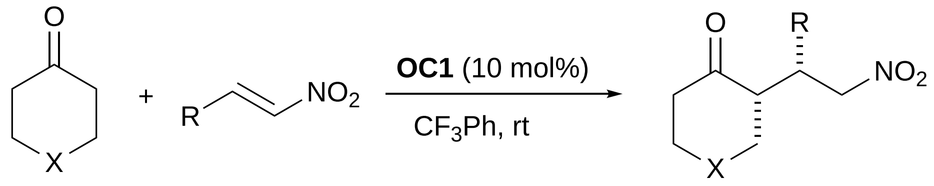


10a

Entry	Catalysts	Solvent	T	Time	Yield[b] (%)	*syn*/*anti*[b]	ee[c] *syn* (%)
1	**OC1**	toluene	rt	48 h	88	94/6	85
2	**OC3**	toluene	rt	3 d	88	94/6	74
3	**OC1**	CF_3Ph	rt	48 h	100	97/3	99
4	**OC3**	CF_3Ph	rt	3 d	84	93/7	91
5	**OC1**	$CHCl_3$	rt	48 h	92	96/4	74
6	**OC1**	THF	rt	48 h	2	> 98/2	79
7	**OC1**	MeCN	rt	48 h	100	95/5	95
8	**OC1**	EtOH	rt	48 h	21	96/4	70
9	**OC1**	H_2O	rt	48 h	60	94/6	90
10	**OC1**	brine	rt	48 h	93	95/5	91
11	**OC1**	CF_3Ph	0 ºC	48 h	54	96/4	91
12	**OC3**	CF_3Ph	0 ºC	48 h	34	96/4	87
13[d]	**OC1**	CF_3Ph	rt	4 d	100	95/5	91

[a] Reaction performed using 0.2 mmol of β-nitrostyrene, 0.4 mmol of ketone and 10 mol% of organocatalyst in the given solvent (2 mL).[b] Determined from the crude reaction mixture by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [c] Determined by chiral HPLC. [d] Catalyst loading 5 mol%.

Table 4 Scope of Michael addition of ketones to *trans*-β-nitroolefins using catalysts **OC1**.[a]



10a-10j

Entry	Product	X	R	Time	Yield[b] (%)	*syn*/*anti* [b]	ee[c] *syn* (%)
1	**10a**	CH_2	Ph	48 h	100	97/3	99
2	**10b**	O	Ph	48 h	100	98/2	94
3	**10c**	AcN	Ph	7 d	90	85/15	91
4[d]	**10d**	CH_2	2-furyl	24 h	96	90/10	94
5	**10e**	CH_2	4-$MeOC_6H_4$	7 d	100	96/4	84
6	**10f**	CH_2	4-MeC_6H_4	48 h	100	98/2	96
7	**10g**	CH_2	4-ClC_6H_4	24 h	100	95/5	98
8	**10h**	CH_2	4-BrC_6H_4	48 h	100	96/4	93
9	**10i**	CH_2	3-BrC_6H_4	36 h	100	95/5	93
10	**10j**	CH_2	2-BrC_6H_4	36 h	100	97/3	94

[a] Reaction performed using 0.2 mmol of nitroolefin, 0.4 mmol of ketone, 10 mol% of **OC1**, in trifluoromethyl benzene (2 mL) at room temperature. [b] Determined from the crude reaction mixture by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [c] Determined by chiral HPLC. [d] Reaction was performed in the absence of light.

The study was extended to other ketones as donor substrates using **OC1** as the organocatalyst. Reactions were conducted at room temperature in the presence of 10 mol% of catalyst and using trifluoromethylbenzene as solvent. Under these conditions cyclic ketones reacted with β-nitrostyrene derivatives to afford the corresponding Michael adducts in high yield (90–100%), diastereo- (*syn*/*anti* 85/15–98/2) and enantioselectivity (84–99% ee) (Table 4).

On the basis of previously reported studies[8c,14] on the origin of regio- and stereoselectivity in Michael additions of pyrrolidine enamines we propose the following model to rationalise the observed stereochemical induction (Figure 3).

The bifunctional pyrrolidine moiety reacts with the aldehyde to form the corresponding *E*-enamine intermediate. Due to the steric overcrowding imposed by the dioxolane moiety the preferential formation of the s-*trans* conformer **A** is expected. Hydrogen bonding interactions of the nitro group with the acidic site at the catalyst favours the formation of a rigid transition state in which the synclinal approach of the nitroolefin from the *si*-face of the enamine produce the 2*R*,3*S* stereoisomer. With the use of ketones as Michael donors is more stable the s-*cis* conformer of the *E*-enamine **B**. In this case the synclinal approach of the nitroolefin in the rigid hydrogen-bonded transition state takes place from the *re*-face of the enamine to produce the observed stereochemistry.

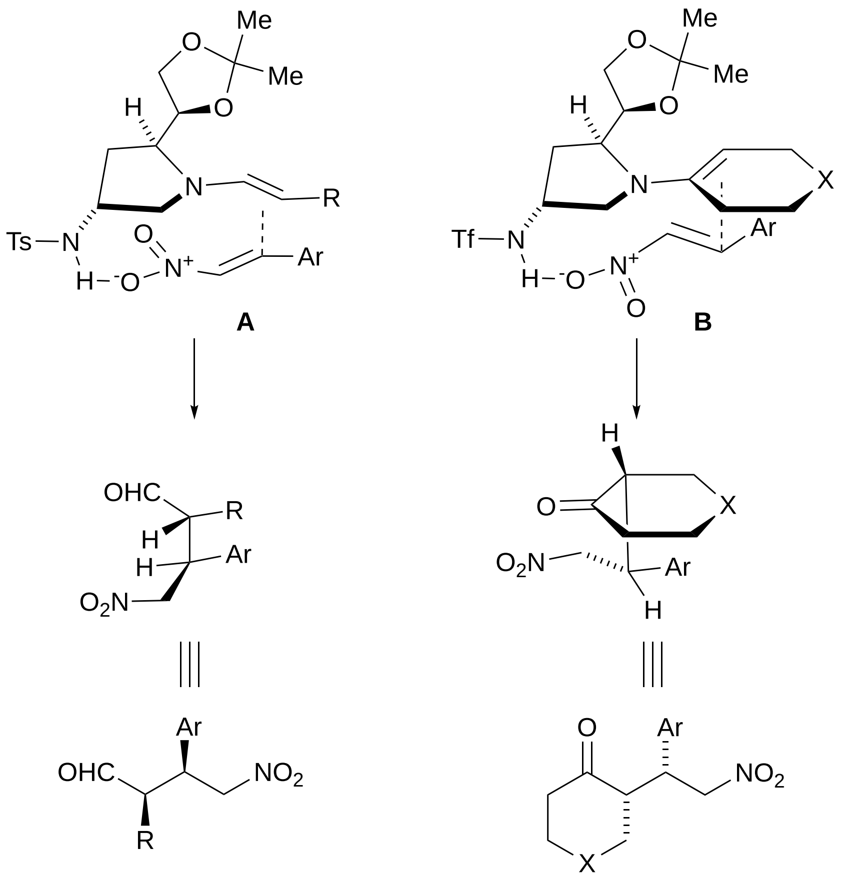


Fig. 3 Proposed model for Michael addition of aldehydes and ketones to nitroolefins catalysed by **OC3** and **OC1**

Conclusions

In summary, novel pyrrolidine-based bifunctional organocatalysts bearing both a sulfonamide group and a sterically demanding group were synthesised from the chiral pool as a chiral source. Iodine-mediated cyclisation of homoallylamines, obtained easily from (*R*)-glyceraldehyde imines, allowed the construction of the conveniently functionalised intermediate pyrrolidine from which sulfonamides of *cis* and *trans* configuration were prepared. Organocatalysts with a *trans* disposition of the two substituents exhibited excellent catalytic efficiency in the Michael addition reaction of aldehydes and ketones to *trans*-β-nitrostyrenes. In the reaction between aldehydes and β-nitrostyrene derivatives the *p*-toluenesulfonamide **OC3** was the most effective organocatalyst and provided Michael adducts with excellent stereoselectivities (up to 98:2 dr and 97% ee). The highest diastereoselectivities (up to 98/2 dr) and enantioselectivities (up to 99% ee) obtained using ketones as donor substrates were obtained with trifluoromethanesulfonamide **OC1** as the catalyst.

Experimental Section

General Information.

All reagents for reactions were of analytical grade and were used as obtained from commercial sources. All solvents were commercial grade and were purified prior to use when necessary. Homoallylamine **1** was prepared according to our previously described procedures.[11]

Whenever possible the reactions were monitored by TLC. TLC analysis was performed on precoated silica gel polyester plates with an F_{254} indicator and products were visualised using ninhydrin, potassium permanganate or ethanolic phosphomolybdic acid solution followed by heating and UV light (254 nm). Column chromatography was performed using silica gel (Kiesegel 60, 230–400 Mesh). Melting points were determined in open capillaries using a Gallenkamp capillary melting point apparatus and are not corrected. FTIR spectra of oils were recorded as thin films on NaCl plates and FTIR spectra of solids were recorded as nujol dispersions on NaCl plates using a Thermo Nicolet Avatar 360 FT-IR spectrophotometer, ν_{max} values expressed in cm^{-1} are given for the main absorption bands. Optical rotations were measured on a Jasco 1020 polarimeter at λ 589 nm and 25 °C in a cell with a 10 cm path length, $[\alpha]_D$ values are given in 10^{-1} $deg{\cdot}cm^2{\cdot}g^{-1}$ and concentrations are given in g/100 mL. ^1H NMR and ^{13}C NMR spectra were acquired on a Bruker AV-300 operating at 300 MHz for ^{1}H NMR, and 75 MHz for ^{13}C NMR or a Bruker AV-400 spectrometer operating at 400 MHz for ^{1}H NMR, 376 MHz for ^{19}F NMR and 100 MHz for ^{13}C NMR. Spectra were acquired at room temperature unless otherwise stated using a 5-mm probe. The chemical shifts (δ) are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard.[15] Coupling constants (J) are quoted in Hertz. The following abbreviations are used: s, singlet; d, doublet; q, quartet; dd, doublet of doublets; m, multiplet; bs, broad singlet; ddd, doublet of doublets of doublets, dddd, doublet of doublet of doublets of doublets. NOESY spectra were acquired in the phase sensitive mode with gradient pulses in the mixing time as 2048 x 256 hipercomplex files with 8 transients for 256 time increments. A mixing time of 900 ms was used and processing was carried out using a sine-bell squared function shifted by p/2 and a states-TPPI method. Special precautions such as degassing of the sample were not taken. High resolution mass spectra were recorded using a Bruker Daltonics MicroToF-Q instrument from methanolic solutions using the positive electrospray ionisation mode (ESI$^+$). HPLC analyses were carried out on a Waters HPLC system consisting of an M-600 low-pressure gradient pump, and an M-2996 photodiode array detector or a Waters HPLC system consisting of an M-600 low-pressure gradient pump, an M-2487 dual wavelength absorbance detector and the Waters Empower chromatography manager software. Commercially available polysaccharide chiral stationary phases Chiralcel® OD-H column, Chiralpak® AS-H column, Chiralpak® IA column and Chiralpak® IC column were used.

(2*S*,4*S*)-1-Benzyl-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-iodopyrrolidine (2c) and (2*S*,4*R*)-1-benzyl-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-iodopyrrolidine (2t).

To a solution of homoallylamine **1** (1.3 g, 5.0 mmol) in toluene (50 mL) at room temperature was added $NaHCO_3$ (2.1 g, 25.0 mmol) and iodine (5,07 g, 20.0 mmol) and the obtained dark brown mixture was stirred for 24 h at the same temperature. Then saturated aqueous Na_2SO_3 (40 mL) was added and the mixture was stirred for 15 min. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 40 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude was dissolved in MeCN (120 mL). After stirring for 4 h at 40 ºC the solvent was removed *in vacuo*. Purification of the residue by silica gel column chromatography (first eluent: Et_2O/hexanes, 1:7; second eluent Et_2O/hexanes, 1:4) yielded 1.2 g (62% yield) of a 60/40 mixture of **2c** and **2t** as a pale yellow oil that was used in the next step without additional purification. In order to characterise both diastereoisomers a small amount of the mixture was purified again by silica gel column chromatography (eluent: Et_2O/hexanes, 1:15). NMR data for (2*S*,4*S*)-1-benzyl-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-iodopyrrolidine (major compound **2c**): ^1H NMR (400 MHz, $CDCl_3$): δ = 1.36 (s, 3H), 1.41 (s, 3H), 2.17 (ddd, *J* = 14.4, 7.2, 7.2 Hz, 1H), 2.71 (ddd, *J* = 14.4, 7.4, 7.4 Hz, 1H), 2.91 (dd, *J* = 11.6, 6.2 Hz, 1H), 3.04 (ddd, *J* = 7.4, 7.4, 6.0 Hz, 1H), 3.17 (dd, *J* = 11.6, 6.8 Hz, 1H), 3.58 (d, *J* = 13.6, 1H), 3.84 (dd, *J* =8.0, 7.2 Hz, 1H), 4.03–4.08 (m, 2H), 4.12–4.19 (m, 1H), 4.23 (ddd, *J* =6.8, 6.0, 6.0 Hz, 1H), 7.23–7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.5, 25.4, 26.8, 41.8, 60.0, 64.9, 65.3, 67.2, 78.6, 109.1, 127.3, 128.5, 128.6, 139.3. NMR data for (2*S*,4*R*)-1-benzyl-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-iodopyrrolidine (minor compound **2t**): ^1H NMR (400

MHz, $CDCl_3$): δ = 1.34 (s, 3H), 1.42 (s, 3H), 2.27–2.46 (m, 2H), 2.82 (dd, *J* = 10.0, 8.8 Hz, 1H), 3.06-3.10 (m, 1H), 3.42 (dd, *J* =10.0, 6.0 Hz, 1H), 3.66–3.71 (m, 2H), 4.00 (dd, *J* = 7.8, 6.6 Hz, 1H), 4.09–4.19 (m, 3H), 7.23–7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.7, 25.3, 26.6, 40.5, 59.8, 64.5, 65.5, 66.9, 77.4, 109.2, 127.3, 128.5, 128.9, 138.9.

(2*S*,4*S*)-4-Azido-1-benzyl-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]pyrrolidine (3c) and (2*S*,4*R*)-4-azido-1-benzyl-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]pyrrolidine (3t).

A solution of a 60/40 mixture of iodopyrrolidines **2c** and **2t** (863 mg, 2.16 mmol), sodium azide (562 mg, 8.64 mmol) in dry DMF (16 mL) was stirred at 70ºC for 4h. Then solvent was removed *in vacuo* and the residue was diluted with water and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue by silica gel column chromatography (eluent: Et_2O/hexanes, 1:4) yielded 613 mg (94% yield) an inseparable 60/40 mixture of **3t** and **3c** as a colourless oil that was used in the next step without additional purification. In order to characterise both diastereoisomers the same synthetic procedure was applied to samples of **2c** and **2t** isolated in the previous step. NMR data for (2*S*,4*R*)-4-azido-1-benzyl-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]pyrrolidine (major compound **3t**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (s, 3H), 1.37 (s, 3H), 1.88 (ddd, *J* = 13.6, 8.4, 5.6 Hz, 1H), 2.01–2.08 (m, 1H), 2.35 (dd, *J* = 10.0, 6.4 Hz, 1H), 2.99 (ddd, *J* = 8.6, 6.2, 3.6 Hz, 1H), 3.12 (dd, *J* = 10.0, 6.0 Hz, 1H), 3.52 (d, *J* = 13.2 Hz, 1H), 3.62 (dd, *J* = 7.6, 7.6 Hz, 1H), 3.90–3.96 (m, 2H), 3.99 (d, *J* = 13.2 Hz, 1H), 4.07–4.11 (m, 1H), 7.16–7.29 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.1, 26.4, 33.2, 58.9, 59.2, 59.6, 63.4, 66.8, 77.1, 109.1, 127.2, 128.4, 128.8, 138.8. (2*S*,4*S*)-4-azido-1-benzyl-2-[(*S*)-2,2-

dimethyl-1,3-dioxolan-4-yl]pyrrolidine (minor compound **3c**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (s, 3H), 1.36 (s, 3H), 1.81 (dddd, *J* = 14.2, 6.0, 2.8, 1.4 Hz, 1H), 2.24 (ddd, *J* = 14.2, 9.2, 7.6 Hz, 1H), 2.42 (dd, *J* =10.8, 5.2 Hz, 1H), 2.83 (ddd, *J* = 9.4, 6.0, 4.8 Hz, 1H), 2.92 (ddd, *J* =10.8, 1.6, 1.6 Hz, 1H), 3.33 (d, *J* = 13.4 Hz, 1H), 3.79–3.84 (m, 2H), 4.01 (dd, *J* = 8.0, 6.4 Hz, 1H), 4.11 (d, *J* =13.4 Hz, 1H), 4.19 (ddd, *J* = 7.6, 6.4, 4.8 Hz, 1H), 7.16–7.28 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.3, 26.6, 34.1, 58.9, 59.4, 59.4, 63.4, 66.8, 77.9, 109.0, 127.2, 128.4, 128.7, 138.7.

(2*S*,4*S*)-4-Amino-1-benzyl-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]pyrrolidine (4c) and (2*S*,4*R*)-4-amino-1-benzyl-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]pyrrolidine (4t).

A suspension of a 60/40 mixture of azidopyrrolidines **3t** and **3c** (613 mg, 2.03 mmol) in EtOH (16 mL) was hydrogenated with molecular hydrogen for 2 h at atmospheric pressure and room temperature in the presence of 10% Pd/C (61.3 mg) as a catalyst. The catalyst was removed by filtration through a Celite® pad and the solvent evaporated in vacuo. CH_2Cl_2 (30 mL) and 1M aqueous NaOH (15 mL) were added and the biphasic solution was stirred for 10 min at room temperature. The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford 480 mg (86% yield) of a 60/40 mixture of **4t** and **4c** as a pale yellow oil which was used in the next step without additional purification. NMR data obtained from the diastereomeric mixture for (2*S*,4*R*)-4-amino-1-benzyl-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]pyrrolidine (major compound **4t**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (s, 3H), 1.39 (s, 3H), 1.52–1.60 (m, 1H), 1.85–1.98 (m, 2H), 2.00–2.07 (m, 2H), 2.96–3.00 (m, 1H), 3.08–3.12 (m, 1H), 3.38–3.49 (m, 2H), 3.63–3.72 (m, 1H), 3.95–4.06 (m, 2H), 4.09–4.13 (m, 1H), 7.18–7.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.1, 26.4, 36.8, 49.7, 59.9*,* 63.2, 63.4, 66.5, 77.5, 108.8, 126.9, 128.1, 128.8, 139.0. NMR data obtained from the diastereomeric mixture for (2*S*,4*S*)-4-amino-1-benzyl-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]pyrrolidine (minor compound **4c**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 3H), 1.42 (s, 3H), 1.52–1.60 (m, 1H), 1.85–1.98 (m, 2H), 2.18 (ddd, *J* = 14.0,10.0, 7.2 Hz, 1H), 2.42 (dd, *J* = 10.0, 4.8, Hz 1H), 2.66–2.70 (m, 1H), 2.73–2.78 (m, 1H), 3.26–3.35 (m, 1H), 3.38–3.49 (m, 1H), 3.63–3.72 (m, 1H), 3.95–4.06 (m, 2H), 4.23 (ddd, *J* = 7.2, 7.2, 2.4 Hz, 1H), 7.18–7.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.0*,* 26.3, 35.9*,* 49.6*,* 58.7*,* 63.2*,* 63.4*,* 66.7*,* 76.4*,* 108.9*,* 126.8*,* 128.1*,* 128.7*,* 139.0.

***N*-{(2*R*,4*S*)-1-Benzyl-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-[(trifluoromethyl)sulfonamido]pyrrolidine (5t) and *N*-{(2*S*,4*S*)-1-benzyl-5-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-[(trifluoromethyl)sulfonamido]pyrrolidine (5c).** Trifluoromethanesulfonic anhydride (277 mL, 1.65 mmol) was added dropwise to a solution of a 60/40 mixture of 4-aminopyrrolidines **4t** and **4c** (456 mg, 1.65 mmol) and Et_3N (276 mL, 1.98 mmol) in CH_2Cl_2 (3.5 mL) at 0 ºC. After stirring for 1h at 0º C the solution was allowed to warm up to room temperature and stirring was continued for 16 h while monitoring by TLC to add Et_3N if necessary. Then reaction mixture was concentrated *in vacuo* and the residue purified by silica gel column chromatography (first eluent: Et_2O/hexanes, 1:2; second eluent Et_2O/hexanes, 1:1) to afford 312 mg (46% yield) of diastereomerically pure **5t** and 206 mg (31% yield) of diastereomerically pure **5c**, 76% overall yield*.* Data for *N*-{(2*R*,4*S*)-1-benzyl-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-[(trifluoromethyl)sulfonamido]pyrrolidine **(5t)**: White solid; mp: 96.6 – 98.5 ºC; $[\alpha]^{25}_D$ = –30.2 (*c* = 1.00, $CHCl_3$); IR (KBr): ν = 1498, 1459, 1353, 1185 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (s, 3H), 1.36 (s, 3H), 1.72

(ddd, *J* = 13.2, 9.2, 7.6 Hz, 1H), 2.19-2.28 (m, 2H), 2.96 (ddd, *J* = 8.0, 4.4, 3.2 Hz, 1H), 3.19 (dd, *J* = 9.2, 6.0 Hz, 1H), 3.52–3.58 (m, 2H), 3.89–3.93 (m, 2H), 4.03–4.12 (m, 2H), 4.40 (bs, 1H), 7.12–7.27 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.0, 26.3, 34.1, 53.2, 58.2, 59.6, 62.2, 66.6, 76.4, 109.5, 119.6 (q, *J* = 320 Hz), 127.6, 128.6, 128.9, 137.9); ^{19}F NMR (376 MHz, $CDCl_3$): δ = –77.55; HRMS (ESI$^+$): calcd. for $C_{17}H_{24}F_3N_2O_4S$ [MH]$^+$ 409.1403; found 409.1420. Data for *N*-{(2*S*,4*S*)-1-benzyl-5-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-[(trifluoromethyl)sulfonamido]pyrrolidine **(5c)**: Colourless oil; $[\alpha]^{25}_D$ = –57.6 (*c* = 1.00, $CHCl_3$); IR (KBr): ν = 3224, 1378, 1193, 1153 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (s, 3H), 1.44 (s, 3H), 1.83 (ddd, *J* = 14.0, 2.4, 2.4 Hz, 1H), 2.10–2.20 (m, 1H), 2.44 (dd, *J* = 9.8, 3.4 Hz, 1H), 2.80 (ddd, *J* = 10.6, 2.4, 1.4 Hz, 1H), 2.88 (dd, *J* = 9.8, 2.2 Hz, 1H), 3.37 (dd, *J* = 8.0, 7.6 Hz, 1H) , 3.51 (d, *J* = 13.6 Hz, 1H), 3.90–3.95 (m, 3H), 4.18 (ddd, *J* = 7.4, 7.4, 1.2 Hz, 1H), 7.17–7.28 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.7, 25.9, 32.4, 53.9, 57.5, 60.4, 62.2, 66.9, 75.0, 110.0, 119.8 (q, *J* = 320 Hz), 127.5, 128.5, 128.6, 138.2; ^{19}F NMR (376 MHz, $CDCl_3$): δ = –77.99; HRMS (ESI$^+$): calcd. for $C_{17}H_{23}F_3N_2O_4SNa$ [MNa]$^+$ 431.1223; found 431.1250.

***N*-{(2*R*,4*S*)-1-Benzyl-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-[(4-methylphenyl)sulfonamido]pyrrolidine (6t) and *N*-{(2*S*,4*S*)-1-benzyl-5-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-[(4-methylphenyl)sulfonamido]pyrrolidine (6c).**

p-Toluensulfonyl chloride (425 mg, 2.23 mmol) was added dropwise to a solution of a 60/40 *trans/cis* mixture of compound **4** (410 mg, 1.48 mmol) and Et_3N (414 mL, 2.97 mmol) in CH_2Cl_2 (3 mL) at 0 ºC. After stirring for 1h at 0º C the solution was allowed to warm up to room temperature and stirring was continued for 12 h. Then reaction mixture was concentrated *in vacuo* and the residue purified by silica gel column chromatography (first eluent: Et_2O/hexanes, 1:1; second eluent Et_2O/hexanes, 2:1) to afford 345 mg (54% yield) of diastereomerically pure **6t** and 231 mg (36% yield) of diastereomerically pure **6c**, 90% overall yield. Data for *N*-{(2*R*,4*S*)-1-benzyl-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-[(4-methylphenyl)sulfonamido]pyrrolidine **(6t)**: White solid; mp: 87.9 – 89.3 ºC; $[\alpha]^{25}_{D}$ = –10.7 (*c* = 1.00, $CHCl_3$); IR (KBr): ν = 3304, 1329, 1160, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.31 (s, 3H), 1.36 (s, 3H), 1.69 (ddd, *J* =13.2, 9.2, 7.6 Hz, 1H), 1.99–2.06 (m, 1H), 2.17 (dd, *J* =8.8, 8.8 Hz, 1H), 2.42 (s, 3H), 2.89–2.94 (m, 1H), 3.02 (dd, *J* = 9.2, 6.4 Hz, 1H), 3.49 (d, *J* =13.2 Hz, 1H), 3.57 (dd, *J* = 7.6, 7.6 Hz, 1H), 3.67–6.76 (m, 1H), 3.91–3.96 (m, 2H), 4.07 (ddd, *J* =6.8, 6.8, 3.2 Hz, 1H), 5.24 (bs, 1H), 7.22–7.30 (m, 7H), 7.73–7.76 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 25.1, 26.3, 33.6, 51.3, 59.1, 59.8, 62.5, 66.5, 76.7, 109.2, 127.2, 128.3, 129.0, 129.8, 137.3, 138.3, 143.6; HRMS (ESI^+): calcd. for $C_{23}H_{31}N_2O_4S$ $[MH]^+$ 431.1999; found 431.2006. Data for *N*-{(2*S*,4*S*)-1-benzyl-5-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-[(4-methylphenyl)sulfonamido]pyrrolidine **(6c)**: White solid; mp: 118.8 – 121.0 ºC; $[\alpha]^{25}_{D}$ = –86.6 (*c* = 1.00, $CHCl_3$); IR (KBr): ν = 3318, 1328, 1156, 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.38 (s, 3H), 1.54 (s, 3H), 1.76–1.81 (m, 1H), 2.12 (ddd, *J* = 13.8, 10.4, 7.0 Hz, 1H), 2.22 (dd, *J* = 9.6, 3.6 Hz, 1H), 2.37 (s, 3H), 2.51–2.55 (m, 1H), 2.73–2.77 (m, 1H), 3.40 (d, *J* = 13.6 Hz, 1H), 3.47 (dd, *J* = 7.6, 7.6 Hz, 1H), 3.78–3.83 (m, 1H), 3.94–4.02 (m, 2H), 4.25 (ddd, *J* = 7.2, 7.2, 1.6 Hz, 1H), 5.95 (d, *J* = 9.6 Hz, 1H), 7.15–7.18 (m, 2H), 7.22–7.33 (m, 5H), 7.66–7.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 24.9, 26.3, 32.8, 51.9, 57.9, 59.3, 62.7, 66.9, 75.2, 109.7, 126.9, 127.2, 128.4, 128.7, 129.6, 138.6, 138.7, 142.9; HRMS (ESI^+): calcd. for $C_{23}H_{31}N_2O_4S$ $[MH]^+$ 431.1999; found 431.2003.

***N*-{(3*R*,5*S*)-5-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]pyrrolidin-3-yl}-1,1,1-trifluoromethanesulfonamide OC1.**

A suspension of pyrrolidine **5t** (294 mg, 0.72 mmol) in EtOH (6 mL) was hydrogenated with molecular hydrogen for 12 h at atmospheric pressure and room temperature in the presence of 10% Pd/C (102.9 mg) as a catalyst. The catalyst was removed by filtration through a Celite® pad and the solvent evaporated *in vacuo*. Purification of the residue by silica gel column chromatography (first eluent: Et_2O/hexanes, 1:1; second eluent EtOAc/EtOH, 7:1) yielded 190 mg (83% yield) of organocatalyst **OC1**. Brownish solid; mp: 178.8 – 181.0 ºC; $[\alpha]^{25}_D$ = +1.88 (*c* = 1.00, MeOH); IR (KBr): ν = 3568, 3497, 3100-2400, 1270, 1202 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6): δ = 1.28 (s, 3H), 1.36 (s, 3H), 2.00–2.15 (m, 2H), 3.05 (ddd, *J* = 11.4, 3.4, 1.0 Hz, 1H), 3.32 (dd, *J* = 11.4, 5.6 Hz, 1H), 3.66 (ddd, *J* =7.6, 7.6, 6.4 Hz, 1H) , 3.77 (dd, *J* = 8.4, 6.0 Hz, 1H), 4.08 (dd, *J* = 8.4, 6.4 Hz, 1H), 4.14–4.20 (m, 1H), 4.23 (ddd, *J* = 6.0, 6.0, 6.0 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6): δ = 25.3, 26.9, 36.7, 54.7, 56.4, 60.3, 67.9, 77.8, 110.0, 121.9 (q, *J* = 320 Hz); ^{19}F NMR (376 MHz, acetone-d_6): δ = –80.00; HRMS (ESI$^+$): calcd. for $C_{10}H_{18}F_3N_2O_4S$ $[MH]^+$ 319.0934; found 319.0927.

***N*-{(3*S*,5*S*)-5-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]pyrrolidin-3-yl}-1,1,1-trifluoromethanesulfonamide OC2.**

A suspension of pyrrolidine **5c** (206 mg, 0.50 mmol) in EtOH (4 mL) was hydrogenated with molecular hydrogen for 12 h at atmospheric pressure and room temperature in the presence of 10% Pd/C (72.9 mg) as a catalyst. The catalyst was removed by filtration through a Celite® pad and the solvent evaporated *in vacuo*. Purification of the residue by silica gel column chromatography (first eluent:

Et_2O/hexanes, 1:1; second eluent EtOAc/EtOH, 7:1) yielded 129 mg (81% yield) of organocatalyst **OC2**. Brownish solid; mp: 187.2 – 187.9 ºC; $[\alpha]^{25}_{D}$ = –3.8 (*c* = 1.00, MeOH); IR (KBr): ν = 3500-2500, 1255, 1189, 1166 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6): δ = 1.27 (s, 3H), 1.34 (s, 3H), 1.71 (ddd, *J* = 13.6, 7.2, 7.2 Hz, 1H), 2.40 (ddd, *J* = 13.6, 8.0, 8.0 Hz, 1H), 2.84 (dd, *J* = 11.2, 6.0 Hz, 1H), 3.19 (dd, *J* = 11.2, 6.8 Hz, 1H), 3.23–3.28 (m, 1H), 3.69–3.76 (m, 1H), 4.01–4.11 (m, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ = 25.6, 27.0, 36.7, 53.7, 56.4, 60.2, 68.2, 79.7, 109.6, 121.0 (q, *J* = 320 Hz); ^{19}F NMR (376 MHz, acetone-d_6): δ = –80.07; HRMS (ESI$^+$): calcd. for $C_{10}H_{18}F_3N_2O_4S$ $[MH]^+$ 319.0934; found 319.0950.

N-{(3*R*,5*S*)-5-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]pyrrolidin-3-yl)} 4-methylbenzenesulfonamide OC3.

A suspension of pyrrolidine **6t** (301 mg, 0.70 mmol) in EtOH (5.6 mL) was hydrogenated with molecular hydrogen for 12 h at atmospheric pressure and room temperature in the presence of 10% Pd/C (105.9 mg) as a catalyst. The catalyst was removed by filtration through a Celite® pad and the solvent evaporated *in vacuo*. Purification of the residue by silica gel column chromatography (eluent: EtOAc/EtOH, 5:1) yielded 219 mg (92% yield) of organocatalyst **OC3**. Brownish solid; mp: 99.8 – 101.3 ºC; $[\alpha]^{25}_{D}$ = +6.4 (*c* = 1.00, $CHCl_3$); IR (KBr): ν = 3561, 3317, 3101, 1327, 1163, 1057 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6): δ = 1.22 (s, 3H), 1.27 (s, 3H), 1.69–1.82 (m, 2H), 2.42 (s, 3H), 2.68 (dd, *J* = 11.2, 4.6 Hz, 1H), 2.88 (dd, *J* = 11.2, 5.6 Hz, 1H), 3.20 (ddd, *J* = 7.2, 7.2, 7.2 Hz, 1H), 3.64 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.66–3.71 (m, 1H), 3.81 (ddd, *J* = 7.2, 6.4 Hz, 6.4 Hz, 1H), 3.95 (dd, *J* = 8.0, 6.4 Hz, 1H), 7.38–7.41 (m, 2H), 7.74–7.77 (m, 2H); ^{13}C NMR (100 MHz, acetone-d_6): δ = 21.4, 25.6, 27.1, 36.5, 53.8, 55.3, 60.1, 68.3, 80.0, 109.4, 127.8, 130.4, 139.7, 143.8; HRMS (ESI$^+$): calcd. for $C_{16}H_{25}N_2O_4S$ [MH]$^+$ 341.1530; found 341.1538.

_N_-{(3_S_,5_S_)-5-[(_S_)-2,2-Dimethyl-1,3-dioxolan-4-yl]pyrrolidin-3-yl)} 4-methylbenzenesulfonamide OC4.

A suspension of pyrrolidine **6c** (168 mg, 0.39 mmol) in EtOH (3 mL) was hydrogenated with molecular hydrogen for 12 h at atmospheric pressure and room temperature in the presence of 10% Pd/C (59.0 mg) as a catalyst. The catalyst was removed by filtration through a Celite® pad and the solvent evaporated *in vacuo*. Purification of the residue by silica gel column chromatography (eluent: EtOAc/EtOH, 5:1) yielded 122 mg (92% yield) of organocatalyst **OC4**. Brownish solid; mp: 122.5 – 123.9 ºC; $[\alpha]^{25}_{D}$ = –10.1 (*c* = 1.00, $CHCl_3$); IR (KBr): ν = 3337, 3100-2500, 1302, 1150, 1074 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6): δ = 1.24 (s, 3H), 1.29 (s, 3H), 1.46 (ddd, *J* = 13.2, 7.6, 7.6 Hz, 1H), 2.10 (ddd, *J* = 13.2, 7.6, 7.6 Hz, 1H), 2.42 (s, 3H), 2.55 (dd, *J* = 11.2, 6.0 Hz, 1H), 2.89 (dd, *J* = 11.2, 6.8 Hz, 1H) , 3.06 (ddd, *J* = 7.6, 7.6, 7.6 Hz, 1H), 3.63-3.70 (m, 2H), 3.91 (ddd, *J* = 6.4, 6.4 Hz, 6.4 Hz, 1H), 3.96 (dd, *J* = 7.6, 6.4 Hz, 1H), 7.38-7.41 (m, 2H), 7.74-7.77 (m, 2H); ^{13}C NMR (100 MHz, acetone-d_6): δ = 21.4, 25.6, 27.1, 36.7, 53.3, 55.3, 60.2, 68.3, 80.2, 109.4, 127.8, 130.4, 139.8, 143.8; HRMS (ESI$^+$): calcd. for $C_{16}H_{25}N_2O_4S$ [MH]$^+$ 341.1530; found 341.1519.

General procedure for the Michael reaction of aldehydes with β-nitroolefins.

A solution of the corresponding organocatalyst **OC1**–**OC4** (0.02 mmol), and aldehyde (0.4 mmol) in the selected solvent (2 mL) was stirred at the specified temperature for 10 min. The nitroolefin (0.2 mmol) was added and stirring was continued for the required time at the same temperature. The reaction was concentrated in vacuo and the residue was analysed by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard[16] to determine the reaction yield and diastereoselectivity. Purification of the residue by silica gel column chromatography yielded the corresponding Michael adducts. Enantioselectivity was determined by chiral HPLC analysis of the purified adducts using a chiral stationary phase.

(*R*)-2-[(*S*)-2-Nitro-1-phenylethyl]pentanal (9a).

Obtained in nearly quantitative yield with a dr 94/6 and 93% ee (entry 1, table 2). Eluent for residue purification Et_2O/hexanes 1:3. Chromatographic and spectroscopic data are in accordance with those previously reported.[17] Chiral HPLC analysis: Chiralcel® OD-H column, hexane/^{i}PrOH 95:5, flow rate 1.0 mL min^{-1}, λ = 220 nm, t_R = 25.8 min (minor) and 32.4 min (major). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79 (t, *J* = 7.2 Hz, 3H), 1.10–1.22 (m, 1H), 1.24–1.39 (m, 2H), 1.41–1.52 (m, 1H), 2.70 (dddd, *J* = 9.2, 9.2, 3.2, 3.2 Hz, 1H), 3.77 (ddd, *J* = 9.6, 9.6, 5.2 Hz, 1H), 4.64 (dd, *J* =12.6, 9.4 Hz, 1H), 4.70 (dd, *J* =12.6, 5.2 Hz, 1H), 7.15–7.18 (m, 2H), 7.25–7.36 (m, 3H), 9.69 (d, *J* = 2.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 19.9, 29.6, 43.2, 53.9, 78.5, 128.1, 128.2, 129.2, 136.9, 203.4.

(2*R*,3*S*)-2-Benzyl-4-nitro-3-phenylbutanal (9b).

Obtained in 94% yield with a dr 95/5 and 88% ee (entry 2, table 2). Eluent for residue purification Et_2O/hexanes 1:3. Chromatographic and spectroscopic data are in accordance with those previously reported.[18] Chiral HPLC analysis: Chiralcel® OD-H column, hexane/EtOH 93:7, flow rate 1.0 mL min^{-1}, λ = 220 nm, t_R = 29.0 min (minor) and 33.1 min (major). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.74–2.84 (m, 2H), 3.14 (dddd; *J* = 8.8, 8.8, 5.9, 2.4 Hz, 1H), 3.86 (ddd, *J* = 8.8, 8.8, 6.0 Hz, 1H), 4.72 (dd, *J* = 12.8, 8.8 Hz, 1H), 4.76 (dd, *J* = 12.8, 6.0 Hz, 1H), 7.04–7.07 (m, 2H), 7.23–7.37 (m, 6H), 7.37–7.43 (m, 2H), 9.73 (d, *J* = 2.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.3, 43.6, 55.4, 78.1, 127.1, 128.2, 128.4, 128.9, 128.9, 129.4, 136.8, 137.3, 203.1.

(2*R*,3*S*)-2-Ethyl-4-nitro-3-phenylbutanal (9c).

Obtained in nearly quantitative yield with a dr 91/9 and 91% ee (entry 3, table 2). Eluent for residue purification Et_2O/hexanes 1:4. Chromatographic and spectroscopic data are in accordance with those previously reported.[19] Chiral HPLC analysis: Chiralpak® IC column, hexane/^{i}PrOH 90:10, flow rate 1.0 mL min^{-1}, λ = 220 nm, t_R = 36.5 min (minor) and 40.3 min (major). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, *J*= 7.4 Hz, 3H), 1.47–1.55 (m, 2H), 2.65–2.71 (m, 1H), 3.79 (ddd, *J* = 9.8, 9.8, 5.0 Hz, 1H), 4.63 (dd, *J* = 12.8, 9.8 Hz, 1H), 4.72 (dd, *J* = 12.8, 4.8 Hz, 1H) , 7.16–7.19 (m, 2H), 7.27–7.37 (m, 3H), 9.72 (d, *J* = 2.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.8, 20.5, 42.8, 55.1, 78.7, 128.1, 128.3, 129.2, 136.9, 203.3.

(2*R*,3*S*)-2-Methyl-4-nitro-3-phenylbutanal (9d).

Obtained in nearly quantitative yield with a dr 95/5 and 91% ee (entry 4, table 2). Eluent for residue purification Et_2O/hexanes 1:2. Chromatographic and spectroscopic data are in accordance with those previously reported.[20] Chiral HPLC analysis: Chiralcel® OD-H column, hexane/^{i}PrOH 80:20, flow rate 1.0 mL min^{-1}, λ = 220 nm, t_R = 18.2 min (minor) and 24.7 min (major). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (d, *J* = 7.2 Hz, 3H), 2.72–2.83 (m, 1H), 3.81 (ddd, *J* = 9.2, 9.2, 5.6 Hz, 1H), 4.68 (dd, *J* = 12.4, 9.2 Hz, 1H), 4.80 (dd, *J* = 12.4, 5.6 Hz, 1H), 7.14–7.18 (m, 2H), 7.26–7.35 (m, 3H), 9.70 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.2, 44.1, 48.5, 78.2, 128.2, 128.2, 129.2, 136.7, 202.4.

(*R*)-2-[(*S*)-2-Nitro-1-phenylethyl]octanal (9e).

Obtained in nearly quantitative yield with a dr 93/7, and 93% ee (entry 5, table 2). Eluent for residue purification Et_2O/hexanes 1:5. Chromatographic and spectroscopic data are in accordance with those previously reported.[21] Chiral HPLC analysis: Chiralcel® OD-H column, hexane/^{i}PrOH 90:10, flow rate 0.5 mL min^{-1}, λ = 220 nm, t_R = 31.4 min (minor) and 38.4 min (major). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82 (t, *J* = 7.2 Hz, 3H), 1.11–1.51 (m, 10H), 2.70 (dddd; *J* = 9.2, 9.2, 4.0, 2.8 Hz, 1H), 3.77 (ddd, *J* = 9.6, 9.6, 5.2 Hz, 1H), 4.64 (dd, *J* = 12.8, 9.6 Hz, 1H), 4.71 (dd, *J* = 12.8, 5.2 Hz, 1H), 7.16–7.19 (m, 2H), 7.26–7.38 (m, 3H), 9.70 (d, *J* = 2.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.5, 26.5, 27.5, 29.2, 31.5, 43.3, 54.0, 78.6, 128.1, 128.3, 129.2, 136.9, 203.4.

(*R*)-2-[(*S*)-2-Nitro-1-phenylethyl]undec-10-enal (9f).

Obtained in nearly quantitative yield with a dr 97/3, and 92% ee (entry 6, table 2). Eluents for residue purification Et_2O/hexanes 1:8 and after Et_2O/hexanes 1:4. Chromatographic and spectroscopic data are in accordance with those previously reported.[19] Chiral HPLC analysis: Chiralpak® IC column, hexane/^{i}PrOH 90:10, flow rate 1.0 mL min^{-1}, λ = 220 nm, t_R = 22.7 min (minor) and 25.1 min (major). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11–1.52 (m, 12H), 1.96–2.02 (m, 2H), 2.69 (dddd, *J* = 9.4, 9.4, 3.8, 2.8 Hz,1H), 3.77 (ddd, *J* = 9.6, 9.6, 5.2 Hz, 1H), 4.63 (dd, *J* = 12.8, 9.4 Hz, 1H), 4.70 (dd, *J* = 12.8, 5.2 Hz, 1H), 4.92 (dddd, *J* = 10.2, 2.4, 1.2, 1.2 Hz, 1H), 4.97 (dddd, *J* = 17.0, 2.4, 1.8, 1.8 Hz, 1H), 4.78 (dddd, *J* = 17.0, 10.2, 6.8, 6.8 Hz, 1H), 7.15–7.18 (m, 2H) , 7.27–7.36 (m, 3H), 9.70 (d, *J* = 2.4, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.4, 27.4, 28.9, 28.9, 29.1, 29.4, 33.8, 43.2, 54.0, 78.6, 114.3, 128.1, 128.3, 129.2, 136.9, 139.2, 203.3.

(2*R*,3*S*)-2-isopropyl-4-nitro-3-phenylbutanal (9g).

Obtained in nearly quantitative yield with a dr 98/2, and 97% ee (entry 7, table 2). Eluent for residue purification Et_2O/hexanes 1:4. Chromatographic and spectroscopic data are in accordance with those previously reported.[22] Chiral HPLC analysis: Chiralpak® IA column, hexane/^{i}PrOH 98:2, flow rate 0.5 mL min^{-1}, λ = 220 nm, t_R = 31.3 min (major) and 40.3 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81 (d. *J* = 6.8 Hz. 3H). 1.03 (d. *J* = 7. 2 Hz. 3H). 1.59–1.70 (m. 1H), 2.70 (ddd, *J* = 10.8, 4.0, 2.4 Hz, 1H), 3.83 (ddd, = 10.4, 10.4, 4.4 Hz, 1H), 4.50 (dd, *J* = 12.4, 10.0 Hz, 1H), 4.60 (dd, *J* = 12.4, 4.4 Hz, 1H), 7.10–7.13 (m, 2H), 7.19–7.30 (m, 3H), 9.86 (d, *J* = 2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.1, 21.8, 28.0, 42.1, 58.9, 79.1, 128.1, 128.2, 129.3, 137.2, 204.5.

(*R*)-2-[(*R*)-1-(Furan-2-yl)-2-nitroethyl]pentanal (9h).

Obtained in 98% yield with a dr 89/11 and 75% ee (entry 8, table 2). Eluent for residue purification Et_2O/hexanes 1:5. Chromatographic and spectroscopic data are in accordance with those previously reported.[20] Chiral HPLC analysis: Chiralcel® OD-H column, hexane/^{i}PrOH 95:5, flow rate 0.8 mL min^{-1}, λ = 220 nm, t_R = 17.3 min (major) and 18.5 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.2 Hz, 3H), 1.20–1.57 (m, 4H), 2.78 (dddd, *J* = 8.2, 8.2, 4.0, 2.0 Hz, 1H), 4.00 (ddd, *J* = 9.0, 8.2, 5.2 Hz, 1H), 4.65 (dd, *J* = 12.8, 5.2 Hz, 1H), 4.72 (dd, *J* = 12.8, 9.2 Hz, 1H), 6.19 (dd, *J* = 3.2, 0.8 Hz, 1H), 6.31 (dd, *J* = 3.2, 1.8 Hz, 1H), 7.37 (dd, *J* = 1.8, 0.8 Hz, 1H), 9.71 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 20.1, 29.2, 37.1, 52.3, 76.2, 108.9, 110.6, 142.8, 150.2, 202.5.

(*R*)-2-[(*S*)-1-(4-Methoxyphenyl)-2-nitroethyl]pentanal (9i).

Obtained in nearly quantitative yield with a dr 83/7 and 89% ee (entry 9, table 2). Eluent for residue purification Et_2O/hexanes 1:5. Chromatographic and spectroscopic data are in accordance with those previously reported.[23] Chiral HPLC analysis: Chiralpak® IC column, hexane/^{i}PrOH 80:20, flow rate 0.8 mL min^{-1}, λ = 220 nm, t_R = 27.6 min (minor) and 30.6 min (major). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80 (t, *J* = 7.2 Hz, 3H), 1.11–1.22 (m, 1H), 1.26–1.40 (m, 2H), 1.42–1.52 (m, 1H), 2.65 (dddd, *J* = 9.4, 9.4, 3.2, 3.2 Hz, 1H), 3.72 (ddd, *J* = 9.8, 9.8, 5.2 Hz, 1H), 3.79 (s, 3H), 4.59 (dd, *J* =12.4, 9.6 Hz, 1H), 4.67 (dd, *J* =12.4, 5.2 Hz, 1H), 6.84–6.88 (m, 2H), 7.06–7.10 (m, 2H), 9.69 (d, *J* = 2.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 19.9, 29.6, 42.6, 54.1, 55.4, 78.8, 114.6, 128.6, 129.2, 159.4, 203.5.

(*R*)-2-[(*S*)-1-(4-Methylphenyl)-2-nitroethyl]pentanal (9j).

Obtained in nearly quantitative yield with a dr 93/7 and 92% ee (entry 10, table 2). Eluent for residue purification Et_2O/hexanes 1:6. Chromatographic and spectroscopic data are in accordance with those previously reported.[20] Chiral HPLC analysis: Chiralpak® IC column, hexane/^{i}PrOH 90:10, flow rate 1.0 mL min^{-1}, λ = 220 nm, t_R = 22.5 min (minor) and 26.1 min (major). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80 (t, *J* = 7.0 Hz, 3H), 1.10–1.23 (m, 1H), 1.24–1.40 (m, 2H), 1.42–1.53 (m, 1H), 2.32 (s, 3H), 2.67 (dddd, *J* = 9.4, 9.4, 3.2, 3.2 Hz, 1H), 3.73 (ddd, *J* = 9.6, 9.6, 5.2 Hz, 1H), 4.61 (dd, *J* = 12.8, 9.6 Hz, 1H), 4.68 (dd, *J* = 12.8, 5.2 Hz, 1H), 7.03–7.06 (m, 2H), 7.13–

7.16 (m, 2H), 9.69 (d, *J* = 2.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 19.9, 21.2, 29.6, 43.0, 54.0, 128.0, 129.9, 133.8, 138.0, 203.5.

(*R*)-2-[(*S*)-1-(4-Chlorophenyl)-2-nitroethyl]pentanal (9k).

Obtained in nearly quantitative yield with a dr 92/8 and 91% ee (entry 11, table 2). Eluent for residue purification Et_2O/hexanes 1:3. Chromatographic and spectroscopic data are in accordance with those previously reported.[24] Chiral HPLC analysis: Chiralpak® IC column, hexane/^{i}PrOH 90:10, flow rate 1.0 mL min^{-1}, λ = 220 nm, t_R = 28.8 min (minor) and 30.6 min (major). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80 (t, *J* = 7.2 Hz, 3H), 1.11–1.23 (m, 1H), 1.24–1.40 (m, 2H), 1.42–1.51 (m, 1H), 2.68 (dddd, *J* = 9.2, 9.2, 3.4, 2.6 Hz, 1H), 3.76 (ddd, *J* = 9.8, 9.8, 5.0 Hz, 1H), 4.61 (dd, *J* = 12.8, 10.0 Hz, 1H), 4.70 (dd, *J* = 12.8, 5.2 Hz, 1H), 7.10–7.14 (m, 2H), 7.30–7.34 (m, 2H), 9.69 (d, *J* = 2.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 19.8, 29.6, 42.6, 53.7, 78.3, 129.5, 129.5, 134.2, 135.5, 202.9.

(*R*)-2-[(*S*)-1-(4-Bromophenyl)-2-nitroethyl]pentanal (9l).

Obtained in 99% yield with a dr 94/6 and 92% ee (entry 12, table 2). Eluent for residue purification Et_2O/hexanes 1:3. Chromatographic and spectroscopic data are in accordance with those previously reported.[20] Chiral HPLC analysis: Chiralcel® OD-H column, hexane/^{i}PrOH 93:7, flow rate 1.0 mL min^{-1}, λ = 220 nm, t_R = 24.4 min (minor) and 26.7 min (major). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80 (t, *J* = 7.0, 3H), 1.12–1.21 (m, 1H), 1.24–1.40 (m, 2H), 1.41–1.50 (m, 1H), 2.68 (dddd, *J* = 9.2, 9.2, 3.6, 2.8 Hz, 1H), 3.75 (ddd, *J* = 9.8, 9.8, 4.8 Hz, 1H), 4.60 (dd, *J* = 12.8, 9.6 Hz, 1H), 4.69 (dd, *J* = 12.8, 4.8 Hz, 1H), 7.04–7.08 (m, 2H), 7.46–7.49 (m, 2H), 9.68 (d, *J* =

2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 19.8, 29.6, 42.7, 53.6, 78.2, 122.2, 129.8, 132.4, 136.0, 202.9.

(*R*)-2-[(*S*)-1-(3-Bromophenyl)-2-nitroethyl]pentanal (9m).

Obtained in nearly quantitative yield with a dr 95/5 and 92% ee (entry 13, table 2). Eluent for residue purification Et_2O/hexanes 1:3. Chromatographic and spectroscopic data are in accordance with those previously reported.[20] Chiral HPLC analysis: Chiralpak® IC column, hexane/^{i}PrOH 95:5, flow rate 1.0 mL min^{-1}, λ = 220 nm, t_R = 39.1 min (minor) and 45.1 min (major). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81 (t, *J* = 7.2 Hz, 3H), 1.13–1.52 (m, 4H), 2.70 (dddd, *J* = 9.2, 9.2, 3.6, 2.4 Hz, 1H), 3.74 (ddd, *J* = 9.6, 9.6, 5.2 Hz, 1H), 4.62 (dd, *J* = 12.8, 9.6 Hz, 1H), 4.70 (dd, *J* = 12.8, 5.2 Hz, 1H), 7.12 (ddd, *J* = 7.8, 1.8, 0.8 Hz, 1H), 7.22 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.33 (dd, *J* = 1.8, 1.8 Hz, 1H), 7.44 (ddd, *J* = 8.0, 2.0, 0.8 Hz, 1H), 9.69 (d, *J* = 2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 19.8, 29.6, 42.8, 53.7, 78.1, 123.3, 126.8, 130.8, 131.2, 131.5, 139.5, 202.8.

(*R*)-2-[(*S*)-1-(2-Bromophenyl)-2-nitroethyl]pentanal (9n).

Obtained in nearly quantitative yield with a dr 95/5 and 92% ee (entry 14, table 2). Eluent for residue purification Et_2O/hexanes 1:6. Spectroscopic data are in accordance with those previously reported.[20] Chiral HPLC analysis: Chiralpak® IC column, hexane/^{i}PrOH/acetone 95:4:1, flow rate 1.0 mL min^{-1}, λ = 220 nm, t_R = 19.9 min (mayor) and 20.8 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 7.0 Hz, 3H), 1.18-1.40 (m, 4H), 2.93-3.00 (m, 1H), 4.33-4.39 (m, 1H), 4.67 (dd, *J* = 13.2, 4.8 Hz, 1H), 4.86 (dd, *J* = 13.2, 9.2 Hz, 1H), 7.16 (ddd, *J* = 8.0, 7.2, 1.6 Hz, 1H), 7.21 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.32 (ddd, *J* = 8.0, 7.2, 1.2 Hz, 1H), 7.61 (dd, *J* = 8.0, 1.2

Hz, 1H), 9.72 (d, J = 2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 20.0, 29.7, 41.9, 53.3, 76.9, 128.2, 129.0, 129.6, 131.1, 134.0, 136.4, 203.3.

General procedure for the Michael reaction of ketones with β-nitroolefins

A solution organocatalyst **OC1** (0.02 mmol), and ketone (0.4 mmol) in trifluoromethyl benzene (2 mL) was stirred at room temperature for 10 min. The nitroolefin (0.2 mmol) was added and stirring was continued for the required time at the same temperature. The reaction was concentrated in vacuo and the residue was analysed by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard[16] to determine the reaction yield and diastereoselectivity. Purification of the residue by silica gel column chromatography yielded the corresponding Michael adducts. Enantioselectivity was determined by chiral HPLC analysis of the purified adducts using a chiral stationary phase.

(*S*)-2-[(*R*)-2-Nitro-1-phenylethyl]cyclohexan-1-one (10a).

Obtained in nearly quantitative yield with a dr 97/3, and 99% ee (entry 1, table 4). Eluent for residue purification Et_2O/hexanes 1:3. Spectroscopic data are in accordance with those previously reported.[25] Chiral HPLC analysis: Chiralpak® IA column, hexane/EtOH/acetone 84/15/1, flow rate 1.0 mL min^{-1}, λ = 220 nm, t_R = 9.8 min (minor) and 16.3 min (major). $[\alpha]^{25}_{D}$ = –25.3 (c = 1.00, $CHCl_3$) [lit.[25] $[\alpha]^{20}_{D}$ = –27.0 (c = 1.00, $CHCl_3$)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10–1.22 (m, 1H), 1.46–1.72 (m, 4H), 1.97–2.03 (m, 1H), 2.31 (ddd, J = 12.8, 12.8, 6.0 Hz, 1H), 2.37–2.42 (m, 1H), 2.61 (ddd, J= 11.0, 11.0, 4.8 Hz, 1H), 3.69 (ddd, J= 10.0, 10.0, 4.4 Hz, 1H), 4.55 (dd, J= 12.4, 10.0 Hz, 1H), 4.87 (dd, J= 12.4, 4.4 Hz, 1H), 7.08–7.26 (m, 5H). ^{13}C NMR

(100 MHz, $CDCl_3$): δ = 25.1, 28.6, 33.3, 42.8, 44.0, 52.6, 79.0, 127.8, 128.3, 129.0, 137.9, 212.0.

(*R*)-3-[(*R*)-2-Nitro-1-phenylethyl]tetrahydro-4H-pyran-4-one (10b).

Obtained in nearly quantitative yield with a dr 98/2, and 94% ee (entry 2, table 4). Eluent for residue purification Et_2O/hexanes 2:1. Spectroscopic data are in accordance with those previously reported.[25] Chiral HPLC analysis: Chiralpak® IA column, hexane/iPrOH 85/15, flow rate 1.0 mL min^{-1}, λ = 210 nm, , t_R = 16.0 min (minor) and 27.1 min (major). $[\alpha]^{25}_D$ = –37.9 (c = 1.00, $CHCl_3$) [lit.[25] $[\alpha]^{25}_D$ = –27.5 (c = 1.00, $CHCl_3$)]. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.58 (ddd, J= 14.0, 4.0, 4.0 Hz, 1H), 2.69 (dddd, J= 14.0, J= 9.6, 6.4, 1.2 Hz, 1H), 2.90 (dddd, J= 10.6, J= 8.8, 5.4, 1.0 Hz, 1H), 3.29 (dd, J= 11.4, 9.0 Hz, 1H), 3.71 (ddd, J= 11.4, 5.2, 1.2 Hz, 1H), 3.79 (ddd, J= 11.2, 10.0, 4.0 Hz, 1H), 3.85 (ddd, J= 10.4, 10.4, 4.4 Hz, 1H), 4.16 (dddd, J= 11.2, 6.4, 4.0, 1.2 Hz, 1H), 4.67 (dd, J= 12.6, 10.2 Hz, 1H), 4.95 (dd, J= 12.6, 4.4 Hz, 1H), 4.19–4.38 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.5, 43.1, 53.4, 69.1, 71.7, 78.8, 128.0, 128.4, 129.4, 136.4, 207.5.

(*R*)-1-Acetyl-3-[(*R*)-2-nitro-1-phenylethyl]piperidin-4-one (10c).

Obtained in 90% yield with a dr 85/15, and 91% ee (entry 3, table 4). Eluent for residue purification EtOAc. Spectroscopic data are in accordance with those previously reported.[26] Chiral HPLC analysis: Chiralpak® IA column, hexane/EtOH/acetone 92/7/1, flow rate 1.5 mL min^{-1}, λ = 210 nm, t_R = 58.1 min (minor) and 61.7 min (major). $[\alpha]^{25}_D$ = +12.9 (*c* = 1.00, CH_2Cl_2) [lit.[26] $[\alpha]_D$ = +20.9 (*c* = 1.00, CH_2Cl_2). ^1H NMR (300 MHz, toluene-d_8, 353 K): δ = 1.55 (s, 3H), 1.95–2.08 (m, 2H), 2.24–2.47 (m, 2H), 2.61–2.73 (m, 1H), 2.94–4.20 (m, 2H), 3.51–3.72 (m, 1H), 4.26 (dd, J = 12.6, 9.3 Hz, 1H), 4.63 ((dd, J= 12.6, 5.0 Hz, 1H) , 6.92–7.08 (m, 5H). ^{13}C NMR (75 MHz, toluene-d_8, 353 K): δ = 20.5, 41.3, 42.4, 43.6 , 47.4 , 52.2, 78.7, 128.1, 128.6, 129.3, 138.0, 168.3, 206.4.

(*S*)-2-[(*S*)-1-(Furan-2-yl)-2-nitroethyl]cyclohexan-1-one (10d).

Obtained in 96% yield with a dr 90/10, and 94% ee (entry 4, table 4). Eluent for residue purification Et_2O/hexanes 1:3. Spectroscopic data are in accordance with those previously reported.[25] Chiral HPLC analysis: Chiralpak® IA column, hexane/EtOH 90/10, flow rate 0.8 mL min^{-1}, λ = 220 nm, t_R = 24.0 min (major) and 31.0 min (minor). $[\alpha]^{25}_D$ = –14.7 (c = 1.00, $CHCl_3$) [lit.[25] $[\alpha]^{20}_D$ = –15.4 (c = 1.00, $CHCl_3$)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22–1.32 (m, 1H), 1.60–1.67 (m, 2H), 1.71–1.78 (m, 1H), 1.80–1.86 (m, 1H), 2.06–2.12 (m, 1H), 2.31–2.39 (m, 1H), 2.42–2.47 (m, 1H), 2.74 (dddd, J = 12.4, 9.2, 5.4, 1.0 Hz, 1H), 3.96 (ddd, J = 9.2, 9.2, 4.8 Hz, 1H), 4.65 (dd, J = 12.4, 9.6 Hz, 1H), 4.78 (dd, J = 12.4, 4.8 Hz, 1H), 6.17 (dd, J = 3.2, 0.4 Hz, 1H), 6.27 (dd, J = 3.2, 2.0 Hz, 1H) , 7.33 (dd, J = 2.0, 0.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.2, 28.3, 32.6, 37.7, 42.7, 51.2, 76.8, 109.1, 110.4, 142.4, 151.0, 211.0.

(*S*)-2-[(*R*)-1-(4-Methoxyphenyl)-2-nitroethyl]cyclohexan-1-one (10e).

Obtained in nearly quantitative yield with a dr 96/4, and 84% ee (entry 5, table 4). Eluents for residue purification Et_2O/hexanes 1:3 and after Et_2O/hexanes 1:1. Spectroscopic data are in accordance with those previously reported.[25] Chiral HPLC analysis: Chiralpak® IA column, hexane/^{i}PrOH 95/5, flow rate 1.0 mL min^{-1}, λ = 220 nm, t_R = 18.8 min (minor) and 22.0 min (major). $[\alpha]^{25}_D$ = –21.9 (c = 1.00, $CHCl_3$) [lit.[25] $[\alpha]^{20}_D$ = –25.1 (c = 1.00, $CHCl_3$)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16–1.26 (m, 1H), 1.53–1.79 (m, 4H), 2.02–2.10 (m, 1H), 2.36 (dddd, *J* = 12.8, 12.8, 6.0, 0.8 Hz, 1H), 2.45 (dddd, *J* = 12.8, 4.0, 4.0, 1.2 Hz, 1H), 2.60–2.67 (m. 1H), 3.70 (ddd, *J* = 10.0, 10.0, 4.4 Hz, 1H), 3.76 (s, 3H), 4.56 (dd, *J* = 12.4, 10.0 Hz, 1H), 4.90 (dd, *J* = 12.4, 4.4 Hz, 1H), 6.81–6.85 (m, 2H), 7.05–7.09 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.1, 28.6, 33.2, 42.8, 43.3, 52.7, 55.3, 79.2, 114.4, 129.3, 129.6, 159.1, 212.2.

(*S*)-2-[(*R*)-1-(4-Methylphenyl)-2-nitroethyl]cyclohexan-1-one (10f).

Obtained in nearly quantitative yield with a dr 98/2, and 96% ee (entry 6, table 4). Eluent for residue purification Et_2O/hexanes 1:3. Chromatographic and spectroscopic data are in accordance with those previously reported.[27] Chiral HPLC analysis: Chiralpak® AS-H column, hexane/^{i}PrOH 90/10, flow rate 1.0 mL min^{-1}, λ = 220 nm, t_R = 11.1 min (minor) and 18.3 min (major). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (dddd, *J* = 12.4, 12.4, 12.4, 3.6 Hz, 1H), 1.51–1.81 (m, 4H), 2.03–2.11 (m, 1H), 2.31 (s, 3H), 2.38 (dddd, *J* = 12.4, 12.4, 6.0, 1.0 Hz, 1H), 2.47 (dddd, *J* = 12.8, 4.8, 3.4, 1.2, 1H), 2.66 (dddd, *J* = 12.0, 10.0, 4.8, 0.8Hz , 1H), 3.72 (ddd, *J* = 10.0, 10.0, 4.8 Hz, 1H), 4.60 (dd, *J* = 12.4, 10.0 Hz, 1H), 4.91 (dd, *J* = 12.4, 4.4H, 1H), 7.03–7.06 (m, 2H), 7.10–7.13 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 25.1, 28.7, 33.3, 42.9, 43.7, 52.7, 79.1, 128.1, 129.7, 134.7, 137.6, 212.2.

(*S*)-2-[(*R*)-1-(4-Chlorophenyl)-2-nitroethyl]cyclohexan-1-one (10g).

Obtained in nearly quantitative yield with a dr 95/5, and 98% ee (entry 7, table 4). Eluent for residue purification Et_2O/hexanes 1:3. Chromatographic and spectroscopic data are in accordance with those previously reported.[27] Chiral HPLC analysis: Chiralpak® AS-H column, hexane/^{i}PrOH 90/10, flow rate 1.0 mL min^{-1}, λ = 220 nm, t_R = 14.8 min (minor) and 24.1 min (major). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17–1.27

(m, 1H), 1.51–1.75 (m, 3H), 1.76–1.82 (m, 1H), 2.05–2.12 (m, 1H), 2.37 (dddd, J = 12.8, 12.8, 6.0, 0.8 Hz, 1H), 2.47 (dddd, J = 12.8, 4.6, 3.4, 1.4 Hz, 1H), 2.64 (dddd, J = 12.2, 9.6, 5.0, 0.8 Hz, 1H), 3.75 (ddd, J = 9.8, 9.8, 4.6 Hz, 1H), 4.59 (dd, J = 12.8, 10.0 Hz, 1H), 4.93 (dd, J = 12.8, 4.6 Hz, 1H), 7.09–7.13 (m, 2H), 7.28–7.31 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.2, 28.6, 33.3, 42.9, 43.5, 52.5, 78.7, 129.3, 129.7, 133.8, 136.4, 211.6.

(*S*)-2-[(*R*)-1-(4-Bromophenyl)-2-nitroethyl]cyclohexan-1-one (10h).

Obtained in nearly quantitative yield with a dr 96/4, and 93% ee (entry 8, table 4). Eluents for residue purification Et_2O/hexanes 1:3 and after Et_2O/hexanes 1:1. Spectroscopic data are in accordance with those previously reported.[25] Chiral HPLC analysis: Chiralpak® IA column, hexane/^{i}PrOH 90/10, flow rate 1.0 mL min^{-1}, λ = 220 nm, t_R = 14.0 min (minor) and 20.4 min (major). $[\alpha]^{25}_D$ = –12.9 (c = 1.00, $CHCl_3$) [lit.[25] $[\alpha]^{20}_D$ = –15.4 (c = 1.00, $CHCl_3$)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 (dddd, J = 12.4, 12.4, 12.4, 3.2 Hz, 1H), 1.53–1.73 (m, 3H), 1.76–1.81 (m, 1H), 2.06–2.11 (m, 1H), 2.36 (ddd, J = 12.4, 12.4, 5.6 Hz, 1H), 2.44–2.48 (m, 1H), 2.61–2.67 (m, 1H), 3.74 (ddd, J = 10.0, 10.0, 4.4 Hz, 1H), 4.59 (dd, J = 12.4, 10.0 Hz, 1H), 4.92 (dd, J = 12.4, 4.4 Hz, 1H), 7.04–7.07 (m, 2H), 7.43–7.46 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.2, 28.5, 33.3, 42.9, 43.5, 52.4, 78.6, 121.8, 130.0, 132.2, 136.9, 211.6.

(*S*)-2-[(*R*)-1-(3-Bromophenyl)-2-nitroethyl]cyclohexan-1-one (10i).

Obtained in nearly quantitative yield with a dr 95/5, and 93% ee (entry 9, table 4). Eluent for residue purification Et_2O/hexanes 1:3. Chromatographic and spectroscopic data are in accordance with those previously reported.[28] Chiral HPLC analysis: Chiralpak® AS-H column, hexane/^{i}PrOH 80/20, flow rate 1.0 mL min^{-1}, λ = 220 nm, t_R

= 11.4 min (minor) and 21.6 min (major). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (dddd, *J* = 12.2, 12.2, 12.2, 3.4 HZ, 1H), 1.52–1.66 (m, 2H), 1.67–1.75 (m, 1H), 1.78–1.83 (m, 1H), 2.05–2.13 (m, 1H), 2.37 (dddd, *J* = 12.8, 12.8, 6.0, 0.8 Hz, 1H), 2.47 (dddd, *J* = 12.8, 4.6, 3.6, 1.6 Hz, 1H), 2.65 (dddd, *J* = 12.4, 9.8, 5.0, 0.8 Hz, 1H), 3.74 (ddd, *J* = 10.0, 10.0, 4.8 Hz, 1H), 4.60 (dd, *J* = 12.8, 10.0 Hz, 1H), 4.93 (dd, *J* = 12.8, 4.8 Hz, 1H), 7.11 (ddd, *J* = 7.6, 1.2, 1.2 Hz, 1H), 7.19 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.32 (dd, *J* = 1.8, 1.8 Hz, 1H), 7.40 (ddd, *J* = 7.8, 2.0, 1.2 Hz, 1H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.2, 28.6, 33.4, 42.9, 43.8, 52.5, 78.5, 123.1, 127.1, 130.6, 131.1, 131.3, 140.4, 211.5.

(*S*)-2-[(*R*)-1-(2-Bromophenyl)-2-nitroethyl]cyclohexan-1-one (10j).

Obtained in nearly quantitative yield with a dr 97/3, and 94% ee (entry 10, table 4). Eluent for residue purification Et_2O/hexanes 1:3. Spectroscopic data are in accordance with those previously reported.[29] $[\alpha]^{25}_D$ = –40.7 (*c* = 0.75, $CHCl_3$) [lit.[29] $[\alpha]^{20}_D$ = –50.8 (*c* = 1.00, $CHCl_3$)]. Chiral HPLC analysis: Chiralpak® IC column, hexane/^{i}PrOH 90/10, flow rate 1.0 mL min^{-1}, λ = 220 nm, t_R = 28.3 min (major) and 33.5 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32-1.42 (m, 1H), 1.53-1.77 (m, 3H), 1.78-1.84 (m, 1H), 2.06-2.14 (m, 1H), 2.38 (dddd, *J* = 12.8, 12.8, 6.0, 0.8 Hz, 1H), 2.47 (dddd, *J* = 12.8, 4.6, 3.2, 1.4 Hz, 1H), 2.82-2.96 (m, 1H), 4.27s-4.34 (m, 1H), 4.85-4.94 (m, 2H), 7.12 (ddd, *J* = 8.0, 7.4, 1.8 Hz, 1H), 7.21 (dd, *J* = 7.6, 1.6 HZ, 1H), 7.29 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.57 (dd, *J* = 8.0, 1.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.4, 28.6, 33.1, 42.9, 43.0 (from HSQC), 52.2 (from HSQC), 77.5, 128.1, 129.2, 133.8, 137.4, 211.7.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 (*a*) B. F. Sun, *Tetrahedron Lett.* **2015**, *56*, 2133–2140; (*b*) A. Ricci, *Asymmetric Organocatalysis at the Service of Medicinal Chemistry*, ISRN Organic Chemistry, vol. 2014, Article ID 531695; (*c*) J. Aleman and S. Cabrera, *Chem. Soc. Rev.* **2013**, *42*, 774–793; (*d*) P. G. Bulger, in *Applications of Organocatalyzed Asymmetric Synthesis*. Comprehensive Chirality, Volume 9: Industrial Applications of Asymmetric Synthesis, ed. D. Huges, Editors-in-Chief: A. M. Carreira and H. Yamamoto, Elsevier Science 2012, p. 228–252.

2 (*a*) Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications, three-volume set, ed. P. I. Dalko, Wiley-VCH, Weinheim, Germany, 2013; (*b*) Comprehensive Chirality, Volume 6: Synthetic Methods V – Organocatalysis, eds. K. Maruoka and M. Shibasaki, Editors-in-Chief: A. M. Carreira and H. Yamamoto, Elsevier Science 2012.

3 (*a*) B. M. Paz, J. Jiang and K. A. Jørgensen, *Chem. Eur. J.* **2015**, *21*, 1846–1853; (*b*) M. C. Holland and R. Gilmour, *Angew. Chem. Int. Ed*. **2015**, *54*, 3862–3871; (*c*) P. Melchiorre, M. Marigo, A. Carlone and G. Bartoli, *Angew. Chem. Int. Ed.* **2008**, *47*, 6138–6171; (*d*) S. Mukherjee, J. W. Yang, S.

Hoffmann and B. List, *Chem. Rev.* **2007**, *107*, 5471–5569; (*e*) B. List, *Chem. Commun*. **2006**, 819–824.

4 See for example: (*a*) L. Albrecht, H. Jiang and K. A. Jorgensen, *Chem. Eur. J.* **2014**, *20*, 358–368; (*b*) L. Q. Lu, X. L. An, J. R. Chen and W. J. Xiao, *Synlett* **2012**, 490–508; (*c*) H. Yang and R. G. Carter, *Synlett* **2010**, 2827–2838; (*d*) X. Liu, L. Lin and X. Feng, *Chem. Commun*. **2009**, 6145–6158.

5 For a recent review on this subject see: A. Y. Sukhorukov, A. A. Sukhanova and S. G. Zlotin, *Tetrahedron* **2016**, *72*, 6191–6281.

6 B. List, P. Pojarliev and H. J. Martin, *Org. Lett*. **2001**, *3*, 2423–2426.

7 J. M. Betancort and C. F. Barbas III, *Org. Lett*. **2001**, *3*, 3737–3740.

8 Some recent reviews: (*a*) A. M. Faísca Phillips, *Curr. Org. Chem*. **2016**, *13,* 687–725; (*b*) R. Somanathan, D. Chavez, F. A. Servin, J. A. Romero, A. Navarrete, M. Parra-Hake, G. Aguirre, C. A. Anaya de Parrodi and J. Gonzalez, *Curr. Org. Chem*. **2012**, *16*, 2440–2461; (*c*) J. L. Vicario, D. Badía, L. Carrillo and E. Reyes, Organocatalytic enantioselective conjugate addition reactions: a powerful tool for the stereocontrolled synthesis of complex molecules, Royal Society of Chemistry, Cambridge, 2010, pp 23-45; (*d*) D. Roca-López, D. Sadaba, I. Delso, R. P. Herrera, T. Tejero and P. Merino, *Tetrahedron: Asymmetry* **2010**, *21*, 2561–2601; (*e*) S. Sulzer-Mosse and A. Alexakis, *Chem. Commun.* **2007**, 3123–3135.

9 (*a*) P. Etayo, R. Badorrey, M. D. Díaz-de-Villegas and J. A. Gálvez, *Adv. Synth. Catal.* **2010**, *352*, 3329–3338; (*b*) A. Castán, R. Badorrey, J. A. Gálvez and M. D. Díaz-de-Villegas, *Beilstein J. Org. Chem.* **2017**, *13*, 612–619.

10 See for example: (*a*) C. He, X. Ren, Y. Feng, Y. Chai, S. Zhang and W. Chen, *Tetrahedron Lett.* **2015**, *56*, 4036–4038; (*b*) J. I. Martínez, E. Reyes, U. Uria, L.

Carrillo and J. L. Vicario, *ChemCatChem* **2013**, *5*, 2240–2247; (*c*) C. Wang, C. Yu, C. Liu, and Y. Peng, *Tetrahedron Lett.* **2009**, *50*, 2363–2366; (*d*) H. Zhang, Y. Chuan, C. Li and Y. Peng, *Adv. Synth. Catal.* **2009**, *351*, 2288–2294; (*e*) Y. M. Chuan, L. Y. Yin, T. M. Zhang and Y. G. Peng, *Eur. J. Org. Chem.* **2011**, 578–583.

11 J. A. Gálvez, M. D. Díaz-de-Villegas, R. Badorrey and M. P. López-Ram-de-Víu, *Org. Biomol. Chem.* **2011**, *9*, 8155–8162.

12 (*a*) A. Feula, S. S. Dhillon, R. Byravan, M. Sangha, R. Ebanks, M. A. H. Salih, N. Spencer, L. Male, I. Magyary, W. P. Deng, F. Müllerc and J. S. Fossey, *Org. Biomol. Chem.* **2013**, *11*, 5083–5093; (*b*) A. Feula, L. Male and J. S. Fossey, *Org. Lett.* **2010**, *12*, 5044–5047.

13 L. Hong, W. Sun, D. Yang, G. Li and R. Wang, *Chem. Rev.* **2016**, *116*, 4006–412.

14 T. Husch, D. Seebach, A. K. Beck and M. Reiher, *Helv. Chim. Acta*, **2017**, *100*, e1700182. And references herein.

15 Residual solvent signals set according to G. R. Fulmer, A. J. M. Miller, N. H. Sherden, H. E. Gottlieb, A. Nudelman, B. M. Stolz, J. E. Bercaw and K. I. Goldberg, *Organometallics* **2010**, *29*, 2176–2179.

16 C. Hellriegel and A. Rück, *Analitix* **2012**, No 4, 8–9.

17 Z. Zheng, B. L. Perkins and B. Ni, *J. Am. Chem. Soc.* **2010**, *132*, 50–51.

18 S. B. Ötvös, I. M. Mándity and F. Fülöp, *ChemSusChem* **2012**, *5*, 266–269.

19 I. Sagamanova, C. Rodríguez-Escrich, I. G. Molnár, S. Sayalero, R. Gilmour and M. A. Pericàs, *ACS Catal.* **2015**, *2015*, 6241–6248.

20 C. He, X. Ren, Y. Feng, Y. Chai, S. Zhang and W. Chen, *Tetrahedron Lett.* **2015**, *56*, 4036–4038.

21 C. Wang, C. Yu, C. L. Liu and Y. G. Peng, *Tetrahedron Lett.* **2009**, *50*, 2363–2366.

22 Y. Wang, D. Li, J. Lin and K. Wei, *RSC Adv*. 2015, 5, 5863–5874.

23 S. Ghosh, Y. Qiao, B. Ni and A. D. Headley, *Org. Biomol. Chem.* **2013**, *11*, 1801–1804.

24 W. H. Wang, T. Abe, X. B. Wang, K. Kodama, T. Hirose and G. Y. Zhang, *Tetrahedron: Asymmetry* **2010**, *21*, 2925–2933.

25 N. Kaplaneris, G. Koutoulogenis, M. Raftopoulou and C. G. Kokotos, *J. Org. Chem.* **2015**, *80*, 5464−5473.

26 C. G. Kokotos, D. Limnios, D. Triggidou, M. Trifonidou, and G. Kokotos, *Org. Biomol. Chem*. **2011**, *9*, 3386−3395.

27 H. W. Zhao, H. L. Li, Y. Y. Yue and Z. H. Sheng, *Eur. J. Org. Chem*. **2013**, 1740−1748.

28 Y. J. Cao, Y. Y. Lai, X. Wang, Y. J. Lia and W. J. Xiao, *Tetrahedron Lett.* **2007**, *48*, 21–24.

29 A. Lu, R. Wu, Y. Wang, Z. Zhou, G. Wu, J. Fang and C. Tang, *Eur. J. Org. Chem*. **2011**, 122−127.