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PAPER

Novel pyrrolidine-thiohydantoins/thioxotetrahydropyrimidinones as highly effective catalysts for the asymmetric Michael addition†

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The synthesis of novel organocatalysts consisting of a pyrrolidine moiety and a thiohydantoin or a thioxotetrahydropyrimidinone ring is described. The compound combining the pyrrolidine with the thioxotetrahydropyrimidinone was found to be a highly effective catalyst for the Michael reaction. Low catalyst loadings (1–2.5%) can be employed leading to quantitative yields and excellent stereoselectivities in the reaction between cyclic ketones and nitroolefins.

Introduction

At the end of the first decade of the 21st century, organocatalysis now constitutes a well recognized methodology complementing transition metal complex-mediated catalysis and biocatalysis in the armoury of asymmetric synthesis.[1] Over the last decade, a wide variety of organocatalysts have been developed presenting distinct mechanisms of action.[2] Among the existing organocatalysts, proline[3] and related aminocatalysts, chiral thioureas initially proposed by Jacobsen[4] and imidazolidinones developed by MacMillan[5] represent the major organocatalyst categories.[6] The five-membered secondary amine structure of pyrrolidine is considered to be a "privileged" structure able to activate carbonyl compounds through the formation of enamine intermediates. In combination with other functional groups, it provides bifunctional molecules such as chiral diamines **1** and **2**,[7] sulfonamide **3**,[8] diarylprolinols **4** and the corresponding TMS ethers,[9] amides like **5**,[10] (Fig. 1) able to catalyze a variety of asymmetric transformations. In addition, it has been demonstrated that compounds containing a primary amino group,[11] like the alanine derivative **6** (Fig. 1),[12] may also catalyse asymmetric reactions, including the Michael reaction. In the last few years, our group proposed 4-substituted prolines[13a,b] and proline sulfonamides,[13c] homoproline and dipeptide sulfonamides,[13d] heterocyclic analogues of homoproline[13e] as well as chiral primary amine-thioureas[13f] as improved catalysts for the aldol and Michael reactions. In an effort to search for new and improved catalytic motives, we focused on developing new bifunctional catalysts combining the secondary amine of the pyrrolidine ring with a new chiral template. To this end, we thought of the thiohydantoin ring or the corresponding six-membered ring as the appropriate scaffold. In the present work, we present the synthesis of novel pyrrolidine-based bifunctional molecules incorporating a thiohydantoin or a 2-thioxotetrahydropyrimidin-4-one ring and the evaluation of these catalysts in the Michael reaction.

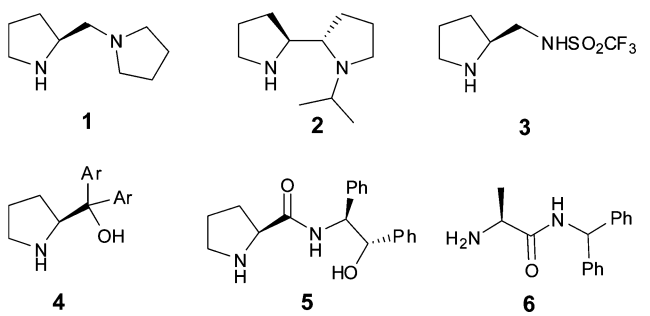

Fig. 1 Some pyrrolidine-based organocatalysts.

Results and discussion

The rationale for the design of the new catalysts is illustrated in Fig. 2. For the construction of the catalyst, apart from the pyrrolidine ring, a chiral template capable of creating either hydrogen bonds or a bulky environment is required. Bearing in mind the amino acid chemistry and the ease of thioureas

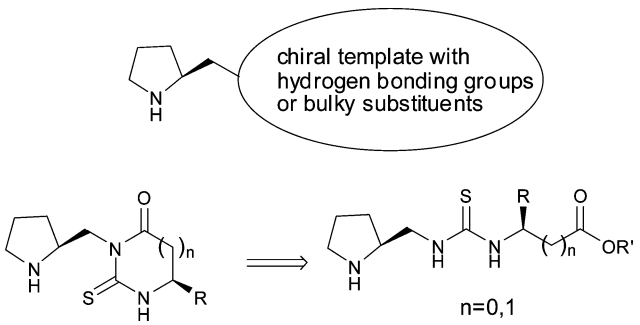

Fig. 2 Design of the new catalysts.

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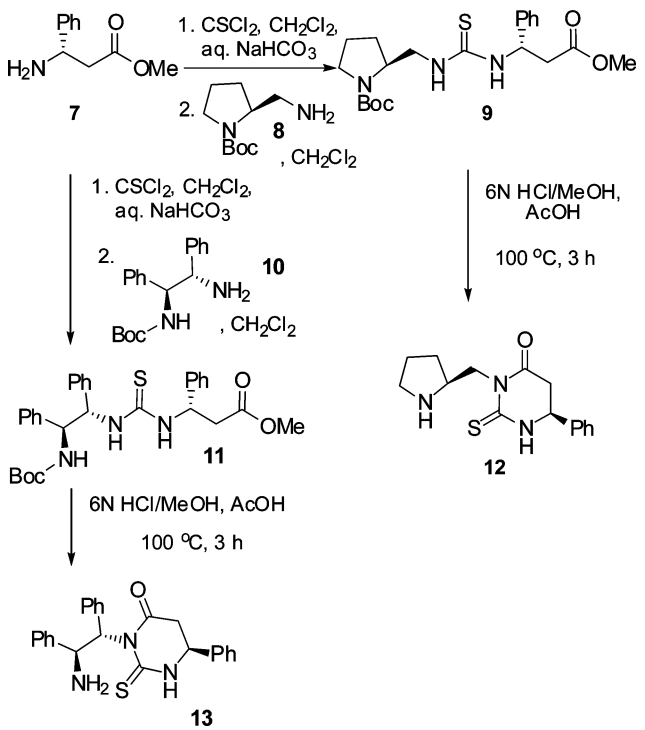
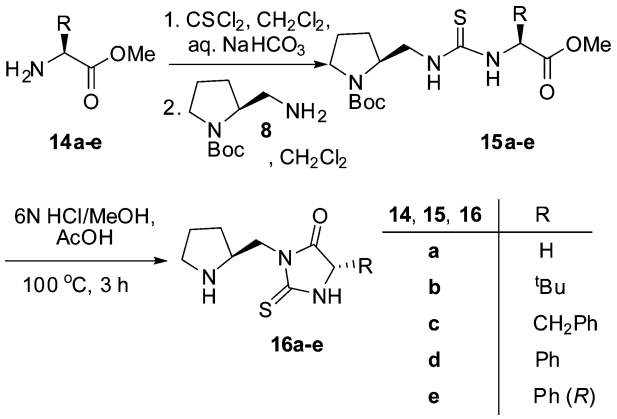
to participate in hydrogen bonding, the thiohydantoin ring or the corresponding six-membered ring of thioxotetrahydropyrimidinone may be formed from thioureas involving α- or β-amino acids (Fig. 2). The commercially available methyl ester of (*S*)-β-phenylalanine (**7**) was converted to the corresponding isothiocyanate by treatment with thiophosgene and reacted with (*S*)-*tert*-butyl-2-(aminomethyl)pyrrolidine-1-carboxylate (**8**) to afford thiourea **9** (Scheme 1). In order to elucidate whether a primary or a secondary amine moiety is optimal for high catalytic activity, the isothiocyanate from **7** also reacted with *tert*-butyl (*1S*, *2S*)-2-amino-1,2-diphenylethylcarbamate (**10**) and thiourea **11** was obtained. It is known that (thio)ureas containing amino acid esters may be cyclized to (thio)hydantoins or 2-(thio)oxotetrahydropyrimidin-4-ones under acidic or basic conditions.[14] Treatment of **9** and **11** with 6 N HCl/MeOH upon heating resulted in the formation of the heterocyclic ring with simultaneous removal of the Boc group providing compounds **12** and **13**. The synthesis of the corresponding five-membered thiohydantoin ring was necessary because five and six-membered rings are known to adopt different conformations, that may result in different reactivities. The synthesis of pyrrolidine/thiohydantoins started from commercially available methyl esters of glycine (**14a**), (*S*)-*tert*-leucine (**14b**), (*S*)-phenylalanine (**14c**), (*S*)-phenylglycine (**14e**) and (*R*)-phenylglycine (**14e**) and is illustrated in Scheme 2, in a similar fashion as in Scheme 1. Altering the reaction conditions in the cyclization step can lead to the Boc-protected compound **17** (Scheme 3) that can be used for studies of the reaction mechanism.

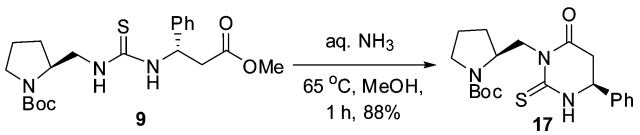


Scheme 1 Synthesis of new catalysts **12** and **13**.

The asymmetric Michael addition is one of the most useful processes for the synthesis of new C–C and C–X bonds. Thus, much effort has been devoted to exploring various organocatalysts for this key transformation.[15] The reaction of cyclohexanone with



Scheme 2 Synthesis of new catalysts **16a–e**.



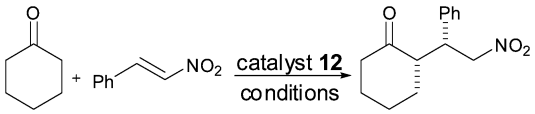
Scheme 3 Synthesis of compound **17**.

trans-β-nitrostyrene was chosen as the model reaction to evaluate the effectiveness of the new catalysts.

At the beginning, catalyst **12** was tested at catalyst loadings from 15% to 2.5% using toluene as the solvent and acetic acid and water as the additives. A catalyst loading of 2.5% was enough to achieve high yield and enantioselectivity (entry 3, Table 1), indicating the high reactivity of the catalysts and their potential use at even lower catalyst loadings. In the absence of additives, only traces of the product were obtained (entry 4, Table 1). Both an acidic additive and H_2O are necessary for the catalytic activity (entry 4 *vs.* 5 and 6, Table 1). The acidic counterpart facilitates the enamine formation which is key for the catalytic cycle, while water should be involved in the hydrolysis of the catalyst from the addition product helping the catalyst turnover. The effect of the reaction solvent was next examined (entries 7–16, Table 1) and it was found that although high enantioselectivities were observed in most cases, the yield varied from low to satisfactory. Polar and chlorinated solvents led to decreased yields while non-polar solvents seem to favour the reaction. Using tetrahydrofuran as the solvent, the product was obtained in a yield comparable to that obtained by using toluene, but the enantiomeric excess was higher (entry 13, Table 1).

An extensive study of various acids instead of acetic acid, highlighted the importance of the nature of the acidic counterpart. Brønsted acids have been reported to facilitate the action of aminocatalysts, improving both the yield and the stereoselectivity.[16] Strong acids like trifluoroacetic acid, citric acid or 2,4-dinitrobenzoic acid did not work leading to traces of the product (entries 2–4, Table 2). Benzoic acid provided low yield, however the introduction of a nitro group, with simultaneous alteration of the acidity of the additive, drastically improved the activity (entries 5–7, Table 2). 4-Nitrobenzoic acid gave excellent results in particular when tetrahydrofuran was used as a solvent (entry 8, Table 2). When the reaction was performed at 0 °C, a decrease in the yield was observed using either acetic acid or 4-nitrobenzoic acid (entries 9 and 10, Table 2), without any improvement in the enantiocontrol of the reaction. It was gratifying to see that under

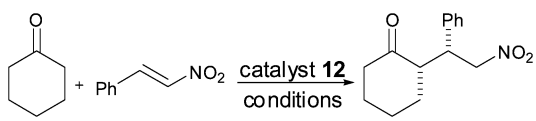
Table 1 Michael reaction between cyclohexanone and *trans*-β-nitrostyrene using catalyst **12**[a]



Entry	Catalyst loading (%)	Solvent	Additives	Yield (%)[b]	*ee* (%)[c]
1	15	toluene	AcOH, H_2O	99	92
2	5	toluene	AcOH, H_2O	99	92
3	2.5	toluene	AcOH, H_2O	95	92
4	2.5	toluene	—	traces	—
5	2.5	toluene	AcOH	62	90
6	2.5	toluene	H_2O	8	88
7	2.5	neat	AcOH, H_2O	41	93
8	2.5	brine	AcOH, H_2O	22	94
9	2.5	Et_2O	AcOH, H_2O	22	94
10	2.5	MeCN	AcOH, H_2O	69	93
11	2.5	DMSO	AcOH, H_2O	17	90
12	2.5	H_2O	AcOH, H_2O	8	88
13	2.5	THF	AcOH, H_2O	92	96
14	2.5	CH_2Cl_2	AcOH, H_2O	78	94
15	2.5	$CHCl_3$	AcOH, H_2O	47	95
16	2.5	$CHCl_3$	AcOH, MeOH	42	93

[a] Reactions were performed using 0.2 mmol nitroolefin, ketone (10 equiv.), acid (15 mol%) and H_2O (2 equiv.) for 18 h. [b] Isolated yield. [c] The enantiomeric excess (*ee*) was determined by chiral HPLC. The diastereomeric ratio (*dr*) was determined by ^{1}H NMR spectroscopy (600 MHz) and found to be 99 : 1 (*syn* : *anti*).

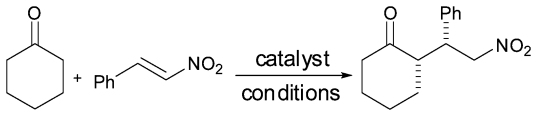
Table 2 Michael reaction between cyclohexanone and *trans*-β-nitrostyrene using catalyst **12**[a]



Entry	Catalyst loading (%)	Solvent	Additive and H_2O	Yield (%)[b]	*ee* (%)[c]
1	2.5	toluene	AcOH	95	92
2	2.5	toluene	TFA	traces	—
3	2.5	toluene	citric acid	traces	—
4	2.5	toluene	2,4-diNBA	traces	—
5	2.5	toluene	$PhCO_2H$	16	89
6	2.5	toluene	2-NBA	61	95
7	2.5	toluene	4-NBA	96	97
8	2.5	THF	4-NBA	100	97
9[d]	2.5	toluene	AcOH	71	97
10[d]	2.5	toluene	4-NBA	67	97
11	1	THF	4-NBA	86	97
12[e]	2.5	THF	4-NBA	98	96
13[f]	1	THF	4-NBA	71	96
14	2.5	THF	4-CBA	95	97
15	2.5	THF	4-TBA	97	97

[a] Reactions were performed using 0.2 mmol nitroolefin, ketone (10 equiv.), acid (15 mol%) and H_2O (2 equiv.) for 18 h. [b] Isolated yield. [c] The enantiomeric excess (*ee*) was determined by chiral HPLC. The diastereomeric ratio (*dr*) was determined by ^{1}H NMR spectroscopy (600 MHz) and found to be 99 : 1 (*syn* : *anti*). [d] The reaction was performed at 0 °C. [e] 2 equiv. of ketone were used, reaction time 48 h, *dr* 98 : 2. [f] 1.2 equiv. of ketone were used, reaction time 48 h, *dr* 98 : 2. 2,4-diNBA: 2,4-dinitrobenzoic acid, 2-NBA: 2-nitrobenzoic acid, 4-NBA: 4-nitrobenzoic acid, 4-CBA: 4-cyanobenzoic acid, 4-TBA: 4-trifluoromethylbenzoic acid.

Table 3 Michael reaction between cyclohexanone and *trans*-β-nitrostyrene using catalyst **12**, **13**, **16a–e** and **17**[a]



Entry	Catalyst	Solvent	Yield (%)[b]	*dr* (syn : anti)[c]	*ee* (%)[d]
1	**12**	toluene	96	99 : 1	97
2	**12**	THF	100	99 : 1	96
3	**16a**	toluene	19	96 : 4	91
4	**16a**	THF	24	96 : 4	92
5	**16b**	toluene	72	99 : 1	95
6	**16b**	THF	100	99 : 1	96
7	**16c**	toluene	92	98 : 2	92
8	**16c**	THF	94	98 : 2	92
9	**16d**	toluene	92	99 : 1	95
10	**16d**	THF	96	99 : 1	95
11	**16e**	toluene	81	99 : 1	94
12	**16e**	THF	91	99 : 1	95
13	**13**[e]	THF	20	60 : 40	50
14	**17**[e]	THF	—	—	—

[a] Reactions were performed using 0.2 mmol nitroolefin, ketone (10 equiv.), 4-NBA (15 mol%) and H_2O (2 equiv.) for 18 h. [b] Isolated yield. [c] The diastereomeric ratio (*dr*) was determined by ^{1}H NMR spectroscopy (600 MHz). [d] The enantiomeric excess (*ee*) was determined by chiral HPLC. [e] 10% mol catalyst was used.

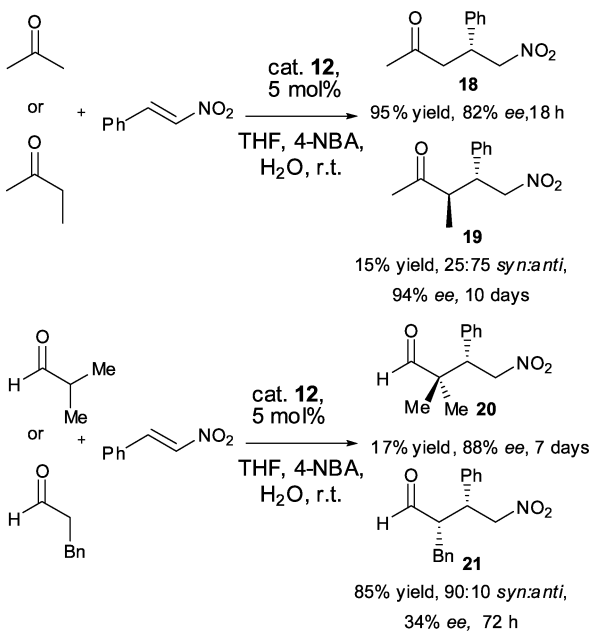
the optimized conditions (tetrahydrofuran, *p*-nitrobenzoic acid and water), the product was obtained in 86% yield and 97% *ee* using even as little as 1% catalyst loading of **12** (entry 11, Table 2). Furthermore, catalyst **12** efficiently catalyzed the reaction even when a slight excess amount of ketone (1.2 to 2 equiv.) was used (entries 12 and 13, Table 2). To fully elucidate the importance of the acid additive, 4-cyanobenzoic acid and 4-trifluoromethylbenzoic acid were tested (entries, 14 and 15, Table 2). In both cases, high yields and stereoselectivities were observed. Comparing the pK_a values (in H_2O) of 4-nitrobenzoic acid (3.44), 4-cyanobenzoic acid (3.55) and 4- trifluoromethylbenzoic acid (3.60), all of which led to excellent results, it seems that an optimum pK_a value of the additive is needed in order to maximise the yield and the enantioselectivity.

In order to shed more light on the required building aspects of a favorable catalyst, we evaluated catalysts **16a–e**, **13** and **17** with different structural features (Table 3). For this study, *p*-nitrobenzoic acid and water, 2.5% catalyst loading and tetrahydrofuran or toluene as solvents were used. When the thioxotetrahydropyrimidinone ring was replaced by the thiohydantoin ring (entry 1 *vs.* 9 and entry 2 *vs.* 10, Table 3) similar results were obtained showing that the two different-sized rings adopted similar conformations in the transition state. The absence of a substituent in the thiohydantoin ring (entry 3 *vs.* 9 and entry 4 *vs.* 10, Table 1) led to decreased selectivities and low yields highlighting the necessity of a substituent on the ring in order to lock its conformation to a much more efficient one for the catalytic activity. Using various substituents such as *tert*-butyl (catalyst **16b**), benzyl (catalyst **16c**) and phenyl (catalyst **16c**), similar results were obtained (entries 5–10, Table 3). Thus, it can be postulated that the nature of the substituent does not seem to be so important for high selectivities, but the conformation of the ring adopted due to the substituent is the important factor. This point is also supported by the fact that catalysts **16d** and **16e**, which have

the phenyl substituent of the thiohydantoin ring in the opposite configuration, furnished the same product enantiomer in similar diastereomeric ratios and *ee*s. Derivative **13** led to poor results regarding both the yield and the stereoselectivities (entry 13, Table 3), while the protected derivative **17** failed to catalyse the Michael reaction (entry 14, Table 3). Both these data indicate that a free secondary amino group is a requirement for the catalytic activity. In conclusion, both the thioxotetrahydropyrimidinone ring and the thiohydantoin ring carrying a phenyl or a bulky substituent work as excellent catalysts for the reaction between cyclohexanone and *trans*-β-nitrostyrene.

To explore the scope and the limitations of the Michael reaction, various nitroolefins and ketones were studied using the pyrrolidine/thioxopyrimidinone **12** and the pyrrolidine/thiohydantoin **16b** as a catalyst and the results are presented in Table 4. Using catalyst **12**, the products of the reaction between cyclohexanone and various nitroolefins were isolated in excellent yields (88–100%) (entries 1, 3, 5, 7, 9, Table 4). In all cases high diastereoselectivities (94 : 6 to 99 : 1) and enantioselectivities (95–97% *ee*) were observed. When other ketones were used, all the products were isolated in high to quantitative yields, high diastereoselectivities (87 : 13 to 98 : 2) and enantioselectivities (95 to 96% *ee*), although elongation of the reaction time was needed to reach reaction completion (entries 11, 13, 15, 17, 19, Table 4). Slight variations were observed when catalyst **16b** was used.

To further study the scope of the new catalyst **12** in Michael additions, acyclic ketones and aldehydes were tested under the optimised conditions for cyclic ketones (Scheme 4). Using 5% catalyst loading, only acetone afforded the desired product in high yield and good enantioselectivity. A more "difficult" substrate like butan-2-one led to high enantioselectivity but low yield after extended reaction time. The use of linear aldehydes was amenable, although good yields and unsatisfactory enantioselectivities were observed. The introduction of geminal substitution in the α-position of the aldehyde led to decreased yields but high *ee*.



Scheme 4 Michael reaction between acyclic ketones and aldehydes with nitrostyrene using catalyst **12**.

To account for the stereochemical outcome of the Michael reaction, a plausible transition-state model is proposed in Fig. 3. The secondary amine of the pyrrolidine ring activates the ketone through the formation of an enamine intermediate. The approach of the electrophile is controlled by the heterocyclic ring through stabilizing interactions, such as hydrogen bonding. Thus, the high enantiocontrol observed can be accounted for by a postulated stabilizing interaction of the heterocyclic ring with the nitroolefin which controls the face of the nucleophilic attack. Thus, the approach occurs in the same way irrespective of the configuration of the stereogenic center of the thiohydantoin ring, leading to the same product enantiomer in both cases (see ESI†). In the absence of the substituent, the front face is not blocked that efficiently.

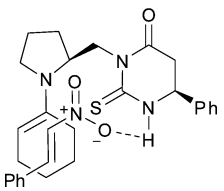


Fig. 3 Proposed transition state.

A great variety of pyrrolidine-based catalysts have been studied for this model Michael addition.[8,13d,17] Although some of the existing catalysts provide the product in high yield and stereoselectivity, two major drawbacks exist. A high catalyst loading (10–30%) as well as a large excess amount of Michael donor (up to 20 equiv. of ketone) has to be applied. Our novel pyrrolidine–thioxopyrimidinone system has as a major advantage in that it works efficiently even at as little as 1–2.5% catalyst loading. In addition, the use of a slight excess of ketones (1.2 to 2 equiv.) may be successfully applied. Recently, a small number of very efficient organocatalysts (1% to 2% catalyst loading) for the Michael reaction of aldehydes to nitroolefins, like tripeptides or diarylprolinol silyl ethers, have appeared in the literature.[16c,18]

Conclusions

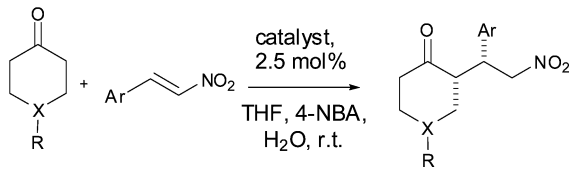
In conclusion, we have developed novel organocatalysts combining the "privileged" pyrrolidine ring with the thioxotetrahydropyrimidinone or the thiohydantoin rings. These novel catalysts are highly effective for the asymmetric Michael addition of cyclic ketones to nitroolefins providing the product in high yields and stereoselectivities. The advantages of the new catalysts are that: (a) they are easily synthesized, and (b) the reaction can be conducted in the presence of as little as 1% catalyst loading. Further studies on exploring the catalytic activity of the novel organocatalysts on other asymmetric transformations are under way.

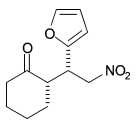
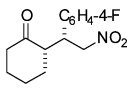
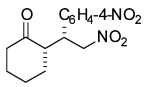
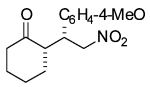
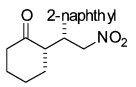
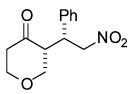
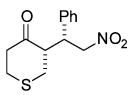
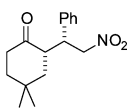
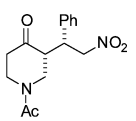
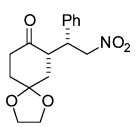
Experimental section

General information

Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on Merck Kieselgel 60 F_{254} 230–400 mesh. Thin-layer chromatography (TLC) was performed on aluminium backed silica plates (0.2 mm, 60 F_{254}). Visualization of the developed chromatogram

Table 4 Michael reaction between cyclic ketones and nitroolefins using catalyst **12** and **16b**[a]



Entry	Product	Catalyst	Time (h)	Yield (%)[b]	*dr* (syn : anti)[c]	*ee* (%)[d]
1		**12**	18	89	94 : 6	95
2		**16b**	18	90	92 : 8	96
3		**12**	18	92	99 : 1	97
4		**16b**	18	91	98 : 2	96
5		**12**	18	100	97 : 3	97
6		**16b**	18	99	98 : 2	96
7		**12**	46	96	98 : 2	96
8		**16b**	46	96	98 : 2	98
9		**12**	18	88	99 : 1	96
10		**16b**	18	85	96 : 4	96
11		**12**	46	98	93 : 7	95
12		**16b**	46	94	95 : 5	96
13		**12**	46	99	97 : 3	95
14		**16b**	46	96	97 : 3	96
15		**12**	46	96	98 : 2	96
16		**16b**	46	98	98 : 2	95
17		**12**	46	92	87 : 13	96
18		**16b**	46	90	87 : 13	96
19		**12**	46	93	98 : 2	95
20		**16b**	46	91	98 : 2	96

[a] Reactions were performed using 0.2 mmol nitroolefin, ketone (10 equiv.), 4-NBA (15 mol%) and H_2O (2 equiv.) for 18 h. [b] Isolated yield. [c] The diastereomeric ratio (*dr*) was determined by ^{1}H NMR spectroscopy (600 MHz). [d] The enantiomeric excess (*ee*) was determined by chiral HPLC.

was performed by fluorescence quenching using phosphomolybdic acid, anisaldehyde or ninhydrin stains. Melting points were determined on a Buchi 530 hot stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury (200 MHz or 50 MHz) or Bruker (600 MHz and 150 MHz respectively) as noted, and are internally referenced to residual protio solvent signals ($CDCl_3$). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, bs = broad signal, bs m = broad signal multiplet), coupling constant and assignment. Wherever rotamers exist, these are presented in brackets. Diastereomeric ratios were determined by ^{1}H NMR (600 MHz). Data for ^{13}C NMR are reported in terms of chemical shift (δ ppm). IR spectra were recorded on a Nicolet 6700 FT-IR

spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were recorded on a Finnigan Surveyor MSQ Plus, with only molecular ions and major peaks being reported with intensities quoted as percentages of the base peak. High Performance Liquid Chromatography (HPLC) was used to determine enantiomeric excesses and was performed on a Agilent 1100 Series apparatus using a Chiralpak®AD-H column. Optical rotations were measured on a Perkin Elmer 343 polarimeter.

General procedure for the synthesis of thioureas 9, 11 and 15a–e

To a stirring solution of amino acid methyl ester hydrochloride (1.00 mmol) in dichloromethane (5 mL), a saturated aqueous solution of $NaHCO_3$ (5 mL) was added at 0 °C and left stirring vigorously for 10 min. The stirring was stopped and thiophosgene (0.10 mL, 1.05 mmol) was added to the organic layer (bottom layer) *via* syringe. The reaction mixture was stirred vigorously at room temperature for 1 h. The two layers were separated and the aqueous layer was extracted with dichloromethane (3 × 5 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated to afford the isothiocyanate with enough purity to be used in the subsequent step. A solution of the isothiocyanate in dichloromethane (15 mL) was added to a stirring solution of the amine (1.00 mmol) in dichloromethane (10 mL) over a period of 5 min at room temperature and the reaction mixture was left stirring until the consumption of the isothiocyanate (0.5–5 h). The solvent was evaporated and the crude product was purified using flash column chromatography eluting with various mixtures of $CHCl_3$: MeOH or CH_2Cl_2 : MeOH.

(*S*)-*tert*-Butyl-2-{[3-((*S*)-3-methoxy-3-oxo-1-phenylpropyl)-thioureido]methyl}pyrrolidine-1-carboxylate (9). Light yellow solid, mp 64–66 °C, 88% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.93 (1H, br d, J = 8.2 Hz, NH), 7.43–7.17 (5H, m, ArH), 6.39 (1H, br s, NH), 5.56 (1H, ddd, J = 11.3, 8.2 and 6.1 Hz, NCH), 4.15–3.99 (1H, m, NCH), 3.72 (3H, s, OCH_3), 3.62–3.21 (4H, m, 4 × NC**H**H), 3.19–3.01 (2H, m, $COCH_2$), 2.01–1.71 (4H, m, 4 × C**H**H), 1.52 [9H, s, $C(CH_3)_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 181.5 (181.3) (C═S), 173.6 (172.4) (C═O), 154.6 (154.2) (OCONH), 135.5 (134.7) (Ar), 129.0 (Ar), 128.1 (Ar), 126.6 (127.0) (Ar), 80.0 [*C*$(CH_3)_3$], 60.3 (60.2) (NCH), 55.9 (NCH), 52.0 (OCH_3), 46.5 (46.4) (NCH_2), 46.1 (45.9) (NCH_2), 36.5 (37.7) (*C*H_2CO), 29.7 (29.6) (CH_2), 28.2 [C(*C*H_3)], 23.5 (23.2) (CH_2); IR (film) 2973, 1744, 1663, 1543, 1508, 1405 cm^{-1}; MS (ESI) 422 (M + H^+, 100%); HRMS exact mass calculated for [M + Na]$^+$ ($C_{21}H_{31}N_3O_4SNa$) requires m/z 444.1933, found m/z 444.1926; $[\alpha]_D$ = −1.5 (c = 1.0, CH_2Cl_2).

(6*S*, 7*S*, *11S*)-Methyl 2,2-dimethyl-4-oxo-6,7,11-triphenyl-9-thioxo-3-oxa-5,8,10-triazatridecan-13-oate (11)

White solid, mp 189–191 °C, 82% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.58–7.49 (1H, br m, NH), 7.38–6.82 (16H, m, NH and ArH), 6.58–6.42 (1H, m, NCH), 5.80–5.48 (1H, br m, NH), 5.38–5.22 (1H, m, NCH), 4.97–4.79 (1H, m, NCH), 3.61 (3H, s, OCH_3), 3.24–2.90 (2H, m, CH_2CO), 1.34 [9H, s, $C(CH_3)_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 181.8 (C═S), 172.3 (C═O), 156.7 (OCONH), 138.1 (Ar), 137.9 (Ar), 135.7 (Ar), 129.0 (Ar), 128.6 (Ar), 128.5 (Ar), 128.4 (Ar), 128.3 (Ar), 127.8 (Ar), 127.4 (Ar), 127.3 (Ar), 126.7 (Ar), 80.4 [*C*$(CH_3)_3$], 63.5 (NCH), 60.3 (NCH), 58.2 (NCH), 52.2 (OCH_3), 37.9 (CH_2), 28.2 [C(*C*H_3)]; IR (film) 3345, 1743, 1682, 1532, 1452 cm^{-1}; MS (ESI) 534 (M + H^+, 100%); HRMS exact mass calculated for [M + Na]$^+$ ($C_{30}H_{35}N_3O_4SNa$) requires m/z 556.2246, found m/z 556.2239; $[\alpha]_D$ = +79.6 (c = 1.0, $CHCl_3$).

(*S*)-*tert*-Butyl-2-{[3-(2-methoxy-2-oxoethyl)thioureido]-methyl}pyrrolidine-1-carboxylate (15a). Light yellow oil, 85% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.86 (1H, br H, NH), 7.12 (0.6H, br s, NH), 6.77 (0.4H, br s, NH), 4.39–4.11 (2H, m, NCH and NC**H**H), 3.96–3.62 (2H, m, 2 × NC**H**H), 3.63 (3H, s, OCH_3), 3.52–3.30 (1H, m, NC**H**H), 3.30–3.08 (2H, m, 2 × NC**H**H), 1.95–1.61 (4H, m, 4 × C**H**H), 1.33 [9H, s, $C(CH_3)_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 182.0 (C═S), 170.1 (C═O), 156.4 (OCONH), 79.9 [*C*$(CH_3)_3$], 56.0 (NCH), 51.9 (OCH_3), 46.8 (NCH_2), 46.6 (NCH_2), 45.7 (NCH_2), 29.2 (CH_2), 28.1 [C(*C*H_3)], 23.4 (CH_2); IR (film) 2974, 1749, 1667, 1553, 1407 cm^{-1}; MS (ESI) 332 (M + H^+, 100%); HRMS exact mass calculated for [M + Na]$^+$ ($C_{14}H_{25}N_3O_4SNa$) requires m/z 354.1464, found m/z 354.1456; $[\alpha]_D$ = −1.8 (c = 1.0, CH_2Cl_2).

(*S*)-*tert*-Butyl-2-{[3-((*S*)-1-methoxy-3,3-dimethyl-1-oxobutan-2-yl)thioureido]methyl} pyrrolidine-1-carboxylate (15b). Light yellow oil, 84% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.04 (1H, br H, NH), 7.13 (0.5H, br s, NH), 6.37 (0.5H, m, NH), 4.97–4.55 (1H, m, NCH), 4.01–3.64 (2H, m, NCH and NC**H**H), 3.60 (3H, s, OCH_3), 3.51–3.32 (1H, m, NC**H**H), 3.31–3.08 (2H, m, 2 × NC**H**H), 1.92–1.57 (4H, m, 4 × C**H**H), 1.35 [9H, s, $C(CH_3)_3$], 0.93 [9H, s, $C(CH_3)_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 181.9 (182.1) (C═S), 171.4 (171.6) (C═O), 156.8 (OCONH), 80.1 (80.0) [*C*$(CH_3)_3$], 65.7 (NCH), 56.0 (NCH), 51.5 (OCH_3), 46.7 (NCH_2), 46.6 (NCH_2), 34.8 [*C*$(CH_3)_3$], 29.2 (CH_2), 28.2 [C(*C*H_3)], 26.5 [C(*C*H_3)], 23.6 (CH_2); IR (film) 2967, 1739, 1664, 1544, 1406 cm^{-1}; MS (ESI) 388 (M + H^+, 100%); HRMS exact mass calculated for [M + Na]$^+$ ($C_{18}H_{33}N_3O_4SNa$) requires m/z 410.2090, found m/z 410.2083; $[\alpha]_D$ = −8.9 (c = 1.0, CH_2Cl_2).

(*S*)-*tert*-Butyl-2-{[3-((*S*)-1-methoxy-1-oxo-3-phenylpropan-2-yl)thioureido]methyl}pyrrolidine-1-carboxylate (15c). Light yellow oil, 89% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.44–7.09 (5H, m, ArH), 5.21 (1H, br s, NCH), 4.11–3.91 (1H, m, NCH), 3.70 (3H, s, OCH_3), 3.57–3.05 (6H, m, 4 × NC**H**H and 2 × C**H**HPh), 2.13–1.56 (4H, m, 4 × C**H**H), 1.47 [9H, s, $C(CH_3)_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 181.5 (181.3) (C═S), 172.5 (172.9) (C═O), 155.4 (OCONH), 136.0 (Ar), 129.1 (Ar), 128.2 (Ar), 126.6 (Ar), 80.1 [*C*$(CH_3)_3$], 60.1 (NCH), 56.0 (56.3) (NCH), 52.0 (OCH_3), 46.6 (46.6) (NCH_2), 46.5 (46.5) (NCH_2), 37.5 (37.4) (CH_2), 29.4 (29.4) (CH_2), 28.2 [C(*C*H_3)], 23.5 (CH_2); IR (film) 2973, 1746, 1662, 1543, 1405 cm^{-1}; MS (ESI) 444 (M + Na^+, 53%), 422 (M + H^+, 100%); HRMS exact mass calculated for [M + Na]$^+$ ($C_{21}H_{31}N_3O_4SNa$) requires m/z 444.1933, found m/z 444.1925; $[\alpha]_D$ = +2.8 (c = 1.0, $CHCl_3$).

(*S*)-*tert*-Butyl-2-{[3-((*S*)-2-methoxy-2-oxo-1-phenylethyl)thio-ureido]methyl}pyrrolidine-1-carboxylate (15d). Light yellow oil, 83% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.62–7.21 (7H, m, ArH and 2 × NH), 5.29–5.02 (1H, m, NCH), 4.11–3.86 (1H, m, NCH), 3.84–3.64 (3H, s, OCH_3), 3.57–3.17 (4H, m, 4 × NC**H**H), 2.05–1.61 (4H, m, 4 × C**H**H), 1.43 [9H, s, $C(CH_3)_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 184.5 (181.5) (C═S), 171.3 (172.7) (C═O), 156.9 (155.0) (OCONH), 135.8 (133.1) (Ar), 128.7 (128.8) (Ar), 128.5 (Ar),

126.7 (127. 6) (Ar), 80.3 (80.4) [*C*(CH_3)$_3$], 62.3 (60.4) (NCH), 56.0 (56.4) (NCH), 52.7 (52.7) (OCH_3), 46.8 (46.9) (NCH_2), 46.0 (46.1) (NCH_2), 29.6 (CH_2), 28.3 [C(*C*H_3)], 23.7 (CH_2); IR (film) 2973, 1744, 1661, 1551, 1406 cm^{-1}; MS (ESI) 408 (M + H^+, 100%); HRMS exact mass calculated for [M + Na]$^+$ ($C_{20}H_{29}N_3O_4SNa$) requires *m/z* 430.1777, found *m/z* 430.1769; $[\alpha]_D = -4.8$ (*c* = 1.0, CH_2Cl_2).

(*S*)-*tert*-Butyl-2-{[3-((*R*)-2-methoxy-2-oxo-1-phenylethyl)thioureido]methyl}pyrrolidine-1-carboxylate (15e). Light yellow solid, mp 67–69 °C, 82% yield ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.99 (1H, br H, NH), 7.51–7.21 (6H, m, ArH and NH), 6.21–5.93 (1H, br m, NCHPh), 4.03–3.77 (1H, m, NCH), 3.68–3.59 (1H, m, NC**H**H), 3.66 (3H, s, OCH_3), 3.51–3.39 (1H, m, NC**H**H), 3.33–3.14 (2H, m, 2 × NC**H**H), 1.99–1.61 (4H, m, 4 × C**H**H), 1.38 [9H, s, C(CH_3)$_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 181.0 (180.9) (C═S), 171.2 (171.0) (C═O), 156.3 (156.0) (OCONH), 135.9 (135.7) (Ar), 128.6 (Ar), 128.3 (Ar), 127.5 (127.4) (Ar), 80.1 [*C*(CH_3)$_3$], 60.2 (60.7) (NCH), 56.4 (55.9) (NCH), 52.5 (52.5) (OCH_3), 46.7 (46.7) (NCH_2), 46.6 (NCH_2), 29.4 (CH_2), 28.2 [C(*C*H_3)], 23.6 (CH_2); IR (film) 2973, 1744, 1662, 1550, 1406 cm^{-1}; MS (ESI) 408 (M + H^+, 100%); HRMS exact mass calculated for [M + Na]$^+$ ($C_{20}H_{29}N_3O_4SNa$) requires *m/z* 430.1777, found *m/z* 430.1769;; $[\alpha]_D = -15.3$ (*c* = 1.0, CH_2Cl_2).

General procedure for the ring closing step

Thiourea (0.5 mmol) was put in a pressure vessel and HCl 6 N in methanol (3 mL) and AcOH (5 mL) were added. The reaction mixture was heated to 100 °C and left stirring at that temperature for 3 h. It was then cooled to room temperature and the pH of the mixture was adjusted to 8 with a solution of $NaHCO_3$ (10%). The resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated to afford the desired product.

(*S*)-6-Phenyl-3-[(*S*)-pyrrolidin-2-ylmethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one (12). Light yellow solid, mp 88–90 °C, 88% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33–7.14 (5H, m, ArH), 5.21 (2H, br m, 2 × NH), 4.43 (1H, ddd, *J* = 14.9, 8.3 and 3.7 Hz, NCH), 3.81–3.59 (2H, m, NCH and NC**H**H), 3.49–3.34 (1H, m, NC**H**H), 3.24 (1H, dd, *J* = 14.0 and 3.6 Hz, NC**H**H), 2.97–2.58 (3H, m, NC**H**H and $COCH_2$), 1.79–1.54 (3H, m, 3 × C**H**H), 1.37–1.20 (1H, m, C**H**H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 184.0 (183.7) (C═S), 174.0 (174.6) (C═O), 135.0 (135.0) (Ar), 129.3 (129.2) (Ar), 128.7 (Ar), 127.4 (Ar), 60.8 (60.5) (NCH), 57.0 (57.0) (NCH), 46.0 (45.8) (NCH_2), 44.9 (NCH_2), 37.3 (CO*C*H_2), 29.4 (29.5) (CH_2), 25.0 (24.9) (CH_2); IR (film) 2927, 1742, 1707, 1658, 1511, 1453 cm^{-1}; MS (ESI) 290 (M + H^+, 100%); HRMS exact mass calculated for [M + H]$^+$ ($C_{15}H_{20}N_3OS$) requires *m/z* 290.1319, found *m/z* 290.1327; $[\alpha]_D = -35.7$ (*c* = 1.0, CH_2Cl_2).

(*S*)-3-[(1*S*, 2*S*)-2-Amino-1,2-diphenylethyl]-6-phenyl-2-thiotetrahydropyrimidin-4-(1*H*)-one (13). Light yellow solid, mp 105–107 °C, 93% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.50–7.42 (1H, m, NH), 7.41–7.02 (15H, m, ArH), 6.87–6.71 (1H, m, NCH), 5.42–5.12 (1H, m, NCH), 4.31–4.05 (1H, m, NCH), 3.28–2.91 (2H, m, CH_2CO); ^{13}C NMR (50 MHz, $CDCl_3$) δ 181.8 (C═S), 172.3 (C═O), 141.5 (Ar), 135.7 (Ar), 134.7 (Ar), 129.5 (Ar), 129.1 (Ar), 129.0 (Ar), 128.5 (Ar), 128.4 (Ar), 128.0 (Ar), 127.7 (Ar), 127.2 (Ar), 126.6 (Ar), 60.5 (NCH), 60.4 (NCH), 58.3 (NCH), 37.7 (CH_2); IR (film) 3412, 1741, 1683, 1497, 1453 cm^{-1}; MS (ESI) 402 (M + H^+, 100%); HRMS exact mass calculated for [M + H]$^+$ ($C_{24}H_{24}N_3OS$) requires *m/z* 402.1640, found *m/z* 402.1647; $[\alpha]_D = -0.6$ (*c* = 1.0, $CHCl_3$).

(*S*)-3-(Pyrrolidin-2-ylmethyl)-2-thioxoimidazolidin-4-one (16a). Light yellow oil, 76% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.43–4.02 (2H, m, NCH and NC**H**H), 3.84–3.78 (1H, m, NC**H**H), 3.69–3.51 (3H, m, 3 × NC**H**H), 3.35–3.27 (1H, m, NC**H**H), 2.31–1.90 (4H, m, 4 × C**H**H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 181.2 (C═S), 176.3 (C═O), 67.4 (NCH), 53.4 (NCH_2CO), 46.4 (NCH_2), 42.5 (NCH_2), 29.7 (CH_2), 26.4 (CH_2); IR (film) 2962, 1742, 1655, 1431 cm^{-1}; MS (ESI) 200 (M + H^+, 11%), 184 (M + H-O^+, 100%), 166 (M + H-H_2S^+, 92%); HRMS exact mass calculated for [2M + H]$^+$ ($C_{16}H_{27}N_6O_2S_2$) requires *m/z* 399.1636, found *m/z* 399.1636; $[\alpha]_D = -44.4$ (*c* = 0.25, CH_2Cl_2).

(*S*)-5-*tert*-Butyl-3-[(*S*)-pyrrolidin-2-ylmethyl)-2-thioxoimidazolidin-4-one (16b). Light yellow oil, 72% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.30 (2H, br s, 2 × NH), 3.90–3.67 (3H, m, 2 × NCH and NC**H**H), 3.64–3.40 (1H, m, NC**H**H), 3.08–2.94 (1H, m, NC**H**H), 2.91–2.76 (1H, m, NC**H**H), 1.95–1.58 (3H, m, 3 × C**H**H), 1.52–1.32 (1H, m, C**H**H), 1.00 [9H, s, C(CH_3)$_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 184.0 (184.2) (C═S), 174.0 (173.5) (C═O), 67.8 (67.9) (NCH), 56.9 (NCH), 46.2 (46.1) (NCH_2), 45.0 (45.1) (NCH_2), 35.4 [*C*(CH_3)$_3$], 29.6 (29.5) (CH_2), 25.5 [C(*C*H_3)], 25.2 (25.1) (CH_2); IR (film) 2962, 1741, 1658, 1508, 1431 cm^{-1}; MS (ESI) 256 (M + H^+, 100%); HRMS exact mass calculated for [M + H]$^+$ ($C_{12}H_{22}N_3OS$) requires *m/z* 256.1483, found *m/z* 256.1479; $[\alpha]_D = -8.8$ (*c* = 1, CH_2Cl_2).

(*S*)-5-Benzyl-3-[(*S*)-pyrrolidin-2-ylmethyl)-2-thioxoimidazolidin-4-one (16c). Light yellow solid, mp 96–98 °C, 80% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.49–6.99 (5H, m, ArH), 6.17–5.50 (2H, br m, 2 × NH), 4.56–4.32 (1H, m, NCH), 3.93–3.57 (2H, m, NCH and NC**H**H), 3.56–3.35 (1H, m, NC**H**H), 3.26 (1H, dd, *J* = 14.0 and 4.0 Hz, C**H**HPh), 3.11–2.59 (3H, m, C**H**HPh and 2 × NC**H**H), 2.05–1.52 (4H, m, 4 × C**H**H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 183.9 (183.6) (C═S), 173.9 (174.5) (C═O), 134.9 (Ar), 129.3 (Ar), 128.8 (Ar), 127.4 (Ar), 60.9 (60.6) (NCH), 57.2 (NCH), 45.8 (45.9) (NCH_2), 44.6 (NCH_2), 37.3 (CH_2), 29.2 (CH_2), 24.8 (24.7) (CH_2); IR (film) 2962, 1741, 1656, 1508, 1431 cm^{-1}; MS (ESI) 290 (M + H^+, 100%); HRMS exact mass calculated for [M + H]$^+$ ($C_{15}H_{20}N_3OS$) requires *m/z* 290.1319, found *m/z* 290.1327; $[\alpha]_D = -16.8$ (*c* = 0.5, $CHCl_3$).

(*S*)-5-Phenyl-3-[(*S*)-pyrrolidin-2-ylmethyl)-2-thioxoimidazolidin-4-one (16d). Light yellow solid, mp 166–168 °C, 85% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.51–7.07 (5H, m, ArH), 6.78 (2H, br s, 2 × NH), 5.29–5.08 (1H, m, NCH), 4.21–3.44 (3H, m, NCH and 2 × NC**H**H), 3.35–3.04 (1H, m, NC**H**H), 2.99–2.50 (1H, m, NC**H**H), 2.07–1.59 (3H, m, 3 × C**H**H), 1.51–1.27 (1H, m, C**H**H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 182.4 (C═S), 172.0 (C═O), 136.4 (Ar), 129.0 (Ar), 128.6 (Ar), 126.9 (Ar), 73.5 (NCH), 58.1 (NCH), 45.2 (NCH_2), 43.0 (NCH_2), 28.9 (CH_2), 25.5 (CH_2); IR (film) 2927, 1742, 1707, 1658, 1511, 1453 cm^{-1}; MS (ESI) 276 (M + H^+, 100%); HRMS exact mass calculated for [M + H]$^+$ ($C_{14}H_{18}N_3OS$) requires *m/z* 276.1170, found *m/z* 276.1165; $[\alpha]_D = +36.8$ (*c* = 1, CH_2Cl_2).

(*R*)-5-Phenyl-3-[(*S*)-pyrrolidin-2-ylmethyl)-2-thioxoimidazolidin-4-one (16e). Light yellow solid, mp 145–147 °C, 82% yield;

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.52–7.06 (5H, m, ArH), 6.17 (2H, br s, 2 × NH), 5.27–5.17 (1H, m, NCH), 4.10–3.89 (1H, m, NCH), 3.80–3.47 (2H, m, 2 × NC**H**H), 3.35–3.04 (1H, m, NC**H**H), 3.04–2.65 (1H, m, NC**H**H), 2.07–1.54 (3H, m, 3 × C**H**H), 1.52–1.34 (1H, m, C**H**H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 182.3 (C═S), 172.0 (C═O), 133.4 (Ar), 129.0 (Ar), 128.7 (Ar), 126.9 (Ar), 73.5 (NCH), 58.1 (NCH), 45.2 (NCH_2), 43.0 (NCH_2), 28.9 (CH_2), 25.4 (CH_2); IR (film) 2960, 1740, 1602, 1490, 1431 cm^{-1}; MS (ESI) 276 (M + H$^+$, 100%); HRMS exact mass calculated for [M + H]$^+$ ($C_{14}H_{18}N_3OS$) requires *m/z* 276.1170, found *m/z* 276.1166; $[\alpha]_D$ = +23.8 (*c* = 0.5, CH_2Cl_2).

General procedure for the ring-closure step under basic conditions

Boc-protected thiourea **9** (0.14 g, 0.33 mmol) was dissolved in methanol (7 mL) in a pressure vessel. Aqueous ammonia (2 drops, 25% NH_3) was added. The reaction mixture was heated at 65 °C and left stirring at that temperature for 1 h. It was then cooled to room temperature and the solvents were evaporated under vacuo. The crude product was purified using flash column chromatography eluting with petroleum ether (40–60 °C) : EtOAc 80 : 20 to afford the desired product.

(*S*)-*tert*-Butyl 2-{[(*S*)-6-oxo-4-phenyl-2-thioxotetrahydropyrimidin-1(2*H*)-yl]methyl}pyrrolidine-1-carboxylate (17). Light yellow solid, mp 94–97 °C, 88% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.02 (0.5H, br s, NH), 7.79 (0.5H, br s, NH), 7.52–7.23 (5H, m, ArH), 4.50–4.21 (2H, m, 2 × NCH), 4.16–3.83 (1H, m, NC**H**H), 3.80–3.49 (1H, m, NC**H**H), 3.47–3.15 (3H, m, 2 × NC**H**H and COC**H**H), 3.14–2.89 (1H, m, COC**H**H), 2.09–1.58 (4H, m, 4 × C**H**H), 1.41 [9H, s, $C(CH_3)_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 183.9 (184.0) (C═S), 173.7 (173.6) (C═O), 154.9 (154.5) (OCONH), 135.2 (135.9) (Ar), 129.1 (129.3) (Ar), 129.0 (128.9) (Ar), 127.4 (127.5) (Ar), 79.0 (79.8) [*C*(CH_3)$_3$], 60.2 (60.5) (NCH), 53.6 (53.7) (NCH), 46.0 (44.5) (NCH_2), 44.0 (42.4) (NCH_2), 37.0 (36.9) (CO*C*H_2), 28.5 (28.4) [C(*C*H_3)$_3$], 28.1 (28.0) (CH_2), 23.3 (22.4) (CH_2); IR (film) 2973, 2929, 1742, 1690, 1501, 1401, 1248 cm^{-1}; MS (ESI) 390 (M + H$^+$, 100%); HRMS exact mass calculated for [M + H]$^+$ ($C_{20}H_{28}N_3O_3S$) requires *m/z* 390.1851, found *m/z* 390.1846; $[\alpha]_D$ = +10.5 (*c* = 1.0, $CHCl_3$).

General procedure for the Michael reaction of cyclohexanones with nitrostyrenes

To a stirring solution of catalyst **12** (0.005 mmol) in THF (1 mL), 4-nitrobenzoic acid (5 mg, 0.03 mmol) and H_2O (8 μL, 0.40 mmol) were added. Nitroolefin (0.20 mmol) was added followed by cyclohexanone (2.00 mmol). The reaction mixture was left stirring for 18 h to 60 h. The solvent was evaporated and the crude product was purified using flash column chromatography eluting with various mixtures of petroleum ether (40–60 °C) : EtOAc to afford the desired product.

(*S*)-2-[(*R*)-3-Nitro-1-phenylethyl]cyclohexanone[13d]. 100% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38–7.05 (5H, m, ArH), 4.93 (1H, dd, *J* = 12.5 and 4.5 Hz, C**H**HNO_2), 4.59 (1H, dd, *J* = 12.5 and 9.9 Hz, C**H**HNO_2), 3.86–3.68 (1H, m, CHPh), 2.75–2.64 (1H, m, CHCO), 2.50–2.35 (2H, m, CHH), 2.16–2.05 (1H, m, C**H**H), 1.81–1.52 (4H, m, 4 × C**H**H), 1.32–1.16 (1H, m, C**H**H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.2 (C═O), 138.0 (Ar), 129.1 (Ar), 128.4 (Ar), 127.9 (Ar), 79.1 (CH_2NO_2), 52.7 (*C*HCO), 44.2 (CO*C*H_2), 42.9 (CHPh), 33.4 (CH_2), 28.8 (CH_2), 25.2 (CH_2); HPLC analysis: Diacel Chiralpak AD-H, hexane/*i*-PrOH 95 : 5, flow rate 1 mL min^{-1}, retention time: 13.21 (minor) and 16.78 (major).

(*S*)-2-[(*S*)-1-(Furan-2-yl)-2-nitroethyl]cyclohexanone[19]. 90% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (1H, s, ArH), 6.31–6.29 (1H, m, ArH), 6.20–6.17 (1H, m, ArH), 4.80 (1H, dd, *J* = 12.5 and 4.8 Hz, C**H**HNO_2), 4.68 (1H, dd, *J* = 12.5 and 9.4 Hz, C**H**HNO_2), 3.98 (1H, td, *J* = 9.4 and 4.8 Hz, CHPh), 2.80–2.72 (1H, m, CHCO), 2.51–2.32 (2H, m, CHH), 2.16–2.07 (1H, m, C**H**H), 1.88–1.61 (4H, m, 4 × C**H**H), 1.34–1.21 (1H, m, C**H**H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.9 (C═O), 151.1 (Ar), 142.3 (Ar), 110.4 (Ar), 109.0 (Ar), 75.2 (CH_2NO_2), 51.2 (*C*HCO), 42.5 (CO*C*H_2), 37.6 (CHAr), 32.5 (CH_2), 28.2 (CH_2), 25.1 (CH_2); HPLC analysis: Diacel Chiralpak AD-H, hexane/*i*-PrOH 95 : 5, flow rate 0.5 mL min^{-1}, retention time: 36.55 (minor) and 29.41 (major).

(*S*)-2-[(*R*)-1-(4-Fluorophenyl)-2-nitroethyl]cyclohexanone[20]. 92% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.18–7.15 (2H, m, ArH), 7.02 (2H, t, *J* = 8.6 Hz, ArH), 4.95 (1H, dd, *J* = 12.5 and 4.5 Hz, C**H**HNO_2), 4.61 (1H, dd, *J* = 12.5 and 10.1 Hz, C**H**HNO_2), 3.78 (1H, td, *J* = 10.1 and 4.5 Hz, CHPh), 2.70–2.63 (1H, m, CHCO), 2.51–2.45 (1H, m, C**H**H), 2.44–2.34 (1H, m, C**H**H), 2.14–2.06 (1H, m, C**H**H), 1.84–1.52 (4H, m, 4 × C**H**H), 1.29–1.17 (1H, m, C**H**H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.7 (C═O), 162.1 (d, *J* = 240 Hz, Ar), 133.4 (Ar), 129.8 (d, *J* = 10 Hz, Ar), 115.8 (d, *J* = 20 Hz, Ar), 78.8 (CH_2NO_2), 52.4 (*C*HCO), 43.2 (CO*C*H_2), 42.7 (CHPh), 33.2 (CH_2), 28.4 (CH_2), 25.0 (CH_2); HPLC analysis: Diacel Chiralpak AD-H, hexane/*i*-PrOH 75 : 25, flow rate 0.7 mL min^{-1}, retention time: 10.44 (minor) and 13.03 (major).

(*S*)-2-[(*R*)-2-Nitro-1-(4-nitrophenyl)ethyl]cyclohexanone[21]. 100% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (2H, d, *J* = 8.7 Hz, ArH), 7.41 (2H, d, *J* = 8.7 Hz, ArH), 5.00 (1H, dd, *J* = 13.0 and 4.4 Hz, C**H**HNO_2), 4.71 (1H, dd, *J* = 13.0 and 10.0 Hz, C**H**HNO_2), 3.94 (1H, td, *J* = 10.0 and 4.4 Hz, CHPh), 2.78–2.69 (1H, m, CHCO), 2.52–2.45 (1H, m, C**H**H), 2.44–2.35 (1H, m, C**H**H), 2.16–2.08 (1H, m, C**H**H), 1.85–1.79 (1H, m, C**H**H), 1.73–1.57 (3H, m, 3 × C**H**H), 1.32–1.22 (1H, m, C**H**H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.8 (C═O), 147.5 (Ar), 145.5 (Ar), 129.3 (Ar), 124.1 (Ar), 78.0 (CH_2NO_2), 52.2 (*C*HCO), 43.7 (CO*C*H_2), 42.7 (CHPh), 33.2 (CH_2), 28.3 (CH_2), 25.1 (CH_2); HPLC analysis: Diacel Chiralpak AD-H, hexane/*i*-PrOH 80 : 20, flow rate 0.5 mL min^{-1}, retention time: 48.57 (minor) and 76.52 (major).

(*S*)-2-[(*R*)-1-(4-Methoxyphenyl)-2-nitroethyl]cyclohexanone[17c]. 96% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.09 (2H, d, *J* = 8.6 Hz, ArH), 6.86 (2H, d, *J* = 8.6 Hz, ArH), 4.92 (1H, dd, *J* = 12.3 and 4.6 Hz, C**H**HNO_2), 4.60 (1H, dd, *J* = 12.3 and 10.0 Hz, C**H**HNO_2), 3.79 (3H, s, OCH_3), 3.73 (1H, td, *J* = 10.0 and 4.6 Hz, CHPh), 2.66 (1H, td, *J* = 10.0 and 4.8 Hz, CHCO), 2.52–2.45 (1H, m, C**H**H), 2.40 (1H, ddd, *J* = 12.8, 12.5 and 5.7 Hz, C**H**H), 2.13–2.04 (1H, m, C**H**H), 1.82–1.52 (4H, m, 4 × C**H**H), 1.30–1.18 (1H, m, C**H**H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.0 (C═O), 158.9 (Ar), 129.5 (Ar), 129.1 (Ar), 114.2 (Ar), 79.0 (CH_2NO_2), 55.1 (OCH_3), 52.6 (*C*HCO), 43.1 (CO*C*H_2), 42.6 (CHPh), 33.1 (CH_2), 28.5 (CH_2), 24.9 (CH_2); HPLC analysis: Diacel Chiralpak AD-H, hexane/*i*-PrOH 95 : 5, flow rate 1.0 mL min^{-1}, retention time: 22.66 (minor) and 27.77 (major).

(*S*)-2-[(*R*)-1-(Naphthaen-2-yl)-2-nitroethyl]cyclohexanone[17c]. 88% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86–7.81 (3H, m, ArH), 7.66 (1H, s, ArH), 7.53–7.48 (2H, m, ArH), 7.28 (1H, dd, J = 8.5 and 1.6 Hz, ArH), 5.05 (1H, dd, J = 12.5 and 4.5 Hz, C**H**HNO$_2$), 4.76 (1H, dd, J = 12.5 and 10.1 Hz, C**H**HNO$_2$), 3.98 (1H, td, J = 10.1 and 4.5 Hz, CHPh), 2.84–2.76 (1H, m, CHCO), 2.55–2.48 (1H, m, C**H**H), 2.42 (1H, td, J = 13.0 and 6.1 Hz, C**H**H), 2.14–2.04 (1H, m, C**H**H), 1.78–1.52 (4H, m, 4 × C**H**H), 1.34–1.23 (1H, m, C**H**H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.8 (C═O), 135.1 (Ar), 133.3 (Ar), 132.8 (Ar), 128.8 (Ar), 127.7 (Ar), 127.6 (Ar), 126.4 (Ar), 126.1 (Ar), 125.2 (Ar), 78.8 (CH_2NO_2), 52.4 (*C*HCO), 44.0 (*C*H$_2$CO), 42.7 (CHPh), 33.2 (CH_2), 28.4 (CH_2), 24.9 (CH_2); HPLC analysis: Diacel Chiralpak AD-H, hexane/*i*-PrOH 95 : 5, flow rate 1.0 mL min^{-1}, retention time: 23.98 (minor) and 27.77 (major).

(*R*)-3-[(*R*)-2-Nitro-1-phenylethyl]dihydro-2*H*-pyran-4-one[22]. 98% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35–7.17 (5H, m, ArH), 4.93 (1H, dd, J = 12.4 and 4.0 Hz, C**H**HNO$_2$), 4.63 (1H, dd, J = 12.4 and 10.0 Hz, C**H**HNO$_2$), 4.11–4.02 (1H, m, CHPh), 3.87–3.66 (3H, m, 3 × OC**H**H), 3.26 (1H, dd, J = 11.4 and 9.4 Hz, OC**H**H), 2.95–2.79 (1H, m, CHCO), 2.73–2.52 (2H, m, CHH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.3 (C═O), 136.2 (Ar), 129.1 (Ar), 128.3 (Ar), 127.8 (Ar), 78.6 (CH_2NO_2), 71.5 (OCH_2), 68.9 (OCH_2), 53.2 (*C*HCO), 42.9 (CO*C*H$_2$), 41.2 (CHPh); HPLC analysis: Diacel Chiralpak AD-H, hexane/*i*-PrOH 85 : 15, flow rate 1 mL min^{-1}, retention time: 13.82 (minor) and 25.75 (major).

(*S*)-3-[(*R*)-2-Nitro-1-phenylethyl]dihydro-2*H*-thiopyran-4-one[17d]. 99% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37–7.17 (5H, m, ArH), 4.75 (1H, dd, J = 12.4 and 4.4 Hz, C**H**HNO$_2$), 4.62 (1H, dd, J = 12.4 and 9.6 Hz, C**H**HNO$_2$), 3.86 (1H, dt, J = 10.4 and 4.4 Hz, CHPh), 3.07–2.92 (3H, m, 3 × SC**H**H), 2.88–2.75 (2H, m, SC**H**H and CHCO), 2.63–2.56 (1H, m, C**H**H), 2.48–2.41 (1H, m, C**H**H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.5 (C═O), 136.5 (Ar), 129.3 (Ar), 128.3 (Ar), 128.1 (Ar), 78.6 (CH_2NO_2), 54.9 (*C*HCO), 44.5 (CO*C*H$_2$), 42.9 (CHPh), 35.1 (SCH_2), 31.6 (SCH_2); HPLC analysis: Diacel Chiralpak AD-H, hexane/*i*-PrOH 85 : 15, flow rate 1 mL min^{-1}, retention time: 12.34 (minor) and 31.06 (major).

(*S*)-4,4-Dimethyl-2-[(*R*)-2-nitro-1-phenylethyl]cyclohexanone. 98% yield; white solid; mp 79–81 °C; IR (film) 2957, 1706, 1551, 1431, 1137 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 (2H, t, J = 7.3 Hz, ArH), 7.19 (1H, t, J = 7.3 Hz, ArH), 7.07 (2H, d, J = 7.3 Hz, ArH), 4.92 (1H, dd, J = 12.4 and 4.6 Hz, C**H**HNO$_2$), 4.57 (1H, dd, J = 12.4 and 9.7 Hz, C**H**HNO$_2$), 3.63 (1H, td, J = 9.7 and 4.6 Hz, CHPh), 2.82–2.78 (1H, m, CHCO), 2.48 (1H, td, J = 13.8 and 6.2 Hz, C**H**HCO), 2.24 (1H, ddd, J = 13.8, 4.5 and 3.1 Hz, C**H**HCO), 1.68 (1H, dtd, J = 9.2, 6.2 and 3.1 Hz, C**H**H), 1.56 (1H, td, J = 13.8 and 4.5 Hz, C**H**H), 1.32–1.29 (1H, m, C**H**H), 1.15 (1H, t, J = 13.8 Hz, C**H**H), 1.06 (3H, s, CH_3), 0.81 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.5 (C═O), 137.8 (Ar), 128.9 (Ar), 128.1 (Ar), 127.7 (Ar), 79.0 (CH_2NO_2), 47.7 (*C*HCO), 45.8 (CO*C*H$_2$), 43.9 (CHPh), 40.6 (CH_2), 39.1 (CH_2), 31.0 [C(CH_3)$_2$], 24.3 (CH_3); MS (ESI) 276 (M + H$^+$, 100%); $[\alpha]_D$ = -105.8 (c = 1, CH_2Cl_2); HPLC analysis: Diacel Chiralpak AD-H, hexane/*i*-PrOH 95 : 5, flow rate 0.5 mL min^{-1}, retention time: 17.81 (minor) and 21.99 (major).

(*S*)-7-[(*R*)-2-Nitro-1-phenylethyl]-1,4-dioxaspiro[4.5]decan-8-one[23]. 93% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36–7.26 (3H, m, ArH), 7.19–7.17 (2H, m, ArH), 4.96 (1H, dd, J = 12.5 and 4.7 Hz, C**H**HNO$_2$), 4.63 (1H, dd, J = 12.5 and 9.8 Hz, C**H**HNO$_2$), 4.01–3.82 (5H, m, CHPh and 4 × OC**H**H), 3.08 (1H, ddd, J = 13.0, 10.1 and 5.5 Hz, CHCO), 2.76–2.68 (1H, m, C**H**H), 2.48 (1H, dd, J = 13.8, 5.1 and 3.5 Hz, C**H**H), 2.06 (1H, ddt, J = 13.0, 6.6 and 3.5 Hz, C**H**H), 1.97 (1H, td, J = 13.0 and 5.1 Hz, C**H**H), 1.70 (1H, ddd, J = 13.0, 5.5 and 3.5 Hz, C**H**H), 1.57 (1H, t, J = 13.4 Hz, C**H**H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.3 (C═O), 137.2 (Ar), 128.9 (Ar), 128.2 (Ar), 127.8 (Ar), 107.0 [*C*(OCH$_2$)$_2$], 78.9 (CH_2NO_2), 64.7 (OCH_2), 64.5 (OCH_2), 48.1 (*C*HCO), 43.4 (CHPh), 39.2 (CH_2), 38.5 (CH_2), 35.0 (CH_2); HPLC analysis: Diacel Chiralpak AD-H, hexane/*i*-PrOH 80 : 20, flow rate 1 mL min^{-1}, retention time: 9.03 (minor) and 14.37 (major).

(*R*)-1-Acetyl-3-[(*R*)-2-nitro-1-phenylethyl]piperidin-4-one. 92% yield; light yellow oil; IR (film) 3012, 2924, 1714, 1648, 1552, 1431 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.44–7.19 (5H, m, ArH), 5.06–4.87 (1H, m, C**H**HNO$_2$), 4.72–4.55 (1H, m, C**H**HNO$_2$), 4.33–4.24 (0.4H, m, NC**H**H), 4.03–3.72 (1.6H, m, NC**H**H and CHPh), 3.58–3.40 (1H, m, NC**H**H), 3.28–3.10 (1H, m, NC**H**H), 3.04–2.68 (2H, m, NC**H**H and CHCO), 2.67–2.43 (2H, m, CHHCO), 2.16 (2H, s, CH_3), 1.82 (1H, s, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 207.5 (207.5) (C═O), 169.2 (169.5) (NCO), 136.4 (136.1) (Ar), 129.5 (129.2) (Ar), 128.7 (128.3) (Ar), 127.7 (128.1) (Ar), 78.6 (CH_2NO_2), 52.2 (51.4) (COCH), 49.5 (NCH_2), 44.9 (45.7) (NCH_2), 41.8 (41.7) ($COCH_2$), 41.2 (41.6) (CHPh), 20.8 (21.3) (CH_3); MS (ESI) 291 (M + H$^+$, 100%); $[\alpha]_D$ = +20.9 (c = 1, CH_2Cl_2); HPLC analysis: Diacel Chiralpak AD-H, hexane/*i*-PrOH 95 : 5, flow rate 1.0 mL min^{-1}, retention time: 75.37 (minor) and 81.15 (major).

(*R*)-5-Nitro-4-phenylpentan-2-one (18)[13f]. 95% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38–7.26 (3H, m, ArH), 7.19–7.14 (2H, m, ArH), 4.69 (1H, dd, J = 12.3 and 7.0 Hz, C**H**HNO$_2$), 4.59 (1H, dd, J = 12.3 and 7.6 Hz, C**H**HNO$_2$), 4.07–3.92 (1H, m, CHPh), 2.91 (2H, d, J = 7.0 Hz, CH_2CO), 2.11 (3H, s, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 205.4 (C═O), 138.8 (Ar), 129.0 (Ar), 127.8 (Ar), 127.3 (Ar), 79.4 (CH_2NO_2), 46.1 (CHPh), 39.0 (CH_2), 30.3 (CH_3); HPLC analysis: Diacel Chiralpak AD-H, hexane/*i*-PrOH 94 : 6, flow rate 1 mL min^{-1}, retention time: 12.54 (minor) and 13.58 (major).

(*3R*,*4R*)-3-Methyl-5-nitro-4-phenyl-pentan-2-one (19)[24]. 15% yield; ^{1}H NMR and ^{13}C NMR were consistent with those reported in the literature;[24] HPLC analysis: Diacel Chiralpak AS-H, hexane/*i*-PrOH 90 : 10, flow rate 1 mL min^{-1}, retention time: 13.84 (major) and 15.98 (minor).

(*S*)-2,2-Dimethyl-4-nitro-3-phenylbutanal (20)[25]. 17% yield; ^{1}H NMR and ^{13}C NMR were consistent with those reported in the literature;[25] HPLC analysis: Diacel Chiralpak AD-H, hexane/*i*-PrOH 85 : 15, flow rate 0.8 mL min^{-1}, retention time: 15.89 (minor) and 20.15 (major).

(2*S*,3*R*)-2-Benzyl-4-nitro-3-phenylbutanal (21)[18b]. 85% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.62 (1H, br s, CHO), 7.35–7.07 (8H, m, ArH), 7.02–6.85 (2H, m, ArH), 4.79–4.51 (2H, m, CHHNO$_2$), 3.75 (1H, td, J = 8.7 and 6.0 Hz, CHPh), 3.11–2.91 (1H, m, CHCO), 2.75–62 (2H, m, CH_2Ph); ^{13}C NMR (50 MHz, $CDCl_3$) δ 203.2 (C═O), 137.5 (Ar), 136.5 (Ar), 129.4 (Ar), 128.9 (Ar), 128.7 (Ar), 128.5 (Ar), 128.0 (Ar), 127.1 (Ar), 78.4

(CH_2NO_2), 55.3 (CHPh), 43.5 (CH), 34.2 (CH_2); HPLC analysis: Diacel Chiralpak AD-H, hexane/*i*-PrOH 97.5 : 2.5, flow rate 1 mL min^{-1}, retention time: 23.86 (minor) and 27.13 (major).

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