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4-Fluoro and 4-Hydroxy Pyrrolidine-thioxotetrahydropyrimidinones: Organocatalysts for Green Asymmetric Transformations in Brine

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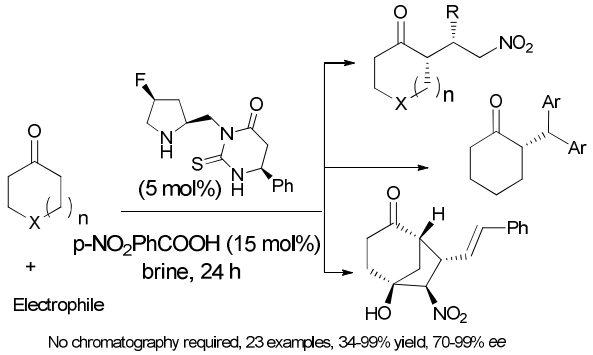
KEYWORDS : Organocatalysis; Green Chemistry; Michael addition; Brine; Fluorine



ABSTRACT : The synthesis of both *trans*- and *cis*- diastereomers of pyrrolidinine-thioxotetrahydropyrimidinone bearing either a fluorine or a hydroxyl group was accomplished. The new compounds were tested for their catalytic properties in a variety of asymmetric organic transformations and compared with the first generation

catalyst. It was found that the new catalysts could efficiently catalyze the reactions in brine, without the use of organic solvent, and by employing an almost stoichiometric amount of reagents. Thus, the products were isolated by simple extractions, avoiding the use of chromatography in excellent yields, diastereoselectivities and enantioselectivities.

INTRODUCTION

After centuries of mis-treating the environment, researchers have turned their attention to finding efficient procedures, where various elements can be wisely employed in order to ensure their use in the distant future. This concept of elemental sustainability can be approached in various ways, like efficient protocols for recycling and recovering or the development of more efficient catalytic protocols (lower catalyst loadings) or even the development of protocols, where these elements can be left out and not used. Along these lines, Organocatalysis[1,2] has provided an excellent alternative on transition-metal-catalysed processes, indicating that elemental sustainability of transition metals can be ensured, just by not using them. In the past few years, we have been actively involved in the field of Organocatalysis, either in developing new organocatalysts and reactions,[3] or providing novel and green oxidation protocols.[4] In one of our endeavours, we designed and synthesized pyrrolidine-thioxotetrahydropyrimidinone **1** (Figure 1), which proved to be a really efficient organocatalyst for the Michael reaction between ketones and nitroolefins.[5] Although numerous catalysts exist for this transformation, the

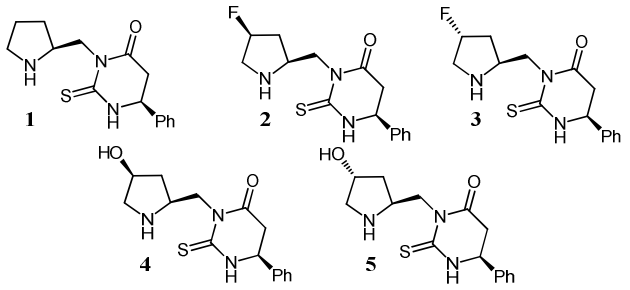


Figure 1. Known and novel organocatalysts utilized in this study.

advantage of **1** was the really low catalyst loading that could be used (1-2.5 mol%). Then, organocatalyst **1** was successfully employed in other reactions,[6] like the α-alkylation of ketones[6a] and the development of novel tandem cyclisations.[6c] However, the main disadvantage of this catalyst resides on the fact that it only works in organic solvents and requires a high reagent ratio (10:1 ketone:nitroalkene).

Fluorine is a very interesting element, possessing unique properties.[7] The incorporation of fluorine into a molecule usually modifies its physical and chemical properties through electronic and stereoelectronic effects. The deep understanding of fluorine effects has led to widespread application of fluorine-containing compounds in a variety of areas. In proline residues, the introduction of fluorine at the 4-position of the pyrrolidine ring influences the puckering of the ring. This effect has been taken advantage in changing the conformation of proline-containing biomolecules in order to study and tune biological processes.[8] Recently, the fluorine effect has been studied in organocatalysis, where benchmark organocatalysts have been modified to carry fluorine atoms and their catalytic properties have been studied.[9] Unfortunately, only a handful of studies related to diaryl prolinols,[9a] imidazolidinones,[9c] proline[9d,e] and aminal-pyrrolidines[9f] have been presented. In most of these examples, the

fluorine-containing molecule was found to improve the catalytic properties, without any major alterations to the reaction conditions. Pyrrolidine ring and five-membered rings in general, are very flexible, so in solution they adopt multiple conformations. In aminocatalysis, some problems arise because every conformer may have different catalytic activity. Fluorine and its gauche effect[10] provide a valuable tool in order to make the pyrrolidine ring more rigid, since the fluorine prefers the axial position in order to maximize the orbital overlap between $\sigma_{C\text{-}F}^{*}$ and $\sigma_{C\text{-}H}$. To achieve this requirement the pyrrolidine ring (4-*cis* substituted prolines) adopts the C^{γ}-endo conformation (Figure 2).[11] Thus, by incorporating a fluorine atom in the 4-position of the pyrrolidine ring, we postulated that the derived enamine would be more planar and thus more reactive towards electrophiles.[12]

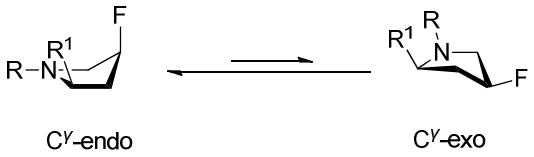
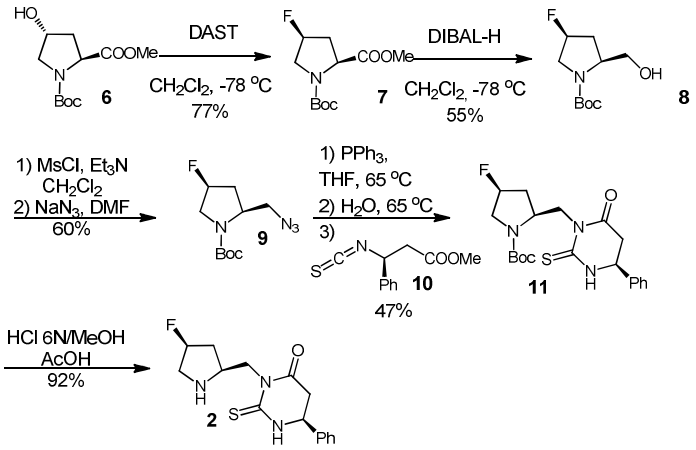


Figure 2. Fluorine effect on the pyrrolidine ring.

Herein, we present the synthesis of four novel organocatalysts (**2**-**5**), bearing either a fluorine or a hydroxyl moiety at the 4-position of the pyrrolidine ring (Figure 1). The comparison of the catalytic properties of the new compounds is also demonstrated in 4 different reactions, highlighting the improved properties and the green character of the novel organocatalysts.

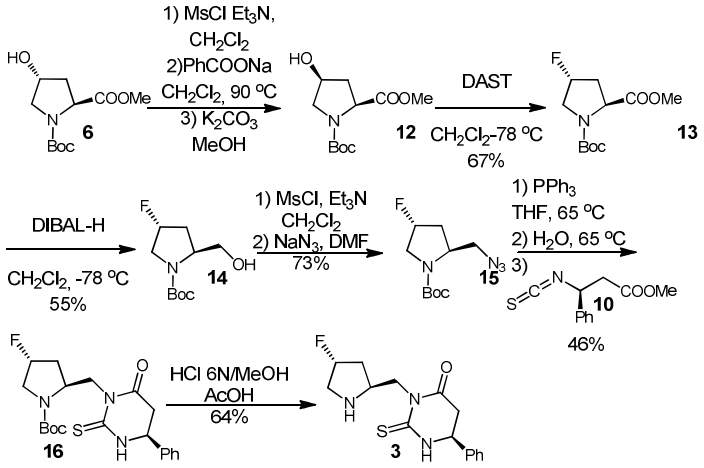
RESULTS AND DISCUSSION

Starting from 4-hydroxy-proline derivative **6**, *cis*-fluoroproline **7** was synthesized (Scheme 1). After reduction of the ester to the corresponding alcohol **8**, azide **9** was obtained after activation of the alcohol via the corresponding mesyl ester. Staudiger reaction followed by coupling with isothiocyanate **10**, provided *cis*-fluoro derivative **11**. After deprotection, *cis*-derivative **2** was obtained.

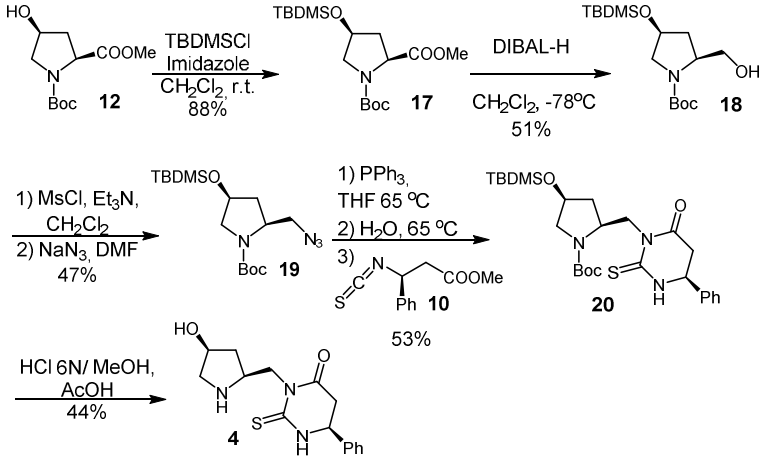


Scheme 1. Synthesis of compound **2**.

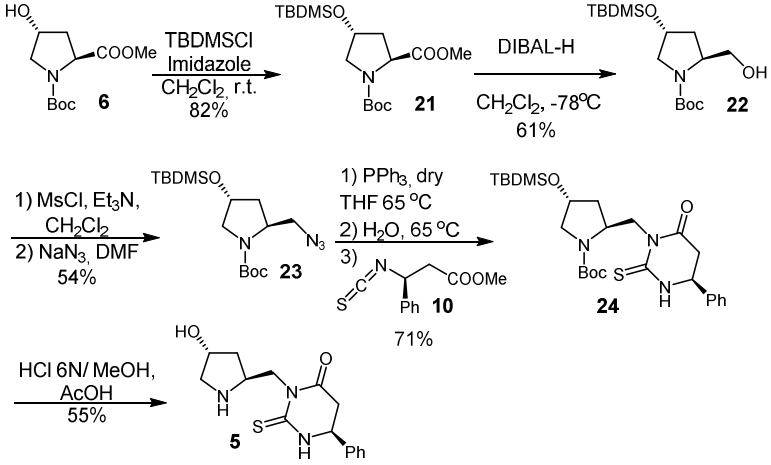
Then, *trans*-fluoro derivative **3** was synthesized (Scheme 2). *cis*-Hydroxyproline **12** was synthesized from **6**. Following a similar synthetic route as before, *trans*-fluoro derivative **3** was obtained. For comparison purposes, the corresponding 4-hydroxy derivatives **4** and **5** were also synthesized (Schemes 3 and 4). It was envisaged that the comparison of the hydroxyl-containing catalysts with the fluoro-contaning catalysts and **1** could provide more information on the effect of fluorine.



Scheme 2. Synthesis of compound **3**.



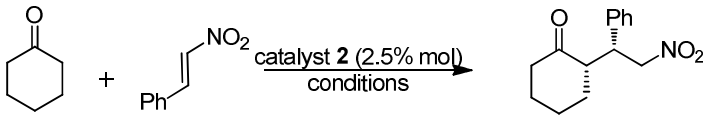
Scheme 3. Synthesis of compound **4**.



Scheme 4. Synthesis of compound **5**.

The asymmetric Michael addition constitutes one of the most powerful methods for the formation of new C-C and C-X bonds in organic synthesis. Especially after the development of organocatalysis, the aforesaid transformation has experienced exponential growth, with a large number of new catalysts exhibiting impressive results in terms of efficiency and selectivity.[13] The Michael reaction between cyclohexanone and *trans-beta*-nitrostyrene is a typical reaction for testing novel organocatalysts. Pyrrolidine-thioxotetrahydropyrimidinone **1** was shown to be an excellent catalyst for the above reaction, where at 2.5 mol% catalyst loading in THF and reagent ratio 10:1 provided the product in excellent yield (97%) and selectivities (98:2 dr and 97% *ee*).[5] As mentioned earlier, catalyst **1** did not work in aqueous media and at lower reagent ratios led to incomplete reactions. Utilizing catalyst **2** in THF, the product was formed in excellent diastereoselectivities and enantioselectivities, but the yield was low (entry 1, Table 1) (for full reaction optimization, see ESI). Utilizing brine as the solvent, the product was obtained in quantitative yield and excellent selectivities in shorter reaction time (entry 2, Table 1). Using only 2.5 mol% catalyst loading, a number of solvents were tested, proving that brine afforded the best results (entries 3-10, Table 1). A variety of acid additives were then tested, none of which led to better results (entries 11-15, Table 1). After identifying the optimum reaction medium for catalyst **2**, catalysts **1** and **3-5** were also tested (Table 2 and ESI). As mentioned before, a clear difference with our first generation catalyst **1**, was the different reaction medium (organic solvents for **1**, but brine for **2**). Catalyst **1** worked in THF, but in brine afforded only traces of the product. In sharp contrast, catalyst **2** afforded the product in excellent yield in brine (entries 1 and 2 vs entries 3-5). Another key aspect was the reagent ratio, since **1** worked only at 10:1 ratio. Catalyst **2** worked equally well at lower reagent ratios (entries 3-5, Table 2).[14] We were happy to

Table 1. Optimization of the conditions for the reaction between cyclohexanone and *beta*-nitrostyrene[a]



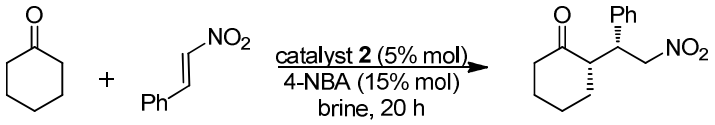
Entry	Solvent	Additive	Yield (%)[b]	dr (*syn:anti*)[c]	*ee* (%)[d]
1[e]	THF	4-NBA	41	97:3	98
2[f, g]	Brine	4-NBA	100	>99:1	99
3[g]	Brine	4-NBA	93	>99:1	99
4	Et_2O	4-NBA	55	>99:1	99
5	Benzene	4-NBA	67	>99:1	98
6	$CHCl_3$	4-NBA	72	99:1	93
7	CH_2Cl_2	4-NBA	87	99:1	99
8	Water	4-NBA	90	99:1	99
9[g]	Brine	4-NBA	70	>99:1	99
10[g]	Brine	AcOH	62	97:3	99
11[g]	Brine	*p*F-PhOH	41	98:2	85
12[g]	Brine	PhCOOH	83	99:1	98
13[g]	Brine	4-TBA	100	97:3	99
14[g]	Brine	4-CBA	95	96:4	99

[a] Reactions were performed using nitroolefin (0.20 mmol), ketone (2.0 mmol), 4-NBA (15% mol) and H_2O (2 equiv.) for 48 h. [b] Yield determined by NMR. [c] The diastereomeric ratio (dr) was determined by ^{1}H-NMR spectroscopy. [d] The enantiomeric excess (*ee*) was determined by chiral HPLC. [e] 10 mol% catalyst loading. [f] 5 mol% catalyst loading. [g] The reaction time was 20 h. 4-NBA: *p*-NO_2-PhCOOH, *p*-F-PhOH: *p*-fluorophenol, 4-TBA: *p*-trifluoromethylbenzoic acid, 4-CBA: *p*-cyanobenzoic acid.

find out even at almost stoichiometric ratios (1.1:1), catalyst **2** performed equally well (entry 5, Table 2). Thus, we were able to establish a green protocol, where a low catalyst loading of 5 mol% could catalyse efficiently the Michael reaction between cyclohexanone and nitrostyrene (in a stoichiometric ratio) in brine. After the completion of the reaction, the product is just extracted from the reaction mixture and no further purification is required. Having already proven that catalyst **2** is more powerful than **1** and provides a green powerful procedure, we tested the other catalysts in two different reaction conditions. *trans*-Fluoro catalyst **3** proved to be a mis-matched case, since both in brine and organic solvent led to inferior results (entries 6 and 7, Table 2, see also ESI). When the fluorine was substituted by the hydroxy group, similar results were observed (entries 8-11, Table 2). Again the *cis*-hydroxy catalyst **4** proved to be the matched case, leading to slightly worse results than catalyst **2** (entries 8 and 9, Table 2). Interestingly, although *trans*-hydroxy catalyst **5** was the mis-matched case, the product was obtained in both organic solvent and brine in slightly better yields and selectivities than fluoro-catalyst **3** (entries 10 and 11 vs 6 and 7, Table 2).

Once the optimum reaction conditions were identified, a variety of ketones and nitrostyrenes were tested in order to study the substrate scope (Scheme 5). A number of nitrostyrenes bearing electron-withdrawing and electron-donating substituents were tested affording products **25a-g** in high yields and excellent selectivities. Then, a variety of cyclic ketones were tested, affording products **25h-l** in similar excellent results. Finally, some difficult substrates (when we utilised catalyst **1**) were tested, affording the products in lower yields and

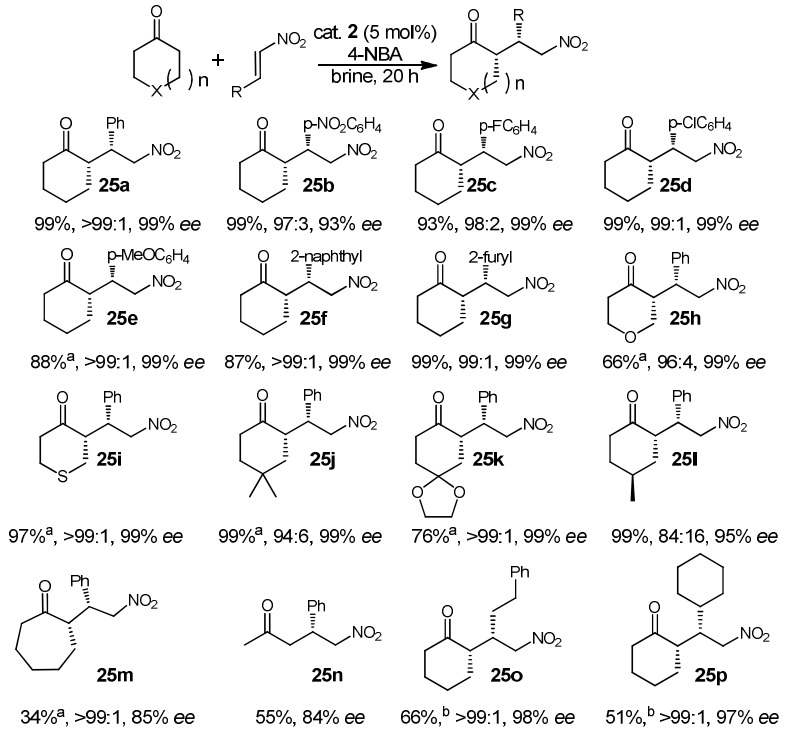
Table 2. Comparison of the catalytic properties of catalysts **2-5** in the reaction between cyclonexanone and *beta*-nitrostyrene.[a]



Entry	Catalyst	Ketone (equiv.)	Yield (%)[b]	dr (*syn:anti*)[c]	*ee* (%)[d]
1[e]	**1**	5	97	99:1	97
2	**1**	5	traces	-	-
3	**2**	5	100	>99:1	99
4	**2**	2	100	>99:1	99
5	**2**	1.1	100	>99:1	99
6[f]	**3**	1.1	56	90:10	88
7[f, g]	**3**	10	23	85:15	92
8[f]	**4**	1.1	86	>99:1	98
9[f, g]	**4**	10	25	>99:1	96
10[f]	**5**	1.1	81	95:5	98
11[f, g]	**5**	10	22	85:15	96

[a] Reactions were performed using nitroolefin (0.20 mmol), ketone, 4-NBA (15 mol%) in brine for 20 h. [b] Yield determined by NMR. [c] The diastereomeric ratio (dr) was determined by ^{1}H-NMR spectroscopy. [*d*] The enantiomeric excess (*ee*) of the major diastereomer was determined by chiral HPLC. [e] The reaction was performed in THF. [f] The reaction time was 48 h. [g] The reaction was performed in CH_2Cl_2. 4-NBA: *p*-NO_2-PhCOOH.

selectivities (products **25m-n**). Aliphatic nitroalkenes could be employed with some success (products **25o-p**). Unfortunately, non-symmetrical ketones, like

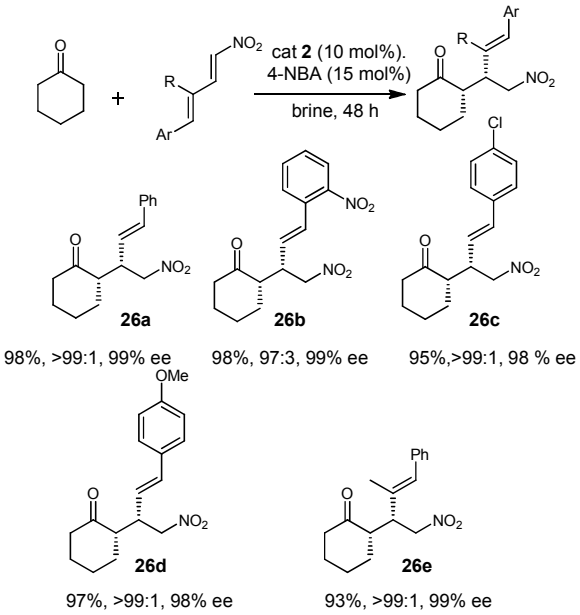


Scheme 5. Michael reaction between ketones and nitrostyrenes utilising catalyst **2.**

2-methyl-cyclohexanone did not give the product of the reaction. It has to be highlighted that in most cases, the product was obtained by simple extractions and no additional purification was necessary.

Since we had earlier demonstrated the catalytic activity of **1** in the reaction between cyclohexanone and nitrodienes,[6b] we tested how catalyst **2** performs in this reaction (Scheme 6).

As before, the reaction was performed in brine, a reaction medium that catalyst **1** could not be employed in earlier. Catalyst **1** can catalyse the reaction in toluene (93% yield, 98:2 dr, 97% *ee*), but it was unable to catalyse the reaction in brine. Similarly to before, catalyst **2** catalysed efficiently this transformation, leading to Michael product **26a** in excellent yield and selectivity. A variety of substituted nitrodienes bearing electron-withdrawing or electron-donating

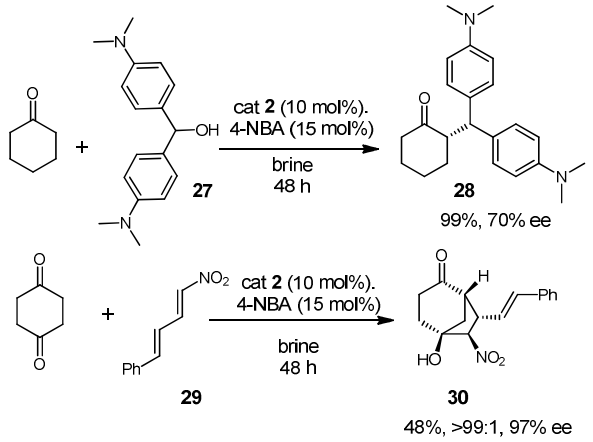


Scheme 6. Michael reaction between ketones and nitrodienes utilising catalyst **2**.

substituents were used successfully, leading to products **26b-d**. Finally, a trisubstituted nitrodiene was employed leading to product **26e**.

Finally, in an effort to test the limits of the novel catalysts, two additional transformations were carried out (Scheme 7). Enantioselective α-alkylation of cyclic ketones is a very difficult reaction,[15] where partial solution was given by catalyst **1** (in CH_2Cl_2 98% yield, 80% *ee*).[6a] Catalyst **2** afforded similar results, but in brine, where catalyst **1** could not catalyse the reaction. The product **28** was obtained in almost quantitative yield and 70% *ee*. Although the enantioselectivity is not excellent, the highest *ee* reported for this transformation is around 80% *ee* (always in organic solvent).[6a] Thus, this is the first time that an α-alkylation of this type is reported in aqueous medium. In addition, a tandem Michael-Henry reaction that was previously catalysed efficiently by catalyst **1**,[6c] was possible to be carried out in brine by employing catalyst **2**. Again as before, catalyst **1** was found to be the only catalyst that could promote efficiently this transformation, but only in organic solvent.[6c]

Novel organocatalyst **2** provided the product as a single diastereomer and in excellent *ee*, but under unoptimised conditions the yield was moderate.



Scheme 7. Other reactions catalysed by **2** in brine.

CONCLUSIONS

In conclusion, four novel organocatalysts were synthesized combining the thioxotetrahydropyrimidinone with a 4-substituted pyrrolidine either by fluorine or a hydroxy moiety. Both *cis* catalysts were a matched case, while *trans* catalysts proved to be a mis-matched case. In comparison to the first generation catalyst (without substituent on the pyrrolidine ring), *cis*-fluoro catalyst **2** proved to catalyse four different transformations more efficiently leading to higher yields and selectivities in low catalyst loadings (5-10 mol%). Striking differences were found between the parent and the novel catalysts. In more detail, the advantage of catalyst **2** in comparison to the parent molecule, was the use of brine as the reaction medium, which leads to greener approaches in synthesis. The fact that all four catalysts provided the product in aqueous environment could be explained by hydrogen bonding interaction between the catalyst and molecules of water. Moreover, the reagent ratio could be reduced to stoichiometric using novel organocatalyst **2** (which

could not be done with catalyst **1**). Thus, this provided a robust, green and efficient protocol to perform these reactions, where the product could be isolated just by simple extractions from the reaction mixture. These results open new avenues on green organocatalytic approaches in performing reactions in aqueous media and we are on the way to taking advantage of these molecules in order to anchor them in a variety of materials in order to recycle the catalyst.

EXPERIMENTAL SECTION

General Remarks

Chromatographic purification of products was accomplished using forced-flow chromatography. Thin-layer chromatography (TLC) was performed on aluminum backed silica plates (0.2 mm, 60 F_{254}). Visualization of the developed chromatogram was performed by fluorescence quenching using phosphomolybdic acid, anisaldehyde or potassium permanganate stains. ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded on 200 MHz, 188 MHz and 50 MHz respectively, and are internally referenced to residual solvent signals. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad signal, bs m = broad signal multiplet), coupling constant and assignment. Data for ^{19}F NMR are internally referenced to trifluoroacetic acid. Data for ^{13}C NMR are reported in terms of chemical shift (δ ppm). Chiral High Performance Liquid Chromatography (HPLC) analyses were performed using an AD-H, OD-H and AS-H columns. The configuration of the products has been assigned by comparison to literature data or assigned by analogy.

(2*S*,4*S*)-1-*tert*-Butyl 2-methyl 4-fluoropyrrolidine-1,2-dicarboxylate (7).[16] To a stirring solution of alcohol **6** (1.20 g, 4.89 mmol) in dry CH_2Cl_2 (5 mL) at -78 ^oC under argon atmosphere, diethylaminosulfur trifluoride (DAST) (1.20 mL, 1.83 g, 11.35 mmol) was added. The reaction was stirred for 30 min at -78 ^oC, and then warmed to room temperature and was allowed to stir for 20 h before being quenched with water (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic phases were dried over Na_2SO_4, and concentrated to yield the crude product. The crude oil was purified by silica gel chromatography ($CHCl_3$/EtOAc, 20:1) to yield the desired product **7**. Pale yellow oil; 0.93 g, 77%; $[\alpha]_D^{20}$ = -48.9 (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 5.07 (1H, dm, *J* = 53.6 Hz), 4.44-4.22 (1H, m), 3.86-3.30 (5H, m), 2.44-2.06 (2H, m), 1.28 (6H, s), 1.33 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.9 (171.6), 153.3 (153.7), 90.8 (d, *J* = 177.6 Hz) [91.9 (d, *J* = 177.4 Hz)], 79.9, 57.3 (56.9), 52.5 (d, *J* = 25.5 Hz) [52.9 (d, *J* = 24.0 Hz)], 51.8, 37.1 (d, *J* = 22.0 Hz) [36.2 (d, *J* = 21.9 Hz)], 27.9 (28.0); ^{19}F NMR (188 MHz, $CDCl_3$) δ -118.1 (1F, m); MS (ESI) *m/z* (%): 248 $[M+H, (100)]^+$.

(2*S*,4*S*)-*tert*-Butyl 4-fluoro-2-(hydroxymethyl)pyrrolidine-1-carboxylate (8). To a stirring solution of **7** (0.59 g, 2.39 mmol) in dry CH_2Cl_2 (10 mL) at -78 ^oC, DIBAL-H (1M in toluene, 6 mL) was added dropwise. The reaction was stirred for 1 h at -78 ^oC and then warmed to room temperature for 16 h before being quenched with MeOH (7 mL) and aq. potassium sodium tartrate (2M, 10 mL). The mixture was stirred vigorously for 30 min. The organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2 (2 x 25 mL). The combined organic phases were washed with brine (40 mL), dried over Na_2SO_4, concentrated under reduced pressure and purified by silica gel chromatography (PE/AcOEt, 8:2) to yield the desired product **8**. Colorless oil; 286 mg, 55% yield; $[\alpha]_D^{20}$ = -26.1 (*c* 1.0, CH_2Cl_2); ^1H NMR

(200 MHz, $CDCl_3$) δ 5.16 (1H, dm, J = 53.2 Hz, CHF), 4.18-3.94 (1H, m), 3.86-3.32 (5H, m), 2.36-2.18 (1H, m), 2.16-1.92 (1H, m), 1.41 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.0, 92.1 (d, J = 176.4 Hz), 80.7 (80.5), 67.3, 58.8, 53.8 (d, J = 21.2 Hz), 34.9 (d, J = 21.2 Hz), 28.2; ^{19}F NMR (188 MHz, $CDCl_3$) δ -116.2 (1F, m); MS (ESI) *m/z* (%): 220 [M+H, (100)]$^+$; HRMS exact mass calculated for [M+Na]$^+$ ($C_{10}H_{18}O_3NFNa^+$) requires *m/z* 242.1163, found *m/z* 242.1163.

(2*S*,4*S*)-*tert*-Butyl 2-(azidomethyl)-4-fluoropyrrolidine-1-carboxylate (9). To a stirring solution of **8** (0.28 g, 1.16 mmol) in dry CH_2Cl_2 (8 mL), Et_3N (0.29 mL, 2.00 mmol) and MsCl (0.15 mL, 1.70 mmol) were added at 0 ^{o}C. After 30 min, the reaction was warmed at room temperature and left stirring at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure and water (12 mL) was added. The crude product was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with aq. $KHSO_4$ (10%, 2 x 20 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to yield the crude mesyl ester. The crude mesyl ester was dissolved in DMF (5 mL) and NaN_3 (0.20 g, 2.00 mmol) was added. The reaction mixture was heated at 60 ^{o}C for 24 h. The reaction mixture was cooled down to room temperature and concentrated under reduced pressure. Water (10 mL) was added and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude oil was purified by silica gel chromatography (PE/AcOEt, 8:2) to yield the desired product **9**. Colorless oil; 87 mg, 60 % yield; $[\alpha]_D^{20}$ = -33.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.19 (1H, dm, J = 53.4 Hz), 4.20-3.80 (2H, m), 3.80-3.40 (2H, m), 3.25-3.05 (1H, m), 2.40-1.81 (2H, m), 1.42 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.0 (153.9), 92.8 (d, J = 176.8 Hz) [92.2 (d, J = 178.7 Hz)], 80.5 (80.8), 55.8, 55.0, 53.4 (d, J = 22.3 Hz) [52.9 (d, J =

23.0 Hz)], 35.3 (d, *J* = 19.7 Hz) [34.5 (d, *J* = 20.3 Hz)], 28.3 (28.2); ^{19}F NMR (188 MHz, $CDCl_3$) δ -116.1 (1F, m); MS (ESI) *m/z* (%): 245 [M+H, (100)]$^+$; HRMS exact mass calculated for [M+Na]$^+$ ($C_{10}H_{17}O_2N_4FNa^+$) requires *m/z* 267.1233, found *m/z* 267.1239.

(2*S*,4*S*)-*tert*-Butyl 4-fluoro-2-(((*S*)-6-oxo-4-phenyl-2-thioxotetrahydropyrimidin-1(2*H*)-yl)methyl)pyrrolidine-1-carboxylate (11). To a stirring solution of azide **9** (85 mg, 0.35 mmol) in dry THF (4 mL) in a pressure vessel, PPh_3 (0.20 g, 0.46 mmol) was added and the reaction mixture was left stirring at 65 ^{o}C for 8 h. Then, H_2O (0.4 mL) was added and the reaction mixture was left stirring at 65 ^{o}C for 16 h. Then, the solvent was removed and the crude amine was used in the next step without purification. A solution of isothiocyanate **10** (135 mg, 0.52 mmol) in dry CH_2Cl_2 (8 mL) was added to a stirring solution of amine (67 mg, 0.30 mmol) in dry CH_2Cl_2 (8 mL) over a period of 5 min at room temperature and the reaction was left stirring for 2 h. The solvent was evaporated and the crude product was purified by silica gel chromatography (PE/EtOAc, 7:3) to yield the desired product **11**. Pale yellow oil; 65 mg, 47% yield; $[\alpha]_D^{20}$ = -13.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36-7.14 (6H, m), 5.19 (1H, dm, *J* = 54.1 Hz), 4.60-4.46 (1H, m), 4.38-4.16 (2H, m), 3.76-3.52 (3H, m), 3.28 (1H, ddd, *J* = 13.8, 7.0 and 1.7 Hz), 3.08-2.78 (1H, m), 2.06-1.92 (2H, m), 1.43 (6H, s), 1.37 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 183.7 (183.8), 173.8 (173.5), 154.4, 134.0, 128.9 (129.0), 128.9 (129.2), 127.3, 93.1 (d, *J* = 175.6 Hz), 79.5 (80.4), 60.6 (60.3), 53.6, 53.2 (d, *J* = 24.9 Hz) [53.3 (d, *J* = 25.7 Hz)], 44.7 (43.5), 36.7 (37.0), 35.6 (d, *J* = 20.3 Hz) [35.5 (d, *J* = 20.1 Hz)], 28.6; ^{19}F NMR (188 MHz, $CDCl_3$) δ -115.6 (1F, m); HRMS exact mass calculated for [M-H]$^-$ ($C_{20}H_{25}F\ N_3O_3S^-$) requires *m/z* 406.1606, found 406.1609.

(*S*)-3-(((2*S*,4*S*)-4-Fluoropyrrolidin-2-yl)methyl)-6-phenyl-2-thioxotetrahydropyrimidin-4(1*H*)-one (2). To a stirring solution of **11** (65 mg, 0.16 mmol) in HCl 6N/MeOH (3 mL) in a pressure vessel, glacial AcOH (5 mL) was added. The reaction mixture was left stirring for 3 h at 100 ^{o}C. After cooling at room temperature, the reaction mixture was treated with aq. $NaHCO_3$ (10%) until pH=8. The crude product was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to yield the desired product **2**. Pale yellow oil; 45 mg, 92% yield; $[\alpha]_D^{20}$ = -13.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40-7.10 (6H, m), 5.05 (1H, dm, *J* = 54.6 Hz), 4.55-4.20 (1H, m), 4.19-3.70 (2H, m), 3.69-2.88 (3H, m), 2.87-2.21 (2H, m), 2.20-1.55 (2H, m), 1.23 (1H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 184.0 (183.7), 174.7 (174.0), 135.6 (135.3), 129.1 (129.0), 128.9 (128.8), 127.5 (127.4), 94.7 (d, *J* = 173.9 Hz) [94.6 (d, *J* = 174.6 Hz)], 61.0 (60.5), 57.1 (56.9), 53.6 (d, *J* = 23.6 Hz) [53.5 (d, *J* = 23.3 Hz)], 44.9, 37.4 (36.9), 37.3 (d, *J* = 21.1 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ -115.6 (1F, m); HRMS exact mass calculated for $[M-H]^-$ ($C_{15}H_{17}F\ N_3OS^-$) requires *m/z* 306.1082, found 306.1080.

(2*S*,4*S*)-1-tert-butyl 2-methyl 4-hydroxypyrrolidine-1,2-dicarboxylate (12). The title compound was obtained following literature procedure and all data for the compound obtained matched literature data.[17]

(2*S*,4*R*)-1-*tert*-Butyl 2-methyl 4-fluoropyrrolidine-1,2-dicarboxylate (13).[18] Following the same procedure as for compound **7**, utilizing compound **12** (1.43 g, 5.83 mmol), to yield the desired product **13.** Pale yellow oil; 0.96 g, 67%; $[\alpha]_D^{20}$ = -70.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.03 (1H, dm, *J* = 52.4 Hz), 4.35-4.12 (1H, m), 3.86-3.14 (5H, m), 2.53-1.67 (2H, m), 1.28 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.7 (172.5), 153.7 (153.1), 90.7 (d, *J* = 178.6 Hz) [91.5 (d, *J* = 178.1 Hz),

80.0 (79.9), 57.2 (56.9), 52.5 (d, J = 22.6 Hz) [52.9 (d, J = 22.6 Hz)], 52.1 (52.3), 37.1 (d, J = 22.4 Hz) [36.2 (d, J = 22.7 Hz)], 27.5 (27.9); ^{19}F NMR (188 MHz, $CDCl_3$) δ -122.6 (1F, m).

(2*S*,4*R*)-*tert*-Butyl 4-fluoro-2-(hydroxymethyl)pyrrolidine-1-carboxylate (14). Following the same procedure as for compound **8**, utilizing compound **13** (0.59 g, 2.39 mmol), to yield the desired product **14**. Colorless oil 286 mg, 55% yield; $[\alpha]_D^{20}$ = -41.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.11 (1H, dm, J = 52.3 Hz), 4.93 (1H, br), 4.25-3.18 (5H, m), 2.44-2.01 (2H, m), 1.44 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.1, 91.0 (d, J = 176.3 Hz), 80.5 (79.6), 65.4, 58.3, 53.3 (d, J = 22.8 Hz), 35.1 (d, J = 21.9 Hz), 28.1; ^{19}F NMR (188 MHz, $CDCl_3$) δ -121.9 (1F, m); HRMS exact mass calculated for $[M+Na]^+$ ($C_{10}H_{18}O_3NFNa^+$) requires *m/z* 242.1163, found *m/z* 242.1167.

(2*S*,4*R*)-*tert*-Butyl 2-(azidomethyl)-4-fluoropyrrolidine-1-carboxylate (15). Following the same procedure as for compound **9**, utilizing compound **14** (405 mg, 1.85 mmol), to yield the desired product **15**. Colorless oil; 331 mg, 73% yield; $[\alpha]_D^{20}$ = -48.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.03 (1H, dm, J = 52.9 Hz), 4.08-3.82 (2H, m), 3.81-3.53 (1H, m), 3.45-2.98 (2H, m), 2.32-1.68 (2H, m), 1.33 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154 (153.7), 91.1 (d, J = 176.8 Hz) [90.7 (d, J = 177.3 Hz)], 79.7 (80.1), 55.0, 53.5 (d, J = 22.5 Hz) [53.1 (d, J = 19.5 Hz)], 51.6, 34.9 (d, J = 21.7 Hz) [36.1 (d, J = 21.7 Hz)], 28.0; ^{19}F NMR (188 MHz, $CDCl_3$) δ -122.0 (1F, m); HRMS exact mass calculated for $[M+Na]^+$ ($C_{10}H_{17}O_2N_4FNa^+$) requires *m/z* 267.1233, found *m/z* 267.1241.

(2*S*,4*R*)-*tert*-Butyl 4-fluoro-2-(((*S*)-6-oxo-4-phenyl-2-thioxotetrahydropyrimidin-1(2*H*)-yl)methyl)pyrrolidine-1-carboxylate (16). Following the same procedure as for compound **11**, utilizing compound **15** (331 mg, 1.35 mmol), to yield the desired

product **16**. Pale yellow oil; 318 mg, 46% yield; $[\alpha]_D^{20}$ = -2.0 (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 8.71(0.4 H, brs), 8.31-8.06 (0.6H, brm), 7.36-7.00 (5H, m), 5.22-4.78 (1H, m), 4.46-4.18 (1H, m), 4.15-3.33 (4H, m), 3.32-2.77 (3H, m), 2.00-1.57 (1H, m), 1.56-1.10 (10H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 183.3 (183.7), 173.6 (173.5), 154.6 (154.3), 135.1 (134.5), 129.5 (129.1), 128.6, 127.4, 91.0 (d, *J* = 177.9 Hz) [91.0 (d, *J* = 177.3 Hz)], 80.4 (79.7), 60.3 (60.0), 55.1, 52.3 (d, *J* = 18.8 Hz) [52.5 (d, *J* = 23.8 Hz)], 43.7 (44.1), 36.4, 35.5 (d, *J* = 21.6 Hz) [20.9 (d, *J* = 20.9 Hz)], 28.1; ^{19}F NMR (188 MHz, $CDCl_3$) δ -122.3 (1F, m); HRMS exact mass calculated for $[M-H]^-$ ($C_{20}H_{25}F\ N_3O_3S^-$) requires *m/z* 406.1606, found 406.1611.

(*S*)-3-(((2*S*,4*R*)-4-Fluoropyrrolidin-2-yl)methyl)-6-phenyl-2-thioxotetrahydropyrimidin-4(1*H*)-one (3). Following the same procedure as for compound **2**, utilizing compound **16** (318 mg, 0.82 mmol), to yield the desired product **3**. Pale yellow oil; 161 mg, 64% yield; $[\alpha]_D^{20}$ = +10.9 (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.38-7.08 (6H, m), 5.07 (1H, dm, *J* = 53.6 Hz), 4.48-4.22 (1H, m), 3.71-3.55 (3H, m), 3.30-2.77 (4H, m), 2.07-1.75 (1H, m), 1.57-1.12 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 183.8 (183.7), 174.0 (173.9), 134.6 (134.9), 129.3 (129.2), 128.7, 127.4, 94.8 (d, *J* = 174.5 Hz), 60.5 (60.3), 54.9 (55.0), 52.5 (d, *J* = 23.1 Hz) [52.4 (d, *J* = 23.1 Hz)], 44.5 (44.6), 37.8 (d, *J* = 21.3 Hz) [37.7 (d, *J* = 23.3 Hz), 37.5; ^{19}F NMR (188 MHz, $CDCl_3$) δ -118.2 (1F, m); HRMS exact mass calculated for $[M-H]^-$ ($C_{15}H_{17}F\ N_3OS^-$) requires *m/z* 306.1082, found 306.1077.

(2*S*,4*S*)-1-*tert*-Butyl 2-methyl 4-((*tert*-butyldimethylsilyl)oxy)pyrrolidine-1,2-dicarboxylate (17). To a stirring solution of alcohol **12** (0.48 g, 1.96 mmol 1.00 g, 4.08 mmol) in dry CH_2Cl_2 (20 mL) at 0 ^oC under argon atmosphere, imidazole (0.40 g, 5.88 mmol) and TBDMSCl (0.36 g, 2.36 mmol) were added. The reaction was stirred for 30 min at 0 ^oC, and then warmed to room temperature and was allowed to

stir for 20 h. Dichloromethane (20 mL) was added and the organic layer was washed with water (30 mL) and brine (30 mL). The organic layer was dried over Na_2SO_4, and concentrated to yield the crude product. The crude oil was purified by silica gel chromatography (PE/EtOAc, 8:2) to yield the desired product **17** as colorless oil (0.60 g, 1.72 mmol, 88% yield); $[\alpha]_D^{20}$ = -30.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.30-4.10 (2H, m), 3.55 (3H, s), 3.54-3.39 (1H, m), 3.27-3.10 (1H, m), 2.24-2.05 (1H, m), 2.00-1.89 (1H, m), 1.32 (3H, s), 1.27 (6H, s), 0.70 (9H, s), -0.11 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.5 (172.0), 153.3 (154.0), 79.5 (79.8), 69.5 (70.4), 57.5 (57.4), 53.9 (54.5), 51.6, 39.3 (38.5), 28.0 (28.1), 25.3, 17.6, -5.2; HRMS exact mass calculated for $[M+H]^+$ ($C_{17}H_{34}O_5NSi^+$) requires *m/z* 360.2201, found 360.2203.

(2*S*,4*S*)-*tert*-Butyl 4-((*tert*-butyldimethylsilyl)oxy)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (18). To a stirring solution of **17** (0.50 g, 1.39 mmol) in dry THF (10 mL) at 0 ^{o}C, $NaBH_4$ (0.50 g, 12.51 mmol) was added. Methanol (8 mL) was added dropwise to the reaction mixture. The reaction was stirred for 1 h at 0 ^{o}C and then warmed to room temperature for 20 h. The reaction was quenched with dropwise addition of aq. NH_4Cl (15 mL). The crude reaction mixture was extracted with AcOEt (3 x 15 mL). The combined organic layers were washed with aq. $NaHCO_3$ (40 mL), brine (40 mL) and dried over Na_2SO_4. The organic solvent were concentrated under reduced pressure and purified by silica gel chromatography (PE/AcOEt, 8:2) to yield the desired product **18** as colorless oil (234 mg, 0.71 mmol, 51% yield); $[\alpha]_D^{20}$ = -14.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.37-4.19 (1H, m), 4.08-3.39 (4H, m), 3.38-3.15 (1H, m), 2.30-2.06 (1H, m), 1.99-1.69 (1H, m), 1.57 (1H, br s), 1.42 (9H, s), 0.84 (9H, s), 0.03 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.7, 79.8 (79.5), 69.5 (70.1), 66.1 (66.8), 58.5 (59.1), 55.6 (55.5), 37.5, 28.1, 25.4, 17.6, -5.2, -5.3; HRMS

exact mass calculated for $[M+Na]^+$ ($C_{16}H_{33}NNaO_4Si^+$) requires *m/z* 354.2071, found 354.2079.

(2*S*,4*S*)-*tert*-Butyl 2-(azidomethyl)-4-((*tert*-butyldimethylsilyl)oxy)pyrrolidine-1-carboxylate (19). Following the same procedure as for compound **9**, utilizing compound **18** (230 mg, 0.69 mmol), to yield the desired product **19** as colorless oil (116 mg, 0.33 mmol, 47% yield); $[\alpha]_D^{20}$ = -10.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.39-4.25 (1H, m), 4.12-3.67 (2H, m), 3.58-3.06 (3H, m), 1.99-1.84 (2H, m), 1.39 (9H, s), 0.79 (9H, s), -0.01 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.7 (154.3), 79.7 (79.5), 69.8 (69.3), 55.4 (56.1), 55.3 (55.1), 52.4 (53.8), 37.8 (38.8), 28.2, 25.4, 17.7, -5.1; HRMS exact mass calculated for $[M+H]^+$ ($C_{16}H_{33}O_3N_4Si$) requires *m/z* 357.2316, found 357.2318.

(2*S*,4*S*)-*tert*-Butyl 4-((*tert*-butyldimethylsilyl)oxy)-2-(((*S*)-6-oxo-4-phenyl-2-thioxotetrahydropyrimidin-1(2*H*)-yl)methyl)pyrrolidine-1-carboxylate (20). Following the same procedure as for compound **11**, utilizing compound **19** (116 mg, 0.33 mmol), to yield the desired product **20** as yellow oil (91 mg, 0.17 mmol, 53% yield); $[\alpha]_D^{20}$ = -22.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38-7.15 (6H, m), 4.54-4.21 (2H, m), 4.20-3.81 (1H, m), 3.78-2.77 (6H, m), 1.90-1.57 (2H, m), 1.49-1.29 (9H, m), 0.85 (9H, s), 0.04 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 183.7 (184.3), 173.2 (173.4), 155.0 (155.2), 136.1 (135.7), 129.0 (129.2), 128.8 (128.7), 128.2 (127.3), 79.1 (79.8), 69.9 (69.6), 60.3 (60.0), 53.8 (54.8), 52.6 (52.7), 52.0 (52.1), 36.7 (36.5), 35.6 (35.4), 28.2, 25.5, 17.7, -4.9, -5.1; HRMS exact mass calculated for $[M-H]^-$ ($C_{26}H_{40}N_3O_4SSi^-$) requires *m/z* 518.2514, found 518.2522.

(*S*)-3-(((2*S*,4*S*)-4-Hydroxypyrrolidin-2-yl)methyl)-6-phenyl-2-thioxotetrahydropyrimidin-4(1*H*)-one (4). Following the same procedure as for compound **2**, utilizing compound **20** (90 mg, 0.17 mmol), to yield the desired product

4 as pale yellow oil; (23 mg, 0.07 mmol, 44% yield); $[\alpha]_D^{20}$ = -19.2 (*c* 0.25, CH_3OH); ^1H NMR (200 MHz, $CDCl_3$) δ 7.39-7.17 (5H, m), 4.44-4.27 (1H, m), 3.93-3.63 (2H, m), 3.49-2.69 (6H, m), 2.09-1.96 (1H, m), 1.69-1.62 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$:CD_3OD) δ 180.8 (181.2), 175.2 (176.1), 131.9 (133.2), 129.1 (129.2), 128.2 (128.4), 127.0 (127.4), 70.7 (69.6), 55.7 (55.0), 53.4 (53.6), 42.8 (43.1), 38.3 (38.2), 36.2 (36.0), 29.2; HRMS exact mass calculated for $[M-H]^-$ ($C_{15}H_{18}N_3O_2S^-$) requires *m/z* 304.1125, found 304.1134.

(2*S*,4*R*)-1-*tert*-Butyl 2-methyl 4-((tert-butyldimethylsilyl)oxy)pyrrolidine-1,2-dicarboxylate (21). Following the same procedure as for compound **17**, utilizing compound **6** (1.00 g, 4.08 mmol), to yield the desired product **21** as a colorless oil (1.20 g, 3.34 mmol, 82%); $[\alpha]_D^{20}$ = -32.9 (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 4.40-4.22 (2H, m), 3.66 (3H, s), 3.58-3.46 (1H, m), 3.39-3.20 (1H, m), 2.20-2.02 (1H, m), 2.02-1.86 (1H, m), 1.39 (3H, s), 1.34 (6H, s), 0.80 (9H, s), -0.01 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.6 (173.4), 153.7 (154.5), 79.9, 69.6 (70.3), 57.9 (57.5), 54.4 (54.7), 51.8, 39.7 (38.8), 28.1 (28.2), 25.6, 17.8, -5.0; MS (ESI) *m/z* (%): 360 [M+H, (100)]$^+$; HRMS exact mass calculated for $[M+H]^+$ ($C_{17}H_{34}O_5NSi^+$) requires *m/z* 360.2201, found 360.2208.

(2*S*,4*R*)-*tert*-Butyl 4-((*tert*-butyldimethylsilyl)oxy)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (22). Following the same procedure as for compound **8**, utilizing compound **21** (2.90 g, 8.10 mmol), to yield the desired product **22** as colorless oil (1.63 g, 5.0 mmol, 61% yield); $[\alpha]_D^{20}$ = -30.9 (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 4.27-4.07 (1H, m), 4.03-3.12 (5H, m), 1.94-1.65 (1H, m), 1.64-1.40 (1H, m), 1.32 (9H, s), 0.72 (9H, s), -0.08 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.8, 79.8, 69.6, 66.2, 58.6, 55.7, 37.5, 28.1, 25.4, 17.6, -5.1, -5.2; HRMS exact mass calculated for $[M+Na]^+$ ($C_{16}H_{33}O_4NSiNa^+$) requires *m/z* 354.2071, found 354.2078.

(2*S*,4*R*)-*tert*-Butyl 2-(azidomethyl)-4-((*tert*-butyldimethylsilyl)oxy)pyrrolidine-1-carboxylate (23). Following the same procedure as for compound **9**, utilizing compound **22** (697 mg, 2.11 mmol), to yield the desired product **23** as colorless oil (408 mg, 1.15 mmol, 54% yield); $[\alpha]_D^{20}$ = -42.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.33-4.22 (1H, m), 4.08-3.88 (1H, m), 3.83-3.07 (4H, m), 1.93-1.79 (2H, m), 1.38 (9H, s), 0.78 (9H, s), -0.02 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.8 (154.4), 79.5 (79.8), 69.9 (69.4), 55.5 (55.4), 54.9, 52.5 (53.8), 37.8 (38.8), 28.2, 25.5, 17.7, -5.1; HRMS exact mass calculated for $[M+Na]^+$ ($C_{16}H_{32}N_4O_3SiNa^+$) requires *m/z* 379.2136, found 379.2144.

(2*S*,4*R*)-*tert*-Butyl 4-((*tert*-butyldimethylsilyl)oxy)-2-(((*S*)-6-oxo-4-phenyl-2-thioxotetrahydropyrimidin-1(2*H*)-yl)methyl)pyrrolidine-1-carboxylate (24). Following the same procedure as for compound **11**, utilizing compound **23** (408 mg, 1.14 mmol), to yield the desired product **24** as pale yellow oil (422 mg, 0.81 mmol, 71% yield); $[\alpha]_D^{20}$ = +3.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.32-6.98 (6H, m), 4.46-4.11 (2H, m), 3.95-3.72 (1H, m), 3.69-2.84 (6H, m), 2.08-1.54 (2H, m), 1.43 (9H, s), 0.83 (9H, s), 0.02 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 183.7 (183.6), 173.6 (173.5), 154.9 (155.0), 135.5 (134.6), 129.1 (129.3), 128.3 (128.6), 126.7 (127.2), 80.4 (79.8), 69.6 (70.0), 60.4 (60.0), 55.0 (53.9), 52.9 (53.3), 52.1 (52.7), 37.6 (37.9), 36.6 (36.9), 28.2, 25.6, 17.7, -4.9, -5.0; HRMS exact mass calculated for $[M-H]^-$ ($C_{26}H_{40}N_3O_4SSi^-$) requires *m/z* 518.2514, found 518.2520.

(*S*)-3-(((2*S*,4*R*)-4-Hydroxypyrrolidin-2-yl)methyl)-6-phenyl-2-thioxotetrahydropyrimidin-4(1*H*)-one (5). Following the same procedure as for compound **2**, utilizing compound **24** (227 mg, 0.44 mmol), to yield the desired product **5** as pale yellow oil (73 mg, 0.24 mmol, 55% yield); $[\alpha]_D^{20}$ = -1.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$:CD_3OD) δ 7.31-7.05 (5H, m), 4.40-4.16 (1H,

m), 3.75-3.43 (3H, m), 3.39-2.59 (5H, m), 1.71-1.54 (1H, m), 1.46-1.25 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$:CD_3OD) δ 183.2 (183.5), 174.5 (174.2), 134.2 (134.1), 129.2 (129.1), 128.3, 127.1, 71.1 (71.0), 55.4 (55.5), 53.8 (53.6), 43.6 (43.5), 38.1 (38.4), 36.2 (36.3), 29.3; HRMS exact mass calculated for $[M-H]^-$ ($C_{15}H_{18}N_3O_2S^-$) requires *m/z* 304.1125, found 304.1131.

General procedure for the Michael reaction between ketones and nitrostyrenes in brine.

To a stirring solution of catalyst **2** (5 mg, 0.016 mmol) and nitroolefin (0.32 mmol), 4-NBA (8.1 mg, 0.049 mmol), brine (1.5 mL) and ketone (0.35 mmol) were added and the reaction mixture was stirred vigorously for 20-48 h. The reaction mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated. In most cases, the product was of sufficient purity (>95%). If the reaction did not reach completion, the product was purified by column chromatography (PE/EtOAc).

(*S*)-2-((*R*)-2-Nitro-1-phenylethyl)cyclohexanone (25a).[5] White solid, 78 mg, 99%; mp 133-134 ^oC; $[\alpha]_D^{20}$ = -27.0 (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.45-7.05 (5H, m), 4.93 (1H, dd, *J* = 12.5 Hz and 4.4 Hz), 4.60 (1H, dd, *J* = 12.3 and 10.3 Hz), 3.83-3.65 (1H, m), 2.78-2.57 (1H, m), 2.54-2.22 (2H, m), 2.17-1.92 (1H, m), 1.90-1.40 (4H, m), 1.38-1.07 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 212.2, 138.0, 129.1, 128.4, 127.9, 79.1, 52.7, 44.2, 42.9, 33.4, 28.8, 25.2; HPLC analysis: 99% *ee*; Diacel Chiralpak® AD-H column, hexane/2-propanol: 95/5, flow rate 1 mL/min, t_R= 17.95 min (minor) and 23.34 min (major).

(*S*)-2-((*R*)-2-Nitro-1-(4-nitrophenyl)ethyl)cyclohexanone (25b).[5] Pale yellow oil, 93 mg, 99%; $[\alpha]_D^{20}$ = -30.3 (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.18 (2H, d, *J* =8.8 Hz), 7.38 (2H, d, *J* = 8.8 Hz), 4.98 (1H, dd, *J* = 13.0 and 4.5 Hz), 4.67 (1H,

dd, *J* = 13.0 and 10.2 Hz), 3.91 (1H, td, *J* = 9.8 and 4.5 Hz), 2.80-2.58 (1H, m), 2.52-2.25 (2H, m), 2.18-2.09 (1H, m), 1.88-1.43 (4H, m), 1.37-1.28 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 210.9, 147.4, 145.5, 129.3, 124.1, 77.9, 52.1, 43.7, 42.7, 33.2, 28.3, 25.1; HPLC analysis: 93% *ee*; Diacel Chiralpak® AD-H column, hexane/2-propanol: 80/20, flow rate 0.5 mL/min, t_R= 39.66 min (minor) and 69.34 min (major).

(*S*)-2-((*R*)-1-(4-Fluorophenyl)-2-nitroethyl)cyclohexanone (25c).[5] White solid, 79 mg, 93%; mp 72-74 °C; $[\alpha]_D^{20}$ = -19.9 (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.18-6.91 (4H, m), 4.91 (1H, dd, *J* = 12.5 and 4.6 Hz), 4.56 (1H, dd, *J* = 12.4 and 10.2 Hz), 3.74 (1H, td, *J* = 10.2 and 4.6 Hz), 2.72-2.54 (1H, m), 2.51-2.23 (2H, m), 2.02-1.90 (1H, m), 1.84-1.43 (4H, m), 1.23-1.17 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 211.7, 162.1 (d, *J* = 240 Hz), 133.4, 129.8 (d, *J* = 10 Hz), 115.8 (d, *J* = 20 Hz), 78.7, 52.4, 43.2, 42.7, 33.2, 28.4, 25.0; ^{19}F NMR (188 MHz, $CDCl_3$): δ -59.4 (1F, m); HPLC analysis 99% *ee*; Diacel Chiralpak® AD-H column, hexane/2-propanol: 75/25, flow rate 0.7 mL/min, t_R= 13.34 min (minor) and 15.51 min (major).

(*S*)-2-((*R*)-1-(4-Chlorophenyl)-2-nitroethyl)cyclohexanone (25d).[19] White solid, 89 mg, 99%; mp 122-124 °C; $[\alpha]_D^{20}$ = -23.7 (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.29 (2H, d, *J* = 8.5 Hz), 7.10 (2H, d, *J* = 8.5 HzH) 4.93 (1H, dd, *J* = 12.6 and 4.6 Hz), 4.58 (1H, dd, *J* = 12.6 and 10.0 Hz), 3.74 (1H, td, *J* = 10.0 and 4.6), 2.73-2.54 (1H, m), 2.52-2.31 (2H, m), 2.21-1.96 (1H, m), 1.85-1.47 (4H, m), 1.22-1.06 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 211.5, 136.2, 133.5, 129.5, 129.1, 78.5, 52.3, 43.3, 42.7, 33.1, 28.1, 25.0; HPLC analysis: 99% *ee*; Diacel Chiralpak® AD-H column, hexane/2-propanol: 90/10, flow rate 0.5 mL/min, t_R= 32.50 min (minor) and 48.88 min (major).

(*S*)-2-((*R*)-1-(4-Methoxyphenyl)-2-nitroethyl)cyclohexanone (25e).[5] White solid, 78 mg, 88%; mp 78-80 °C; $[\alpha]_D^{20}$ = -25.1 (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ

7.06 (2H, d, J = 8.6 Hz), 6.83 (2H, d, J = 8.8 Hz), 4.90 (1H, dd, J = 12.3 and 4.6 Hz), 4.56 (1H, dd, J = 12.3 and 10.1 Hz), 3.79-3.62 (4H, m), 2.72-2.54 (1H, m), 2.47-2.25 (2H, m), 2.17-1.97 (1H, m), 1.83-1.43 (4H, m), 1.32-1.15 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 212.0, 158.9, 129.5, 129.1, 114.2, 79.0, 55.1, 52.6, 43.1, 42.6, 33.1, 28.5, 24.9; HPLC analysis: 99% *ee*; Diacel Chiralpak® AD-H column, hexane/2-propanol: 95/5, flow rate 1 mL/min, t_R= 24.68 min (minor) and 31.42 min (major).

(*S*)-2-((*R*)-1-(Naphthalen-2-yl)-2-nitroethyl)cyclohexanone (25f).[5] White solid, 83 mg, 87%; mp 91-93 ^{o}C; $[\alpha]_D^{20}$ = -36.2 (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.87-7.71 (3H, m), 7.66-7.57 (1H, s), 7.53-7.39 (2H, m), 7.28 (1H, dd, J = 8.5 and 1.8 Hz), 5.02 (1H, dd, J = 12.5 Hz and 4.5 Hz), 4.72 (1H, dd, J = 12.5 and 10.0 Hz), 3.94 (1H, td, J = 10.0 and 4.5 Hz), 2.85-2.68 (1H, m), 2.58-2.28 (2H, m), 2.18-1.97 (1H, m), 1.80-1.53 (4H, m), 1.37-1.19 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 211.8, 135.1, 133.3, 132.8, 128.8, 127.7, 127.6, 126.4, 126.1, 125.2, 78.8, 52.4, 44.0, 42.7, 33.2, 28.4, 24.9; HPLC analysis: 99% *ee*; Diacel Chiralpak® AD-H column, hexane/2-propanol: 95/5, flow rate 1 mL/min, t_R= 33.85 min (minor) and 39.89 min (major).

(*S*)-2-((*S*)-1-(Furan-2-yl)-2-nitroethyl)cyclohexanone (25g).[5] White solid, 75 mg, 99%; mp 76-78 ^{o}C; $[\alpha]_D^{20}$ = -15,4 (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.41-7.20 (1H, m), 6.34-6.07 (2H, m), 4.86-4.53 (2H, m), 4.04-3.83 (1H, m), 2.83-2.60 (1H, m), 2.54-2.23 (2H, m), 2.18-2.08 (1H, m), 1.93-1.49 (4H, m), 1.42-1.10 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 210.9, 151.1, 142.3, 110.4, 109.0, 75.2, 51.2, 42.5, 37.6, 32.5, 28.2, 25.1; HPLC analysis: 99% *ee*; Diacel Chiralpak® AD-H column, hexane/2-propanol: 95/5, flow rate 0.5 mL/min, t_R= 37.39 min (major) and 45.46 min (minor).

(*R*)-3-((*R*)-2-Nitro-1-phenylethyl)dihydro-2H-pyran-4(3H)-one (25h).[5] White solid, 53 mg, 66%; mp 97-99 ^{o}C; $[\alpha]_D^{20}$ = -27.5 (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz,

$CDCl_3$): δ 7.38-7.10 (5H, m) 4.93 (1H, dd, J = 12.7 and 4.6 Hz), 4.63 (1H, dd, J = 12.7 and 10.1 Hz), 4.22-4.03 (1H, m), 3-90-3.60 (3H, m), 3.25 (1H, dd, J = 11.4 and 8.9 Hz), 3.00-2.77 (1H, m), 2.76-2.38 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 207.3, 136.2, 129.1, 128.3, 127.8, 78.6, 71.5, 68.9, 53.2, 42.9, 41.2; HPLC analysis: 99% *ee*; Diacel Chiralpak® AD-H column, hexane/2-propanol: 85/15, flow rate 1 mL/min, t_R= 29.22 min (minor) and 41.48 min (major).

(*S*)-3-((*R*)-2-Nitro-1-phenylethyl)dihydro-2H-thiopyran-4(3H)-one (25i).[5] White solid, 82 mg, 97%; mp 132-134 ^oC; $[\alpha]_D^{20}$ = -26.9 (c 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.37-7.17 (5H, m), 4.75 (1H, dd, J = 12.4 and 4.4 Hz), 4.62 (1H, dd, J = 12.4 and 9.6 Hz), 3.86 (1H, dt, J = 9.6 και 4.4 Hz), 3.07-2.92 (3H, m), 2.88-2.75 (2H, m), 2.63-2.56 (1H, m), 2.48-2.41 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 209.5, 136.5, 129.3, 128.3, 128.1, 78.6, 54.9, 44.5, 42.9, 35.1, 31.6; HPLC analysis: 99% *ee*; Diacel Chiralpak® AD-H column, hexane/2-propanol : 85/15, flow rate 1 mL/min, t_R= 23.48 min (minor) and 41.94 min (major).

(*S*)-4,4-Dimethyl-2-((*R*)-2-nitro-1-phenylethyl)cyclohexanone (25j).[5] White solid, 87 mg, 99%; mp 79-81 ^oC; $[\alpha]_D^{20}$ = -105.8 (*c* 1, CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$): δ 7.38-7.08 (5H, m), 4.99 (1H, dd, J = 12.3 and 4.6 Hz), 4.61 (1H, dd, J = 12.3 and 9.7 Hz), 3.69 (1H, td, J = 9.7 and 4.6 Hz), 2.86 (1H, ddd, J = 13.3, 9.6 and 5.4 Hz), 2.55 (1H, ddd, 13.5, 13.4 6.5 Hz), 2.29 (1H, ddd, J = 13.5, 4.6 and 2.9 Hz), 1.83-1.55 (2H, m), 1.44-1.16 (2H, m), 1.12 (3H, s), 0.87 (3H, s);^{13}C NMR (50 MHz, $CDCl_3$): δ 212.6, 137.7, 128.9, 128.1, 127.7, 79.0, 47.6, 45.8, 43.8, 40.6, 39.1, 31.0, 24.2; HPLC analysis: 99% *ee*; Diacel Chiralpak® AD-H column, hexane/2-propanol: 95/5, flow rate 0.5 mL/min, t_R= 32.02 min (minor) and 35.16 min (major).

(*S*)-7-((*R*)-2-nitro-1-phenylethyl)-1,4-dioxaspiro[4.5]decan-8-one (25k).[5] White solid, 74 mg, 76%; mp 117-119 ^oC; $[\alpha]_D^{20}$ = -13.9 (c 1, $CHCl_3$); ^1H NMR (200 MHz,

$CDCl_3$): δ 7.36-7.26 (3H, m), 7.19-7.17 (2H, m), 4.96 (1H, dd, J = 12.5 and 4.7 Hz), 4.63 (1H, dd, J = 12.5 and 9.8 Hz), 4.01-3.82 (5H, m), 3.08 (1H, ddd, J = 13.0, 10.1 and 5.5 Hz), 2.78-2.68 (1H, m), 2.48 (1H, dd, J = 13.8, 5.1 and 3.5 Hz), 2.06 (1H, ddt, J = 13.0, 6.6 and 3.5 Hz), 1.97 (1H, td, J = 13.0 and 5.1 Hz), 1.70 (1H, ddd, J = 13.0, 5.5 and 3.5 Hz), 1.57 (1H, t, J = 13.4 Hz);^{13}C NMR (50 MHz, $CDCl_3$): δ 201.3, 137.2, 128.9, 128.2, 127.8, 107.0, 78.9, 64.7, 64.5, 48.1, 43.4, 39.2, 38.5, 35.0; HPLC analysis: 99% *ee*,; Diacel Chiralpak® AD-H column, hexane/2-propanol : 80/20, flow rate 1 mL/min, t_R= 15.82 min (minor) and 20.92 min (major).

(2*S*,4*S*)-4-Methyl-2-((*R*)-2-nitro-1-phenylethyl)cyclohexanone (25l).[20] Pale yellow oil, 83 mg, 99%; $[\alpha]_D^{20}$ = -49.6 (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.36-7.26 (3H, m), 7.18-7.16 (2H, m), 4.73-4.56 (2H, m), 3.84-3.76 (1H, m), 2.77-2.69 (1H, m), 2.50 (2H, t, J = 6.6 Hz), 2.12-1.94 (2H, m), 1.68-1.56 (1H, m), 1.50-1.35 (2H, m), 0.97 (3H, d, J = 6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 213.0, 137.3, 129.1, 128.0, 79.1, 50.0, 44.1, 38.6, 37.9, 34.4, 26.5, 19.4; HPLC analysis: 95% *ee*,; Diacel Chiralpak® OD-H column, hexane/2-propanol : 90/10, flow rate 0.5 mL/min, t_R= 42.46 min (minor) and 48.27 min (major).

(*S*)-2-((*R*)-2-Nitro-1-phenylethyl)cycloheptanone (25m).[21] Colorless oil, 28 mg, 34%; $[\alpha]_D^{20}$ = -4.0 (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.35-7.27 (3H, m), 7.18-7.17 (2H, m), 4.67-4.53 (2H, m), 3.68 (1H, ddd, J = 10.3, 8.5 and 5.2 Hz), 3.01 (1H, td, J =10.3 and 3.3 Hz), 2.59-2.49 (2H, m), 1.94-1.86 (2H, m), 1.79-1.42 (3H, m), 1.27-1.14 (3H, m) ^{13}C NMR (50 MHz, $CDCl_3$): δ 214.7, 137.7, 129.0, 128.1, 127.9, 78.7, 53.7, 45.5, 43.4, 29.9, 28.6, 28.5, 23.9 ; HPLC analysis: 85% *ee*; Diacel Chiralpak® AD-H column, hexane/2-propanol : 98/2, flow rate 1 mL/min, t_R= 25.03 min (minor) and 35.10 min (major).

(*R*)-5-Nitro-4-phenylpentan-2-one (25n).[5] White solid, 36 mg, 55%; mp 120-122 ^{o}C; $[\alpha]_D^{20}$ = +3.5 (c 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.38-7.26 (3H, m), 7.19- 7.14 (2H, m), 4.69 (1H, dd, J = 12.3 Hz and 7.0 Hz), 4.59 (1H, dd, , J = 12.3 Hz and 7.6 Hz), 4.07-3.92 (IH, m), 2.91 (2H, d, J = 7.0 Hz), 2.11 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 205.4, 138.8, 129.0, 127.8, 127.3, 79.4, 46.1, 39.0, 30.3; HPLC analysis: 84% *ee*; Diacel Chiralpak® AD-H column, hexane/2-propanol : 94/6, flow rate 1 mL/min, t_R= 21.41 min (minor) and 23.30 min (major).

***(S)*-2-((*S*)-1-Nitro-4-phenylbutan-2-yl)cyclohexan-1-one (25o)**.[22] Colorless oil, 58 mg, 66%; $[\alpha]_D^{20}$ = -10.9 (*c* 0.5, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.35-7.12 (5H, m), 4.61 (1H, dd, J = 12.4 and 5.8 Hz), 4.44 (1H, dd, J = 12.4 and 6.4 Hz), 2.72-2.63 (3H, m), 2.55-2.51 (1H, m), 2.39-2.25 (2H, m), 2.14-2.05 (2H, m), 1.95-1.43 (6H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 211.1, 141.1, 128.5, 128.2, 126.1, 76.9, 51.4, 42.5, 37.0, 33.5, 31.3, 30.2, 27.6, 25.2; HPLC analysis: 98% *ee*; Diacel Chiralpak® AD-H column, hexane/2-propanol : 98/2, flow rate 0.5 mL/min, t_R= 49.46 min (major) and 63.11 min (minor).

(*S*)-2-((*S*)-1-Cyclohexyl-2-nitroethyl)cyclohexan-1-one (25p).[19] Colorless oil, 41 mg, 51%; $[\alpha]_D^{20}$ = -31.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.65 (1H, dd, J = 13.9 and 5.9 Hz), 4.36 (1H, dd, J = 13.9 and 5.9 Hz), 2.90-2.22 (4H, m), 2.20-2.02 (2H, m), 2.00-1.90 (1H, m), 1.84-1.48 (8H, m), 1.44-0.83 (6H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 211.6, 76.5, 50.8, 42.6, 38.8, 32.2, 31.4, 30.0, 27.8, 26.4, 26.3, 26.2, 25.3; HPLC analysis: 97% *ee*; Diacel Chiralpak® AD-H column, hexane/2-propanol : 95/5, flow rate 1.0 mL/min, t_R= 19.48 min (major) and 25.38 min (minor).

General procedure for the Michael reaction between ketones and nitrodienes in brine.

To a stirring solution of catalyst **2** (5 mg, 0.016 mmol) and nitroolefin (0.16 mmol), p-NBA (4 mg, 0.024 mmol), brine (1.5 mL) and ketone (0.18 mmol) were added and the reaction mixture was stirred vigorously for 44 h. The reaction mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated. In most cases, the product was of sufficient purity (>95%). If the reaction did not reach completion, the product was purified by column chromatography (PE/EtOAc).

(*S*)-2-((*S*,*E*)-1-Nitro-4-phenylbut-3-en-2-yl)cyclohexanone (26a).[6b] White solid, 43 mg, 98%; mp 120-122 ^oC; $[\alpha]_D^{20}$ = -66.7 (*c* 0.1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.35-7.18 (5H, m), 6.49 (1H, d, *J* = 15.8 Hz,), 6.01 (1H, dd, *J* = 15.8 and 9.5 Hz), 4.67 (1H, dd, *J* = 11.9 and 5.0 Hz), 4.56 (1H, dd, *J* = 11.9 and 8.2 Hz), 3.42-3.27 (1H, m), 2.60-2.30 (3H, m), 2.21-2.03 (2H, m), 1.96-1.82 (1H, m), 1.73-1.54 (3H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 211.2, 136.2, 134.4, 128.5, 127.9, 126.4, 125.6, 78.0, 51.6, 42.6, 41.9, 32.6, 28.1, 25.0; HPLC analysis: 99% *ee*; Diacel Chiralpak® AS-H column, hexane/2-propanol: 85/15, flow rate 0.8 mL/min, t_R= 18.40 min (minor) and 24.28 min (major).

(*S*)-2-((*S*,*E*)-1-Nitro-4-(2-nitrophenyl)but-3-en-2-yl)cyclohexanone (26b).[6b] Yellow oil, 50 mg, 98%; $[\alpha]_D^{20}$ = -42.4 (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.96 (1H, d, *J* = 7.8 Hz), 7.61-7.36 (3H, m), 6.96 (1H, d, *J* = 15.7 Hz), 6.01 (1H, dd, *J* = 15.7 and 9.4 Hz), 4.76-4.79 (2H, m), 3.49-3.31 (1H, m), 2.66-2.54 (1H, m), 2.49-2.32 (2H, m), 2.28-2.04 (2H, m), 1.98-1.89 (1H, m), 1.80-1.47 (3H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 211.2, 147.3, 133.4, 132.5, 131.2, 130.2, 129.3, 128.5, 124.5, 77.6, 51.5, 42.6, 41.9, 32.6, 28.1, 25.1; HPLC analysis: 99% *ee*; Diacel Chiralpak® OD-H column, hexane/2-propanol: 95/5, flow rate 0.8 mL/min, t_R= 59.44 min (minor) and 67.84 min (major).

(*S*)-2-((*S*,*E*)-4-(4-Chlorophenyl)-1-nitrobut-3-en-2-yl)cyclohexanone (26c).[6b] White solid, 47 mg, 95%; mp 118-119 ^{o}C; $[\alpha]_D^{20}$ = -49.9 (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.26-7.24 (4H, m), 6.44 (1H, d, *J* = 15.8 Hz), 5.99 (1H, dd, *J* = 15.8 and 9.5 Hz), 4.67 (1H, dd, *J* = 11.9 and 4.9 Hz), 4.55 (1H, dd, *J* = 11.9 and 8.4 Hz), 3.41-3.25 (1H, m), 2.60-2.33 (3H, m), 2.20-2.04 (2H, m), 1.94-1.86 (1H, m), 1.75-1.58 (2H, m), 1.53-1.39 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 211.2, 134.6, 133.5, 133.1, 128.7, 127.6, 126.3, 77.9, 51.5, 42.6, 41.9, 32.6, 28.0, 25.0; HPLC analysis: 98% *ee*; Diacel Chiralpak® AD-H column, hexane/2-propanol: 95/5, flow rate 0.8 mL/min, t_R= 43.12 min (minor) and 52.40 min (major).

(*S*)-2-((*S*,*E*)-4-(4-Methoxyphenyl)-1-nitrobut-3-en-2-yl)cyclohexanone (26d).[6b] Yellow solid, 47 mg, 97%; mp 136-137 ^{o}C; $[\alpha]_D^{20}$ = -64.2 (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.26 (2H, d, *J* = 8.8 Hz), 6.82 (2H, d, *J* = 8.8 Hz), 6.40 (1H, d, *J* = 15.8 Hz), 5.83 (1H, dd, *J* = 15.8 and 9.6 Hz), 4.64 (1H, dd, *J* = 11.8 and 4.9 Hz), 4.52 (1H, dd, *J* = 11.8 and 8.3 Hz), 3.77 (3H, s), 3.37-3.21 (1H, m), 2.57-2.29 (3H, m), 2.22-2.00 (2H, m), 1.93-1.79 (1H, m), 1.73-1.55 (3H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 211.5, 159.3, 133.8, 128.9, 127.6, 123.2, 113.9, 78.2, 55.3, 51.6, 42.6, 42.0, 32.6, 28.1, 25.0; HPLC analysis: 98% *ee*; Diacel Chiralpak® AD-H column, hexane/2-propanol: 95/5, flow rate 0.8 mL/min, t_R= 53.68 min (minor) and 62.45 min (major).

(*S*)-2-((*R*,*E*)-3-Methyl-1-nitro-4-phenylbut-3-en-2-yl)cyclohexanone (26e).[6b] Colorless oil, 43 mg, 93%; $[\alpha]_D^{20}$ = -45.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.35-7.10 (5H, m), 6.39 (1H, s), 4.82 (1H, dd, *J* = 11.2 and 4.2 Hz), 4.42 (1H, t, *J* = 11.2 Hz), 3.34 (1H, td, *J* = 11.2, 4.2 Hz), 2.54-2.32 (3H, m), 2.14-1.99 (2H, m), 1.91-1.61 (6H, m), 1.56-1.41 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 212.0, 136.8, 132.6, 131.4, 128.9, 128.1, 126.7, 76.9, 49.8, 48.0, 42.7, 33.0, 28.5, 24.9, 13.8;

HPLC analysis: 99% *ee*; Diacel Chiralpak® AD-H column, hexane/2-propanol: 98/2, flow rate 0.8 mL/min, t_R= 30.47 min (minor) and 37.97 min (major).

(*S*)-2-(Bis(4-(dimethylamino)phenyl)methyl)cyclohexanone (28).[6a] Into a round-bottom flask, catalyst **2** (4.3 mg, 0.014 mmol), bis(4-(dimethylamino)phenyl)methanol **27** (37.8 mg, 0.14 mmol), p-NBA (3.5 mg, 0.021 mmol), brine (1.5 mL) and cyclohexanone (137 mg, 1.39 mmol) were added and the reaction mixture was stirred vigorously for 44 h. The reaction mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated. The crude product was purified by silica gel chromatography (PE/AcOEt, 8:2) to yield the desired product as white solid (48.2 mg, 0.14 mmol, 99%); mp 156-159 ^oC; $[\alpha]_D^{20}$ = -82.3 (*c* 0.025, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.15-7.05 (4H, m), 6.70-6.60 (4H, m), 4.17 (1H, d, J = 11.5 Hz_2), 3.29-3.18 (1H, m), 2.91-2.82 (12H, m), 2.53-2.23 (2H, m), 1.98-1.76 (4H, m), 1.68-1.44 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 213.3, 148.8, 148.6, 132.3, 131.7, 128.6, 128.0, 112.7, 55.3, 48.8, 41.9, 40.6, 32.8, 39.1, 23.6; HPLC analysis: 70% ee; Diacel Chiralpak® AD-H column, hexane/2-propanol: 95/5, flow rate 0.3 mL/min, t_R= 79.47 min (minor) and 82.54 min (major).

(1*S*,5*S*,6*R*,7*S*)-5-Hydroxy-6-nitro-7-((*E*)-styryl)bicyclo[3.2.1]octan-2-one (30).[6c] Into a round-bottom flask, catalyst **7** (4.7 mg, 0.015 mmol), ((1*E*,3*E*)-4-nitrobuta-1,3-dien-1-yl)benzene (26.8 mg, 0.15 mmol), p-NBA (3.8 mg, 0.023 mmol), brine (1 mL) and cyclohexane-1,4-dione (22.3 mg, 0.20 mmol) were added and the reaction mixture was stirred vigorously for 44 h. The reaction mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated. The crude product was purified by silica gel chromatography (PE/AcOEt, 8:2) to yield the desired product as white solid (21 mg, 0.072 mmol,

48%); $[\alpha]_D^{20}$ = -19.1 (*c* 0.5, CH_3OH); mp 142-144 °C; ^1H NMR (200 MHz, acetone-d_6): δ 7.42-7.23 (5H, m), 6.66 (1H, d, *J* = 16.1 Hz), 6.32 (1H, dd, *J* = 16.1 Hz and 6.8 Hz), 5.30 (1H, d, *J* = 5.9 Hz), 5.19 (1H, s), 4.15- 4.01 (1H, m), 3.04-2.93 (1H, m), 2.65-2.42 (3H, m), 2.37-2.15 (3H, m); ^{13}C NMR (50 MHz, acetone-d_6): δ 208.4, 137.3, 133.9, 129.3, 128.6, 127.2, 125.7, 95.5, 79.0, 54.7, 50.3, 41.0, 38.1, 35.3; HPLC analysis: 97% ee; Diacel Chiralpak® AD-H column, hexane/2-propanol: 90/10, flow rate 0.7 mL/min, t_R= 38.24 min (major) and 45.83 min (minor).

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Notes

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SUPPORTING INFORMATION

Supporting Information: Complete list of optimization experiments, NMR data and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org/.

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