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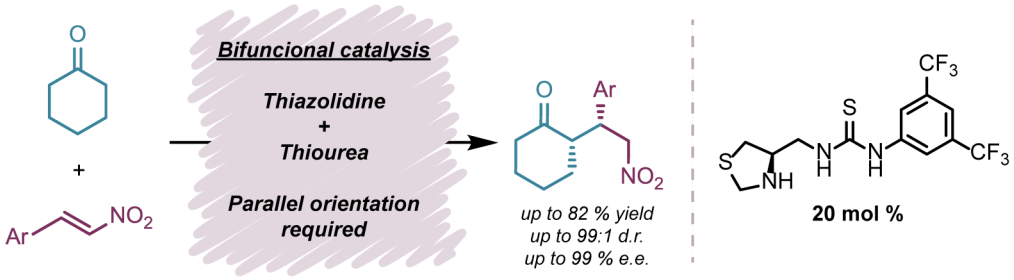

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Asymmetric Michael Reaction Promoted by Chiral Thiazolidine-Thiourea Catalyst

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The authors declare no conflict of interest.

Abstract: In this work, we report the synthesis and characterization of three new thiazolidine- and thiourea-based chiral organocatalysts. These compounds were successfully applied in asymmetric Michael addition reactions between different ketones and nitrostyrenes leading to products in up to 85% yield, >96:4 *r.d.* and 97% *e.e.* Computational studies were used to better visualize the proposed transition state and explain the observed stereoselectivities. One of the new catalysts was also successfully applied in an aldol addition between cyclohexanone an *p*-nitrobenzaldehyde leading to product in 80% yield, >96:4 *d.r.* and 80% *e.e.*

Keywords: Thiourea, Thiazolidine, Asymmetric Michael Reaction, Asymmetric Aldol Reaction.

Introduction

With growing interest for enantioenriched compounds, the search for methodologies that can deliver asymmetric molecules in high yields with selectivity is becoming increasingly important. In this context, after all the work developed since the organocatalyzed aldol reaction reported by List, Barbas *et al.* in 2000,[1] organocatalysis is now recognized as one of the most important tools in organic synthesis, performing a large number of asymmetric organic reactions very efficiently.[2]

L-Proline and its derivatives are one of the most explored groups in organocatalysis. This natural amino acid, which presents a five-member ring containing a secondary amine, is responsible for efficiently catalysing several organic reactions.[3] Its sulfur analogue, (*R*)-thiazolidine-4-

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carboxylic acid, is rarely explored in asymmetric catalysis, despite the high potential presented when it is applied: the thiazolidine moiety has demonstrated pyrrolidine-like activity, forming enamine intermediaries from ketones and catalysing aldol additions stereoselectively.[4]

The stereoselectivity in aminocatalysis can be highly improved with the presence of a hydrogen-bonding directing group in the compound. When double-hydrogen-bound motifs are synthesized, the efficiency of the catalysts can be modulated by the type of scaffold and the distance between the units. Thioureas are the most applied groups in this context, and over the last few years several modifications were performed in an attempt to improve their catalytic activity. [5]

Interested in obtaining an efficient organocatalytic system, we synthesized three catalysts containing both thiourea and thiazolidine moieties, varying the linker between them through simple and already stablished synthetic routes. The role of these linkers in the conformation of the compounds and consequently in their catalytic activity was evaluated in order to develop an optimized catalytic method.

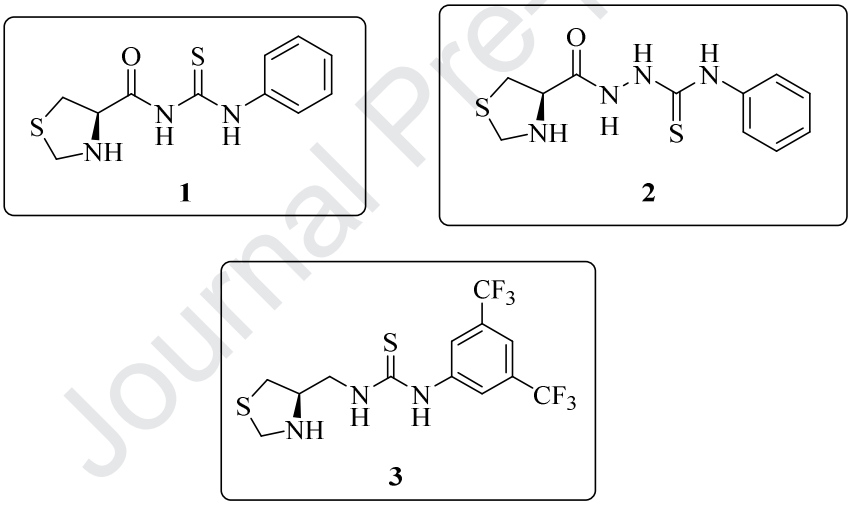

Figure 1. New thiazolidine-thiourea organocatalysts.

Results and discussion

Initially, catalysts **1** and **2**, containing a carbonyl group linker between the five-member cycle and the thiourea portions, were synthesized from (*R*)-thiazolidine-4-carboxylic acid, **4** (Scheme 1). Compound **1** was prepared through a coupling reaction with phenylthiourea catalysed by boric acid, while compound **2** was obtained through esterification and a posterior multicomponent protocol with hydrazine and phenyl isothiocyanate. These two simple and straightforward methodologies can lead to the products with good global yields without the necessity of protection and deprotection steps.

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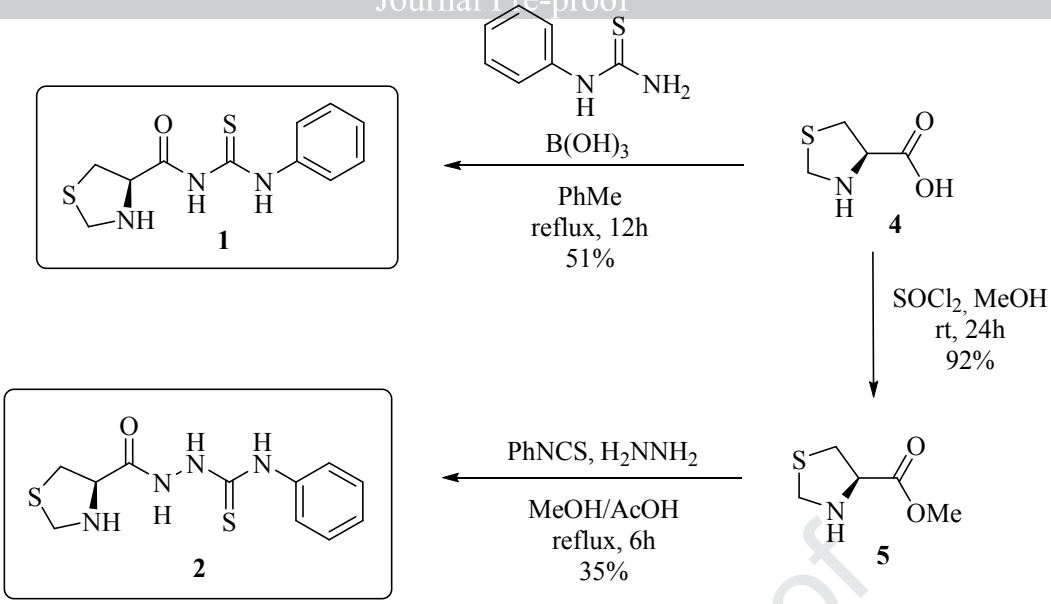
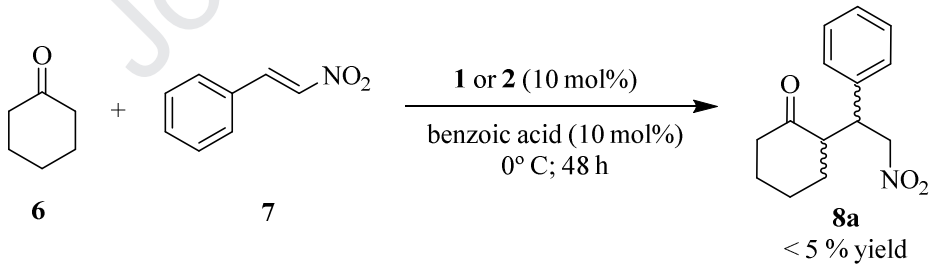


Scheme 1. Synthesis of compounds **1** and **2** from (*R*)-thiazolidine-4-carboxylic acid.

The prepared compounds were then applied in a classical Michael protocol using cyclohexanone and *β*-nitrostyrene as substrates and benzoic acid as an additive (Scheme 2). However, even after 48 hours of reaction the compound **8a** was formed in less than 5% yield, demonstrating that the conformation adopted by the compounds were probably not ideal to promote the reaction. These results were corroborated by previous reports,[6] which showed that systems containing a carbonyl moiety as linker between thiourea and pyrrolidine portions were inefficient as Michael catalysts.



Scheme 2. Application of compounds 1 and 2 as catalysts in Michael addition.

Another report, by Tang *et al.*[7] presented a new catalyst with a methylene group as the linker and a substituted aromatic ring. This catalyst promoted the Michael addition with excellent yields and stereoselectivity. With this in mind, we redesigned our synthetic route to obtain compound **3** in order to investigate the role of the thiazolidine cycle in this type of catalyst. The methylene moiety was obtained through a borane-dimethylsulfide reduction of the protected compound **9**. After tosylation of the alcohol group and a nucleophilic substitution with sodium azide, a Staudinger

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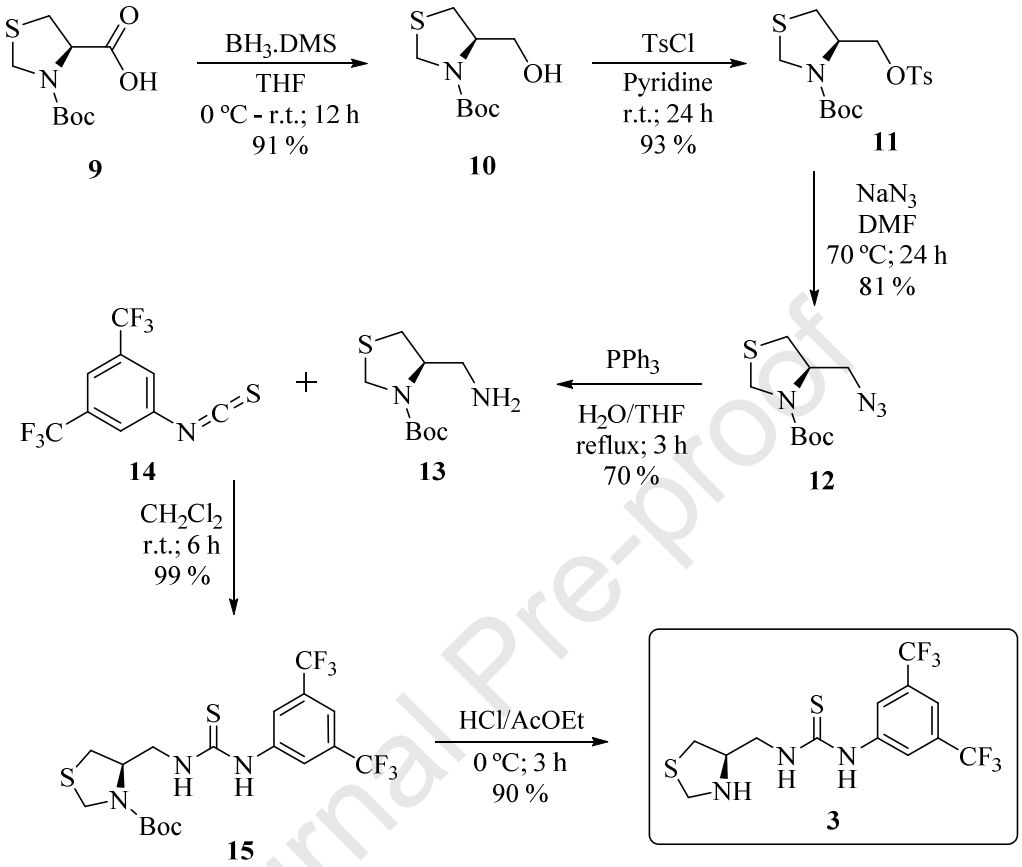
protocol was performed to generate compound **13**. The primary amine group was then reacted with isothiocyanate **14**, and the removal of the Boc group with HCl led to the potential catalyst **3** with high overall yield.



Scheme 3. Synthetic route to prepare compound **3**.

Catalyst **3** was then tested in the Michael addition reaction using the same conditions applied previously. After 72 hours of reaction, the product was obtained with yield of 70% and excellent stereoselectivity (Table 1, entry 1). This result indicates that the insertion of a more flexible link between the two catalytic sites can dramatically improve the catalytic activity of the compound, probably because more effective conformations are allowed. Moreover, the addition of electron withdrawing substituents in the phenyl ring can increase the acidity of the hydrogens in the thiourea portion, improving the efficiency of the hydrogen-bond catalysis.

Other additives were also tested (Table 1, entries 2-5) and butyric acid presented an improvement in the catalytic system. But in terms of yield and stereoselectivity, none of them presented better results than benzoic acid. When both catalyst and additive loads were increased to 20 mol%, the yield was improved and both enantiomeric excess and diastereomeric ratio were not influenced (entry 6). Interestingly, when only the catalyst load was increased, the reaction yield

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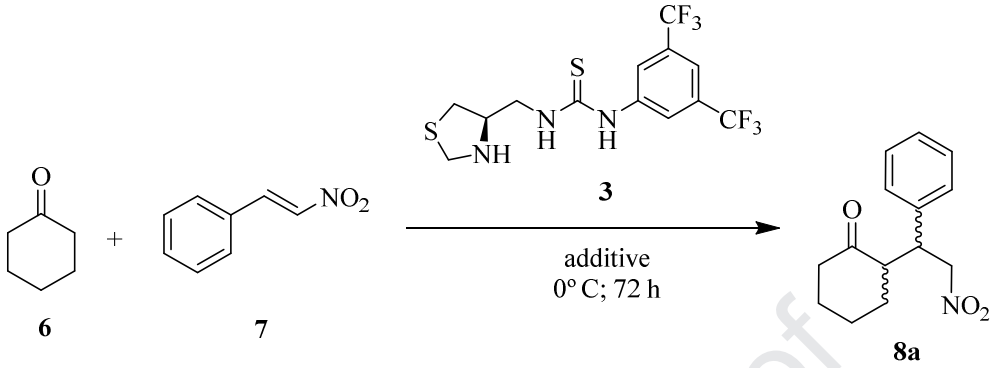
dropped considerably, and when only 5 mol% of additives was added there was no product formation. The same was observed for the reaction performed without additive.

Table 1. Screening of additives and load of catalyst in the Michael addition catalysed by **3**.



Entry	Catalyst 3 (mol%)	Additive	Additive (mol %)	Yield[b] (%)	*d.r.*[c]	*e.e.*[d] (%)
1	10	Benzoic acid	10	70	96:4	97
2	10	Butyric acid	10	21	92:8	97
3	10	Acetic acid	10	49	91:9	96
4	10	Trifluoroacetic acid	10	50	96:4	97
5	10	*p*-Nitrobenzoic acid	10	55	95:5	95
6	20	Benzoic acid	20	80	96:4	97
7	20	Benzoic acid	10	15	96:4	97
8	20	Benzoic acid	5	-	-	-
9	20	Benzoic acid	-	-	-	-

[a] The reactions were performed using cyclohexanone (10 mmol; 0.5 mL), catalyst **3**, additive and *β*-nitrostyrene (0.25 mmol); [b] Yield of isolated product; [c] Determined by ^{1}H NMR spectroscopy; [d] Determined by HPLC analysis using a chiral stationary phase.

An optimization of the reaction conditions, such as solvent, temperature and time, was also realized. Solvents with hydrogen bond acceptors in their structures, such as THF, methanol and DMF, can interact with the thiourea moiety of the catalyst and deactivate it. These interactions can explain the absence of product when all of these solvents were used in the reaction (Table 2, entries 1-3). When an apolar solvent was used (Table 2, entry 4), high stereoselectivity was still obtained, but the yield decreased to 21%. Brine was also tested as a solvent, based on several reports that it was capable of creating a better environment to catalysis due to salting-out effect,[4,8] but the results for both the yield and stereoselectivity were lower than in the neat medium (Table 2, entry 5).

An increase in the reaction yield without loss of stereoselectivity was observed with the passage of time. However, after 72 hours of reaction, the increase in yield was almost insignificant.

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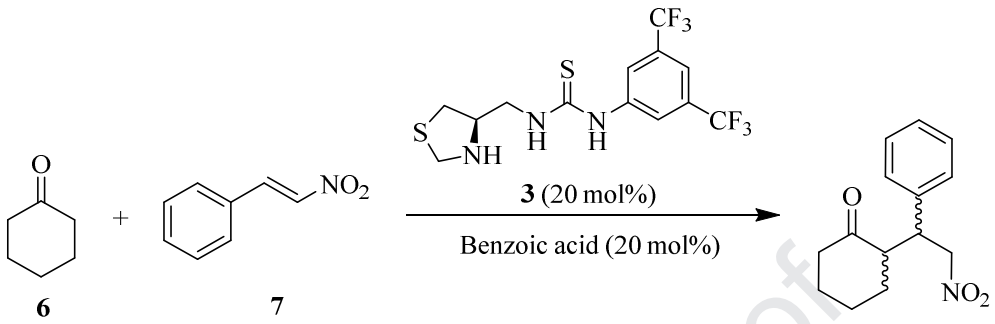
In an effort to reach higher selectivity, a reaction was performed at -10 ºC, but the yield dropped to 51%, while at 20 ºC the stereoselectivity was affected (Table 2, entries 7-12).

Table 2. Optimization of time, solvent and temperature in the Michael addition reaction catalysed by **3**.



6 **7** **8a**

Entry	Time (h)	Solvent	Temperature (ºC)	Yield[b] (%)	*d.r.*[c]	*e.e.*[d] (%)
1	72	THF	0	-	-	-
2	72	DMF	0	-	-	-
3	72	Methanol	0	-	-	-
4	72	Toluene	0	21	96:4	97
5	72	Brine	0	62	90:10	78
6	72	Neat	0	80	96:4	97
7	12	Neat	0	trace	-	-
8	24	Neat	0	15	96:4	97
9	48	Neat	0	56	96:4	97
10	96	Neat	0	83	96:4	97
11	72	Neat	-10	51	96:4	97
12	72	Neat	20	74	90:10	75

[a] The reactions were performed using cyclohexanone (10 mmol; 0.5 mL), catalyst **3** (0.05 mmol), benzoic acid (0.05 mmol), and *β*-nitrostyrene (0.25 mmol); [b] Yield of isolated product; [c] Determined by ^{1}H NMR spectroscopy; [d] Determined by HPLC analysis using a chiral stationary phase.

With the optimized conditions in hand, different ketones and nitroolefins were submitted to the catalysed reaction (Table 3). When a five-membered cyclic ketone was used (Table 3, entry 2), both diastereo- and enantioselectivities decreased. Lower enantioselectivity was also observed when acetone was used as the Michael donor (Table 3, entry 3). These results are explainable by the

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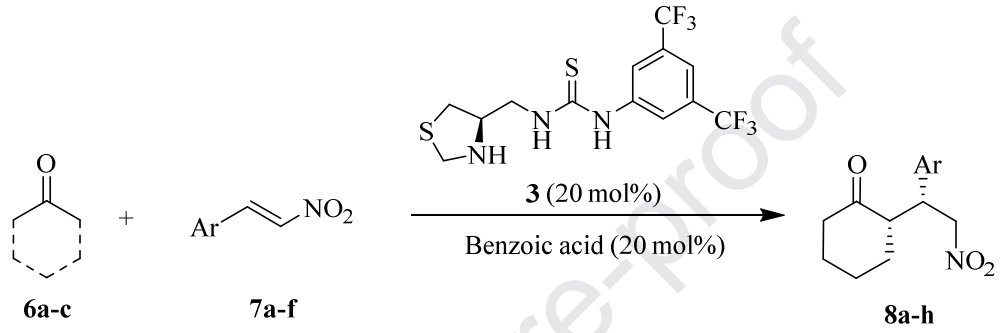
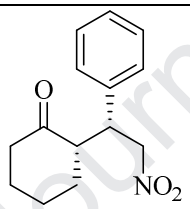
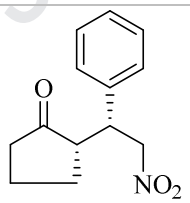
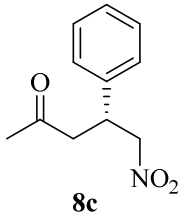
higher stability presented by the enamine derived from cyclohexanone, giving it better stereochemistry control. When electron-rich aromatic systems were used as olefin substituents (Table 3, entries 4 and 5), good yields and stereoselectivities were obtained, especially for the thiophenyl group. Electron-withdrawing groups in all ring positions were tolerated (Table 3, entries 6-8), and in the case of the *p*-bromophenyl substituent, only one of the four possible stereoisomers was observed. Even when the highly reactive *m*-nitrophenyl-substituted olefin was employed the product could be obtained in good enantio- and diastereoselectivity.

Table 3. Scope of different ketones and nitroolefins in the catalysed Michael addition.



6a-c **7a-f** **8a-h**

Entry	Product	Yield[b] (%)	*r.d.*[c] (syn:anti)	*e.e.*[d] (%)
1	 **8a**	80	96:4	97 (*syn*)
2	 **8b**	52	85:15	76 (*syn*) : 64 *(anti)*
3	 **8c**	75	-	69

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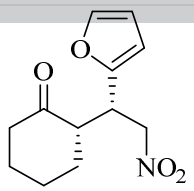
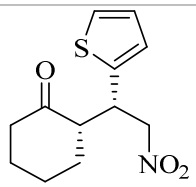
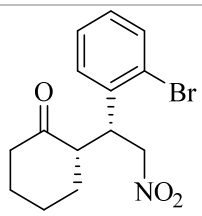
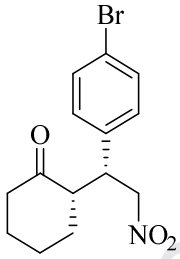
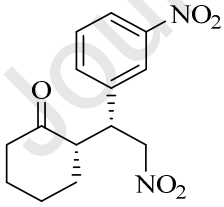
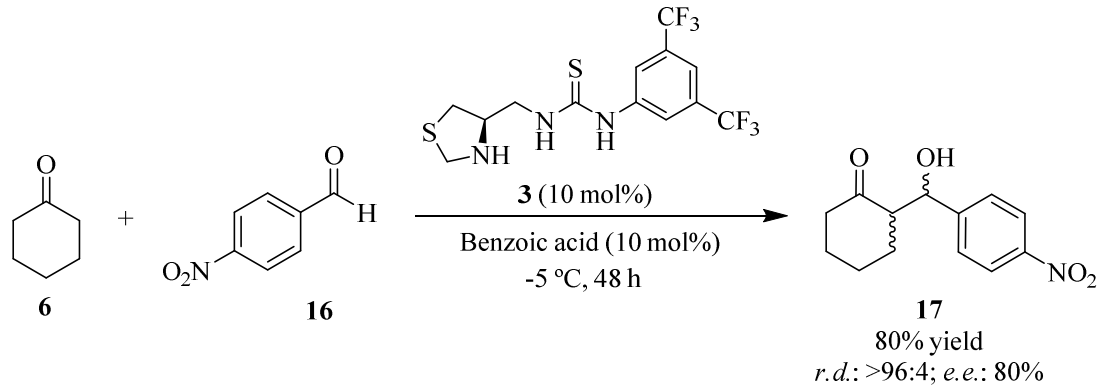
4	 **8d**	82	95:5	76 (*syn)*
5	 **8e**	85	95:5	96 *(*syn)
6	 **8f**	76	>99:1	96 *(syn)*
7	 **8g**	81	>99:1	99 *(syn)*
8	 **8h**	77	93:7	90 *(syn)*

[a] The reactions were performed using ketone (10 mmol; 0.5 mL), catalyst **3** (0.05 mmol), benzoic acid (0.05 mmol), and olefin (0.25 mmol); [b] Yield of isolated product; [c] Determined by ^{1}H NMR spectroscopy; [d] Determined by HPLC analysis using a chiral stationary phase.

To demonstrate the catalyst versatility, compound **3** was also employed in the aldol asymmetric reaction between cyclohexanone and *p*-nitrobenzaldehyde (Scheme 4). When 10 mol% of catalyst was used along with 10 mol% of benzoic acid, the product could be obtained in 80% yield, excellent *anti* selectivity of >96:4, and good enantiomeric excess of 80%. Previously synthesized compounds **1** and **2** were also applied in this reaction but could not afford the aldol product.



Scheme 4. Aldol asymmetric reaction catalysed by **3**.

The influence of a carbonyl group in the catalytic efficiency of the synthesized compounds was investigated through DFT calculations (Figure 2) using the Gaussian 03 program package (B3LYP/6-31G(d) basis set; solvent was accounted for using the PCM method). Conformational studies were realized to evaluate the spatial arrangement of compounds **1** and **3** in the cyclohexanone medium. The minimum energy conformers calculated for the two compounds are shown in Figure 1. It can be easily noted that the carbonyl group present in catalyst **1** leads to a more planar structure, in which thiazolidine and thiourea moieties are parallel to each other. This conformation does not provide a good approximation of the reaction substrates, which could explain the inefficiency of the compound in Michael and aldol tests. Even if the compound was capable of promoting the reaction, it is not possible to observe any steric or electronic hindrance to induce stereocontrol in the formed product. In the proposed conformation for compound **3**, the N-H bonds of the thiourea portion are parallel, and thiazolidine is displaced from the molecule plane. This calculation suggests a better conformation for accomplishing the reaction, because the two substrates can be oriented by the bifunctional catalyst in one favoured disposition.

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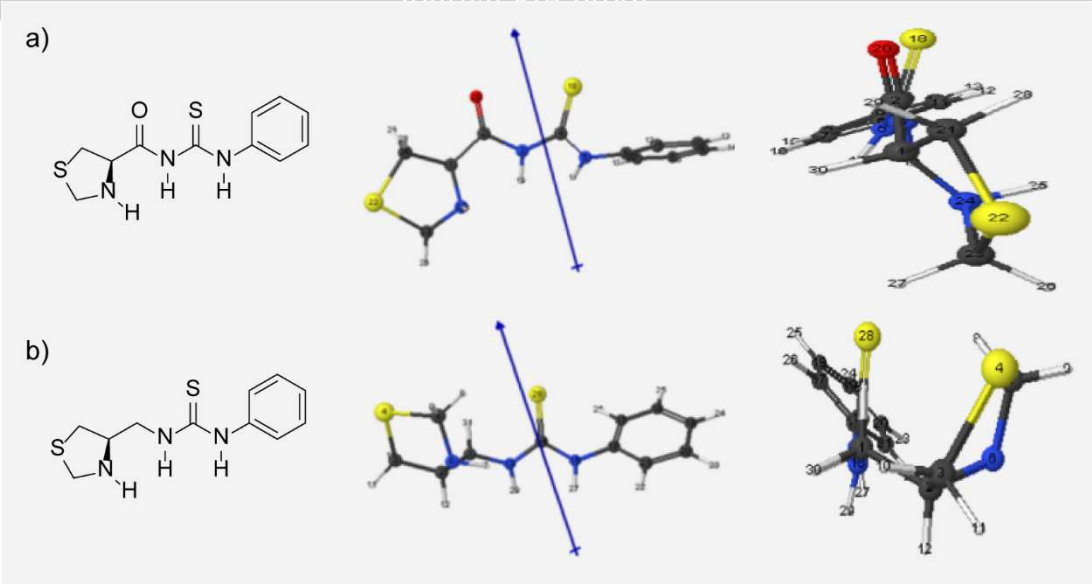
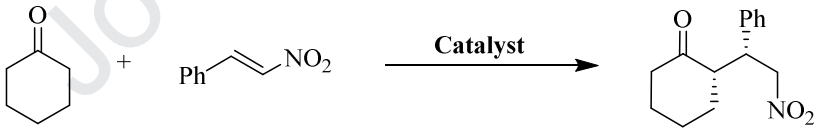


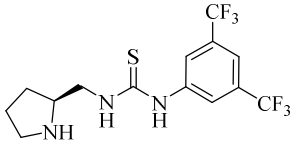
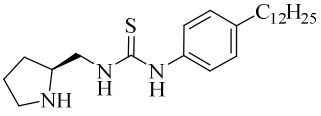
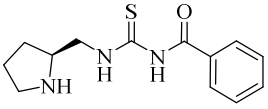
Figure 2. DFT-calculated minimum energy conformers calculated for compounds a) **1** and b) **3**.

Since Tang's catalyst,[7] several bifunctional catalysts containing the pyrrolidine and thiourea moieties were reported in the literature, presenting outstanding performance in asymmetric catalysis (Table 4). These reports can reassure the importance of the union of amine and hydrogen bond catalysis, since the results are strongly related to the catalysts structures. Our proposed bifunctional catalyst (Table 4, entry 7), based on previous results of our research group,[4] that incorporates a thiazolidine moiety in the structure, produced comparable or even better results than the catalysts mentioned in the asymmetric Michael addition.

Table 4. Different catalysts employed in the asymmetric Michael reaction in the last years.



6a **7a** **8a**

Entry	Catalyst	Time (h)	Yield (%)	*d.r.* (syn:anti)	*e.e.* (%)	Ref.
1		38	93	96:4	90	[7]
2		8	91	100:00	92	[9]
3		12	92	99:1	94	[10]

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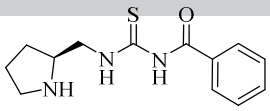
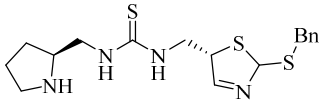
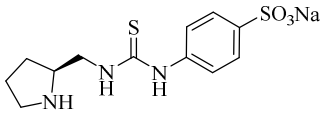
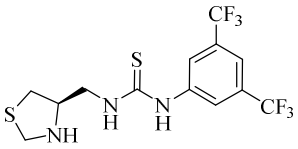
4		15	92	98:2	98	[11]
5		48	72	99:1	95%	[12]
6		60	86	97:3	90	[13]
7		48	80	96:4	97	Our catalyst

Conclusions

Three different methodologies were developed to synthesize bifunctional catalysts containing thiazolidine and thiourea groups in their structures. A versatile protocol was developed to catalyse Michael additions between cyclic or aliphatic ketones and aromatic aldehydes, yielding products with high stereocontrol. The same catalyst could be employed to efficiently catalyse asymmetric aldol reactions. The presence of a more flexible methylene group as a linker between the two catalytic portions was proved necessary, because the compounds containing carbonyl groups in the linker were not able to provide the product. This inability could be explained by conformational studies of compounds **1** and **3**, which showed the different dispositions created by the presence or absence of a carbonyl group. The importance of flexibility in the structure to lead the catalyst to a more convenient conformation is then highlighted.

Experimental Section

The ^{1}H NMR, ^{13}C NMR, 2D-COSY NMR and 2D-HMQC NMR spectra were recorded on 300 MHz spectrometers Varian Inova 300 and Varian VNMRS 300. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. All enantiomeric excesses were obtained from HPLC using chiral stationary phase in a Shimadzu LC-20AT chromatograph. Optical rotations were obtained in a Perkin Elmer Polarimeter 341. Infrared spectra were obtained in a Varian 640-IR spectrometer. All of the column chromatography separations were done using silica gel Fluka, 100-200 Mesh. Solvents were purified by the usual methods. Other reagents were obtained from commercial source and used without further purification. The organic extracts were dried over anhydrous sodium sulfate. Evaporation of solvent was performed under reduced pressure.

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***(R)*-*N*-(Phenylcarbamothioyl)thiazolidine-4-carboxamide (1)**

In a 50 mL two-neck round bottom flask, equipped with a Dean-Stark trap and a condenser, compound **4** (2.0 mmol) was added over toluene (10 mL). Then, boric acid (0.9 mmol, 0.055 g) and 1-phenylthiourea (2.2 mmol, 0.334 g) were added and the reaction was heated up to 120 ºC under strong stirring. The reaction became homogeneous after it reached reflux temperature. The reaction was monitored by TLC until complete consumption of the starting material was completed (12 h). An azeotropic distillation was performed under reduced pressure using methanol to remove toluene and then the mixture was diluted with ethyl acetate (30 mL) and washed with HCl 10 % (v/v) solution (2 x 20 mL). The residue was submitted to purification by column chromatography using a 70:30 hexane:ethyl acetate solution as eluent. A white solid was obtained as the product. Yield: 51%. M.P. = 180-183 ºC. $[\alpha]_D^{20}$ = -24 (c 1, CH_2Cl_2). FTIR (ATR): 3500 cm^{-1}, 1567 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.54-7.42 (m, 3H); 7.50-7.38 (m, 2H); 5.43 (d, 1H, *J* = 9.3 Hz); 4.65 (dd, 1H, *J* = 9.0 Hz); 4.51 (d, 1H, *J* = 9.6 Hz); 3.39 (dd, 1H, *J* = 12.0 Hz; 6.9 Hz); 3.17 (dd, 1H, *J* = 9.0 Hz; 8.3 Hz); 1.25 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 185.1; 170.5; 132.8; 129.3; 129.1; 66.3; 49.9; 31.1. HRMS calcd. for $(M+K)^+$ 306.0500, found 307.0201.

***(R)*-N-phenyl-2-(thiazolidine-4-carbonyl) hydrazinecarbothioamide (2)**

In a 50 mL round-bottom flask containing methanol the reagents were added in the following order: compound **5** (5.0 mmol, 0.576 g), hydrazine monohydrate (5.0 mmol, 0.15 mL), phenyl isothiocyanate (5.0 mmol, 0.9 mL). Catalytic acetic acid was added, and the mixture was heated to reflux (90 ºC) under magnetic stirring. The reaction was monitored by TLC and finished in 6 h. The white solid product was obtained after filtration from the crude reaction and washed with cold methanol. Yield: 35%. M.P. = 203-206 ºC. $[\alpha]_D^{20}$ = -3 (c 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.54-7.42 (m, 3H); 7.50-7.38 (m, 2H); 5.42 (d, 1H, *J* = 9.3 Hz); 4.64 (dd, 1H, *J* = 9.1 Hz); 4.53 (d, 1H, *J* = 9.6 Hz); 3.35 (dd, 1H, *J* = 12.0 Hz; 6.9 Hz); 3.19 (dd, 1H, *J* = 9.0 Hz; 8.3 Hz); 1.23 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 185.1; 170.5; 132.8; 129.3; 129.1; 66.3; 49.9; 31.1. HRMS: calcd. for $(M+2H)^{2+}/2$ 142.0300, found 142.0309.

(*R*)-tert-butyl 4-((3-(3,5-bis(trifluoromethyl)phenyl)thioureido)methyl)thiazolidine-3-carboxylate (15)

In a 10 mL one-neck round bottom flask containing dichloromethane (10 mL) at 0 ºC, compound **13** (1.1 mmol, 0.131 g) and the isothiocyanate **14** (1.2 mmol, 0.25 mL) were added. The reaction was stirred under room temperature for 2-3 hours until consumption of starting material was completed. Then, the solution was concentrated under reduced pressure and the residue was purified with column chromatography using as eluent a mixture 80:20 (hexane: ethyl acetate), affording a white crystalline solid. Yield: 99%. M.P.: 140 ºC. $[\alpha]_D^{20}$ = +35° (c 1, CH_2Cl_2). ^{1}H NMR (300 MHz,

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$CDCl_3$) δ: 8.38 (s, 1H); 7.58 (s, 2H); 4.24 (d, 2H, *J* = 7.2 Hz); 3.67 (m, 2H); 3.17 (d, 1H, *J* = 5.41 Hz); 2.81 (d, 1H, *J* = 10.0 Hz); 1.40 (s, 9H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 179.1; 154.7; 141.0; 131.7; 128.5; 124.9; 123.5; 121.3; 118.1; 82.6; 59.6; 48.6; 46.4; 34.9; 28.1.

1-(3,5-bis(trifluoromethyl)phenyl)-3-(((*R*)-thiazolidin-4-yl)methyl)thiourea) (3)

In a round bottom flask containing compound **15** (0.32 mmol, 0.156 g), a solution of HCl 3M in ethyl acetate (8 mL) was added. The reaction was stirred at 0 ºC for 1h. After, $NaHCO_{3(sat)}$ solution was added until pH 6-7. The solution was extracted with dichloromethane (3 x 20 mL). The organic phase was dried over Na_2SO_4, filtered and the solvent was evaporated. The product was afforded as a white crystal solid. Yield: 90%. M.P.: 112-114 ºC. $[\alpha]_D^{20}$ = + 43° (c 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.00 (s, 1H); 7.70 (s, 2H); 7.60 (s, 1H); 7.10 (s, 1H); 4.08-3.95 (m, 3H); 3.71 (s, 1H); 3.30 (m, 1H); 2.98 (m, 1H); 2.62 (m, 1H); 2.20 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 180.1; 139.3; 132.4; 124.1; 123.2; 121.4; 118.9; 62.9; 52.5; 46.0; 36.1. HRMS (ESI) calcd. for $(M+H)^+$ 390.0533, found 390.0525.

General procedure for organocatalytic asymmetric Michael reaction

In a round bottom flask containing the solvent, the ketone (5 mmol), catalyst **3** (0.05 mmol, 0.020 g) and additive were added and stirred at 0 °C for 30 min. After this, the nitroolefin (0.25 mmol) was added and the reaction was stirred for the desired time at the specified temperature. Then it was treated with $NH_4Cl_{(sat)}$ solution (10 mL) and the aqueous phase was extracted with dichloromethane (2 x 15 mL). The organic phase was dried over Na_2SO_4, filtered and the solvent was evaporated. The residue was purified through column chromatography using as eluent an 80:20 mixture of hexane:ethyl acetate as eluent.

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