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# Synthesis of New 5-Aryl-1,3,4-Oxadiazol-Thioureas and Oxadiazol-Thioxopyrimidinones Derivatives of Monoterpenes and Evaluation of their Catalytic Efficiency for Strecker-type and Epoxide Ring Opening Reactions

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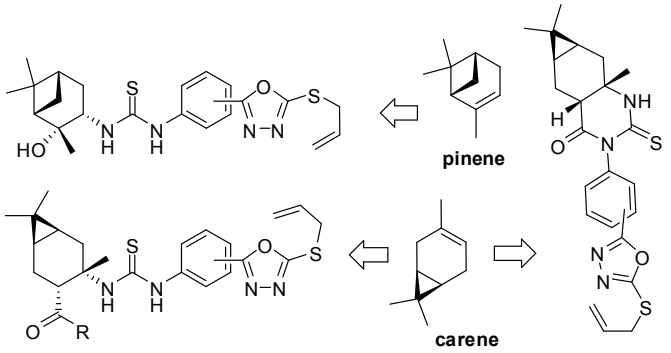
**Graphical Abstract**




**Abstract**: New and easily accessible oxadiazol-thioureas **8-11**, **12, 13** and oxadiazol-thioxopyrimidinones **14, 15** have been successfully synthesized and applied as organocatalysts in the selected Strecker-type and epoxide ring opening reactions. It has been demonstrated that oxadiazol-thioureas (**8**, **9**, **11** and **12**) and oxadiazol-thioxopyrimidinones (**14** and **15**) are significantly more active in the epoxide ring opening than in the Strecker-type reaction. These results provide insights in the future design and development of highly active and enantioselective thiourea-based organocatalysts for the selected reaction types.

**Keywords**: bifunctional organocatalyst, (+)-3-carene, (+)-α-pinene, 5-aryl-1,3,4-oxadiazoles.

## 1. Introduction

The synthesis of optically active compounds through asymmetric catalysis with chiral bifunctional compounds is an important and rapidly growing area of modern synthetic organic chemistry[1,2]. Cooperative catalysis with chiral thiourea-based bifunctional molecules has recently been recognized as a new and exciting strategy in asymmetric organocatalysis[3]. In particular, impressive progress has been made in the development of highly enantioselective secondary and tertiary amine-thiourea bifunctional organocatalysts for a diverse range of reactions[4].

On the other hand, monoterpene-derived amines are readily accessible[5a-e] and could easily be converted to chiral thioureas and thioxopyrimidinones as well[5d,e]. These subjects encouraged us to incorporate monoterpene auxiliaries with 1,3,4-oxadiazols functionality, which could be potentially copolymerized with natural monoterpenes[6a-c] to simplify the catalytic (if active) recovery.

This encouraged us to synthesize and investigate the potential of the new oxadiazol-thioureas **8-11**, **12, 13** and oxadiazol-thioxopyrimidinones **14, 15** as possible organocatalytic motifs for Strecker-type and epoxide ring opening reactions.

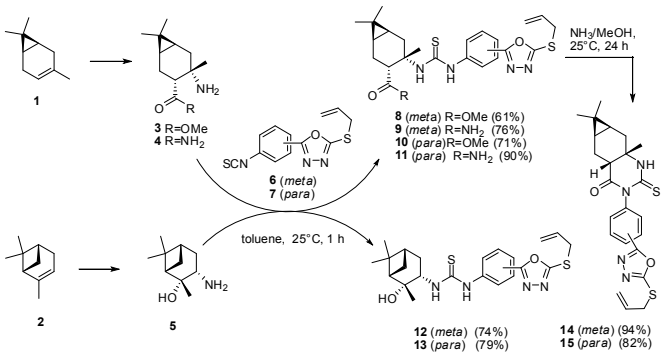
## 2. Results and Discussion

### 2.1. *Synthesis of New 5-Aryl-1,3,4-Oxadiazol-Thioureas and Oxadiazol-Thioxopyrimidinones Catalysts*

The synthesis of new oxadiazol-thioureas **8-11**, **12, 13** and oxadiazol-thioxopyrimidinones **14, 15** was accomplished as summarized in Scheme 1.

The isothiocyanates **6** and **7** were prepared by treatment of known mercaptans[7] with allyl bromide analogously to a published method[8].

The (+)-3-carene **1** *via* known amines **3** and **4** [5b-d] were converted to the corresponding 5-aryl-[1,3,4]oxadiazolthioureas **8-11** with the isothiocyanatosulfides (**6** and **7)** with good yields. Using a similar method, [1,3,4]oxadiazolthioureas **12** and **13** were also synthesized from (+)-α-pinene **2** *via* amine **5**. Next, the thioureaesters (**8** and **10)** were converted into the 2-thioxo-4-pyrimidinones (**14** and **15)** by a $NH_3$/MeOH catalyzed cyclization procedure.

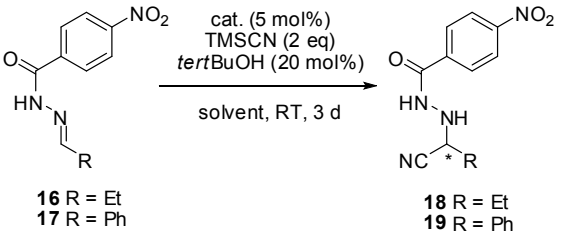



**Scheme 1.** Synthesis of oxadiazol-thioureas and oxadiazol-thioxopyrimidinones organocatalysts.

### *2.2. Application of New Catalysts in Strecker-type and Epoxide ring Opening Reactions*

The catalytic properties of different oxadiazol-thioureas **8-11**, **12, 13** and oxadiazol-thioxopyrimidinones **14, 15** were examined in the known Strecker-type[9] and cyclohexene oxide opening[10] reactions. As a first model of transformation, we studied the Strecker-type reaction (Scheme 2) of hydrazone (**16)** with TMSCN, in the presence of 5% mol of oxadiazol-thioureas (**8-11, 12, 13),** with oxadiazol-thioxopyrimidinones **(14, 15)** as chiral catalysts, and with *tert*-butanol.

We also studied the solvents effect on chemical yield and selectivity of the reaction. With this aim, the transformation was carried out in three different solvents: toluene, $CH_2Cl_2$ and MeOH. The reaction proceeded for 3 days at room temperature. The products were separated chromatographically on $SiO_2$ columns.




**Scheme 2.** Strecker-type reaction.

Oxadiazol-thioureas catalysts **8, 9, 10, 12** and **13** showed negative results as no conversion was observed in all the solvents. It is important to note that catalyst **11** was the only compound from oxadiazol-thioureas row, which afforded the formation of the product in good yields. The conversion and, as a consequence, the yield of the target product was considerably improved from 50% to 74% in the presence of this catalyst (Table 1, entry 1). Preliminary results were also not promising for oxadiazol-thioxopyrimidinone **14**. It turned out to be completely inactive when the reaction was carried out in $CH_2Cl_2$. However, this catalyst showed reactivity when toluene and MeOH were used as solvents, affording 30% and 16% yields respectively (Table 1, entry 2). Oxadiazol-thioxopyrimidinone **15** was active in the chosen reaction in all solvents, though the target product (**18**) was isolated in low yields ranging from 13% to 21 % (Table 1, entry 3).

The results are shown in Table 1.

**Table 1.** Screening of solvents in the Strecker-type reaction (Scheme 2), catalyzed by oxadiazol-thiourea **11** and oxadiazol-thioxopyrimidinones **14, 15.**

| Entry | Catalyst [a] | Yield of **18** [%][b] | | |
|---|---|---|---|---|
| | | Toluene | $CH_2Cl_2$ | MeOH |
| 1 | **11** | 50 | 66 | 74 |
| 2 | **14** | 30 | - | 16 |
| 3 | **15** | 21 | 13 | 15 |

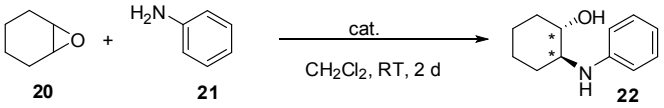
[a]No reaction was observed in the presence of 10% mol of thioureas **8, 9, 10, 12, 13**. [b]Yield of isolated product after column chromatography on $SiO_2$.

Regarding the stereochemistry of this model reaction, no influence of the catalyst's chirality was observed, as all products were obtained in racemic form. From these results, hydrazones having other functional groups could be applied to this reaction and we expected to obtain enantio-enriched amines **19** under these reaction conditions. However, under similar conditions no conversion in all cases of the sterically more hindered derivative **17** was observed.

We expected that a mechanism for oxadiazol-thioureas catalyzed imine hydrocyanation would be similar to that reported by Jacobsen et al.[11] and would involve formation of

an iminium/cyanide ion pair that is bound to catalyst through multiple noncovalent interactions. However, our studies have shown that, for a Strecker-type reaction, not only the electronic features of the thiourea catalyst but also the solvents have a profound effect on the outcome of the reaction. Such as the outcome, a less reactive substrate (**8, 9, 10, 12** and **13)** would not achieve better results.

As a next model reaction, the epoxide ring opening of cyclohexene oxide (**20**) with aniline (**21**) in $CH_2Cl_2$ (Scheme 3) in the presence of 10 mol% of the catalysts **8–11, 12-15** was investigated. The reaction proceeded in 2 days at room temperature. The products were separated chromatographically on $SiO_2$ columns.




**Scheme 3.** Epoxide ring opening reaction.

Oxadiazol-thiourea **10** was the first catalyst evaluated in this reaction. Unfortunately it showed very low reactivity and the yield of target product was 4% (Table 2, entry 3).

The application of N-formyl-L-proline as an organocatalyst for the epoxide ring opening reaction was reported in 2010[10]. With the aim to increase the yield of the product we additionally employed 5 mol% of *N*-formyl-(*S*)-proline in further experiments. Fortunately, *N*-formyl-(*S*)-proline (5 mol%) in combination with oxadiazol-thioureas **8, 9, 11, 12** as cocatalyst afforded the corresponding amino-alcohol **22** in 80, 74, 79, 73% yield (Table 2, entry 1, 2, 4, 5) and 81% yield with oxadiazol-thioxopyrimidinones **14** and **15** (Table 2, entry 7, 8). The lowest result concerning reactivity was obtained in the case of oxadiazol-thiourea **13,** with 30% yield (Table 2, entry 6).

As we highlighted in Scheme 3, in this model reaction, the *trans*-configured amino-alcohol **22** was obtained as a racemic mixture in all cases.

The results are summarized in Table 2.

## Conclusions

The effect of the new 5-aryl-1,3,4-oxadiazol-thioureas and oxadiazol-thioxopyrimidinones derivatives of (+)-3-carene and (+)-α-pinene in the Strecker-type and epoxide ring opening reactions was studied. In the cases of oxadiazol-thioxopyrimidinones or oxadiazol-thioureas, good conversions (up to 74% or 81%) but low enantio-selectivities were obtained. It is reasonable to speculate that the reaction mechanism involves unexpected initial hydrogen-bonding interactions of the C=N group of oxadiazol instead of thioureas or thioxopyrimidinones group of catalysts with hydrazone or cyclohexene oxide core to yield the corresponding intermediate, which is then trapped by different-type reaction with TMSCN or aniline.

**Table 2.** Screening of the epoxide ring opening reaction (Scheme 3) catalyzed by oxadiazol-thioureas **8-11, 12, 13** and oxadiazol-thioxopyrimidinones **14**, **15**.

| Entry | Catalyst | Yield of **22** [%][a] |
|---|---|---|
| 1 | **8** | 80 |
| 2 | **9** | 74 |
| 3 | **10** | 4 |
| 4 | **11** | 79 |
| 5 | **12** | 73 |
| 6 | **13** | 30 |
| 7 | **14** | 81 |
| 8 | **15** | 81 |

[a]Yield of isolated product after column chromatography on $SiO_2$.

These experiments show that, on its own, the Lewis basic bifunctional group in **8, 9, 11-15** is not able to facilitate the reaction with a good yield, and thus, the prerequisite for high yield is that the catalyst possess both a formamide group and a carboxylic moiety of *N*-formyl-(*S*)-proline. Direct activation of imine by the thiourea was proposed earlier[2,11]. Our data are consistent with a mechanism involving on the weakness of the system. For example, the non-covalent interactions mismatching. However, we believe that the good chirality induced by novel derivatives of 5-aryl-1,3,4-oxadiazol should involve multiple noncovalent interactions including hydrogen-bonding interactions of the C=N group as well as NH or $NH_2$ group of chiral core such type of bifunctional organocatalyst for creating a chiral pocket which influences the selectivity. Tracer experiments to clarify the mechanisms and further studies on the reactivity of novel 5-aryl-1,3,4-oxadiazol-thioureas as organocatalysts are in progress.

## 3. Experimental

### 3.1 General

Solvents and reagents were purchased from Aldrich (Germany), Across (Belgium) Lancaster (Great Britain), dried and distilled prior to use. Glassware dried in an oven and reaction conducted under $N_2$ atmosphere. Thin-layer chromatography was carried out on Merck aluminum sheets, silica gel 60 $F_{254}$. Column chromatography was performed on Fluka silica gel 60, 70–230 mesh. Melting points were determined on a Boëtius melting point apparatus (PHMK, VEB Wägetechnik Rapido, Radebeul, Germany) and are uncorrected. IR spectra were acquired on apparatus "Perkin-

Elmer Spectrum 100 FTIR". $^{1}H$ and $^{13}C$ NMR spectra have been recorded for DMSO-$d_6$ or $CDCl_3$ 2-% solution on a "Bruker -Avance III" (400.13 and 100.61 MHz). Chemical shifts δ are given in ppm referring to the signal center using the solvent peaks. The specific rotation has been recorded on "Jasco-P-2000" in $CHCl_3$. Enantiomeric excess of the products was determined by chiral HPLC analysis in comparison with reliable racemic material. Chiral HPLC measurements were performed using the Agilent 1200 Series enginery: Vacuum Degasser G1322-90010, Quaternary Pump G1311-90010, Thermostated Column Compartment G1316-90010, Diode Array and Multiple Wavelength Detector SL G1315-90012, Standard and Preparative Autosampler G1329-90020 and Agilent Chemstation for evaluation of the chromatographic runs. Compartment G1316-90010, Diode Array and Multiple Wavelength Detector SL G1315-90012, Standard and Preparative Autosampler G1329-90020 and Agilent Chemstation for evaluation of the chromatographic runs.

### 3.2. *2-Allylsulfanyl-5-(3-isothiocyanatophenyl)-[1,3,4]oxadiazole (6)*

To 5-(3-isothiocyanato-phenyl)-1,3,4-oxadiazole-2-thiol[7] (1.000 g, 4.25 mmol, 1.0 eq) and triethylamine (0.430 g, 0.589 ml, 4.25 mmol, 1.0 eq) in acetone (20 ml) was added a solution of allyl bromide (0.514 g, 0.367 ml, 4.25 mmol) in acetone (5 ml). The reaction mixture was stirred for 2 h at ambient temperature, the solvent was evaporated, the residue was dissolved in chloroform, then washed with water and dried over $Na_2SO_4$. The chloroform was evaporated under reduced pressure and the precipitate obtained was washed with small amount of acetone resulting in **6** (1.000 g, 3.63 mmol, 85 %) as a yellow colored solid. Mp: 43-45°C. IR (ν/cm$^{-1}$): 1560 (C=N), 2134 (NCS), 2556 ($SCH_2$). $^{1}H$ NMR (δ ppm, DMSO-$d_6$, 400 MHz): 3.98 (d, *J* = 6.8 Hz, 2H), 5.2 (d, *J* = 10.0 Hz, 1H), 5.39 (d, *J* = 16.8 Hz, 1H), 5.95 - 6.06 (m, 1H), 7.53 - 7.93 (m, 4H). $^{13}C$ NMR (δ ppm, DMSO-$d_6$, 100 MHz): 35.1, 119.7, 123.7, 125.1, 125.7, 129.4, 131.4, 131.9, 132.8, 164.1, 164.3. Anal. Calcd. for $C_{12}H_9N_3OS_2$: C, 52.34; H, 3.29; N, 15.26. Found: C, 52.36; H, 3.32; N, 15.33 %.

### 3.3. *2-Allylsulfanyl-5-(4-isothiocyanatophenyl)-[1,3,4]oxadiazole (7)*

Prepared in analogy to **6** from 5-(4-isothiocyanatophenyl)-1,3,4-oxadiazole-2-thiol[8] (1.000 g, 4.25 mmol, 1.0 eq). After evaporation of the acetone at reduced pressure, the precipitate obtained was washed with water and acetone to give compound **7 (**1.100 g, 3.99 mmol, 94 %) as a white solid. Mp: 119-120°C. IR (ν/cm$^{-1}$): 1603 (C=N), 2108 (NCS), 2566 ($SCH_2$).$^{1}H$ NMR (δ ppm, DMSO-$d_6$, 400 MHz): 3.97 (d, *J* = 6.8 Hz, 2H), 5.19 (d, *J* = 10.4 Hz, 1H), 5.38 (dd, $J_1$ = 1.2 Hz, $J_2$ = 17.2 Hz, 1H), 5.95 - 6.05 (m, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 8.02 (d, *J* = 8.4 Hz, 2H). $^{13}C$ NMR (δ ppm, DMSO-$d_6$, 100 MHz): 35.1, 119.7, 122.4, 127.3, 128.3, 132.9, 133.7, 136.5, 163.9, 164.8. Anal. Calcd. for $C_{12}H_9N_3OS_2$: C, 52.34; H, 3.29; N, 15.26. Found: C, 52.36; H, 3.26; N, 15.28 %.

### 3.4. *Methyl (-)-(1S,3R,4S,6S)-4-{3-[3-(5-allylsulfanyl-[1,3,4]oxadiazol-2-yl)-phenyl]-thioureido}-4,7,7-trimethyl-bicyclo[4.1.0]heptane-3-carboxylate (8)*

Isothiocyanate **6** (0.650 g, 2.36 mmol, 1.0 eq) was added to a solution of amino ester **3** (0.501 g, 2.37 mmol, 1.0 eq) in anhydrous toluene (10 ml). After stirring the reaction mixture for 1 h at room temperature (the reaction was monitored by means of TLC), the solvent was evaporated to dryness and the obtained residue was purified by column chromatography over silica gel ($CH_2Cl_2$), resulting in **8** (0.700 g, 1.44 mmol, 61 %) as a colorless solid. Mp: 92-93 °C. IR (ν/cm$^{-1}$): 1198 ($C(CH_3)_2$), 1188 (C=S), 1362 ($CO_2CH_3$), 1602 (C=N), 2561($SCH_2$), 3088 (C-NH-). $[\alpha]_D^{20}$ = - 3.3 (c = 0.0115). $^{1}H$ NMR (δ ppm, DMSO-$d_6$, 400 MHz): 0.66 (dd, $J_1$ = 9.3 Hz, $J_2$ = 15.0 Hz, 1 H), 0.77 (t, *J* = 8.6 Hz, 1 H), 0.85 - 0.86 (m, 1 H), 0.95 (s, 3 H), 1.06 (s, 3 H), 1.51 (s, 3 H), 1.77 (dd, $J_1$ = 7.9 Hz, $J_2$ = 14.7 Hz, 1 H), 1.94 - 1.95 (m, 1 H), 2.08 - 2.10 (m, 1 H), 3.60 (s, 3 H), 3.94 (d, *J* = 7.2 Hz, 2 H), 4.19 (dd, $J_1$ = 5.4 Hz, $J_2$ = 15.1 Hz, 1 H), 5.21 (d, *J* = 10.1 Hz, 1 H), 5.40 (d, *J* = 17.1 Hz, 1 H), 6.01 - 6.03 (m, 1 H), 7.19 (s, 1 H), 7.48 (t, *J* = 7.9 Hz, 1 H), 7.71 (dd, $J_1$ = 8.8 Hz, $J_2$ = 16.5 Hz, 2 H), 8.02 (s, 1 H), 9.93 (s, 1 H). $^{13}C$ NMR (δ ppm, DMSO-$d_6$, 100 MHz): 15.3, 16.8, 17.3, 18.1, 20.0, 23.4, 27.9, 28.4, 50.4, 51.4, 53.9, 54.6, 119.3, 121.0, 121.8, 123.7, 126.5, 129.3, 132.1, 140.0, 162.9, 165.1, 175.6, 179.4. Anal. Calcd. for $C_{24}H_{30}N_4O_3S_2$: C 59.23; H 6.21; N 11.51; S 13.18. Found: C 58.75; H 5.91; N 11.08; S 12.82 %.

### 3.5. *(-)-(1S,3R,4S,6S)-4-{3-[3-(5-allylsulfanyl-[1,3,4]oxadiazol-2-yl)-phenyl]-thioureido}-4,7,7-trimethyl-bicyclo[4.1.0]heptane-3-carboxamide (9)*

Prepared as a colorless solid in analogy to thiourea **8** by reaction of the amine **4** and the isothiocyanate **6** in 76 % yield. Mp: 166-167°C. IR (ν/cm$^{-1}$): 1193 ($C(CH_3)_2$), 1188 (C=S), 1690 ($CONH_2$), 1608 (C=N), 2561($SCH_2$), 3087 (C-NH-). $[\alpha]_D^{20}$ = - 8.9 (c = 0.0184). $^{1}H$ NMR (δ ppm, $CDCl_3$, 400 MHz): 0.72 - 0.75 (m, 1 H), 0.60 (t, *J* = 8.9 Hz, 1 H), 0.95 (s, 3 H), 0.98 - 1.00 (m, 1 H), 1.07 (s, 3 H), 1.52 (s, 3 H), 1.73 - 1.76 (m, 2 H), 1.98 - 1.99 (m, 1 H), 3.93 (d, *J* = 6.94 Hz, 2 H), 4.20 (s, 2 H), 5.25 (d, *J* = 10.3 Hz, 1 H), 5.41 (d, *J* = 16.5 Hz, 1 H), 5.97 (s, 1 H), 6.01 - 6.03 (m, 1 H), 7.37 (s, 1 H), 7.45 (s, 1 H), 7.35 (t, *J* = 7.8 Hz, 1 H), 7.84 (d, *J* = 7.6 Hz, 1 H), 7.88 (s, 1 H), 8.01 (s, 1 H). $^{13}C$ NMR (δ ppm, $CDCl_3$, 100 MHz): 15.5, 17.2, 17.7, 18.1, 21.2, 23.4, 28.4, 35.2, 50.7, 55.7, 119.9, 122.8, 124.3, 124.8, 128.1, 128.3, 130.5, 131.6, 138.0, 164.1, 165.2, 178.6, 179.7. Anal. Calcd. for $C_{23}H_{29}N_5O_2S_2$: C 58.57; H 6.20; N 14.85; S 13,60. Found: C 58.34; H 6.11; N 14.48; S 13.37 %.

### 3.6. *Methyl (-)-(1S,3R,4S,6S)-4-{3-[4-(5-allylsulfanyl-[1,3,4]oxadiazol-2-yl)-phenyl]-thioureido}-4,7,7-trimethyl-bicyclo[4.1.0]heptane-3-carboxylate (10)*

Prepared as a yellow colored solid in analogy to thiourea **8** by reaction of the amine **3** and the isothiocyanate **7** in 71 % yield. Mp: 136-137°C. IR (ν/cm$^{-1}$): 1191 ($C(CH_3)_2$), 1185 (C=S), 1362 ($CO_2CH_3$), 1602 (C=N), 2561($SCH_2$), 3087 (C-NH-). $[\alpha]_D^{20}$ = - 71.2 (c = 0.019). $^{1}H$ NMR (δ ppm, DMSO-$d_6$, 400 MHz): 0.68 (t, *J* = 8.7 Hz, 1 H), 0.81 - 0.83 (m, 1 H), 0.94 (s, 3 H), 1.04 (s, 3 H), 1.52 (s, 3 H), 1.79 (dd, $J_1$ = 7.8 Hz, $J_2$ = 14.6 Hz, 1 H), 1.96 - 1.97 (m, 1 H), 2.13 - 2.14 (m, 1 H), 3.64 (s, 3 H), 3.92 (d, *J* = 7.2 Hz, 2 H), 4.16 (dd, $J_1$ = 5.2 Hz, $J_2$ = 15.0 Hz, 1 H), 5.20 (d, *J* = 10.2 Hz, 1 H), 5.39 (d, *J*

= 16.8 Hz, 1 H), 5.47 (s, 1 H), 5.99 - 6.02 (m, 1 H), 7.26 (s, 1 H), 7.68 (d, *J* = 8.8 Hz, 2 H), 7.90 (d, J = 8.8 Hz, 2 H), 10.04 (s, 1 H). $^{13}$C NMR (δ ppm, $CDCl_3$, 100 MHz): 15.2, 17.2, 17.8, 18.1, 20.9, 23.4, 27.0, 28.5, 35.3, 50.3, 52.0, 55.8, 119.9, 121.3, 124.3, 126.4, 128.3, 131.7, 139.8, 163.9, 165.3, 176.8, 179.5, 193.1. Anal. Calcd. for $C_{24}H_{30}N_4O_3S_2$: C 59.23; H 6.21; N 11.51; S 13,18. Found: C 58.64; H 5.95; N 11.21; S 12.74 %.

### 3.7.*(-)-(1S,3R,4S,6S)-4-{3-[4-(5-allylsulfanyl-[1,3,4]oxadiazol-2-yl)-phenyl]-thioureido}-4,7,7-trimethyl-bicyclo[4.1.0]heptane-3-carboxamide (11)*

Prepared as a white solid in analogy to thiourea **8** by reaction of the amine **4** and the isothiocyanate **7** in 90 % yield. Mp: 141-142°C. IR (ν/cm$^{-1}$): 1193 ($C(CH_3)_2$), 1188 (C=S), 1690 ($CONH_2$), 1608 (C=N), 2561($SCH_2$), 3085 (C-NH-). $[\alpha]_D^{20}$ = - 62.3 (c = 0.0117). $^1$H NMR (δ ppm, $CDCl_3$, 400MHz): 0.66 (t, *J* = 9.0 Hz, 1 H), 0.72 (dd, $J_1$ = 9.4 Hz, $J_2$ = 15.3 Hz, 1 H), 0.95 (s, 3 H), 0.99 - 1.00 (m, 1 H), 1.06 (s, 3 H), 1.55 (s, 3 H), 1.73 - 1.78 (m, 3 H), 1.96 - 1.97 (m, 1 H), 3.93 (d, *J* = 7.1 Hz, 2 H), 4.29 (s, 1 H), 5.25 (d, *J* = 10.1 Hz, 1 H), 5.41 (d, *J* = 17.0 Hz, 1 H), 5.89 (s, 2 H), 6.02 (d, *J* = 3.1 Hz, 1 H), 7.38 (d, *J* = 8.4 Hz, 2 H), 7.84 (s, 1 H), 8.01 (d, *J* = 8.7 Hz, 2 H), 8.17 (s, 1 H). $^{13}$C NMR (δ ppm, $CDCl_3$, 100 MHz): 15.4, 17.3, 17.7, 18.2, 21.3, 23.3, 28.4, 28.6, 35.3, 50.7, 55.8, 119.8, 120.8, 124.5, 128.1, 128.3, 131.7, 140.1, 163.8, 165.4, 178.4, 179.5. Anal. Calcd. for $C_{23}H_{29}N_5O_2S_2$: C 58,57; H 6,20; N 14,85; S 13,60. Found: C 58,12; H 6.09; N 14.35; S 12.98 %.

### 3.8. *(+)-1-[3-(5-Allylsulfanyl-[1,3,4]oxadiazol-2-yl)-phenyl]-3-[(1S,2R,3S,5S)-(2-hydroxy-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl]-thiourea (12)*

Prepared as a colorless solid in analogy to thiourea **8** by reaction of the aminoalcohol **5** and the isothiocyanate **6** in 74 % yield. Mp: 126-127°C. IR (ν/cm$^{-1}$): 1197 ($C(CH_3)_2$), 1186 (C=S), 1608 (C=N), 2561($SCH_2$), 3620(C-OH), 3087 (C-NH). $[\alpha]_D^{20}$= + 13.7 (c = 0.02, chloroform). $^1$H NMR (δ ppm, $CDCl_3$, 400 MHz): 1.18 (s, 3 H), 1.33 (s, 3 H), 1.42 (d, *J* = 10.4 Hz, 2 H), 1.48 - 1.15 (m, 3 H), 2.00 (s, 1 H), 2.02 (d, *J* = 6.0 Hz, 2 H), 2.18 - 2.20 (m, 1 H), 2.77 (t, *J* = 11.5 Hz, 1 H), 3.95 (d, *J* = 6.8 Hz, 2 H), 4.81 (dd, $J_1$ = 8.7 Hz, $J_2$ = 16.4 Hz, 1 H), 5.27 (d, *J* = 9.8 Hz, 1 H), 5.43 (d, *J* = 16.9 Hz, 1 H), 6.03 - 6.05 (m, 1 H), 7.49 (s, 2 H), 7.60 (d, *J* = 7.4 Hz, 1 H), 7.65 (s, 1 H), 8.06 (s, 1 H), 8.61 (s, 1 H). $^{13}$C NMR (δ ppm, $CDCl_3$, 100 MHz): 23.9, 28.4, 29.00, 30.1, 35.1, 35.7, 38.9, 40.7, 53.9, 55.0, 75.0, 119.9, 120.7, 122.6, 124.7, 125.8, 130.4, 131.6, 138.7, 163.6, 165.1, 179.4. Anal. Calcd. for $C_{22}H_{28}N_4O_2S_2$: C 59.43; H 6.35; N 12.60; S 14.42. Found: C 58.72; H 6.10; N 11.97; S 14.23 %.

### 3.9. *(+)-1-[4-(5-Allylsulfanyl-[1,3,4]oxadiazol-2-yl)-phenyl]-3-[(1S,2R,3S,5S)-(2-hydroxy-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl]-thiourea (13)*

Prepared as a colorless solid in analogy to thiourea **8** by reaction of the aminoalcohol **5** and the isothiocyanate **7** in 79 % yield. Mp: 83-84°C. IR (ν/cm$^{-1}$): 1198 ($C(CH_3)_2$), 1187 (C=S), 1609 (C=N), 2565 ($SCH_2$), 3621 (C-OH), 3085 (C-NH). $[\alpha]_D^{20}$= + 19.78 (c = 0.017). $^1$H NMR (δ ppm, $CDCl_3$, 400 MHz): 1.12 (s, 3 H), 1.31 (s, 3 H), 1.35 (d, *J* = 10.4 Hz, 1 H), 1.40 (s, 3 H), 1.52 (dd, $J_1$ = 6.3 Hz, $J_2$ = 13.7 Hz, 1 H), 1.92 (s, 1 H), 2.02 (d, *J* = 5.8 Hz, 2 H), 2.23 (m, 1 H), 2.82 (t, *J* = 11.6 Hz, 1 H), 3.93 (d, *J* = 7.0 Hz, 2 H), 4.87 (dd, $J_1$ = 8.6 Hz, $J_2$ = 16.5 Hz, 1 H), 5.25 (d, *J* = 10.0 Hz, 1 H), 5.41 (d, *J* = 17.1 Hz, 1 H), 6.01 - 6.03 (m, 1 H), 7.40 (d, *J* = 8.5 Hz, 2 H), 7.58 (d, *J* = 7.7 Hz, 1 H), 8.01 (d, *J* = 8.6 Hz, 2 H), 8.21 (s, 1 H). $^{13}$C NMR (δ ppm, $CDCl_3$, 100 MHz): 27.8, 28.1, 28.8, 29.6, 30.0, 35.3, 35.5, 38.2, 39.0, 50.6, 40.7, 54.2, 54.8, 119.9, 120.2, 123.0, 129.3, 131.6, 140.3, 163.8, 165.2, 179.1. Anal. Calcd. for $C_{22}H_{28}N_4O_2S_2$: C 59.43; H 6.35; N 12.60; S 14.42. Found: C 58.69; H 6.14; N 12.21; S 14.19 %.

### 3.10. *Typical Procedure for the Cyclization of the Thioureas*

The appropriate thiourea (1.04 mmol) was dissolved in methanol (5 ml). Five drops of methanol containing 25% $NH_3$ were added to the solution. After standing for 1 day at room temperature, the resulting white crystalline product was filtered off then washed with methanol to finish the target compound.

### 3.10.1. *(-)-(4aR,5aS,6aS,7aS)-4-[3-(5-Allylsulfanyl-[1,3,4]oxadiazol-2-yl)-phenyl]-6,6,7a-trimethyl-2-thioxo-perhydrocyclopropa[g]quinazolin-4-one (14)*

Prepared from the thiourea **8** as a white solid in 94 % yield. Mp: 204-205°C. IR (ν/cm$^{-1}$): 1197 ($C(CH_3)_2$), 1186 (C=S), 1609 (C=N), 1715 (C=O), 2565($SCH_2$), 3085 (C-NH). $[\alpha]_D^{20}$= - 150.68 (c = 0.019). $^1$H NMR (δ ppm, DMSO-$d_6$, 400 MHz): 0.85 (d, *J* = 4.1 Hz, 2 H), 0.93 (s, 3 H), 1.03 (dd, $J_1$ = 11.0 Hz, $J_2$ = 15.5 Hz, 1 H), 1.07 (s, 3 H), 1.35 (s, 3 H), 1.95 - 1.98 (m, 2 H), 2.16 (t, *J* = 9.4 Hz, 1 H), 2.46 (dd, $J_1$ = 6.6 Hz, $J_2$ = 15.4 Hz, 1 H), 3.95 (d, *J* = 6.9 Hz, 2 H), 5.22 (d, *J* = 9.9 Hz, 1 H), 5.40 (d, *J* = 16.8 Hz, 1 H), 6.01 - 6.02 (m, 1 H), 7.24 (d, *J* = 8.5 Hz, 2 H), 8.01 (d, *J* = 8.6 Hz, 2 H), 10.00 (s, 1 H). $^{13}$C NMR (δ ppm, DMSO-$d_6$, 100 MHz): 15.5, 16.7, 17.7, 17.8, 19.8, 26.7, 28.3, 28.6, 35.1, 40.7, 44.3, 51.4, 119.6, 123.1, 126.8, 130.8, 132.3, 142.1, 163.3, 165.2, 170.9, 180.2. Anal. Calcd. for $C_{23}H_{26}N_4O_2S_2$: C 60.77; H 5.76; N 12.32; S 14.11. Found: C 59.47; H 5.68; N 12.11; S 13.95 %.

### 3.10.2. *(-)-(4aR,5aS,6aS,7aS)-4-[4-(5-Allylsulfanyl-[1,3,4]oxadiazol-2-yl)-phenyl]-6,6,7a-trimethyl-2-thioxo-perhydrocyclopropa[g]quinazolin-4-one (15)*

Prepared from the thiourea **10** as a white solid in 82 % yield. Mp: 229-230°C. IR (ν/cm$^{-1}$): 1198 ($C(CH_3)_2$), 1187 (C=S), 1607 (C=N), 1715 (C=O), 2565 ($SCH_2$), 3088 (C-NH). $[\alpha]_D^{20}$ = - 96.53 (c = 0.015, chloroform). $^1$H NMR (δ ppm, DMSO-$d_6$, 400 MHz): 0.84 - 0.85 (m, 2 H), 0.93 (s, 3 H), 1.03 (dd, $J_1$ = 11.6 Hz, $J_2$ = 15.2 Hz, 1 H), 1.07 (s, 3 H), 1.36 (s, 3 H), 2.00 (d, *J* = 6.6 Hz, 2 H), 2.17 (t, *J* = 8.8 Hz, 1 H), 2.46 (dd, $J_1$ = 6.6 Hz, $J_2$ = 15.8 Hz, 1 H), 3.94 (d, *J* = 7.1 Hz, 2 H), 5.20 (d, *J* = 10.1 Hz, 1 H), 5.40 (d, *J* = 16.9 Hz, 1 H), 5.99 - 6.00 (m, 1 H), 7.25 (d, *J* = 8.2 Hz, 1 H), 7.57 (d, *J* = 7.8 Hz, 1 H), 7.60 (s, 1 H), 7.98 (d, *J* = 8.3 Hz, 1 H), 9.99 (s, 1 H). $^{13}$C NMR (δ ppm, DMSO-$d_6$, 100 MHz): 15.1, 16.4, 17.4, 17.5, 19.5, 26.3, 27.9, 28.2, 34.8, 43.8, 51.1, 95.8, 119.3, 125.8,

127.5, 132.2, 133.0, 139.7, 142.3, 163.3, 164.7, 170.9, 179.8. Anal. Calcd. for $C_{23}H_{26}N_4O_2S_2$: C 60.77; H 5.76; N 12.32; S 14.11. Found: C 58.84; H 5.60; N 11.88; S 13.98 %.

### 3.11. *Strecker-Type Reaction of hydrazine and TMSCN, mediated by oxadiazol-thioureas 8-11, 12, 13 and oxadiazol-thioxopyrimidinones 14, 15:*

#### *N'-(1-cyanopropyl)-4-nitrobenzohydrazide (18)*

The appropriate catalyst (6.8 μmol, 0.05 eq) was added to a solution of the respective hydrazone (**16** or **17**) (135.6 μmol, 1.00 eq) in a mixture of the corresponding solvent (3 ml) and *tert*-butanol (2.0 mg, 2.58 μl, 27.1 μmol, 0.20 eq) at ambient temperature. After stirring for 20 min, trimethylsilyl cyanide (26.9 mg, 33.9 μl, 271.2 μmol, 2.00 eq) was added to the reaction mixture and the stirring continued for 72 h at room temperature. The mixture was directly transferred for purification by column chromatography over silica gel (petrol ether/ ethyl acetate/ dichloromethane 5:4:1). The solvent was evaporated under reduced pressure and resulting in **18** (13-74 % yields) as a yellow colored oil. $^1$H NMR (δ ppm, DMSO-$d_6$, 300 MHz): 1.00 (t, 3H, $J$ = 7 Hz), 2.42 - 2.29 (m, 2H), 4.00 - 4.10 (m, 1H), 6.08 (t, 1H, $J$ = 5 Hz), 8.04 (d, 2H, $J$ = 9 Hz), 8.30 (d, 2H, $J$ = 9 Hz), 10.55 (d, 1H, $J$ = 6 Hz). $^{13}$C NMR (δ ppm, DMSO-$d_6$, 100 MHz): 10.01, 24.09, 52.97, 119.99, 123.66, 128.79, 138.27, 149.22, 164.39. EI-MS: $m/z$ = 248 $[M]^+$.

No conversion was observed in the case of hydrazone **17.**

### 3.12. *Epoxide Ring Opening Reaction of Cyclohexene Oxide with Aniline, mediated by oxadiazol-thioureas 8-11, 12, 13 and oxadiazol-thioxopyrimidinones 14, 15:*

#### *2-(phenylamino)phenol (22)*

A solution of cyclohexene oxide **20** (24.6 mg, 25.4 μl, 250.7 μmol, 1.0 eq), aniline **21** (46.6 mg, 45.6 μl, 500.4 μmol, 2.0 eq) and catalyst **10** (12.5 mg, 25.7 μmol, 0.1 eq) in dichloromethane (125 μl) was stirred for 48 h at ambient temperature. The mixture was directly purified over silica gel by column chromatography (petrol ether/ ethyl acetate 5:1). The reactions with the catalysts **8**, **9**, **11** and **12**-**15** (each 25.1 μmol, 0.1 eq) were carried out under the same conditions, except that *N*-formyl-(*S*)-proline (1.8 mg, 12.6 μmol, 0.05 eq) was additionally employed in the experiments. Physico-chemical properties of the compound **22** were in accordance with the literature data[12].

## 4. Conclusions

In summary, new oxadiazol-thioureas **8-11**, **12, 13** and oxadiazol-thioxopyrimidinones **14**, **15** have been prepared successfully from (+)-3-carene and (+)-α-pinene derivatives and applied as catalysts in such organic transformations as Strecker-type and epoxide ring opening reactions. Interestingly enough, some oxadiazol-thioureas (**8**, **9**, **11** and **12**) and oxadiazol-thioxopyrimidinones (**14** and **15**) have shown higher reactivity in the epoxide ring opening (73-81% yields), than in Strecker-type reaction.

These results provide useful insights in the further design and development of highly active and enantioselective thiourea-based organocatalysts for the selected organic transformations.

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