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New bifunctional carbohydrate-like thiourea derivatives – design and first application in organocatalysis

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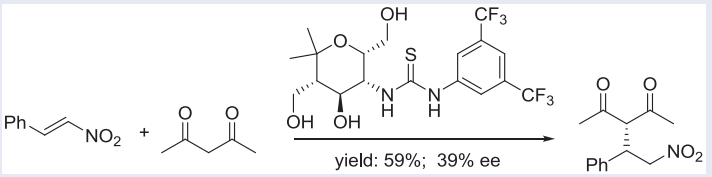
ABSTRACT

From easily available aminopyran and aminooxepane derivatives and 2,5-bis(trifluoromethyl)phenyl isothiocyanate the corresponding thiourea derivatives were prepared. One compound was further modified by introducing a tertiary amino group. The four catalysts were then examined as catalysts in a Michael addition of acetylacetone to β-nitrostyrene. A 1:1 mixture of one of these thioureas with an (*S*)-prolinol derivative was also tested as catalyst, but no synergetic effect was found. The best yield achieved was 88% and the highest ee amounted to 39%. In a preliminary experiment, the aldol reaction of acetone with isatin was investigated. One catalyst provided the expected aldol product in low yield, but in excellent enantioselectivity.

GRAPHICAL ABSTRACT



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The asymmetric organocatalysis with its various activation modes has become a fundamental strategy in creation of stereo-defined molecules including the construction of complex biomolecules and natural products.[1] One of the most efficient and widely used class of organocatalysts are bifunctional thiourea derivatives. Since the first investigation of bifunctional thiourea and its derivatives introduced by Jorgensen, Takemoto, Schreiner and other, much attention has been found on the application of this organocatalytic system.[2] Among the various functionalized thiourea catalysts bearing at least one chiral moiety, growing attention has been paid more recently to carbohydrate-substituted thiourea derivatives.[3] In 2014, one of the first reports emerged on employing bifunctional thiourea catalysts, such as **1**, having a carbohydrate unit (Figure 1). It

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Dedicated to the memory of Dr. Maurice Taszarek.

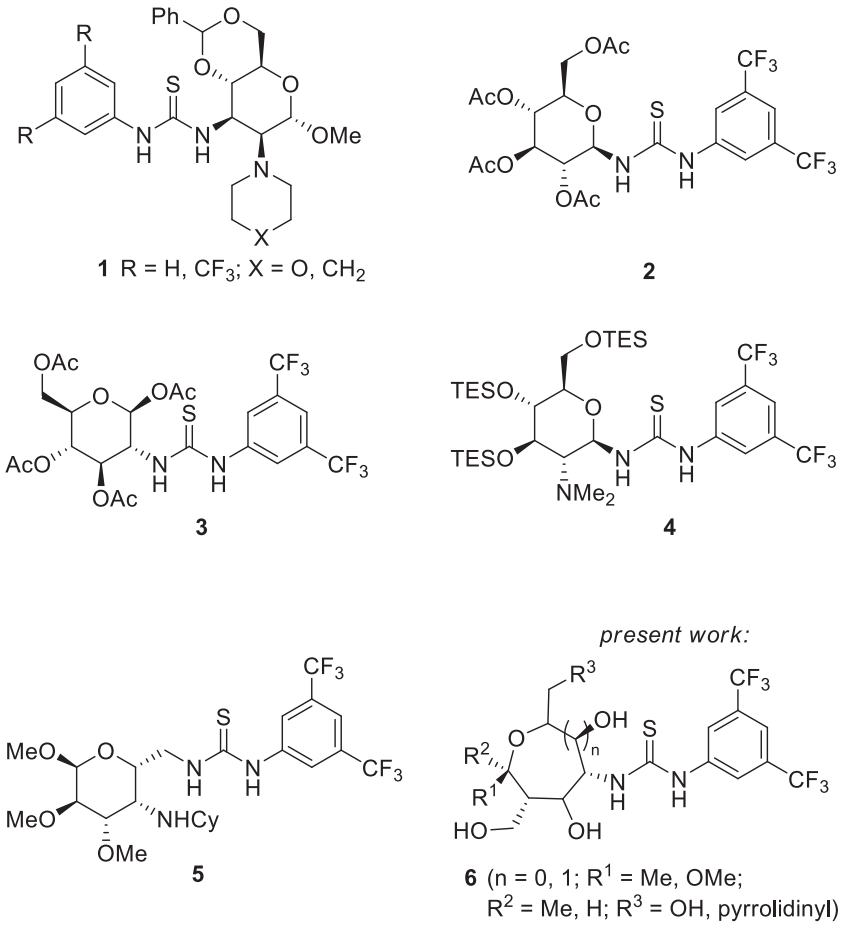
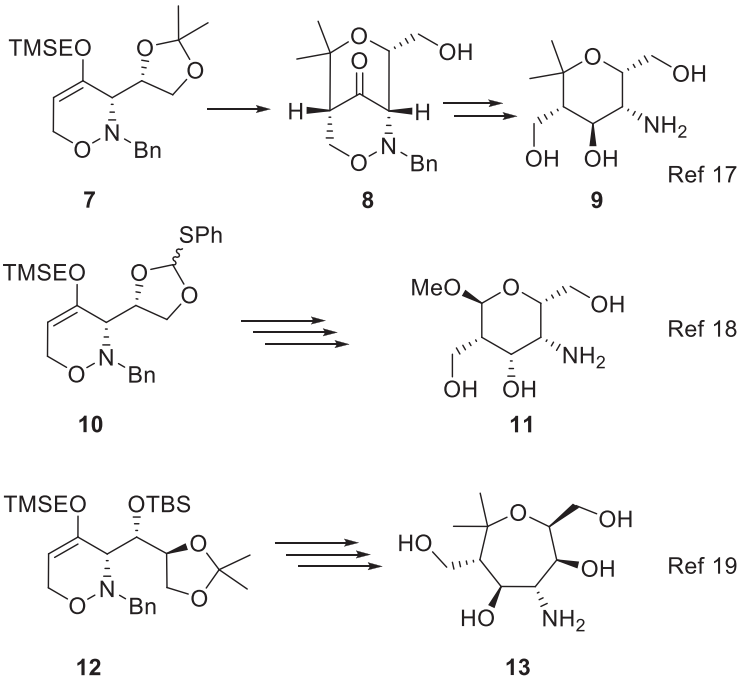


Figure 1. Selected examples of literature known carbohydrate-substituted thiourea derivatives and catalyst type **6** investigated in this study.

was applied by Ágoston and Fügedi to the conjugate addition of acetylacetone to β-nitrostyrene.[4] After this study, further thiourea catalysts bearing a carbohydrate moiety, for example **2**–**5**, have been designed as suitable hydrogen-bonding organocatalysts and were tested in various asymmetric reactions, including decarboxylative Mannich reactions, Michael additions, aza-Henry reaction and additions of malonates to imines.[5–12] Stimulated by these results, we were interested to replace the carbohydrate unit by a stereodefined carbohydrate-mimetic moiety that are rapidly accessible by our established approach via 1,2-oxazines,[13] creating thiourea derivatives of type **6**. Moreover, the newly designed catalysts of type **6** should be tested in typical organocatalytic processes.

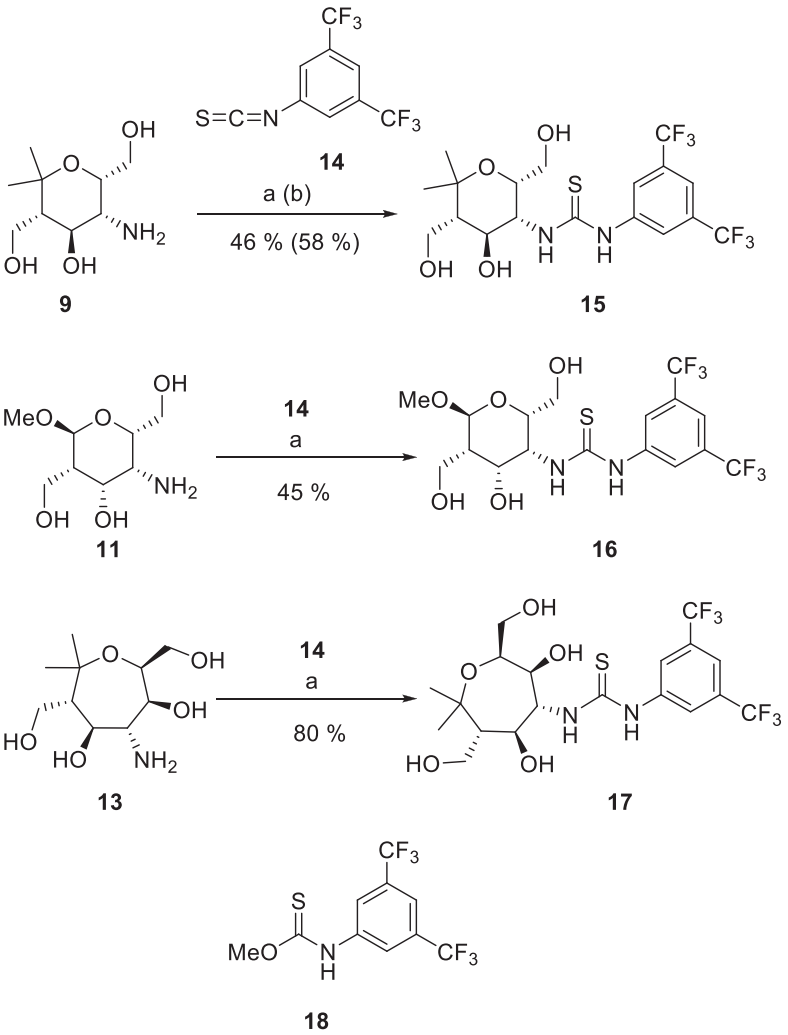
In the course of our research, we have constantly reported on the preparation of enantiopure 3,6-dihydro-2*H*-1,2-oxazines[14] and their application as synthetically useful chiral building blocks.[14–16] A serendipitous but important discovery during these studies was the Lewis-acid promoted rearrangement of 4-(2-trimethylsilyl)ethoxy-substituted 3,6-dihydro-2*H*-1,2-oxazines such as **7**, **10** or **12** (Scheme 1). Our study herein commenced with the selection of the amino-substituted pyran and oxepane derivatives



Scheme 1. Syntheses of amino-substituted pyran and oxepane derivatives.

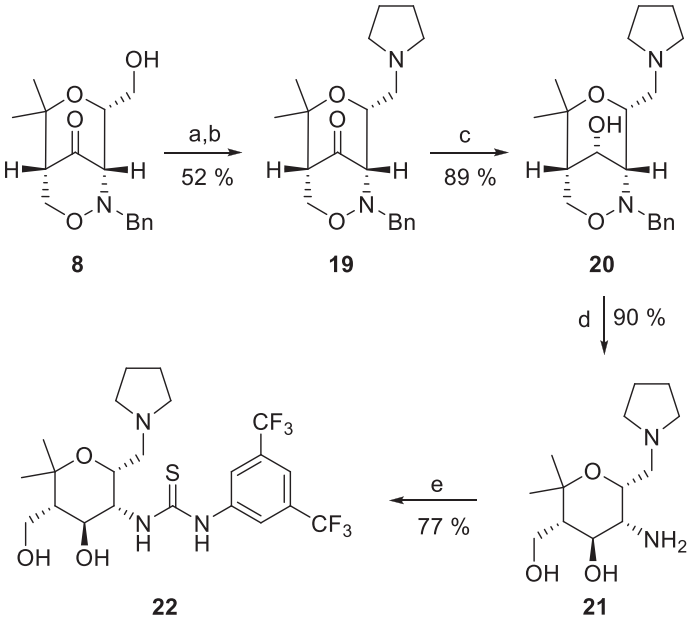
9, **11** and **13**, previously synthesized in short reaction sequences from corresponding enantiopure compounds **7**, **10** and **12**. The Lewis-acid induced rearrangement of 2*H*-1,2-oxazine **7** using TMSOTf as promoter afforded the bicyclic ketone **8** in good yield. The plausible mechanism of this rearrangement was already discussed in details in former reports.[17] After subsequent stereoselective reduction of ketone **8** with $NaBH_4$ in ethanol followed by hydrogenolysis of the corresponding alcohol intermediate with palladium on charcoal the aminopyran derivative **9** was obtained in excellent yield. A similar reaction sequence starting form precursor **10** was applied to the preparation of aminopyran **11** containing an anomeric center.[18] Similarly, to the synthesis of **9**, the desired aminooxepane **13** was achieved in a five-step reaction sequence starting from 3,6-dihydro-2*H*-1,2-oxazine **12**.[19]

Having the required primary amine precursors in hand, we adopted an operative simple procedure to prepare the desired chiral thioureas **15**–**17**.[4] The reaction of amino-substituted pyran derivative **9** with an excess of 2,5-bis(trifluoromethyl)phenyl isothiocyanate **14** (1.5 equiv) in methanol afforded after a short reaction time (1.5 h) the thiourea derivative **15** in 46% yield (Scheme 2, conditions a). The moderate yield was probably caused by the formation of the side product **18**, an adduct of **14** and methanol. A better yield of **15** was achieved by running the reaction in isopropanol (conditions b). The additions of aminopyran **11** and aminooxepane **13** to **14** gave the expected thioureas **16** and **17**, respectively, in moderate to very good yields. The obtained thioureas bear additional free hydroxyl groups that might be valuable due to additional hydrogen bonding in a cooperative catalytic process.[3,20] Moreover, the installation of a basic moiety, for example a tertiary amino group, in our designed catalysts **15**–**17** could additional activate nucleophiles in the reactions.[2d]

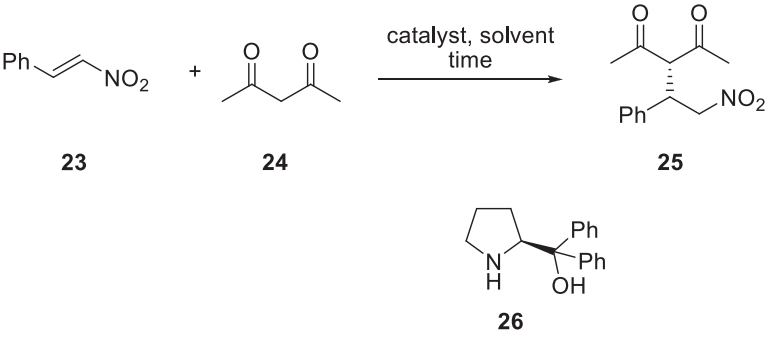


Scheme 2. Additions of aminopyrans **9** and **11** and of aminooxepane **13** to isothiocyanate **14** leading to bifunctional thioureas **15**–**17**. Reagents and conditions: a) MeOH, 0 °C, 1.5 h. b) *i*PrOH, 0 °C, 1.5 h.

In order to address the role of an additional tertiary amino group in the organocatalyst, we prepared the bifunctional thiourea derivative **22** bearing a pyrrolidinyl moiety. Starting from bicyclic ketone **8** (Scheme 3) mesylation of the primary alcohol function gave the corresponding mesylate intermediate that was treated with an excess of pyrrolidine (5 equiv) in 1,4-dioxane at 100 °C (17 h) leading to compound **19** in 52% yield (over two steps). Surprisingly, only under these fairly harsh conditions, we were able to introduce the cyclic amine without problems. When the reaction was performed using typically milder conditions (room temperature, shorter reaction time), the substitution failed and only starting material was recovered. The subsequent steps were achieved according to established protocols. The stereoselective reduction of ketone **19** using sodium borohydride gave the alcohol **20** as a single diastereomer that was then subjected to a palladium-catalyzed hydrogenolysis to afford the pyran derivative **21** in excellent yield.



Scheme 3. Synthesis of thiourea derivative **22** bearing a tertiary amino group. Reagents and conditions: (a) MsCl, NEt_3, CH_2Cl_2, 0 °C, 4 h; (b) pyrrolidine, 1,4-dioxane, 100 °C, 17 h; (c) $NaBH_4$, EtOH, 0 °C to room temp, 3 h; (d) H_2, Pd/C, *i*PrOH, room temp., 3.5 d; (e) isothiocyanate **14**, *i*PrOH, 0 °C to room temp., 17 h.



Scheme 4. Michael addition of acetylacetone (**24**) to β-nitrostyrene (**23**).

Table 1 Michael addition of acetylacetone (**24**) to β-nitrostyrene (**23**) in the presence of thiourea catalysts.

Entry	Catalyst	Solvent	Time (h)	Yield (%)[a]	$[\alpha]_D$	Ee (%)[b]
1	**15**	CH_2Cl_2	159	59	+60	39
2	**16**	CH_2Cl_2, MeOH	159	13	+12	9
3	**17**	CH_2Cl_2, MeOH	93	56	+5.2	3
4	**17** + **26**	CH_2Cl_2, MeOH	48	66	−9.1	−5
5	**26**	CH_2Cl_2, MeOH	48	50	+8.3	4
6	**22**	CH_2Cl_2	69	88	+26	15

[a]Yields after chromatography.
[b]Determined by HPLC analysis using a chiral column (see experimental section).

Finally, applying the optimized conditions with isopropanol as solvent, the addition of **21** and isothiocyanate **14** furnished the desired thiourea derivative **22** in 77% yield.

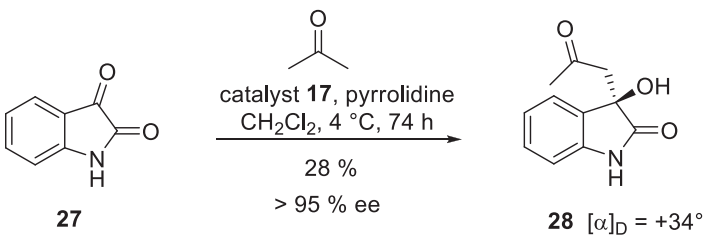
In a preliminary study, the thiourea derivatives **15**–**17** and **22** were evaluated as organocatalysts in a typical Michael addition of acetylacetone (**24**) to β-nitrostyrene (**23**) that furnished adduct **25** (Scheme 4, Table 1). The conjugate addition reaction was carried out with 10 mol-% of catalyst **15** at room temperature in dichloromethane to afford **25** in 59% yield and with an enantiomeric excess of 39% (Table 1, entry 1). Under the same conditions, catalysts **16** and **17** were also tested (Table 1, entries 2 and 3). Both catalysts showed dramatically reduced enantioselectivities (3–9% ee). At this point, we encountered solubility problems and solvent screening identified that the addition of methanol (10 vol-%) was necessary. The use of this protic solvent may cause the lower enantioselectivities by interfering with the hydrogen bonds.

The self-assembly of several components, in particular of two chiral compounds, to deliver a highly active catalytic species, is an attractive method in stereoselective synthesis.[21] We therefore performed the Michael addition under the influence of a 1:1 mixture of thiourea **17** and prolinol derivative (*S*)-**26** (entry 4).[22] This result has to be compared with that of thiourea derivative **17** only (entry 3) and of (*S*)-**26** (entry 5). The catalyst system of **17** and (*S*)-**26** afforded product **25** in a slightly improved yield of 66%, but all reactions gave disappointingly low enantioselectivities with ee values between 3 and −5%, close to the analytical error. In consequence, a desired synergetic effect caused by the chosen catalyst system was not observed. Nevertheless, it is remarkable that the reaction time with the catalyst mixture of entry 4 was significantly shorter than that of entry 3 (48 h instead of 93 h).

Next, we tested thiourea compound **22** bearing a tertiary amino group at the pyran moiety (Table 1, entry 6). The use of this catalyst resulted in the formation of **25** with the best yield of 88% in a reasonable reaction time, albeit in a lower ee of only 15% compared with the catalyst **15**.

The enantiomeric excesses of product **25** were established by HLPC using chiral column (chiralpak IA) and the absolute configuration was determined by comparison of the optical rotation value with those reported in the literature.[23] It was found that in almost all cases the (+)-enantiomer (*S*)-**25** was preferentially formed.

After these disillusioning low stereoselectivities obtained in Michael additions to **25**, we briefly examined a second asymmetric carbon-carbon bond forming reaction with our bifunctional thiourea derivatives. For this purpose, we choose the enantioselective aldol reaction of isatin **27** with acetone.[5,24] The aldol reactions were performed using 1-2 mol-% of catalysts **15**–**17** in the presence of 10 mol-% of pyrrolidine at 4 °C in dichloromethane (Scheme 5). Monitoring the reaction by TLC indicated complete



27 **28** $[\alpha]_D$ = +34°

Scheme 5. Aldol reaction of isatin (**27**) with acetone catalyzed by **17**.

conversion of **27** after 74 hours in all cases. Unfortunately, the chromatographic separation of the polar aldol product **28** and the employed catalyst turned out to be very difficult. Only in the case of the aldol reaction with catalyst **17,** we were able to isolate pure **28** in moderate 28% yield (additional material of **28** was still in mixed fractions). The measured optical rotation of product **28** was in the same range as that reported in the literature[25] and it indicates an excellent enantioselectivity in the range of >95% ee for this sample.[26] An unambiguous confirmation of this ee value by chiral HPLC so far failed. Although this transformation looks very promising, detailed investigations are required for its optimization.

In summary, starting from easily available aminopyran and aminooxepane derivatives **9**, **11**, **13** and **21** and 2,5-bis(trifluoromethyl)phenyl isothiocyanate **14,** we have prepared the bifunctional thioureas **15**–**17** and **22** bearing a carbohydrate-like moiety. These new potential organocatalysts were tested for the first time in the Michael addition of **24** to **23** leading to the addition product **25** in up to 88% yield. The moderate enantioselectivity observed in the conjugate addition induced by catalyst **15** certainly needs improvement. A further option is the application of other asymmetric transformations as briefly demonstrated by the applied aldol reaction of **27** with acetone that provided a sample of **28** with excellent ee.

Experimental

General methods

Reactions were generally performed under argon in flame-dried flasks. Solvents and reagents were added by syringes. Solvents were dried using standard procedures. Reagents were purchased and were used as received without further purification unless stated. Reactions were monitored by thin-layer chromatography (TLC). Products were purified by flash chromatography (FLC) on silica gel (32–63 μm). Unless otherwise stated, yields refer to chromatographically homogeneous and spectroscopically pure materials (^{1}H-NMR spectroscopy). NMR spectra were recorded with JEOL (ECX 400, Eclipse 500) instruments. Chemical shifts are reported relative to TMS (^{1}H: $\delta = 0.00$ ppm) and $CDCl_3$ (^{13}C: $\delta = 77.0$ ppm). Integrals are in accordance with assignments; coupling constants are given in Hz. Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), m (multiplet), m_c (centered multiplet), dd (doublet of doublet), br s (broad singlet). MS and HRMS analyses were performed with a Varian Ionspec QFT-7 instrument (ESI-FT ICRMS). Elemental analyses were carried out with a Vario EL Elemental Analyzer. Optical rotations ($[\alpha]_D$) were determined with Perkin–Elmer 141 or Perkin–Elmer 241 polarimeters at the temperatures given. Melting points were measured with a Reichert apparatus (Thermovar) and are uncorrected.

The starting materials **9**,[17] **11**,[18] **13**,[19] and the prolinol derivative **26**[27] were prepared according to literature procedures.

General Procedure 1, syntheses of thiourea derivatives

The corresponding aminopyran or aminooxepane derivative (1.0 equivalent) and isothiocyanate **14** (1.0 equivalent) were dissolved in methanol or isopropanol (2-8 mL/mmol substrate) at 0 °C. After stirring the mixture for 1.5 h at this temperature, the solvent

was removed under reduced pressure. The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 15:1) to give the corresponding thiourea product.

1-[3,5-Bis(trifluoromethyl)phenyl]-3-[(2S,3R,4S,5S)-4-hydroxy-2,5-bis(hydroxyl-methyl)-6,6-dimethyltetrahydro-2H-pyran-3-yl]thiourea (15)

According to the general procedure 1, pyran derivative **9** (282 mg, 1.38 mmol), and isothiocyanate **14** (374 mg, 1.38 mmol) in methanol (7 mL) were used. The crude product was purified by column chromatography to give **15** (305 mg, 46%) as colorless crystals, mp. 83–86 °C, and **18** (160 mg, 38%) as colorless wax. Product **15**: $[\alpha_D^{20}] + 45.0$ (*c* 0.5, MeOH). ^{1}H NMR (CD_3OD, 500 MHz): δ = 1.27, 1.46 (2 s, 3 H each, Me), 1.78 (*q*, *J* = 5.3 Hz, 1 H, 5″-H), 3.56 (dd, *J* = 11.6, 7.1 Hz, 1 H, 2″-CH_2), 3.66-3.72 (*m*, 2 H, 2″-CH_2, 5″-CH_2), 3.75 (dd, *J* = 11.1, 5.7 Hz, 1 H, 5″-CH_2), 4.05 (*t*, *J* = 4.7 Hz, 1 H, 4″-H), 4.19-4.25 (*m*, 1 H, 2″-H), 4.63-4.66 (*m*, 1 H, 3″-H), 7.63 (*s*, 1 H, 4′-H), 8.21 ppm (*s*, 2 H, 2′-H). ^{13}C NMR (CD_3OD, 125.8 MHz): δ = 26.5, 27.6 (2 q, Me), 49.4 (d, C-5″), 58.0 (d, C 3″), 62.8 (*t*, 2″-CH_2), 63.2 (*t*, 5″-CH_2), 70.8 (d, C-2″), 72.6 (d, C-4″), 75.8 (*s*, C-6″), 117.8 (d, C-4′), 123.7 (d, C-2′), 124.7 (*q*, $^1J_{CF}$ = 271.9 Hz, CF_3), 132.6 (*q*, $^2J_{CF}$ = 32.9 Hz, C-3′), 141.5 (*s*, C-1′), 182.8 ppm (*s*, C-2). ^{19}F NMR (CD_3OD, 376 MHz): δ = −60.4 ppm (*s*, CF_3). IR (ATR): ν = 3500-3100 (OH, NH), 3100-2895 (=C-H, C-H), 1275 cm^{-1} (C = S). HRMS (ESI-TOF) calcd for $C_{18}H_{23}F_6N_2O_5S$ $[M+H]^+$: 477.1277, found: 477.1325. Elemental analysis calc (%) for $C_{18}H_{22}F_6N_2O_5S$ (476.4): C 45.38, H 4.65, N 5.88, S 6.73; found: C 45.38, H 4.66, N 5.92, S 7.24. Product **18**: ^{1}H NMR (CD_3OD, 400 MHz): δ = 4.07 (*s*, 3 H, OMe), 7.69 (*s*, 1 H, 4-H), 8.30 ppm (br s, 2 H, 2-H). ^{13}C NMR (CD_3OD, 125.8 MHz): δ = 56.4 (*q*, OMe), 117.0 (d, C-4), 121.1 (d, C-2), 123.3 (*q*, $^1J_{CF}$ = 277.2 Hz, CF_3), 131.7 (*q*, $^2J_{CF}$ = 37.4 Hz, C-3′), 189.5 ppm (*s*, C = S); the signal of C-1′ could not be detected. IR (ATR): ν = 3300-3200 (N-H), 3100-2900 (=C-H, C-H), 1280 cm^{-1} (C = S). Elemental analysis calc (%) for $C_{10}H_7F_6NOS$ (303.2): C 39.61, H 2.33, N 4.62, S 10.57; found: C 39.64, H 2.54, N 4.69, S 10.04.

1-[3,5-Bis(trifluoromethyl)phenyl]-3-[(2S,3S,4R,5S,6S)-3,5-dihydroxy-2,6-bis-(hydroxy-methyl)-7,7-dimethyloxepan-4-yl]thiourea (17)

According to the general procedure 1, oxepane derivative **13** (353 mg, 1.50 mmol), and isothiocyanate **14** (407 mg, 1.50 mmol) in methanol (8 mL) were used. The crude product was purified by column chromatography to give **17** (605 mg, 80%) as pale pink solid, mp. 165 °C, $[\alpha_D^{20}]$ -20.5 (*c* 0.7, MeOH). ^{1}H NMR (CD_3OD, 500 MHz, 300 K): δ = 1.35 (2 s, 3 H each, Me), 2.00-2.08 (*m*, 1 H, 6″-H), 3.53–3.72 (*m*, 5 H, 2″-H, 2″-CH_2, 6″-CH_2), 3.85 (dd, *J* = 7.8, 2.9 Hz, 1 H, 5″-H), 3.95 (m_c, 1 H, 3″-H), 4.58–4.70 (*m*, 1 H, 4″-H), 7.56 (*s*, 1 H, 4′-H), 8.07 ppm (*s*, 2 H, 2′-H). ^{13}C NMR (CD_3OD, 125.8 MHz, 300 K): δ = 21.2, 31.6 (2 q, Me), 59.8 (d, C-6″), 63.6* (*t*, 2″-CH_2, 6″-CH_2), 67.7 (d, C-4″), 73.7, 74.9 (2 d, C-2″, C-5″), 77.4 (*s*, C-7″), 118.1 (d, C-4′), 124.4 (d, C-2′), 124.7 (*q*, $^1J_{CF}$ = 273.5 Hz, CF_3), 132.8 (*q*, $^2J_{CF}$ = 40.9 Hz, C-3′), 143.0 (*s*, C-1′), 184.2 ppm (*s*, C-2); *intensity of the peak corresponds to two C atoms. ^{19}F NMR (CD_3OD, 376 MHz): δ = −64.3 ppm (*s*, CF_3). IR (ATR): ν = 3500–3100 (O-H, N-H), 3100–2850 (=C-H, C-H), 1275 cm^{-1} (C = S). HRMS (ESI–TOF): calcd for $C_{19}H_{25}F_6N_2O_5S$ $[M+H]^+$: 507.1400, found: 507.1383. Elemental analysis calc (%) for $C_{19}H_{24}F_6N_2O_5S$ (506.5): C 45.06, H 4.78, N 5.53, S 6.33; found: C 45.00, H 4.79, N 5.46, S 6.48.

Michael addition of acetylacetone to β-nitrostyrene

To a solution of β-nitrostyrene **23** (30 mg, 0.20 mmmol) in dichloromethane (1 mL) or dichloromethane/methanol (1 mL/0.1 mL), the corresponding organocatalyst (0.20 mmol) was added under argon atmosphere at room temperature. The solution was stirred for 5 min, then acetylacetone **24** (24 µL, 0.23 mmol) was added and stirring was continued for the time indicated in Table 1 of the main text. The solution concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel (hexane/ethyl acetate, 3:1) to give the product **25**. The ratio of the formed enantiomers was determined by chiral HPLC (chiralpak IA, 4.6x250 mm; 5% isopropanol/hexane; flow 1 mL/min, 25 bar; UV 215 nm, RI).

$[\alpha_D{}^{20}] + 60$ (*c* 0.59, CH_2Cl_2); 39% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.91$, 2.25 (2 s, 3 H each, Me), 4.19 (ddd, $J = 10.9$, 8.1, 6.4 Hz, 1 H, PhCH), 4.57 (d, $J = 10.9$ Hz, 1 H, COCH), 4.68–4.75 (*m*, 2 H, CH_2), 7.11-7.63 ppm (*m*, 5 H, Ph). The NMR data are in accordance to those reported in the literature.[4]

Acknowledgments

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