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Graphical Abstract

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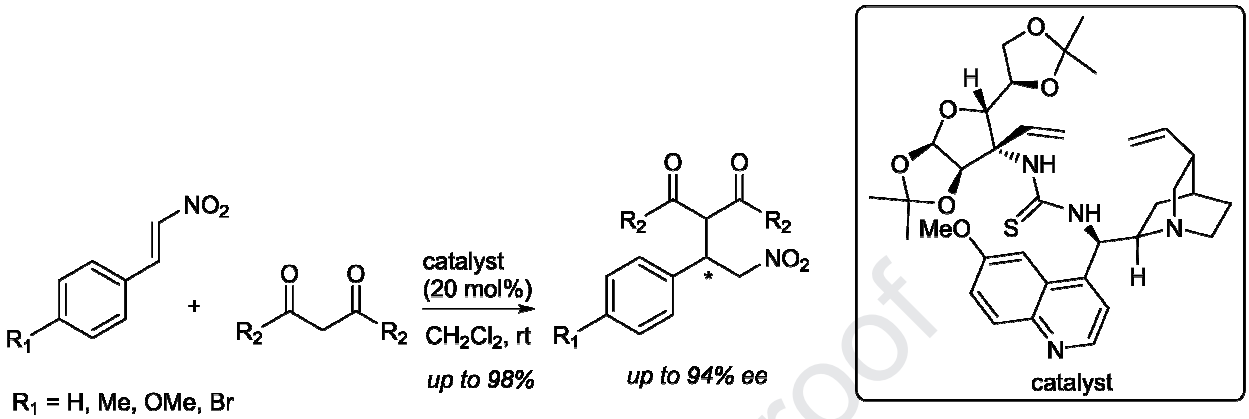

Novel carbohydrate-based thioureas as organocatalysts for asymmetric Michael addition of 1,3-dicarbonyl compounds to nitroolefins

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[†]This work is dedicated to the memory of Professor Jozef Gonda (1957-2019)

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ABSTRACT

A series of novel carbohydrate-derived thioureas were synthesized and examined as catalysts for the asymmetric Michael addition of symmetrical 1,3-dicarbonyl compounds, including dimethyl malonate, to several *trans*-*β*-nitrostyrenes. High enantioselectivities (up to 94% *ee*) as well as high yields (up to 98%) were attained using a bifunctional organocatalyst bearing a cinchona-based alkaloid unit.

1. Introduction

Chiral bifunctional organocatalysts, which combine a thiourea group as a hydrogen-bond donor moiety with a Lewis base, are commonly used in asymmetric catalysis.[1] In 2003 Takemoto and coworkers[1f,2] described the prototype of such a catalyst and evaluated in Michael reaction of malonates to nitroolefins (Fig. 1). The high stereocontrol of the reaction is explained as a synergistic effect of both parts of the catalyst cooperatively activating the

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nucleophile and the electrophile simultaneously.[2] The effectivity of Takemoto's catalyst[2a] inspired several synthetic groups and many different chiral scaffolds have been employed in the synthesis of related structures[1e,1g,2b,3] (Fig. 1).

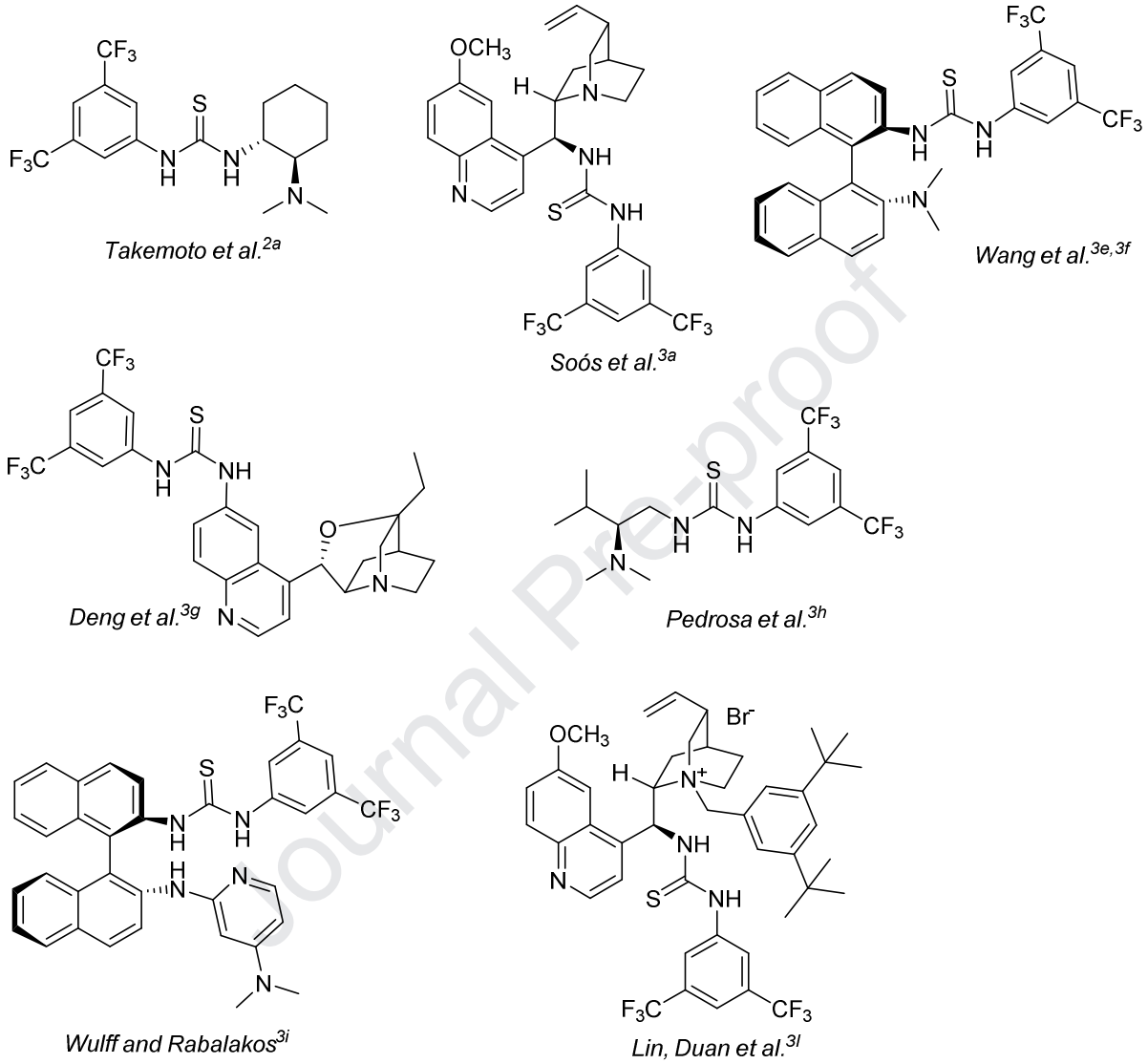


Figure 1. Several examples of thiourea-based bifunctional catalysts bearing chiral scaffolds.

In the last decade, growing attention has been focused on the preparation of thiourea-based bifunctional organocatalysts having a monosaccharide unit.[4] In general, carbohydrates are very useful chiral precursors due to their optical purity and stereodiversity as well as their high degree of functionality for optimizing catalyst performance. Ma and coworkers[4a] published the synthesis of the first thiourea catalysts bearing carbohydrate core scaffold and a primary amino group (Fig. 2). The promising catalytic potential was later extended by the

synthesis of related catalysts bearing various amine basic moiety and monosaccharide or disaccharide part.[4b,4g,4j-k] Most of Ma's group catalysts have been evaluated successively in direct Michael additions.[4a-b,4g] Various groups have been working on bifunctional carbohydrate-based catalysts (some of them are illustrated in Figure 2) and their catalytic potential has been evaluated in various asymmetric transformations, including Michael,[4a-i,4l-n,5a,5c,5e] Mannich[4h,4j] and Biginelli[5b] reactions, cyanation of carbonyl compounds[5d] and a one-pot sequential conjugate addition/dearomative fluorination process.[4k]

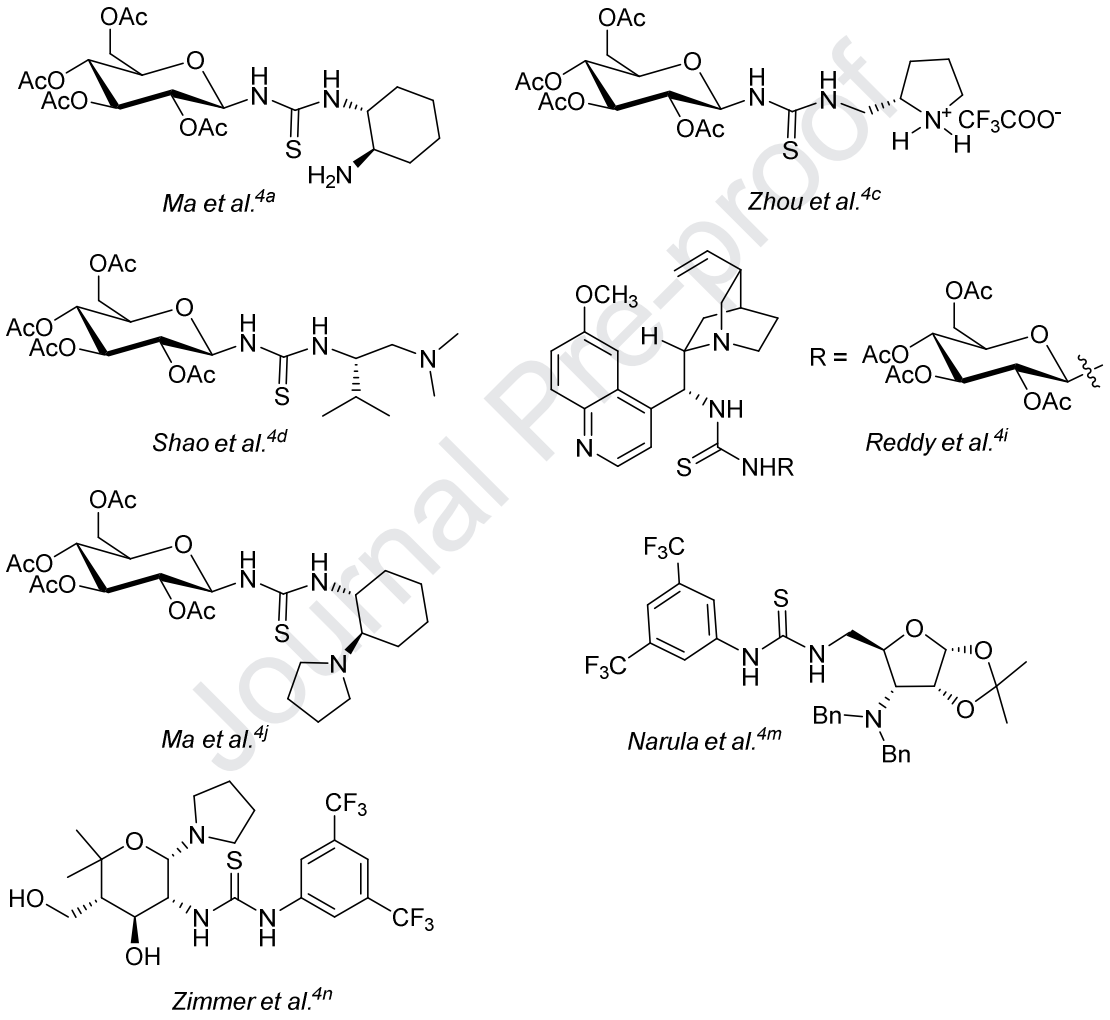


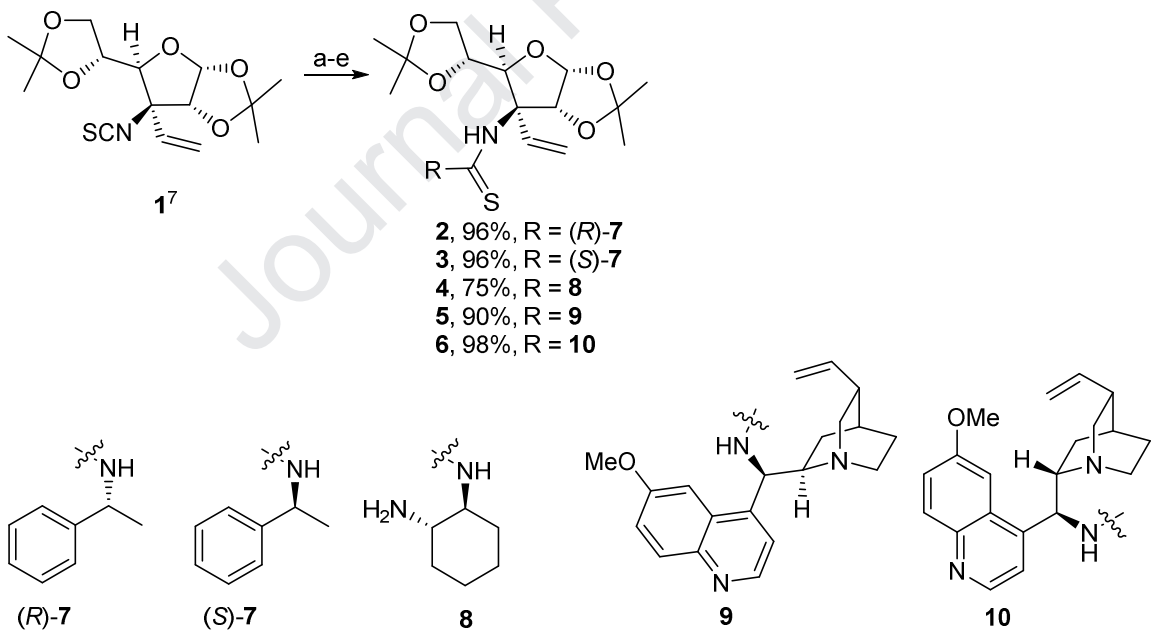
Figure 2. Examples of thiourea-derived bifunctional catalysts with carbohydrate units.

Inspired by the various sugar-derived bifunctional thiourea conjugates in several asymmetric catalytic processes,[4,5] we decided to synthesize novel thiourea catalysts **2-6** that combined a bulky D-glucofuranose scaffold with a chiral amino unit, including cinchona alkaloid moieties

(Scheme 1). The successful application of the furanose- and pyranose- derived organocatalysts reported in literature[4m,6] leads us to examine the effect of substituents attached to designed glucofuranose-thiourea linkage and investigate their catalytic performance. Recently, we reported a catalytic activity of the prepared bifunctional hybrids in the enantioselective Michael addition of symmetrical 1,3-dicarbonyl compounds **11**, **14**, and dimethyl malonate **15** to both unsubstituted **12a** and substituted *β*-nitrostyrenes **12b-d** (*vide infra*).

2. Results and discussion

As shown in Scheme 1, the preparation of catalysts **2-6** was achieved in a single-step procedure by treatment of the known 3-deoxy-1,2:5,6-di-*O*-*i*sopropylidene-3-isothiocyanato-3-*C*-vinyl-*α*-D-glucofuranose **1**[7] with the corresponding commercially available amines **7-10** in very good yields (75-98%, Scheme 1).

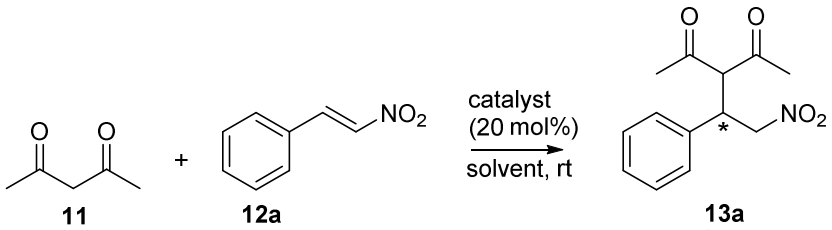


Scheme 1. *Reagents and conditions:* (a) (*R*)-**7**, THF, rt, 1 h; (b) (*S*)-**7**, THF, rt, 1 h; (c) **8**, CH_2Cl_2, rt, 1.5 h; (d) **9**.3 HCl, E_3N, THF, rt, 48 h; (e) **10**.3 HCl, Et_3N, THF, rt, 24 h.

With thioureas **2-6** in hand, we started our investigation of their catalytic activity on the model Michael addition. The screening of the reaction was carried out with pentane-2,4-dione

11, *trans*-nitrostyrene **12a**, and 20 mol% of the prepared catalysts in CH_2Cl_2 at room temperature. The obtained results are summarized in Table 1.

Table 1. Catalyst and solvent screening of the asymmetric Michael addition of pentane-2,4-dione **11** to *trans*-nitrostyrene **12a**



Entry	Catalyst	Solvent	Time (days)	Yield[a] **13a** (%)	*ee*[b] (%) config.[c]
1	**2**	CH_2Cl_2	7	4	6 (*R*)
2	**3**	CH_2Cl_2	7	3	rac.[d]
3	**4**	CH_2Cl_2	7	7	rac.[d]
4	**5**	CH_2Cl_2	1	98	88 (*R*)
5[e]	**5**	CH_2Cl_2	1	87	88 (*R*)
6[f]	**5**	CH_2Cl_2	1	70	93 (*R*)
7	**5**	toluene	1	80	87 (*R*)
8	**5**	MeOH	1	73	21 (*R*)
9	**5**	MeCN	1	63	66 (*R*)
10	**5**	THF	1	83	66 (*R*)
11	**6**	CH_2Cl_2	1	75	60 (*S*)

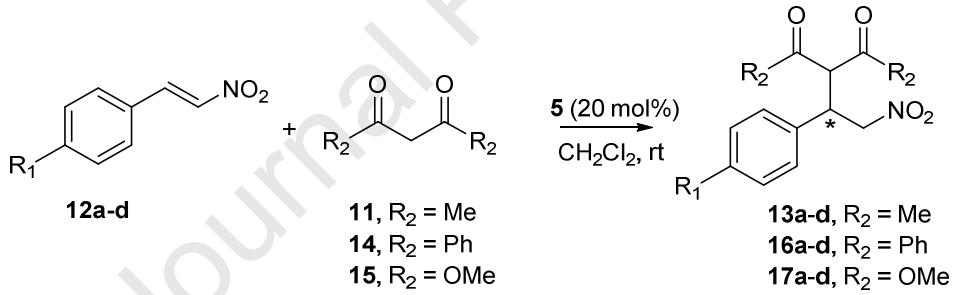
[a] Isolated yield. [b] Determined by chiral HPLC analysis. [c] Determined by comparison of the HPLC retention times and optical rotations values with reported data (Ref.[8]). [d] Racemic sample. [e] In the presence of 5 mol% of the catalyst **5**. [f] Reaction was performed at -20 °C.

Model Michael reaction catalyzed by **2-4** was very slow and afforded the corresponding addition product **13a** in very low yield as a racemic mixture (Table 1, entries 2-3) or with only 6% enantiomeric excess after seven days (Table 1, entry 1). Among the tested catalysts cinchona-based catalyst **5** emerged as the most effective catalyst, affording (*R*)-configured adduct **13a** in an excellent yield (98%) and high 88% *ee* with a significant shortening of the reaction time to one day (Table 1, entry 4). On the other hand, its diastereoisomeric partner **6** was found to be less-active in terms of enantioselectivity (60% *ee*, Table 1, entry 11), providing the Michael product **13a** in only 75% yield with the opposite (*S*)-stereochemistry. The screening of solvents revealed dichloromethane as the most suitable solvent from all

tested (Table 1, entries 4-10). Catalyst loading was successfully reduced to 5 mol% without any loss of enantioselectivity in slightly lower yield (Table 1, entry 5). Performing the reaction at low temperature (-20 °C) were also investigated afforded the best enantioselective results (93% *ee*) but only 70% of product was formed (Table 1, entry 6). The absolute configuration of **13a** was determined by comparison of the HPLC and optical rotation data in the literature for both enantiomers of **13a**.[8]

Having identified the bifunctional thiourea **5** as a promising catalyst, we focused our attention on evaluating the synthetic potential of **5** in the Michael addition of the symmetrical 1,3-dicarbonyl compounds **11** and **14**, including dimethyl malonate **15**, to both unsubstituted **12a** and substituted *β*-nitrostyrenes **12b-d** with methyl-, methoxy- and bromo- groups on the phenyl ring (Table 2). For this screening we used previously optimized reaction conditions of the model study (20 mol% of catalyst, CH_2Cl_2, room temperature).

Table 2. Enantioselective 1,4-addition of Michael donors **11**, **14** and **15** to various *β*-nitrostyrenes **12a-d** catalyzed by **5**



Entry	Nitroolefin	Michael donor	Time (h)	Yield[a] (%)	*ee*[b] (%) config.[c]
1	**12a** (R_1 = H)	**11** (R_2 = Me)	24	98 (**13a**)	88 (*R*)
2	**12b** (R_1 = Me)	**11** (R_2 = Me)	24	96 (**13b**)	86 (*R*)
3	**12c** (R_1 = OMe)	**11** (R_2 = Me)	24	91 (**13c**)	94 (*R*)
4	**12d** (R_1 = Br)	**11** (R_2 = Me)	24	81 (**13d**)	92 (*R*)
5	**12a** (R_1 = H)	**14** (R_2 = Ph)	24	82 (**16a**)	88 (*R*)
6[e]	**12a** (R_1 = H)	**14** (R_2 = Ph)	24	73 (**16a**)	89 (*R*)
7	**12b** (R_1 = Me)	**14** (R_2 = Ph)	24	75 (**16b**)	80 (*R*)
8	**12c** (R_1 = OMe)	**14** (R_2 = Ph)	24	80 (**16c**)	76 (*R*)
9	**12d** (R_1 = Br)	**14** (R_2 = Ph)	24	29 (**16d**)	60 (*R*)
10	**12a** (R_1 = H)	**15** (R_2 = OMe)	48	14 (**17a**)	8 (*R*)
11	**12b** (R_1 = Me)	**15** (R_2 = OMe)	48	11 (**17b**)	11 (*R*)
12	**12c** (R_1 = OMe)	**15** (R_2 = OMe)	48	42 (**17c**)	17 (*R*)

13	**12d** (R_1 = Br)	**15** (R_2 = OMe)	48	27 (**17d**)	13[d]

[a] Isolated yield. [b] Determined by chiral HPLC analysis. [c] Determined by comparison with reported data - HPLC retention times and optical rotation values (Refs.[8,9]). [d] The absolute configuration not assigned. [e] In the presence of 5 mol% of the catalyst **5**.

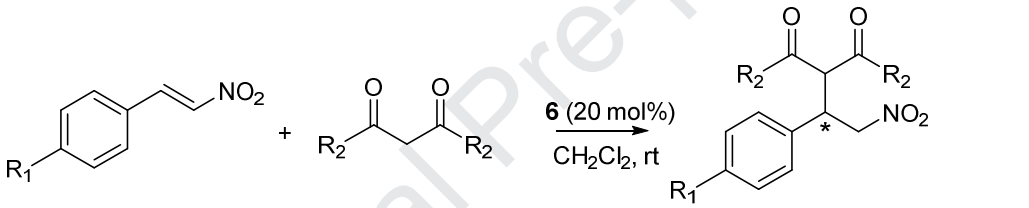
As given in Table 2, in the case of Michael addition of pentane-2,4-dione **11** to **12b-d**, all of the *para*-substituted nitroolefins used was found to furnish adducts **13b-d** in very good yields (81-96%) and enantioselectivities (86-94% *ee*). The best level of selectivity (94% *ee*) was observed for the reaction between **11** and *β*-nitrostyrene **12c** bearing an electron-donating group on the phenyl core when compared to the model reaction (Table 1, entry 1 *versus* entry 3). On the other hand, 1,3-dicarbonyl compound **14** yielded with the corresponding olefins **12b-c** products **16b-d** with relatively lower enantioselectivities (76-80% *ee*). The chemical yields were good and ranged from 75 to 80% (Table 2, entries 7-8). The ability of **5** to catalyze the enantioselective 1,4-addition between **12d** and **14** was significantly reduced and expected product **16d** was obtained in only 29% yield with 60% *ee* (Table 2, entry 9). A promising result of the Michael addition regarding selectivity (88% *ee*) and effectivity (82% yield) was observed in the case of the unsubstituted olefin **12a** (Table 2, entry 5). It should be noted that also in this case the amount of catalyst had no significant effect on the course of the reaction. After reducing the catalyst loading from 20 mol% to 5 mol% the selectivity remains the same and the chemical yield gently decreased (89% *ee*, 73%, Table 2, entry 6).

For extending the substrate scope of the Michael addition, we also investigated the reaction of nitrostyrenes **12a-d** with dimethyl malonate **15** as the Michael donor. The use of **15** as a catalyst led to a dramatic loss of stereocontrol providing the corresponding products **17a-d** in very small yields ranged from 11 to 42% (Table 2, entries 10-13). The different reactivity of malonate **15** toward the Michael addition by comparison with 1,3-dicarbonyl compounds **11** and **14** could be explained by the lower acidity of the methylene group protons in the case of **15**.

To make a comparison between thioureas **5** and **6**, we also turned our attention to the catalytic activity of **6**. The use of **6** allowed the conversion of both unsubstituted and substituted *β*-nitrostyrenes **12a** and **12c** with the 1,3-diketones **11** and **14** into the corresponding adducts **13a**, **13c**, **16a** and **16c** in good yields (up to 85%), but a significant decrease of enantioselectivity was noticed (16-60% *ee*, Table 3, entries 1-4).

The absolute configuration of the aforementioned products was assigned by comparison of the HPLC retention times[8, 9] and opposite optical rotation values with the published data[8c] (see ESI), revealing the (*S*)-stereochemistry of the prevalent antipode in all cases (Table 3). Our screening showed that the absolute configuration of the Michael products is controlled by the (*R*)-configured C-9/C-8 stereocenters in the bulky 9-amino-9-deoxyquinidine moiety of **5** (Table 2). Surprisingly, thiourea **6** bearing the (8*S*,9*S*)-9-amino-9-deoxy-epiquinine fragment was found to be a poorer catalyst for preferring the formation of the opposite enantiomer. The obtained results indicate that the proper conformation of the cinchona alkaloid-derived scaffolds is probably necessary for successful asymmetric induction, while a furanose template is beneficial for the tuning of the catalyst.

Table 3. Bifunctional cinchona organocatalyst **6** catalyzed Michael reaction of nitrostyrenes **12a**, **12c** with donors **11** and **14**



12a, R_1 = H
12c, R_1 = OMe

11, R_2 = Me
14, R_2 = Ph

13a, R_1 = H, R_2 = Me
13c, R_1 = OMe, R_2 = Me
16a, R_1 = H, R_2 = Ph
16c, R_1 = OMe, R_2 = Ph

Entry	Catalyst	Nitrostyrenes	Michael donor	Time (h)	Yield[a] (%)	*ee*[b] (config.)[c]
1	**6**	**12a** (R_1 = H)	**11** (R_2 = Me)	24	75 (**13a**)	60 (*S*)
2	**6**	**12c** (R_1 = OMe)	**11** (R_2 = Me)	24	85 (**13c**)	44 (*S*)
3	**6**	**12a** (R_1 = H)	**14** (R_2 = Ph)	24	78 (**16a**)	16 (*S*)
4	**6**	**12c** (R_1 = OMe)	**14** (R_2 = Ph)	24	31 (**16c**)	40 (*S*)

[a] Isolated yield. [b] Determined by chiral HPLC analysis. [c] Determined by comparison with reported data - HPLC retention times and optical rotation values (Refs.[8,9]).

3. Conclusion

In conclusion, five novel glucofuranose-based thiourea organocatalysts **2**-**6** were synthesized from the commercially available amines **7**-**10** and the known isothiocyanate **1** developed in our laboratory. The initial screening of their catalytic activity on the model Michael addition showed the promising potential of the bifunctional catalyst **5**, bearing a quinidine-derived

cinchona alkaloid scaffold. Thiourea **5** proved to be a highly efficient catalyst for the Michael addition of 1,3-dicarbonyl compounds to nitrostyrenes to afford the corresponding adducts with good-to-high enantioselectivities (up to 94% *ee*) in excellent yields (up to 98%), without any additive. Catalyst loading screening study revealed that only 5 mol% is sufficient to catalyze the reaction, and decrease the reaction temperature to -20 °C slightly improved the enantiomeric enrichment but resulted in lower yield. Further studies, aimed at the reaction mechanism and scope of this novel catalyst, are currently in progress.

4. Experimental section

4.1. General methods

All reagents bought from commercial sources (Aldrich or Acros Organics) were used as sold without further purification. Solvents were dried and purified before use according to standard procedures. Yields refer to chromatographically purified and spectroscopically pure compounds, unless otherwise stated. All reactions were performed under an atmosphere of nitrogen. Reactions were monitored by thin layer chromatography (TLC) using Merck silica gel 60 F_{254} analytical plates and visualized by fluorescence quenching under UV light (254 nm). In addition, TLC plates were stained with a dipping solution of basic potassium permanganate solution, or ethanolic acidic solution of *p*-anisaldehyde followed by heating. Chromatographic purification was performed on silica gel, Kieselgel 60 (0.040–0.063 mm, 230–400 mesh, Merck). Solvents for chromatography (*n*-hexane, EtOAc, DCM, MeOH) were distilled before use. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury Plus 400 FT NMR (400.13 MHz for ^{1}H and 100.61 MHz for ^{13}C) spectrometer in deuterated solvents ($CDCl_3$ and CD_3OD). NMR data are reported as follows: δ are given in parts per million (ppm), for ^{1}H relative to TMS (δ = 0.00 ppm) as the internal standard or to the solvent signals CD_3OD (δ = 4.84 ppm or δ = 3.31 ppm) and for ^{13}C relative to $CDCl_3$ (δ = 77.00 ppm) or CD_3OD (δ = 49.05 ppm). The multiplicity of the ^{13}C NMR signals concerning the ^{13}C-^{1}H coupling was determined by the HSQC and HMBC method. Chemical shifts (in ppm) and coupling constants (in Hz) were obtained by first-order analysis; assignments were derived from COSY and H/C correlation spectra. Infrared (IR) spectra were measured with a Nicolet 6700 FT-IR spectrometer and are listed in ν values (cm^{-1}), only selected maximum absorbances are reported. High-resolution mass spectra (HRMS) were recorded on a micrOTOF-Q II quadrupoletime of flight hybrid mass spectrometer (Bruker Daltonics).

Optical rotations were measured on a P-2000 Jasco polarimeter and reported as follows: $[\alpha]_D$ (*c* in grams per 100 mL, solvent). Melting points were obtained on a Kofler hot block and are uncorrected. The enantiomeric excesses were determined by HPLC analysis on chiral columns (Chiralpak-IA, Lux 5μm i-Amylose-1) using *n*-hexane/*i*-PrOH as a mobile phase. The corresponding HPLC analyses were performed on a Shimadzu HPLC system, including the following instruments: LC-20AD pump and refractive index detector RID-10A. Nitrostyrenes **12a-d** were synthesized according to the known procedure[10b] and their spectroscopic data and other relevant characteristics were in good accord with those reported in the literature for the same compounds.[10]

*4.1.1. Preparation of catalyst **2***

To a solution of **1**[7] (0.10 g, 0.305 mmol) in dry THF (4 mL) was added (*R*)-(+)-α-methylbenzylamine (*R*)-**7** (47 μL, 0.366 mmol). After being stirred for 1 h at room temperature, the solvent was evaporated, and the residue was flash-chromatographed through a short column of silica gel (*n*-hexane/EtOAc, 4:1) to give 0.13 g (96%) of compound **2** as a white amorphous solid; $[\alpha]_D^{21}$ +61.1 (*c* 1.12, $CHCl_3$). IR (neat) *v* 3340, 2984, 2931, 1531 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 1.25 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.55 (d, *J* = 6.9 Hz, 3H, CH_3), 4.02 (d, *J* = 7.8 Hz, 1H, H-4), 4.07 (dd, *J* = 8.7, 5.0 Hz, 1H, H-6), 4.09–4.16 (m, 1H, H-6), 4.23–4.30 (m, 1H, H-5), 4.49 (s, 1H, H-2), 5.47 (d, *J* = 11.0 Hz, 1H, H-8), 5.50–5.64 (m, 2H, H-8, CH), 5.76 (s, 1H, H-1), 5.96 (d, *J* = 17.7, 11.0 Hz, 1H, H-7), 6.36 (s, 1H, NH), 6.87 (d, *J* = 7.2 Hz, 1H, NH), 7.23–7.37 (m, 5H, Ph); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 21.7 (CH_3), 25.3 (CH_3), 26.3 (CH_3), 26.7 (CH_3), 26.8 (CH_3), 55.8 (CH), 67.3 (C-6), 70.1 (C-3), 73.1 (C-5), 81.6 (C-4), 86.7 (C-2), 103.7 (C-1), 110.5 (C_q), 113.1 (C_q), 121.1 (C-8), 126.4 (2 × CH_{Ph}), 127.6 (CH_{Ph}), 128.7 (2 × CH_{Ph}), 131.3 (C-7), 142.5 (C_i), 180.6 (C=S). ESI-HRMS: *m/z* calcd for $C_{23}H_{33}N_2O_5S$ $[M + H]^+$ 449.2105, found 449.2126.

*4.1.2. Preparation of catalyst **3***

Using the same procedure as described for the synthesis of **2**, the corresponding isothiocyanate **1**[7] (0.10 g, 0.305 mmol) and (*S*)-(–)-α-methylbenzylamine (*S*)-**7** (47 μL, 0.366 mmol) afforded after flash chromatography on silica gel (*n*-hexane/EtOAc, 4:1) 0.13 g (96%) of compound **3** as a white amorphous solid; $[\alpha]_D^{21}$ +82.8 (*c* 0.92, $CHCl_3$). IR (neat) *v* 3354, 2984, 2932, 1536 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 1.25 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.54 (d, *J* = 6.9 Hz, 3H, CH_3), 4.01 (d, *J* = 7.8 Hz, 1H,

H-4), 4.05 (dd, *J* = 8.8, 5.0 Hz, 1H, H-6), 4.09–4.16 (m, 1H, H-6), 4.23–4.31 (m, 1H, H-5), 4.49 (s, 1H, H-2), 5.47 (d, *J* = 11.0 Hz, 1H, H-8), 5.51–5.63 (m, 2H, H-8, CH), 5.75 (s, 1H, H-1), 5.96 (dd, *J* = 17.8, 11.0 Hz, 1H, H-7), 6.32 (s, 1H, NH), 6.85 (d, *J* = 7.4 Hz, 1H, NH), 7.38–7.23 (m, 5H, Ph); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.7 (CH_3), 25.3 (CH_3), 26.3 (CH_3), 26.7 (CH_3), 26.8 (CH_3), 55.8 (CH), 67.3 (C-6), 70.1 (C-3), 73.1 (C-5), 81.6 (C-4), 86.7 (C-2), 103.7 (C-1), 110.6 (C_q), 113.1 (C_q), 121.1 (C-8), 126.5 (2 × CH_{Ph}), 127.6 (CH_{Ph}), 128.7 (2 × CH_{Ph}), 131.3 (C-7), 142.5 (C_i), 180.7 (C=S). ESI-HRMS: *m/z* calcd for $C_{23}H_{33}N_2O_5S$ $[M + H]^+$ 449.2105, found 449.2131.

*4.1.3. Preparation of catalyst **4***

(1*R*,2*R*)-(−)-1,2-diaminocyclohexane **8** (0.17 g, 1.527 mmol) was added to a solution of isothiocyanate **1**[7] (0.10 g, 0.305 mmol) in dry CH_2Cl_2 (4 mL). After being stirred for 1.5 h at room temperature, the mixture was concentrated, and the residue was chromatographed on silica gel (CH_2Cl_2/MeOH, 10:1). This procedure yielded 0.10 g (75%) of compound **4** as white crystals; mp 128–130 °C; $[\alpha]_D^{21}$ +68.6 (*c* 0.98, $CHCl_3$). IR (neat) *v* 3319, 3272, 2985, 2933, 2858, 1556 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02–1.37 (m, 10H, 2 × CH_2, 2 × CH_3), 1.44 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.64–1.76 (m, 2H, CH_2), 1.92–2.09 (m, 2H, CH_2), 2.31 (br s, 2H, NH_2), 2.44–2.55 (m, 1H, CH), 3.99–4.16 (m, 4H, H-4, 2 × H-6, CH), 4.27–4.36 (m, 1H, H-5), 4.59 (br s, 1H, H-2), 5.47–5.60 (m, 2H, 2 × H-8), 5.88 (d, *J* = 3.4 Hz, 1H, H-1), 5.97 (dd, *J* = 17.7, 11.0 Hz, 1H, H-7), 6.40 (br s, 1H, NH), 6.61 (br s, 1H, NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.9 (CH_2), 25.0 (CH_2), 25.3 (CH_3), 26.4 (CH_3), 26.7 (CH_3), 26.9 (CH_3), 32.3 (CH_2), 34.7 (CH_2), 55.8 (CH), 62.8 (CH), 67.4 (C-6), 70.0 (C-3), 73.0 (C-5), 81.8 (C-4), 86.7 (C-2), 103.8 (C-1), 110.5 (C_q), 113.0 (C_q), 120.8 (C-8), 131.3 (C-7), 181.5 (C=S). ESI-HRMS: *m/z* calcd for $C_{21}H_{36}N_3O_5S$ $[M + H]^+$ 442.2370, found 442.2379.

*4.1.4. Preparation of catalyst **5***

A solution of (9*R*)-6'-methoxycinchonan-9-amine trihydrochloride **9**.3 HCl (0.10 g, 0.231 mmol) in dry THF (9 mL) was treated with Et_3N (96 μL, 0.693 mmol) at room temperature. Then isothiocyanate **1**[7] (83 mg, 0.254 mmol) was added and stirring was continued for 48 h at the same temperature. After completion of the reaction, the solvent was evaporated, and the residue was subjected to flash chromatography on silica gel (CH_2Cl_2/MeOH, 98:2) to afford 0.135 g (90%) of compound **5** as a white amorphous solid; $[\alpha]_D^{21}$ +154.5 (*c* 0.92, $CHCl_3$). IR (neat) *v* 3315, 2983, 2935, 1621 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 1.00–1.10 (m, 1H, H-

7), 1.13–1.23 (m, 1H, H-7), 1.29 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.57–1.67 (m, 3H, H-4, 2 × H-5), 2.31–2.40 (m, 1H, H-3), 2.93–3.05 (m, 3H, 2 × H-6, H-2), 3.26–3.33 (m, 1H, H-8), 3.34–3.36 (m, 2H, H-9, H-2), 3.94–4.05 (m, 5H, OCH_3, H-4", H-6"), 4.06–4.12 (m, 1H, H-6"), 4.45 (dd, *J* = 11.9, 6.1 Hz, 1H, H-5"), 5.02–5.16 (m, 3H, H-2", H-8", *H*-CH_2), 5.17–5.28 (m, 2H, H-8", *H*-CH_2), 5.78 (s, 1H, H-1"), 5.88–6.00 (m, 2H, H-7", CH), 6.24 (br s, 1H, NH), 7.43 (d, *J* = 9.2 Hz, 1H, H-7'), 7.48 (d, *J* = 4.6 Hz, 1H, H-3'), 7.93 (d, *J* = 9.2 Hz, 1H, H-8'), 7.99 (s, 1H, H-5'), 8.67 (d, *J* = 4.6 Hz, 1H, H-2'); NH not seen; ^{13}C NMR (101 MHz, CD_3OD) δ 25.6 (CH_3), 26.5 (C-7), 26.6 (CH_3), 26.9 (2 × CH_3), 27.4 (C-5), 28.8 (C-4), 40.3 (C-3), 49.0 (C-2), 49.9 (C-9), 50.2 (C-6), 56.6 (OCH_3), 61.2 (C-8), 68.0 (C-6"), 71.0 (C-3"), 74.2 (C-5"), 83.2 (C-4"), 86.5 (C-2"), 104.0 (C-5'), 105.4 (C-1"), 111.2 (C_q), 113.6 (C_q), 115.2 (CH_2), 119.3 (C-8"), 120.9 (C-3'), 124.0 (C-7'), 130.1 (C-4a'), 131.2 (C-8'), 132.9 (C-7"), 141.8 (CH), 145.2 (C-8a'), 148.2 (C-2', C-4'), 159.6 (C-6'), 183.7 (C=S); HSQC correlation: H-2/C-2, HMBC correlation: CH/C-2. ESI-HRMS: *m/z* calcd for $C_{35}H_{47}N_4O_6S$ $[M + H]^+$ 651.3211, found 651.3243.

4.1.5. Preparation of catalyst ***6***

According to the same procedure described for the preparation of **5**, 9-amino-(9-deoxy)-*epi*-quinine trihydrochloride **10**.3 HCl (0.12 g, 0.277 mmol), Et_3N (0.12 mL, 0.831 mmol) and isothiocyanate **1**[7] (0.10 g, 0.305 mmol) provided after chromatography on silica (CH_2Cl_2/MeOH, 98:2) 0.176 g (98%) of compound **6** as a white amorphous solid; $[\alpha]_D^{21}$ – 52.6 (*c* 0.34, $CHCl_3$). IR (neat) *v* 3332, 2930, 2360, 1723, 1525 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 0.88 (dd, *J* = 13.1, 6.6 Hz, 1H, H-7), 1.29 (s, 6H, 2 × CH_3), 1.35–1.42 (m, 4H, CH_3, H-7), 1.50 (s, 3H, CH_3), 1.57–1.74 (m, 3H, H-4, 2 × H-5), 2.28–2.38 (m, 1H, H-3), 2.69–2.82 (m, 2H, H-2, H-6), 3.20–3.32 (m, 3H, H-2, H-8, H-9), 3.35–3.52 (m, 1H, H-6), 3.96 (dd, *J* = 8.5, 5.8 Hz, 1H, H-6"), 4.01 (s, 3H, OCH_3), 4.02–4.12 (m, 2H, H-4", H-6"), 4.36 (dd, *J* = 11.5, 6.2 Hz, 1H, H-5"), 4.92–5.04 (m, 2H, CH_2), 5.13 (s, 1H, H-2"), 5.33-5.47 (m, 2H, 2 × H-8"), 5.74 (d, *J* = 3.0 Hz, 1H, H-1"), 5.82 (dd, *J* = 16.3, 8.9 Hz, 1H, CH), 6.01–6.16 (m, 2H, H-7", NH), 7.44 (d, *J* = 9.2 Hz, 1H, H-7'), 7.49 (d, *J* = 4.6 Hz, 1H, H-3'), 7.93 (d, *J* = 9.2 Hz, 1H, H-8'), 8.01 (s, 1H, H-5'), 8.66 (d, *J* = 4.6 Hz, 1H, H-2'); NH not shown; ^{13}C NMR (101 MHz, CD_3OD) δ 25.5 (CH_3), 26.6 (C-7), 26.7 (CH_3), 26.9 (CH_3), 27.0 (CH_3), 28.7 (C-5), 28.9 (C-4), 40.9 (C-3), 42.5 (C-6), 49.1 (C-9), 56.5 (OCH_3), 56.9 (C-2), 62.1 (C-8), 67.8 (C-6"), 71.1 (C-3"), 74.2 (C-5"), 82.9 (C-4"), 86.3 (C-2"), 104.3 (C-5'), 105.4 (C-1"),111.2 (C_q), 113.7 (C_q), 115.0 (CH_2), 120.2 (C-8"), 121.0 (C-3'), 123.6 (C-7'), 130.2 (C-4a'), 131.2 (C-8'), 132.8 (C-7"), 142.6 (CH), 145.0 (C-8a'), 148.3 (C-2', C-4'), 159.5 (C-6'), 182.5 (C=S); HSQC

correlation: H-9/C-9. ESI-HRMS: *m/z* calcd for $C_{35}H_{47}N_4O_6S$ $[M + H]^+$ 651.3211, found 651.3220.

4.1.6. General procedure for the catalytic Michael addition

To a solution of the corresponding nitroolefin (50 mg, **12a-d**) in dry CH_2Cl_2 (1.5 mL) was added organocatalyst (20 mol%, **2-6**) and 1,3-dicarbonyl compound (2 eq, **11**, **14**, **15**). After being stirred at room temperature, the resulting mixture was concentrated, and the residue was subjected to flash chromatography on silica gel. The enantiomeric excess was determined by HPLC analysis on chiral columns (Chiralpak-IA, Lux i-Amylose-1) using *n*-hexane/*i*-PrOH as the mobile phase. The corresponding HPLC chromatograms are listed in ESI.

Conflicts of interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at [it will be filed by the Editorial office].

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Highlights

- Novel cinchona derived glucofuranose-based thiourea catalysts were developed.
- The Michael reaction provided the corresponding products in excellent yields with a high degree of enantioselectivity (up to 94% ee).
- The resulting stereochemistry of Michael adducts was controlled by the quinuclidine part of the bifunctional catalyst.

Novel carbohydrate-based thioureas as organocatalysts for asymmetric Michael addition of 1,3-dicarbonyl compounds to nitroolefins

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Conflicts of interest

The authors declare no conflicts of interest.

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