Synthesis of 2-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)-3-((dimethylamino)methyl)camphor Organocatalysts

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ABSTRACT In a stereo-divergent synthesis, three novel camphor-derived bifunctional thiourea organocatalysts **7–9** have been prepared in five steps starting from (+)-camphor. In addition, borneol-derived bifunctional thiourea organocatalysts **19/19'** have been prepared in three steps from (1*S*)-(+)-camphorquinone. Novel organocatalysts **7–9**, **19/19'** have been evaluated in a model reaction of *Michael* addition of dimethyl malonate to *trans*-β-nitrostyrene with low to moderate enantioselectivities (20%–60% ee). Configuration of all novel compounds has been meticulously determined using nuclear magnetic resonance (NMR) techniques. *Chirality 24:412–419, 2012.* © 2012 Wiley Periodicals, Inc.

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INTRODUCTION

Camphor is one of nature's privileged scaffolds, which is readily available in both enantiomeric forms. It undergoes a wide variety of chemical transformations that functionalize, at first glance, inactivated positions.[1,2] All of the aforementioned makes camphor a very desirable starting material for the preparation of a wide variety of compounds ranging from natural products[1,2] to chiral auxiliaries,[3,4] ligands in asymmetric synthesis,[5–9] NMR shift reagents,[10] and so on.

Bifunctional (thio)urea derivatives comprise the bulk of noncovalent organocatalysts, which can achieve electrophile and nucleophile binding and activation through hydrogen-bonding interactions. The preferred substituent is the electron-poor 3,5-bis(trifluoromethyl)phenyl-group attached through thiourea functionality to a suitable chiral scaffold.[11–26] Concerning the camphor-derived noncovalent organocatalysts, the vast majority represent the pyrrolidinyl–camphor-derived bifunctional organocatalysts, where both camphor and pyrrolidine chiral frameworks, connected with an appropriate linker, act in synergy (Fig. 1).[27–36]

To the best of our knowledge, we could not find any 3,5-bis(trifluoromethyl)phenyl thiourea-derived bifunctional organocatalysts with camphor as the exclusive chiral framework. Considering camphor's vast potential for chemical manipulation and our previous experiences with monofunctional camphor-derived thioureas prompted us to investigate the possibility to prepare novel bifunctional thiourea camphor derivatives, preferably in a stereo-divergent synthesis. Thus, herein, we report our results on the synthesis, structural characterization, and catalyst evaluation of novel camphor-thiourea-derived bifunctional organocatalysts.

EXPERIMENTAL

Materials and Methods

Melting points were determined on a Kofler micro hot stage and on SRS OptiMelt MPA100—Automated Melting Point System (Stanford Research Systems, Sunnyvale, CA, USA). The NMR spectra were obtained on a Bruker UltraShield 500 plus (Bruker, Billerica, MA, USA) at 500 MHz for ^{1}H and 126 MHz for ^{13}C nucleus, using DMSO-d_6 and $CDCl_3$ with TMS as the internal standard, as solvents. Mass spectra were recorded on an Agilent 6224 Accurate Mass TOF LC/MS (Agilent Technologies, Santa Clara, CA, USA) and infrared (IR) spectra on a Perkin-Elmer Spectrum BX FTIR spectrophotometer (Waltham, MA, USA). Microanalyses were performed on a Perkin-Elmer CHN Analyzer 2400 II (PerkinElmer, Waltham, MA, USA). Catalytic hydrogenation was performed on a Parr Pressure Reaction Hydrogenation Apparatus (Moline, IL, USA). Column chromatography was performed on silica gel (Silica gel 60 (Sigma-Aldrich, St. Louis, MO, USA), particle size: 0.035–0.070 mm). Medium-pressure liquid chromatography (MPLC) was performed with Büchi Flash Chromatography System (BUCHI Labortechnik AG, Flawil, Switzerland) (Büchi Fraction Collector C-660, Büchi Pump Module C-605, Büchi Control Unit C-620) on silica gel (LiChrosphere® Si 60 (12 μm) and/or LiChroprep® Si 60 (15–25 μm) (Merck, KGaA, Darmstadt, Germany)); column dimensions (wet filled): 22 × 460 mm, 36 × 460 mm, and 40 × 460 mm; backpressure: 10–20 Bar; detection: UV 254 nm. High-performance liquid chromatography (HPLC) analyses were performed on an Agilent 1260 Infinity LC (Agilent Technologies, Santa Clara, CA, USA) by using CHIRALPAK AD-H (0.46 cm ø × 25 cm) as chiral column. Low temperatures were maintained using Julabo FT902 immersion cooler (JULABO Labortechnik GmbH, Seelbach, Germany).

(+)-Camphor (**1**), *tert*-butoxy bis(dimethylamino)methane, anhydrous DMF, 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (**6**), *p*-toluidine hydrochloride (**10**), (1*S*)-(+)-camphorquinone (**16**), dimethyl malonate (**20**),*trans*-β-nitrostyrene (**21**), and 10% palladium on charcoal are commercially available (Sigma-Aldrich, St. Louis, MO, USA). (1*S*,4*S*,3*E*)-3-((Dimethylamino)methylene)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**2**),[37] (1*S*,4*R*,3*E*)-3-(hydroxyimino)-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-one (**17**),[38] and (1*S*,2*R*,3*R*,4*R*)-3-amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (**18**)[39] were prepared following the literature procedure.

The source of chirality is as follows: (+)-camphor (**1**) (Sigma-Aldrich), product number 21300, purum, natural, 97.0% (GC, sum of enantiomers), $[\alpha]_D^{20} = +42.5 \pm 2.5$ (c = 10, EtOH), mp 176–180 °C, ee not specified and

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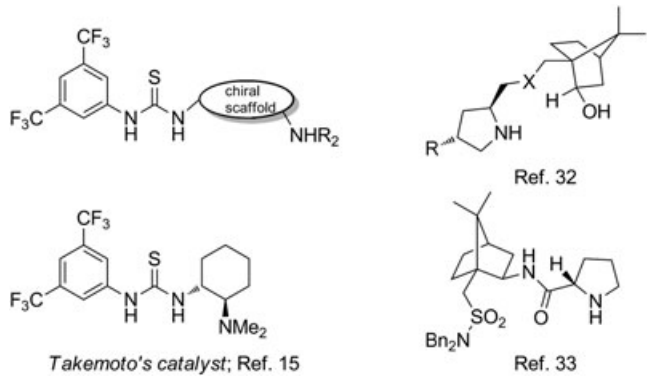


Fig. 1. General outline and an example of a bifunctional thiourea organocatalyst and selected examples of camphor-derived bifunctional organocatalysts.

(1*S*)-(+)-camphorquinone (**16**) (Sigma-Aldrich), product number 272078, 99%, $[\alpha]_D^{20} = +100$ (c = 1.9, PhMe); mp 197–201 °C, ee not specified.

Syntheses

***N,N*-Dimethyl-1-((1R,2R,4S)-4,7,7-trimethyl-3-oxobicyclo[2.2.1]heptan-2-yl)methanaminium chloride (3)[40] and *N,N*-dimethyl-1-((1R,2S,4S)-4,7,7-trimethyl-3-oxobicyclo[2.2.1]heptan-2-yl)methanaminium chloride (3')[40].** To a solution of (1*S*,4*S*,3*E*)-3-((dimethylamino)methylene)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**2**)[37] (1.5 g, 7.24 mmol) in anhydrous EtOH (40 ml) under Argon, Pd–C (10%, 450 mg) and HCl (5 ml, 2 M in EtOAc, 10 mmol) were added. The reaction vessel was flushed with H_2, and the reaction mixture was hydrogenated in a *Paar* hydrogenator (P = 4 Bar) at room temperature for 3 h. The reaction mixture was filtered through a plug of Celite® and washed with EtOH (100 ml). Volatile components were evaporated *in vacuo* to give a crude mixture of ammonium salts **3/3'** (100% conversion), which was used in the following transformation without further purification/separation. Yield: 100% conversion (**3/3'** = 78:22) of dirty white solid. Electron ionization high-resolution mass spectrometry (EI-HRMS): *m/z* = 210.1851 (M^+); $C_{13}H_{24}NO^+$ requires: *m/z* = 210.1852 (M^+). ^{1}H-NMR (500 MHz, DMSO-d_6) for **3**: δ 0.83 (*s*, Me); 0.86 (*s*, Me); 0.98 (*s*, Me); 1.12–1.18 (*m*, 1H of CH_2); 1.51–1.58 (*m*, 1H of CH_2); 1.63–1.81 (*m*, 2H of CH_2); 2.33 (*t*, *J* = 4.1 Hz, H-C(4)); 2.77 (*s*, N*Me*$_2$H$^+$); 2.93–2.98 (*m*, H-C(3)); 3.22 (*d*, *J* = 7.6 Hz, H_2-C(3')); 10.31 (*s*, NMe$_2$*H*$^+$). ^{1}H-NMR (500 MHz, DMSO-d_6) for **3'**: δ 0.68 (*s*, Me); 0.82 (*s*, Me); 0.91 (*s*, Me); 1.43–1.49 (*m*, 1H of CH_2); 1.92–1.98 (*m*, 1H of CH_2); 2.24 (*d*, *J* = 4.0 Hz, H-C(4)); 2.41 (*dd*, *J* = 3.5; 6.3 Hz, H-C(3)); 2.76 (*s*, N*Me*$_2$H$^+$);10.51 (s, NMe$_2$*H*$^+$).

(1S,3R,4R,2E)-3-((Dimethylamino)methyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one oxime (4)[41] and (1S,3S,4R,2E)-3-((dimethylamino)methyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one oxime (4')[41]. To a solution of **3/3'** (**3**:**3'** = 78:22, 7.2 mmol) in EtOH (70 ml), pyridine (6.3 ml, 78.8 mmol) and $NH_2OH{\cdot}HCl$ (6.95 g, 100 mmol) were added, and the resulting mixture was refluxed for 24 h. Volatile components were thoroughly evaporated *in vacuo*, and to the residue, $NaHCO_3$ (aq. sat. 100 ml) was added followed by extraction with CH_2Cl_2 (3 × 100 ml). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and volatile components evaporated *in vacuo*. The residue was dried on high vacuum to give a crude mixture of oximes **4/4'**, which was used in the following transformation without further purification/separation. Yield: 1.4 g (86%, **4**:**4'** = 84:16) of dirty white solid. EI-HRMS: *m/z* = 225.1949 (MH^+); $C_{13}H_{25}N_2O$ requires: *m/z* = 225.1961 (MH^+); ^{1}H-NMR (500 MHz, $CDCl_3$) for **4**: δ 0.85 (*s*, Me); 0.93 (*s*, Me); 1.02 (*s*, Me); 1.34 (*t*, *J* = 9.4 Hz, 1H of CH_2); 1.42–1.47 (*m*, 1H of CH_2); 1.63–1.75 (*m*, 2H of CH_2); 1.86 (*t*, *J* = 4.0 Hz, 1H-C(4)); 2.26 (*dd*, *J* = 2.4; 12.5 Hz, Ha-C(3')); 2.37 (*s*, NMe_2); 2.55 (*dd*, *J* = 11.3; 12.4 Hz, Hb-C(3')); 2.82–2.87 (*m*, H-C(3)); 12.54 (br *s*, OH). ^{1}H-NMR (500 MHz, $CDCl_3$) for **4'**: δ 0.89 (*s*, Me); 0.89 (*s*, Me); 1.04 (*s*, Me); 2.35 (s, NMe_2). ^{13}C-NMR (126 MHz, $CDCl_3$) for **4**: δ 12.3, 18.8, 19.1, 21.0, 32.3, 40.7, 45.3, 47.2, 48.3, 53.2, 59.9, 167.3.

(1S,4R)-3-((Dimethylamino)methyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine (5)[41]. To a solution of oxime **4/4'** (**4**:**4'** = 84:16, 1.2 g, 5.35 mmol) in anhydrous *n*PrOH (25 ml) under Argon under reflux, sodium (*ca.* 200 mg) was added. Before all the added sodium reacted, another chunk of sodium (*ca.* 200 mg) was added, followed by addition of further sodium to ensure a continuous evolution of hydrogen for 1 h. After all the sodium reacted, volatile components were evaporated *in vacuo*, and to the residue, H_2O (100 ml) was added followed by extraction with EtOAc (3 × 70 ml). Combined organic phase was dried over anhydrous Na_2SO_4, filtered, and volatile components evaporated *in vacuo* to give the crude amine **5**, as a mixture of stereoisomers in a ratio of 54:29:17 and in 100% conversion. The amine mixture was used in the following transformation without further purification/separation. Yield: 1 g (89%) of yellowish brown oil. EI-HRMS: *m/z* = 211.2170 (MH^+); $C_{13}H_{27}F_6N_2$ requires: *m/z* = 211.2169 (MH^+).

Preparation of 2-(3-(3,5-Bis(trifluoromethyl)phenyl) thioureido)-3-((dimethylamino)methyl)-camphor Stereoisomers 7, 8, and 9

To a solution of crude mixture of amines **5** (632 mg, 3 mmol) in anhydrous Et_2O (20 ml) at 0 °C, 1-isothiocyanato-3,5-bis(trifluoromethyl) benzene (**6**) (418 µl, 2.2 mmol) was added, and the resulting mixture was stirred for 30 min at 0 °C and further 24 h at room temperature. The reaction mixture was passed through a plug of Silica gel 60 (length of 5 cm) and washed with EtOAc/Et_3N/MeOH = 100:2:1 to elute all the products. Volatile components were evaporated *in vacuo*, and the residue was separated by MPLC (EtOAc/Et_3N/MeOH = 100:2:1). Fractions containing the separated products were combined and volatile components evaporated *in vacuo* to give **7**, **8**, and **9**, respectively. Fractions containing mixtures of products or not fully separated products were discarded.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((1S,2R,3R,4R)-3-((dimethylamino)methyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl) thiourea (7). **7** elutes first from the column. Yield: 439 mg (41%) of white solid; mp 50–58 °C. $[\alpha]_D^{r.t.} = -121.4$ (c = 0.12, CH_2Cl_2) ($C_{22}H_{29}F_6N_3S$ requires: C, 54.87; H, 6.07; N, 8.73 and found: C, 55.22; H, 6.24; N, 8.65); EI-HRMS: *m/z* = 480.1917 ($M\text{-}H^+$); $C_{22}H_{28}F_6N_3S$ requires: *m/z* = 480.1914 ($M\text{-}H^+$); ν_{max} (KBr) 3438, 2956, 1636, 1496, 1472, 1382, 1278, 1204, 1174, 1134, 1107, 1002, 884, 701, 681 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 0.84 (*s*, 2×Me); 0.99 (*s*, Me); 1.16–1.22 (*m*, 1H of CH_2); 1.42–1.59 (*m*, 3H of CH_2); 1.70 (br *s*, H-C(4)); 2.11 (*s*, NMe_2); 2.18–2.26 (*m*, H-C(3), Ha-C(3')); 2.43 (*t*, *J* = 12.5 Hz, Hb-C(3')); 4.11 (*dd*, *J* = 6.0; 7.8 Hz, H-C(2)); 7.71 (*s*, 1H of Arl); 7.78 (*d*, *J* = 8.7 Hz, H-N(2')); 8.32 (*s*, 2H of Arl); 10.16 (br *s*, NH). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 11.9, 19.6, 19.7, 20.6, 36.0, 44.7, 45.4, 46.6, 47.4, 50.1, 60.2, 65.4, 115.7 (br *s*), 121.1 (br *s*), 123.3 (*q*, *J* = 272.7 Hz), 130.1, (*q*, *J* = 32.8 Hz), 142.0, 180.7.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((1S,2S,3S,4R)-3-((dimethylamino)methyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl) thiourea (8). **8** elutes second from the column. Yield: 64 mg (6%) of white solid; mp 50–57 °C. $[\alpha]_D^{r.t.} = +108.7$ (c = 0.12, CH_2Cl_2) ($C_{22}H_{29}F_6N_3S$ requires: C, 54.87; H, 6.07; N, 8.73 and found: C, 55.83; H, 6.11; N, 8.69); EI-HRMS: *m/z* = 480.1914 ($M\text{-}H^+$); $C_{22}H_{28}F_6N_3S$ requires: *m/z* = 480.1914 ($M\text{-}H^+$); ν_{max} (KBr) 3416, 2958, 1635, 1541, 1502, 1473, 1383, 1278, 1178, 1133, 1107, 1025, 1002, 883, 700, 682 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 0.80 (*s*, Me); 0.84 (*s*, Me); 0.97 (*s*, Me); 1.16–1.25 (*m*, 1H of CH_2); 1.26–1.35 (*m*, 1H of CH_2); 1.37–1.43 (*m*, H-C(4)); 1.60–1.68 (*m*, H-C(3), 1H of CH_2); 1.73–1.81 (*m*, 1H of CH_2); 2.09 (*s*, NMe_2); 2.31 (*dd*, *J* = 3.3; 11.9 Hz, Ha-C(4')); 2.46 (*dd*, *J* = 9.4; 12.3 Hz, Hb-C(4')); 4.81 (*t*, *J* = 6.9 Hz, H-C(2)); 7.72 (*s*, 1H of Arl); 8.27 (*s*, 2H of Arl); 8.29 (*d*, *J* = 9.5 Hz, H-N(2')); 9.92 (*s*, NH). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 13.7, 19.7, 21.1, 27.7, 29.9, 45.3, 47.4, 48.4, 49.6, 50.4, 63.9, 64.6, 115.7 (br *s*), 121.3 (br *s*), 123.3 (*q*, *J* = 272.8 Hz), 130.2, (*q*, *J* = 33.0 Hz), 142.0, 181.1.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((1S,2S,3R,4R)-3-((dimethylamino)methyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl) thiourea (9). **9** elutes third from the column. Yield: 341 mg (32%) of white solid; mp 48–56 °C. $[\alpha]_D^{r.t.} = +141.7$ (c = 0.16, CH_2Cl_2) ($C_{22}H_{29}F_6N_3S$ requires: C, 54.87; H, 6.07; N, 8.73 and found: C, 54.88; H, 6.37; N, 8.60); EI-HRMS: *m/z* = 480.1913 ($M\text{-}H^+$); $C_{22}H_{28}F_6N_3S$ requires: *m/z* = 480.1914 ($M\text{-}H^+$); ν_{max} (KBr) 3422, 2961, 1625, 1541, 1474, 1385, 1278, 1225, 1177, 1133, 1108, 1001, 883, 700, 682 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 0.76 (*s*, Me); 0.90 (*s*, Me); 0.99 (*s*, Me); 1.30–1.58 (*m*, 4H of CH_2); 1.68 (br *s*, H-C(4)); 1.95 (*dd*, *J* = 5.5; 12.0 Hz, Ha-C(3')); 2.09 (*s*, NMe_2); 2.32 (*t*, *J* = 11.7 Hz, Hb-C(3')); 2.43–2.50 (*m*, H-C(3)); 4.76 (*t*, *J* = 9.9 Hz, H-C(2)); 7.72 (*s*, 1H of Arl); 7.94 (*d*, *J* = 9.2 Hz, H-N(2')); 8.39 (*s*, 2H of Arl); 10.13 (br *s*, NH). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 14.1, 18.2, 19.7, 19.9, 27.6, 35.2, 45.3, 46.2, 47.0, 49.5, 56.0, 58.4, 115.7 (br *s*), 121.0 (br *s*), 123.3 (*q*, *J* = 272.7 Hz), 130.1, (*q*, *J* = 32.7 Hz), 142.0, 181.3.

(1S,4S,3Z)-1,7,7-Trimethyl-3-((p-tolylamino)methylene)bicyclo[2.2.1]heptan-2-one (11) and (1S,4S,3E)-1,7,7-trimethyl-3-((p-tolylamino)methylene)bicyclo[2.2.1]heptan-2-one (11'). To a solution of (1*S*,4*S*,3*E*)-3-((dimethylamino)methylene)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**2**) (196 mg, 0.947 mmol) in anhydrous EtOH (2 ml), *p*-toluidine hydrochloride (**10**) (136 mg, 0.947 mmol) was added, and the mixture was stirred at room temperature for 24 h. The resulting precipitate was collected by filtration and washed with cold EtOH (1 ml, 0 °C) to give the product as a mixture of major (*Z*)-isomer **11** and minor (*E*)-isomer **11'**. Yield: 140 mg (54%, **11/11'** = 92:8) of dirty white solid; mp 171–181 °C. $[\alpha]_D^{r.t.}$ = +363.7 (c = 0.08, CH_2Cl_2) ($C_{18}H_{23}NO$ requires: C, 80.26; H, 8.61; N, 5.20 and found: C, 80.22; H, 8.85; N, 5.20); EI-HRMS: *m/z* = 268.1708 ($M\text{-}H^·$); $C_{18}H_{22}NO$ requires: *m/z* = 268.1707 ($M\text{-}H^·$); ν_{max} (KBr) 3423, 3304, 2956, 2867, 1696, 1603, 1583, 1525, 1500, 1473, 1451, 1385, 1368, 1301, 1251, 1218, 1201, 1170, 1106, 1076, 1014, 947, 896, 827, 812, 793 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) for **11**: δ 0.85 (*s*, Me); 0.91 (*s*, Me); 0.97 (*s*, Me); 1.35–1.43 (*m*, 2H of CH_2); 1.66 (*t*, *J* = 10.1 Hz, 1H of CH_2); 2.00–2.09 (*m*, 1H of CH_2); 2.28 (*s*, Me); 2.44 (*d*, *J* = 3.6 Hz, H-C(4)); 6.83 (*d*, *J* = 8.4 Hz, 2H of Arl); 6.94 (*d*, *J* = 12.1 Hz, H-C(3')); 7.07 (*d*, *J* = 8.2 Hz, 2H of Arl); 9.71 (*d*, *J* = 11.9 Hz, NH). ^{1}H-NMR (500 MHz, $CDCl_3$) for **11'**: δ 0.86 (*s*, Me); 0.95 (*s*, Me); 2.62 (*d*, *J* = 3.5 Hz, H-C(4)); 6.13 (*d*, *J* = 13.3 Hz, NH); 7.58 (*d*, *J* = 13.4 Hz, H-C(3')). ^{13}C-NMR (126 MHz, $CDCl_3$) for **11**: δ 9.3, 19.3, 20.7, 20.8, 28.6, 30.4, 49.2, 49.9, 58.8, 114.6, 114.7, 130.3, 131.4, 132.8, 138.9, 208.6.

Catalytic Hydrogenation of a Mixture of 11 and 11'

To a solution of enaminones **11/11'** (**11**:**11'** = 92:8, 330 mg, 1.23 mmol) in anhydrous EtOH (70 ml) under Ar, Pd–C (10%, 180 mg) and HCl (1.5 ml, 2 M in EtOAc, 3 mmol) were added. The reaction vessel was flushed with H_2, and the reaction mixture was hydrogenated in *Paar* hydrogenator (P = 4 Bar) at room temperature for 3 h. The reaction mixture was filtered through a plug of Celite® and washed with EtOH (100 ml). Volatile components were evaporated *in vacuo*, and the residue was dissolved in EtOAc (200 ml) and washed with $NaHCO_3$ (aq. sat. 10 ml). The organic phase was dried over anhydrous Na_2SO_4, filtered, and volatile components evaporated *in vacuo* to give a mixture of *p*-toluidine **12**, **12'**, **13** and the corresponding saturated derivatives **14**, **14'**, **15** (all the starting material **11/11'** was consumed). The crude reaction mixture was partially separated by column chromatography (Silica gel 60; (1) EtOAc/petroleum ether = 1:2 to elute the *p*-toluidine derivatives (200 mg, **12**:**12'**:**13** = 42:26:32) and (2) EtOAc/MeOH = 10:1 to elute the cyclohexyl derivatives (45 mg, the ratio of **14**:**14'**:**15**, their presence was determined only by HRMS)). *p*-Toluidine derivatives were partially separated by MPLC (EtOAc/petroleum ether = 1:2) to give a mixture ketone epimers **12** and **12'** in a 70:30 ratio and an amino alcohol **13**. Mixture of compounds **14**, **14'**, and **15** has not been preparatively separated (LC–MS analysis).

(1S,3S,4R)-1,7,7-Trimethyl-3-((p-tolylamino)methyl)bicyclo[2.2.1]heptan-2-one (12) and (1S,3R,4R)-1,7,7-trimethyl-3-((p-tolylamino)methyl)bicyclo[2.2.1]heptan-2-one (12'). **12/12'** elute first from the column. Yield: 79 mg (23%, **12/12'** = 70:30) of dirty white solid; mp 60–64 °C. $[\alpha]_D^{r.t.}$ = +83.3 (c = 0.11, CH_2Cl_2) ($C_{18}H_{25}NO$ requires: C, 79.66; H, 9.28; N, 5.16 and found: C, 79.90; H, 9.46; N, 5.19); EI-HRMS: *m/z* = 272.2025 (MH^+); $C_{18}H_{26}NO$ requires: *m/z* = 272.2009 (MH^+); ν_{max} (KBr) 3376, 2964, 2870, 1732, 1620, 1583, 1522, 1466, 1407, 1390, 1374, 1318, 1304, 1270, 1250, 1211, 1182, 1124, 1092, 1044, 1023, 932, 850, 822, 806 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) for **12**: δ 0.87 (*s*, Me); 0.91 (*s*, Me); 0.95 (*s*, Me); 1.34–1.40 (*m*, 1H of CH_2); 1.44–1.52 (*m*, 1H of CH_2); 1.61–1.67 (*m*, 1H of CH_2); 1.97–2.05 (*m*, H-C(4), 1H of CH_2); 2.19 (*t*, *J* = 7.0 Hz, H-C(3)); 2.23 (*s*, Me); 3.24 (*dd*, *J* = 7.0; 12.7 Hz, Ha-C(3')); 3.41 (*dd*, *J* = 7.0; 12.7 Hz, Hb-C(3')); 4.15 (br *s*, NH); 6.55–6.60 (*m*, 2H of Arl); 6.99 (*d*, *J* = 8.0 Hz, 2H of Arl). ^{1}H-NMR (500 MHz, $CDCl_3$) for **12'**: δ 1.00 (*s*, Me); 1.52 – 1.59 (*m*, 1H of CH_2); 1.68–1.75 (*m*, 1H of CH_2); 1.78–1.87 (*m*, 1H of CH_2); 2.14–2.17 (*m*, H-C(4)); 2.73 (*dd*, *J* = 7.1; 12.1 Hz, H-C(3)); 3.11 (*dd*, *J* = 7.8; 12.2 Hz, Ha-C(3')); 3.33 (*dd*, *J* = 7.4; 12.2 Hz, Hb-C(3')). ^{13}C-NMR (126 MHz, $CDCl_3$) for **12**: δ 9.4, 20.5, 20.6, 21.9, 29.2, 29.4, 46.7, 47.0, 47.3, 53.9, 58.1, 113.5, 127.0, 129.9, 145.5, 221.1. ^{13}C-NMR (126 MHz, $CDCl_3$) for **12'**: δ 9.6, 19.3, 19.7, 20.7, 31.3, 43.1, 46.1, 46.2, 49.0, 59.1, 113.6, 127.2, 129.9, 145.9, 220.8.

(1S,2R,3S,4R)-1,7,7-Trimethyl-3-((p-tolylamino)methyl)bicyclo[2.2.1]heptan-2-ol (13). **13** elutes second from the column. Yield: 58 mg (17%) of dirty white solid; mp 69–72 °C. $[\alpha]_D^{r.t.}$ = +102.2 (c = 0.09, CH_2Cl_2) ($C_{18}H_{27}NO$ requires: C, 79.07; H, 9.95; N, 5.12 and found: C, 79.19; H, 10.24; N, 5.11); EI-HRMS: *m/z* = 274.2162 (MH^+); $C_{18}H_{28}NO$ requires: *m/z* = 274.2165 (MH^+); ν_{max} (KBr) 2947, 1616, 1516, 1483, 1459, 1389, 1366, 1349, 1293, 1242, 1211, 1182, 1129, 1112, 1090, 1056, 982, 909, 872, 824, 816 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.82 (*s*, Me); 0.94 (*s*, Me); 1.00 – 1.08 (*m*, 2H of CH_2); 1.19 (*s*, Me); 1.45 – 1.51 (*m*, 1H of CH_2); 1.60 (*d*, *J* = 3.8 Hz, H-C(4)); 1.70–1.78 (*m*, 1H of CH_2); 1.94–2.01 (*m*, H-C(3)); 2.24 (*s*, Me); 3.03 (br *s*, NH, OH); 3.18 (*dd*, *J* = 5.3; 12.0 Hz, Ha-C(3')); 3.55 (*t*, *J* = 11.5 Hz, Hb-C(3')); 3.81 (*d*, *J* = 7.9 Hz, H-C(2)); 6.60 (*d*, *J* = 8.0 Hz, 2H of Arl); 6.99 (*d*, *J* = 8.0 Hz, 2H of Arl). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 11.7, 20.6, 21.8, 22.3, 30.0, 33.6, 45.8, 47.0, 49.2, 49.8, 50.1, 81.2, 114.3, 127.5, 129.9, 146.2.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((1R,2S,3R,4S)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]-heptan-2-yl)thiourea (19) and 1-(3,5-bis(trifluoromethyl)phenyl)-3-((1R,2R,3S,4S)-3-hydroxy-4,7,7-trimethylbicyclo [2.2.1]heptan-2-yl)thiourea (19'). To a solution of crude (1*S*,2*R*,3*R*,4*R*)-3-amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol[38,39] (**18**) (88 mg, 0.52 mmol) in anhydrous Et_2O (10 ml) at 0 °C, 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (**6**) (97 µl, 0.52 mmol) was added, and the resulting mixture was stirred for 30 min at 0 °C and further 24 h at room temperature. Volatile components were evaporated *in vacuo*, and the residue was purified by column chromatography (Silica gel 60; (1) EtOAc/petroleum ether = 1:9 to elute the nonpolar impurities and (2) EtOAc/petroleum ether = 1:5 to elute the product). Fractions containing the product were combined and volatile components evaporated *in vacuo* to give **19/19'**. Yield: 115 mg (50%; **19/19'** = 89:11) of white solid; mp 173–176 °C. $[\alpha]_D^{r.t.}$ = –74.3 (c = 0.07, CH_2Cl_2) ($C_{19}H_{22}F_6N_2OS$ requires: C, 51.81; H, 5.03; N, 6.36 and found: C, 52.02; H, 5.10; N, 6.39); EI-HRMS: *m/z* = 441.1425 (MH^+); $C_{19}H_{23}F_6N_2OS$ requires: *m/z* = 441.1430 (MH^+); ν_{max} (KBr) 3440, 2962, 1624, 1560, 1508, 1471, 1383, 1345, 1291, 1278, 1178, 1127, 1094, 1055, 968, 888, 710, 683 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6) for **19**: δ 0.76 (*s*, Me); 0.88 (*s*, Me); 1.01 (*s*, Me); 1.03–1.14 (*m*, 2H of CH_2); 1.42–1.49 (*m*, 1H of CH_2); 1.60–1.67 (*m*, 1H of CH_2); 1.99 (*d*, *J* = 5.3 Hz, H-C(4)); 3.70 (*dd*, *J* = 6.1; 7.6 Hz, H-C(2)); 4.02 (*dd*, *J* = 5.9; 7.7 Hz, H-C(3)); 5.81 (*d*, *J* = 5.8 Hz, OH); 7.70 (*s*, 1H of Arl); 7.94 (*d*, *J* = 5.7 Hz, H-N(2')); 8.43 (*s*, 2H of Arl); 10.73 (*s*, NH). ^{1}H-NMR (500 MHz, DMSO-d_6) for **19'**: δ 0.82 (*s*, Me); 0.94 (*s*, Me); 1.25–1.32 (*m*, 1H of CH_2); 1.35–1.40 (*m*, 1H of CH_2); 1.79–1.85 (*m*, 1H of CH_2); 2.18 (*t*, *J* = 4.1 Hz, H-C(4)); 3.90 (*dd*, *J* = 5.0; 10.1 Hz, H-C(2)); 4.41–4.46 (*m*, H-C(3)); 5.66 (*d*, *J* = 5.2 Hz, OH); 7.81 (*d*, *J* = 6.1 Hz, H-N(2')); 10.74 (*s*, NH). ^{13}C-NMR (126 MHz, DMSO-d_6) for **19**: δ 11.6, 21.0, 21.6, 25.6, 32.6, 45.9, 48.8, 49.8, 60.9, 77.4, 115.5 (br *s*), 120.7 (br *s*), 123.3 (*q*, *J* = 272.7 Hz), 130.2, (*q*, *J* = 32.7 Hz), 142.2, 178.8.

General Procedure for Organocatalytic Michael Addition Reaction

Dimethyl malonate (**20**) (2.5 mmol, 292 µl) was added to a solution of catalyst **7–9**, **19/19'** (0.1 mmol, 10 mol%), and *trans*-β-nitrostyrene (**21**) (149 mg, 1 mmol) in toluene (1.5 ml) at room temperature or at −30 °C, and the mixture was stirred for 1 day or 3 days. The reaction mixture was passed through a plug of Silica gel 60 (7 × 2 cm (ø); EtOAc/petroleum ether = 1:1) to remove the catalyst. Volatile components were evaporated *in vacuo*, and the residue was used for the determination of conversion (^{1}H-NMR($CDCl_3$)) and HPLC analysis. Characterization of *Michael* addition product (**22**): HPLC analysis: CHIRALPAK AD-H, *n*-Hexane/*i*-PrOH = 80:20, flow rate: 1.0 ml/min, 25 °C, UV: λ = 210 nm, *t* (minor) = 11 min, *t* (major) = 13 min. Absolute configuration was determined by comparing the relative retention time of the HPLC analysis with the reported data.[24]

RESULTS AND DISCUSSION

Syntheses

The title bifunctional camphor-derived organocatalysts **7–9** were prepared in five steps starting from (+)-camphor (**1**). Following the literature procedure,[37] (+)-camphor (**1**) was transformed into 3-((dimethylamino)methylene)camphor (**2**). Next, catalytic hydrogenation of enaminone **2** in EtOH in the presence of 10% Pd–C and excess HCl gave the corresponding ammonium salt as a mixture of the major *endo*-epimer **3**[40] and the minor *exo*-epimer **3'**[40] in a ratio of 78:22 and in 100% conversion. The observed formation of the major *endo*-epimer for a closely related transformation has been proposed previously.[37] Treatment of ammonium salts **3/3'** under conditions used by *Page*[42] ($NH_2OH{\cdot}HCl$, pyridine) gave the corresponding oximes **4/4'**[41]

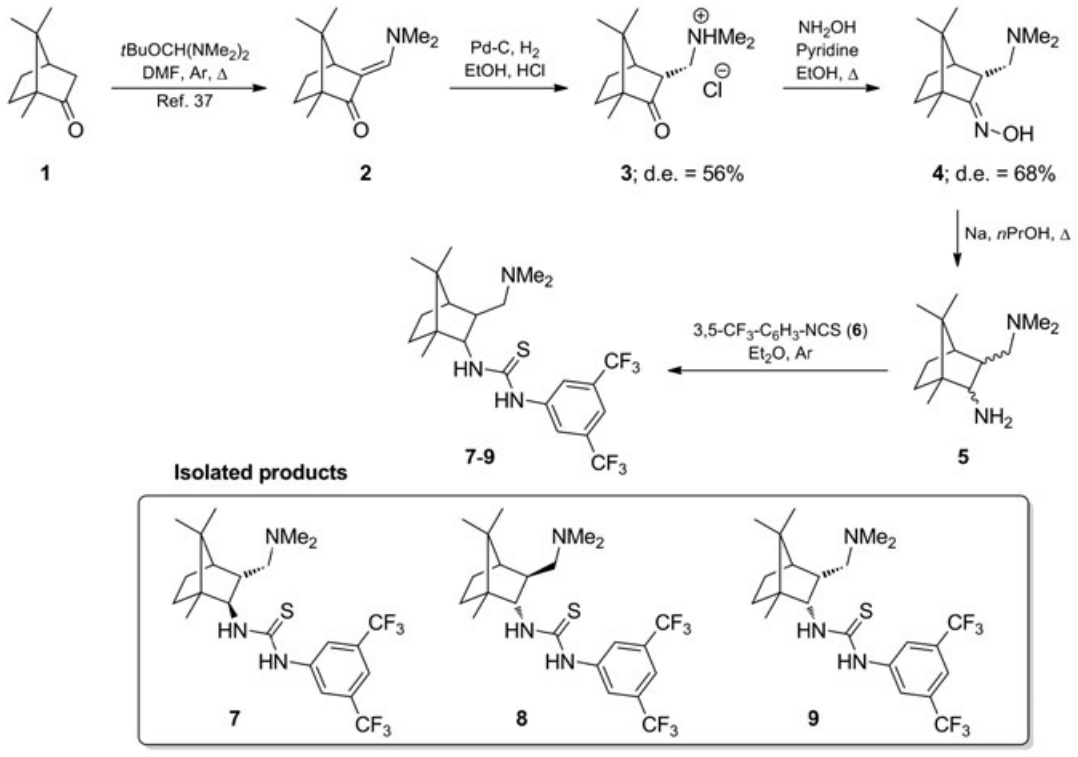
with a slight change of epimer composition (**4/4'** = 84:16) in 86% yield. Hine and coworkers reported the preparation of (1*R*,2*S*,3*R*,4*R*)-diamine **5**,[41] via reduction of oximes **4/4'** with excess $LiAlH_4$ under reflux for 48 h. To obtain diamine **5** in a stereo-divergent way in a short reaction time, the crude oximes **4/4'** were reduced with Na[37] in *n*PrOH to give a mixture of diamines **5** in full conversion and in 54:29:17 stereoisomer ratio. Because of the overlap of the signals in ^{1}H-NMR spectra, the stereochemistry assignation was impossible. Finally, the mixture of diamine stereoisomers **5** in anhydrous Et_2O was reacted with 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (**6**), which, after chromatographic separation, gave 2-thiourea derivatives **7**, **8**, and **9** in 41%, 6%, and 32% yield, respectively (Scheme 1).

The dimethylamino group in enaminone **2** and in other enaminones and related 3-(dimethylamino)propenoates undergoes a facile acid-catalyzed substitution with various amines, especially amines less basic than dimethylamine (i.e., aromatic and heteroaromatic amines) as well as with other *N*-nucleophile, *C*-nucleophile, and *O*-nucleophile.[43–45] Following the synthetic route in Scheme 1 might lead to a significant increase in the number of potential bifunctional organocatalysts. Thus, enaminone **2** was treated with *p*-toluidine hydrochloride (**10**), which yielded the expected dimethylamino substitution product as a mixture of the major (*Z*)-product **11** and the minor (*E*)-product **11'** in a 92:8 ratio and in 54% yield as a filterable precipitate. As shown previously, the (*E*)-enaminone and the (*Z*)-enaminone readily interconvert (the equilibrium is especially solvent dependent).[44] Next, catalytic hydrogenation of **11/11'** in EtOH in the presence of 10% Pd–C and excess HCl gave, unlike in the case of hydrogenation of **2**, a complex mixture of products. Partial chromatographic separation of the reaction mixture gave products containing the *p*-toluidine group intact (compounds **12/12'** and **13**; the major products) and the corresponding 4-methyl-cyclohexyl derivatives (compounds **14/14'** and **15**; the minor products). Further chromatographic separation of compounds **12/12'/13** yielded ketone epimers **12/12'** in a 70:30 ratio as an inseparable mixture in 23% yield and amino alcohol **13** in 17% yield. The mixture of compounds **14/14'** and **15** was preparatively not separated, and their identity was confirmed only by mass spectroscopy (LC–MS). Changing the conditions of hydrogenation (solvent, reaction time, and acid used) consistently produced similarly complex mixtures of products. Further transformation of ketones **12/12'** has not been pursued (Scheme 2).

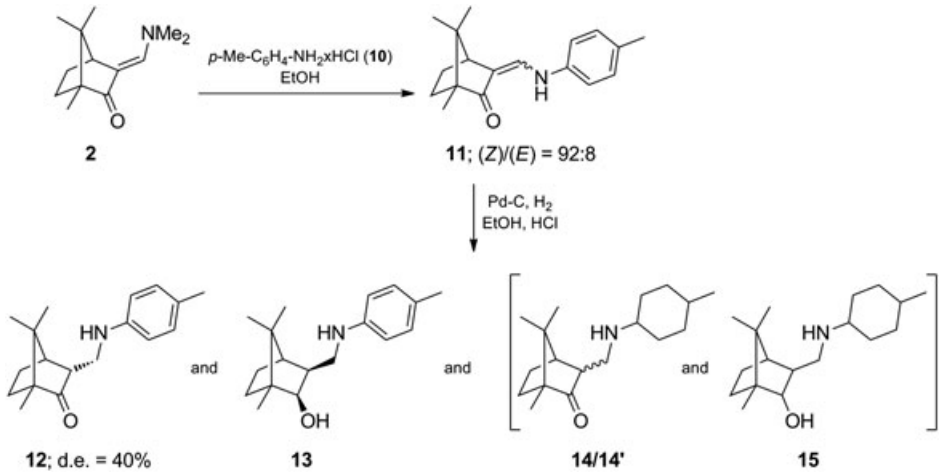
Finally, a borneol-derived bifunctional thiourea organocatalyst **19** has been prepared in three steps from (1*S*)-(+)-camphorquinone (**16**). Following the literature procedure, (1*S*)-(+)-camphorquinone (**16**) was first transformed into the corresponding keto oxime **17**,[38] followed by reduction with $LiAlH_4$ to give the amino alcohol **18**.[39] The crude **18** was treated with 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (**6**) to give borneol-derived thiourea stereoisomers **19** and **19'** in a 89:11 ratio and in 50% yield. Stereoisomers **19/19'** could not be separated neither by chromatography nor by crystallization. The crude **18** must have contained impurities of a minor stereoisomer, which eventually led to **19'** (Scheme 3).

Structure Determination

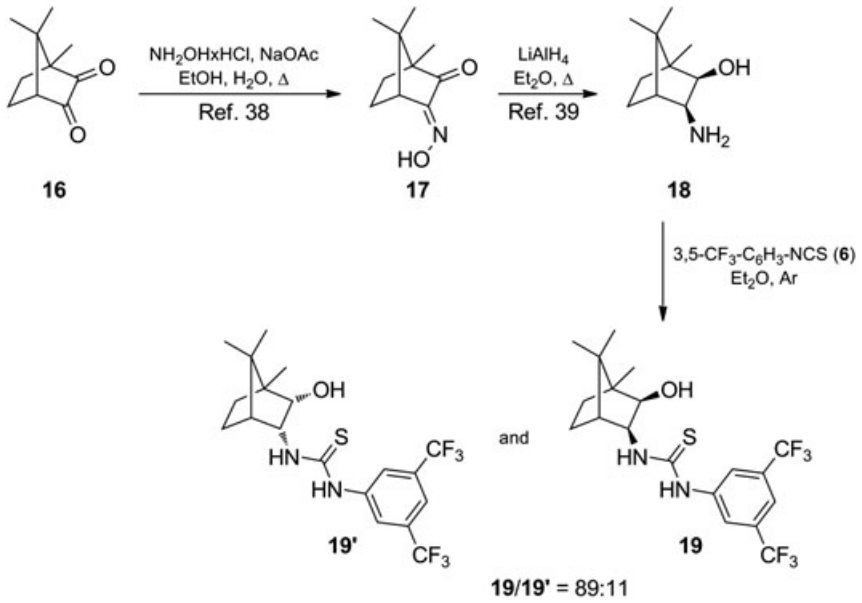
The structures of compounds **3/3'**,[40] **4/4'**,[41] and **5**[41] were determined by ^{1}H-NMR, and/or ^{13}C-NMR, and/or



Scheme 1. Preparation of camphor-derived bifunctional thiourea organocatalysts **7–9**.



Scheme 2. Catalytic hydrogenation of dimethylamino substitution product **11/11'**.



Scheme 3. Preparation of borneol—thiourea derivatives **19/19'**.

MS-HRMS. They were prepared following procedures different from the literature procedures and used as crude compounds in the following transformations. The structures of novel compounds **7–9**, **11/11'**, **12/12'**, **13** and **19/19'** were determined by spectroscopic methods (IR, NMR spectroscopy (^{1}H-NMR and ^{13}C-NMR, DEPT 90 and 135, COSY, HSQC, HMBC, and NOESY experiments) and MS-HRMS) and by elemental analyses for C, H, and N. Identities of compounds **14/14'** and **15** were confirmed by MS-HRMS.

The (2*E*)-configuration of oximes **4/4'** was ascribed on the basis of the configuration of closely related oximes.[37] The (*Z*)-configuration around the C=C bond in the enaminone **11** was determined on the basis of NOE between H-C(3') and H-C(4) in the NOESY spectra. Accordingly, the (*E*)-configuration around the C=C bond in the enaminone **11'** was determined on the basis of the NOE between NH and *H*-C(4). Similarly, the configuration(s) at position(s) 2 and/or 3 of compounds **4**, **7–9** **12/12'**, **13**, and **19/19'** was/were determined on the basis of NOE observed in NOESY spectra between the corresponding key proton signals. See also the Supporting information for ^{1}H-NMR, ^{13}C-NMR data, and selected parts of NOESY spectra (Fig. 2).

Organocatalyst Performance

Compounds **7–9**, **19/19'** have been evaluated as organocatalysts in a model reaction of *Michael* addition of dimethyl malonate to *trans*-β-nitrostyrene (Table 1). An equivalent of *trans*-β-nitrostyrene (**21**), 2 equivalents of dimethyl malonate (**20**), and 10% of catalyst in toluene were used.[24] Borneol derivatives **19/19'** gave no traces of the corresponding product **22** because of the lack of the basic functionality in the catalyst (Entry 1). All three catalysts **7–9** gave the addition product **22** of the same (*R*)-configuration[24] with low to moderate enantioselectivities (20.0%–60.1% ee).

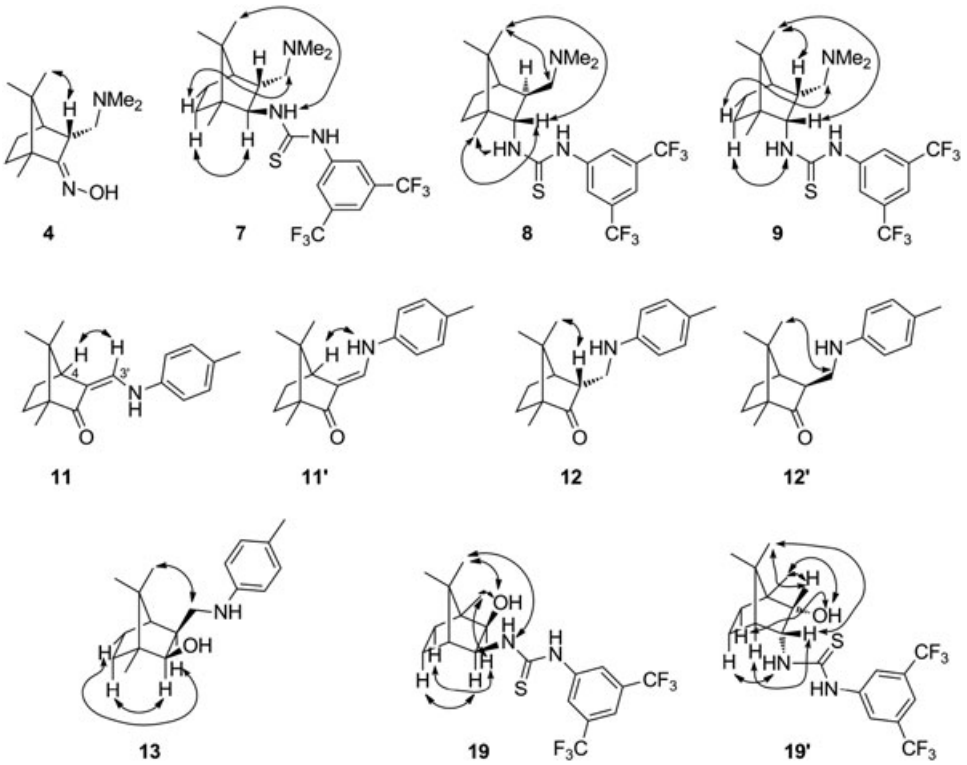
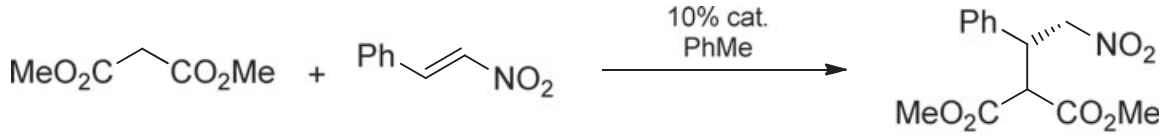


Fig. 2. Key NOE observed in NOESY spectra of compounds **4**, **7–9**, **11/11'**, **12/12'**, **13**, and **19/19'** for the determination of configuration.

TABLE 1. Organocatalytic enantioselective addition of dimethyl malonate to *trans*-β-nitrostyrene



20 **21** **22**

Entry	Catalyst	*T* (°C)	*t* (days)	Conversion (%)[a]	ee (%)[b]
1	**19/19'**	r.t.	3	–	–
2	**7**	r.t.	1	98	49.0; (*R*)
3	**8**	r.t.	1	99	20.0; (*R*)
4	**9**	r.t.	1	99	60.1; (*R*)
5	**7**	−30	3	58	53.7; (*R*)
6	**8**	−30	3	85	21.7; (*R*)
7	**9**	−30	3	86	45.0; (*R*)

[a]Conversion was determined using ^{1}H-NMR.
[b]ee was determined using CHIRALPAK AD-H.

Lowering the reaction temperature in the case of catalyst **7** slightly increased the selectivity (Entries 2 and 5), whereas in the case of catalyst **9**, lowering of the temperature actually decreased the selectivity (Entries 4 and 7). The selectivity of catalyst **8** stayed equally low regardless of the reaction temperature (Entries 4 and 6). In all cases, lowering of the reaction temperature led to incomplete conversions albeit the prolonged reaction times.

CONCLUSIONS

Starting from (+)-camphor (**1**), three novel bifunctional thiourea organocatalysts **7–9** have been prepared using stereo-divergent straightforward transformations. Borneol derivatives **19/19'** have been prepared in three steps from (1*S*)-(+)-camphorquinone (**16**). Acid-catalyzed substitution of the dimethylamino group of enaminone **2** with various nucleophiles could potentially lead to a diversity-oriented

catalyst preparation. Attempt to reduce the substitution product **11/11'** leads to a complex mixture of products including the desired *p*-tolylaminomethyl derivative **12/12'** albeit in low yield. Configurations of all novel compounds have been meticulously determined using NMR techniques. Finally, novel organocatalysts **7–9**, **19/19'** have been evaluated in a model reaction of *Michael* addition of dimethyl malonate to *trans*-β-nitrostyrene with low to moderate enantioselectivities (20%–60% ee). No stereochemical model for the explanation of the observed selectivities has been postulated.

LITERATURE CITED

1. Money T. Camphor: a chiral starting material in natural product synthesis. Nat Prod Rep 1985;2:253–289.
2. Money T. Remote functionalization of camphor: application to natural product synthesis. In: Organic Synthesis: Theory and Applications, Vol. 3. JAI Press Inc.; 1996. p 1–83.
3. Oppolzer W. Camphor derivatives as chiral auxiliaries in asymmetric synthesis. Tetrahedron 1987;43:1969–2004.
4. Oppolzer W. Camphor as a natural source of chirality in asymmetric synthesis. Pure Appl Chem 1990;62:1241–1250.
5. Matlin SA, Lough WJ, Chan L, Abram DMH, Zhou Z. Asymmetric induction in cyclopropanation with homogeneous and immobilized chiral metal β-diketonate catalysts. J Chem Soc Chem Commun 1984;1038–1040.
6. Chapuis C, Jurczak J. Asymmetric Diels-Alder reactions of cyclopentadiene with N-crotonoyl- and N-acryloyl-4,4-dimethyl-1,3-oxazolidin-2-one, mediated by chiral Lewis acids. Helv Chim Acta 1987;70:436–440.
7. Tomioka K. Asymmetric synthesis utilizing external chiral ligands. Synthesis 1990;541–549.
8. Noyori R, Kitamura M. Enantioselective addition of organometallic reagents to carbonyl compounds: transfer, duplication and intesification of chirality. Angew Chem Int Ed Engl 1991;30:34–48.
9. Brown HC, Ramachandran PV. The boron approach to asymmetric synthesis. Pure Appl Chem 1991;63:307–316.
10. Goering HL, Eikenberry JN, Koermer GS. Tris[3-(trifluoromethylhydroxymethylene)-d-camphorato]europium(III). A chiral shift reagent for direct determination of enantiomeric compositions. J Am Chem Soc 1971;93:5913–5914.
11. Sigman MS, Jacobsen EN. Schiff base catalysts for the asymmetric Strecker reaction identified and optimized from parallel synthetic libraries. J Am Chem Soc 1998;120:4901–4902.
12. Sigman MS, Vachal P, Jacobsen EN. A general catalyst for the asymmetric Strecker reaction. Angew Chem Int Ed 2000;39:1279–1281.
13. Schreiner PR, Wittkopp A. H-bonding additives act like Lewis acid catalysts. Org Lett 2002;4:217–220.
14. Wittkopp A, Schreiner PR. Metal-free, noncovalent catalysis of Diels-Alder reactions by neutral hydrogen bond donors in organic solvents and in water. Chem Eur J 2003;9:407–414.
15. Okino T, Hoashi Y, Takemoto Y. Enantioselective Michael reaction of malonates to nitroolefins catalyzed by bifunctional organocatalysts. J Am Chem Soc 2003;125:12672–12673.
16. Sohtome Y, Tanatani A, Hashimoto Y, Nagasawa K. Development of bis-thiourea-type organocatalyst for asymmetric Baylis-Hillman reaction. Tetrahedron Lett 2004;45:5589–5592.
17. Sohtome Y, Hashimoto Y, Nagasawa K. Guanidine-thiourea bifunctional organocatalyst for the asymmetric Henry (nitroaldol) reaction. Adv Synth Catal 2005;347:1643–1648.
18. Herrera RP, Sgarzani V, Bernardi L, Ricci A. Catalytic enantioselective Friedel-Crafts alkylation of indoles with nitroalkenes by using a simple thiourea organocatalyst. Angew Chem Int Ed 2005;44:6576–6579.
19. Vakulya B, Varga S, Csampai A, Soos T. Highly enantioselective conjugate addition of nitromethane to chalcones using bifunctional cinchona organocatalysts. Org Lett 2005;7:1967–1969.
20. Wang J, Li H, Yu X, Zu L, Wang W. Chiral binaphthyl-derived amine-thiourea organocatalyst-promoted asymmetric Morita-Baylis-Hillman reaction. Org Lett 2005;7:4293–4296.
21. McCooey SH, Connon SJ. Urea- and thiourea-substituted cinchona alkaloid derivatives as highly efficient bifunctional organocatalysts for the asymmetric addition of malonate to nitroalkenes: inversion of configuration at C9 dramatically improves catalyst performance. Angew Chem Int Ed 2005;44:6367–6370.
22. Cao C-L, Ye M-C, Sun X-L, Tang Y. Pyrrolidine-thiourea as a bifunctional organocatalyst: highly enantioselective Michael addition of cyclohexanone to nitroolefins. Org Lett 2006;8:2901–2904.
23. Berkessel A, Roland K, Neudörfl JM. Asymmetric Morita-Baylis-Hillman reaction catalyzed by isophoronediamine-derived bis(thio)urea organocatalysts. Org Lett 2006;8:4195–4198.
24. Okino T, Hoashi Y, Furukawa T, Xu X, Takemoto Y. Enantio- and diastereoselective michael reaction of 1,3-dicarbonyl compounds to nitroolefins catalyzed by a bifunctional thiourea. J Am Chem Soc 2005;127:119–125.
25. Wanka L, Cabrele C, Vanejews M, Schreiner PR. γ-Aminoadamantanecarboxylic acids through direct C-H bond amidations. Eur J Org Chem 2007;1474–1490.
26. Yamaoka Y, Miyabe H, Takemoto Y. Catalytic enantioselective Petasis-type reaction of quinolines catalyzed by a newly designed thiourea catalyst. J Am Chem Soc 2007;129:6686–6687.
27. Bellis E, Kokotos G. 4-Substituted prolines as organocatalysts for Aldol reactions. Tetrahedron 2005;61:8669–8676.
28. Tzeng Z-H, Chen H-Y, Huang C-T, Chen K. Camphor containing organocatalysts in asymmetric Aldol reaction on water. Tetrahedron Lett 2008;49:4134–4137.
29. Tzeng Z-H, Chen H-Y, Reddy RJ, Huang C-T, Chen K. Highly diastereo- and enantioselective direct Aldol reactions promoted by water-compatible organocatalysts bearing a pyrrolidinyl-camphor structural scaffold. Tetrahedron 2009;65:2879–2888.
30. Reddy RJ, Kuan H-H, Chou T-Y, Chen K. Novel prolinamide-camphor-containing organocatalysts for direct asymmetric Michael addition of unmodified aldehydes to nitroalkenes. Chem Eur J 2009;15:9294–9298.
31. Magar DR, Chang C, Ting Y-F, Chen K. Highly enantioselective conjugate addition of ketones to alkylidene malonates catalyzed by a pyrrolidinyl-camphor-derived organocatalyst. Eur J Org Chem 2010;2062–2066.
32. Ting Y-F, Chang C, Reddy RJ, Magar DR, Chen K. Pyrrolidinyl-camphor derivatives as a new class of organocatalyst for direct asymmetric Michael addition of aldehydes and ketones to β-nitroalkenes. Chem Eur J 2010;16:7030–7038.
33. Rani R, Peddinti RK. Camphor-10-sulfonamide-based prolinamide organocatalyst for the direct intermolecular Aldol reaction between ketones and aromatic aldehydes. Tetrahedron. Asymmetry 2010; 21:775–779.
34. Rani R, Peddinti RK. Michael reaction of ketones and β-nitrostyrenes catalyzed by camphor-10-sulfonamide-based prolinamide. Tetrahedron. Asymmetry 2010;21:2487–2492.
35. Liu P-M, Magar DR, Chen K. Highly efficient and practical pyrrolidine-camphor-derived organocatalysts for the direct α-amination of aldehydes. Eur J Org Chem 2010;5705–5713.
36. Anwar S, Lee P-H, Chou T-Y, Chang C, Chen K. Pyrrolidine-linker-camphor assembly: bifunctional organocatalysts for efficient Michael addition of cyclohexanone to nitroolefins under neat conditions. Tetrahedron 2011;67:1171–1177.
37. Grošelj U, Golobič A, Stare K, Svete J, Stanovnik B. Synthesis and structural elucidation of novel camphor derived thioureas. Chirality 2012;24:307–317.
38. Bonner MP, Thornton ER. Asymmetric aldol reactions. A new camphor-derived chiral auxiliary giving highly stereoselective Aldol reactions of both lithium and titanium(IV) enolates. J Am Chem Soc 1991;113:1299–1308.
39. White JD, Wardrop DJ, Sundermann KF. Preparation of (2S)-(-)-3-exo-(dimethylamino)isoborneol [(2S)-(-)-DAIB]. Organic Synth 2002;79:130–134.
40. Minardi G, Schenone P. N-substituted 3-aminomethylbornan-2-ones. Il Farmaco 1970;25(7):519–532.
41. Hine J, Li W-S, Zeigler JP. Catalysis of alpha -hydrogen exchange. 20. Stereoselective bifunctional catalysis of dedeuteration of cyclopentanone-2,2,5,5-d_4 by (1R,2S,3R,4R)-3-dimethylaminomethyl-1,7,7-trimethyl-2-norbornanamine. J Am Chem Soc 1980;102:4403–4409.
42. Page PCB, Murrell VL, Limousin C, Laffan DDP, Bethell D, Slawin AMZ, Smith TAD. The first stable enantiomerically pure chiral N-H oxaziridines: synthesis and reactivity. J Org Chem 2000;65: 4204–4207.

43. Stanovnik B, Svete J. Synthesis of heterocycles from alkyl 3-(dimethylamino)propenoates and related enaminones. Chem Rev 2004;104: 2433–2480.
44. Grošelj U, Bevk D, Jakše R, Meden A, Pirc S, Rečnik S, Stanovnik B, Svete J. Synthesis and properties of N-substituted (1R,5S)-4-aminomethylidene-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-2-ones. Tetrahedron. Asymmetry 2004;15:2367–2383.
45. Grošelj U, Rečnik S, Meden A, Stanovnik B, Svete J. Synthesis and transformations of some N-substituted (1R,4S)-3-aminomethylidene-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ones. Acta Chim. Slov. 2006;53:245–256.