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Scientific paper

Synthesis of Bifunctional Amine-Squaramide Organocatalysts Derived from 3-((Dimethylamino) methylene)camphor

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Abstract

Four bifunctional, noncovalent amine-squaramide organocatalysts were prepared from camphor in five steps. The stereochemistry of the prepared catalysts was thoroughly analyzed using various spectroscopic techniques. Their organocatalytic activity was investigated in the Michael addition of acetylacetone to *trans*-β-nitrostyrene. The addition product was formed in complete conversion and with an enantioselectivity of up to 77% *ee*. In the reactions catalyzed by the 2-*exo*-3-*endo* catalysts, the major (*S*)-enantiomer was formed, whereas in the presence of 2-*endo*-3-*endo* catalysts, the (*R*)-enantiomer was formed as the major product.

Keywords: Camphor, Enaminone, Asymmetric organocatalysis, Bifunctional noncovalent organocatalysts, Squaramide organocatalysts, Michael addition

1. Introduction

The noncovalent bifunctional organocatalyst with thiourea H-bond donor introduced by Takemoto in 2003[1] and the squaramide catalyst developed by Rawal in 2008[2] and their numerous analogs have become the workhorses of noncovalent organocatalysis,[3–7] as they enable the simultaneous activation and coordination of both electrophilic and nucleophilic reactants.[7,8] A typical and most commonly used organocatalyst of this type is a derivative of a chiral 1,2-diamine based on cyclohexane-1,2-diamine[9] or privileged cinchona alkaloids.[10–12] Although several H-bond donors have been described in the literature,[13–15] thiourea and squaramide remain the most common and best H-bond donors.[3–7,16,17] Hydrogen bond donors based on thiourea and squaramide have been very successfully introduced into noncovalent bifunctional quaternary ammonium salt phase-transfer organocatalysts.[18–21]

In the course of our extensive research on camphor-diamine building blocks and their application for the synthesis of noncovalent bifunctional organocatalysts with thiourea or squaramide double H-bond donors,[22–24] we were able to develop highly efficient squaramide organocatalysts based on camphor-derived 1,3-diamine for the addition of 1,3-dicarbonyl nucleophiles and heterocyclic pyrrolone nucleophiles to nitroalkene acceptors.[25,26] In contrast, their thiourea analogs proved to be inferior to the squaramide organocatalysts.[22] While amine-thiourea organocatalysts derived from 3-((dimethylamino)methylene)camphor have already been reported,[23] the corresponding squaramide analogs have not yet been prepared and their organocatalytic activity has not yet been investi-

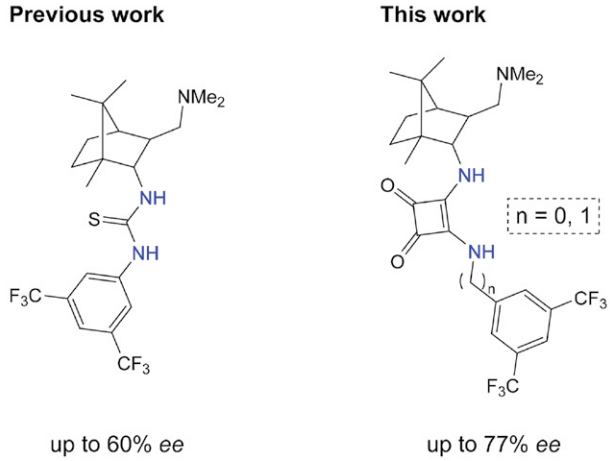


Figure 1. 3-((Dimethylamino)methylene)camphor-derived thiourea and squaramide organocatalysts.

gated (Figure 1). In this work, we present the synthesis of camphor-derived noncovalent bifunctional squaramide organocatalysts **8a**,**b** and **9a**,**b** and their catalytic activity in the addition of acetylacetone to *trans*-β-nitrostyrene.

2. Experimental

2. 1. Materials and Measurements

Solvents for extractions and chromatography were of technical grade and were distilled prior to use. Extracts were dried over technical grade anhydrous Na_2SO_4. Melting points were determined on a Kofler micro hot stage and on SRS OptiMelt MPA100 – Automated Melting Point System (Stanford Research Systems, Sunnyvale, California, 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 $CDCl_3$ and DMSO-d_6 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), IR spectra on a Perkin-Elmer Spectrum BX FTIR spectrophotometer (Perkin-Elmer, Waltham, MA, USA). Column chromatography (CC) was performed on silica gel (silica gel 60, particle size: 0.035–0.070 mm (Sigma-Aldrich, St. Louis, MO, USA)). HPLC analyses were performed on an Agilent 1260 Infinity LC (Agilent Technologies, Santa Clara, CA, USA) using CHIRALPAK AD-H (0.46 cm ø × 25 cm) as chiral column (Chiral Technologies, Inc., West Chester, PA, USA). Catalytic hydrogenation was performed on a Parr Pressure Reaction Hydrogenation Apparatus (Moline, IL, USA). The optical rotation of optical active substances was measured on a Perkin-Elmer 241 MC Polarimeter (Perkin-Elmer, Waltham, MA, USA) equipped with a Na lamp (sodium emission lines at 589.0 nm) at 20 °C. All the commercially available chemicals used were purchased from Sigma-Aldrich (St. Louis, MO, USA).

2. 2. Synthesis of 3-((3,5-Bis(trifluoromethyl) benzyl)amino)-4-(((1*S*,2*S*,3*R*,4*R*)-3-((dimethylamino)methyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl) amino)cyclobut-3-ene-1,2-dione (8a) and 3-((3,5-Bis(trifluoromethyl)benzyl)amino)-4-(((1*S*,2*S*,3*R*,4*R*)-3-((dimethylamino)methyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl) amino)cyclobut-3-ene-1,2-dione (8b)

To a solution of diamine **5** (1.21 mmol, 254 mg) in anhydrous CH_2Cl_2 (3 mL) under argon at 25 °C was added 3-((3,5-bis(trifluoromethyl)benzyl)amino)-4-ethoxycyclobut-3-ene-1,2-dione (**6**) (1.1 equiv., 1.331 mmol, 489 mg). The resulting reaction mixture was stirred at 25 °C for 24 h. The volatiles were evaporated *in vacuo* and the residue was purified by column chromatography. First column chromatography: silica gel 60; (i) EtOAc/MeOH/Et_3N = 20:1:0.5 to elute less polar impurities; (ii) EtOAc/MeOH/Et_3N = 10:1:0.5 to elute the combined products **8a** and **8b**. The fractions containing products **8a** and **8b** were combined and the volatiles were evaporated *in vacuo*. The residue was purified by a second column chromatography: silica gel 60; CH_2Cl_2/MeOH/Et_3N = 40:1:1 to separate products **8a** and **8b**. The fractions containing the pure separated products were combined separately and the volatiles were evaporated *in vacuo*.

Compound **8a**. Elutes first from the column. Yield: 296 mg (0.557 mmol, 46%) of white solid; m.p. 248–253 °C. $[\alpha]_D^{r.t.}$ = –149.6 (0.26, $CHCl_3$). EI-HRMS: *m/z* = 532.2390 (MH^+); $C_{26}H_{32}F_6N_3O_2$ requires: *m/z* = 532.2393 (MH^+); IR ν_{max} 3293, 2959, 2770, 1801, 1673, 1580, 1539, 1467, 1379, 1348, 1277, 1167, 1132, 1046, 902, 874, 843, 816, 726, 703, 682 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.71 (s, 3H), 0.83 (s, 3H), 0.95 (s, 3H), 1.00–1.09 (m, 1H), 1.34–1.44 (m, 1H), 1.46–1.57 (m, 2H), 1.69 (s, 1H), 2.12 (s, 6H), 2.16 (s, 1H), 2.21–2.30 (m, 1H), 2.34–2.41 (m, 1H), 3.47–3.57 (m, 1H), 4.88 (dd, *J* = 15.6, 5.9 Hz, 1H), 4.98 (dd, *J* = 15.4, 6.8 Hz, 1H), 7.15 (br s, 1H), 7.85 (br s, 1H), 8.07 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 11.58, 19.60, 19.80, 20.68, 35.32, 45.37, 45.08, 45.68, 46.82, 47.25, 50.08, 60.26, 66.71, 121.29, 123.30 (q, *J* = 272.9 Hz), 128.52, 130.54 (q, *J* = 32.6 Hz), 142.65, 166.82, 168.42, 182.48, 182.62.

Compound **8b**. Elutes second from the column. Yield: 109 mg (0.205 mmol, 17%) of yellowish semisolid. $[\alpha]_D^{r.t.}$ = –27.5 (0.28, $CHCl_3$). EI-HRMS: *m/z* = 532.2391 (MH^+); $C_{26}H_{32}F_6N_3O_2$ requires: *m/z* = 532.2393 (MH^+); IR ν_{max} 3236, 2949, 1797, 1658, 1583, 1534, 1480, 1379, 1346, 1277, 1170, 1130, 902, 843, 813, 704, 682 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.72 (s, 3H), 0.89 (s, 3H), 0.94 (s, 3H), 1.24–1.37 (m, 2H), 1.45–1.56 (m, 1H), 1.59–1.67 (m, 2H), 2.16 (br s, 6H), 2.38–2.46 (m, 3H), 4.44 (t, *J* = 10.5 Hz, 1H), 4.89 (dd, *J* = 15.5, 6.0 Hz, 1H), 4.99 (dd, *J* = 15.6, 7.0 Hz, 1H), 7.82 (br s, 1H), 8.07 (s, 3H), 8.39 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 13.74, 18.15, 19.50, 19.97, 26.29, 36.07, 44.79, 45.67, 46.35, 47.58, 49.95, 56.63, 58.92, 121.19, 123.31 (q, *J* = 272.8 Hz), 128.34, 130.50 (q, *J* = 33.0 Hz), 142.83, 167.25, 169.44, 182.55, 182.61.

2. 3. Synthesis of 3-((3,5-Bis(trifluoromethyl) phenyl)amino)-4-(((1*S*,2*S*,3*R*,4*R*)-3-((dimethylamino)methyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl) amino)cyclobut-3-ene-1,2-dione (9a) and 3-((3,5-Bis(trifluoromethyl)phenyl)amino)-4-(((1*S*,2*S*,3*R*,4*R*)-3-((dimethylamino)methyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl) amino)cyclobut-3-ene-1,2-dione (9b)

To a solution of diamine **5** (1.21 mmol, 254 mg) in anhydrous CH_2Cl_2 (3 mL) under argon at 25 °C was added

3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-ethoxycyclobut-3-ene-1,2-dione (**7**) (1.1 equiv., 1.331 mmol, 470 mg). The resulting reaction mixture was stirred at 25 °C for 24 h. The volatiles were evaporated *in vacuo* and the residue was purified by column chromatography. First column chromatography: silica gel 60; (i) Et_2O/MeOH/Et_3N = 20:1:0.5 to elute less polar impurities; (ii) Et_2O/MeOH/Et_3N = 10:2:0.5 to elute the combined products **9a** and **9b**. The fractions containing products **9a** and **9b** were combined and the volatiles were evaporated *in vacuo*. The residue was purified by a second column chromatography: silica gel 60; CH_2Cl_2/MeOH/Et_3N = 40:1:1 to separate products **9a** and **9b**. The fractions containing the pure separated products were combined separately and the volatiles were evaporated *in vacuo*.

Compound **9a**. Elutes first from the column. Yield: 125 mg (0.242 mmol, 20%) of yellowish semisolid. $[\alpha]_D^{r.t.}$ = –88.3 (0.3, $CHCl_3$). EI-HRMS: *m/z* = 518.2237 (MH^+); $C_{25}H_{30}F_6N_3O_2$ requires: *m/z* = 518.2237 (MH^+); IR ν_{max} 2956, 1792, 1690, 1600, 1550, 1436, 1376, 1329, 1276, 1178, 1130, 933, 879, 847, 826, 700, 678, 619 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 0.77 (s, 3H), 0.87 (s, 3H), 1.04 (s, 3H), 1.07–1.13 (m, 1H), 1.38–1.45 (m, 1H), 1.49–1.60 (m, 2H), 1.72–1.76 (m, 1H), 2.15 (s, 6H), 2.20–2.34 (m, 2H), 2.35–2.43 (m, 1H), 3.57 (d, *J* = 5.5 Hz, 1H), 7.59 (br s, 1H), 7.66 (s, 1H), 8.11 (s, 2H), 10.37 (br s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 11.67, 19.82, 19.90, 20.66, 35,46, 44.96, 45.46, 46.83, 47.36, 50.22, 60.23, 67.39, 114.71, 118.14, 123.20 (q, *J* = 272.7 Hz), 131.33 (q, *J* = 32.9 Hz), 141.13, 162.09, 169.84, 180.29, 184.38.

Compound **9b**. Elutes second from the column. Yield: 50 mg (0.0968 mmol, 8%) of yellowish semisolid. $[\alpha]_D^{r.t.}$ = –37.1 (0.07, $CHCl_3$). EI-HRMS: *m/z* = 518.2235 (MH^+); $C_{25}H_{30}F_6N_3O_2$ requires: *m/z* = 518.2237 (MH^+); IR ν_{max} 3355, 2955, 1793, 1685, 1606, 1567, 1505, 1472, 1441, 1375, 1329, 1275, 1173, 1129, 1007, 932, 903, 881, 846, 798, 703, 686, 671 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 0.75 (s, 3H), 0.91 (s, 3H), 0.98 (s, 3H), 1.24–1.31 (m, 1H), 1.34–1.43 (m, 1H), 1.49–1.59 (m, 1H), 1.71 (s, 1H), 1.87–1.95 (m, 1H), 2.45 (br s, 6H), 2.52–2.62 (m, 3H), 4.52 (t, *J* = 10.2 Hz, 1H), 7.62 (s, 1H), 8.27 (s, 2H), 8.96 (br s, 1H), 12.05 (br s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 13.61, 18.24, 19.46, 20.08, 35.52, 44.23, 46.65, 47.64, 50.44, 56.44, 59.86, 114.28, 117.42, 123.23 (q, *J* = 272.8 Hz), 131.38 (q, *J* = 32.9 Hz), 141.79, 162.75, 168.80, 180.23, 184.11 (one signal missing).

2. 4. Organocatalyzed Addition of Acetylacetone to *trans*-β-Nitrostyrene

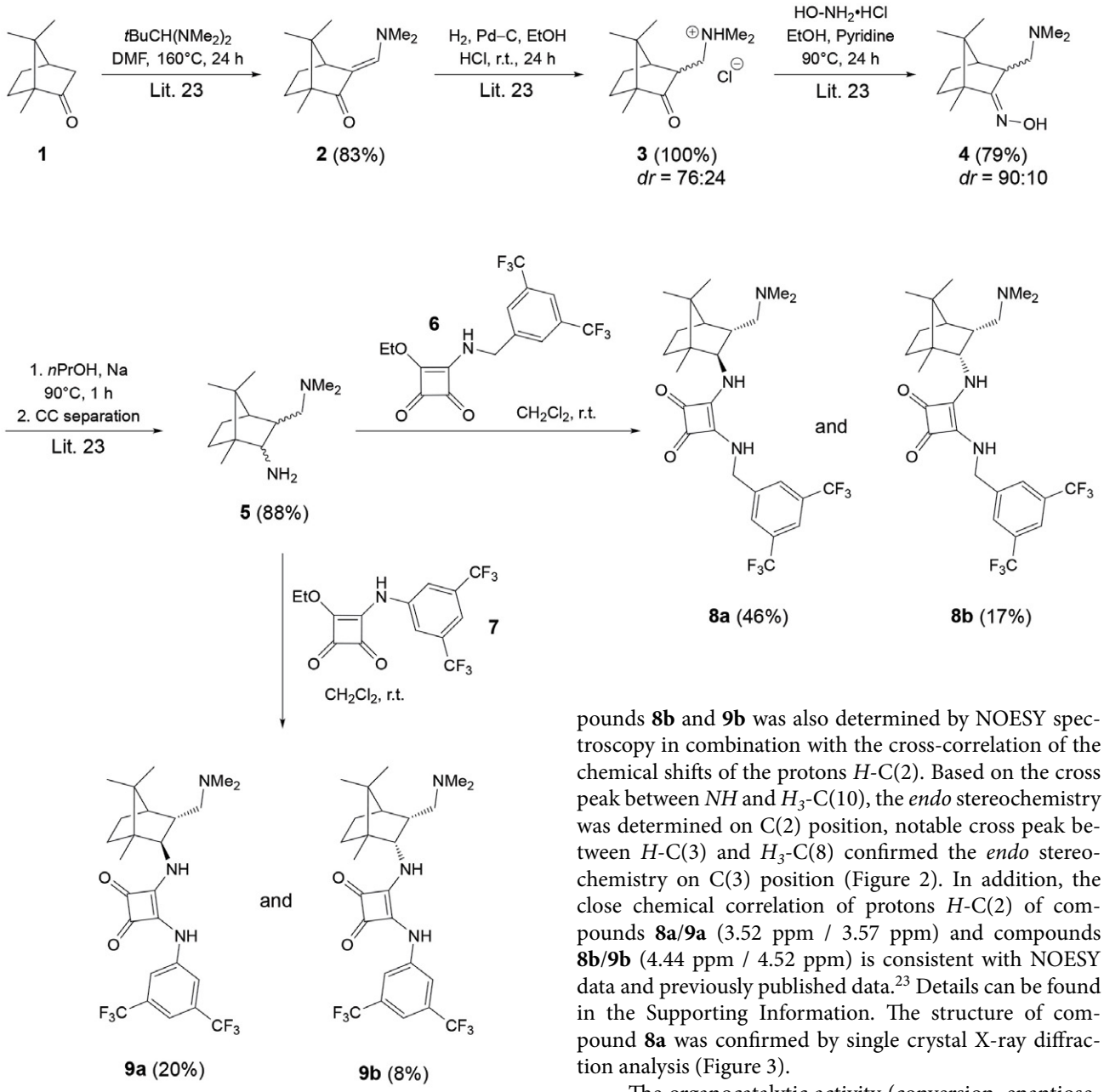
To a solution of *trans*-β-nitrostyrene (**A**) (14.9 mg, 0.1 mmol) in anhydrous CH_2Cl_2 (1 mL) or anhydrous toluene (1 mL) under argon, a catalyst (10 mol%) was added, followed by the addition of acetylacetone (**B**) (15.4 μL, 0.15 mmol). The resulting reaction mixture was stirred under argon for 24 h at 25 °C. After 24 h, an aliquot of 100 μL of the reaction mixture was withdrawn to determine the reaction conversion by ^1H NMR (in $CDCl_3$). The remainder of the reaction mixture was used to isolate the addition product **C**. The residue was purified by column chromatography (silica gel 60, EtOAc/petroleum ether = 1:2). The reaction mixture was transferred directly to the top of the column without prior evaporation of the volatile components. The fractions containing product **C** were combined and the volatiles were evaporated *in vacuo*. The enantioselectivity was determined by chiral HPLC analysis (chiral column CHIRALPAK AD-H, mobile phase: *n*-hexane/*i*-PrOH = 90:10, flow rate: 1.0 mL/min; λ = 210 nm).

2. 5. X-Ray Crystallography

Single-crystal X-ray diffraction data was collected on Agilent Technologies SuperNova Dual diffractometer with an Atlas detector using monochromated Mo-Kα radiation (λ = 0.71073 Å) at 150 K. The data was processed using CrysAlis PRO.[28] Using Olex2.1.2.,[29] the structures were solved by direct methods implemented in SHELXS[30] or SHELXT[31] and refined by a full-matrix least-squares procedure based on F^2 with SHELXT-2014/7.[32] All nonhydrogen atoms were refined anisotropically. Hydrogen atoms were placed in geometrically calculated positions and were refined using a riding model. The drawings and the analysis of bond lengths, angles and intermolecular interactions were carried out using Mercury[33] and Platon.[34] Structural and other crystallographic details on data collection and refinement for compound **8a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC Deposition Number **2336641**. These data are available free of charge at https://www.ccdc.cam.ac.uk/structures/, accessed on 04 March 2024 (or from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

3. Results and Discussion

The starting diamine **5** was prepared as a mixture of diastereomers in four steps (Scheme 1) in 57% yield following the procedures from our previous work.[23] Thus, (1*R*)-(+)-camphor (**1**) was treated with Bredereck's reagent to give enaminone **2**, which was catalytically hydrogenated in the presence of anhydrous hydrochloric acid in ethanol to give amino-ketone hydrochloride **3** as a mixture of two diastereomers in the ratio 76:24. The subsequent reaction with hydroxylamine gave oxime **4** (*dr* = 90:10), while the final reduction with sodium in *n*-propanol gave an inseparable mixture of diastereomeric diamines **5** in the ratio 62:28:10.[23] Treatment of the diastereomeric mixture of amine **5** with squaramate **6**[35] and **7**[36] gave, after extensive purification by column chromatography, diastereomerically pure catalysts **8a** (46% yield)/**8b** (17% yield) and **9a** (20% yield)/**9b** (8% yield), respectively (Scheme 1).



Scheme 1. Synthesis of camphor-derived bifunctional amine-squaramide organocatalysts **8** and **9**.

The structures of compounds **8a**,**b**, and **9a**,**9b** were confirmed by spectroscopic methods (^{1}H and ^{13}C NMR, 2D NMR, IR, and high-resolution mass spectrometry). The 2-*exo*-3-*endo* stereochemistry of compounds **8a** and **9a** was determined by NOESY spectroscopy (Figure 2). Based on cross peaks in NOESY spectra the *exo* stereochemistry on the C(3) position was determined (cross peak between *H*-C(2) and H_3-C(10) as well as *NH* and H_3-C(8)). The *endo* stereochemistry on the C(2) position was determined based on the cross peak between *H*-C(3) and H_3-C(8). The 2-*endo*-3-*endo* stereochemistry of compounds **8b** and **9b** was also determined by NOESY spectroscopy in combination with the cross-correlation of the chemical shifts of the protons *H*-C(2). Based on the cross peak between *NH* and H_3-C(10), the *endo* stereochemistry was determined on C(2) position, notable cross peak between *H*-C(3) and H_3-C(8) confirmed the *endo* stereochemistry on C(3) position (Figure 2). In addition, the close chemical correlation of protons *H*-C(2) of compounds **8a**/**9a** (3.52 ppm / 3.57 ppm) and compounds **8b**/**9b** (4.44 ppm / 4.52 ppm) is consistent with NOESY data and previously published data.[23] Details can be found in the Supporting Information. The structure of compound **8a** was confirmed by single crystal X-ray diffraction analysis (Figure 3).

The organocatalytic activity (conversion, enantioselectivity) of camphor-derived organocatalysts **8a**,**b** and **9a**,**b** was investigated in the 1,4-addition of acetylacetone (**B**) to *trans*-β-nitrostyrene (**A**).[25,27] The reactions were carried out in anhydrous dichloromethane at 25 °C for 24 h with 10 mol% of the catalyst (Scheme 2). The 2-*exo*-3-*endo* catalysts **8a** and **9a** afforded the addition product **C** in complete conversion and with good (*S*)-enantioselectivity, *i.e.* 77% *ee* and 71% *ee*, respectively. In contrast, incomplete conversion (94% and 30%, respectively) with reversed (*R*)-enantioselectivity (62% *ee* and 4% *ee*, respectively) was obtained with the 2-*endo*-3-*endo* catalysts **8b** and **9b**. The catalytic performance of the best catalyst **8a** was additionally carried out in anhydrous toluene, where 40% conversion and 57% *ee* were obtained. The squaramide-based catalysts **8a** and **9a** outperformed the

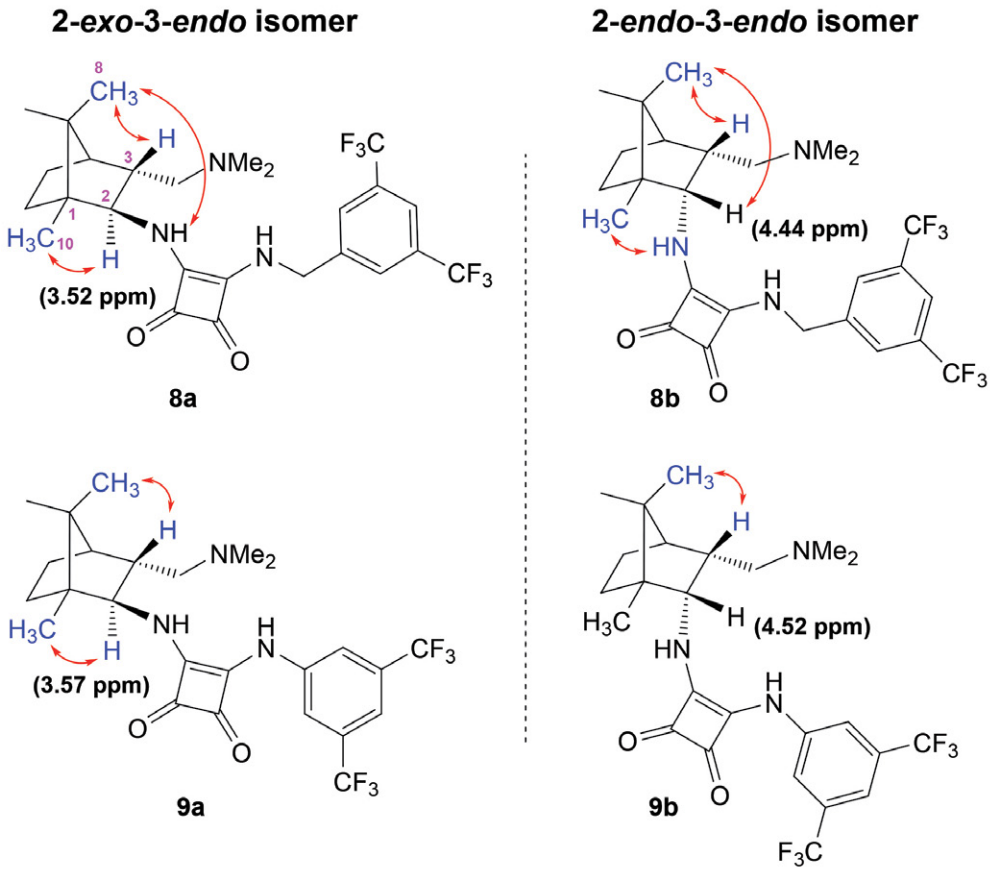


Figure 2. Structure determination by NOESY spectroscopy and cross-correlation of chemical shifts of proton *H*-C(2).

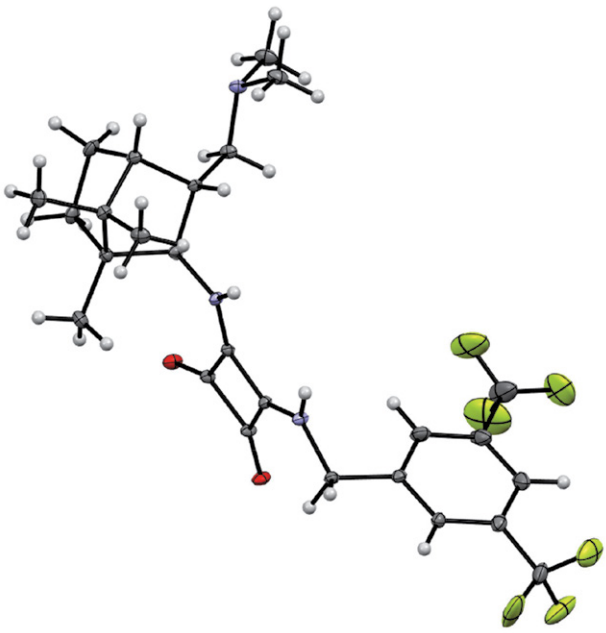


Figure 3. Molecular structure of product **8a** without solvent (2·$CHCl_3$). Thermal ellipsoids are shown at 50% probability.

previously reported thiourea-based catalysts (up to 60% *ee*).[23]

4. Conclusion

The bifunctional noncovalent squaramide organocatalysts **8a**,**b** and **9a**,**b**, prepared from camphor in five steps, were fully characterized and their organocatalytic activity in the addition of acetylacetone to *trans*-β-nitrostyrene was evaluated. The best performing catalyst **8a** gave the addition product **C** in 77% *ee* with (*S*)-enantioselectivity and complete conversion.

Supplementary Material

Crystal data and structure refinement for compound **8a** and copies of IR, HRMS, ^{1}H NMR, ^{13}C NMR and 2D spectra of the products are presented in the supporting information.

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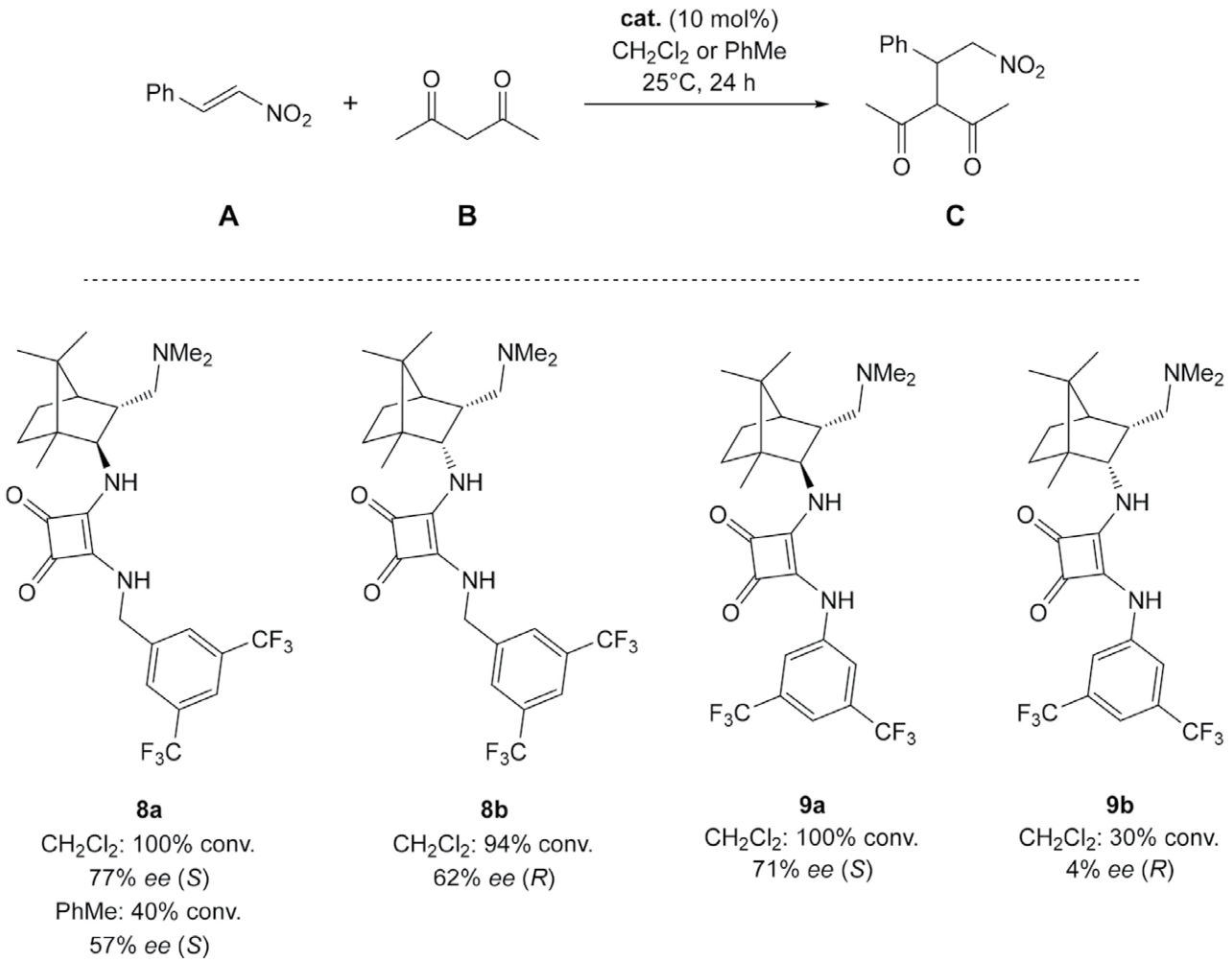

Scheme 2. The organocatalytic activity of organocatalysts **8a**,**b** and **9a**,**b** in the 1,4-addition of acetylacetone (**B**) to *trans*-β-nitrostyrene (**A**).

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Conflicts of interest

There are no conflicts to declare.

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Povzetek

V petih sinteznih korakih so bili iz kafre pripravljeni štirje bifunkcionalni, nekovalentni amin-skvaramidni organokatalizatorji. Stereokemija pripravljenih katalizatorjev je bila temeljito analizirana z različnimi spektroskopskimi tehnikami. Organokatalitska aktivnost katalizatorjev je bila ovrednotena v modelni reakciji Michaelove adicije acetilacetona na *trans*-β-nitrostiren. Adicijski produkt je nastal s popolno konverzijo in z enantioselektivnostjo do 77 % *ee*. Pri reakciji acetilacetona na *trans*-β-nitrostiren se v prisotnosti 2-*ekso*-3-*endo* katalizatorjev tvori večinski (*S*)-enantiomer, v prisotnosti 2-*endo*-3-*endo* katalizatorjev pa večinski (*R*)-enantiomer.