Synthesis of Six-Membered N-Heterocyclic Carbene Precursors Based on Camphor

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Article

Synthesis of Six-Membered N-Heterocyclic Carbene Precursors Based on Camphor

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Abstract: The *endo*- and *exo*-N-heterocyclic carbene precursors based on camphor were prepared diastereoselectively in five synthetic steps starting from (1*S*)-(+)-ketopinic acid. The obtained N-heterocyclic carbene precursors were investigated in an asymmetric benzoin reaction. All new compounds were fully characterized and the absolute configurations were determined by X-ray diffraction and NOESY measurements.

Keywords: ketopinic acid; amidation; reduction; diamines; N-heterocyclic carbene precursors; asymmetric catalysis; amidinium salts; hydrolysis

1. Introduction

Camphor is a privileged chiral pool building block available in both enantiomeric forms, which undergo a wide range of different chemical transformations. These include fragmentation reactions and rearrangements, such as the Wagner-Meerwein rearrangement, which functionalize at first glance inactivated positions (Figure 1) and enable the synthesis of structurally and functionally very different products [1,2].

Numerous camphor derivatives have found their application in the field of asymmetric synthesis and catalysis. For example, camphorsultam has been widely used as an efficient chiral auxiliary [3,4], while the α-aminoisoborneol derivatives DAIB [5] and MIB [6] have been used as efficient ligands for the enantioselective addition of organozinc reagents to aldehydes. In the field of asymmetric organocatalysis [7,8], the first efficient camphor-derived organocatalyst was published in 2005 [9]. Both, covalent and non-covalent organocatalysts based on camphor backbone were developed [10]. While the first efficient N-heterocyclic carbene (NHC) organocatalyst was introduced by Enders and Kallfass in 2002 [11], efficient camphor-based NHC analogues appeared from 2008 [12–20]. The NHC precursors developed by You [13] and Rafiński [19] are particularly efficient in enantioselective catalysis (Figure 1).

Recently, we prepared camphor-derived 1,2-, 1,3-, and 1,4-diamines as potential building blocks for bifunctional organocatalysts with camphor as the exclusive chiral scaffold [21]. These camphor-derived diamines were used for the preparation of bifunctional non-covalent thiourea and squaramide organocatalysts [21,22] and bifunctional quaternary ammonium salt phase transfer organocatalysts [23]. The camphor-1,3-diamine-derived squaramide organocatalyst exhibited excellent catalytic activity in enantioselective conjugative additions of 1,3-dicarbonyls and α-amino acid-derived pyrrolin-4-ones to *trans*-β-nitrostyrenes [22,24]. In extension, we reasoned that camphor-based 1,3-diamines [21,22] could be transformed into cyclic amidinium salts as interesting non-racemic precursors of NHC. In this article, we report the synthesis of a novel type of six-membered NHC precursors in five steps from commercially available (1*S*)-(+)-ketopinic acid (Figure 1).

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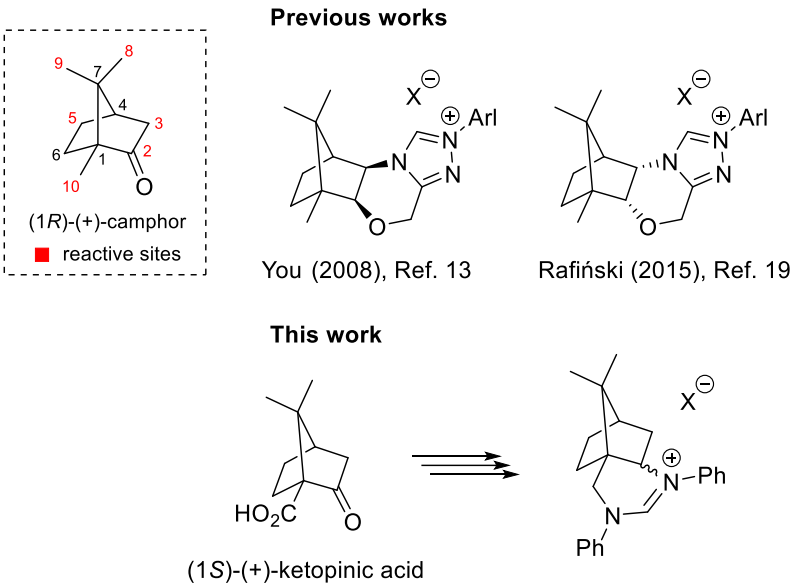

Figure 1. Efficient camphor-derived N-heterocyclic carbene precursors (top); six-membered N-heterocyclic carbene precursors (bottom).

2. Results and Discussion

2.1. Synthesis

The starting point for the synthesis was commercially available (1*S*)-(+)-ketopinic acid (**1**) (Scheme 1), which can alternatively be prepared from the much cheaper (1*S*)-(+)-10-camphorsulfonic acid according to procedures described in the literature [25,26,27]. First, (1*S*)-(+)-ketopinic acid (**1**) was treated with thionyl chloride. After removal of volatiles, crude acid chloride **2** was reacted with aniline in the presence of excess triethylamine in anhydrous toluene to give amide **3** [28] in 94% yield. Treatment of ketone **3** with excess aniline in the presence of catalytic amounts of *para*-toluenesulfonic acid with azeotropic removal of water using 4 Å molecular sieves gave imine **4** in 49% yield. Attempts to reduce both amide and imine functionality in one step to obtain diamines **6a**/**6b** with excess $LiAlH_4$ or BH_3•THF resulted in complex product mixtures. Therefore, sequential reduction was performed. Diastereoselective reduction of imine **4** with $NaCNBH_3$ [29] in methanol in the presence of acetic acid afforded *exo*-aminoamide **5a** in 91% yield and high diastereoselectivity (*dr* 93:7). Reduction of imine **4** with sodium [21,22] in *n*-propanol at 95°C gave a mixture of products containing *endo*-epimer **5b** in an estimated 94% combined yield. The diastereoselectivity of the reduction could not be determined. Reduction of imine **4** with Zn in the presence of KOH and catalytic hydrogenation with Pd-C in methanol failed. Reduction of epimeric amides **5a** and **5b** with excess $LiAlH_4$ gave diamines **6a** and **6b** in 64% and 61% yields, respectively. Diamines **6a** and **6b** were isolated with a diastereoselectivity of 99:1 and 90:10, respectively. Finally, the cyclic amidinium salts **7a–c** were isolated in 65–72% yield by treating diamines **6a** and **6b** in triethyl orthoformate in the presence of ammonium tetrafluoroborate or ammonium chloride at elevated temperature [30,31]. The *exo*-amidinium slats **7a** and **7b** were isolated in 99:1 *dr*, while the *endo*-salt **7c** was isolated in 91:9 *dr* (Scheme 1). Recrystallization of **7c** from *i*-PrOH did not improve the diastereomeric ratio.

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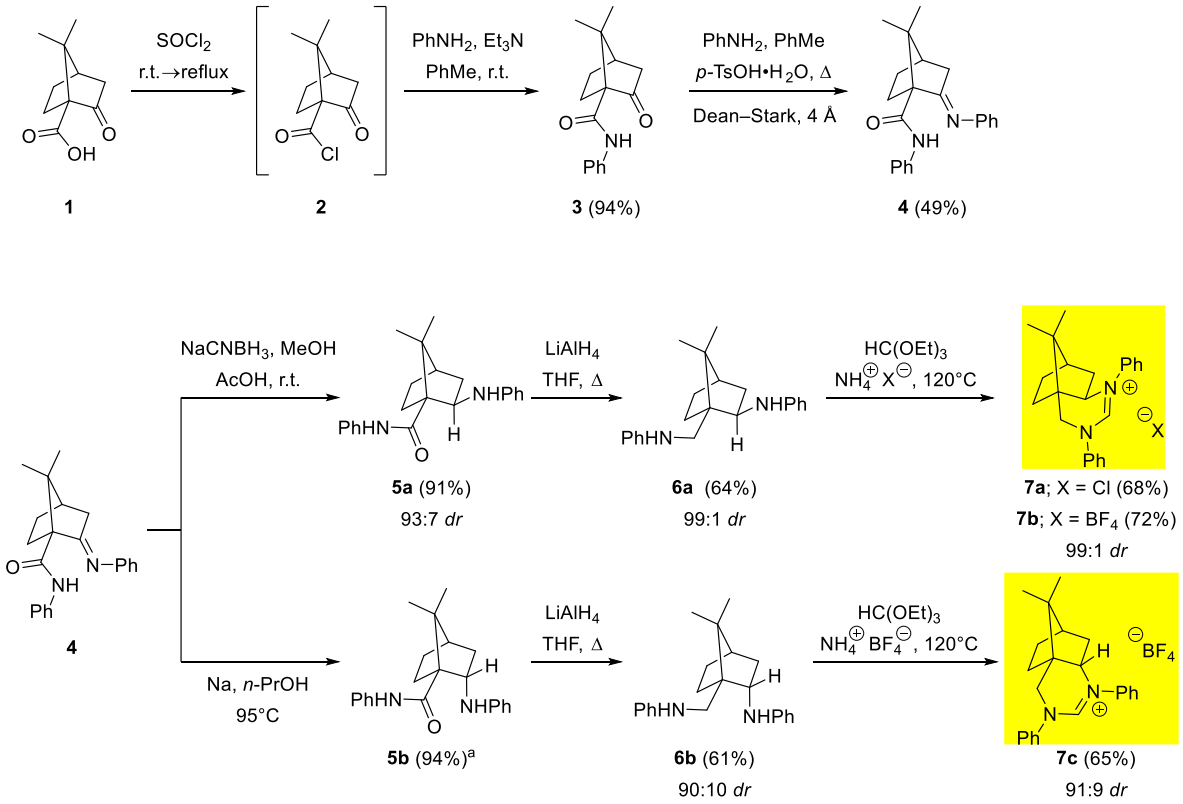


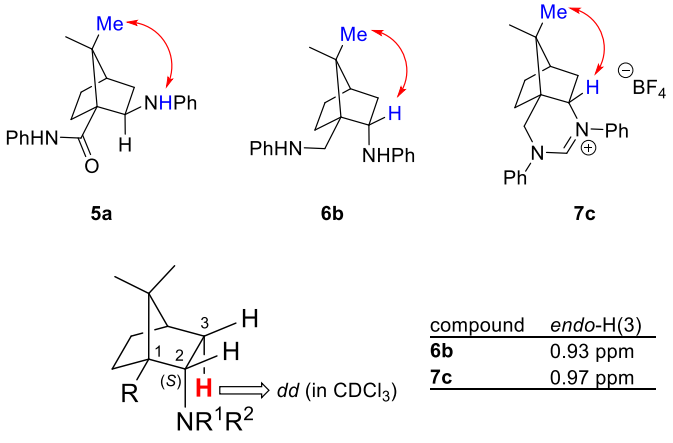
Scheme 1. Synthesis of NHC precursors **7a–c**; [a] *dr* could not be determined.

2.2. Structure determination

The new compounds were characterized by spectroscopic methods (^{1}H and ^{13}C NMR, 2D NMR, HRMS, and IR). Compound **5b** could not be isolated in pure form and was used in further transformation without additional purification.

The configuration of the newly formed stereocenter at C-2 for *endo*-isomers **6b** and **7c** was determined by NOESY spectroscopy. The NOEs between the *exo*-H(2) and the 8-Me group agreed with the (2*S*) configuration (Figure 2). Similarly, the (2*R*) configuration at the chiral C-2 center of compound **5a** was in line with the cross peak between the 8-Me group and the *exo*-H-N proton observed in the NOESY spectra [32]. The *endo*-stereochemistry of isomers **6b** and **7c** was additionally confirmed based on the chemical shift and multiplicity correlations of the *endo*-H(3) proton at position 3, which appears as a doublet of doublet at 0.93 and 0.97 ppm, respectively (Figure 2) [21,23,32].

The structures of compounds **4** and **7a** were also determined by single crystal X-ray analysis (Figure 3) [32].



compound	*endo*-H(3)
6b	0.93 ppm
7c	0.97 ppm

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Figure 2. Determination of the absolute configuration at the C-2 based on the observed NOE correlation spectroscopy cross peaks (top) and chemical shift correlations in the series of C-2 *endo*-isomers (bottom).

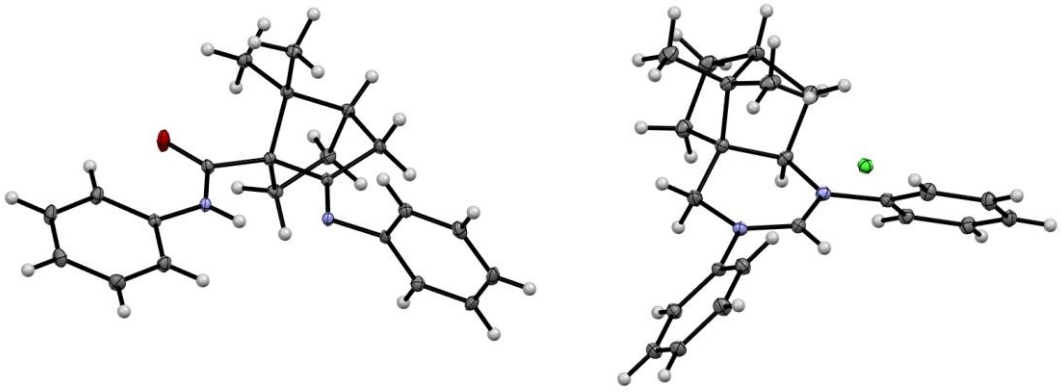

Figure 3. Molecular structures of compound **4** (left) and **7a** (right). Thermal ellipsoids are shown at 50% probability.

2.3. Performance of camphor-derived NHC precursors in benzoin reaction

The model reaction for evaluating the efficiency of the procatalyst **7a–c** was the benzoin reaction with benzaldehyde, in which 10 mol% of the procatalyst was used (Scheme 2). Various bases were used for the *in situ* formation of the nucleophilic carbene catalyst. With aqueous Na_2CO_3 [33] as base, no reaction took place and the NHC precursors remained unchanged. Since the estimated pKa values of the amidinium salts **7a–c** are in the range of 24 to 26 [34,35,36], stronger bases were used to obtain NHCs. Reactions in the presence of *t*BuONa, LiHDMS and LDA in anhydrous THF or 1,4-dioxane [37] did not give the benzoin product, while the amidinium salts **7a–c** decomposed presumably due to traces of water present in the reaction mixture or during workup. The attempts to confirm the formation of the carbene catalyst *in situ* (in the NMR tube) were also unsuccessful, only the decomposition products were observed. To verify the hydrolysis of the amidinium salt **7** under basic conditions and to identify the decomposition product, the amidinium salt ***ent*-7c** (*dr* = 82:18; prepared from (1*R*)-(–)-ketopinic acid) was hydrolyzed in a mixture of THF and water with two equivalents of NaOH. After 18 hours, the amidinium starting salt ***ent*-7c** was quantitatively hydrolyzed to an aminoamide mixture **8**/**8′** in the ratio 81:19. Crystallization of the crude product yielded single crystals of **8** (*dr* = 95:5) suitable for X-ray analysis, which confirmed the structure of the hydrolyzed product **8** (Figure 4). The absolute configuration at position 2 was additionally confirmed by NOESY measurement [21,23,32]. The amidinium salts ***ent*-7c** are hydrolytically unstable even in the presence of traces of water and are therefore not suitable as precursors of NHCs under applied reaction conditions.

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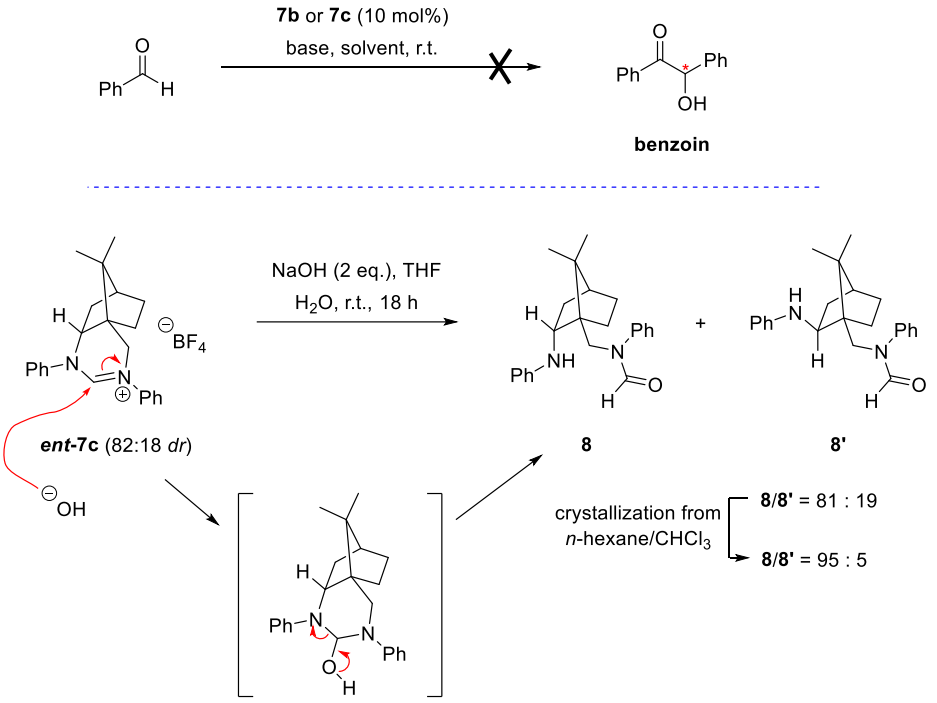

Scheme 2. Benzoin reaction (top) and opening of the amidinium salt **7c** (bottom).

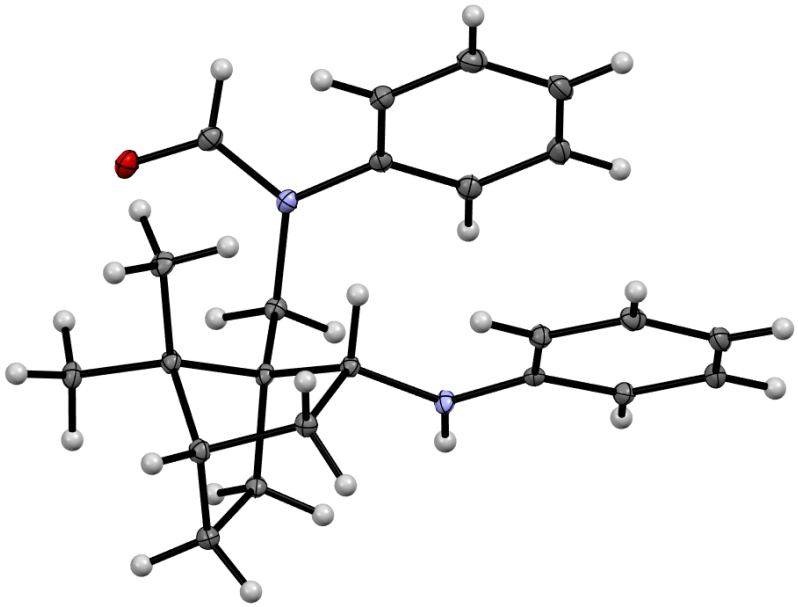

Figure 4. Molecular structure of compound **8**. Thermal ellipsoids are shown at 50% probability.

3. Conclusions

Starting from (1*S*)-(+)-ketopinic acid, three NHC precursors based on camphor were prepared in a diastereoselective five-step synthesis. Both the *exo*- and *endo*-diastereomer of the NHC precursors were also analyzed in an asymmetric benzoin reaction. The desired benzoin product was not observed under any reaction conditions. On the other hand, we have shown that the amidinium salt procatalysts **7** decompose under basic conditions. All new compounds were fully characterized,

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including determination of the absolute configuration by X-ray diffraction, NOESY measurements and NMR data correlation.

4. Materials and Methods

4.1. Materials and General Methods

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, United States). The NMR spectra were obtained on a Bruker UltraShield 500 plus (Bruker, Billerica, Massachusetts, United States) at 500 MHz for ^1H and 126 MHz for ^{13}C nucleus, using $CDCl_3$ 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, California, United States), IR spectra on a Perkin-Elmer Spectrum BX FTIR spectrophotometer (PerkinElmer, Waltham, Massachusetts, United States). Column chromatography (CC) was performed on silica gel (Silica gel 60, particle size: 0.035-0.070 mm (Sigma-Aldrich, St. Louis, Missouri, United States)). All the commercially available chemicals used were purchased from Sigma-Aldrich (St. Louis, Missouri, United States).

4.1.1. Synthesis of (1R,4R)-7,7-dimethyl-2-oxo-N-phenylbicyclo[2.2.1]heptane-1-carboxamide (3) [28]

$SOCl_2$ (8 mL) was added to the flask containing (1*S*)-(+)-ketopinic acid (**1**) (20 mmol, 3.644 g) under argon. The reaction mixture was stirred for 2 h at room temperature and then for 1 h under reflux. Excess $SOCl_2$ was evaporated *in vacuo*. The crude acid chloride **2** was immediately reacted further.

To a solution of acid chloride **2** (20 mmol) in anhydrous toluene at 0°C (20 mL) were added dropwise aniline (20 mmol, 1.823 mL) and Et_3N (7 mL). The reaction mixture was stirred at room temperature for 20 hours. Ethyl acetate (20 mL) was added to the reaction mixture, followed by extraction with NaCl (aq. sat., 2 × 10 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and the volatiles were evaporated *in vacuo*. The crude amide **3** was further reacted without additional purification. The crude amide **3** can, if needed, be purified by recrystallization from EtOH. Yield: 3.838 g (18.8 mmol, 94%) of white solid. ^1H-NMR (500 MHz, $CDCl_3$) δ (ppm): 1.04 (*s*, 3H) 1.34 (*s*, 3H), 1.45 – 1.52 (*m*, 1H), 1.68 – 1.75 (*m*, 1H), 2.05 (*d*, *J*=18.8 Hz, 1H), 2.12 (*t*, *J*=4.5 Hz, 1H), 2.16 – 2.25 (*m*, 1H), 2.55 – 2.65 (*m*, 2H), 7.07 – 7.12 (m, 1H), 7.29 – 7.35 (*m*, 2H), 7.59 – 7.64 (*m*, 2H), 9.70 (br *s*, 1H).

4.1.2. Synthesis of (1R,4R,E)-7,7-dimethyl-N-phenyl-2-(phenylimino)bicyclo[2.2.1]heptane-1-carboxamide (4)

To a solution of amide **3** (10 mmol, 2.573 g) in anhydrous toluene (40 mL) under argon were added aniline (50 mmol, 4.556 mL) and *para*-toluenesulfonic acid monohydrate (2 mmol, 380 mg). The flask was fitted with a Dean–Stark trap filled with activated 4 Å molecular sieves and a reflux condenser. The reaction mixture was refluxed for 20 h. To a cooled reaction mixture were added EtOAc (30 mL) and H_2O (30 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic phase was washed with brine (10 mL), dried under anhydrous Na_2SO_4, filtered, and the volatiles were evaporated *in vacuo*. The crude product was purified by CC (Silica gel 60, EtOAc/petroleum ether = 1:5). The fractions containing pure product **4** were combined and the volatiles evaporated *in vacuo*. Yield: 1.629 g (4.9 mmol, 49%) of orange solid; mp = 138–140°C. $[\alpha]_D^{r.t.}$ = +76.9 (0.13, $CHCl_3$). EI-HRMS: *m*/*z* = 333.1956 (MH^+); $C_{22}H_{25}N_2O$ requires: *m*/*z* = 333.1961 (MH^+); ν_{max} 3238, 3177, 3116, 3022, 3000, 2970, 2954, 1680, 1594, 1547, 1487, 1455, 1443, 1391, 1375, 1322, 1297, 1253, 1229, 1206, 1196, 1154, 1102, 1073, 1041, 1026, 966, 905, 885, 870, 833, 816, 790, 760, 712, 695, 662 cm^{-1}. ^1H-NMR (500 MHz, $CDCl_3$) δ (ppm): 1.05 (*s*, 3H), 1.37 (*s*, 3H), 1.34 – 1.41 (*m*, 1H), 1.83 (*ddd*, *J*=4.8, 9.4, 13.7 Hz, 1H), 1.91 – 1.99 (*m*, 2H), 2.10 – 2.19 (*m*, 1H), 2.41 (*dt*, *J*=4.1, 18.1, 1H), 2.67 – 2.76 (*m*, 1H), 6.81 – 6.91 (*m*, 2H), 7.03 – 7.09 (*m*, 1H), 7.13 – 7.19 (*m*, 1H), 7.26 – 7.34 (*m*, 2H), 7.35 – 7.42 (*m*, 2H), 7.58 – 7.67 (*m*, 2H), 11.49 (*s*, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm): 19.64, 20.51,

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27.58, 30.56, 35.99, 43.28, 50.25, 60.70, 118.93, 119.26, 119.35, 123.05, 123.82, 128.10, 128.13, 128.64, 128.67, 128.70, 137.88, 148.56, 168.45, 182.04.

4.1.3. Synthesis of (1R,2R,4R)-7,7-dimethyl-N-phenyl-2-(phenylamino)bicyclo[2.2.1]heptane-1-carboxamide (5a)

$NaCNBH_3$ (12 mmol, 794 mg, ω = 0.95) was added to a solution of imine **4** (332 mg, 1 mmol) in anhydrous MeOH (15 mL) under argon. Then a catalytic amount of anhydrous acetic acid (0.2 mL) was added and the reaction mixture was stirred at room temperature for 5 h. The reaction was stopped by adding a saturated solution of $NaHCO_3$ (5 mL) and EtOAc (10 mL), and the phases were separated. The aqueous phase was extracted with EtOAc (10 mL) and the combined organic phase was washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and the volatiles were evaporated *in vacuo*. Yield: 304 mg (0.91 mmol, 91%, *dr* 93:7) of dirty white solid; mp = 174–175°C. $[\alpha]_D^{r.t.}$ = –10.6 (0.12, $CHCl_3$). EI-HRMS: *m*/*z* = 335.2112 (MH^+); $C_{22}H_{27}N_2O$ requires: *m*/*z* = 335.2118 (MH^+); ν_{max} 3333, 2954, 1652, 1601, 1519, 1498, 1439, 1388, 1308, 1245, 1180, 1104, 1072, 869, 746, 690 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 1.10 (*s*, 3H), 1.22 – 1.29 (*m*, 1H), 1.31 (*s*, 3H), 1.46 – 1.53 (*m*, 1H), 1.81 – 1.87 (*m*, 1H), 1.89 (*t*, *J*=4.3 Hz, 1H), 1.91 – 1.98 (*m*, 1H), 2.15 (*dd*, *J*=8.6, 12.8 Hz, 1H), 2.58 (*td*, *J*=4.6, 12.4 Hz, 1H), 3.58 (*dt*, *J*=5.0, 9.3 Hz, 1H), 4.09 (*d*, *J*=4.9 Hz, 1H), 6.62 – 6.68 (*m*, 2H), 6.74 – 6.79 (*m*, 1H), 6.97 – 7.02 (*m*, 1H), 7.13 – 7.23 (*m*, 6H), 8.92 (br *s*, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm): 21.48, 21.50, 26.91, 31.65, 42.35, 45.79, 50.79, 58.43, 63.09, 114.36, 119.09, 120.52, 123.98, 128.71, 129.52, 138.04, 147.47, 171.17.

4.1.4. Synthesis of (1R,2S,4R)-7,7-dimethyl-N-phenyl-2-(phenylamino)bicyclo[2.2.1]heptane-1-carboxamide (5b)

Imine **4** (3 mmol, 997 mg) was dissolved in *n*-PrOH (100 mL) and the mixture was heated to 95°C. Then the first sodium piece was added to the reaction mixture, followed by another sodium piece after the first sodium piece had reacted, then the third, and so on. After 2 hours at 95°C, when the last sodium piece had reacted, H_2O (100 mL) and Et_2O (100 mL) were added to the cooled reaction mixture and the phases were separated. The aqueous phase was extracted with Et_2O (2 × 100 mL) and the combined organic phase was dried over anhydrous Na_2SO_4, filtered, and the volatiles evaporated *in vacuo*. The crude amine **5b** was further reacted without additional purification. Yield: 943 mg (2.82 mmol, 94%,) of grey oil.

Synthesis of (1*S*,2*R*,4*R*)-7,7-dimethyl-*N*-phenyl-1-((phenylamino)methyl)bicyclo[2.2.1]-heptan-2-amine (**6a**)

To a solution of compound **5a** (0.6 mmol, 201 mg) in anhydrous THF (2 mL) under argon at room temperature was added $LiAlH_4$ (2.4 M in THF, 1.0 mL) dropwise. After addition, the reaction mixture was stirred for 20 h at 60°C. The reaction was cooled (0°C) and quenched by careful addition of a mixture of H_2O and THF in a 1:5 ratio. The reaction mixture was filtered and the cake was washed with EtOAc (3 × 15 mL). The collected liquid was dried over anhydrous Na_2SO_4, filtered, and the volatiles were evaporated *in vacuo*. The crude product was purified by CC (Silica gel 60, EtOAc/petroleum ether = 1:10). The fractions containing the pure product **6a** were combined and the volatiles were evaporated *in vacuo*. Yield: 123 mg (0.384 mmol, 64%, *dr* 99:1) of dirty white semisolid. $[\alpha]_D^{r.t.}$ = –123.7 (0.12, $CHCl_3$). EI-HRMS: *m*/*z* = 321.2323 (MH^+); $C_{22}H_{29}N_2$ requires: *m*/*z* = 321.2325 (MH^+); ν_{max} 3412, 3050, 2951, 2876, 1600, 1499, 1429, 1387, 1369, 1302, 1251, 1180, 1152, 1096, 1073, 1028, 992, 866, 744, 689 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 0.99 (*s*, 3H), 1.17 (*s*, 3H), 1.21 – 1.28 (*m*, 1H), 1.46 – 1.53 (*m*, 1H), 1.70 – 1.87 (*m*, 4H), 1.91 – 1.99 (*m*, 1H), 3.20 (*d*, *J*=12.4 Hz, 1H), 3.29 (*d*, *J*=12.3 Hz, 1H), 3.50 – 3.56 (*m*, 1H), 3.69 (br *s*, 1H), 4.05 (br *s*, 1H), 6.55 – 6.62 (*m*, 4H), 6.68 (*t*, *J*=7.3 Hz, 2H), 7.08 – 7.19 (*m*, 4H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm): 21.12, 21.24, 27.41, 34.22, 40.72, 43.58, 46.13, 47.69, 51.93, 59.63, 113.42, 113.53, 117.47, 117.64, 129.27, 129.39, 147.58, 149.05.

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4.1.5. Synthesis of (1S,2S,4R)-7,7-dimethyl-N-phenyl-1-((phenylamino)methyl)bicyclo[2.2.1]-heptan-2-amine (6b)

To a solution of compound **5b** (0.5 mmol, 201 mg) in anhydrous THF (2 mL) under argon at room temperature was added $LiAlH_4$ (2.4 M in THF, 1.0 mL) dropwise. After addition, the reaction mixture was stirred for 20 h at 60°C. The reaction was cooled (0°C) and quenched by careful addition of a mixture of H_2O and THF in a 1:5 ratio. The reaction mixture was filtered and the cake was washed with EtOAc (3 × 15 mL). The collected liquid was dried over anhydrous Na_2SO_4, filtered, and the volatiles were evaporated *in vacuo*. The crude product was purified by CC (Silica gel 60, EtOAc/petroleum ether = 1:10). The fractions containing the pure product **6b** were combined and the volatiles were evaporated *in vacuo*. Yield: 98 mg (0.305 mmol, 61%, *dr* 90:10) of grey semisolid. $[\alpha]_D^{r.t.}$ = +25.0 (0.15, $CHCl_3$). EI-HRMS: *m*/*z* = 321.2323 (MH^+); $C_{22}H_{29}N_2$ requires: *m*/*z* = 321.2325 (MH^+); ν_{max} 3403, 3050, 3020, 2951, 2875, 1600, 1499, 1430, 1388, 1372, 1310, 1276, 1252, 1179, 1153, 1100, 1072, 1045, 1028, 992, 866, 744, 689, 617 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 0.93 (*dd*, *J*=3.8, 13.1 Hz, 1H), 1.03 (*s*, 3H), 1.08 (*s*, 3H), 1.29 – 1.36 (*m*, 1H), 1.61 – 1.69 (*m*, 1H), 1.73 (*t*, *J*=4.6 Hz, 1H), 1.84 – 1.92 (m, 1H), 2.00 – 2.07 (*m*, 1H), 2.44 – 2.52 (*m*, 1H), 3.18 (*d*, *J*=11.7 Hz, 1H), 3.24 (*d*, *J*=11.7 Hz, 1H), 3.88 – 3.94 (*m*, 1H), 4.01 (*s*, 1H), 4.37 (*s*, 1H), 6.48 – 6.54 (*m*, 2H), 6.62 – 6.68 (*m*, 3H), 6.70 – 6.75 (*m*, 1H), 7.08 – 7.19 (*m*, 4H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm): 19.53, 20.54, 25.30, 28.31, 39.32, 45.67, 46.91, 48.80, 51.27, 58.44, 113.07, 114.48, 117.28, 118.31, 129.23, 129.48, 148.13, 149.17.

4.1.6. Synthesis of (7R,8aR)-9,9-dimethyl-1,3-diphenyl-3,5,6,7,8,8a-hexahydro-4H-4a,7-methanoquinazolin-1-ium chloride (7a)

A mixture of diamine **6a** (0.25 mmol, 80 mg, *dr* 99:1), triethyl orthoformate (1.5 mL), and NH_4Cl (0.26 mmol, 13 mg) was stirred for 5 h at 120°C. The reaction mixture was cooled to room temperature and then Et_2O (5 mL) was added. The resulting precipitate was filtered off, and the filter cake was washed thoroughly with CH_2Cl_2. The filtrate was dried over anhydrous Na_2SO_4, filtered, and the volatiles were evaporated *in vacuo*. The product **6a** was recrystallized from *i*-PrOH at room temperature by slow evaporation. Yield: 62 mg (0.170 mmol, 68%, *dr* 99:1) of white solid; mp = 143–146°C. $[\alpha]_D^{r.t.}$ = +3.6 (0.14, $CHCl_3$). EI-HRMS: *m*/*z* = 331.2166 (M^+); $C_{23}H_{27}N_2$ requires: *m*/*z* = 331.2169 (M^+); ν_{max} 3013, 2953, 2933, 2880, 1663, 1592, 1497, 1455, 1381, 1330, 1300, 1240, 1212, 1030, 934, 767, 728, 704, 638 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 1.03 (*s*, 3H), 1.15 (*s*, 3H), 1.30 – 1.38 (*m*, 1H), 1.66 (*dd*, *J*=8.6, 13.7 Hz, 1H), 1.70 – 1.76 (*m*, 1H), 1.80 – 1.91 (*m*, 4H), 3.61 (*d*, *J*=13.9 Hz, 1H), 4.83 (*d*, *J*=13.9 Hz, 1H), 4.93 (*dd*, *J*=4.8, 8.7 Hz, 1H), 7.39 – 7.44 (*m*, 2H), 7.45 – 7.51 (*m*, 4H), 7.57 – 7.62 (*m*, 2H), 7.64 – 7.69 (*m*, 2H), 8.06 (*s*, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm): 20.12, 20.21, 26.58, 32.21, 34.18, 45.66, 46.16, 47.97, 48.61, 60.65, 124.17, 124.70, 129.32, 129.40, 130.20, 130.33, 138.82, 141.81, 152.01.

4.1.7. Synthesis of (7R,8aR)-9,9-dimethyl-1,3-diphenyl-3,5,6,7,8,8a-hexahydro-4H-4a,7-methanoquinazolin-1-ium tetrafluoroborate (7b)

A mixture of diamine **6a** (0.25 mmol, 80 mg, *dr* 99:1), triethyl orthoformate (1.5 mL), and NH_4BF_4 (0.26 mmol, 27 mg) was stirred for 5 h at 120°C. The reaction mixture was cooled to room temperature and then Et_2O (5 mL) was added. The resulting precipitate was filtered off, and the filter cake was washed thoroughly with CH_2Cl_2. The filtrate was dried over anhydrous Na_2SO_4, filtered, and the volatiles were evaporated *in vacuo*. The product **6a** was recrystallized from *i*-PrOH at room temperature by slow evaporation. Yield: 75 mg (0.180 mmol, 72%, *dr* 99:1) of grayish white solid; mp = 280–285°C. $[\alpha]_D^{r.t.}$ = +30.8 (0.25, $CHCl_3$). EI-HRMS: *m*/*z* = 331.2170 (M^+); $C_{23}H_{27}N_2$ requires: *m*/*z* = 331.2169 (M^+); ν_{max} 2956, 2921, 1663, 1591, 1494, 1380, 1319, 1297, 1229, 1049, 1030, 916, 766, 696 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 1.04 (*s*, 3H), 1.13 (*s*, 3H), 1.31 – 1.38 (*m*, 1H), 1.64 – 1.92 (*m*, 6H), 3.61 (*d*, *J*=14.3 Hz, 1H), 4.46 (*d*, *J*=14.3 Hz, 1H), 4.55 (*dd*, *J*=5.3, 8.1 Hz, 1H), 7.37 – 7.53 (*m*, 10H), 7.85 (*s*, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm): 20.22, 20.25, 26.56, 32.24, 34.35, 45.65, 46.12, 47.98, 48.05, 60.03, 123.99, 124.42, 129.52, 129.67, 130.42, 130.55, 138.69, 141.72, 151.62.

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4.1.8. Synthesis of (4aS,7R)-9,9-dimethyl-1,3-diphenyl-3,5,6,7,8,8a-hexahydro-4H-4a,7-methanoquinazolin-1-ium tetrafluoroborate (7c)

A mixture of diamine **6a** (0.25 mmol, 80 mg, *dr* 90:10), triethyl orthoformate (1.5 mL), and NH_4BF_4 (0.26 mmol, 27 mg) was stirred for 5 h at 120°C. The reaction mixture was cooled to room temperature and then Et_2O (5 mL) was added. The resulting precipitate was filtered off, and the filter cake was washed thoroughly with CH_2Cl_2. The filtrate was dried over anhydrous Na_2SO_4, filtered, and the volatiles were evaporated *in vacuo*. The product **6a** was recrystallized from *i*-PrOH at room temperature by slow evaporation. Yield: 68 mg (0.1625 mmol, 65%, *dr* 91:9) of grayish white solid; mp = 238–240°C. $[\alpha]_D^{r.t.}$ = –25.5 (0.13, $CHCl_3$). EI-HRMS: *m*/*z* = 331.2163 (M^+); $C_{23}H_{27}N_2$ requires: *m*/*z* = 331.2169 (M^+); ν_{max} 3082, 3064, 2952, 2881, 1645, 1591, 1494, 1457, 1419, 1396, 1368, 1330, 1285, 1232, 1162, 1050, 1026, 968, 829, 770, 753, 697, 656, 627 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 0.97 (*dd*, *J*=5.9, 13.8 Hz, 1H), 1.08 (*s*, 3H), 1.20 (*s*, 3H), 1.23 – 1.29 (*m*, 1H), 1.69 – 1.78 (*m*, 1H), 1.87 – 2.00 (*m*, 3H), 2.19 – 2.28 (*m*, 1H), 3.49 (*d*, *J*=12.8 Hz, 1H), 4.44 (*d*, *J*=12.8 Hz, 1H), 4.91 (*dd*, *J*=6.0, 11.1 Hz, 1H), 7.36 – 7.54 (*m*, 10H), 7.83 (*s*, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm): 18.49, 20.07, 27.41, 28.05, 30.79, 45.49, 46.37, 47.61, 54.91, 59.40, 124.54, 124.78, 129.49, 129.70, 130.29, 130.41, 139.33, 141.95, 152.66.

4.1.9. Synthesis of N-(((1S,2S,4R)-7,7-dimethyl-2-(phenylamino)bicyclo[2.2.1]heptan-1-yl)methyl)-N-phenylformamide (8) and N-(((1S,2R,4R)-7,7-dimethyl-2-(phenylamino)bicyclo[2.2.1]heptan-1-yl)methyl)-N-phenylformamide (8′)

To a solution of ***ent*-7c** (0.0239 mmol, 10 mg, *dr* 82:18) in THF (1 mL) was added H_2O (100 µL) and NaOH (0.0478 mmol, 1.9 mg). The resulting reaction mixture was stirred for 18 h at room temperature. The reaction mixture was diluted with Et_2O (20 mL) and washed with H_2O (1 mL) and brine (1 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and the volatiles were evaporated *in vacuo*. Yield: 6 mg (0.0172 mmol, 72%, *dr* 81:19) of colorless semisolid. ^{1}H-NMR (500 MHz, $CDCl_3$) for **8′**: δ (ppm): 0.73 – 0.79 (*m*, 1H), 0.93 (*s*, 3H), 3.04 (*dd*, *J*=4.7, 7.3, 1H), 3.61 (*d*, *J*=11.1, 1H), 4.64 (*d*, *J*=14.9, 1H), 4.81 (*s*, 1H), 6.51 – 6.56 (*m*, 2H), 8.17 (s, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$) for **8′**: δ (ppm): 20.93, 21.01, 30.45, 35.33, 41.41, 43.11, 45.69, 48.85, 53.55, 59.23, 113.14, 116.55, 125.27, 127.41, 129.13, 129.64, 141.60, 147.75, 163.82.

The crude product was additionally crystallized from a mixture of $CHCl_3$ and *n*-heptane by slow evaporation of chloroform at room temperature. Compound **8**: Yield: 3 mg (0.0086 mmol, 36%, *dr* 95:5) of white solid; mp = 144–146°C. EI-HRMS: *m*/*z* = 349.2275 (M^+); $C_{23}H_{29}N_2O$ requires: *m*/*z* = 349.2274 (M^+); ν_{max} 3383, 2965, 2943, 2863, 1660, 1592, 1517, 1495, 1432, 1390, 1358, 1313, 1257, 1215, 1180, 1128, 1069, 1022, 988, 917, 866, 826, 748, 691, 670 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) for **8**: δ (ppm): 0.89 (*s*, 3H), 0.87 – 0.93 (*m*, 1H), 1.03 (*s*, 3H), 1.14 – 1.21 (*m*, 1H), 1.44 – 1.52 (*m*, 1H), 1.61 – 1.77 (*m*, 3H), 2.29 – 2.38 (*m*, 1H), 3.63 (*d*, *J*=9.0, 1H), 3.87 (*d*, *J*=14.8, 1H), 4.07 (*s*, 1H), 4.14 (*d*, *J*=14.8, 1H), 6.43 – 6.48 (*m*, 2H), 6.66 (*t*, *J*=7.3, 1H), 7.09 – 7.16 (*m*, 4H), 7.17 – 7.21 (*m*, 1H), 7.29 – 7.36 (*m*, 2H), 8.31 (*s*, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$) for **8**: δ (ppm): 19.31, 20.14, 25.48, 27.95, 38.60, 44.43, 45.84, 48.67, 53.67, 56.60, 113.50, 117.18, 123.62, 126.57, 129.22, 129.71, 142.15, 148.49, 163.72.

4.2. General procedure for the catalytic asymmetric benzoin condensation reaction with benzaldehyde

To a solution/suspension of amidinium salt 7 (10 mol%) in anhydrous THF or 1,4-dioxane (in the case of Na_2CO_3, water was used as solvent), benzaldehyde (0.75 mmol) and then base (10 mol%; *t*BuONa, LiHDMS and LDA (1 M in THF/hexanes)) were added. The resulting reaction mixture was stirred for 24 h at room temperature. The reaction mixture was concentrated under reduced pressure. Part of the residue was used for ^{1}H-NMR measurements, the rest was subjected to column chromatography.

4.3. X-ray Crystallography

Single-crystal X-ray diffraction data was collected on Agilent Technologies SuperNova Dual diffractometer with an Atlas detector using monochromated Cu-Kα radiation (λ = 1.54184 Å) at 150 K. The data was processed using CrysAlis PRO [38]. Using Olex2.1.2. [39], the structures were solved

by direct methods implemented in SHELXS [40] or SHELXT [41] and refined by a full-matrix least-squares procedure based on F2 with SHELXT-2014/7 [42]. All nonhydrogen atoms were refined anisotropicallly. 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 [43] and Platon [44]. Structural and other crystallographic details on data collection and refinement for compounds **4**, **7a**, and **8** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC Deposition Numbers **2302865**, **2302861** and **2307379**, respectively. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. Copies of ^{1}H- and ^{13}C-NMR spectra; Copies of NOESY spectra; Copies of HRMS reports; Copies of IR spectra, Structure determination by X-ray diffraction analysis.

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Sample Availability: Samples of the compounds **7a–c** are available from the authors.

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