Carane amino alcohols as organocatalysts in asymmetric aldol reaction of isatin with acetone

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Carane-derived β-amino alcohols with amino and hydroxy groups at positions 3 and 4 differing in their mutual arrangement and configuration were synthesized. Their application as organocatalysts in the asymmetric aldol reaction of isatin with acetone allowed one to obtain adducts with up to 84% enantiomeric excess.

Key words: amino alcohols, 3-carene, asymmetric synthesis, organocatalysts, aldol reaction, isatin.

β-Amino alcohols possess a wide range of biological activity,[1—3] they are successfully used in asymmetric synthesis, playing the role of chiral building blocks, chiral auxiliaries and catalysts. Amino alcohols and amino diols synthesized based on α- and β-pinene, 3-carene, menthone,[4] and limonene[5] catalyze addition of diethylzinc to aldehydes with different structures.[6—9]

The review[10] summarizes a multitude of examples of application of amino alcohols, α-amino acids (first of all proline), and chiral amines as organocatalysts in asymmetric aldol reactions leading to biologically active compounds.

In the present work, carane-derived amino alcohols were obtained based on the natural 3-carene **1** (Scheme 1) through epoxides **2** and **7** synthesized according to the known procedures.[11,12] Epoxide ring opening with sodium azide in refluxing methanol led to the mixtures of azido alcohols **3** and **4**,[13] **8** and **9**[14] in the ratio of 1 : 1. Their reduction with an equimolar amount of $LiAlH_4$ in diethyl ether gave the corresponding amino alcohols in 59—82% yields. The spectral characteristics of amino alcohols **5** and **6** agree with those described in the literature.[15] Compounds **10** and **11** were synthesized for the first time.

The IR spectrum of amino alcohol **10** exhibits characteristic absorption bands attributed to the stretching vibrations of the NH_2 group in the region of 3356 cm^{-1}, the OH group in the region of 3082 cm^{-1}, as well as to the bending vibrations of the NH_2 and OH groups in the region of 1597 and 1448 cm^{-1}, respectively. The presence of these functional groups in compound **11** was also confirmed by the absorption bands of the corresponding stretching (3350 and 3201 cm^{-1}) and bending (1583—1456 cm^{-1}) vibrations of these group bonds.

The ^1H NMR spectra ($CDCl_3$) of amino alcohols **10** and **11**, together with the signals for the terpene fragment, exhibit singlets for the NH_2 and OH groups in the region of δ 1.8 and 1.4, respectively. A total number of signals in the ^{13}C NMR spectra of compounds **10** and **11** corresponds to the number of carbon atoms in their molecules. In the spectrum of amino alcohol **11**, the signal for the tertiary carbon atom C(4) at the OH group was found in the low-field region at δ 72, while the signal of the quaternary atom C(3) bonded to the NH_2 group has greater upfield shift at δ 50. Quite the opposite pattern is observed in the spectrum of compound **10**, where the signal for the atom C(4) bonded to the NH_2 group is found in the region of higher field at δ 55, while the atom C(3) bonded to the OH group is observed in the region of low field at δ 72. The structures of amino alcohols **10** and **11** were confirmed by X-ray diffraction studies (Fig. 1).

The catalytic activity of amino alcohols **5**, **6**, **10**, and **11** was studied in the asymmetric aldol reaction of isatin **12** with acetone (Scheme 2).

Earlier,[16] it was shown that the vicinal amino alcohols such as leucinol and valinol are efficient organocatalysts of the reaction of isatin and its derivatives with acetone.

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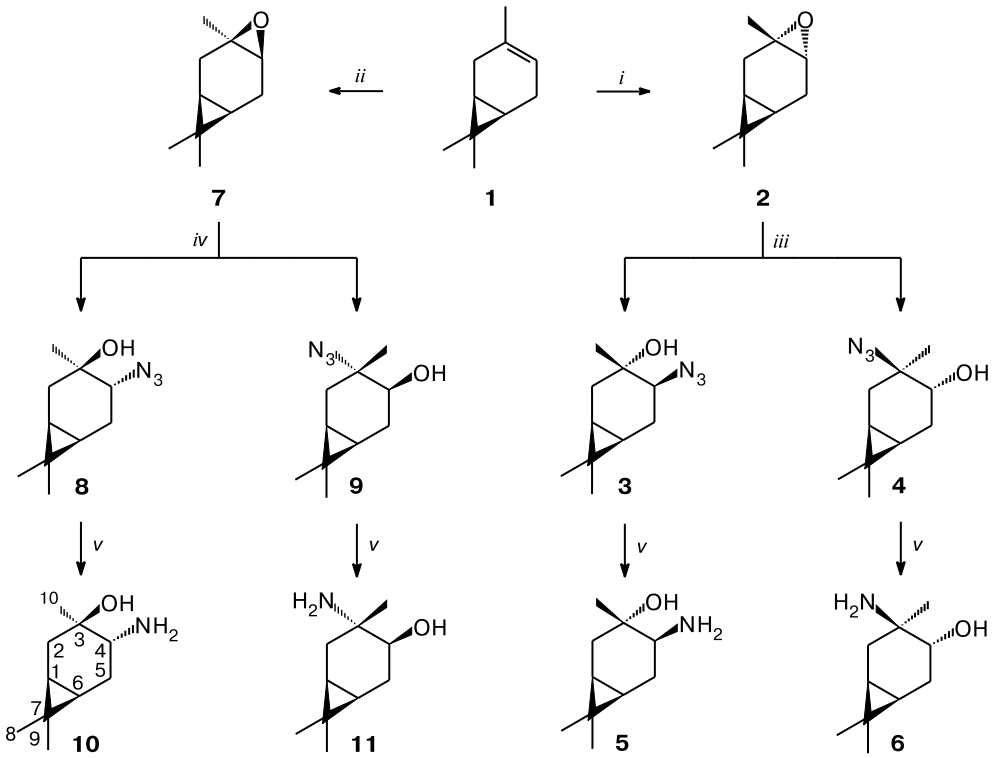
Scheme 1



Reagents and conditions: *i*. *m*-chloroperbenzoic acid (*m*-CPBA), $CHCl_3$; *ii*. 1) NBS, $CaCO_3$, 2) Bu^tOK, Bu^tOH; *iii*. NaN_3, MeOH; *iv*. NaN_3, MeOH; *v*. $LiAlH_4$, Et_2O.

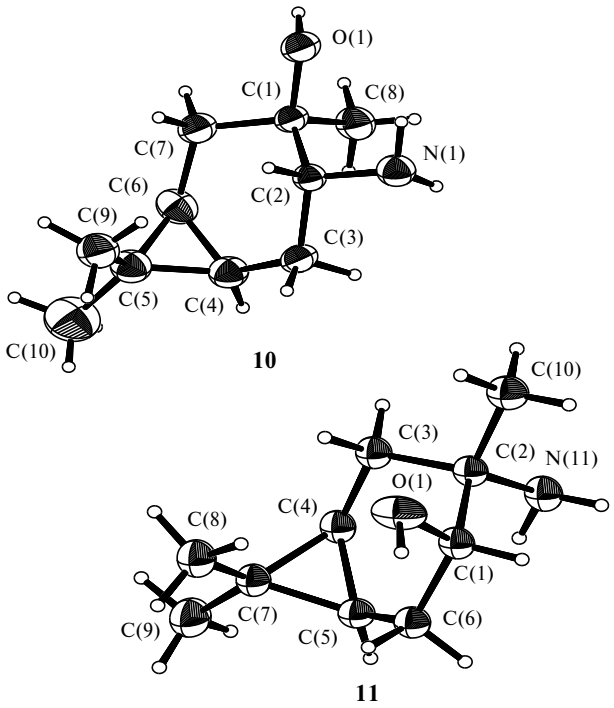
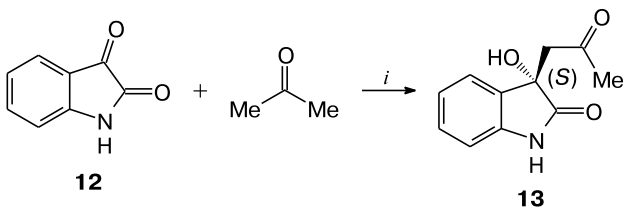


Fig. 1. General view of molecules **10** and **11** according to the X-ray diffraction data.

Scheme 2



Reagents and conditions: *i*. A catalyst (20 mol.%), 20 °C; CH_2Cl_2.

However, (*S*)-isomers of 3-acetonyl-3-hydroxyindolone **13** (see Scheme 2) and convolutamydine A (inhibitor of leukemia cell discrimination) are predominantly formed in their presence, while the natural biological active isomer of the latter has an (*R*)-configuration.

Our preliminary experiments (Table 1) showed that the most efficient organocatalyst is the amino alcohol **5** with the sterically nonhindered NH_2 group occupying a *syn*-position with respect to the cyclopropane fragment of the molecule. In its presence, the reaction reached completion within 24 h, leading to (*S*)-isomer of product **13** with 84% enantiomeric excess. Compound **6**, in which the amino group is sterically hindered (attached to the quater-

Table 1. Aldol reaction of isatin with acetone in the presence of 20 mol.% amino alcohols **5**, **6**, **10**, and **11** at 20 °C

Catalyst	τ*/h	Y (%)**	*ee* (%)
11	120	74	0
10	21	77	39 (*R*)
10	96	95	49 (*R*)
6	100	60	5 (*S*)
5	50	95	77 (*S*)
5	24	95	84 (*S*)

* τ is the reaction time.
** Y is the product yield.

nary carbon atom C(3)), catalyzes aldol coupling with a minimum enantiomeric excess (5%). A racemate is formed in the presence of compound **11**. Note that when the catalyst **10** is used, the required (*R*)-isomer is formed, but with moderate enantiomeric excesses (39% and 49%). In order to increase enantioselectivity, we plan to continue our experiments on optimization of the reaction conditions (by variation of temperature, reaction time, solvents, catalyst concentration).

In conclusion, 3-carene was used as a basis for the synthesis of a series of vicinal amino alcohols, their application as organocatalysts in the asymmetric aldol reaction of isatin with acetone was studied for the first time. The highest yield of the product and its enantiomeric excess were obtained in the presence of (+)-4β-amino-3α-hydroxy-*cis*-carane **5**.

Experimental

IR spectra were recorded on a Shimadzu IR Prestige 21 Fourier-transform spectrometer. Melting points were determined on a Gallencamp-Sanyo heating stage. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-300 spectrometer (300.17 and 75.48 MHz, respectively) in $CDCl_3$. Thin-layer chromatography was carried out on Sorbfil plates, visualizing agents were a 10% solution of phosphomolybdic acid in EtOH, a 3% solution of vanillin in ethanol, iodine, UV light. Column chromatography was carried out on Alfa Aesar silica gel (0.06—0.2 mm) and neutral aluminum oxide from Acros. HPLC analysis was carried out using Chiralpak AD-H chiral columns (hexane : 2-propanol = = 8 : 2). Elemental analysis was carried out on a EA 1110 CHNS-O automated analyzer. Optical rotation angles were determined on a Kruss P3002RS automated polarimeter (Germany). (+)-3-Carene ($[\alpha_D^{20}]$ = +17.1° (neat)) and commercial 98% isatin purchased from Sigma-Aldrich were used in the work.

X-ray diffraction study of compounds **10** and **11** was carried out on a Xcalibur 3 automated four-circle diffractometer with a CCD detector (Multi-User Center of the IOC of the Ural Branch of the Russian Academy of Sciences) according to the standard procedure[17] (ω-scan technique with a 1° step at monochromatized MoKα radiation and T = 295(2) K). Empirical correction for absorption was introduced. The structures were solved by direct statistical method and refined by the full-matrix least squares method with respect to F^2 using anisotropic approximation parameters for all the nonhydrogen atoms, using the SHELXL program.[18] Hydrogen atoms of the C—H bonds were placed in geometrically calculated position and refined in isotropic approximation. The effect of anomalous scattering was neglected. The results of the X-ray diffraction experiments were deposited with the Cambridge Crystallographic Data Center (CCDC 1519876—1519877) and are available free of charge upon request at www.ccdc.cam.ac.uk/data_request/cif.

(+)-(1*S*,3*S*,4*R*,6*R*)-3,4-Epoxy-3,7,7-trimethylbicyclo[4.1.0]-heptane (2) ($[\alpha_D^{20}]$ = +12.0° (*c* 1.0; EtOH), Ref. 11: $[\alpha_D^{20}]$ = = +13.9° (neat)) was obtained from 3-carene **1**. The spectral data are similar to those described in the literature.[11]

(1*S*,3*S*,4*S*,6*R*)-4-Azido-3,7,7-trimethylbicyclo[4.1.0]heptan-3-ol (3) and (1*R*,3*R*,4*R*,6*S*)-4-azido-4,7,7-trimethylbicyclo-[4.1.0]heptan-3-ol (4) were synthesized based on *trans*-3,4-epoxycarane **2**. The spectral characteristics correspond to those described in the literature.[13]

The spectral data for **(+)-4β-amino-3α-hydroxy-*cis*-carane (5)** ($[\alpha_D^{26}]$ = +62.6° (*c* 1.0; $CHCl_3$), Ref. 15: $[\alpha_D^{25}]$ = +35.0° (*c* 1.8; $CHCl_3$)) and **(–)-3β-amino-4α-hydroxy-*trans*-carane (6)** ($[\alpha_D^{26}]$= –9.0° (*c* 1.0; $CHCl_3$), Ref. 15: $[\alpha_D^{25}]$ = –8.0° (*c* 1.0; $CHCl_3$)) agree with those described in the literature.[15]

(–)-(1*S*,3*R*,4*S*,6*R*)-3,4-Epoxy-3,7,7-trimethylbicyclo[4.1.0]-heptane (7) was synthesized from 3-carene **1**. The spectral data correspond to those described in the literature.[12]

(1*S*,3*R*,4*R*,6*R*)-4-Azido-3,7,7-trimethylbicyclo[4.1.0]heptan-3-ol (8) and **(1*R*,3*S*,4*S*,6*S*)-4-azido-3,7,7-trimethylbicyclo-[4.1.0]heptan-3-ol (9)** were obtained from *cis*-3,4-epoxycarane **7**. The spectral characteristics are similar to those described in the literature.[13]

Reduction of azido alcohols 8 and 9. A solution of azido alcohol (1.14 g, 5.8 mmol) in Et_2O (15 mL) was added dropwise to a suspension of $LiAlH_4$ (0.22 g, 5.8 mmol) in Et_2O (10 mL) cooled to –5 °C, and the mixture was stirred for 2 h. Then, a 5% aqueous NaOH (15 mL) was added, the resulting mixture was extracted with Et_2O, the extract was washed with brine, dried with Na_2SO_4, and recrystallized from a mixture of hexane and diethyl ether to obtain compounds **9** and **10**.

(1*S*,3*R*,4*R*,6*R*)-4-Amino-3,7,7-trimethylbicyclo[4.1.0]heptan-3-ol (4α-amino-3β-hydroxy-*trans*-carane) (10). White needle-like crystals, the yield was 75%, R_f 0.30 (1 : 1, C_6H_6 : Pr^iOH), m.p. 61 °C, $[\alpha_D^{26}]$ = –34.3° (*c* 1.0, $CHCl_3$). IR (KBr, ν/cm^{-1}): 3356, 1597 (NH_2), 3082, 1448 (OH). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.58 (t, 1 H, H(6), J = 8.3 Hz); 0.70 (td, 1 H, H(1), J = 9.5 Hz, J = 5.0 Hz); 0.96 (s, 6 H, Me(8), Me(9)); 1.10 (s, 3 H, Me(10)); 1.18 (dd, 1 H, H(2α), J = 14.1 Hz, J =5.0 Hz); 1.42 (dd, 1 H, H(5α), J = 14.5 Hz, J =11.1 Hz, J =8.3 Hz); 1.79 (br.s, 3 H, NH_2, OH); 1.98 (dd, 1 H, H(2β), J = 14.1 Hz, J = 9.5 Hz); 2.05 (dd, 1 H, H(5β), J = 14.5 Hz, J = 7.2 Hz); 2.35 (dd, 1 H, H(4), J = 11.1 Hz, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 15.52 (C(8)), 17.56 (C(7)), 19.08 (C(10)), 20.23 (C(1)), 20.56 (C(6)), 28.85 (C(9)), 30.30 (C(5)), 34.29 (C(2)), 55.43 (C(4)), 71.94 (C(3)). Found (%): C, 70.56; H, 11.59; N, 8.74. $C_{10}H_{19}NO$. Calculated (%): C, 70.96; H, 11.31; N, 8.27.

X-ray diffraction study of compound 10. A monoclinic crystal, space group $P2_1$, a = 9.7323(7) Å, b = 8.9751(5) Å, c = 12.1117(6) Å, β = 97.720(5)°, V = 1048.35(11) Å^3, for a compound with molecular formula $C_{10}H_{19}NO$, M = 169.26, Z = 2, μ(MoKα)= 0.068 mm^{-1}. On the scattering angle

$5.06 < 2\theta < 56.56°$ there were collected 5281 reflections, 2684 of which were independent ($R_{int} = 0.0295$), including 1956 with $I > 2\sigma(I)$. The final parameters of refinement: $R_1 = 0.0734$, $wR_2 = 0.1287$ (on all the reflection), $R_1 = 0.0481$, $wR_2 = 0.1110$ (on the reflections with $I > 2\sigma(I)$). $S = 1.008$. $\Delta\rho_{\bar{e}} = 0.15/-0.16$ ē Å^{-3}.

(1*R*,3*S*,4*S*,6*S*)-4-Amino-4,7,7-trimethylbicyclo[4.1.0]heptan-3-ol (3α-amino-4β-hydroxy-*cis*-carane) (11). White orthorhombic crystals, the yield was 72%, R_f 0.34 (1 : 1, C_6H_6: Pr^iOH), m.p. 80 °C, $[\alpha_D^{26}] = +75.0°$ (*c* 1.0, $CHCl_3$). IR (KBr, ν/cm^{-1}): 3350, 1583 (NH_2), 3201,1456 (OH). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.51 (td, 1 H, H(6), $J = 9.1$ Hz, $J = 2.5$ Hz); 0.66 (td, 1 H, H(1), $J = 9.1$ Hz, $J = 6.0$ Hz); 0.99 (s, 3 H, Me(9)); 1.02 (s, 3 H, Me(10)); 1.05 (s, 3 H, Me(8)); 1.32 (dd, 1 H, H(2α), $J = 14.7$ Hz, $J = 5.9$ Hz); 1.42 (br.s, 3 H, NH_2, OH); 1.41—1.54 (m, 2 H, H(5α), H(2β)); 2.27 (ddd, 1 H, H(5β), $J = 16.2$ Hz, $J = 9.1$ Hz, $J = 7.0$ Hz); 3.35 (br.d, 1 H, H(4), $J = 7.0$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 15.24 (C(8)), 17.59 (C(1)), 17.88 (C(7)), 18.27 (C(6)), 25.69 (C(5)), 26.25 (C(10)), 28.52 (C(2)), 28.92 (C(9)), 50.69 (C(3)), 72.72 (C(4)). Found (%): C, 70.52; H, 11.85; N, 8.27. $C_{10}H_{19}NO$. Calculated (%): C, 70.96; H, 11.31; N, 8.27.

X-ray diffraction study of compound 11. An orthorhombic crystal, space group $P2_12_12_1$, $a = 6.0826(3)$ Å, $b = 12.6526(8)$ Å, $c = 13.2163(8)$ Å, $V = 1017.14(10)$ Å^3, for a compound with the molecular formula $C_{10}H_{19}NO$ $M = 169.26$, $Z = 4$, $\mu(MoK\alpha) = 0.070$ mm^{-1}. On the scattering angle $6.16 < 2\theta < 61.92°$ there were collected 3517 reflections, 1643 of which were independent ($R_{int} = 0.0192$), including 1281 with $I > 2\sigma(I)$. The final parameters of refinement: $R_1 = 0.0642$, $wR_2 = 0.1496$ (on all the reflections), $R_1 = 0.0451$, $wR_2 = 0.1312$ (on reflections with $I > 2\sigma(I)$). $S = 1.038$. $\Delta\rho_{\bar{e}} = 0.22/-0.12$ ē Å^{-3}.

Aldol reaction of isatin with acetone catalyzed by amino alcohols 5, 6, 10, and 11. Water (4.4 μL, 0.244 mmol) and a solution of acetone (0.3 mL) in dichloromethane (1.2 mL) were sequentially added to a mixture of isatin **12** (0.122 mmol) and a catalyst (0.024 mmol). The reaction mixture was stirred at room temperature (see Table 1), then dichloromethane was evaporated. The residue was subjected to chromatography on neutral alumina, using a gradient of light petroleum ether, EtOAc, and MeOH as an eluent. The ratio of enantiomers of product **13** was determined by HPLC on a chiral column. The spectral data for compound **13** are similar to those described in the literature.[16]

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