Enantioselective synthesis of β-hydroxy ketones from heterocyclic aldehydes in water catalyzed by a recyclable organocatalyst bearing an ionic liquid moiety

*D. E. Siyutkin, A. S. Kucherenko, and S. G. Zlotin**

N. D. Zelinsky of Organic Chemistry, Russian Academy of Sciences,
47 Leninsky prosp., 119991 Moscow, Russian Federation.
Fax: +7 (499) 135 5328. E-mail: zlotin@ioc.ac.ru

The aldol reactions of cyclic (heterocyclic) ketones and heterocyclic aldehydes catalyzed by (4*R*,*S*)-4-hydroxyproline modified with a ionic liquid moiety proceed with high yields and diastereo- and enantioselectivity in the presence of water. The catalyst retained its activity and selectivity for at least five cycles.

Key words: organocatalysis, asymmetric aldol reaction, water, β-hydroxy ketones, heterocyclic aldehydes, catalyst regeneration, ionic liquids.

Chiral heterocyclic compounds bearing the β-hydroxy group possess useful types of biological activity[1a,b] and are used as intermediates in the synthesis of natural compounds.[1c,d] A direct method for their preparation can be the asymmetric aldol reaction involving carbonyl compounds of the heterocyclic series. It was found that aldol reactions between aldehydes and ketones proceed efficiently in the presence of chiral organic amino compounds, including amino acids and their derivatives, named organocatalysts.[2] In spite of the vigorous development of studies in the field of organocatalysis followed after this discovery,[3] data on the involvement of aldehydes of the heterocyclic series in the asymmetric aldol reaction are rare.[4] In particular, it was established that heterocyclic aldols catalyzed by proline derivatives **1**—**7** bearing hydrophobic substituents are formed with high enantiometric purity in the presence of water.[4b,5] Catalysts **4**—**7** immobilized on dendrimer[6a] and polymeric groups[6b—d] can be recovered and multiply used in the reaction.

Proline derivatives **8a** and **9a** bearing moieties of ionic liquids with long-chain alkyl groups, which have been synthesized by us previously, belong to the same type of catalysts. They catalyze aldol reactions between cycloalkanones and aromatic aldehydes in aqueous media[7] but have not been used earlier in reactions with heterocyclic aldehydes.

In order to compare the activity and selectivity of the catalysts bearing amphiphilic ionic groups with the corresponding parameters of catalysts **1**—**7** in the formation of heterocyclic aldols, we studied compound **9a** in the reactions of cyclohexanone (**10a**) with nicotinaldehyde (**11a**), 5-nitrofurane-2-carboxaldehyde (**11b**), and 5-nitrothiophene-2-carboxaldehyde (**11c**), whose structural fragments occur in most of important biologically active substances[8] (Scheme 1). The reactions were carried out in an aqueous medium at room temperature at the molar ratio ketone : aldehyde = 3 : 1. The amount of catalyst **9a** was 15 mol.%, and the amount of water was 110 equivalents over the aldehyde. Under the conditions studied, aldols **12a**—**c** were formed in high yields (62—94%) and with good *anti*-diastereo- (*dr* 86 : 14—97 : 3) and enantioselectivity (*ee* of *anti*-isomers is 88—99%) (Table 1). The yields and the *dr* or *ee* values of known products **12a**,**b** were comparable with or exceeded those obtained earlier by the action of arginine in a ionic liquid medium[9] or catalysts **1** and **2** in an aqueous medium. In the catalytic system proposed, the reactions proceeded with a higher rate than in the presence of catalysts **1** (see Ref. 5b) and **2** (see Ref. 4b) and required no additives of an organic solvent or a surfactant for the intensification of the process.

Compound **9a** is not almost inferior in all parameters to catalysts **4**—**7** immobilized on the polymers and dendrimer and used earlier in the reactions with cyclohexanone with isonicotinaldehyde[6a] and furfural.[5a,6a—d] It is noteworthy that catalyst **9a** can easily be recovered. After the extraction of product **12c** with diethyl ether, new portions of reactants **9a** **10a** and **11c** were added to the remainder suspension of **9a** in water, and the process was carried out again. After fivefold repetition of the recovery—reaction sequence, no decrease in the selectivity and yield of product **12c** was observed.

Under the conditions studied, compound **9a** catalyzes the aldol reactions between aldehyde **11c** and other cyclic

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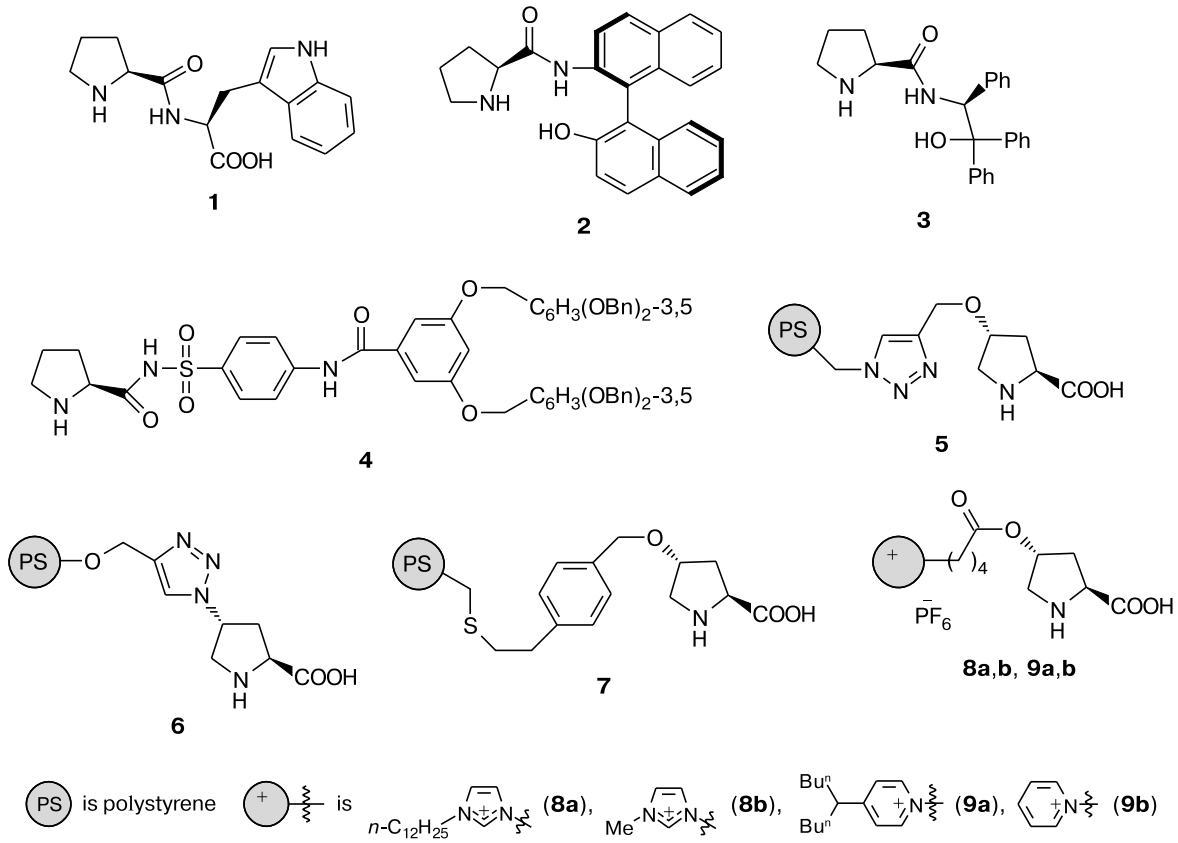
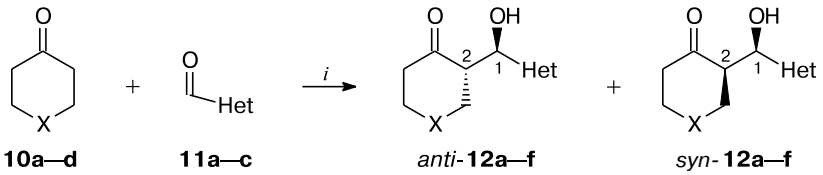


Scheme 1



i. Catalyst, H_2O, 20 °C.

(heterocyclic) ketones, including cyclopentanone (**10b**), 1,4-dioxaspiro[4.5]decan-8-one (**10c**) and 1-Cbz-piperidin-4-one (**10d**), which afford the corresponding aldols **12d—f** in high yield and with high enantioselectivity. The reactions with six-membered cyclic ketones **10c**,**d**, as well as the reaction with cyclohexanone (**10a**), are highly *anti*-diastereoselective (*dr anti*/*syn* = 93 : 7), whereas in the reaction with cyclopentanone (**10b**) this parameter is noticeably lower, which is, most likely, due to conformational features of cyclopentanone.[4b,5b,6] We did not determine the absolute configuration of newly synthesized aldols **12c—f**, being oily compounds. However, the configurations (2*S*, 1′*R*), (7*S*, 1′*R*), and (3*S*, 1′*R*) can be ascribed with rather high probability to the prevailing enantiomers of *anti*-aldols **12** for compounds **12c**,**d**, **12e**, and **12f**, respectively, by analogy to the most part of aldol reactions catalyzed by proline derivatives and involving cyclic (heterocyclic) ketones.[6,10]

The necessary prerequisite for the reaction between ketones and heterocyclic aldehydes in water to occur efficiently is a low solubility in water of the reactants and catalyst. Acetone and butan-2-one, which are unrestrictedly miscible with water, do not interact with aldehyde **11c** in the presence of catalyst **9a**. Hydrophilic salts **8b** and **9b** bearing no long-chain alkyl substituents, unlike amphiphilic salt **9a**, do not catalyze the reaction between compounds **10a** and **11c** under the conditions studied. Water plays an important role in providing the efficient stereocontrol of the reaction. When the aldol reactions catalyzed by salt **9a** are carried out in a medium of the reactants without water, the diastereo- and enantioselectivity values decrease by 5—10%. It is most likely

Table 1. Aldol reaction of heteroaromatic aldehydes **11** and cyclic (heterocyclic) ketones **10** in the presence of catalyst **9a**

12	X	Het	Catalyst (mol.%)	τ/h	Yield (%) (cycle)	*dr* (*anti*/*syn*)	*ee* (*anti*/*syn*)	Reference
a	—CH_2—	3-Py	**9a** (15)	8	62	88/12	88/—	—[b]
			Arg (10)[a]	—	38	81/19	89/—	9
b	—CH_2—	5-NO_2-2-furyl	**9a** (15)	8	94	86/14	92/75	—[b]
			1 (20)	12	90	53/47	85/83	5b
			2 (10)	24	99	96/4	79/—	4b
c	—CH_2—	5-NO_2-2-thienyl	**9a** (15)	4	83 (1), 85 (2), 81 (3), 80 (4), 82 (5)	96/4—97/3	98—99/74—75	—[b]
d	σ-bond	The same	The same	20	92	62/38	90/52	—[b]
e		The same	The same	20	90	93/7	98/50	—[b]
f	—N(Cbz)—	The same	The same	20	87	93/7	93/—	—[b]

[a] The reaction was carried out in the ionic liquid 1-butyl-1-methylpyrrolidinium trifluoromethanesulfonate in the presence of TsOH (10 mol.%).
[b] Results of this work.

that amphiphilic catalyst **9a**, which is poorly soluble in water and organic solvents, is localized, under the reaction conditions, at the interface of the organic and aqueous phases, where the stereocontrolled catalytic transformation occurs.[7]

Thus, we developed an efficient method for the synthesis of chiral β-hydroxy ketones of the heterocyclic series from heteroaromatic aldehydes and cyclic (heterocyclic) ketones in the presence of water catalyzed by hydroxyproline ester **9a** bearing a moiety of the hydrophobic ionic liquid. The method is experimentally simple and provides high selectivity retaining upon the multiple use of the catalyst.

Experimental

NMR spectra were recorded on a Bruker AM 300 instrument (300.13 MHz {^{1}H} and 75.5 MHz {^{13}C}) in $CDCl_3$. Chemical shifts of the ^{1}H nuclei were determined relative to Me_4Si as an internal standard, and ^{13}C chemical shifts were determined relative to the signal of $CDCl_3$. Elemental analysis was carried out on a Perkin—Elmer 2400 microanalyzer. The conversion of the reactants and purity of the products were monitored by TLC on Silufol plates using *n*-hexane/EtOAc (2 : 1 or 1 : 1) as eluent. The chromatograms were visualized under UV irradiation. Compounds **12a**—**f** were purified using column chromatography on silica gel (Acros, 0.035—0.070) using *n*-hexane—EtOAc (3 : 1) as eluent. Compounds **12a** (see Ref. 9) and **12b** (see Ref. 5b) were identified by the comparison of the ^{1}H NMR spectra with the literature data. The *dr* values of aldols were determined by the ^{1}H NMR spectra, and the signals of diastereomers were assigned by the spin-spin coupling constant $^3J_{H(1),H(2)}$: $J < 3$ Hz (δ = 5.51—5.59) for *syn*-diastereomers and $J = 6.6$—9.5 Hz (δ = 5.02—5.24) for *anti*-diastereomers (see Scheme 1). The *ee* values were determined by HPLC on a Stayer chromatograph. Racemic forms of the corresponding aldols obtained by the action of *rac*-proline in ketone (for **12c** and **12d**) or DMF (for **12e** and **12f**) served as standards. The starting compounds **10** and **11** (Acros) were introduced into the reaction without additional purification.

Asymmetric aldol reaction (general procedure). Ketone **10** (0.3 mmol) and aldehyde **11** (0.1 mmol) were added to a suspension of catalyst **9** (0.015 mmol, 3.4 mg) in water (11 mmol, 0.2 mL). The reaction mixture was stirred at 23 °C, the organic part was extracted with Et_2O (2×2.5 mL), and the combined extracts were dried with $MgSO_4$. The solvent was removed under reduced pressure (30 °C, 15 Torr), and products **12** were isolated by column chromatography as a mixture of *anti*- and *syn*-diastereomers. New portions of ketone **10a** and aldehyde **11c** were added to the mixture of **9a** and water remained after the extraction of product **12c**, and the process was repeated. The yields and the diastereo- (*dr*) and enantioselectivity (*ee*) values of products **12** are listed in Table 1.

2-[Hydroxy(5-nitro-2-thienyl)methyl]cyclohexanone (12c). Light yellow oil. ^{1}H NMR of *anti*-isomer, δ: 1.61—1.77 (m, 3 H, CH_2, HCH); 1.85—1.98 (m, 2 H, CH_2); 2.11—2.21 (m, 1 H, HCH); 2.32—2.56 (m, 2 H, CH_2CO); 2.59—2.76 (m, 1 H, CHCO); 4.15 (d, OH, J = 4.0 Hz); 5.02—5.06 (m, 1 H, CHOH, J = 7.0 Hz); 6.89 (d, 1 H, CHSCHNO$_2$, J = 3.7 Hz); 7.81 (d, 1 H, $CHNO_2$, J = 4.4 Hz). ^{1}H NMR of *syn*-isomer, δ: 1.61—1.77 (m, 3 H, CH_2, HCH); 1.85—1.98 (m, 2 H, CH_2); 2.11—2.21 (m, 1 H, HCH); 2.32—2.56 (m, 2 H, CH_2CO); 2.59—2.76 (m, 1 H, CHCO); 3.29 (d, OH, J = 4.0 Hz); 5.56 (s, 1 H, CHOH); 6.84 (d, 1 H, CHSCHNO$_2$, J = 3.7 Hz); 7.84 (d, 1 H, $CHNO_2$, J = 4.0 Hz). ^{13}C NMR of *anti*-isomer, δ: 24.6, 27.6, 30.5, 42.5, 57.3, 71.0, 123.9, 128.0, 151.0, 154.3, 214.0. ^{13}C of *syn*-isomer, δ: 24.6, 27.6, 30.5, 42.5, 56.7, 68.2, 121.9, 128.7, 150.4, 155.6, 213.1. Found (%): C, 52.03; H, 5.24; N, 5.34. $C_{11}H_{13}NO_4S$. Calculated (%): C, 51.75; H, 5.13; N, 5.49. R_f 0.41 (*n*-hexane—EtOAc, 2 : 1). HPLC (Chiralcel OJ-H column, eluent *n*-hexane—Pr^{i}OH (7 : 3), λ = 254 nm, v = 0.8 mL min^{-1}), τ/min: 9.0 (*anti*), 10.4 (*ent-anti*), 11.3 (*syn*), 17.1 (*ent-syn*).

2-[Hydroxy(5-nitro-2-thienyl)methyl]cyclopentanone (12d). Light yellow oil. ^{1}H NMR of *anti*-isomer, δ: 1.73—1.90 (m, 1 H, HCH); 1.92—2.27 (m, 4 H, 2CH_2); 2.37—2.50 (m, 1 H, HCH); 2.50—2.62 (m, 1 H, CHCO); 4.86 (s, 1 H, OH); 5.01 (d, 1 H, CHOH, J = 9.5 Hz); 6.88 (d, 1 H, CHSCHNO$_2$, J = 4.0 Hz); 7.80 (d, CHNO$_2$, J = 4.0 Hz). ^{1}H NMR of *syn*-isomer, δ: 1.73—1.90 (m, 1 H, HCH); 1.92—2.27 (m, 4 H, 2 CH_2); 2.37—2.50 (m, 1 H, HCH); 2.50—2.62 (m, 1 H, CHCO); 2.95 (d, 1 H, OH, J = 5.5 Hz); 5.51 (s, 1 H, CHOH); 6.88 (d, 1 H, CHSCHNO$_2$, J = 4.0 Hz); 7.83 (d, CHNO$_2$, J = 4.0 Hz). ^{13}C NMR of *anti*-isomer, δ: 22.0, 24.9, 38.8, 55.0, 68.3, 122.8, 130.1, 148.8, 159.5, 217.5 ^{13}C of *syn*-isomer, δ: 20.0, 22.0, 38.6, 54.7, 66.8, 122.6, 130.4, 148.8, 161.2, 217.2. Found (%): C, 49.98; H, 4.68; N, 5.70. $C_{10}H_{11}NO_4S$. Calculated (%): C, 49.78; H, 4.60; N, 5.81. R_f 0.40 (*n*-hexane—EtOAc, 2 : 1). HPLC (Chiralcel OJ-H column, eluent *n*-hexane—Pr^{i}OH (7 : 3), λ = 254 nm, v = 0.8 mL min^{-1}), τ/min: 9.8 (*anti*), 11.2 (*ent-anti*), 11.6 (*syn*), 12.9 (*ent-syn*).

7-[Hydroxy(5-nitro-2-thienyl)methyl]-1,4-dioxaspiro[4.5]-decan-8-one (12e). Light yellow oil. ^{1}H NMR of *anti*-isomer, δ: 1.74—2.15 (m, 4 H, CH_2CCH_2); 2.42—2.83 (m, 2 H, CH_2CO); 2.98—3.13 (m, 1 H, CHCO); 3.92—4.05 (m, 4 H, OCH_2CH_2O); 4.08 (d, 1 H, OH, J = 4.0 Hz); 5.02—5.11 (m, 1 H, CHOH, J = 6.6 Hz); 6.89 (d, 1 H, CHSCHNO$_2$, J = 4.0 Hz); 7.80 (d, 1 H, CHNO$_2$, J = 4.4 Hz). ^{1}H NMR of *syn*-isomer, δ: 1.74—2.15 (m, 4 H, CH_2CCH_2); 2.42—2.83 (m, 2 H, CH_2CO); 2.98—3.13 (m, 1 H, CHCO); 3.29 (d, 1 H, OH, J = 3.7 Hz); 3.92—4.05 (m, 4 H, OCH_2CH_2O); 5.59 (s, 1 H, CHOH); 6.83 (d, 1 H, CHSCHNO$_2$, J = 4.4 Hz); 7.84 (d, 1 H, CHNO$_2$, J = 4.4 Hz). ^{13}C NMR of *anti*-isomer, δ: 33.3, 34.2, 38.4, 52.9, 64.7, 64.9, 67.7, 107.2, 121.9, 128.8, 150.6, 155.2, 211.0. ^{13}C NMR of *syn*-isomer, δ: 34.3, 37.4, 38.7, 53.3, 64.7, 64.9, 70.6, 106.8, 124.0, 128.2, 151.3, 153.8, 212.2. Found (%): C, 50.08; H, 4.96; N, 4.28. $C_{13}H_{15}NO_6S$. Calculated (%): C, 49.83; H, 4.83; N, 4.47. R_f 0.26 (*n*-hexane—EtOAc, 2 : 1). HPLC (Chiralcel OJ-H column, eluent *n*-hexane—Pr^{i}OH (7 : 3), λ = 254 nm, v = 0.8 mL min^{-1}), τ/min: 16.1 (*anti*), 16.9 (*ent-anti*), 18.2 (*syn*), 20.8 (*ent-syn*).

1-Benzyloxycarbonyl-3-[hydroxy(5-nitro-2-theinyl)methyl]-piperidin-4-one (12f). Light yellow oil. ^{1}H NMR of *anti*-isomer, δ: 2.46—2.96 (m, 2 H, CH_2CO); 3.05—3.45 (m, 2 H, NCH_2CH_2); 4.05—4.25 (m, 2 H, NCH_2CH); 5.05—5.24 (m, 3 H, CHOH, CH_2Ph); 6.63—6.95 (m, 1 H, CHSCHNO$_2$); 7.21—7.43 (m, 5 H, C_6H_5); 7.62—7.90 (m, 1 H, CHNO$_2$). ^{1}H NMR of *syn*-isomer, δ: 2.46—2.96 (m, 2 H, CH_2CO); 3.05—3.45 (m, 2 H, NCH_2CH_2); 4.05—4.25 (m, 2 H, NCH_2CH); 5.05—5.24 (m, 2 H, CH_2Ph); 5.58 (s, 1 H, CHOH); 6.63—6.95 (m, 1 H, CHSCHNO$_2$); 7.21—7.43 (m, 5 H, C_6H_5); 7.62—7.90 (m, 1 H, CHNO$_2$). ^{13}C NMR of *anti*-isomer, δ: 41.4, 43.2, 43.7, 56.4, 67.7, 68.0, 124.1, 128.0, 128.1, 128.3, 128.5, 136.0, 151.4, 154.3, 183.1, 208.9. ^{13}C NMR of *syn*-isomer, δ: 41.4, 43.2, 43.7, 55.9, 66.9, 68.0, 122.1, 128.0, 128.3, 128.5, 128.7, 136.0, 150.8, 155.3, 183.1, 207.7. Found (%): C, 55.60; H, 4.87; N, 7.08. $C_{18}H_{18}N_2O_6S$. Calculated (%): C, 55.38; H, 4.65; N, 7.18. R_f 0.39 (*n*-hexane—EtOAc, 1 : 1). HPLC (Chiralcel OJ-H column, eluent *n*-hexane—Pr^{i}OH (7 : 3), λ = 254 nm, v = 0.8 mL min^{-1}), τ/min: 9.8 (*anti*), 10.4 (*syn*), 10.9 (*ent-anti*), 11.5 (*ent-syn*).

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