Tetrahedron 70 (2014) 3707–3713

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Evaluation of mono- and dipeptides as organocatalysts for enantioselective aldol reaction

Cigdem Yolacan *, Murat Emrah Mavis, Feray Aydogan

Department of Chemistry, Yildiz Technical University, Davutpasa Campus, Esenler, 34010 Istanbul, Turkey

ARTICLE INFO

Article history:
Received 27 January 2014
Received in revised form 21 March 2014
Accepted 7 April 2014
Available online 13 April 2014

Keywords:
Aldol reaction
Tetrahydroisoquinoline-3-carboxylic acid
Proline
Organocatalysis
Asymmetric synthesis

ABSTRACT

Catalytic activities of (3*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (THIQA)-based mono- and dipeptides and their L-proline analogs in asymmetric aldol reaction were investigated. THIQA-based dipeptides showed better enantioselectivity than proline analogs, whereas proline-based dipeptides gave higher yield in the aldol reaction of cyclohexanone with several aldehydes in dichloromethane at −10 °C in the presence of benzoic acid.

1. Introduction

Asymmetric carbon–carbon bond formation reactions catalyzed by chiral organic molecules have become an important area in organic synthesis. The aldol reaction is the most important one of these type of reactions in modern organic synthesis as a key step in natural product synthesis and for rapid access to polyoxygenated compounds. This useful reaction facilitates the construction of larger complex molecules with new stereogenic centers from smaller ones.[1] Since the first example of a nonmetallic small-molecule catalyst for direct intermolecular asymmetric aldol reactions by List et al.,[2] many new nonmetallic organocatalysts have been developed dramatically for this reaction.[3–7] Organocatalysts have several advantages over transition-metal catalysts and enzymes. They are usually robust, inexpensive, readily available, and non-toxic. Because of their robustness they often do not require demanding reaction conditions like inert gas atmosphere and anhydrous solvent.[8–11] Especially, proline amide derivatives have attracted special interest from researchers as organocatalysts because of their high enantioselective activities.[12–17] These derivatives have the proline ring to form an enamine intermediate and the amide NH proton to form a hydrogen bond, which is necessary for the enantioselectivity.[18] This derivatisation also improves the solubility of the catalyst in organic solvents, which is the important drawback of proline[19] and allows the structural modifications, therefore improves the catalyst properties by varying the stereo and electronic effects of the terminal amide to affect the ability of hydrogen bonding formation between the catalysts and substrates.[20]

Although many proline[7,21–25] and some hydroxyproline[26,27] mono- and diamides have been synthesized and investigated for their catalytic activity in asymmetric aldol reactions, as far as we know, other ring systems such as tetrahydroisoquinoline have not been investigated for this asymmetric transformation. Thus, we decided to investigate the catalytic activity of new mono- and dipeptides derived from (3*S*)-1,2,3,4-tetrahydroisoquinolin-3-carboxylic acid (THIQA) in the asymmetric direct aldol reaction.

2. Results and discussion

THIQA-derived mono- and dipeptides are known well in the literature for their biological activities,[28–33] but, as far as we know, they have not been used as catalysts for aldol reaction. New THIQA-based mono- (**4**) and dipeptides (**8a**,**b**) (Fig. 1) were prepared by the amidation reaction of THIQA (**1**), which was easily prepared starting from commercially available L-phenylalanine,[32] with L-*tert*-leucine methyl ester and/or (*S*)-2-amino-3-phenyl-1-propanol. The

* Corresponding author. Tel.: +90 212 383 42 13; fax: +90 212 383 41 06; e-mail address: cigdemyolacan@hotmail.com (C. Yolacan).

0040-4020/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2014.04.016

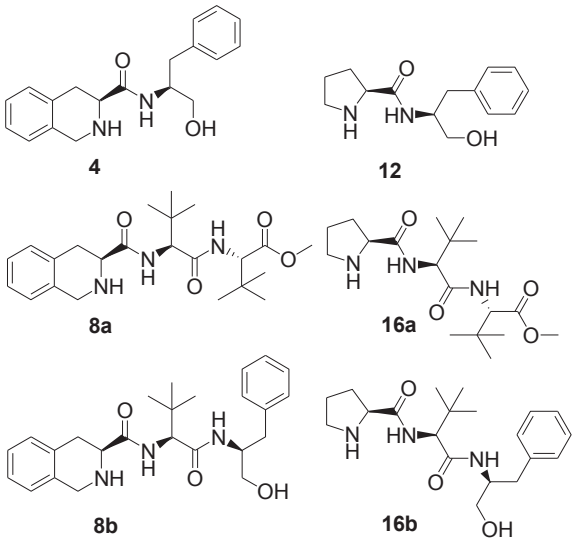


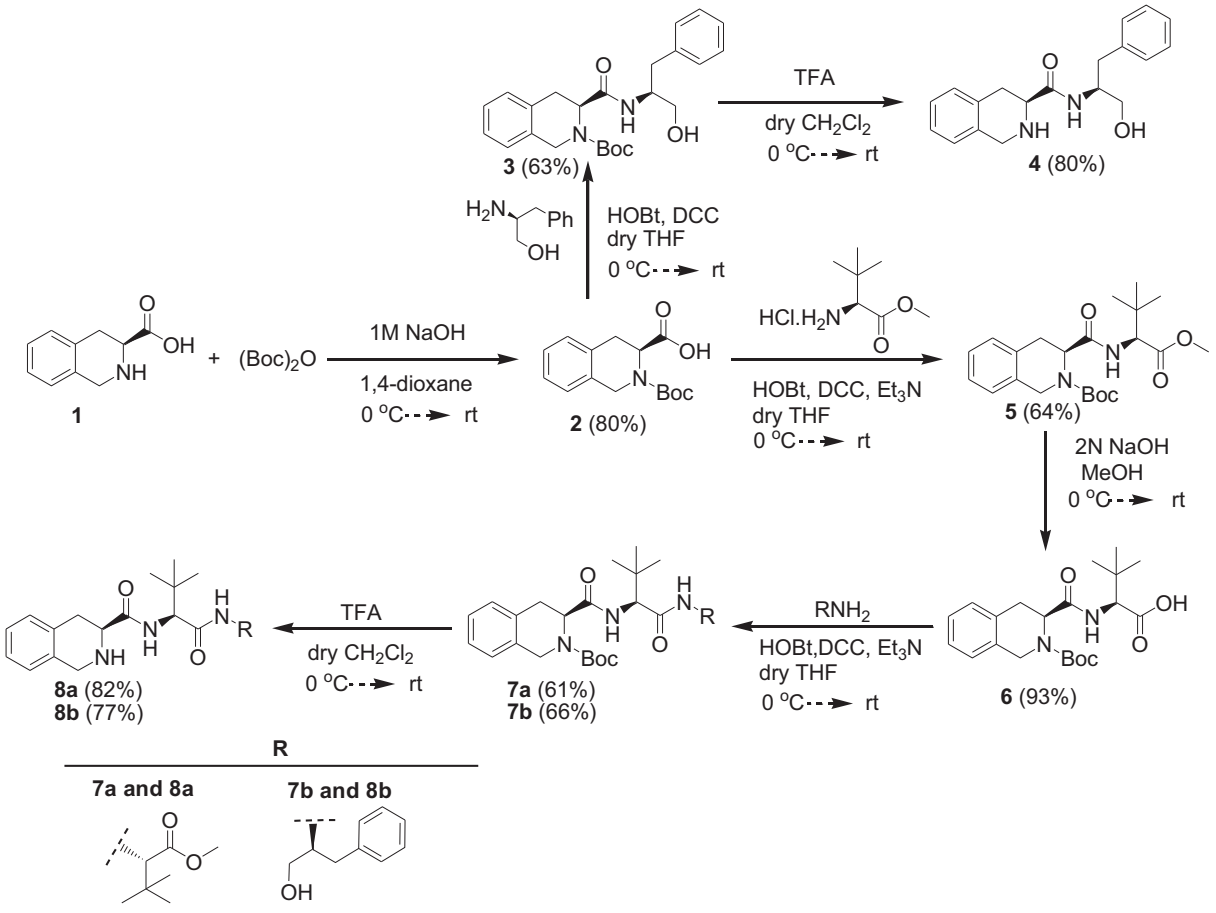
Fig. 1. Proline- and THIQA-based mono- and dipeptides.

synthetic pathway of catalyst **4** and **8a**,**b** outlined in Scheme 1, included protection of THIQA, amidation with L-*tert*-leucine methyl ester, hydrolysis of the ester group, a second amidation, and deprotection of the Boc group by modified literature procedures.[33,34] The proline based mono- (**12**) and dipeptides (**16a**,**b**) (Fig. 1) were also synthesized by a similar synthetic pathway (Scheme 2) to compare their catalytic activities with catalysts **4** and **8a**,**b**. All of the compounds, except compound **12**,[35] were unknown in the literature. The structures of the compounds were determined by their spectroscopic data.

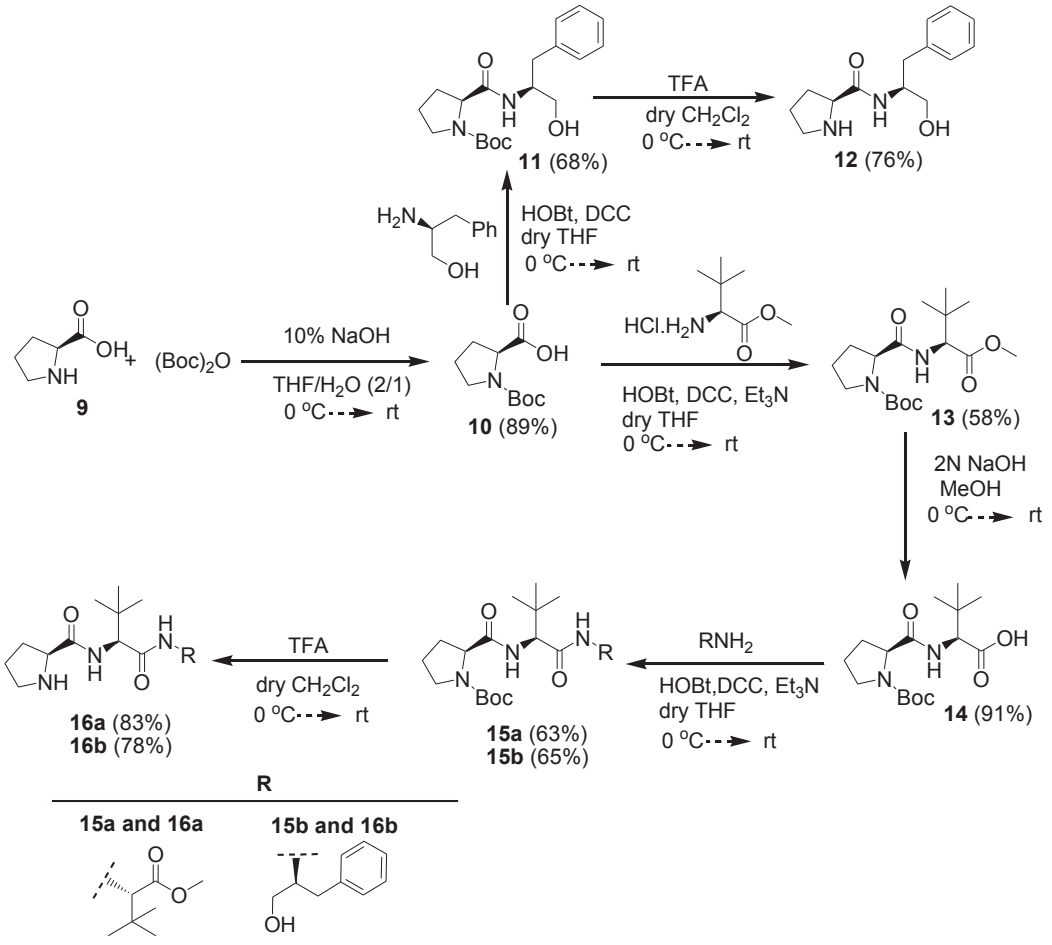
The aldol reactions of 4-nitrobenzaldehyde and cyclohexanone in tetrahydrofuran (THF) at different temperatures in the presence of benzoic acid were used to evaluate the catalysts. Although catalysts **8a** and **8b** showed similar diastereoselectivities, reactions with the catalyst **8a** gave the best enantioselectivity based on the *anti* isomer, whereas the best yields were obtained with the proline-based catalyst **16a** as shown in Table 1. Besides THF, other solvents were screened with catalysts **8a** and **16a**. The results are given in Table 2. The enantioselectivity was not improved considerably by the tested solvents but the yield was 80% in DCM at −10 °C with catalyst **8a**. However, the yield was higher with the proline-based dipeptide **16a** than the THIQA analog **8a** under this conditions. This may be because of difficulty in the formation of the enamine intermediate. Higher enantioselectivity of **8a** may be attributed to the more stable transition state of the THIQA-dipeptide (Scheme 3). The dipeptide structure of the catalyst contributes to the activation of the aldehyde via co-catalyst.

With this promising result, different acid additives were investigated with the same amount of catalyst (10 mol %) in DCM at −10 °C. Benzoic acid gave the best enantioselectivity and yield among the tested acids (Table 3).

Finally, the aldol reactions of different aliphatic ketones with aromatic aldehydes were investigated under the optimized conditions with catalyst **8a** (Table 4). The aldol products are known in the literature, and their spectroscopic data are in agreement with the literature data.[36–38]

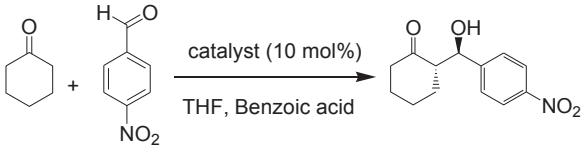


Scheme 1. Synthesis of catalysts **4** and **8a**,**b**.



Scheme 2. Synthesis of catalysts **12** and **16a**,**b**.

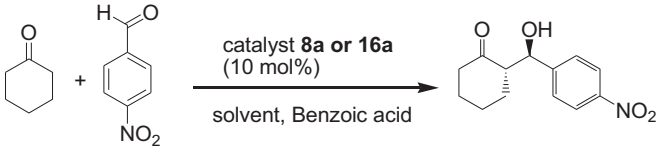
Table 1
Screening of organocatalysts for the aldol reaction



Catalyst	Temperature (°C)	Reaction time (h)	Yield[a] (%)	dr[b] (*anti*/*syn*)	ee[c] (%) (*anti*)
8a	rt	24	65	80:20	87
16a	rt	24	98	63:37	49
8b	rt	24	71	80:20	75
16b	rt	24	90	74:26	68
4	rt	24	53	57:43	65
12	rt	24	86	77:23	74
8a	0	48	62	77:23	88
16a	0	48	98	60:40	56
8b	0	48	58	84:16	82
16b	0	48	94	82:18	73
4	0	48	68	77:23	81
12	0	48	80	79:21	69
8a	−10	72	68	83:17	86
16a	−10	72	97	68:32	62
8b	−10	72	43	84:16	77
16b	−10	72	90	80:20	65
4	−10	72	49	74:26	68
12	−10	72	70	76:24	81

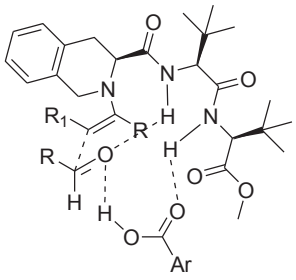
[a] Combined yields of isolated diastereomers.
[b] Determined by ^{1}H NMR of crude product.
[c] Determined by chiral-phase HPLC analysis of the *anti* product.

Table 2
Solvent effect on the aldol reaction with catalysts **8a** and **16a**



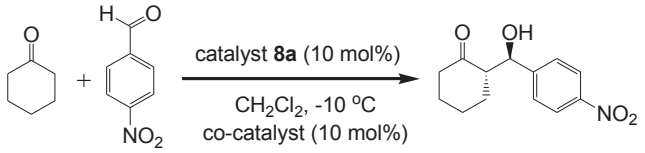
Catalyst	Solvent	Temperature (°C)	Reaction time (h)	Yield[a] (%)	dr[b] (*anti*/*syn*)	ee[c] (%) (*anti*)
8a	CH_2Cl_2	rt	24	66	57:43	85
16a	CH_2Cl_2	rt	24	97	59:41	36
8a	CH_2Cl_2	0	48	31	68:32	84
16a	CH_2Cl_2	0	48	97	59:41	35
8a	*CH_2Cl_2*	*−10*	*72*	*80*	*75:25*	*90*
8a	CH_2Cl_2	−10	72	15	68:32	71[d]
16a	CH_2Cl_2	−10	72	97	67:33	75
8a	CH_2Cl_2	−20	96	69	81:19	85
8a	Toluene	rt	24	58	63:37	84
16a	Toluene	rt	24	98	53:47	25
8a	Toluene	0	48	49	80:20	90
16a	Toluene	0	48	94	68:32	73
8a	Toluene	−10	72	49	77:23	88
16a	Toluene	−10	72	98	75:25	78
8a	Toluene	−20	96	50	84/16	90
8a	H_2O	rt	24	76	66/34	78
16a	H_2O	rt	24	85	55:45	36
8a	H_2O	0	48	71	80:20	82
16a	H_2O	0	48	94	76:24	64

[a] Combined yields of isolated diastereomers.
[b] Determined by ^{1}H NMR of crude product.
[c] Determined by chiral-phase HPLC analysis of the *anti* product.
[d] Without benzoic acid.



Scheme 3. Proposed transition state.

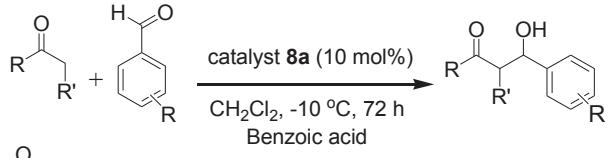
Table 3
The effect of acid additives



Acid co-catalyst (10 mol %)	Reaction time (h)	Yield[a] (%)	dr[b] (*anti*/*syn*)	ee[c] (%) (*anti*)
—	72	15	68:32	71
Benzoic acid	72	80	75:25	90
TFA	72	56	82:18	87
Acetic acid	72	67	80:20	86
Tartaric acid	72	65	83:17	76

[a] Combined yields of isolated diastereomers.
[b] Determined by ^{1}H NMR of crude product.
[c] Determined by chiral-phase HPLC analysis of the *anti* product.

Table 4
The aldol reactions with various aldehydes



	ArCHO	Yield[a] (%)	dr[b] (*anti*/*syn*)	ee[c] (%) (*anti*)
Cyclohexanone	2-Nitrobenzaldehyde	67	98:2	89
Cyclohexanone	3-Nitrobenzaldehyde	81	87:13	87
Cyclohexanone	4-Cyanobenzaldehyde	63	84:16	83
Cyclohexanone	4-Bromobenzaldehyde	nr	—	—
Cyclohexanone	4-Chlorobenzaldehyde	nr	—	—
Cyclohexanone	Benzaldehyde	nr	—	—
Cyclohexanone	4-Nitrobenzaldehyde	80	75:25	90
Cyclopentanone	4-Nitrobenzaldehyde	71	28:72	50[d]
Acetone	4-Nitrobenzaldehyde	74	—	83
Ethyl methyl ketone	4-Nitrobenzaldehyde	34[e]	70:30	50

[a] Combined yields of isolated diastereomers.
[b] Determined by ^{1}H NMR of crude product.
[c] Determined by chiral-phase HPLC analysis of the *anti* product.
[d] *syn* isomer.
[e] Based on the 4-hydroxy-3-methyl-4-(4-nitrophenyl)butan-2-one regioisomer.

While electron poor nitrobenzaldehydes and cyanobenzaldehyde gave good enantioselectivity, benzaldehyde, chlorobenzaldehyde, and bromobenzaldehyde did not gave any reaction under these optimized conditions. Different ketones such as cyclopentanone, acetone, and ethyl methyl ketone were also investigated for their aldol reactions with 4-nitrobenzaldehyde under the same conditions. Among these ketones, especially, acetone showed good enantioselectivity, while the other ketones gave good diastereoselectivities. Diastereomeric ratios were determined from the ^{1}H NMR of the crude products and enantiomeric excesses were determined by chiral HPLC analysis of *anti* products by using the methods from the literature.[36–38]

3. Conclusion

In conclusion, the catalytic activity of new chiral THIQA-based mono- and dipeptides in direct aldol reaction of cyclohexanone was investigated and compared with those of L-proline mono- and dipeptide analogs for the first time. It was shown that the enantioselectivity of THIQA-based dipeptide was better than the proline analog. These type organocatalysts may have potential to be a new class of catalysts for asymmetric aldol reaction.

4. Experimental

4.1. General information

All reagents were of commercial quality and reagent quality solvents were used without further purification. IR spectra were determined on a Perkin Elmer, Spectrum One FT-IR spectrometer. NMR spectra were recorded on Varian Unity Inova 500 MHz spectrometer and Bruker Avance III 500 MHz spectrometer. Chemical shifts δ are reported in parts per million (ppm) with TMS as internal standard and the solvents are $CDCl_3$ and CD_3OD. Column chromatography was conducted on silica gel 60 (40–63 μM). TLC was carried out on aluminum sheets precoated with silica gel 60F_{254} (Merck). LC/MS spectra were obtained on a Finnigan LC/MS instrument. Elemental analysis were carried out on Thermo Flash EA 1112 series apparatus. Optical rotations were measured with Bellingham Stanley ADP-410 Polarimeter. Chiral HPLC analysis were performed with Shimadzu HPLC (Daicel Chiralpak AD and AD-H columns) equipped with SPD-20A detector and isopropanol/*n*-hexane mixtures as the eluent. The protection of THIQA[39,40] and L-proline[41,42] was carried out according to the literature procedure.

4.2. Synthesis of the catalysts

4.2.1. General procedure for amidation reactions. At 0 °C and with stirring, to the solution of *N*-Boc-THIQA (**2**) or L-*N*-Boc-proline (**10**) (0.92 mmol) in dry THF (10 mL), HOBt (1.0 mmol) was added, and stirred for 10 min, then DCC (1.0 mmol) was added (mixture A). In another reaction flask, to the suspension of L-*tert*-leucine methyl ester hydrochloride (1.02 mmol) in dry THF (5 mL), triethylamine (0.5 mL) was added and stirred at room temperature for 1 h (mixture B). The reaction mixtures A and B were combined (in the case of (*S*)-2-amino-3-phenyl-1-propanol, the amino alcohol (1.02 mmol) was added directly to the mixture A). The reaction mixture was stirred at room temperature for 24 h, and the reaction was monitored by TLC. The formed precipitate of DCU was removed by filtration, and the filtrate was evaporated under vacuum. The residue was dissolved in 50 mL of ethyl acetate, the formed solution was washed successively with saturated aqueous solution of $NaHCO_3$ (30 mL×3), 5% aqueous solution of $KHSO_4$ (30 mL×3), and brine (30 mL×3), and dried with anhydrous Na_2SO_4. After filtration, the filtrate was evaporated under vacuum to give the crude products, which were purified by column chromatography on silica gel.

4.2.2. General procedure for deprotection of Boc group. To the solution of *N*-Boc-protected compounds (**3**, **7a**, **b**, **11**, **15a**, **b**) (1.0 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C, trifluoroacetic acid (27.0 mmol) was added dropwise over 5 min while stirring. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 2 h then 2 M K_2CO_3 was added to adjust to basic pH. The

organic phase was washed with water, dried over $MgSO_4$, filtrated, and evaporated to give the pure compounds.

4.2.3. General procedure for hydrolysis of ester group. At 0 °C to the solution of compound **5** or **13** (1.0 mmol) in methanol (5 mL), 2 N aqueous NaOH was added to adjust the pH to 11. The reaction mixture was stirred at 0 °C for 3 h, and at room temperature for 24 h, then adjusted to pH 2 with aqueous solution of $KHSO_4$. The solution was evaporated under vacuum to remove methanol, and extracted with ethyl acetate (30 mL×3). The combined ethyl acetate was successively washed with brine (20 mL×2) and dried with anhydrous Na_2SO_4. After filtration, the filtrate was evaporated to provide compounds **6** and **14**, which were used without any further purification.

*4.2.4. (S)-tert-Butyl 3-((S)-1-hydroxy-3-phenylpropan-2-ylcarbamoyl)-3,4-dihydro-isoquinoline-2(1H)-carboxylate (**3**).* White solid, yield 63%, mp 142–143 °C; $[\alpha]_D^{20}$ −29.7 (*c* 1.0, $CHCl_3$). Found: C, 70.35; H, 7.26; N, 6.85. $C_{24}H_{30}N_2O_4$ requires C, 70.22; H, 7.37; N, 6.82%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.80 (br s, 1H), 2.58–2.70 (m, 2H), 3.02–3.27 (m, 2H), 3.45–3.49 (m, 1H), 3.53–3.62 (m, 1H), 4.00 (br s, 1H), 4.07–4.34 (m, 1H), 4.45–4.49 (m, 1H), 4.57–4.75 (m, 1H), 6.03 (br s, 1H), 6.98 (br s, 2H), 7.05–7.24 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.9, 28.6, 36.8, 44.6, 52.2, 52.9, 64.3, 81.4, 126.4, 126.8, 127.3, 127.8, 128.4, 128.8, 129.4, 133.6, 137.1, 137.3, 155.8, 172.5; IR (ATR) ν 3380, 3302, 1662, 1654, 1644 cm^{-1}.

*4.2.5. (3S)-1,2,3,4-Tetrahydro-N-((S)-1-hydroxy-3-phenylpropan-2-yl)isoquinoline-3-carboxamide (**4**).* White solid, yield 80%, mp 125–126 °C; $[\alpha]_D^{20}$ −78.5 (*c* 0.56, MeOH); Found: C, 73.59; H, 7.17; N, 8.96. $C_{19}H_{22}N_2O_2$ requires C, 73.52; H, 7.14; N, 9.03%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.05 (br s, 1H), 2.53–2.58 (m, 1H), 2.71–2.76 (m, 1H), 2.85–2.89 (m, 1H), 3.05–3.09 (m, 1H), 3.42–3.46 (m, 1H), 3.54–3.58 (m, 1H), 3.65–3.71 (m, 2H), 3.81–3.84 (br d, 1H, *J*=17.0 Hz), 4.12 (br s, 1H), 6.94 (br s, 1H), 7.06–7.09 (m, 3H), 7.12–7.14 (m, 3H), 7.18–7.22 (m, 2H), 7.41 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.6, 36.0, 46.1, 51.8, 55.2, 63.9, 124.4, 125.2, 125.6, 127.5, 127.6, 128.0, 128.1, 133.2, 135.0, 136.5, 173.0; ESI$^{(-)}$-MS: *m*/*z*=311.1(M+1); IR (ATR) ν 3309, 3282, 3193, 1649 cm^{-1}.

*4.2.6. (S)-tert-Butyl 3-((S)-1-(methoxycarbonyl)-2,2-dimethylpropylcarbamoyl)-3,4-dihydro-isoquinoline-2(1H)-carboxylate (**5**).* Colorless viscous oil, yield 64%; $[\alpha]_D^{20}$ −9.5 (*c* 1.27, $CHCl_3$). Found: C, 65.26; H, 8.06; N, 6.87. $C_{22}H_{32}N_2O_5$ requires C, 65.32; H, 7.97; N, 6.93%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.58 (s, 9H), 1.39 (s, 9H), 2.98–3.01 (m, 1H), 3.23–3.26 (m, 1H), 3.59 (s, 3H), 4.18 (d, 1H, *J*=9.5 Hz), 4.34–4.85 (m, 3H), 6.15 and 6.64 (br s, 1H, NH rotamers), 7.08–7.12 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.9, 27.2, 31.2, 33.3, 43.8, 50.6, 55.7, 58.6, 80.3, 125.2, 126.0, 126.7, 127.0, 132.8, 154.0, 169.2, 169.7, 170.3; IR (ATR) ν 3345, 1737, 1682 cm^{-1}.

*4.2.7. (S)-[({(S)-2-[tert-Butoxycarbonyl]-1,2,3,4-tetrahydroisoquinolin-3-yl}carbonyl)amino]-3,3-dimethylbutanoic acid (**6**).* Colorless oil, yield 93%; $[\alpha]_D^{20}$ −10.0 (*c* 0.6, $CHCl_3$); Found: C, 64.63; H, 7.81; N, 7.09. $C_{21}H_{30}N_2O_5$ requires C, 64.59; H, 7.74; N, 7.17%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.55 (s, 9H), 1.43 (s, 9H), 3.02–3.11 (m, 1H), 3.29–3.36 (m, 1H), 4.24 (d, 1H, *J*=9.5 Hz), 4.38–4.85 (m, 3H), 6.26 and 6.63 (br s, 1H, NH rotamers), 7.20 (br s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.9, 27.2, 31.2, 33.3, 43.8, 55.8, 58.6, 80.6, 125.2, 126.1, 126.8, 127.0, 132.7, 154.2, 170.6, 170.7, 173.8; IR (ATR) ν 3420, 1729, 1702, 1675 cm^{-1}.

*4.2.8. (S)-tert-Butyl 3-((S)-1-((S)-1-methoxy-3,3-dimethyl-1-oxobutan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamoyl)-3,4-dihydroisoquinoline-2-(1H)-carboxylate (**7a**).* White solid, yield 61%, mp 155–157 °C; $[\alpha]_D^{20}$ −24.8 (*c* 1.0, $CHCl_3$). Found: C, 64.91; H, 8.42; N, 8.07. $C_{28}H_{43}N_3O_6$ requires C, 64.97; H, 8.37; N, 8.12%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.46 (s, 9H), 0.86 (s, 9H), 1.37 (s, 9H), 2.97–3.00 (m, 1H), 3.28 (br d, 1H, *J*=15.0 Hz), 3.62 (s, 3H), 4.02–4.08 (m, 1H), 4.27 (d, 1H, *J*=8.5 Hz), 4.35–4.62 (m, 3H), 6.20–6.25 (m, 1H, NH rotamers), 6.45 and 6.61 (br s, 1H, NH, rotamers), 7.11 (br s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.8, 25.7, 27.4, 31.0, 33.3, 33.6, 44.3, 50.7, 55.1, 58.9, 59.5, 80.2, 124.6, 125.1, 126.2, 127.5, 132.4, 132.6, 153.9, 168.7, 170.0, 170.5; IR (ATR) ν 3309, 1740, 1701, 1652 cm^{-1}.

*4.2.9. (S)-tert-Butyl 3-(((S)-1-hydroxy-3-phenylpropan-2-ylcarbamoyl)-2,2-dimethylpropylcarbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (**7b**).* White solid, yield 66%, mp 118–119 °C; $[\alpha]_D^{20}$ −20.0 (*c* 1.0, $CHCl_3$). Found: C, 68.76; H, 7.82; N, 8.06. $C_{30}H_{41}N_3O_5$ requires C, 68.81; H, 7.89; N, 8.02%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.57 (s, 9H), 1.55 (s, 9H), 2.77–2.83 (m, 2H), 3.10 (dd, 1H, *J*=15.0, 6.5 Hz), 3.27 (br s, 1H), 3.49–3.66 (m, 2H), 3.73–3.76 (m, 1H), 3.99–4.22 (br s, 1H), 4.39–4.45 (m, 1H), 4.63–4.74 (m, 2H), 6.22 and 6.41 (br s, 1H, NH, rotamers), 6.48 and 6.56 (br s, 1H, NH, rotamers), 7.19–7.25 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.3, 28.3, 31.4, 33.1, 36.8, 45.5, 52.9, 56.4, 62.0, 63.4, 81.8, 125.9, 126.4, 126.6, 127.1, 128.1, 128.5, 129.2, 133.6, 133.8, 138.0, 155.8, 169.6, 171.8; IR (ATR) ν 3351, 3264, 1674, 1662, 1631 cm^{-1}.

*4.2.10. (S)-Methyl 2-((S)-3,3-dimethyl-2-((S)-1,2,3,4-tetrahydroisoquinoline-3-carboxamido)butanamido)-3,3-dimethylbutanoate (**8a**).* White solid, yield 82%, mp 76–78 °C; $[\alpha]_D^{20}$ −20.3 (*c* 2.3; CH_2Cl_2); Found: C, 66.18; H, 8.39; N, 10.11. $C_{23}H_{35}N_3O_4$ requires C, 66.16; H, 8.45; N, 10.06%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (s, 9H), 0.89 (s, 9H), 1.88 (br s, 1H), 2.78–2.83 (m, 1H), 3.14 (dd, 1H, *J*=16.2, 6.0 Hz), 3.57–3.61 (m, 1H), 3.65 (s, 3H), 3.90–3.99 (m, 2H), 4.24 (d, 1H, *J*=9.5 Hz), 4.30 (d, 1H, *J*=9.5 Hz), 6.39 (br d, 1H, *J*=8.5 Hz), 6.98–7.01 (m, 1H), 7.06–7.10 (m, 3H), 7.89 (br d, 1H, *J*=9.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.4, 25.5, 30.2, 33.4, 33.6, 45.7, 50.7, 55.0, 59.2, 59.3, 124.6, 125.3, 125.7, 127.8, 133.1, 134.7, 169.4, 170.6, 172.0; ESI$^{(-)}$-MS: *m*/*z* 418.3 (M+1); IR (ATR) ν 3311, 1740, 1642 cm^{-1}.

*4.2.11. (S)-N-((S)-1-((S)-1-Hydroxy-3-phenylpropan-2-ylcarbamoyl)-2,2-dimethylpropyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (**8b**).* White solid, yield 77%, mp 186–188 °C; $[\alpha]_D^{20}$ −43.4 (*c* 0.7, MeOH). Found: C, 70.93; H, 7.81; N, 9.96. $C_{25}H_{33}N_3O_3$ requires C, 70.89; H, 7.85; N, 9.92%; ^{1}H NMR (500 MHz, CD_3OD) δ 0.90 (s, 9H), 2.58–2.62 (m, 1H), 2.81–2.87 (m, 2H), 3.07 (dd, 1H, *J*=16.5, 4.5 Hz), 3.43 (br d, 2H, *J*=5.5 Hz), 4.02 (dd, 1H, *J*=12.2, 5.0 Hz), 4.05–4.09 (m, 1H), 4.18 (br s, 1H), 4.25 (br s, 2H), 7.03–7.08 (br s, 1H), 7.11–7.22 (m, 9H); ^{13}C NMR (125 MHz, CD_3OD) δ 27.1, 31.2, 35.2, 37.9, 45.5, 54.0, 56.4, 62.6, 64.4, 127.2, 127.6, 128.5, 129.1, 129.3, 129.4, 129.9, 130.4, 132.0, 139.9, 169.5, 171.6; ESI$^{(-)}$-MS: *m*/*z* 424.3 (M+1); IR (ATR) ν 3420, 3260, 1671, 1636 cm^{-1}.

*4.2.12. (S)-tert-Butyl 2-((S)-1-hydroxy-3-phenylpropan-2-ylcarbamoyl)pyrrolidine-1-carboxylate (**11**).* White solid, yield 68%, mp 152–154 °C; $[\alpha]_D^{20}$ −84.0 (*c* 1.0, $CHCl_3$). Found: C, 65.53; H, 8.07; N, 8.09. $C_{19}H_{28}N_2O_4$ requires C, 65.49; H, 8.10; N, 8.04%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.63–1.77 (m, 2H), 1.95–2.17 (m, 2H), 2.76–2.97 (m, 2H), 3.27–3.37 (m, 2H), 3.55–3.70 (m, 2H), 4.16–4.21 (br s, 2H), 6.23 and 6.67 (br s, 1H, NH rotamers), 7.12–7.23 (m, 3H), 7.28–7.31 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.2, 27.3, 28.6, 35.9, 46.0, 51.7, 59.5, 64.1, 79.7, 125.7, 127.5, 128.0, 136.6, 171.4, 172.3; IR (ATR) ν 3363, 3333, 1670, 1648 cm^{-1}.

*4.2.13. (2S)-N-((S)-1-Hydroxy-3-phenylpropan-2-yl)pyrrolidine-2-carboxamide (**12**).* White solid, yield 76%, mp 102–104 °C; $[\alpha]_D^{20}$ −30.0 (*c* 0.4, MeOH); [lit.[35] yield 82%, mp 104.4–105.9 °C; [α] −63.0 (*c* 0.5, EtOH)]; ^{1}H NMR (500 MHz, CD_3OD) δ 1.87–1.94 (m, 3H),

2.23–2.33 (m, 1H), 2.64–2.69 (m, 1H), 2.80–2.84 (m, 1H), 3.14–3.20 (m, 1H), 3.24–3.29 (m, 1H), 3.41–3.44 (m, 1H), 3.47–3.50 (m, 1H), 4.00–4.05 (m, 2H), 7.07–7.09 (m, 1H), 7.13–7.18 (m, 4H); IR (ATR) ν 3503, 3251, 1656 cm^{-1}.

*4.2.14. (S)-tert-Butyl 2-((S)-1-(methoxycarbonyl)-2,2-dimethylpropylcarbamoyl)pyrrolidine-1-carboxylate (**13**).* Yellow oil, yield 58%; $[\alpha]_D^{20}$ −71.0 (*c* 1.52, $CHCl_3$). Found: C, 59.71; H, 8.87; N, 8.14. $C_{17}H_{30}N_2O_5$ requires C, 59.63; H, 8.83; N, 8.18%; ^1H NMR (500 MHz, $CDCl_3$) δ 0.96 (s, 9H), 1.48 (s, 9H), 1.80–1.88 (m, 2H), 2.16–2.20 (m, 1H), 2.36–2.42 (m, 1H), 3.31–3.49 (m, 2H), 3.71 (s, 3H), 4.25–4.46 (m, 2H), 7.65 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.9, 25.4, 27.3, 28.9, 33.3, 45.9, 50.6, 57.4, 58.6, 80.5, 170.1, 170.6, 172.1; IR (ATR) ν 3333, 1740, 1686 cm^{-1}.

*4.2.15. (2S)-2-({[(2S)-1-(tert-Butoxycarbonyl)pyrrolidin-2-yl]carbonyl}amino)-3,3-dimethylbutanoic acid (**14**).* Yellow oil, yield 91%; $[\alpha]_D^{20}$ −60.0 (*c* 0.5, $CHCl_3$). Found: C, 58.59; H, 8.65; N, 8.50. $C_{16}H_{28}N_2O_5$ requires C, 58.52; H, 8.59; N, 8.53%; ^1H NMR (500 MHz, $CDCl_3$) δ 1.00 (s, 9H), 1.47 (s, 9H), 1.90 (br s, 2H), 2.16–2.20 (m, 2H), 2.35–2.38 (m, 2H), 3.33–3.50 (m, 1H), 4.28–4.45 (m, 1H), 6.68 and 7.65 (br s, 1H, NH rotamers); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.6, 25.5, 27.3, 30.0, 33.3, 46.0, 58.6, 62.6, 79.6, 170.8, 171.5, 173.5; IR (ATR) ν 3322, 1724, 1662 cm^{-1}.

*4.2.16. (S)-tert-Butyl 2-((S)-1-((S)-1-methoxy-3,3-dimethyl-1-oxobutan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamoyl)pyrrolidine-1-carboxylate (**15a**).* White solid, yield 63%, mp 88–89 °C; $[\alpha]_D^{20}$ −52.9 (*c* 1.0, $CHCl_3$). Found: C, 60.68; H, 8.98; N, 9.26. $C_{23}H_{41}N_3O_6$ requires C, 60.64; H, 9.07; N, 9.22%; ^1H NMR (500 MHz, $CDCl_3$) δ 0.86 (s, 18H), 1.46 (s, 9H), 1.90 (br s, 2H), 2.15–2.18 (m, 1H), 2.28–2.35 (m, 1H), 3.33–3.49 (m, 2H), 3.71 (s, 3H), 4.14–4.17 (m, 1H), 4.26–4.35 (m, 1H), 4.40 (d, 1H, *J*=8.5 Hz), 6.22 and 6.36 (br s, 1H, NH, rotamers), 6.80 and 7.59 (br s, 1H, NH rotamers); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.1, 26.7, 27.0, 27.9, 30.2, 32.4, 33.0, 46.4, 51.6, 59.9, 60.2, 66.7, 80.5, 155.8, 170.1, 171.7, 172.5; IR (ATR) ν 3349, 3297, 1742, 1701, 1643 cm^{-1}.

*4.2.17. (S)-tert-Butyl 2-((S)-1-((S)-1-hydroxy-3-phenylpropan-2-ylcarbamoyl)-2,2-dimethylpropylcarbamoyl)pyrrolidine-1-carboxylate (**15b**).* White solid, yield 65%, mp 178–179 °C; $[\alpha]_D^{20}$ −81.5 (*c* 1.0, $CHCl_3$). Found: C, 65.11; H, 8.57; N, 9.04. $C_{25}H_{39}N_3O_5$ requires C, 65.05; H, 8.52; N, 9.10%; ^1H NMR (500 MHz, $CDCl_3$) δ 0.92 (s, 9H), 1.50 (s, 9H), 1.89–1.93 (m, 2H), 2.10–2.18 (m, 2H), 2.81–2.91 (m, 2H), 3.39–3.54 (m, 3H), 3.61–3.70 (m, 1H), 3.98–4.14 (m, 1H), 4.25 (br s, 2H), 6.65 (br d, 1H, *J*=8.0 Hz), 6.89–6.96 (m, 1H), 7.18–7.26 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.7, 27.1, 28.3, 31.9, 32.7, 37.1, 47.3, 52.9, 60.8, 62.6, 63.7, 81.4, 126.3, 128.4, 129.2, 138.1, 155.9, 169.9, 172.3; IR (ATR) ν 3371, 3335, 1678, 1641 cm^{-1}.

*4.2.18. (S)-Methyl 2-((S)-3,3-dimethyl-2-((S)-pyrrolidine-2-carboxamido)butanamido)-3,3-dimethylbutanoate (**16a**).* Colorless oil, yield 83%; $[\alpha]_D^{20}$ −42.9 (*c* 2.3, CH_2Cl_2). Found: C, 60.87; H, 9.31; N, 11.83. $C_{18}H_{33}N_3O_4$ requires C, 60.82; H, 9.36; N, 11.82%; ^1H NMR (500 MHz, $CDCl_3$) δ 0.95 (s, 9H), 0.99 (s, 9H), 1.25 (br s, 1H), 1.70–1.77 (m, 2H), 1.90–1.96 (m, 1H), 2.13–2.22 (m, 1H), 2.96–3.01 (m, 1H), 3.04–3.09 (m, 1H), 3.72 (s, 3H), 3.82–3.85 (m, 1H), 4.31–4.33 (d, 1H, *J*=9.0 Hz), 4.35–4.37 (d, 1H, *J*=8.5 Hz), 6.67 (br d, 1H, *J*=8.5 Hz), 8.33 (br d, 1H, *J*=8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.1, 26.5, 26.6, 30.9, 34.3, 34.6, 47.2, 51.7, 60.0, 60.3, 60.4, 170.5, 171.7, 174.5; $ESI^{(-)}$-MS: *m*/*z*=356.2 (M+1); IR (ATR) ν 3312, 1741, 1645 cm^{-1}.

*4.2.19. (2S)-N-((S)-1-((S)-1-Hydroxy-3-phenylpropan-2-ylcarbamoyl)-2,2-dimethyl-propyl)pyrrolidine-2-carboxamide (**16b**).* White solid, yield 78%, mp 174–176 °C; $[\alpha]_D^{20}$ −49.2 (*c* 0.65, MeOH). Found: C, 66.41; H, 8.68; N, 11.67. $C_{20}H_{31}N_3O_3$ requires C, 66.45; H, 8.64; N, 11.62%; ^1H NMR (500 MHz, CD_3OD) δ 0.89 (s, 9H), 1.62–1.69 (m, 1H), 1.80–1.96 (m, 2H), 2.18–2.26 (m, 1H), 2.56–2.60 (m, 1H), 2.81–2.85 (m, 1H), 3.19–3.22 (m, 1H), 3.27–3.32 (m, 1H), 3.42 (d, 2H, *J*=5.5 Hz), 4.06–4.09 (m, 1H), 4.13 (s, 1H), 4.18–4.21 (m, 1H), 7.03–7.06 (m, 1H), 7.13 (br d, 4H, *J*=4.5 Hz), 7.92 (br d, 1H, *J*=9.0 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 25.0, 27.1, 31.2, 35.1, 37.9, 47.5, 53.9, 60.8, 62.9, 64.4, 127.1, 129.2, 130.4, 139.9, 169.3, 171.6; $ESI^{(-)}$-MS: *m*/*z*=362.2 (M+1); IR (ATR) ν 3416, 3285, 1669, 1644 cm^{-1}.

4.2.20. General procedure for aldol reaction. The catalyst **8a** (0.1 mmol) and benzoic acid (0.1 mmol) were dissolved in CH_2Cl_2, and the solution was stirred at −10 °C for 30 min. Then, aldehyde (1.0 mmol) and ketone (10.0 mmol) were added and the reaction mixture was stirred at −10 °C for 72 h. After the evaporation of solvent, the crude products were purified by column chromatography using EtOAc/hexane. The enantioselectivity was determined by chiral HPLC with a Chiralpack AD or AD-H column (UV detection set at 254 nm, *i*-PrOH/hexane as eluent).

Acknowledgements

We thank Yildiz Technical University Scientific Research Foundation (2011-01-02-KAP-02) for financial support.

References and notes

1. Bisai, V.; Bisai, A.; Singh, V. K. *Tetrahedron* **2012**, *68*, 4541.
2. List, B.; Lemer, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395.
3. Heravi, M. M.; Asadi, S. *Tetrahedron: Asymmetry* **2012**, *23*, 1431.
4. Vishnumaya, M. R.; Singh, V. K. *J. Org. Chem.* **2009**, *74*, 4289.
5. Ma, X.; Da, C. S.; Yi, L.; Jia, Y. N.; Guo, Q. P.; Che, L. P.; Wu, F. C.; Wang, J. R.; Li, W. P. *Tetrahedron: Asymmetry* **2009**, *20*, 1419.
6. Bellis, E.; Kokotos, G. *Tetrahedron* **2005**, *61*, 8669.
7. Guillena, G.; Najera, C.; Ramon, D. J. *Tetrahedron: Asymmetry* **2007**, *18*, 2249.
8. Seayed, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719.
9. Pellisier, H. *Tetrahedron* **2007**, *63*, 9267.
10. Bertelsen, S.; Jorgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178.
11. Aleman, J.; Cabrera, S. *Chem. Soc. Rev.* **2013**, *42*, 774.
12. Wang, Q. W.; Peng, L.; Fu, J. Y.; Huang, Q. C.; Wang, L. X.; Xu, X. Y. *ARKIVOC* **2010**, *ii*, 340.
13. Fu, J. Y.; Huang, Q. C.; Wang, Q. W.; Wang, L. X.; Xu, X. Y. *Tetrahedron Lett.* **2010**, *51*, 4870.
14. Enders, D.; Chow, S. *Eur. J. Org. Chem.* **2006**, *71*, 4578.
15. Fuentes, J. A.; Lebl, T.; Slawin, A. M. Z.; Clarke, M. L. *Chem. Sci.* **2011**, *2*, 1997.
16. Kanemitsu, T.; Umehara, A.; Haneji, R.; Nagata, K.; Itoh, T. *Tetrahedron* **2012**, *68*, 3893.
17. Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790.
18. Revelou, P.; Kokotos, C. G.; Moutevelis-Minakakis, P. *Tetrahedron* **2012**, *68*, 8732.
19. Robak, M. T.; Herbage, M. A.; Elman, J. A. *Tetrahedron* **2011**, *67*, 4412.
20. Chen, F.; Huang, S.; Zhang, H.; Liu, F.; Peng, Y. *Tetrahedron* **2008**, *64*, 9585.
21. Xu, J. W.; Fu, X. K.; Hu, X. Y.; Wu, C. L. *Catal. Lett.* **2011**, *141*, 1156.
22. Tang, G.; Gun, U.; Altenbach, H. J. *Tetrahedron* **2012**, *68*, 10230.
23. Berkessel, A.; Koch, B.; Lex, J. *Adv. Synth. Catal.* **2004**, *346*, 1141.
24. Mino, T.; Omura, A.; Uda, Y.; Wakui, K.; Haga, Y.; Sakamoto, M.; Fujita, T. *Tetrahedron: Asymmetry* **2011**, *22*, 2024.
25. Thorat, P. B.; Goswami, S. V.; Khade, B. C.; Bhusare, S. R. *Tetrahedron Lett.* **2012**, *53*, 6083.
26. Zhang, T.; Zhang, Y.; Li, Z.; Song, Z.; Liu, H.; Tao, J. *Chin. J. Chem.* **2013**, *31*, 247.
27. Subba Reddy, B. V.; Bhavani, K.; Raju, A.; Yadav, J. S. *Tetrahedron: Asymmetry* **2011**, *22*, 881.
28. Cavalli, A.; Lizzi, F.; Bongarzone, S.; Brun, R.; Krauth-Siegel, R. L.; Bolognesi, M. L. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3031.
29. Zhang, X.; Zhang, J.; Zhang, L.; Feng, J.; Xu, Y.; Yuan, Y.; Fang, H.; Xu, W. *Bioorg. Med. Chem.* **2011**, *19*, 6015.
30. Chen, K. X.; Njoroge, F. G.; Pichardo, J.; Prongay, A.; Butkiewicz, N.; Yao, N.; Madison, V.; Girijavallabhan, V. *J. Med. Chem.* **2006**, *49*, 567.
31. Hirth, B. H.; Qiao, S.; Cuff, L. M.; Cochran, B. M.; Pregel, M. J.; Gregory, J. S.; Sneddon, S. F.; Kane, J. L., Jr. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2087.
32. Wang, H.; Peng, L.; Zhao, M.; Liu, J.; Zhang, X.; Wang, Y.; Wu, J.; Li, L.; Peng, S. *Bioorg. Med. Chem.* **2011**, *19*, 871.
33. Cheng, S.; Zhang, X.; Wang, W.; Zhao, M.; Zheng, M.; Chang, H. W.; Wu, J.; Peng, S. *Eur. J. Med. Chem.* **2009**, *44*, 4904.
34. Suyama, T. L.; Gerwick, W. H. *Org. Lett.* **2006**, *8*, 4541.

35. Tang, Z.; Jiang, F.; Yu, L. T.; Cui, X.; Gong, L. Z.; Mi, A. Q.; Jiang, Y. Z.; Wu, Y. D. *J. Am. Chem. Soc.* **2003**, *125*, 5262.
36. Gauchot, V.; Schmitzer, A. R. *J. Org. Chem.* **2012**, *77*, 4917.
37. Zhao, Q.; Lam, Y. H.; Kheirabadi, M.; Xu, C.; Houk, K. N.; Schafmeister, C. E. *J. Org. Chem.* **2012**, *77*, 4784.
38. Lei, M.; Shi, M.; Li, G.; Chen, S.; Fang, W.; Ge, Z.; Cheng, T.; Li, R. *Tetrahedron* **2007**, *63*, 7892.
39. Toselli, N.; Fortrie, R.; Martin, D.; Buono, G. *Tetrahedron: Asymmetry* **2010**, *21*, 1238.
40. Charton, J.; Gassiot, A. C.; Melnyk, P.; Mizzi, S. G.; Sergheraert, C. *Tetrahedron Lett.* **2004**, *45*, 7081.
41. Thomas, C. A.; Erach, R. T.; Bann, J. G. *Chem. Commun.* **2009**, 3366.
42. Budesinsky, M.; Ragnarsson, U.; Lankiewicz, L.; Grehn, L.; Slaninova, J.; Havacek, J. *Amino Acids* **2005**, *29*, 151.