Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters 47 (2006) 5717–5721
Tetrahedron Letters

Synthesis of some new tertiary amines and their application as co-catalysts in combination with L-proline in enantioselective Baylis–Hillman reaction between *o*-nitrobenzaldehyde and methyl vinyl ketone

Hongying Tang, Guofeng Zhao,* Zhenghong Zhou,* Qilin Zhou and Chuchi Tang

State Key Laboratory of Elemento-Organic Chemistry, Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, PR China

Received 20 March 2006; revised 1 June 2006; accepted 2 June 2006
Available online 23 June 2006

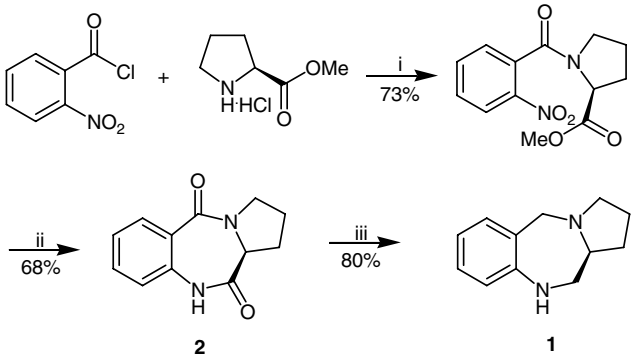
Abstract—A chiral benzodiazepine derivative **1** was synthesized starting from *o*-nitrobenzoyl chloride and methyl L-prolinate hydrochloride. Diastereomeric (1*R*,2*R*,1′*S*)-(+)-2-[*N*-methyl-*N*-(α-phenylethyl)amino]cyclohexanol **3a** and (1*S*,2*S*,1′*S*)-(+)-2-[*N*-methyl-*N*-(α-phenylethyl)amino]cyclohexanol **3b** were synthesized starting from (*S*)-α-phenylethylamine and cyclohexene oxide via ring-opening, diastereomer separation and N-methylation. (*S*,*S*)-octahydrodipyrrolo[1,2-*a*:1′,2′-*d*]pyrazin **5** was synthesized from methyl L-prolinate. Chiral tertiary amines **1**, **3a**, **3b** and **5** almost cannot catalyze the Baylis–Hillman reaction between *o*-nitrobenzaldehyde and methyl vinyl ketone (MVK). However, they functioned as efficient catalysts for this reaction in the presence of L-proline. The corresponding adducts were obtained in good yields with enantioselectivity of 83% ee, 81% ee, 51% ee and 66% ee, respectively.

Recently, chiral tertiary amines catalyzed asymmetric Baylis–Hillman (B–H) reaction has attracted much attention, and significant progress has been witnessed in this area.[1] All the tertiary amines employed as the catalysts in this reaction can be classified into the following three categories: (1) Chiral tertiary amine without free hydroxyl group which functions as a nucleophile to promote the Michael addition on to the activated alkenes.[2] (2) The second class represents chiral tertiary amine containing a free hydroxyl group. The existence of suitably positioned hydroxyl group can stabilize the enolate intermediate via a hydrogen-bonding interaction involving the hydroxyl group and the enolate formed in the reaction.[3] (3) The third type refers to chiral tertiary amine in combination with a Lewis acid or Brønsted acid which act as co-catalyst in the B–H reaction.[4] Only a few examples of tertiary amine without free hydroxyl groups have been documented because of their poor enantioselectivities. The best result (75% ee) in the coupling of methyl vinyl ketone (MVK) with aromatic aldehyde was obtained by Hayashi et al.[2d] The second type of tertiary amine catalysts seems more important and efficient. Among them, the alkaloids quinine or quinidine and their derivatives demonstrated good catalytic activity. Hatakeyama and co-workers, employing a quinidine derivative as the catalyst, attained an enantioselectivity of up to 91% ee. However, the activated alkene was limited to 1,1,1,3,3,3-hexafluoro-2-propyl acrylate.[3f–i] Shi and Jiang re-investigated the same catalyst. The enantioselectivities of 92% ee and 49% ee were obtained when α-naphthyl acrylate and MVK were used as the substrate, respectively.[3j] Krishna et al. reported L-prolinol catalyzed B–H reaction of MVK with arylaldehydes in which up to 78% ee was obtained.[3k] Recently, some examples of the third type of catalysts were reported. Barret et al. reported chiral pyrrolizidine catalyzed reaction of ethyl vinyl ketone and aromatic aldehydes. The best enantioselectivity of 72% ee was observed in the presence of $NaBF_4$.[4a] Achiral weak base imidazole and L-proline co-catalyzed B–H reaction between MVK and arylaldehydes was examined by Shi et al. Although an obvious rate acceleration of the reaction was observed, the enantioselectivities of the reaction were quite low (5–10% ee).[4b] Shi documented Hatakeyama catalyst, in combination with L- or D-proline, LiOTf, $LiClO_4$, catalyzed reaction

* Corresponding authors. Fax: +86 22 2350 8939/3438 (Z.Z.); e-mail: z.h.zhou@nankai.edu.cn

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.06.023

between MVK and aldehyde. No obvious improvements in enantioselectivity were achieved compared with the reaction without the additive.[3j] Miller and co-workers developed an efficient co-catalytic system of L-proline and peptides for the asymmetric B–H reaction of MVK and aromatic aldehydes. The corresponding adducts were formed with up to 81% ee. This was the best result for MVK-based B–H reaction prior to this report.[4c] The combination of DABCO (1,4-diaza-bicyclo[2.2.2]octane) and a chiral Lewis acid formed upon the treatment of D-camphor-derived diimino ligand and $La(OTf)_3$ provided high enantioselectivity (up to 95% ee) in acrylate-based B–H reaction.[4d] Most recently, Miller and co-workers realized catalytic asymmetric intramolecular B–H reaction in which ee of up to 84% was achieved.[4e] Although only a few examples were documented for the third type of catalysts, which is supposed to mediate the reaction via dual activation of the electrophile and the nucleophile,[5] it is attracting more and more attention from organic chemists because of its efficacy on rate acceleration and enantioselectivity improvement in asymmetric B–H reactions. Herein, we wish to report the synthesis of some new chiral tertiary amines and their application as co-catalysts in combination with L-proline in enantioselective B–H reaction between *o*-nitrobenzaldehyde and methyl vinyl ketone.



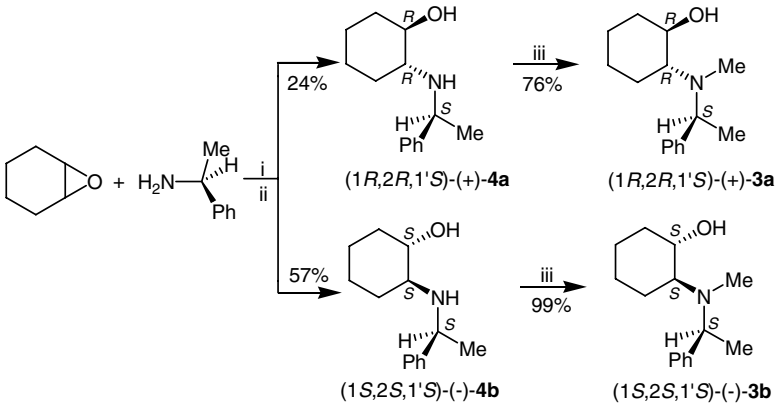
Scheme 1. Reagents and conditions: (i) Et_3N/CH_2Cl_2, 0 °C; (ii) Fe/AcOH, 110 °C; (iii) $LiAlH_4$/THF, −10 °C–rt, N_2.

Chiral tricyclic benzodiazepine **1** was synthesized starting from *o*-nitrobenzoic acid and methyl L-prolinate hydrochloride (Scheme 1). A lot of procedures have been reported for the synthesis of **2**, in which the common starting material is 2-azidobenzoic[6] acid or anthranilic acid (2-aminobenzoic acid),[7] respectively. The use of *o*-nitrobenzoic acid as the starting material shortens the access to **2**. Most importantly, **2** was obtained with good chemical yield in the key reduction ring-closing step utilizing the cheap and readily available iron filings as the reductant. Further reduction of **2** provided **1**.[8,9] This convenient and practical method may be useful for the synthesis of chiral benzodiazepine pharmaceuticals.

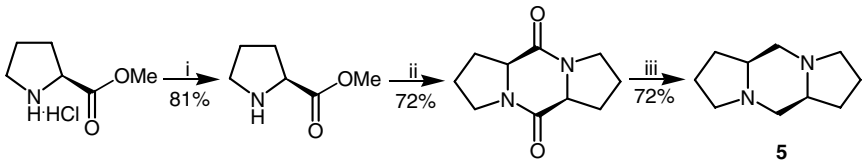
Diastereomeric (1*R*,2*R*,1′*S*)-(+)-2-[*N*-methyl-*N*-(α-phenylethyl)amino]cyclohexanol **3a** and (1*S*,2*S*,1′*S*)-(+)-2-[*N*-methyl-*N*-(α-phenylethyl)amino]cyclohexanol **3b** were synthesized according to the synthetic route outlined in Scheme 2. Overman and Sugai[10] first examined the ring-opening of cyclohexene oxide with (*R*)- or (*S*)-α-phenylethylamine in the presence of $AlMe_3$. A pair of diastereomer (1:1 molar ratio) was obtained after flash chromatography separation. Bianchini and co-workers[11] carried out this reaction in an autoclave at high temperature (160 °C). The separation of diastereomeric amines **4** was accomplished by fractional crystallization of the corresponding hydrochloride. According to Juaristic's and co-workers procedure,[12] the ring-opening of cyclohexene oxide took place smoothly in the presence of anhydrous lithium perchlorate. The corresponding diastereomeric 2-aminocyclohexanols **4a** (major, 57%) and **4b** (minor, 24%) were separated through column chromatography on silica gel. Further N-methylation of **4a** and **4b** with formaldehyde and formic acid afforded **3a** and **3b**, respectively.[13]

Following Breitmaier and Zadel's procedure,[14,15] dimerization of methyl L-prolinate and then reduction of the corresponding cyclic dipeptide gave (*S*,*S*)-(+)-octahydrodipyrrolo[1,2-*a*:1′,2′-*d*]pyrazin **5** (Scheme 3).

The catalytic activity of the prepared tertiary amines **1**, **3** and **5** was preliminarily examined using the reaction of *o*-nitrobenzaldehyde and MVK as a model.[16] Chiral

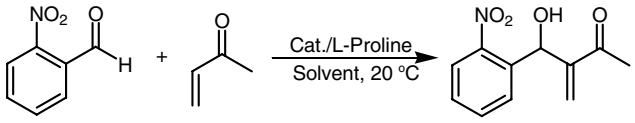


Scheme 2. Reagents and conditions: (i) $LiClO_4$/MeCN, reflux, 18 h; (ii) Separation of diastereomer via column chromatography; (iii) HCO_2H/HCHO, reflux, 4 h.



Scheme 3. Reagents and conditions: (i) K_2CO_3, 0 °C; (ii) 105 °C; (iii) $LiAlH_4$/THF, −10 °C–rt, N_2.

Table 1. Chiral amine/L-proline co-catalyzed B–H reaction between MVK and *o*-nitrobenzaldehyde



Entry	Catalyst (mol %)	L-Proline (mol %)	Solvent	Time (day)	Yield[a] (%)	ee[b] (%)	Configuration[c]
1	**1**(5)	10	THF	5	80	63	*S*
2	**1**(5)	10	MeCN	3	53	75	*S*
3	**1**(5)	10	DMF	3	34	52	*S*
4	**1**(5)	10	$CHCl_3$/THF (v/v, 1:4)	5	82	58	*R*
5	**1**(5)	10	$CHCl_3$/THF (v/v, 4:1)	5	68	83	*S*
6	**1**(30)	60	$CHCl_3$/THF (v/v, 4:1)	4	63	76	*S*
7	**1**(3)	6	$CHCl_3$/THF (v/v, 4:1)	5	71	45	*S*
8	**1**(5)	2.5	$CHCl_3$/THF (v/v, 4:1)	6	45	53	*S*
9	**3a**(30)	30	$CHCl_3$/THF (v/v, 4:1)	6	66	81	*S*
10	**3a**(40)	40	$CHCl_3$/THF (v/v, 4:1)	4	84	74	*S*
11	**3a**(30)	30	$CHCl_3$/THF (v/v, 4:1)	7	35	54	*S*
12	**3b**(30)	30	$CHCl_3$/THF (v/v, 4:1)	7	61	51	*S*
13	**5**(5)	5	$CHCl_3$/THF (v/v, 4:1)	5	79	66	*S*
14	**5**(5)	10	$CHCl_3$/THF (v/v, 4:1)	5.5	61	47	*S*

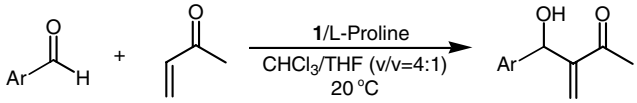
[a] Isolated yield.
[b] Determined by HPLC analysis on a chiralcel AD-H column, hexane–2-propanol = 90:10, flow rate 0.7 mL/min, t_R = 32.8 and 36.6 min.
[c] Determined by comparison of the specific rotation value with the literature value.[2d]

tertiary amine **1** itself exhibited poor catalytic activity for the reaction when used alone. Almost racemic product was obtained with only 10% yield after stirring for 9 days at room temperature. Catalysts **3a**, **3b** and **5** can not promote the reaction at all by themselves. No reaction was detected even after stirring for 2 weeks at 20 °C. However, dramatic improvements on the reaction rate as well as enantioselectivitiy were observed using chiral amine **1**, **3a**, **3b** and **5** in combination with L-proline as the co-catalytic system. The corresponding adduct was obtained not only in good yield but also with the best enantioselectivity for MVK-base B–H reaction. The results are listed in Table 1.

The influence of solvent, catalyst loading and molar ratio of catalyst to L-proline on the reaction was systematically investigated. As shown in Table 1, the reaction conducted best in $CHCl_3$/THF (v/v, 4:1) at 20 °C. The optimal catalyst loading and molar ratio of catalyst to L-proline was varied depending on the catalyst employed. The catalytic system in combination of amine **1** (5 mol %) with L-proline (10 mol %) provided ee value of 83% (entry 5). The cooperative catalyst consists of 30 mol % of chiral amine **3a** and 30 mol % of L-proline affording enantioselectivity of 81% ee (entry 9). Under the same condition, diastereomeric **3b** provided much lower selectivity (51% ee, entry 12). This result implies that **3b** and L-proline is a mismatched pair of co-catalyst. The combination of **5** (5 mol %) and L-proline (5 mol %) produced the product only with 66% ee (entry 13).

Based on these results, the scope of the aldehydes was preliminarily investigated. A set of aromatic aldehydes were employed to the coupling of MVK under the optimized reaction conditions using **1** and L-proline as the co-catalyst. The results are listed in Table 2. This co-catalyst system was also effective to the tested aldehydes. The corresponding adducts were obtained in good yields with moderate enantioselectivities.

Table 2. **1**/L-proline co-catalyzed B–H reaction between MVK and aromatic aldehydes



Entry	Ar	Time (days)	Yield[a] (%)	ee[b] (%)
1	1-Nitro-2-naphthyl	5	70	46
2	3-MeO-2-$NO_2C_6H_3$	10	66	52
3	3-$NO_2C_6H_3$	4	76	59
4	4-Cl-2-$NO_2C_6H_3$	5	54	32
5	2-F-4-ClC_6H_3	5	66	31

[a] Isolated yield.
[b] Determined by HPLC analysis on a chiralcel AD-H column.

In conclusion, an efficient new route for the preparation of chiral benzodiazepine **1** has been developed starting from readily available raw materials. Diastereomeric 2-aminocyclohexanols **3a** and **3b** were synthesized starting from (*S*)-α-phenylethylamine and cyclohexene oxide. (*S*,*S*)-Octahydrodipyrrolo-[1,2-*a*:1′,2′-*d*]pyrazin **5** was synthesized from methyl L-prolinate. The preliminary screening of the catalysts **1**, **3a**, **3b** and **5** revealed that these compounds exhibited almost no catalytic activity for the reaction of *o*-nitrobenzaldehyde and MVK without the coexistence of L-proline. However, dramatic improvements on the reaction rate as well as enantioselectivity were observed with the introduction of L-proline to form a co-catalytic system. The combination of **1** and L-proline gave the product with ee value of 83%. The L-proline-**3a** combination provided the product with an enantioselectivity of 81% ee. At present, these represent the best result for the MVK-based B–H reaction. The L-Pro-**3b** and L-Pro-**5** combination also afforded the product with selectivity of 51% ee and 66% ee, respectively. These results revealed that the co-catalytic function of the tertiary amine and L-proline played an important role in the reaction. Further extending of this catalytic system to other aldehydes or activated alkenes and the exact mechanistic explanation for this reaction are ongoing in our laboratory.

Acknowledgements

We are grateful to the National Natural Science Foundation of China (No. 20472033) and the Ph.D. Programs and the Key Science and Technology Project of Ministry of Education of China for generous financial support for our programs.

References and notes

1. (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811; (b) Cai, J. X.; Zhou, Z. H.; Tang, C. C. *Chem. Res. (Chinese)* **2001**, *12*, 54; (c) Langer, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3049.
2. (a) Oishi, T.; Hirama, M. *Tetrahedron Lett.* **1992**, *33*, 639; (b) Oishi, T.; Oguri, H.; Hirama, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1241; (c) Barrett, A. G. M.; Dozzo, P.; White, A. J. P.; Williams, D. J. *Tetrahedron* **2002**, *58*, 7303; (d) Hayashi, Y.; Tamura, T.; Shoji, M. *Adv. Synth. Catal.* **2004**, *346*, 1106.
3. (a) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653; (b) Bailey, M.; Marko, I. E.; Olis, W. D.; Rassmussen, P. R. *Tetrahedron Lett.* **1990**, *31*, 4509; (c) Gilbert, A.; Heritage, T. W.; Isaacs, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 969; (d) Marko, I. E.; Giles, P. R.; Hindley, N. J. *Tetrahedron* **1997**, *53*, 1015; (e) Brzezinski, L. J.; Rafel, S.; Leaky, J. W. *Tetrahedron* **1997**, *53*, 16423; (f) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219; (g) Iwabuchi, Y.; Sugihara, T.; Esumi, T.; Hatakeyama, S. *Tetrahedron Lett.* **2001**, *42*, 7867; (h) Iwabuchi, Y.; Furukawa, M.; Esumi, T.; Hatakeyama, S. *Chem. Commun.* **2001**, 2030; (i) Iwabuchi, Y.; Hatakeyama, S. *Synth. Org. Chem. Jpn.* **2002**, *60*, 1; (j) Shi, M.; Jiang, J. K. *Tetrahedron: Asymmetry* **2002**, *13*, 1941; (k) Krishna, P. R.; Kannan, V.; Reddy, P. V. N. *Adv. Synth. Catal.* **2004**, *346*, 603.
4. (a) Barrett, A. G. M.; Cook, A. S.; Kamimura, A. *Chem. Commun.* **1998**, 2533; (b) Shi, M.; Jiang, J. K.; Li, C. Q. *Tetrahedron Lett.* **2002**, *43*, 127; (c) Imbriglio, J. E.; Vasbinder, M. M.; Miller, S. J. *Org. Lett.* **2003**, *5*, 3741; (d) Yang, K. S.; Lee, W. D.; Pan, J. F.; Chen, K. M. J. *Org. Chem.* **2003**, *68*, 915; (e) Aroyan, C. E.; Vasbinder, M. M.; Miller, S. J. *Org. Lett.* **2005**, *7*, 3849.
5. Ma, J. A.; Cahard, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4566.
6. (a) Molina, P.; Diaz, I.; Tarraga, A. *Tetrahedron* **1995**, *51*, 5617; (b) Kamal, A.; Reddy, B. S. P.; Reddy, B. S. N. *Tetrahedron Lett.* **1996**, *37*, 6803; (c) Ohmeyer, M. H. J. WO 9701560; *Chem. Abstr.* **1997**, *126*, 171624; (d) Kamal, A.; Damayanthi, Y.; Reddy, B. S. N.; Lakminarayana, B.; Reddy, B. S. P. *Chem. Commun.* **1997**, 1015; (e) Kamal, A.; Laxman, E.; Laxman, N.; Venugopal, R. N. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2311; (f) Kamal, A.; Laxman, E.; Arifuddin, M. *Tetrahedron Lett.* **2000**, *41*, 7743; (g) Kamal, A.; Reddy, K. S.; Prasad, B. R.; Babu, A. H.; Ramana, A. V. *Tetrahedron Lett.* **2004**, *45*, 6517; (h) Kamal, A.; Ramana, A. V.; Reddy, K. S.; Ramana, K. V.; Haribabu, A.; Prasad, B. R. *Tetrahedron Lett.* **2004**, *45*, 8187; (i) Kamal, A.; Reddy, K. L.; Devaiah, V.; Shankaraiah, N. *Synlett.* **2004**, 2533.
7. (a) Schultz, A. G.; McCloskey, P. J.; Sundararaman, P.; Springer, J. P. *Tetrahedron Lett.* **1985**, *26*, 1619; (b) Nagasaka, T.; Koseki, Y.; Hamaguchi, F. *Tetrahedron Lett.* **1989**, *30*, 1871; (c) Feigel, M.; Lugert, G.; Manero, J.; Bremer, M. *Zeit. Natur., B Chem. Sci.* **1990**, *45*, 258; (d) Kamal, A. *J. Org. Chem.* **1991**, *56*, 2237; (e) Akssira, M.; Boumzebra, M.; Kasmi, H.; Dahdouh, A.; Roumestant, M. L.; Viallefont, P. *Synth. Commun.* **1993**, *23*, 2265.
8. Vedejs, E.; Lee, N. K. *J. Am. Chem. Soc.* **1995**, *117*, 891.
9. Experimental data of compound **1**: Mp 102–104 °C, $[\alpha]_D^{20}$ −177.7 (*c* 1.0, $CHCl_3$). Anal. Calcd For $C_{12}H_{16}N_2$: C, 76.60; H, 8.51; N, 14.89. Found: C, 76.57; H, 8.50; N, 14.71. ^1H NMR (δ, $CHCl_3$, 300 MHz): 1.41–1.54 (m, 1H), 1.75–1.99 (m, 3H), 2.44–2.63 (m, 2H), 2.75 (dd, 1H, $J = 12.6$, 9.6 Hz, one proton of NCH_2), 3.16 (dt, 1H, $J = 8.4$, 2.7 Hz, CH), 3.33 (dd, 1H, $J = 12.6$, 1.5 Hz, one proton of NCH_2), 3.52 (d, 1H, $J = 13.5$ Hz, one proton of $PhCH_2$), 3.83 (d, 1H, $J = 13.5$ Hz, one proton of $PhCH_2$), 3.86 (br, 1H, NH), 6.72 (dd, 1Harom, $J = 7.8$ Hz, 0.6 Hz), 6.83 (dt, 1Harom, $J = 7.5$ Hz, 1.2 Hz), 7.04–7.13 (m, 2Harom).
10. Overman, L. E.; Sugai, S. *J. Org. Chem.* **1985**, *50*, 4154.
11. Barbaro, P.; Bianchini, C.; Sernau, V. *Tetrahedron: Asymmetry* **1996**, *7*, 843.
12. Anaya de Parrodi, C.; Moreno, G. E.; Quintero, L.; Juaristic, E. *Tetrahedron: Asymmetry* **1998**, *9*, 2093.
13. Experimental data of compound **3a** and **3b**: For **3a**, mp 72–74 °C, $[\alpha]_D^{20}$ +45.2 (*c* 1.0, MeOH). Anal. Calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00. Found: C, 77.45; H, 9.84; N, 6.07. ^1H NMR (δ, $CHCl_3$, 300 MHz): 0.98–1.16 (m, 4H), 1.40 (d, 3H, $J = 6.9$ Hz), 1.57–1.68 (m, 3H), 2.00–2.05 (m, 1H), 2.25 (s, 3H), 2.20–2.29 (m, 1H), 3.34 (dt, 1H, $J = 5.2$ and 9.9 Hz), 3.72 (q, 1H, $J = 6.9$ Hz), 3.89 (br, 1H), 7.21–7.34 (m, 5Harom); For **3b**, oil, $[\alpha]_D^{20}$ −68.2 (*c* 1.0, MeOH). Anal. Calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00. Found: C, 77.20; H, 9.90; N, 6.16. ^1H NMR (δ, $CHCl_3$, 300 MHz): 1.17–1.27 (m, 4H), 1.36 (d, 3H, $J = 6.9$ Hz), 1.57–1.72 (m, 3H), 2.05 (s, 3H), 2.13–2.16 (m, 1H), 2.62–2.70 (m, 1H), 3.41 (dt, 1H, $J = 5.2$ and 9.9 Hz), 3.69 (q, 1H, $J = 6.9$ Hz), 3.95 (br, 1H), 7.24–7.34 (m, 5Harom).
14. Zadel, G.; Breitmaier, E. *Chem. Ber.* **1994**, *127*, 1323.
15. Experimental data of compound **5**: mp 48–52 °C, $[\alpha]_D^{20}$ +7.2 (*c* 2.3, $CHCl_3$). ^1H NMR (δ, $CHCl_3$, 300 MHz):

1.56–1.84 (m, 8H), 2.37–2.48 (m, 4H), 2.55–2.57 (m, 4H), 2.76–2.83 (m, 2Harom).

16. General procedure for the chiral amine/L-proline co-catalyzed reaction: To a solution of aldehyde (2 mmol), chiral amine and L-proline in 2.5 mL of solvent was added MVK (6 mmol). Then the resulting mixture was stirred at 20 °C for completion of the reaction (monitored by TLC). After removal of solvent, the residue was purified by column chromatography on silica gel (200–300 mesh, gradient eluted with petroleum ether/ethyl acetate) to afford the product.