Asymmetric α-Amination of Chiral Protected β-Hydroxyaldehydes Catalyzed by Proline

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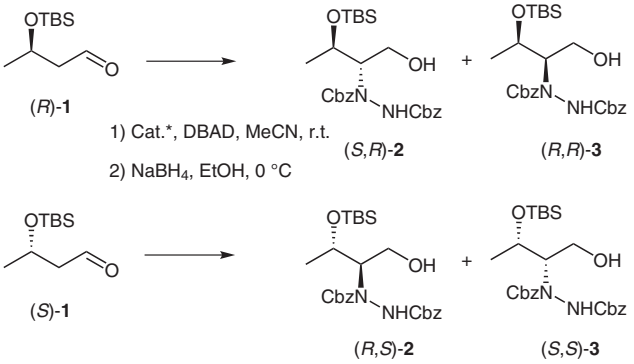
Abstract: Proline-catalyzed α-amination of a variety of chiral β-hydroxyaldehydes followed by reduction step afforded the corresponding chiral 2-hydrazino-1,3-diols in good yields, enantioselectivities and diastereoselectivities.

Key words: amination, organocatalysis, diastereoselectivity, β-hydroxyaldehyde, 2-hydrazino-1,3-diol, azodicarboxylate

α-Functionalization of carbonyl compounds catalyzed by chiral primary or secondary amines has emerged as a powerful method to create carbon–carbon or carbon–heteroatom bonds.[1,2] In this field, electrophilic α-amination[3] which was first reported by Jørgensen[4] and List[5] independently in 2002 is an efficient transformation to form C–N bond stereoselectively. Either aliphatic[4,5] or α-branched[6] aldehydes or ketones[7] undergo this reaction with azodicarboxylate and various organocatalysts such as cyclic amino acids derivatives.[8] α-Amino carbonyl derivatives are obtained in good yields and excellent enantioselectivities. As a result, this reaction has been employed in several natural product syntheses.[9] However α-amination of chiral β-functionalized aldehydes has not been investigated to date. Herein, we report the asymmetric α-amination of protected β-hydroxyaldehydes catalyzed by proline and its derivatives which provide diastereoselectively enantioenriched vicinal amino alcohol in good yields.

The amination reaction of the two antipodes of 3-*tert*-butyldimethylsilyloxybutanal[10] (**1**) with dibenzyl azodicarboxylate (DBAD) in the presence of proline-type catalysts was selected as a model. The *anti*- or *syn*-2-hydrazino-1,3-diols, **2** or **3**, respectively, were isolated after reduction of the aldehyde using $NaBH_4$ in ethanol (Scheme 1).



Scheme 1

Starting from enantiopure (*R*)-**1**, the electrophilic amination organocatalyzed by L-proline afforded the *anti*-(*S*,*R*)-**2** compound as the major diastereomer (Table 1).[11]

First, the reaction was run using 10 mol% catalytic loading and *anti*-(*S*,*R*)-**2** was isolated in 62% yield and a diastereomeric ratio of 90:10 (Table 1, entry 1). Increasing the catalyst loading to 20 mol% gave a better result and the expected *anti*-2-hydrazino-1,3-diol (*S*,*R*)-**2** was obtained in shorter reaction time with 88% yield and an excellent diastereomeric ratio of 94:6 (entry 2).[12]

The same reaction was performed using an achiral organocatalyst such as pyrrolidine (20 mol%); under these conditions, the diastereomeric excess did not exceed 8% (*anti*/*syn*, 54:46).

Then, D-proline was tested as chiral organocatalyst, and the *syn*-(*R*,*R*)-**3** compound was obtained as the major diastereomer in a diastereomeric ratio (*anti*/*syn*) of 8:92 (entry 3). This observation suggests a matched-mismatched effect.

When substrate (*S*)-**1** was used, similar results were observed. *syn*-2-Hydrazino-1,3-diol (*S*,*S*)-**3** or *anti*-2-hydrazino-1,3-diol (*R*,*S*)-**2** were obtained as the major diastereomers with L-proline or D-proline as catalyst, respectively (entries 4 and 5).

Finally, when the reaction was conducted at 0 °C, no improvement in terms of yield or selectivity was observed (entry 6).

Then, different catalysts were tested for this reaction such as the *tert*-butoxyprolines **I** and **II**[13] and the α,α-diarylprolinol silyl ether **III**[14] (Figure 1).

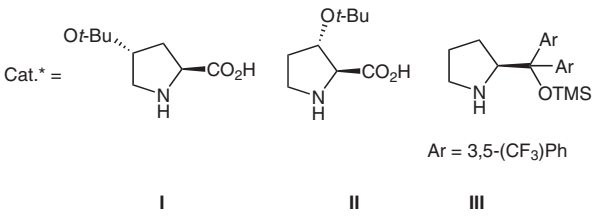


Figure 1

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Table 1 α-Amination of (*R*)- and (*S*)-3-*tert*-Butyldimethylsilyloxybutanal (*R*)-**1** and (*S*)-**1** Organocatalyzed by L- and D-Proline

Entry	Substrate	Catalyst	Time	Yield	*anti*/*syn*[a]	Major product
1	(*R*)-**1**	L-Pro (10 mol%)	3.5 h	62%	90:10	(*S*,*R*)-**2**
2	(*R*)-**1**	L-Pro (20 mol%)	2.5 h	88%	94:6	(*S*,*R*)-**2**
3	(*R*)-**1**	D-Pro (20 mol%)	2.5 h	69%	8:92	(*R*,*R*)-**3**
4	(*S*)-**1**	L-Pro (20 mol%)	2.5 h	72%	8:92	(*S*,*S*)-**3**
5	(*S*)-**1**	D-Pro (20 mol%)	2.5 h	84%	94:6	(*R*,*S*)-**2**
6	(*S*)-**1**	L-Pro (20 mol%)	8 h at 0 °C	53%	18:82	(*S*,*S*)-**3**

[a] Determined by ^{1}H NMR analysis of the crude product.

The use of catalyst **I** for the amination of (*R*)-**1** did not improve the diastereoselectivity (*anti*/*syn*, 94:6) but a lower yield of 66% was noticed (Table 2, entry 1). A moderate yield was also obtained with the catalyst **II** and the diastereoselectivity in favor of the aminated product (*S*,*R*)-**2** decreased (*anti*/*syn*, 78:28; entry 2). Finally, as expected the catalyst **III** induced the opposite configuration for the created aminated center giving the *syn* diastereomer (*R*,*R*)-**3** in a ratio of 9:91 and a yield of 75% (entry 5). This last experiment was run with a longer reaction time (i.e. 24 h).

The matched-mismatched effect was observed as precedently starting from (*S*)-**1**. The catalysts **I** and **II** favored the *syn* diastereomer (*S*,*S*)-**3** with the ratios of 11:89 and 33:67, respectively (entries 4 and 5). The *anti* diastereomer (*R*,*S*)-**2** was isolated after 24 hours with a very good yield of 93% and a diastereomeric ratio of 93:7 (entry 6). This methodology affords a straightforward access to the four possible stereomers of protected threoninol derivatives **2** and **3** in good yields up to 88% and high diastereoselectivities (*anti*/*syn*) of 94:6 and 8:92, respectively.[15] The *anti*/*syn* mixture could be easily separated by medium-pressure liquid chromatography to afford each diastereomer as an enantiopure compound. We examined this transformation with a variety of functionalized chiral β-hydroxyaldehydes.

The results are summarized in Table 3. A hindered aldehyde containing cyclic acetal (**4**) obtained from commercially available methyl (4*S*)-2,2-dimethyl-1,3-dioxolane-4-acetate after reduction of the ester group to aldehyde, was submitted to the α-amination reaction. The *anti*-α-hydrazino alcohol **5** was obtained with a moderate yield of 65% and excellent diastereoselectivity (*anti*/*syn*, 95:5; entry 1). In contrast, the formation of the compound **6** was observed without *syn* selectivity showing a great enhancement of the mismatched effect (entry 2). To compare the influence of protecting groups on the starting material, we synthesized the functionalized butanal **7** derived from the corresponding β-hydroxyester[16] after TBS protection of the secondary alcohol and reduction of the ester group. When the reaction was conducted with L-proline, the product **8** was obtained in 82% yield and a diastereomeric ratio (*anti*/*syn*) of 88:12 (entry 3). If D-proline was used, the *syn* diastereomer **9** was the major compound and isolated in 74% yield with a diastereomeric ratio (*anti*/*syn*) of 18:82 (entry 4). The enamine intermediate formed with the aldehyde **7** and D-proline might be less conformationally constrained compared to that obtained with the aldehyde **4** as shown by the lower mismatched effect. Finally, the functionalized pentanal **10** prepared from the corresponding β-hydroxyester[17] after TBS protection of the secondary alcohol and reduction of the ester group was tested. The use of D-proline gave product **11** in 61% yield and a *anti*/*syn* ratio of 85:15 and the use of L-proline furnished the *syn* diastereomer **12** with a comparable yield of 63% and a diastereomeric ratio (*anti*/*syn*) of 17:83.

In conclusion, the α-amination of chiral β-hydroxyaldehydes organocatalyzed by L- or D-proline followed by a reduction of the aldehyde functionality was proved to be an efficient access to the four possible stereomers of the corresponding 2-hydrazino-1,3-diols with an excellent control of the stereoselectivity. This transformation could be easily performed at room temperature using 20 mol% of catalyst loading.

Table 2 Catalyst Screening for the α-Amination of (*R*)- and (*S*)-3-*tert*-Butyldimethylsilyloxybutanal (*R*)-**1** and (*S*)-**1**

Entry	Substrate	Catalyst	Time	Yield	*anti*/*syn*[a]	Major product
1	(*R*)-**1**	**I** (20 mol%)	1.5 h	66%	94:16	(*S*,*R*)-**2**
2	(*R*)-**1**	**II** (20 mol%)	0.75 h	64%	72:28	(*S*,*R*)-**2**
3	(*R*)-**1**	**III** (20 mol%)	24 h	75%	9:91	(*R*,*R*)-**3**
4	(*S*)-**1**	**I** (20 mol%)	1.5 h	62%	11:89	(*S*,*S*)-**3**
5	(*S*)-**1**	**II** (20 mol%)	0.75 h	82%	33:67	(*S*,*S*)-**3**
6	(*S*)-**1**	**III** (20 mol%)	24 h	93%	93:7	(*R*,*S*)-**2**

[a] Determined by ^{1}H NMR analysis of the crude product.

Acknowledgment

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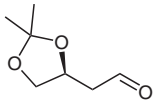
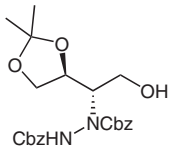
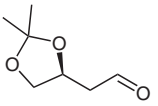
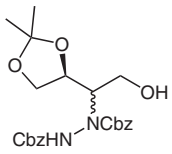
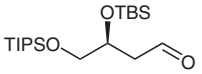
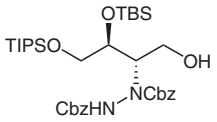
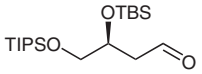
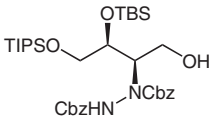
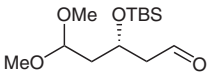
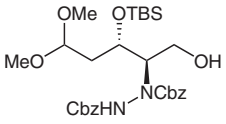
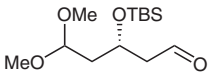
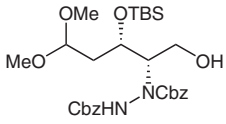
Table 3 α-Amination of Functionalized Chiral β-Hydroxyaldehydes

Entry	Substrate	Catalyst	Yield	*anti*/*syn*[a]	Major product
1	 **4**	L-Pro	65%	95:5	 **5**
2	 **4**	D-Pro	70%	50:50	 **6**
3	 **7**	L-Pro	82%	88:12	 **8**
4	 **7**	D-Pro	74%	18:82	 **9**
5	 **10**	D-Pro	61%	85:15	 **11**
6	 **10**	L-Pro	63%	17:83	 **12**

[a] Determined by ^{1}H NMR analysis of the crude product.

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(10) 3-*tert*-Butyldimethylsilyloxybutanal (**1**) was synthesized in two steps (TBS protection and DIBAL-H reduction of the ester moiety) from ethyl 3-hydroxybutyrate commercially available in both enantiomeric forms.

(11) To determine the relative configuration of *anti*-**2**, we synthesized this compound via diastereoselective electrophilic amination method from ethyl (*R*)-3-hydroxybutyrate using LDA, $ZnBr_2$ and DBAD. For this reaction, see: Genêt, J. P.; Jugé, S.; Mallart, S. *Tetrahedron Lett.* **1998**, *29*, 6765.

(12) **General Procedure for the Organocatalytic α-Amination**: Dibenzylazodicarboxylate (1 mmol) and D- or L-proline (0.2 mmol, 20 mol%) in MeCN (10 mL) were treated with an aldehyde (1.5 mmol) at r.t. The reaction mixture was stirred at this temperature until the yellow color of the azodicarboxylate had disappeared. The mixture was treated with EtOH (10 mL) and $NaBH_4$ (40 mg) and was stirred for 5 min at 0 °C. The reaction was worked up with aq NH_4Cl solution and EtOAc. The organic layers were dried ($MgSO_4$), filtered, and concentrated. Medium-pressure column chromatography on silica gel with EtOAc–pentane

mixture (1:4) gave the desired *anti*- or *syn*-2-hydrazino-1,3-diol as a single diastereomer.

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(15) **Characterization of Selected Compounds**:
Compound **2**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.01–0.05 (m, 6 H), 0.86 (s, 9 H), 1.08–1.16 (m, 3 H), 3.51–3.99 (m, 4 H), 4.15–4.33 (m, 1 H), 5.16–5.29 (m, 4 H), 6.54 (s, 1 H), 7.28–7.37 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.1, –4.3, 17.7, 21.1, 25.6, 59.1, 59.6, 66.3, 67.0, 67.4, 68.1, 68.3, 68.5, 127.5, 127.7, 128.0, 128.1, 128.3, 128.4, 128.5, 135.0, 135.4, 135.6, 156.0, 157.0, 158.2, 158.9. MS (ESI): *m*/*z* = 525.4 [M + Na^+]. IR: 3409, 3272, 2955, 2856, 1722, 1268, 1097, 833, 777, 696 cm^{-1}. Anal. Calcd for $C_{26}H_{38}N_2O_6Si$: C, 62.12; H, 7.62; N, 5.57. Found: C, 62.06; H, 7.55; N, 5.48. $[\alpha]_D^{25}$ –25 (*c* = 1, CH_2Cl_2) for (*S*,*R*)-**2**; $[\alpha]_D^{25}$ +24 (*c* = 1, CH_2Cl_2) for (*R*,*S*)-**2**.
Compound **3**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = (–0.01)–0.05 (m, 6 H), 0.81–0.82 (m, 9 H), 1.08–1.18 (m, 3 H), 3.48–4.04 (m, 4 H), 4.20–4.38 (m, 1 H), 5.14–5.30 (m, 4 H), 6.69–6.74 (m, 1 H), 7.32–7.37 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.3, –5.2, –4.3, –4.2, 17.6, 21.2, 21.3, 25.5, 25.6, 59.7, 59.8, 64.1, 65.8, 68.1, 68.2, 68.5, 68.7, 127.6, 128.0, 128.1, 128.2, 128.4, 128.5, 135.2, 135.5, 135.8, 156.3, 156.9, 157.6, 158.2. MS (ESI): *m*/*z* = 525.4 [M + Na^+]. IR: 3401, 3270, 2953, 2855, 1721, 1256, 1072, 836, 776, 696 cm^{-1}. Anal. Calcd for $C_{26}H_{38}N_2O_6Si$: C, 62.12; H, 7.62; N, 5.57. Found: C, 62.02; H, 7.35; N, 5.55. $[\alpha]_D^{25}$ –3 (*c* = 1, CH_2Cl_2) for (*R*,*R*)-**3**; $[\alpha]_D^{25}$ +3 (*c* = 1, CH_2Cl_2) for (*S*,*S*)-**3**.

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