Asymmetric α-Amination of Aldehydes and Ketones Catalyzed by *tert*-Butoxy-L-Proline

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Abstract: Asymmetric electrophilic α-amination of aldehydes and ketones is described using *trans*-3-*tert*-butoxy-L-proline and *trans*-4-*tert*-butoxy-L-proline as efficient catalysts. Good yields and high enantioselectivities are obtained working at 0°C or at room temperature with a catalyst loading of only 5 mol%.

Keywords: Electrophilic amination, organocatalysis, *tert*-butoxyproline, azodicarboxylate, α-hydrazinoalcohol.

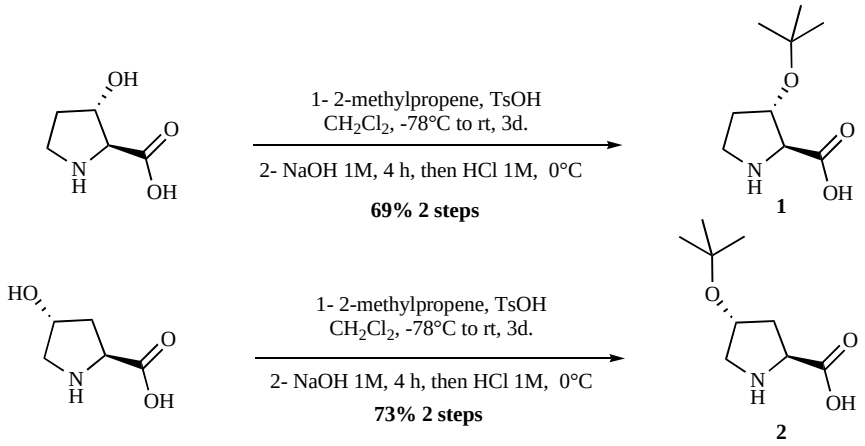
INTRODUCTION

The stereocontrol of C-N bond formation is of great interest in organic synthesis due to the large presence of amino group functionalities in biologically active molecules. Several stereoselective methods have been described in the literature involving nucleophilic or electrophilic nitrogen reagents [1]. The last few years have seen the great emergence of organocatalysis as new metal-free asymmetric reaction [2]. Various known reactions have been developed using this process [3] and notably α-functionalization of carbonyl compounds [4]. Jorgensen [5] and List [6] both reported the first examples of electrophilic amination of aldehydes using proline and dialkyl azodicarboxylate. We [7] and others [8] have shown that this reaction could be extended to functionalized aldehydes or ketones using different organocatalysts.

Proline is one of the most popular catalyst for this kind of transformation. However, its poor solubility in organic solvents remained a limitation in regard with the loading of catalyst required (10 to 50 mol%). One of the great tasks in organocatalysis is to conceive new highly reactive catalysts which afford high level of enantioselectivity. We report herein the use of 3- and 4-*tert*-butoxyproline as efficient catalysts for α-amination of carbonyl compounds.

RESULTS AND DISCUSSION

Organocatalysis, by using small and readily available molecules as catalysts, constitue a great application to the concept of green chemistry. In this context, development of new organocatalysts requires straightforward synthesis without the use of protecting groups and purification steps. Starting from natural 3- and 4-hydroxyproline, *trans*-3-*tert*-butoxy-L-proline **1** [9] and *trans*-4-*tert*-butoxy-L-proline **2** [10] were obtained in 2 steps respectively in 69 and 73% yield (Scheme **1**).



Scheme 1.

The reaction of 6,6-dimethoxyhexanal with dibenzyl azodicarboxylate was chosen as a model reaction to test the

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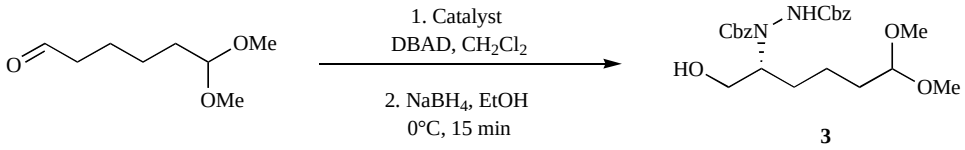


Scheme 2.

efficiency of catalysts **1** and **2** in the electrophilic amination reaction (Scheme **2**). The corresponding hydrazino aldehyde was reduced *in situ* using $NaBH_4$ in EtOH [11] and the enantiomeric excess of **3** was determined on the crude hydrazino alcohol [12]. The results are summarized in Table **1**.

In the presence of 10 mol% L-proline at 0°C, the α-aminated alcohol was obtained in 76% yield and 94% ee (entry 1). When the reactions were carried out in the presence of the catalysts **1** and **2**, higher reactivities were observed (entries 2 and 3) : the reaction time decreased dramatically and enantioselectivities were slightly elevated. This result prompted us to lower the loading of catalyst. When the reaction was conducted using 5 mol% of **1** at room temperature, the enantiomeric excess dropped to 71% and the expected product **3** was obtained in 67% yield (entry 4). At 0°C, the kinetic of the reaction was slower. 22 hours were necessary to perform the amination step but the chemical yield and the enantioselectivity were higher compared to those obtained at room temperature: 80% yield and 82% ee (entry 5).

The electrophilic amination of 6,6-dimethoxyhexanal performed at room temperature in presence of **2** 5 mol%, afforded **3** in 78% yield and 88% ee (entry 6). Lowering temperature to 0°C increased the efficiency of the catalyst providing **3** in 84% yield and 94% ee (entry 7). This result validated our attempt to find a highly reactive catalyst for the electrophilic amination reaction.

The antipode of **1**, *trans*-3-*tert*-butoxy-D-proline, was also tested as catalyst. We previously reported the synthesis of *trans*-3-hydroxy-D-proline by a classical way of enantioselective catalytic hydrogenation of functionalized β-ketoester and diastereoselective electrophilic amination of the resulting β-hydroxyester [13]. *Trans*-3-hydroxy-D-proline was protected in two steps as precedently to give the enantiomer of **1** [14]. α-Amination of 6,6-dimethoxyhexanal using this catalyst afforded the enantiomer of **3** with comparable yield and enantioselectivity.

Then, we studied electrophilic amination of different aliphatic aldehydes in presence of the catalysts **1** and **2** (Table **2**).

The reactions involving *trans*-3-*tert*-butoxy-L-proline **1** afforded the expected aminated products in good yields and moderate to good enantioselectivities, up to 87% ee (entries 1, 3 and 5).

When the reaction was catalyzed by *trans*-4-*tert*-butoxy-L-proline **2**, the level of enantiocontrol was good to excellent. The amination of propionaldehyde provided compound **4** in 68% yield and 93% ee [15] (entry 2). The hydrazino alcohol **5** derived from heptanal was synthesized in 75% yield and 95% ee [16] (entry 4). Finally, the best result was obtained with 5,5-dimethoxypentanal and compound **6** was isolated in 69% yield and 97% ee [17] (entry 6).

The reaction was further applied to more challenging substrates (Table **3**). The efficiency of catalysts **1** and **2** was tested using cyclic and acyclic ketones. L-Proline [8a] as well as 4-siloxy-L-proline [8f] are known to catalyze α-amination of ketones. *Trans*-3- and *trans*-4-*tert*-butoxy-L-proline proved to be very efficient using only 5 mol% of catalyst loading at room temperature.

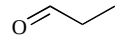
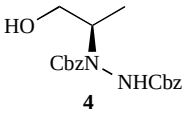
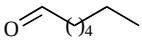
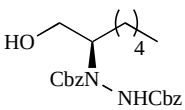
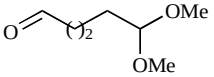
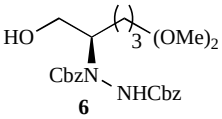
The electrophilic amination of butanone with DBAD led to the 3-hydrazinobutanone **7** as a sole product (entries 1 and 2). The formation of the 1-hydrazino regioisomer was precedently reported when DEAD was used as electrophilic aminating reagent [8a]. These results could be compare with what was obtained using L-proline 20 mol% as catalyst and DBAD as reagent [7a]. We observed similar e.e. and increased chemical yields probably due to the best solubilities of the catalysts **1** and **2** in the reaction mixture. Compound **7** was obtained in 65% yield and 90% ee [18]

Table 1. α-Amination Reaction of 6,6-Dimethoxyhexanal with DBAD Catalyzed by *trans*-3-*tert*-butoxy-L-proline 1 and *trans*-4-*tert*-butoxy-L-proline 2[a]

Entry	Catalyst	Temp.	Time	Yield (%)	Ee (%)
1	L-Prol (10 mol%)	0°C	16h	76%	94%
2	1 (10 mol%)	0°C	4h30	74%	94%
3	2 (10 mol%)	0°C	3h30	71%	96%
4	1 (5 mol%)	r.t.	55 min	67%	71%
5	1 (5 mol%)	0°C	22h	80%	82%
6	2 (5 mol%)	r.t.	3h30	78%	88%
7	2 (5 mol%)	0°C	22h	84%	94%

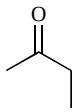
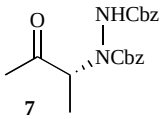
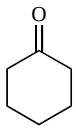
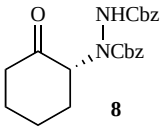
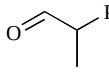
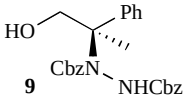
[a]Reactions were conducted with DBAD (1.0 equiv), and carbonyl compound (1.5 equiv) in CH_2Cl_2.

Table 2. α-Amination Reaction of Various Aldehydes with DBAD Catalyzed *trans*-3-*tert*-butoxy-L-proline 1 and *trans*-4-*tert*-butoxy-L-proline 2 (5 mol%)[a]

Entry	Aldehyde	Catalyst	Time	Product	Yield (%)	Ee (%)
1		1	1h50	 **4**	74%	80%
2		2	1h15[b]		68%	93%
3		1	2h20	 **5**	72%	87%[c]
4		2	3h10		75%	95%[c]
5		1	14h	 **6**	68%	83%
6		2	14h		69%	97%

[a]Unless otherwise shown, reactions were conducted with catalyst **1** or **2** (5 mol%), DBAD (1.0 equiv), and carbonyl compound (1.5 equiv) in CH_2Cl_2 at 0°C.
[b]reaction was conducted at room temperature.
[c]Determined before reduction step on the α-aminoaldehyde.

Table 3. α-Amination Reaction of α, α-Disubstituted Aldehydes or Ketones with DBAD Catalyzed by *trans*-3-*tert*-butoxy-L-proline (1) and *trans*-4-*tert*-butoxy-L-proline (2)[a]

Entry	Starting mat.	Catalyst	Time	Product	Yield (%)	Ee (%)
1		1	40h	 **7**	63%	84%
2		2	40h		65%	90%
3		1	40h	 **8**	71%	86%
4		2	40h		72%	90%
5		1	4h	 **9**	76%	45%
6		2	14h		61%	77%

[a]Unless otherwise shown, reactions were conducted with catalyst **1** or **2** (5 mol%, for entries 1 to 4 and 30 mol% for entries 5 and 6), DBAD (1.0 equiv), and carbonyl compound (1.5 equiv) in CH_2Cl_2 at r.t.

using **2** as catalyst (entry 2). The electrophilic amination of cyclohexanone with DBAD in the presence of **1** and **2** 5 mol% as catalysts gave similar or even better results compared to those obtained respectively with with 4-silyloxy-L-proline 10 mol% [8f] or L-proline 20 mol% [7a]. The aminated product **8** was isolated in 72% yield and 90% ee [19] using **2** as catalyst (entry 4).

α-Amination reaction of α,α-disubstituted aldehydes was previously reported using 50 mol% of proline [8b,d,g] or 30 mol% of silyloxyproline [8f]. While the amination of 2-phenylpropanal in the presence of the catalyst **1** gave low enantioselectivity (entry 5), the use of *trans*-4-*tert*-butoxy-L-proline **2** (30 mol%) afforded a similar result compared to the one reported in the literature : 61% yield and 77% ee [20] (entry 6).

CONCLUSION

In summary, *trans*-3-*tert*-butoxy-L-proline **1** and *trans*-4-*tert*-butoxy-L-proline **2** proved to be efficient catalysts for the electrophilic α-amination of carbonyl compounds. The loading of catalyst was lowered to 5 mol%. Various aldehydes were aminated at 0°C affording the hydrazino derivatives in good yields and high level of enantioselectivities.

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[9] *Trans*-3-*tert*-butoxy-L-proline **1**: 2-Methyl-propene (4 mL) was condensed into a pear-shaped flask at -78 °C and then added to a suspension of *trans*-3-hydroxy-L-proline (0.130 g, 0.99 mmol) and *p*-toluenesulfonic acid hydrate (0.736 g, 3.86 mmol) in dichloromethane (5 mL) at -78 °C. The reaction was stirred for 3 days, allowing the mixture to come to room temperature. The reaction mixture was then cooled to 0 °C, vented carefully, and then poured into a separatory funnel and washed twice with a saturated aqueous solution of $NaHCO_3$. The combined aqueous layers were extracted once with dichloromethane, and the combined organic layers were then washed once with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was suspended in 1 M NaOH (6.5 mL) and stirred until the reaction mixture became homogeneous, that is, for about 4h. The reaction mixture was then cooled to 0 °C and acidified with HCl (1M) (6.5mL). The mixture was stirred at 0 °C for 30 min then concentrated *in vacuo*. The product was isolated after elution on Dowex 50WX8-200 ion exchange column (NH_4OH, 1N) to yield compound **1** as a white solid (0.128 g, 69 % over two steps); mp 200-202°C; $[\alpha]_D^{22}$ = + 12.4 (c 1; MeOH); IR υ 3441, 3098, 2976, 1586, 1452, 1386, 1363, 1195, 1094, 1015, 872 cm^{-1}; ^1H NMR (300 MHz, MeOD) δ 4.49 (m; 1H); 3,85 (d, *J* = 2.3 Hz, 1H); 3.36 (m; 2H); 1.93 (m; 2H); 1.17 (s; 9H); ^{13}C NMR (75 MHz, MeOD) δ 171.8, 76.5, 74.5, 68.3, 44.4, 31.8, 27.3; Anal. calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.54; H, 8.94; N, 6.91.

[10] *Trans*-4-*tert*-butoxy-L-proline **2:** 2-Methyl-propene (8 mL) was condensed into a pear-shaped flask at -78 °C and then added to a suspension of *trans*-4-hydroxy-L-proline (0.500 g, 3.81 mmol) and *p*-toluenesulfonic acid hydrate (2.81 g, 14.81 mmol) in dichloromethane (20 mL) at -78 °C. The reaction was stirred for 3 days, allowing the mixture to come to room temperature. The reaction mixture was then cooled to 0 °C, vented carefully, and then poured into a separatory funnel and washed twice with a saturated aqueous solution of $NaHCO_3$. The combined aqueous layers were extracted once with dichloromethane, and the combined organic layers were then washed once with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was suspended in 1 M NaOH (30 mL) and stirred until the reaction mixture became homogeneous, that is, for about 4h. The reaction mixture was then cooled to 0 °C and acidified with HCl (1M) (30 mL). The mixture was stirred at 0 °C for 30 min then concentrated *in vacuo*. The product was isolated after elution on Dowex 50WX8-200 ion exchange column (NH_4OH, 1N) to yield compound **2** as a white solid (0.520 g, 73 % over two steps); mp 204-206°C; $[\alpha]_D^{22}$ = + 34.6 (c 1; MeOH); IR υ 3484, 3119, 2977, 1593, 1465, 1393, 1362, 1195, 1109, 1022, 898 cm^{-1}; ^1H NMR (300 MHz, MeOD) δ 4.61 (m; 1H); 4.30 (t, *J* = 8.7 Hz, 1H); 3,59 (dd, *J* = 5.0, 2.1 Hz, 1H); 3,26 (dd, *J* = 5.0, 2.1 Hz, 1H); 2.31 (m; 2H); 1.26 (s; 9H); ^{13}C NMR (75 MHz, MeOD) δ 174.0, 76.1, 69.9, 59.9, 52.1, 36.9, 27.1; Anal. calcd for $C_9H_{17}NO_3$:C, 57.73; H, 9.15; N, 7.48. Found: C, 57.46; H, 8.98; N, 7.63.

[11] General procedure for the amination step: Dibenzylazodicarboxylate (1 mmol) and catalyst (5 mol% or 10 mol%) in dichloromethane (3 mL) were treated with an aldehyde (1.5 mmol) at 0°C or room temperature. The reaction mixture was stirred until the yellow color of the azodicarboxylate had disappeared. The mixture was treated with ethanol (3 mL) and $NaBH_4$ (1.05 mmol) and was stirred for 15 min. at 0°C. The reaction was worked up with aqueous ammonium chloride solution and ethyl acetate. The organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography on silica gel ($EtOAc/CH_2Cl_2$ 1/2) afforded the alcohols.

[12] Compound **3**: the enantiomeric excess was determinated by HPLC analysis of the crude product using Chiralpack AD-H; Eluant: heptane/propan-2-ol: 90/10 + 0,2% TFA; flow 0.5 ml/min; λ 260 nm; T 25°C; τ_{minor} = 52.07 min, τ_{major} = 55.31 min.

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[14] *Trans*-3-*tert*-butoxy-D-proline: $[\alpha]_D^{22}$ = - 12.3 (c 1; MeOH).

[15] Compound **4**: the enantiomeric excess was determinated by HPLC analysis of the crude product using Chiralpack AD-H; Eluant: heptane/propan-2-ol: 90/10 + 0,2% TFA; flow 0.5 ml/min; λ 260 nm; T 25°C; τ_{minor} = 41.68 min, τ_{major} = 37.90 min.

[16] Compound **5**: the enantiomeric excess was determined before reduction step on the α-aminoaldehyde by HPLC analysis using Chiralpack OD-H; Eluant: heptane/propan-2-ol: 93/7; flow 0.9 ml/min; λ 260 nm; T 25°C; τ_{minor} = 33.23 min, τ_{major} = 42.30 min.

[17] Compound **6**: the enantiomeric excess was determinated by HPLC analysis of the crude product using Chiralpack AD-H; Eluant: heptane/propan-2-ol: 90/10 + 0,2% TFA; flow 0.5 ml/min; λ 260 nm; T 25°C; τ_{minor} = 58.67 min, τ_{major} = 53.28 min.

[18] Compound **7**: the enantiomeric excess was determinated by HPLC analysis of the crude product using Chiralpack OD-H; Eluant: heptane/propan-2-ol: 93/7; flow 0.9 ml/min; λ 260 nm; T 25°C; τ_{minor} = 64.75 min, τ_{major} = 50.03 min

[19] Compound **8**: the enantiomeric excess was determinated by HPLC analysis of the crude product using Chiralpack OD-H; Eluant: heptane/propan-2-ol: 93/7; flow 0.9 ml/min; λ 260 nm; T 25°C; τ_{minor} = 35.72 min, τ_{major} = 48.37 min

[20] Compound **9**: the enantiomeric excess was determinated by HPLC analysis of the crude product using Chiralpack AD-H; Eluant: heptane/propan-2-ol: 90/10 + 0,2% TFA; flow 0.5 ml/min; λ 260 nm; T 25°C; τ_{minor} = 85.11 min, τ_{major} = 80.11 min.