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# Enantioselective α-Amination of Branched Aldehydes Promoted by Simple Chiral Primary Amino Acids

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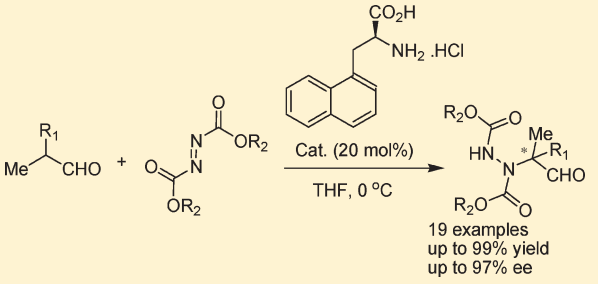
Supporting Information

**ABSTRACT:** A series of simple chiral primary amino acids were first successfully applied to promote the enantioselective α-amination of branched aldehydes with azadicarboxylates and the desired adducts bearing quaternary stereogenic centers were obtained in excellent yields (up to 99%) and enantioselectivities (up to 97% ee).




Optically active nitrogen-containing units, widely existing in natural products and pharmaceuticals,[1j] are versatile and important building blocks in organic synthesis. Particularly, α-amino carbonyl compounds with chiral quaternary stereogenic centers can be easily transferred to α-amino alcohols and α-amino acids.[2] α-Amino acids and their derivatives are key intermediates to construct biological molecules and pharmaceuticals, such as anti-HIV drug atazanavir[3] and ACE (angiotensin converting enzyme) inhibitor perindopril,[4] and also efficient catalysts in asymmetric catalysis. The significance of these interesting structures has stimulated chemists to develop numerous new efficient methods to access these important molecules, such as hydrosilylation of α-imino esters,[5] α-aminooxy[6] and α-amination[7] of carbonyl compounds, etc. Among them, the amination of branched aldehydes is one of the straightforward methods to obtain α,α-disubstituted amino acids, which are difficult to be constructed for highly steric hindrance. The first enantioselective example of α-amination of branched aldehydes is reported by Bräse group[7g] and moderate results are obtained in the presence of 50 mol % L-proline or L-azetidinecarboxylic acid. Continually, Barbas[7k] disclosed the α-amination of 3-(4-bromophenyl)-2-methylpropanal catalyzed by chiral L-proline-derived tertrazole in 95% yield and 80% ee. Recently, Bräse reported that microwave irradiation could accelerate this conversion and increase the yields and enantioselectivities (up to 99% yield and 91% ee).[7h,j] To the best of our knowledge, the catalysts of this transformation are only involved L-proline and its derivatives, and no satisfactory protocol has been reported, and very recently, we reported a α-amination of branched aldehydes promoted by chiral proline-derived amide thiourea bifunctional catalyst in excellent yields (up to 99%) and enantioselectivities (up to 97% ee).[8] It is still desirable to develop new efficient and simple catalytic systems for this conversion.

Since the last century, amino acids have been attracting organic chemists' attentions because they are simple, cheap and easily obtained.[9] Typically, L-proline has been widely used as an efficient catalyst in asymmetric reactions.[10,11] Except L-proline, primary amino acids in some cases show higher activities than L-proline for the easy formation of imines and enamines between catalysts and carbonyl substrates, and are also effective catalysts.[12] Since Eder, Sauer and Wiechert[13] first disclosed that L-phenylalanine catalyzed asymmetric Michael addition of the vinyl ketones to the cyclic 1,3-diketones in 1971, many exciting progresses have been made on chiral primary amino acids catalyzed asymmetric reactions.[14] As a part of our continuing work in asymmetric catalysis,[15] herein, we wish to report our original work on the amination of branched aldehydes catalyzed by primary amino acids (Figure 1) in excellent yields and enantioselectivities.

For further investigation on this α-amination, we choose the reaction of 2-phenylpropionaldehyde (**2a**) and diethyl azadicarboxylate (DEAD) (**3a**) as a model reaction to determine the optimal conditions and the results were summarized in Table 1. Catalyst screenings in $CH_3CN$ gave poor to excellent yields (21−99%) and moderate enantioselectivities (8−72% ee) (Table 1, entries 1−19). 3-(1-Naphthyl) alanine hydrochloride (**1p**), providing the desired product in better results (92% yield

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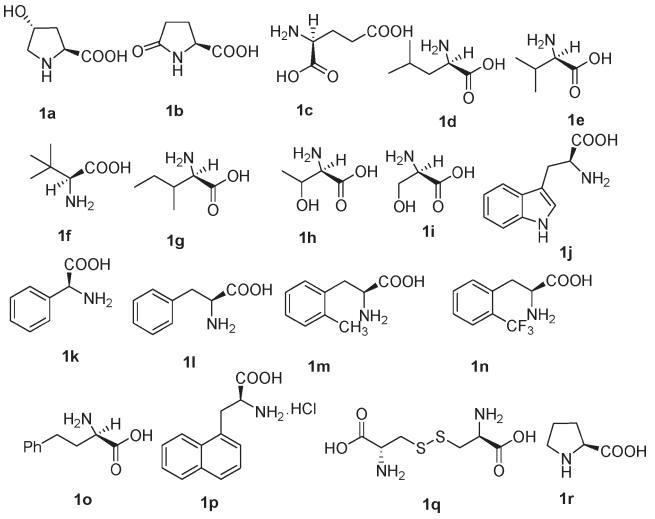
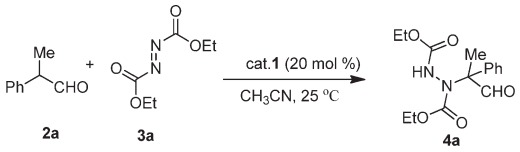



**Figure 1.** Chiral primary amino acid catalysts evaluated.

**Table 1. Screening of Chiral Primary Amino Acid Catalysts**[a]



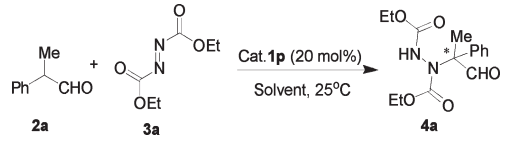

| entry | catalyst | time (h) | yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|
| 1 | **1a** | 72 | 26 | 8 |
| 2 | **1b** | 72 | 21 | 46 |
| 3 | **1c** | 72 | 62 | 57 |
| 4 | **1d** | 168 | 98 | 67 |
| 5 | **1e** | 168 | 98 | 66 |
| 6 | **1f** | 156 | 98 | 69 |
| 7 | **1g** | 168 | 91 | 64 |
| 8 | **1h** | 168 | 94 | 38 |
| 9 | **1i** | 144 | 84 | 50 |
| 10 | **1j** | 48 | 90 | 47 |
| 11 | **1k** | 156 | 50 | 37 |
| 12 | **1l** | 12 | >99 | 66 |
| 13 | **1m** | 5 | 99 | 63 |
| 14 | **1n** | 5 | 99 | 60 |
| 15 | **1o** | 144 | 78 | 60 |
| 16 | **1p** | 6 | 92 | 72 |
| 17[d] | **1p** | 3 | 73 | 50 |
| 18 | **1q** | 144 | 98 | 47 |
| 19 | **1r** | 88 | 77 | 69 |

[a] Unless otherwise specified, all reactions were carried out with 2-phenylpropionaldehyde (**2a**, 0.30 mmol), azodicarboxylate (**3a**, 0.20 mmol), the catalyst (20 mol %) in $CH_3CN$ (1.0 mL) at 25 °C. [b] Isolated yield. [c] Determined by HPLC with a Chiralpak-AS column and the absolute configuration of **4c** was assigned as R.[7i] [d] $Et_3N$ (20 mol %) added.

and 72% ee, Table 1, entry16), was chosen for further investigation.

Then a series of solvents were evaluated and the results were presented in Table 2. All solvents gave moderate to good yields (45−99%) and enantioselectivities (46−88% ee). Arene, alkane

**Table 2. Screening of Solvents**[a]




| entry | solvent | time (h) | yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|
| 1 | toluene | 144 | 81 | 59 |
| 2 | *o*-xylene | 144 | 48 | 60 |
| 3 | cyclohexane | 53 | 45 | 57 |
| 4 | n-hexane | 48 | 61 | 58 |
| 5 | $CH_2Cl_2$ | 22 | 50 | 54 |
| 6 | DCE | 71 | 68 | 58 |
| 7 | $CHCl_3$ | 53 | 78 | 53 |
| 8 | $CHCl_2CHCl_2$ | 45 | 98 | 46 |
| 9 | $CHCl_2CH_2Cl$ | 53 | 90 | 51 |
| 10 | $Et_2O$ | 28 | 91 | 74 |
| 11 | THF | 28 | 77 | 88 |
| 12 | dioxane | 23 | 67 | 85 |
| 13 | MTBE | 71 | 99 | 81 |
| 14 | $CH_3OCH_2CH_2OCH_3$ | 30 | 74 | 83 |
| 15 | EtOAc | 28 | 78 | 82 |
| 16 | MeOH | 10 | 93 | 53 |

[a] Unless otherwise specified, all reactions were carried out with **2a** (0.30 mmol), **3a** (0.20 mmol), **1p** (20 mol %) in solvent (1.0 mL) at 25 °C. [b] Isolated yield. [c] Determined by HPLC with a Chiralpak-AS column.

and haloalkane solvents afforded moderate enantioselectivities (46−60% ee, Table 2, entries 1−9). Ethers and ester gave good yields and enantioselectivities, while polar solvent methanol gave only moderate enantioselectivity (53% ee, Table 2, entry 16). Particularly, THF delivered the highest enantioselectivity (88% ee) at room temperature (Table 2, entry 11), and was chosen as an optimal candidate solvent for further screenings.

Continually, reaction temperature, the amount of **2a** and catalyst loading were studied, and the results were presented in Table 3. Lowering temperature to 0 °C, the enantioselectivity increased to 90% ee (Table 3, entry 1), while further cooled to −40 °C, no significant improvements were observed, even after prolonging reaction time to 98 h (Table 3, entry 3). Decreasing the catalyst loading to 10 mol % (Table 3, entry 5), the enantioselectivities were not significantly lowered. The molar ratio of **2a** to **3a** was also studied and 2.0 equiv **2a** gave the highest yield (98%, Table 3, entry 6). Through those screenings, the optimized reaction conditions were found to be reaction of 1.0 equiv **3a** with 2.0 equiv **2a**, in the presence of 20 mol % of **1p** in THF at 0 °C.

Under the optimized reaction conditions, a range of branched aldehydes were evaluated and the results were listed in Table 4. In general, various α,α-disubstituted aldehydes reacted smoothly with azodicarboxylates in excellent yields (up to 99%) and enantioselectivities (up to 97% ee, Table 4, entries 1−19). Aliphatic substituted aldehydes afforded lower yields (Table 4, entries 2, 3) compared with aromatic substituted ones (Table 4, entries 4−19). By contrast, the enantioselectivities were more sensitive to steric hindrance than electrical properties of the substituents on the aromatic, and the ortho substituted aldehydes required longer reaction time and gave lower yields due to the


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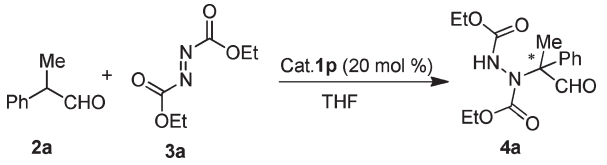
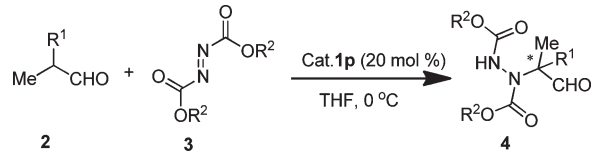
**Table 3. Screening of Temperature and the Loading of 2a**[a]




| entry | cat. loading (%) | 2a (equiv) | temp. (°C) | time (h) | yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|---|
| 1 | 20 | 1.5 | 0 | 21 | 88 | 90 |
| 2 | 20 | 1.5 | −10 | 51 | 79 | 89 |
| 3 | 20 | 1.5 | −40 | 98 | 82 | 72 |
| 4 | 15 | 1.5 | 0 | 32 | 86 | 91 |
| 5 | 10 | 1.5 | 0 | 32 | 73 | 91 |
| 6 | 20 | 2.0 | 0 | 21 | 98 | 91 |

[a] Unless otherwise specified, all reactions were carried out with **2a**, **3a** (0.20 mmol), and the catalyst **1p** in THF (1.0 mL). [b] Isolated yield. [c] Determined by HPLC with a Chiralpak-AS column.

**Table 4. Scope of Substrates**[a]




| entry | $R^1$ | $R^2$ | product | time (h) | yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|---|
| 1 | Ph (**2a**) | *i*-Pr | **4a**-*i*-Pr | 32 | 82 | 95 |
| 2 | *n*-Pr (**2b**) | Et | **4b**-Et | 15 | 64 | —[d] |
| 3 | *n*-Pr (**2b**) | *i*-Pr | **4b**-*i*-Pr | 15 | 88 | —[d] |
| 4 | *p*-$NO_2$Ph (**2c**) | Et | **4c**-Et | 24 | 99 | 85 |
| 5 | *p*-BrPh (**2d**) | Et | **4d**-Et | 22 | 96 | 90 |
| 6 | *p*-BrPh (**2d**) | *i*-Pr | **4d**-*i*-Pr | 34 | 77 | 93 |
| 7 | *p*-FPh (**2e**) | Et | **4e**-Et | 18 | 99 | 94 |
| 8 | *p*-FPh (**2e**) | *i*-Pr | **4e**-*i*-Pr | 34 | 63 | 96 |
| 9 | *m*-ClPh (**2f**) | Et | **4f**-Et | 22 | 96 | 89 |
| 10 | *m*-ClPh (**2f**) | *i*-Pr | **4f**-*i*-Pr | 34 | 72 | 96 |
| 11 | *o*-ClPh (**2g**) | Et | **4g**-Et | 24 | trace | nd |
| 12 | *o*-ClPh (**2g**) | *i*-Pr | **4g**- *i*-Pr | 58 | 29 | 91 |
| 13 | *p*-$CH_3O$Ph (**2h**) | Et | **4h**-Et | 23 | 98 | 85 |
| 14 | *p*- $CH_3$Ph (**2i**) | Et | **4i**-Et | 22 | 83 | 97 |
| 15 | *p*- $CH_3$Ph (**2i**) | i-Pr | **4i**-*i*-Pr | 19.5 | 91 | 96 |
| 16 | *o*- $CH_3$Ph (**2j**) | Et | **4j**-Et | 40.5 | 87 | 96 |
| 16 | 2-Naphthyl (**2k**) | Et | **4k**-Et | 22 | 92 | 91 |
| 17 | 2-Naphthyl (**2k**) | i-Pr | **4k**-*i*-Pr | 34 | 86 | 94 |
| 18 | Ph (**2a**) | *t*-Bu | **4l**- *t*-Bu | 72 | 33 | 92 |
| 19 | *p*-BrPh (**2d**) | *t*-Bu | **4 m**- *t*-Bu | 72 | 45 | 85 |

[a] Unless otherwise specified, all reactions were carried out with **2** (0.4 mmol), azodicarboxylate (**3**, 0.20 mmol), and the catalyst **1p** (0.04 mmol) in THF (1.0 mL) at 0 °C. [b] Isolated yield. [c] Determined by HPLC with a Chiralpak column. [d] The ee values could not be determined by our methods.

larger steric hindrance (Table 4, entries 11, 12). Aromatic substituted aldehydes bearing electron-withdrawing or electron-donating on aromatic ring both gave the desired products in satisfactory enantioselectivities (85−97% ee, Table 4, entries 4−19). With diisopropyl azodicarboxylate (DIAD) in hand, the effects of substituents on the aromatic were investigated and good results (29−91% yields, and 91−96% ee, Table 4) were also obtained. When using ditert-butyl azodicarboxylate (DBAD) as nitrogen source, only moderate yields and good enantioselectivities were obtained due to its larger steric hindrance (Table 4, entries 18, 19).

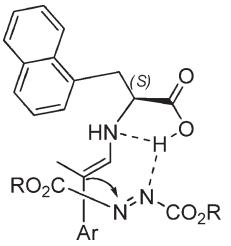



**Figure 2.** Proposed transition state model.

The absolute configuration of the α-amination product **4c**−**Et**, was determined to be R by comparison with the optical rotation of the reported compound.[7i]

Based on the experimental results and the absolute configuration of products, we suggested a plausible bifunctional catalytic mechanism involving hydrogen binding and enamine formation as shown in Figure 2. Aldehyde was activated by the amine group via the formation of enamine transition state and azodicarboxylate might be directed and activated by hydrogen binding interaction with nitrogen atom (Figure 2).

In summary, we have successfully found the simple, cheap and commercially available chiral primary amino acid, especially 3-(1-naphthyl) alanine hydrochloride (**1p**), is a highly efficient and enantioselective catalyst for the direct asymmetric α-amination of branched and hindered aldehydes with azodicarboxylates in excellent yields (up to 99%) and enantioselectivities (up to 97% ee). This work provided an effective method for the construction of nitrogen-containing compounds with quaternary stereocenters, especially optically active and pharmaceutically important amino acids and amino alcohols. Further applications of those catalysts in other reactions and new pharmaceutical preparations are currently underway in our laboratory.

## EXPERIMENTAL SECTION

Typical experimental procedure for the amination of branched aldehydes with azodicarboxylates: A stirred solution of catalyst **1** (20 mol %), and aldehydes **2** (0.40 mmol) in THF (1.0 mL) was cooled to 0 °C and azodicarboxylates **3** (0.2 mmol) was added at the same temperature. The reaction mixture was stirred at 0 °C for the time indicated. After the azodicarboxylate was consumed as indicated (monitored by TLC and the decolorization of azodicarboxylate was also observed), the reaction solution was concentrated in vacuo. The crude product was purified by column chromatography on silica gel (eluent PE/EtOAc = 8:1) to afford pure α-aminated products **4**. All known products were identified by spectroscopic data ($^1$H and $^{13}$C NMR) which are in good agreement with those reported.[7,8]

**Compound 4a-Et**[7,8]**.** The ee was determined by chiral HPLC analysis (AS-H, *i*-PrOH/hexane = 20/80, 220 nm, 1.0 mL/min, $t_r$ (major) = 15.765 min, $t_r$ (minor) = 21.165 min). $[\alpha]_D^{20}$ = +39.3 (c 0.300, $CH_2Cl_2$). $^1$H NMR (300 MHz, $CDCl_3$): δ1.20−1.24 (m, 6H), 1.72, 1.79 (2s, 3H), 4.13−4.18 (m, 4H), 6.64 (br, 1H), 7.31−7.55 (m, 5H), 9.58, 9.74 (2s, 1H) ppm.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## ■ ASSOCIATED CONTENT

**Supporting Information.** Detailed experimental procedures, characterization data, and copies of $^1$H NMR and HPLC spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

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## ■ ACKNOWLEDGMENT

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