Benzo[*d*]imidazole and Aliphatic α-Amino Acid Derived Primary Amines in Asymmetric Aldol Reactions

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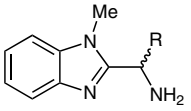
Abstract: Starting from essential α-amino acids, four new benzo[*d*]imidazole and alkyl-chain-substituted primary amines were synthesized. The reaction sequence involves activation of the Boc-amino acid carboxylic acid, reaction with *o*-phenylenediamine, and subsequent cyclization to benzo[*d*]imidazole. N-Methylation and final Boc group removal afforded four new primary amines. The synthesized amines were preliminarily applied as organocatalysts in an asymmetric version of the aldol reaction between 4-nitrobenzaldehyde and acetone/cyclohexanone, achieving chemical yields of 40–64% and ee and de values up to 65 and 96%, respectively.

Key words: benzo[*d*]imidazole, primary amine, α-amino acid, asymmetric aldol reaction, organocatalysis

Carbon–carbon bond-forming reactions undoubtedly represent the most desired and used synthetic tool of organic chemists. Among such reactions, a process accompanied by the formation of a new stereogenic center is of high interest. The aldol reaction, which provides general access to β-hydroxycarbonyl compounds, represents such a case.[1] Although well known for more than 160 years, the aldol reaction is still a versatile tool that is used for the construction of a range organic substances such as natural products (epothilone), pharmaceuticals (atorvastatin, erythromycin, steroids), explosives (pentaerythritol tetranitrate), and α,β-unsaturated carbonyl compounds (reactive substrates). Hence, the development of novel and improved protocols and catalysts remains in demand. In addition to many other catalysts that have been developed to date such as transition-metal catalysts, homo/heterogeneous catalysts, Brønsted and Lewis acids/bases, and biocatalysts, direct aldol reactions can also be organocatalyzed by amines.[1,2] The most widely known and used are secondary amines such as proline-derived catalysts.[3] However, within the last two decades, extensive synthetic efforts have also been devoted to the application of primary amines as catalysts.[4] Such primary amines can also be derived from α-amino acids.[5] Inspired by the molecule of histidine, we also focused our recent synthetic attempts on the development of new chiral imidazole derivatives. In this context, various essential α-amino acids were utilized as chiral, readily available, and inexpensive starting material.[6] It has also been shown that five-membered imidazole, which features a variety of useful properties such as the presence of two lone electron pairs on the nitrogen atoms, acid/base properties, imidazole tautomerism, metal ion chelating abilities, and straightforward synthesis, may act as an active part of a chiral ligand and be applied in asymmetric catalysis.[7] We report herein the design, synthesis, and further application of benzo[*d*]imidazole derivatives **1**–**4** featuring aliphatic α-amino acid pendants at C2 (Figure 1).



1, R = Me (*S*), (*R*), (±)
2, R = *i*-Pr (*S*)
3, R = *i*-Bu (*S*)
4, R = *s*-Bu (*S*)

Figure 1 General structure of α-amino acid and benzo[*d*]imidazole derived primary amines **1**–**4**

The construction of benzo[*d*]imidazole derivatives **1**–**4** started from commercially available Boc-protected (*S*)-alanine, (*R*)-alanine, (±)-alanine, (*S*)-valine, (*S*)-leucine, and (*S*)-isoleucine, which were activated as their mixed anhydride ($ClCOOMe/Et_3N/DMF$)[6a,c] and subsequently treated with *o*-phenylenediamine to afford amino-amides **5**–**8** in yields of 76–82% (Scheme 1). Their cyclization to benzo[*d*]imidazole derivatives **9**–**12** was carried out in acetic acid.[8] Subsequent N-alkylation was performed to avoid benzimidazole tautomerism. Thus, benzo[*d*]imidazole derivatives **9**–**12** were treated with lithium bis(trimethylsilyl)amide (LHMDS) and iodomethane to provide N-methyl derivatives **13**–**16** in isolated yields of 58–86%.[7h] Finally, primary amines **1**–**4** were gained by Boc group removal using trifluoroacetic acid (TFA).[8] The complete reaction sequence is outlined in Scheme 1 and resembles that used to generate BocGly derivative described by Lazarus et al.[9] Table 1 shows the structures, absolute configurations, and yields of all intermediates and final products. It should be noted that a similar reaction sequence can also be drawn for Cbz-protected α-amino acids, however, in contrast to our previous observations,[6a,c] Cbz group removal in the last step turned out to be very sluggish and low-yielding. The chemical and optical purities of all target compounds were verified by ^1H, ^{13}C NMR, HRMS (MALDI), and by chiral phase HPLC analysis (see the Supporting Information).

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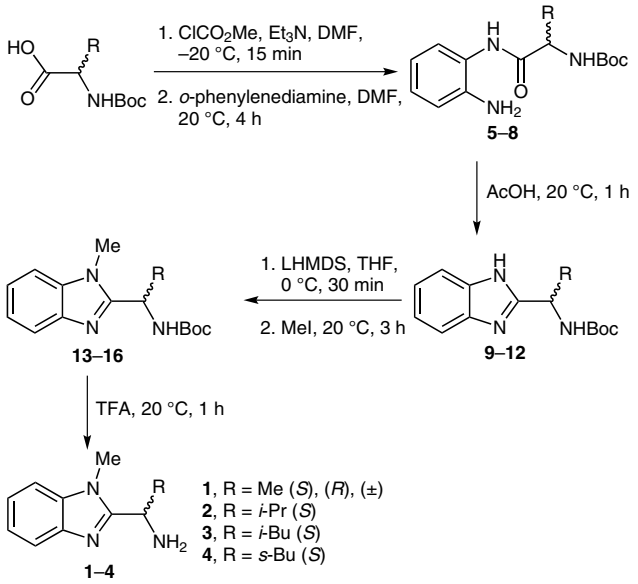
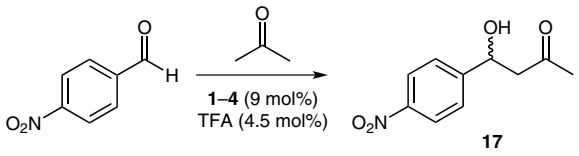


Scheme 1 Synthetic pathway leading to primary amines **1**–**4**

Table 1 Structure, Absolute Configurations, and Yields of Primary Amines **1**–**4** and Intermediates **5**–**16**

α-Amino acid	R	Configuration	Yield (%)			
			5–8	**9–12**	**13–16**	**1–4**
(±)-Ala	Me	±	76	78	86	45
(*R*)-Ala	Me	*R*	78	82	76	48
(*S*)-Ala	Me	*S*	76	75	66	45
(*S*)-Val	*i*-Pr	*S*	82	71	58	61
(*S*)-Leu	*i*-Bu	S	71	66	65	39
(*S*)-Ile	*s*-Bu	*S*	80	76	64	36

All the synthesized primary amines **1**–**4** were further studied as organocatalysts in the direct aldol reaction. The initial screening was carried out in an acid-catalyzed reaction utilizing 4-nitrobenzaldehyde acceptor and acetone donor. The reaction and the achieved results are summarized in Scheme 2 and Table 2.



Scheme 2 Asymmetric aldol reaction with acetone

After initial elaboration, all reactions were carried out on a 1 mmol scale with 9 mol% catalyst and a reaction time/temperature of 24 h/20 °C. According to the observations on benzoimidazole-pyrrolidine (BIP) ligand made by Vincent et al.,[10] TFA (4.5 mol%) was used as a proton source. Such standard conditions allowed the structure–catalytic activity of the synthesized amines **1**–**4** to be investigated. Aldol products **17** were isolated by column chromatography and the enantiomeric excesses were determined by HPLC.[12] The reaction catalyzed by racemic alanine-derived amine (±)-**1** afforded aldol product **17** in a yield of 51% and with the anticipated 0% ee (Table 2, entry 1). Corresponding catalysts (*R*)-**1** and (*S*)-**1** afforded aldols **17** in yields of 40 and 46%, respectively, and modest optical purities of 20 and 32% ee (Table 2, entries 2 and 3). The observed variation in ee is due to optically impure catalyst (*R*)-**1** (86% ee, see also the Supporting Information). This optical impurity was introduced from starting (*R*)-alanine. Whereas amine (*R*)-**1** afforded aldol **17** with absolute configuration (*S*), catalyst (*S*)-**1** provided (*R*)-**17**. In general, all organocatalysts having (*S*)-configuration provided (*R*)-aldol, whereas amine (*R*)-**1** provided the opposite enantiomer (*S*)-**17**. This is consistent with the results reported by Vincent et al.[10]

Table 2 Aldol Reaction with Acetone[11]

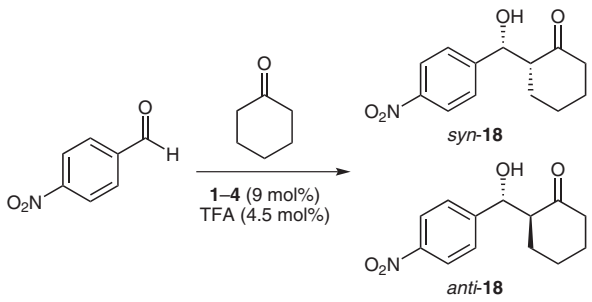
Entry	Catalyst	Yield (%)[a]	Configuration[b]	ee (%)[c]
1	(±)-**1**	51	±	0
2	(*R*)-**1**	40	*S*	20[d]
3	(*S*)-**1**	46	*R*	32
4	(*S*)-**2**	48	*R*	49
5	(*S*)-**3**	51	*R*	59
6	(*S*)-**4**	59	*R*	65

[a] Isolated chemical yield after column chromatography (SiO_2; EtOAc–hexane, 1:1).
[b] Determined on the basis of the optical rotation of aldol **17**.3a
[c] Determined by chiral phase HPLC analysis (Chiralpak AS-H).[12]
[d] Lower ee due to optical impurity of (*R*)-**1** (86% ee).

Interestingly, the attained enantiomeric excesses increased with increasing steric bulk of the R-substituent. The highest ee values of 59 and 65% were achieved for the aldol reaction catalyzed with leucine- and isoleucine-derived amines (*S*)-**3** and (*S*)-**4**, bearing isobutyl and *sec*-butyl R-substituents (Table 2, entries 5 and 6). Thus, the stereochemical outcome of the aldol reaction can be significantly tuned by changing the α-amino acid appended to benzimidazole C2.

The catalytic activity of primary amines **1**–**4** was further evaluated in the aldol reaction performed on cyclohexanone (Scheme 3). The reaction conditions used were identical to those employed with acetone donor.[11] The reaction outcomes are summarized in Table 3. The isolated chemical yields ranged from 46 to 64% and increased slightly with extensions of the R-substituent. In contrast to the aldol reaction with acetone, the aldol reaction with cyclohexanone afforded aldol **18** as a set of *syn* and *anti* diastereoisomers. The attained *syn*/*anti* ratios and de values for optically pure organocatalysts **1**–**4** varied from 2:97 to 17:83 and from 94 to 66%, respectively. The *anti*-diastereoisomer **18** was predominantly isolated irrespec-

tive of the structure of the catalyst used. The aldol reaction catalyzed by alanine-derived amines (±)-**1**, (*R*)-**1**, and (*S*)-**1**, afforded 0/0, 32/29, and 23/32% ee values for *syn*/*anti* diastereoisomers, respectively. Whereas the attained ee values for the *syn*-stereoisomers were all modest 23–32%, those of the dominant *anti*-**18** ranged from 29 to 62%. By using (*S*)-catalysts **1**–**4**, the (2*S*,1′*R*) and (2*R*,1′*R*) *anti*/*syn* enantiomers were isolated in enantiomeric excess. The highest ee values (62 and 39%) were achieved within the aldol reaction catalyzed by valine- and isoleucine-derived amines (*S*)-**2** and (*S*)-**4**. Hence, branching of the R-substituent seems to be crucial.



Scheme 3 Asymmetric aldol reaction with cyclohexanone

Table 3 Aldol Reaction with Cyclohexanone[11]

Entry	Catalyst	Yield (%)[a]	*syn*/*anti*[b]	ee (*syn*) (%)[c]	ee (*anti*) (%)[c]
1	(±)-**1**	48	2:98	0	0
2	(*R*)-**1**	46	3:97	32 (2*S*,1′*S*)	29 (2*R*,1′*S*)
3	(*S*)-**1**	49	17:83	23 (2*R*,1′*R*)	32 (2*S*,1′*R*)
4	(*S*)-**2**	51	7:93	32 (2*R*,1′*R*)	62 (2*S*,1′*R*)
5	(*S*)-**3**	60	4:96	23 (2*R*,1′*R*)	32 (2*S*,1′*R*)
6	(*S*)-**4**	64	8:92	31 (2*R*,1′*R*)	39 (2*S*,1′*R*)

[a] Isolated chemical yield after column chromatography (SiO_2; EtOAc–hexane, 1:1).
[b] Determined by ^{1}H NMR and chiral phase HPLC analysis (Chiralpak AD-H).[12]
[b] Absolute configurations were determined by comparison of chiral phase HPLC analysis with reported data.[4h]

In conclusion, we have demonstrated that 1-methylbenzo[*d*]imidazole linked to α-amino acid residues represent an interesting class of chiral amines that organocatalyze direct aldol reactions. Their straightforward synthesis involved reaction of activated Boc-protected α-amino acid with *o*-phenylenediamine, cyclization to benzo[*d*]imidazole, N-methylation, and Boc-group removal. The stereochemical outcomes of the aldol process can be affected by the configuration and steric bulk of the α-amino acid residue. The highest enantiomeric excesses achieved were 65 and 62% for the aldol reaction between 4-nitrobenzaldehyde and acetone or cyclohexanone, respectively. In view of the current wide interest in optically pure amines, we believe that amines **1**–**4** would serve as useful building blocks for further elaboration.

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(8) **Synthesis of (*S*)-4; Typical Procedure**: Methyl chloroformate (1.6 mL, 21.2 mmol) was added to a mixture of (*S*)-*N*-Boc-ILe (4.9 g, 21.2 mmol), triethylamine (3.0 mL, 21.2 mmol), and DMF (18 mL) at –20 °C. After 15 min stirring, *o*-phenylenediamine (2.3 g, 21.2 mmol) was added and the reaction was stirred at 20 °C for 4 h. The solvent was evaporated and the residue was partitioned between H_2O and EtOAc. The organic layer was washed with $NaHCO_3$ (5% aq.), brine, H_2O, dried (Na_2SO_4), and the solvent was evaporated to afford amino-amide **8** (5.7 g, 80%).
A solution of **8** (5.7 g, 20.0 mmol) in glacial AcOH (10 mL) was heated at 65 °C for 1 h, then the solvent was evaporated and the residue was partitioned between H_2O and EtOAc. The organic layer was washed with H_2O, dried (Na_2SO_4), and the solvent was evaporated. Crystallization of the residue from Et_2O–hexane afforded benzo[*d*]imidazole derivative **12** (3.9 g, 76%).
Derivative **12** (1.2 g, 3.8 mmol) dissolved in anhydrous THF (20 mL) was treated with LHMDS (1 M in THF, 3.8 mL, 3.8 mmol) at 0 °C for 30 min, whereupon iodomethane (0.25 mL, 4.0 mmol) was added and the reaction was stirred at 20 °C for 3 h. The reaction was diluted with H_2O and extracted with EtOAc. The organic layer was dried (Na_2SO_4), the solvents were evaporated, and the residue was purified by column chromatography (SiO_2; EtOAc–hexane, 1:1) to gave *N*-methyl derivative **16** (772 mg, 64%).
Boc derivative **16** (730 mg, 2.3 mmol) was treated with TFA (1 mL) at 20 °C for 1 h, then Et_2O–hexane (1:1) was added to the reaction mixture until the product precipitated. The crude product was filtered and purified by column chromatography (SiO_2; EtOAc–CH_2Cl_2–MeOH, 1:1:0.2) to afford (*S*)-**4** (180 mg, 36%) as a viscous oil. $[\alpha]_D^{20}$ –21.8 (*c* 1, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.85 (d, *J* = 6.4 Hz, 3 H, CH_2CH_3), 0.90 (t, *J* = 7.2 Hz, $CHCH_3$), 1.19 and 1.75 (2 × m, 2 × 1 H, CH_2), 1.90 (m, 1 H, CH), 3.85 (s, 3 H, NCH_3), 4.03 (d, *J* = 7.6 Hz, 1 H, NH_2CH), 7.20–7.55 (m, 2 H, CH_{Ar}), 7.56 (d, *J* = 7.0 Hz, 1 H, CH_{Ar}), 7.62 (d, *J* = 7.0 Hz, 1 H, CH_{Ar}). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 11.20, 15.78, 24.06, 29.80, 39.92, 52.30, 110.02, 118.51, 121.35, 121.62, 135.68, 141.92, 157.67. MALDI-HRMS (DHB): *m*/*z* $[M+H]^+$ calcd for $C_{13}H_{20}N_3^+$: 218.1652; found: 218.1645.

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(11) **Aldol Reaction; General Procedure:** A solution of catalyst **1**–**4** (0.09 mmol) in acetone or cyclohexanone (7.5 mL) was treated with TFA (3.5 μL, 0.045 mmol) at 20 °C for 5 min, whereupon 4-nitrobenzaldehyde (151 mg, 1.0 mmol) was added and the reaction was stirred for 24 h. The solvent was evaporated and the residue was purified by column chromatography (SiO_2; EtOAc–hexane, 1:1).

(12) Enantiomeric excesses were determined by chiral phase HPLC. For **17**: Daicel Chiralpak AS-H; *n*-hexane–*i*-PrOH, 70:30; flow rate 0.5 mL/min; λ = 254 nm, t_R = 25.32, 33.65 min. For **18**: Daicel Chiralpak AD-H; *n*-hexane–*i*-PrOH, 80:20; flow rate 0.5 mL/min; λ = 254 nm; t_R = 22.69 (*syn*), 24.34 (*syn*), 26.35 (*anti*), 33.26 (*anti*) min.

