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Towards a Series of Chiral Primary Amines Bearing α-Amino Acid and Benzo[*d*]imidazole Pendants, and Their Application in Asymmetric Aldol Reactions

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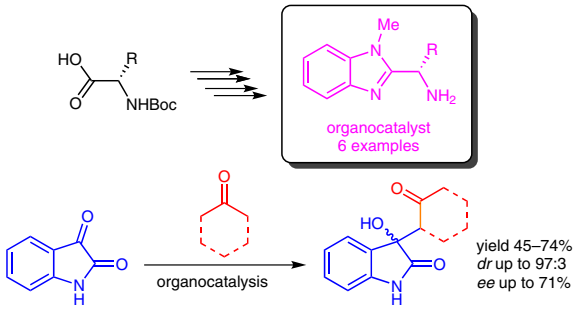

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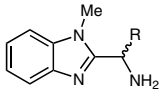
Abstract A straightforward reaction path towards chiral primary amines bearing α-amino acid and benzo[*d*]imidazole pendants has been developed. Six starting essential α-amino acids were converted into the target chiral amines in a four-step synthesis. The prepared amines were screened as organocatalysts in the direct asymmetric aldol reaction between 4-nitrobenzaldehyde or isatin and acetone or cyclohexanone. The aldol adducts were obtained in good chemical yields, diastereoselectivity up to 97:3 (reactions with cyclohexanone), and enantioselectivity up to 71% *ee*. Trifluoroacetic acid and benzoic acid proved to be the best cocatalysts for the aldol process on 4-nitrobenzaldehyde and isatin, respectively.

Key words α-amino acids, benzo[*d*]imidazoles, amines, organocatalysis, aldol reaction

The field of organocatalyzed asymmetric reactions has been rapidly developing in the recent years. The methodology for such reactions generally involves an optically pure and readily available organic substance as organocatalyst, is metal free, and can also be considered as nontoxic and environmentally friendly.[1] Amines represent a group of reactive and valuable organic compounds that can also be used as organocatalysts.[2,3] One of the most widely explored types of organocatalysts are undoubtedly secondary amines derived from proline.[4] Besides these successful catalysts, various primary amines have also been recently introduced as suitable organocatalysts.[5] Their parent backbone is often derived from an α-amino acid as a suitable and readily available source of chirality.[6] In this respect, our recent synthetic attempts were focused on the development of new chiral imidazole derivatives bearing various essential α-amino acid pendants.[7] Five-membered imidazole, which features a variety of useful properties including the presence of two lone electron pairs on the nitrogen atoms, acid/base properties, imidazole tautomerism, metal ion chelating ability, and easy synthesis, may act as an active part of a chiral ligand and be applied in asymmetric catalysis.[8] Hence, based on our recent preliminary communication,[9] we report herein a straightforward synthetic methodology towards a series of primary amines **5a–h** bearing α-amino acid and benzo[*d*]imidazole pendants (Figure 1), and their applications as organocatalysts in asymmetric aldol reactions.



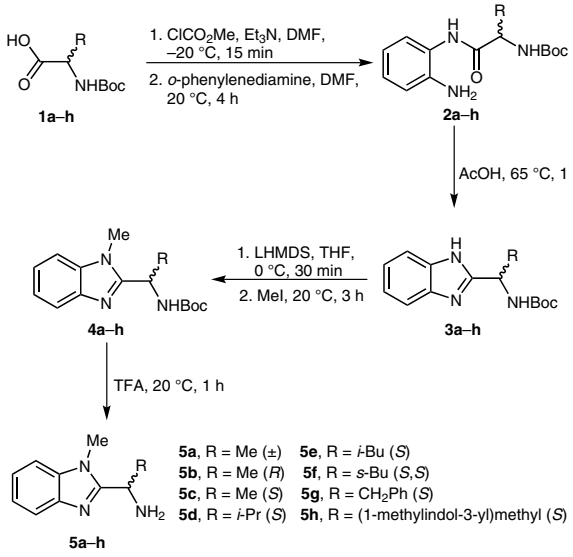
5a, R = Me (±) **5e**, R = *i*-Bu (*S*)
5b, R = Me (*R*) **5f**, R = *s*-Bu (*S*,*S*)
5c, R = Me (*S*) **5g**, R = CH_2Ph (*S*)
5d, R = *i*-Pr (*S*) **5h**, R = (1-methylindol-3-yl)methyl (*S*)

Figure 1 General structure of target primary amines **5a–h** bearing α-amino acid and benzo[*d*]imidazole pendants

The aldol reaction, known for more than 160 years, is one of the most-explored fundamental carbon–carbon bond-forming reactions.[10] This synthetic tool allows the stereoselective formation of aldol products with stereogenic centers at the α- and β-carbon atoms. These aldol products are immensely valuable in the synthesis of architecturally interesting and biologically important natural products, particularly of polyoxygenated compounds. Hence, an availability of various strategies, protocols, and catalysts for asymmetric aldol reactions seems to be necessary.[1a] The classical aldol reaction is highly atom-economical but suffers from low chemo- and regioselectivity. Besides transition-metal catalysts, homo-/heterogenous catalysts, Brønsted and Lewis acids/bases, and biocatalysts, organocatalysis utilizing small organic molecules seems to be a suitable strategy towards asymmetric aldol reactions. Organo-

catalyzed aldol reactions have been utilized for the construction of miscellaneous organic substances including natural products (epothilone), pharmaceuticals (atorvastatin, erythromycin, steroids), explosives (pentaerythritol tetranitrate), and α,β-unsaturated carbonyl compounds (reactive substrates). Among these and many others, 3-hydroxy-2-oxindole is one of the key structural units found in a large variety of natural products and drug candidates, having a wide spectrum of biological activities.[11] In particular, the 3-alkyl-3-hydroxy-2-oxindole structural motif is of great importance in medicinal chemistry. This motif can be found in many drugs and natural products, such as TMC-95A–D,[11d,12] donaxaridine,[13] the convolutamydines,[13] dioxibrassinine,[14] and 3′-hydroxyglucoisatisin.[15] These molecules display diverse biological and pharmacological activities, such as potent antioxidant, anticonvulsant, anticancer, anti-HIV, and neuroprotective properties. The most straightforward synthetic approach towards 3-substituted 3-hydroxy-2-oxindoles is via nucleophilic addition to isatin (aldol process). In 2005, Tomasini and co-workers reported the first enantioselective aldol reaction of isatin with acetone using 10% of a dipeptide containing a secondary amine at the N-terminus.[16] Quinidine thiourea may also serve as an organocatalyst for the reaction of inactivated ketones and activated carbonyl compounds.[17] Primary amines, as well as carbohydrate-derived alcohols, were successfully screened as organocatalysts in enantioselective aldol processes between isatins and cyclohexanone or acetophenone.[18,19] Especially primary amines turned out to efficiently catalyze aldol processes of isatin derivatives[20–24] and, therefore, we focused our further attention on utilizing amines **5a–h** in asymmetric aldol reactions to afford 3-substituted 3-hydroxyindolin-2-ones in a single operational method.

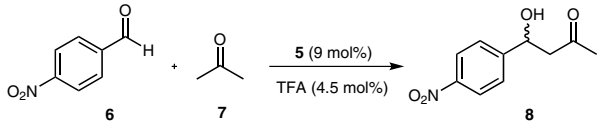
The synthesis of benzo[*d*]imidazole-derived primary amines **5a–h** was carried out via the reaction path shown in Scheme 1.[9] Commercially available, Boc-protected (±)-alanine, (*R*)-alanine, (*S*)-alanine, (*S*)-valine, (*S*)-leucine, (*S*,*S*)-isoleucine, (*S*)-phenylalanine, and (*S*)-1-methyltryptophan (**1a–h**) were used as starting materials. These *N*-Boc-α-amino acids were activated via mixed anhydride ($ClCO_2Me$, Et_3N, DMF) and then treated with *o*-phenylenediamine to afford amino amides **2a–h** in 71–84% yield. Amides **2a–h** were directly cyclized to the benzo[*d*]imidazole derivatives **3a–h** by treatment with acetic acid. Subsequent *N*-alkylation was performed to avoid benzo[*d*]imidazole tautomerism. Thus, the benzo[*d*]imidazole derivatives **3a–h** were treated with lithium hexamethyldisilazide and iodomethane to provide the *N*-methyl derivatives **4a–h** in 50–86% isolated yield. In contrast to products **4a–f** and **4h**, a partial racemization of phenylalanine derivative **4g** was observed during this step (52% *ee*). Unfortunately, all attempted alternative *N*-alkylation systems, including those using Et_3N and Na_2CO_3, also resulted in partial racemization of **4g**.[25] Finally, target amines **5a–g** were obtained by Boc group removal using trifluoroacetic acid. Boc group removal from **4g** was accompanied by further racemization, and **5g** was obtained with only 20% *ee*. Chemical and optical purities of all target compounds and intermediates were verified by ^1H NMR, ^{13}C NMR, HR-MALDI-MS, and chiral-phase HPLC analysis (see the Supporting Information).



Scheme 1 Synthesis of primary amines **5a–h**

All synthesized primary amines, except **5g**, were studied as organocatalysts in the direct aldol reaction. The initial screening was carried out utilizing an acid-catalyzed reaction with 4-nitrobenzaldehyde (**6**) as acceptor and acetone (**7**) as donor (Table 1). Trifluoroacetic acid was used as a proton source. The optimized reaction catalyzed by racemic amine (±)-**5a** derived from alanine afforded aldol product **8** in 51% yield and with the anticipated 0% *ee* (Table 1, entry 1). The corresponding catalysts (*R*)-**5b** and (*S*)-**5c** afforded aldol product **8** in 40% and 46% yield, respectively, and modest optical purity of 32% *ee* in both cases (Table 1, entries 2 and 3). In general, all organocatalysts having *S*-configuration provided the *R*-configured aldol, while amine (*R*)-**5b** provided the opposite (*S*)-**8** enantiomer. This is in agreement with the observations of Vincent and co-workers.[26] In the series of amines bearing aliphatic residues (**5b–f**), the attained enantiomeric excess steadily increased with increasing bulkiness of the R substituent (Table 1, entries 2–6). Hence, the highest enantiomeric excess of 65% was achieved with amine **5f** derived from isoleucine (Table 1, entry 6). On the contrary, attachment of a heterocyclic (indolyl) moiety, as in catalyst **5h** derived from tryptophan, reduced the stereochemical outcome of this aldol process very significantly (Table 1, entry 7).

Table 1 Aldol Reaction of 4-Nitrobenzaldehyde with Acetone[a]



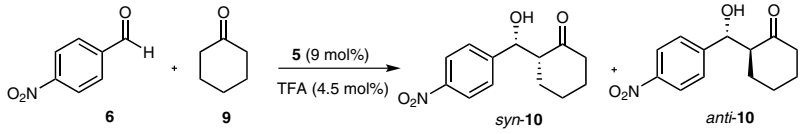
Entry	Catalyst	Yield[b] (%)	Config.[c]	*ee*[d] (%)
1	**5a**	51	±	0
2	**5b**	40	*S*	32
3	**5c**	46	*R*	32
4	**5d**	48	*R*	49
5	**5e**	51	*R*	59
6	**5f**	59	*R*	65
7	**5h**	51	*R*	3

[a] Reaction conditions: **6** (1.0 mmol), **7** (7.5 mL), **5** (0.09 mmol), TFA (3.5 µL, 0.045 mmol), 25 °C, 24 h.
[b] Isolated chemical yield after silica gel column chromatography (EtOAc/hexane, 1:1).
[c] Determined from the optical rotation of aldol **8**.[4a]
[d] Determined by chiral-phase HPLC analysis (Chiralpak AS-H column).[9]

The catalytic activities of primary amines **5a–f**,**h** were further evaluated in the aldol process performed with cyclohexanone (**9**) (Table 2). The isolated chemical yields ranged from 46% to 64% and slightly increased with the extension of the catalyst R substituent. The aldol process with **9** afforded product **10** as a set of *syn*- and *anti*-diastereoisomers with *anti*-**10** dominant, regardless of the structure of the catalyst used. The reaction catalyzed by amines **5a**, **5b**, and **5c** derived from alanine afforded 0/0%, 32/29%, and 23/32% *ee* for the *syn*/*anti*-diastereoisomers, respectively (Table 2, entries 1–3). The absolute configuration of the obtained aldol products depends on the configuration of the catalyst used (e.g., **5b** vs **5c**). Whereas the attained *ee* for the *syn*-stereoisomers is modest (10–32%), the *ee* values for the dominant *anti*-**10** range from 29% to 62%. The highest enantiomeric excesses of 62% and 39% were achieved with the aldol reaction catalyzed by amines **5d** and **5f** derived from valine and isoleucine, respectively (Table 2, entries 4 and 6). Hence, branching of the R substituent seems to be crucial.

In addition, we have investigated the catalytic performance of amines **5a–f**,**h** in the direct aldol reaction of isatin (**11**). Both acetone (**7**) and cyclohexanone (**9**) were used as donors (Table 3 and 4). In initial optimization attempts, a model reaction was carried out between **11** and **7** using 10 mol% of catalyst **5** (Table 3). It has been well documented that additives may improve the catalytic efficiency via fast enamine formation.[28] Accordingly, we examined trifluoroacetic, acetic, and benzoic acids as proton sources (30 mol%).[5a] As seen in Table 3, addition of benzoic acid resulted in better catalytic efficiency (attained chemical yields and enantioselectivities) than the other two acid additives. Under these conditions, the aldol process between isatin (**11**) and acetone (**7**) utilizing the catalyst **5**/$PhCO_2H$ system afforded product **12** in 56–74% yield and 3–24% *ee* (Table 3). A clear trend in increasing enantioselectivity, from 4% to 24% *ee* (Table 3, entries 4 → 7 → 10 → 13 → 16), can be seen within the series of amines **5b–f** with aliphatic residues. This is in accordance with the observation made for the aldol reaction of 4-nitrobenzaldehyde (**6**) with acetone (Table 1). The highest chemical yields of **12** (74% and 70%) and enantioselectivities (16% and 24% *ee*) were obtained for the most sterically hindered catalysts **5e** and **5f** derived from leucine and isoleucine, respectively (Table 3, entries 13 and

Table 2 Aldol Reaction of 4-Nitrobenzaldehyde with Cyclohexanone[a]

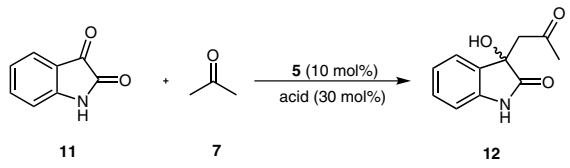


Entry	Catalyst	Yield[b] (%)	*syn*/*anti*,[c] *de*	*ee*[d] (%) (*syn*)	*ee*[d] (%) (*anti*)
1	**5a**	48	2:98, 96	0	0
2	**5b**	46	3:97, 94	32 (2*S*,1′*S*)	29 (2*R*,1′*S*)
3	**5c**	49	17:83, 66	23 (2*R*,1′*R*)	32 (2*S*,1′*R*)
4	**5d**	51	7:93, 86	32 (2*R*,1′*R*)	62 (2*S*,1′*R*)
5	**5e**	60	4:96, 92	23 (2*R*,1′*R*)	32 (2*S*,1′*R*)
6	**5f**	64	8:92, 84	31 (2*R*,1′*R*)	39 (2*S*,1′*R*)
7	**5h**	49	12:88, 76	10 (2*R*,1′*R*)	36 (2*S*,1′*R*)

[a] Reaction conditions: **6** (1.0 mmol), **9** (7.5 mL), **5** (0.09 mmol), TFA (3.5 µL, 0.045 mmol), 25 °C, 72 h.
[b] Isolated chemical yield after silica gel column chromatography (EtOAc/hexane, 1:1).
[c] Determined by ^1H NMR and chiral-phase HPLC analysis (Chiralpak AD-H column).[9]
[d] Absolute configuration was determined by comparison of chiral-phase HPLC analyses with reported data.[5h]

16). Similar to the aldol reaction of **6** with acetone (Table 1), amine **5h** bearing the tryptophan pendant showed very low catalytic performance (Table 3, entries 17–19).

Table 3 Optimization Study of the Model Aldol Reaction of Isatin with Acetone[a]



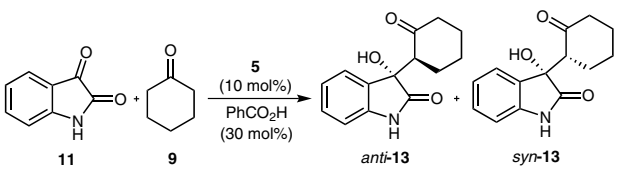
11 7 12

Entry	Catalyst	Acid	Yield[b] (%)	Config.[c]	*ee*[d] (%)
1	**5a**	$PhCO_2H$	56	±	0
2	**5b**	TFA	58	*R*	1
3	**5b**	AcOH	64	*R*	2
4	**5b**	$PhCO_2H$	65	*R*	4
5	**5c**	TFA	64	*S*	1
6	**5c**	AcOH	66	*S*	2
7	**5c**	$PhCO_2H$	68	*S*	4
8	**5d**	TFA	57	*S*	3
9	**5d**	AcOH	59	*S*	5
10	**5d**	$PhCO_2H$	67	*S*	6
11	**5e**	TFA	62	*S*	12
12	**5e**	AcOH	64	*S*	15
13	**5e**	$PhCO_2H$	74	*S*	16
14	**5f**	TFA	67	*S*	18
15	**5f**	AcOH	72	*S*	22
16	**5f**	$PhCO_2H$	70	*S*	24
17	**5h**	TFA	61	*S*	1
18	**5h**	AcOH	62	*S*	1
19	**5h**	$PhCO_2H$	66	*S*	3

[a] Reaction conditions: **11** (0.10 mmol), **7** (1 mL), **5** (0.01 mmol), acid cocatalyst (0.03 mmol), 5 °C, 96 h.
[b] Isolated chemical yield after silica gel column chromatography (EtOAc/hexane, 1:1).
[c] Absolute configuration was determined by comparison of chiral-phase HPLC analyses with reported data.[27]
[d] Determined by chiral-phase HPLC analysis (Chiralcel OJ-H column).[27]

In contrast to reactions with acetone, the reaction of isatin (**11**) with cyclohexanone (**9**) required a little longer reaction time for completion (108 vs 96 h). The aldol products **13** were isolated in 46–60% yield as a set of *syn*- and *anti*-diastereoisomers (Table 4). The attained *syn*/*anti* ratio for the optically pure organocatalysts **5b–f** ranged from 97:3 to 55:45 (94% to 10% *de*). Whereas amines **5a–c** derived from alanine provided the aldol adducts **13** in about 50% yield with low diastereo- and enantioselectivity (Table 4, entries 1–3), the valine, leucine, and isoleucine derivatives **5d–f** showed significantly improved stereochemical outcomes (Table 4, entries 4–6). Amine **5d** derived from valine showed the highest diastereoselectivity (94% *de*), while the leucine and isoleucine derivatives **5e** and **5f** afforded *syn*-**13** with the highest enantioselectivities of 62% and 71% *ee*.

Table 4 Aldol Reaction of Isatin with Cyclohexanone[a]

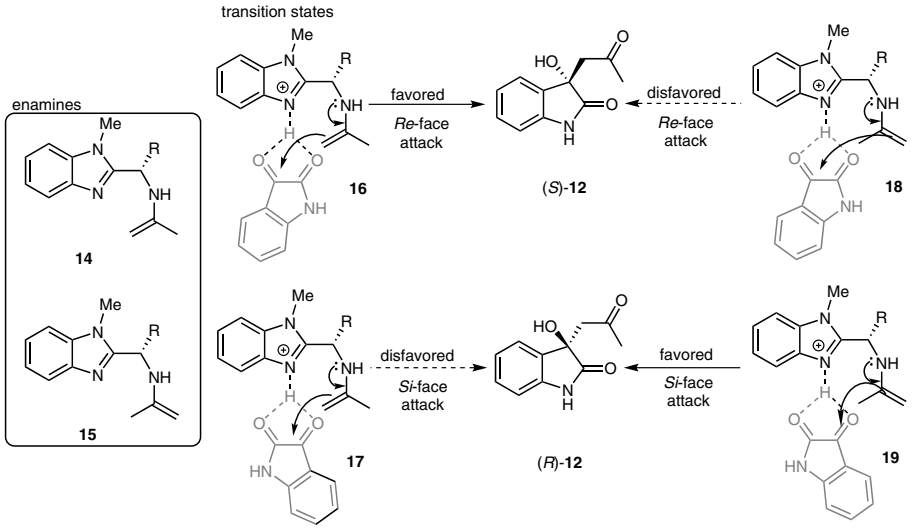


11 9 *anti*-13 *syn*-13

Entry	Catalyst	Yield[b] (%)	*syn*/*anti*[c], *de*	*ee*[d] (%) (*anti*)	*ee*[d] (%) (*syn*)
1	**5a**	51	60:40, 20	0	0
2	**5b**	48	55:45, 10	6	7 (3*S*,1′*R*)
3	**5c**	50	80:20, 60	4	7 (3*R*,1′*S*)
4	**5d**	60	97:3, 94	25	36 (3*R*,1′*S*)
5	**5e**	46	89:11, 78	49	62 (3*R*,1′*S*)
6	**5f**	48	83:17, 66	45	71 (3*R*,1′*S*)

[a] Reaction conditions: **11** (0.10 mmol), **9** (1 mL), **5** (0.01 mmol), $PhCO_2H$ (0.03 mmol), 5 °C, 108 h.
[b] Isolated chemical yield after silica gel column chromatography (EtOAc/hexane, 1:1).
[c] Determined by ^1H NMR and chiral-phase HPLC analysis (Chiralcel OJ-H column).[27]
[d] Determined by comparison of chiral-phase HPLC analyses with reported data.[27]

Based on our observations and the absolute configuration of obtained aldol **12**, a plausible catalytic model for the reaction of isatin (**11**) with acetone (**7**) is proposed (Scheme 2). As a first step, primary amine **5** reacts with ketone **7** to form an enamine intermediate. In principle, and according to a recent mechanistic investigation by Kočovský and coworkers,[29] both the *syn*- and *anti*-rotamers **14** and **15** can be envisaged. Whereas the *anti*-enamine **15** is kinetically favored, the *syn*-enamine **14** is thermodynamically more stable and, under equilibrium conditions, the subsequent aldol process will proceed mainly via **14**. Two principal roles of the cocatalyst (acid) can be envisaged: i) acceleration of the formation of enamines **14** and **15**, and ii) also protonation of the nitrogen atom of the benzimidazole backbone to form the benzimidazolium salt. The benzimidazolium ion is most likely hydrogen-bonded to the carbonyl groups of isatin (**11**), which influences their reactivity and also brings the reacting species close together for the cross-aldol reaction. The transition states for both enamines **14** and **15** shown in Scheme 2 suggest easiest access of **14** to attack **11** via the *Re*-face (transition state **16**), which leads to the formation of (*S*)-**12**. On the contrary, enamine **15** would attack **11** via the *Si*-face (transition state **19**) leading to (*R*)-**12**. These two concurrent modes of attack are reflected in the low enantioselectivities obtained in the aldol reaction between acetone and **11** (Table 3, maximal 24% *ee*).



Scheme 2 Structure of enamines **14** and **15** and proposed transition states **16–19** for the aldol reaction between isatin and acetone catalyzed by primary amines **5**

In contrast, the reaction of **11** with cyclohexanone (**9**) afforded aldol **13** with up to 71% *ee* (Table 4). Whereas in amines **5a–f** the aliphatic R substituent is only involved as a bulky substituent without protonation/coordination capability, in tryptophan derivative **5h** another transition state involving the indolyl residue can be envisaged. Most likely, this accounts for the low stereochemical performance of this derivative.

In conclusion, we have developed a facile synthetic access to chiral primary amines bearing α-amino acid and benzo[*d*]imidazole pendants. Starting from commercially available Boc-protected α-amino acids, six new derivatives were synthesized in a four-step reaction sequence. The alanine derivative was prepared as a racemic mixture and as both optically pure enantiomers. The phenylalanine derivative **5g** underwent racemization during the reaction sequence and, therefore, was not further evaluated. The other prepared amines were investigated as organocatalysts in aldol reactions of 4-nitrobenzaldehyde and isatin with acetone and cyclohexanone. Trifluoroacetic acid and benzoic acid proved to be well-suited proton sources for these two aldol reactions organocatalyzed by amines **5a–f**,**h**, providing the products both in good chemical yields and with enantiomeric excesses up to 71%. The reaction with cyclohexanone provides a set of diastereoisomers with up to 94% *de*. Moreover, the prepared amines proved to be tunable organocatalysts. Whereas their absolute configuration predestines the stereochemical configuration of the formed aldol product, their structure, bulkiness of the R substituent, significantly affects the asymmetric induction.

The starting Boc-protected α-amino acids **1a–h** are commercially available. Enantiomeric excesses were determined by HPLC analysis with a Chiralpak AS-H, Chiralpak AD-H, or Daicel Chiralcel OJ-H column. The aldol reactions with 4-nitrobenzaldehyde were carried out following our earlier procedure.[9] Evaporation and concentration in vacuo were performed at water aspirator pressure. Column chromatography was carried out with silica gel 60 (particle size 0.040–0.063 mm, 230–400 mesh; Merck) and commercially available solvents. TLC was conducted on Merck aluminum sheets coated with silica gel 60 F_{254}, with visualization by UV lamp (254 or 360 nm). Melting points were measured on a Büchi B-540 melting point apparatus in open capillaries and are uncorrected. NMR spectra were recorded in DMSO-d_6 or $CDCl_3$ at 500 or 400 MHz (for ^{1}H NMR) and at 125 or 100 MHz (for ^{13}C NMR) with Bruker Avance III 500 or Bruker Avance 400 instruments at 25 °C. Chemical shifts are reported in ppm relative to the signal for TMS. Coupling constants are given in hertz. Apparent resonance multiplicities are described as s (singlet), br s (broad singlet), d (doublet), dd (doublet of doublet), dt (doublet of triplet), t (triplet), q (quartet), and m (multiplet). Residual solvent signals in the NMR spectra were used as the internal reference ($CDCl_3$: 7.25 and 77.23 ppm for ^{1}H and ^{13}C NMR, respectively; DMSO-d_6: 2.55 and 39.51 ppm for ^{1}H and ^{13}C NMR, respectively). Optical rotation values were measured on a Perkin Elmer 341 instrument; concentration *c* is given in g/100 mL MeOH. IR spectra were recorded on a Thermo Nicolet iS50 FTIR spectrometer (Thermo Fisher Scientific, Waltham, MA). High-resolution MALDI mass spectra were measured on a MALDI LTQ Orbitrap XL mass spectrometer (Thermo Fisher Scientific, Bremen, Germany) equipped with a nitrogen UV laser (337 nm, 60 Hz). The LTQ Orbitrap instrument was operated in the positive ion mode over a normal mass range (*m*/*z* 50–1500) with the following settings for tuning parameters: resolution 100000 at *m*/*z* = 400, laser energy 17 mJ, number of laser shots 5. 2,5-Dihydroxybenzoic acid (DHB) was used as the matrix. Mass spectra were averaged over the whole MS record (30 s) for all measured samples.

Benzo[*d*]imidazole Derivatives 3a–h; General Procedure

Methyl chloroformate (1.6 mL, 21.2 mmol) was added to a mixture of a Boc-protected α-amino acid **1a–h** (21.2 mmol), Et_3N (3.0 mL, 21.2 mmol), and DMF (18 mL) at –20 °C. After 15 min of stirring, *o*-phenylenediamine (2.3 g, 21.2 mmol) was added and the reaction mixture was stirred at 20 °C for 4 h. The volatiles were evaporated and the res-

idue was partitioned between water and EtOAc. The organic layer was washed with 5% aq $NaHCO_3$, brine, and water, then dried (Na_2SO_4), and the solvent was evaporated to afford the corresponding amino amide **2a–h** (71–84% yield).

A solution of crude compound **2a–h** (20.0 mmol) in glacial AcOH (10 mL) was heated at 65 °C for 1 h, then the volatiles were evaporated and the residue was partitioned between water and EtOAc. The organic layer was washed with water, then dried (Na_2SO_4), and the solvent was evaporated. Crystallization of the residue (Et_2O/hexane) afforded the corresponding benzo[*d*]imidazole derivative **3a–h** as a solid (64–82% yield).

(±)-*tert*-Butyl 1-(1*H*-Benzo[*d*]imidazol-2-yl)ethylcarbamate (3a)

Synthesized from (±)-*N*-Boc-Ala amino amide **2a** (5.60 g, 20.0 mmol). White solid; yield: 4.10 g (78%); mp 232–234 °C; $[\alpha]_D^{20}$ 0 (*c* 1, MeOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.2 (s, 1 H, NH_{bim}), 7.54 (m, 2 H, CH_{Ar}), 7.41 (d, *J* = 7.8 Hz, 1 H, N*H*Boc), 7.17 (d, *J* = 5 Hz, 2 H, CH_{Ar}), 4.91 (m, 1 H, BocNHC*H*), 1.52 (d, *J* = 7.0 Hz, 3 H, CH_3), 1.44 (s, 9 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.44, 155.11, 142.93, 134.28, 121.72, 120.98, 118.44, 111.28, 78.25, 45.05, 28.25, 20.17.

HR-MALDI-MS (DHB): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{20}N_3O_2^+$: 262.15500; found: 262.15419.

(*R*)-*tert*-Butyl 1-(1*H*-Benzo[*d*]imidazol-2-yl)ethylcarbamate (3b)

Synthesized from (*R*)-*N*-Boc-Ala amino amide **2b** (5.60 g, 20.0 mmol). White solid; yield: 4.30 g (82%); mp 220–222 °C; $[\alpha]_D^{20}$ +13.1 (*c* 1, MeOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.1 (s, 1 H, NH_{bim}), 7.53 (m, 2 H, CH_{Ar}), 7.41 (d, *J* = 6 Hz, 1 H, N*H*Boc), 7.17 (s, 2 H, CH_{Ar}), 4.90 (br s, 1 H, BocNHC*H*), 1.52 (d, *J* = 6.5 Hz, 3 H, CH_3), 1.45 (s, 9 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.35, 157.06, 155.90, 155.73, 121.45, 121.12, 109.21, 108.21, 78.78, 49.45, 45.66, 28.58, 27.00, 20.78, 17.69.

HR-MALDI-MS (DHB): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{20}N_3O_2^+$: 262.15500; found: 262.15388.

(*S*)-*tert*-Butyl 1-(1*H*-Benzo[*d*]imidazol-2-yl)ethylcarbamate (3c)

Synthesized from (*S*)-*N*-Boc-Ala amino amide **2c** (5.60 g, 20.0 mmol). White solid; yield: 3.94 g (75%); mp 228–230 °C; $[\alpha]_D^{20}$ –13.5 (*c* 1, MeOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.1 (s, 1 H, NH_{bim}), 7.58 (d, *J* = 6.8 Hz, 1 H, CH_{Ar}), 7.48 (d, *J* = 6.8 Hz, 1 H, CH_{Ar}), 7.41 (d, *J* = 7.8 Hz, 1 H, N*H*Boc), 7.14–7.20 (m, 2 H, CH_{Ar}), 4.89 (m, 1 H, BocNHC*H*), 1.51 (d, *J* = 7.0 Hz, 3 H, CH_3), 1.45 (s, 9 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.37, 155.05, 142.89, 134.23, 129.62, 121.68, 120.92, 118.39, 111.22, 108.43, 78.09, 44.99, 28.21, 20.11.

HR-MALDI-MS (DHB): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{20}N_3O_2^+$: 262.15500; found: 262.15504.

(*S*)-*tert*-Butyl 1-(1*H*-Benzo[*d*]imidazol-2-yl)-2-methylpropylcarbamate (3d)

Synthesized from (*S*)-*N*-Boc-Val amino amide **2d** (6.15 g, 20.0 mmol). White solid; yield: 4.12 g (71%); mp 248–250 °C; $[\alpha]_D^{20}$ –42.4 (*c* 1, MeOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.2 (s, 1 H, NH_{bim}), 7.59 (d, *J* = 7.0 Hz, 1 H, CH_{Ar}), 7.50 (d, *J* = 6.5 Hz, 1 H, N*H*Boc), 7.22 (d, *J* = 9 Hz, 1 H, CH_{Ar}), 7.17–7.23 (m, 2 H, CH_{Ar}), 4.59 (t, *J* = 8.2 Hz, 1 H, BocNHC*H*), 2.23 (m, 1 H, C*H*(CH_3)$_2$), 1.42 (s, 9 H), 0.95 (d, *J* = 6.7 Hz, 3 H, CH_3), 0.83 (d, *J* = 6.7 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.41, 154.99, 142.90, 133.84, 124.48, 121.67, 120.96, 118.42, 111.18, 78.04, 55.15, 51.87, 32.05, 28.14, 19.28, 18.57.

HR-MALDI-MS (DHB): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{24}N_3O_2^+$: 290.18630; found: 290.18652.

(*S*)-*tert*-Butyl 1-(1*H*-Benzo[*d*]imidazol-2-yl)-3-methylbutylcarbamate (3e)

Synthesized from (*S*)-*N*-Boc-Leu amino amide **2e** (6.45 g, 20.0 mmol). White solid; yield: 4.03 g (66%); mp 186–188 °C; $[\alpha]_D^{20}$ –32.3 (*c* 1, MeOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.1 (s, 1 H, NH_{bim}), 7.53 (m, 2 H, CH_{Ar}), 7.34 (d, *J* = 8.5 Hz, 1 H, N*H*Boc), 7.17 (d, *J* = 5.1 Hz, 2 H, CH_{Ar}), 4.86 (q, *J* = 7.8 Hz, 1 H, BocNHC*H*), 1.77 (m, 2 H, CH_2), 1.62 (m, 1 H, C*H*), 1.43 (s, 9 H), 0.95 (t, *J* = 6.6 Hz, 6 H, CH(CH_2)$_3$).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 174.82, 156.22, 155.36, 121.40, 78.11, 77.94, 51.86, 47.70, 43.07, 28.25, 24.41, 22.94, 22.76, 21.84.

HR-MALDI-MS (DHB): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{26}N_3O_2^+$: 304.20195; found: 304.20100.

(1*S*,2*S*)-*tert*-Butyl 1-(1*H*-Benzo[*d*]imidazol-2-yl)-2-methylbutylcarbamate (3f)

Synthesized from (*S*,*S*)-*N*-Boc-Ile amino amide **2f** (6.45 g, 20.0 mmol). Yellowish solid; yield: 4.65 g (76%); mp 188–190 °C; $[\alpha]_D^{20}$ –17.5 (*c* 1, MeOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.2 (s, 1 H, NH_{bim}), 7.55 (br s, 2 H), 7.26 (d, *J* = 8.8 Hz, 1 H, N*H*Boc), 7.16–7.19 (m, 2 H, CH_{Ar}), 7.03 (d, *J* = 8.4 Hz, 1 H, CH_{Ar}), 4.66 (t, *J* = 8.3 Hz, 1 H, BocNHC*H*), 2.00 (m, 1 H, C*H*), 1.53 (m, 1 H, CH_2), 1.41 (s, 9 H), 1.22 (m, 1 H, CH_2), 0.88 (m, 3 H, CHCH_3), 0.77 (d, *J* = 6.7 Hz, 3 H, CH$_2$CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.96, 155.65, 143.59, 134.46, 122.33, 121.64, 119.09, 111.86, 78.72, 54.55, 38.95, 28.82, 28.60, 25.46, 16.22, 11.95, 11.65.

HR-MALDI-MS (DHB): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{26}N_3O_2^+$: 304.20195; found: 304.20152.

(*S*)-*tert*-Butyl 1-(1*H*-Benzo[*d*]imidazol-2-yl)-2-phenylethylcarbamate (3g)

Synthesized from (*S*)-*N*-Boc-Phe amino amide **2g** (7.12 g, 20.0 mmol). White solid; yield: 5.35 g (79%); mp 180–182 °C; $[\alpha]_D^{20}$ –10.4 (*c* 1, MeOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.28 (br s, 1 H, NH_{bim}), 7.56 (br, s, 1 H, N*H*Boc), 7.44 (d, *J* = 8.7 Hz, 1 H, CH_{Ar}), 7.29 (m, 4 H, CH_{Ar}), 7.17–7.25 (m, 4 H, CH_{Ar}), 5.04 (m, 1 H, BocNHC*H*), 2.78–3.22 (m, 2 H, CHCH_2Ph), 1.34 (s, 9 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.92, 155.80, 143.59, 138.80, 134.78, 129.86, 128.70, 126.83, 122.45, 121.68, 119.15, 111.96, 78.70, 51.48, 28.80.

HR-MALDI-MS (DHB): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{24}N_3O_2^+$: 338.18630; found: 338.18640.

(*S*)-*tert*-Butyl 1-(1*H*-Benzo[*d*]imidazol-2-yl)-2-(1-methyl-1*H*-indol-3-yl)ethylcarbamate (3h)

Synthesized from (*S*)-*N*-Boc-1-MeTrp amino amide **2h** (8.20 g, 20.0 mmol). Yellowish solid; yield: 5.00 g (64%); mp 204–206 °C; $[\alpha]_D^{20}$ –30.5 (*c* 1, MeOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.2 (s, 1 H), 7.48–7.64 (m, 3 H, CH_{Ar}), 7.39 (t, *J* = 9.5 Hz, 1 H), 7.15–7.22 (m, 3 H, CH_{Ar}), 7.02–7.05 (m, 2 H, CH_{Ar}), 5.81 (s, 1 H), 5.08 (q, *J* = 7.5 Hz, 1 H, BocNHC*H*), 3.73 (s, 3 H, NCH_3), 3.48 (dd, *J* = 14.5, 5.7 Hz, 1 H, CHCH_2Trp), 3.24 (dd, *J* = 14.5, 8.7 Hz, 1 H, CHCH_2Trp), 1.36 (s, 9 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.61, 155.27, 143.03, 136.49, 134.20, 127.85, 127.76, 121.80, 121.05, 121.03, 118.68, 118.54, 118.39, 111.34, 109.90, 109.54, 78.07, 50.41, 32.31, 29.76, 28.18.

HR-MALDI-MS (DHB): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{27}N_4O_2^+$: 391.21285; found: 391.21269.

***N*-Methylbenzo[*d*]imidazole Derivatives 4a–h; General Procedure**

The appropriate benzo[*d*]imidazole **3a–h** (3.8 mmol) dissolved in anhydrous THF (20 mL) was treated with 1 M LHMDS in THF (3.8 mL, 3.8 mmol) at 0 °C for 30 min, whereupon MeI (0.25 mL, 4.0 mmol) was added and the reaction mixture was stirred at 20 °C for 3 h. Then, the mixture was diluted with water and extracted with EtOAc. The organic layer was dried (Na_2SO_4), the solvents were evaporated, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:1) to afford the *N*-methyl derivative **4a–h** as a solid (50–86% yield).

(±)-*tert*-Butyl 1-(1-Methyl-1*H*-benzo[*d*]imidazol-2-yl)ethylcarbamate (4a)

Synthesized from (±)-*N*-Boc-Ala BIM **3a** (1.00 g, 3.8 mmol). White solid; yield: 0.90 g (86%); mp 134–136 °C; $[\alpha]_D^{20}$ 0 (*c* 1, MeOH); R_f = 0.5.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (m, 1 H, CH_{Ar}), 7.29–7.40 (m, 3 H, CH_{Ar}), 5.56 (d, *J* = 8.5 Hz, 1 H, N*H*Boc), 5.19–5.26 (m, 1 H, BocNHC*H*), 3.86 (s, 3 H, NCH_3), 1.69 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.49 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.58, 155.27, 142.22, 135.94, 122.88, 122.37, 119.65, 109.54, 80.03, 42.99, 29.97, 28.52, 21.02.

HR-MALDI-MS (DHB): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{22}N_3O_2^+$: 276.17065; found: 276.16979.

(*R*)-*tert*-Butyl 1-(1-Methyl-1*H*-benzo[*d*]imidazol-2-yl)ethylcarbamate (4b)

Synthesized from (*R*)-*N*-Boc-Ala BIM **3b** (1.00 g, 3.8 mmol). Yellowish solid; yield: 0.80 g (76%); mp 138–140 °C; $[\alpha]_D^{20}$ +84.1 (*c* 1, MeOH); R_f = 0.5.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77–7.80 (m, 1 H, CH_{Ar}), 7.29–7.40 (m, 3 H, CH_{Ar}), 5.61 (d, *J* = 8.7 Hz, 1 H, N*H*Boc), 5.19–5.26 (m, 1 H, BocNHC*H*), 3.85 (s, 3 H, NCH_3), 1.69 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.50 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.55, 155.25, 142.15, 135.89, 122.85, 122.33, 119.60, 109.53, 80.00, 42.95, 29.95, 28.49, 20.98.

HR-MALDI-MS (DHB): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{22}N_3O_2^+$: 276.17065; found: 276.16956.

(*S*)-*tert*-Butyl 1-(1-Methyl-1*H*-benzo[*d*]imidazol-2-yl)ethylcarbamate (4c)

Synthesized from (*S*)-*N*-Boc-Ala BIM **3c** (1.00 g, 3.8 mmol). Yellowish solid; yield: 0.70 g (66%); mp 128–130 °C; $[\alpha]_D^{20}$ –84.8 (*c* 1, MeOH); R_f = 0.5.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (m, 1 H, CH_{Ar}), 7.22–7.33 (m, 3 H, CH_{Ar}), 5.49 (d, *J* = 8.6 Hz, 1 H, N*H*Boc), 5.12–5.19 (m, 1 H, BocNHC*H*), 3.79 (s, 3 H, NCH_3), 1.62 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.42 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.58, 155.29, 142.23, 135.96, 122.89, 122.38, 119.67, 109.56, 80.06, 43.02, 29.98, 28.54, 21.05.

HR-MALDI-MS (DHB): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{22}N_3O_2^+$: 276.17065; found: 276.16937.

(*S*)-*tert*-Butyl 2-Methyl-1-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)propylcarbamate (4d)

Synthesized from (*S*)-*N*-Boc-Val BIM **3d** (1.10 g, 3.8 mmol). Yellow solid; yield: 0.67 g (58%); mp 114–116 °C; $[\alpha]_D^{20}$ –62.1 (*c* 1, MeOH); R_f = 0.7.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (s, 1 H, CH_{Ar}), 7.78–7.80 (m, 1 H, CH_{Ar}), 7.33–7.42 (m, 2 H, CH_{Ar}), 5.49 (d, *J* = 9.6 Hz, 1 H, N*H*Boc), 4.86 (t, *J* = 5.8 Hz, 1 H, BocNHC*H*), 3.89 (s, 3 H, NCH_3), 2.30–2.39 (m, 1 H, C*H*(CH_3)$_2$), 1.48 (s, 9 H), 1.12 (d, *J* = 6.7 Hz, 3 H, CH_3), 0.99 (d, *J* = 6.7 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.91, 155.23, 142.47, 135.53, 122.69, 122.37, 119.57, 109.68, 79.87, 52.47, 33.66, 30.18, 28.51, 19.77, 18.58.

HR-MALDI-MS (DHB): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{26}N_3O_2^+$: 304.20195; found: 304.20202.

(*S*)-*tert*-Butyl 3-Methyl-1-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)butylcarbamate (4e)

Synthesized from (*S*)-*N*-Boc-Leu BIM **3e** (1.16 g, 3.8 mmol). White solid; yield: 0.79 g (65%); mp 102–104 °C; $[\alpha]_D^{20}$ –41 (*c* 1, MeOH); R_f = 0.6.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.73 (m, 1 H, CH_{Ar}), 7.29–7.34 (m, 1 H, CH_{Ar}), 7.23–7.29 (m, 2 H, CH_{Ar}), 5.19 (d, *J* = 9.3 Hz, 1 H, N*H*Boc), 5.12 (m, 1 H, BocNHC*H*), 3.83 (s, 3 H, NCH_3), 1.86 (m, 2 H, CH_2), 1.70 (m, 1 H, C*H*), 1.40 (s, 9 H), 0.99 (d, *J* = 6.5 Hz, 3 H, CH(CH_2)$_3$), 0.95 (d, *J* = 6.6 Hz, 3 H, CH(CH_2)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.80, 135.68, 134.61, 129.62, 122.78, 122.35, 119.66, 109.64, 79.99, 45.10, 44.29, 30.03, 28.51, 24.93, 23.13, 22.44.

HR-MALDI-MS (DHB): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{28}N_3O_2^+$: 318.21760; found: 318.21729.

(1*S*,2*S*)-*tert*-Butyl 2-Methyl-1-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)butylcarbamate (4f)

Synthesized from (*S*,*S*)-*N*-Boc-Ile BIM **3f** (1.16 g, 3.8 mmol). Yellow solid; yield: 0.78 g (64%); mp 104–106 °C; $[\alpha]_D^{20}$ –73.5 (*c* 1, MeOH); R_f = 0.6.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (m, 1 H, CH_{Ar}), 7.34 (m, 1 H, CH_{Ar}), 7.23–7.29 (m, 2 H, CH_{Ar}), 5.39 (d, *J* = 9.5 Hz, 1 H, N*H*Boc), 4.82 (t, *J* = 9.0 Hz, 1 H, BocNHC*H*), 3.82 (s, 3 H, NCH_3), 2.05 (m, 1 H, C*H*), 1.71 (m, 1 H, CH_2), 1.39 (s, 9 H), 1.20 (m, 1 H, CH_2), 0.91 (t, *J* = 7.4 Hz, 3 H, CHCH_3), 0.85 (d, *J* = 6.7 Hz, 3 H, CH$_2$CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.84, 155.45, 142.53, 135.46, 122.66, 122.37, 119.56, 109.72, 79.88, 51.51, 39.95, 30.20, 28.51, 24.99, 15.97, 11.40.

HR-MALDI-MS (DHB): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{28}N_3O_2^+$: 318.21760; found: 318.21717.

(*S*)-*tert*-Butyl 1-(1-Methyl-1*H*-benzo[*d*]imidazol-2-yl)-2-phenylethylcarbamate (4g)

Synthesized from (*S*)-*N*-Boc-Phe BIM **3g** (1.29 g, 3.8 mmol). White solid; yield: 0.67 g (50%); mp 132–134 °C; $[\alpha]_D^{20}$ –18.8 (*c* 1, MeOH); 52% *ee*; R_f = 0.8.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80–7.83 (m, 1 H, CH_{Ar}), 7.23–7.34 (m, 7 H, CH_{Ar}), 7.09 (m, 1 H, CH_{Ar}), 5.72 (d, *J* = 8.8 Hz, 1 H, N*H*Boc), 5.24 (m, 1 H, BocNHC*H*), 3.4–3.55 (m, 2 H, CHCH_2Ph), 3.33 (s, 3 H, NCH_3), 1.47 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.56, 142.43, 136.90, 129.62, 128.65, 127.03, 122.77, 122.41, 119.55, 109.55, 49.14, 42.73, 29.40, 28.52.

HR-MALDI-MS (DHB): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{26}N_3O_2^+$: 352.20195; found: 352.20187.

(*S*)-*tert*-Butyl 1-(1-Methyl-1*H*-benzo[*d*]imidazol-2-yl)-2-(1-methyl-1*H*-indol-3-yl)ethylcarbamate (4h)

Synthesized from (*S*)-*N*-Boc-1-MeTrp BIM **3h** (1.49 g, 3.8 mmol). Brown solid; yield: 0.99 g (64%); mp 164–166 °C; $[\alpha]_D^{20}$ –20.1 (*c* 1, MeOH); R_f = 0.5.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 7.5 Hz, 1 H, CH_{Ar}), 7.49 (d, *J* = 7.8 Hz, 1 H, CH_{Ar}), 7.15–7.28 (m, 5 H, CH_{Ar}), 6.99 (t, *J* = 7.5 Hz, 1 H, CH_{Ar}), 6.66 (s, 1 H, N*H*Boc), 5.78 (br s, 1 H), 5.34 (q, *J* = 7.8 Hz, 1 H, BocNHC*H*), 3.61 (s, 3 H, NCH_3), 3.54 (dd, *J* = 14.0, 5.4 Hz, 1 H, CHCH_2Trp), 3.40 (dd, *J* = 14.0, 9.4 Hz, 1 H, CHCH_2Trp), 3.20 (s, 3 H, NCH_3), 1.41 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.49, 155.36, 136.98, 135.32, 129.94, 128.10, 127.82, 122.78, 122.51, 121.83, 119.34, 118.98, 109.73, 109.41, 109.29, 79.99, 48.13, 32.82, 32.16, 29.75, 28.54.

HR-MALDI-MS (DHB): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{29}N_4O_2^+$: 405.22850; found: 405.22849.

Primary Amines 5a–h; General Procedure

The appropriate Boc derivative **4a–h** (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 collected by filtration and purified by silica gel column chromatography (EtOAc/CH_2Cl_2/MeOH, 1:1:0.2) to afford **5a–h** as a viscous oil or as a solid (36–61% yield).

(±)-1-(1-Methyl-1*H*-benzo[*d*]imidazol-2-yl)ethanamine (5a)

Synthesized from (±)-*N*-Boc-Ala BIM-*N*-Me **4a** (0.64 g, 2.3 mmol). Yellow oil; yield: 0.19 g (45%); $[\alpha]_D^{20}$ 0 (*c* 1, MeOH); R_f = 0.2.

IR (HATR): 3100, 3050, 2998, 1681, 1479, 1458, 1335, 1258, 1128, 742 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.73 (m, 1 H, CH_{Ar}), 7.22–7.32 (m, 3 H, CH_{Ar}), 4.33 (q, *J* = 6.7 Hz, 1 H, NH_2CH), 3.79 (s, 3 H, NCH_3), 1.57 (d, *J* = 6.7 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.09, 141.76, 136.06, 121.64, 121.19, 118.59, 109.79, 43.64, 29.62, 23.34, 23.04.

HR-MALDI-MS (DHB): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{14}N_3^+$: 176.11823; found: 176.11749.

(*R*)-1-(1-Methyl-1*H*-benzo[*d*]imidazol-2-yl)ethanamine (5b)

Synthesized from (*R*)-*N*-Boc-Ala BIM-*N*-Me **4b** (0.64 g, 2.3 mmol). Yellow oil; yield: 0.20 g (48%); $[\alpha]_D^{20}$ +4.0 (*c* 1, MeOH); R_f = 0.2.

IR (HATR): 3100, 3050, 2932, 1684, 1630, 1456, 1395, 1331, 740 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.61 (d, *J* = 7.4 Hz, 1 H, CH_{Ar}), 7.54 (d, *J* = 7.5 Hz, 1 H, CH_{Ar}), 7.18–7.27 (m, 2 H, CH_{Ar}), 4.33 (q, *J* = 6.7 Hz, 1 H, NH_2CH), 3.86 (s, 3 H, NCH_3), 1.49 (d, *J* = 6.5 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.91, 141.76, 136.06, 121.67, 121.22, 118.60, 109.82, 43.62, 29.63, 22.93.

HR-MALDI-MS (DHB): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{14}N_3^+$: 176.11823; found: 176.11766.

(*S*)-1-(1-Methyl-1*H*-benzo[*d*]imidazol-2-yl)ethanamine (5c)

Synthesized from (*S*)-*N*-Boc-Ala BIM-*N*-Me **4c** (0.64 g, 2.3 mmol). Yellow oil; yield: 0.18 g (45%); $[\alpha]_D^{20}$ –4.2 (*c* 1, MeOH); R_f = 0.2.

IR (HATR): 3100, 3030, 2933, 1680, 1457, 1335, 1128, 741 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.61 (d, *J* = 7.4 Hz, 1 H, CH_{Ar}), 7.54 (d, *J* = 7.4 Hz, 1 H, CH_{Ar}), 7.14–7.27 (m, 2 H, CH_{Ar}), 4.31 (q, *J* = 6.7 Hz, 1 H, NH_2CH), 3.86 (s, 3 H, NCH_3), 1.49 (d, *J* = 6.6 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.10, 141.75, 136.05, 121.61, 121.16, 118.57, 109.77, 43.63, 29.61, 23.05.

HR-MALDI-MS (DHB): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{14}N_3^+$: 176.11823; found: 176.11816.

(*S*)-2-Methyl-1-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)propan-1-amine (5d)

Synthesized from (*S*)-*N*-Boc-Val BIM-*N*-Me **4d** (0.70 g, 2.3 mmol). Yellow solid; yield: 0.29 g (61%); mp 80–82 °C; $[\alpha]_D^{20}$ –11.4 (*c* 1, MeOH); R_f = 0.3.

IR (HATR): 3060, 2961, 2860, 1683, 1612, 1467, 1200, 1126, 740 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.61 (d, *J* = 7.4 Hz, 1 H, CH_{Ar}), 7.55 (d, *J* = 7.7 Hz, 1 H, CH_{Ar}), 7.19–7.26 (m, 2 H, CH_{Ar}), 3.90 (d, *J* = 7.0 Hz, 1 H, NH_2CH), 3.84 (s, 3 H, NCH_3), 2.05–2.13 (m, 1 H, C*H*(CH_3)$_2$), 1.01 (d, *J* = 6.7 Hz, 3 H, CH_3), 0.88 (d, *J* = 6.7 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 158.25, 141.93, 135.75, 121.55, 121.28, 118.52, 109.97, 53.52, 33.33, 29.76, 19.87, 18.23.

HR-MALDI-MS (DHB): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{18}N_3^+$: 204.14952; found: 204.14897.

(*S*)-3-Methyl-1-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)butan-1-amine (5e)

Synthesized from (*S*)-*N*-Boc-Leu BIM-*N*-Me **4e** (0.73 g, 2.3 mmol). Viscous oil; yield: 0.20 g (39%); $[\alpha]_D^{20}$ –15 (*c* 1, MeOH); R_f = 0.2.

IR (HATR): 3040, 3030, 2958, 2810, 1678, 1454, 1201, 1133, 746 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.61 (d, *J* = 7.7 Hz, 1 H, CH_{Ar}), 7.55 (d, *J* = 7.9 Hz, 1 H, CH_{Ar}), 7.19–7.27 (m, 2 H, CH_{Ar}), 4.23 (t, *J* = 6.8 Hz, 1 H, NH_2CH), 3.86 (s, 3 H, NCH_3), 1.75 (m, 2 H, CH_2), 1.67 (m, 1 H, C*H*), 0.93 (d, *J* = 6.0 Hz, 6 H, CH(CH_3)$_2$).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 158.39, 141.86, 135.97, 121.79, 121.39, 118.63, 110.00, 46.14, 45.52, 29.75, 24.43, 23.06, 22.29.

HR-MALDI-MS (DHB): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{20}N_3^+$: 218.16517; found: 218.16497.

(1*S*,2*S*)-2-Methyl-1-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)butan-1-amine (5f)

Synthesized from (*S*,*S*)-*N*-Boc-Ile BIM-*N*-Me **4f** (0.73 g, 2.3 mmol). Viscous oil; yield: 0.18 g (36%); $[\alpha]_D^{20}$ –21.8 (*c* 1, MeOH); R_f = 0.2.

IR (HATR): 3330, 3250, 2965, 1678, 1558, 1471, 1202, 1180, 1130, 744, 721 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.62 (d, J = 7.0 Hz, 1 H, CH_{Ar}), 7.56 (d, J = 7.0 Hz, 1 H, CH_{Ar}), 7.20–7.55 (m, 2 H, CH_{Ar}), 4.03 (d, J = 7.6 Hz, 1 H, NH_2CH), 3.85 (s, 3 H, NCH_3), 1.90 (m, 1 H, CH), 1.19 and 1.75 (2 × m, 2 × 1 H, CH_2), 0.90 (t, J = 7.2 Hz, 3 H, CHCH_3), 0.85 (d, J = 6.4 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 157.67, 141.92, 135.68, 121.62, 121.35, 118.51, 110.02, 52.30, 39.92, 29.80, 24.06, 15.78, 11.20.

HR-MALDI-MS (DHB): m/z [M + H]$^+$ calcd for $C_{13}H_{20}N_3^+$: 218.16517; found: 218.16473.

(*S*)-1-(1-Methyl-1*H*-benzo[*d*]imidazol-2-yl)-2-phenylethanamine (5g)

Synthesized from (*S*)-*N*-Boc-Phe BIM-*N*-Me **4g** (0.81 g, 2.3 mmol). Oil; yield: 0.22 g (38%); $[\alpha]_D^{20}$ –6.2 (*c* 1, MeOH); 20% *ee*; R_f = 0.3.

IR (HATR): 3100, 3050, 2926, 1676, 1460, 1261, 1122, 733, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82–7.85 (m, 1 H, CH_{Ar}), 7.27–7.35 (m, 6 H, CH_{Ar}), 7.13–7.15 (m, 2 H, CH_{Ar}), 4.44 (t, J = 7.2 Hz, 1 H, NH_2CH), 3.45 (s, 3 H, NCH_3), 3.23–3.34 (m, 2 H, CHCH_2Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.04, 142.19, 137.79, 129.53, 128.84, 127.07, 122.71, 122.39, 119.56, 109.46, 50.96, 44.77, 29.58.

HR-MALDI-MS (DHB): m/z [M + H]$^+$ calcd for $C_{16}H_{18}N_3^+$: 252.14952; found: 252.14904.

(*S*)-1-(1-Methyl-1*H*-benzo[*d*]imidazol-2-yl)-2-(1-methyl-1*H*-indol-3-yl)ethanamine (5h)

Synthesized from (*S*)-*N*-Boc-1-MeTrp BIM-*N*-Me **4h** (0.94 g, 2.3 mmol). Yellow oil; yield: 0.38 g (53%); $[\alpha]_D^{20}$ –7.5 (*c* 1, MeOH); R_f = 0.2.

IR (HATR): 3070, 2924, 1612, 1520, 1470, 1326, 1123, 1006, 844, 738 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.80 (m, 1 H, CH_{Ar}), 7.53 (d, J = 7.8 Hz, 1 H, CH_{Ar}), 7.22–7.32 (m, 5 H, CH_{Ar}), 7.08 (t, J = 7.4 Hz, 1 H, CH_{Ar}), 6.86 (s, 1 H), 4.51 (t, J = 7.1 Hz, 1 H, NH_2CH), 3.73 (s, 3 H, NCH_3), 3.56 (s, 3 H, NCH_3), 3.45 (dd, J = 16.0, 7.1 Hz, 1 H, CHCH_2Trp), 3.35 (dd, J = 14.2, 8.2 Hz, 1 H, CHCH_2Trp).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.41, 142.13, 137.24, 135.90, 128.24, 127.91, 122.67, 122.34, 121.94, 119.58, 118.70, 110.08, 109.39, 109.04, 49.66, 33.92, 32.87, 31.94, 29.88.

HR-MALDI-MS (DHB): m/z [M + H]$^+$ calcd for $C_{19}H_{21}N_4^+$: 305.17783; found: 305.17652.

Aldol Reaction of Isatin with Ketones; General Procedure

A solution of catalyst **5a**–**f**,**h** (0.01 mmol) in acetone (**7**) or cyclohexanone (**9**) (1 mL) was treated with benzoic acid (0.03 mmol) at 5 °C, whereupon isatin (**11**) (0.015 g, 0.10 mmol) was added and the mixture was stirred for 96 or 108 h. The progress of the reaction was monitored by TLC. In the case of acetone, the remaining **7** was then removed in vacuo and the mixture was purified by silica gel column chromatography (EtOAc/hexane, 1:1) to afford aldol product **12** as a pale yellow solid; mp 170–172 °C. The crude mixture after reactions with cyclohexanone (**9**) was directly subjected to silica gel column chromatography (EtOAc/hexane, 1:1) to afford aldol product **13** as a pale yellow solid; mp 177–179 °C.

Aldol Product 12

The enantiomeric excess of compound **12** was determined by HPLC analysis (Daicel Chiralcel OJ-H column; flow 0.8 mL·min^{-1}; *n*-hexane/*i*-PrOH, 80:20): t_R = 24.6 (major), 22.0 (minor) min; 24% *ee* for the reaction catalyzed by **5f**. The absolute configuration of compound **12** was assigned by comparison of chiral-phase HPLC analyses with reported data.[27]

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.2 (s, 1 H), 7.28 (d, J = 7.4 Hz, 1 H), 7.22 (dt, J_t = 7.6 Hz, J_d = 1.3 Hz, 1 H), 6.95 (dt, J_t = 7.5 Hz, J_d = 1.0 Hz, 1 H), 6.82 (d, J = 7.6 Hz, 1 H), 6.03 (s, 1 H), 3.32 (d, J = 16.6 Hz, 1 H), 3.04 (d, J = 16.6 Hz, 1 H), 2.04 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 205.86, 178.81, 143.14, 132.12, 129.63, 124.30, 121.89, 110.07, 73.27, 50.86, 31.18.

HR-MALDI-MS (DHB): m/z [M + Na]$^+$ calcd for $C_{11}H_{11}NNaO_3^+$: 228.06311; found: 228.06326.

Aldol Product 13

The enantiomeric excess of product **13** was determined by HPLC analysis (Daicel Chiralcel OJ-H column; flow 0.8 mL·min^{-1}; *n*-hexane/*i*-PrOH, 85:15): t_R (major diastereoisomer) = 21.2 (major), 28.1 (minor) min; 71% *ee* for the reaction catalyzed by **5f**; t_R (minor diastereoisomer) = 16.7 (major), 18.6 (minor) min; 45% *ee* for the reaction catalyzed by **5f**.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.19 (s, 1 H), 7.12–7.20 (m, 1 H), 6.73–6.84 (m, 2 H), 5.81 (s, 1 H), 3.05 (dd, J = 13.2, 5.2 Hz, 1 H), 2.55–2.58 (m, 1 H), 2.25–2.31 (m, 1 H), 1.3–1.8 (m, 5 H), 1.23 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 209.75, 179.35, 144.06, 131.49, 129.22, 125.44, 121.46, 110.04, 74.50, 58.01, 42.11, 34.02, 27.27, 25.09, 24.66.

HR-MALDI-MS (DHB): m/z [M + Na]$^+$ calcd for $C_{14}H_{15}NNaO_3^+$: 268.09441; found: 268.09464.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588107.

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