Practical Proline-catalyzed asymmetric Mannich reaction of aldehydes with *N*-Boc-imines

Jung Woon Yang, Michael Stadler & Benjamin List

Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, 45470 Mülheim an der Ruhr, Germany. Correspondence should be addressed to B.L. (list@mpi-muelheim.mpg.de).

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This protocol describes a procedure for the synthesis of α, β-branched-b-amino aldehydes via Proline-catalyzed asymmetric Mannich reaction of aldehydes with *N-tert*–butoxycarbonyl-imines. The crystalline β-amino aldehydes are formed in good yields and extremely high levels of diastereo- and enantioselectivities without the need for chromatographic purification and are readily oxidized to the corresponding β-amino acids. The protocol can be completed in approximately 14 h on small scales or up to 30 h on larger scales.

INTRODUCTION

Enantiomerically pure β-amino carbonyl compounds such as β-amino acids and their derivatives are pharmaceutically highly relevant and versatile chiral building blocks for the synthesis of many nitrogen-containing, biologically important compounds[1]. One way to obtain these compounds is through the Mannich reaction[2–4]. Asymmetric Mannich-type reactions of imines with carbonyl compounds are amongst the most important C–C bond-forming reactions in organic synthesis. The first catalytic enantioselective Mannich-type reaction was discovered by Kobayashi *et al.*[5]. A direct Mannich reaction of unmodified ketones using a lanthanum catalyst was discovered in 1999 by Shibasaki and co-workers[6]. In 2000, we have discovered the Proline-catalyzed asymmetric Mannich reaction, which provides *syn*-β-amino ketones in good to excellent yields and high enantioselectivities from different ketones, aldehydes and amines[7–9]. (For the use of aldehyde nucleophiles with a preformed imine see ref. 8. For a three-component Mannich reaction using aldehyde nucleophiles, see ref. 9.) Originally, the Proline-catalyzed Mannich reaction required the use of anilines as the amine component. Since the N-substituent is usually employed as protecting group, it should be easily removable after the reaction has taken place. However, the removal of the most commonly used *p*-methoxyphenyl group from nitrogen often requires drastic oxidative conditions involving harmful reagents such as ceric ammonium nitrate that are not compatible with all substrates[10]. This results in a considerable limitation of the generality of the methodology. We have now employed the *tert*-butoxycarbonyl (Boc)-group as an easily removable protecting group

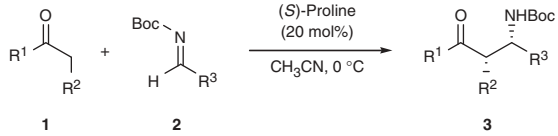

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Figure 1 | General reaction scheme of the Proline-catalyzed asymmetric Mannich-type reaction of aldehydes with *N*-Boc-imines. Boc, *tert*-butoxycarbonyl.

to overcome this drawback[11]. Independently, Enders reported Mannich reactions of one ketone with two *N*-Boc-imines[12,13].

We found the reaction of unmodified aldehydes and acetone with simple preformed aromatic *N*-Boc-imines to give chiral β-amino aldehydes and ketones in high levels of diastereo- and enantioselectivities (**Fig. 1**). Moreover, the products of the reaction either precipitate from the reaction mixture and can be collected *via* filtration or are obtained by an aqueous workup/organic extraction process as stable, crystalline solids. Purification can be achieved by trituration with cool hexanes.

As indicated by the data in **Table 1**, the reaction is highly diastereoselective giving *syn*-Mannich products with greater than 99:1 *syn* to *anti* selectivity and in 59–91% isolated yields for different imine substrates. The enantioselectivities are also remarkably high (greater than 99:1 *er*) over a range of imines including electron-poor and electron-rich imines.

When the benzaldehyde-derived *N*-Boc-imine **2a** (R^3 = Ph) was treated with a twofold excess of hexanal in the presence of 20 mol% (*S*)- Proline in acetonitrile (CH_3CN) at 0 °C, the desired product **3a**

TABLE 1 | Proline-catalyzed asymmetric Mannich reaction of aldehydes with *N-tert*-butoxycarbonyl-imines[a]

Entry	Mannich product	R^1	R^2	R^3	Yield (%)	Syn:anti	Enantiomeric ratio
1	3a	H	*n*-Bu	Ph	75	>99:1	>99:1[b]
2	3b	H	Me	Ph	91	>99:1	>99:1
3	3c	H	*i*-Pr	Ph	88	>99:1	>99:1
4	3d	H	*i*-Pr	4-MeO-C_6H_4	80	>99:1	>99:1
5	3e	H	*i*-Pr	4-Cl-C_6H_4	59	99:1	99:1
6	3f	H	*i*-Pr	2-Naphthyl	82	>99:1	>99:1[c]
7	3g[d]	H	*i*-Pr	2-Furyl	74	97:3	99:1
8	3h[e]	Me	H	Ph	73	—	>99:1

[a]Yields, diastereoselectivities and enantioselectivities of precipitated products. [b]Crude enantiomeric ratio (*er*) 99:1. [c]Crude *er* 96:4. [d]Product isolated by chromatography. [e]Reaction run at room temperature in acetone.

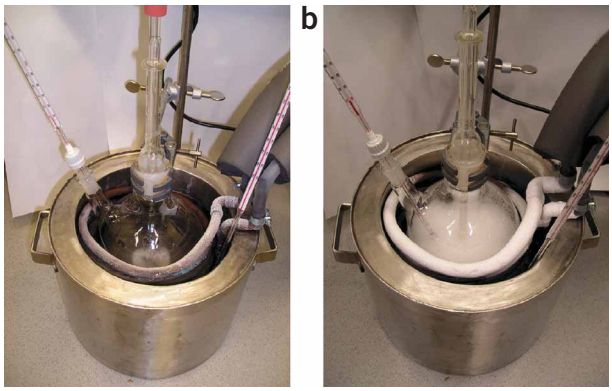


Figure 2 | The reaction setup of hexanal with benzaldehyde-derived *N*-Boc-imine **2a** in the presence of (*S*)-Pro (20 mol%) in acetonitrile. (**a**) Reaction mixture after mixing all compounds. (**b**) Reaction mixture after completion the reaction (24 h). Boc, *tert*-butoxycarbonyl.

precipitated and could be collected by filtration (**Fig. 2**) in 75% yield with extremely high diastereoselectivity (greater than 99:1 *dr*) and enantioselectivity (greater than 99:1 *er*) (**Table 1**, entry 1). Similarly, the reaction of the 2-naphthaldehyde-derived *N*-Boc-imine **2f** (R^3 = 2-naphthyl) with isovaleraldehyde resulted in the formation of the crystalline product **3f** with the same diastereoselectivity (greater than 99:1) and enantioselectivity (greater than 99:1) after precipitation (entry 6).

These selectivities are not entirely based on an enrichment during precipitation, since a sample obtained through aqueous/organic workup was analyzed to possess an *er* of 99:1. The reaction of the benzaldehyde-derived *N*-Boc-imine **2a** with propionaldehyde proceeded smoothly to afford the desired adduct in 91% yield with the same level of diastereoselectivity and enantioselectivity (entry 2). In this case, Mannich product **3b** did not precipitate, but its isolation was accomplished by the aqueous workup/organic extraction route (see Step 10B in the PROCEDURE). The residue was then triturated with cool hexanes to give the pure crystalline product. The Mannich products **3c**, **3d** and **3e** were also purified in a similar manner, giving excellent diastereoselectivities and enantioselectivities (entries 4 and 5). Furan-derived Mannich product **3g** was isolated by column chromatography (entry 7). Acetone was found to undergo the reaction with similar enantioselectivity. Treating the benzaldehyde-derived *N*-Boc-imine **2a** with (*S*)-Proline (20 mol%) in acetone gave the corresponding Mannich product **3h** in good yield and close to perfect enantioselectivity.

Conversion to the corresponding β-amino acid proceeds straightforwardly via oxidation and deprotection (**Fig. 3**)[14]. The procedure is not covered in this protocol.

The experimental procedure reported below details the synthesis of **3a** (entry 1 in **Table 1**) starting from the benzaldehyde-derived *N*-Boc-imine **2a** and hexanal. However, please note that the same procedure applies to the syntheses of all products designated as **3b–3h** in **Table 1** (see in particular alternative Steps 10A and B).

MATERIALS

REAGENTS

- (*S*)-Proline (Acros, cat. no. 15762)
- *N*-Boc imines **2a–2h** synthesized according to known methods[15–17]
- Hexanal (Avocado, cat. no. A16265) (see REAGENT SETUP)
- Isovaleraldehyde (Acros, cat. no. 16397) (see REAGENT SETUP)
- Propionaldehyde (Sigma-Aldrich, cat. no. 538124) (see REAGENT SETUP)
- Anhydrous CH_3CN (Fluka, cat. no. 00695)
- Hexane
- Ethyl acetate
- Diethyl ether
- Magnesium sulfate ($MgSO_4$)
- *p*-Anisaldehyde (for TLC stain)
- Acetic acid (for TLC stain)
- Concentrated sulfuric acid (for TLC stain)
- Optional: silica gel 60 (spherical, 40–63 μm; Merck, cat. no. 9385)
- Heptane and i-PrOH for HPLC analysis

EQUIPMENT

- 1 l-two-necked round-bottom flask
- Cooling circulator for 0 °C (Haake), big enough to cool a 1-l round bottom flask
- Mechanical stirrer
- Rotary evaporator (Büchi)
- 2-l beaker
- Büchner funnel
- Suction flask
- Filter papers
- Precoated plastic sheets for TLC (POLYGRAM SIL G/UV_{254}; Macherey-Nagel, ref. 805 021)
- Separatory funnels
- 50- or 100-ml round bottom flasks
- 250-ml brown glass jar with screw cap (for storing the TLC stain)
- Heat gun (Steinel HG 2000 E)
- Spatula
- High vacuum pump (for drying the products)
- Optional: column for chromatography
- ^{1}H-NMR and ^{13}C-NMR spectrometers
- HPLC apparatus (Shimadzu LC-2010C System)
- Chiral column (CHIRALPAK AS-H, Daicel)

REAGENT SETUP

Purify hexanal, isovaleraldehyde and propionaldehyde by distillation under argon atmosphere before use.

PROCEDURE

1| Weigh 10.26 g (50 mmol) benzaldehyde-derived *N*-Boc imine **2a** into a 1-l two-necked round bottom flask.

2| Dissolve the imine in 500 ml of anhydrous CH_3CN.

3| Add 12.4 ml (100 mmol) freshly distilled hexanal all at once.

4| Equip the flask with a mechanical stirrer and an internal thermometer. Make sure that the stirrer is thoroughly mixing the solution.

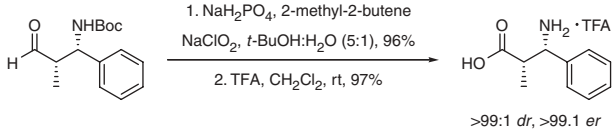


Figure 3 | Synthesis of α, β-branched-β-amino acid. Boc, *tert*-butoxycarbonyl.

BOX 1 | PREPARATION AND USE OF A *P*-ANISALDEHYDE STAIN FOR TLC VISUALIZATION

1. Fill a 250-ml, brown screw cap glass jar with a wide mouth with 100 ml acetic acid.
2. Add a magnetic stir bar and stir vigorously while adding 1 ml *p*-anisaldehyde.
3. Continue stirring and add 2 ml of concentrated sulfuric acid dropwise. Then stop the stirrer and cap the glass.

■ **PAUSE POINT**: The stain solution thus prepared has a shelf life of approximately 1 or 2 months.

4. To develop a TLC plate, submerge the plate in the stain using tweezers.
5. Remove excess liquid with a paper towel.
6. Gently heat the plate with a heat gun until the stains are developed.

Note: Acetic acid and especially concentrated sulfuric acid may cause severe burns upon contact with skin. Please make sure that you are working in a well-ventilated hood and that you are wearing a lab coat and eye protection.

5| The internal temperature of the flask is maintained at 0 °C using a cryostat (depending on your cooling equipment, it might be necessary to choose a slightly lower external temperature, e.g., −5 °C).

▲ **CRITICAL STEP** Given the propensity of its temperature to fluctuate, do not use an ice-bath for cooling. The temperature of 0 °C has to be maintained throughout the reaction as higher temperatures will lead to lower diastereoselectivity.

6| Weigh out 1.15 g (10 mmol) (*S*)-Proline onto a piece of weighing paper.

7| When the solution has reached an internal temperature of 0 °C, remove the thermometer and quickly add the Proline all at once using a funnel. Then re-equip with the thermometer. Proline is rather insoluble in CH_3CN, so you will initially observe a heterogeneous solution that will become homogenous within approximately 30 min of vigorous stirring.

■ **PAUSE POINT** The reaction mixture can be left stirring overnight at 0 °C.

8| Check the reaction progress by TLC (use a *p*-anisaldehyde stain as detailed in **Box 1** for visualization) or gas chromatography-mass spectrometry.

■ **PAUSE POINT** Let the reaction proceed for 8–12 h if it is carried out on a small scale (0.5 mmol). However, on 50 mmol scale, the reaction will take longer to complete and should be left to stir for 24 h. Please note that since the products are stable, prolonged reaction times are unproblematic.

9| Upon completion of the reaction, pour the reaction mixture into a 2-l beaker, containing approximately 1.5 l dH_2O. Use additional water to flush out the precipitated product from the flask. Please note that a precipitate will not necessarily form at this stage of the procedure if the desired product is other than **3a** (see INTRODUCTION).

10| For the isolation of the product, use method A in case the desired product precipitates as a solid, and method B if precipitation does not occur (as, e.g., when preparing product **3b**).

(A) Isolating precipitated product

(i) Equip a suction flask with a Büchner funnel and filter paper. Clamp the flask securely.
(ii) Attach the flask to an aspirator trap connected to an aspirator.
(iii) Wet the filter paper with a small volume of dH_2O. This should cause the filter paper to flatten snugly on the bottom of the funnel. Check to make sure that this occurs.
(iv) Without releasing suction, pour the mixture to be filtered into the funnel. The white solid is sucked as dry as possible before proceeding with Step 11.

(B) Isolating nonprecipitated product

(i) Transfer the water/CH_3CN solution into a suitably sized separation funnel.
(ii) Extract three times with diethyl ether (approximately 500 ml each time).
(iii) Combine the organic layers, and then wash once by extracting with a saturated aqueous solution of sodium chloride (approximately 500 ml).
(iv) To dry the organic fractions, add $MgSO_4$ and shake the flask. Repeat this until the added sulfate does not clump together any more, but is free-flowing. Then wait an additional 10–20 min, occasionally shaking the flask.
(v) Filter off the $MgSO_4$ and evaporate the solvent using a rotary evaporator (apply approximately 850 mbar and 40 °C to remove the ether, then lower the pressure to remove other volatile compounds), until you obtain a white solid.

11| Cool approximately 200 ml hexanes in an Erlenmeyer flask to between −60 and −70 °C using a cooling bath of dry ice/isopropyl alcohol.

12| Put the white solid obtained in Step 10 into a suitably big mortar and add the cool hexane. Triturate this mixture to make sure there is no impurity trapped inside clusters of product.

▲ CRITICAL STEP Work fast in this step, as the hexane will heat up, and this might result in lower yields due to the product partially dissolving in hexane.

13| Filter the mixture over a Büchner flask as described in Step 10A.

14| Repeat Steps 11–13 until TLC indicates pure Mannich product (usually, one repetition is enough). When the product is clean, proceed with Step 16. If you do not obtain satisfactory results, proceed with Step 15.

15| (Optional) Although purification is normally achieved using the method described above, in exceptional cases (such as preparation of compound **3g**), purification via chromatography is necessary. The following describes the chromatography performed on a 0.5 mmol scale of compound **3g**: (i) pack a column with an internal diameter of 1.5 cm with approximately 10 g silica gel, using ethyl acetate/hexane 20/80 vol/vol. (ii) Dissolve the compound in as little ethyl acetate/hexane 20/80 mixture as possible, and load the solution on top of the column. Cover the top with a layer of sea sand. (iii) Elute the column under a pressure of approximately 0.2 bar pressure with ethyl acetate/hexane 20/80 vol/vol. Collect samples of approximately 15 ml using test tubes. (iv) Identify the fractions containing the product by TLC, combine them and evaporate the solvent using a rotary evaporator at a bath temperature of 40 °C. At this temperature, hexane will evaporate at approximately 350 mbar, and ethyl acetate at 220 mbar.

16| Weigh out a round bottom flask, add the product, and dry under high vacuum until the weight is constant.
Note: Make sure to use a round bottom flask without scratches or cracks when working with high vacuum. The presence of these imperfections may cause the flask to implode when evacuated.
■ PAUSE POINT The reaction vessel can be left overnight under vacuum at room temperature (20–25 °C) to attain complete dryness of the product. The product can be stored in a fridge for several months without decomposition.

● TIMING
Steps 1–4, 30 min
Step 5, approximately 45 min
Steps 6–7, 5 min
Step 8, 8–24 h
Steps 9–14, 90 min
Step 15, 2 h
Step 16, 3 h to overnight

ANTICIPATED RESULTS

Analytical data

***tert*-Butyl (1*S*,2*S*)-2-formyl-1-phenylhexylcarbamate (3a in Table 1)**
mp: 139–140 °C; $[\alpha]^{20}_D$ −14.2 ($c = 1.01$, $CHCl_3$); (ethyl acetate:hexane 25:75 vol/vol): $R_f = 0.43$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (d, $J = 2.4$ Hz, 1H), 7.36-7.32 (m, 2H), 7.29-7.21 (m, 3H), 5.21-5.10 (m, 1H), 5.10-5.00 (m, 1H), 2.74-2.65 (m, 1H), 1.76-1.63 (m, 1H), 1.53-1.18 (m, 6H), 1.41 (s, 9H), 0.85 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.4, 154.7, 139.3, 128.4, 127.4, 126.5, 79.6, 56.4, 54.3, 29.2, 28.0, 24.9, 22.3, 13.4; HRMS (ESI) (*m/z*) [M+Na$^+$] calcd for $C_{18}H_{27}NO_3Na$ 328.188606, found 328.188316. The enantiomeric ratio was determined to be >99:1 by chiral HPLC (Chiralpak AS-H column, 2% *i*-PrOH/heptane, 0.50 ml min^{-1}, 220 nm, tR (minor 33.5 min), tR (major 44.1 min).

***tert*-Butyl (1*S*,2*S*)-2-methyl-3-oxo-1-phenylpropylcarbamate (3b)**
mp: 133–135 °C; $[\alpha]^{20}_D$ +11.5 ($c = 1.00$, $CHCl_3$); (ethyl acetate:hexane 15:85 vol/vol): $R_f = 0.33$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 7.37-7.24 (m, 5H), 5.16 (m, 2H), 2.86 (m, 1H), 1.41 (s, 9H), 1.07 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 155.1, 128.7, 127.6, 126.6, 80.0, 54.7, 51.5, 28.3, 9.2; HRMS (ESI) (*m/z*) [M+Na$^+$] calcd for $C_{15}H_{21}NO_3Na$ 286.141350, found 286.141365. The enantiomeric ratio was determined to be >99:1 by chiral HPLC (Chiralpak AS-H column, 2% *i*-PrOH/heptane, 0.50 ml min^{-1}, 220 nm, tR (minor 44.7 min), tR (major 60.5 min).

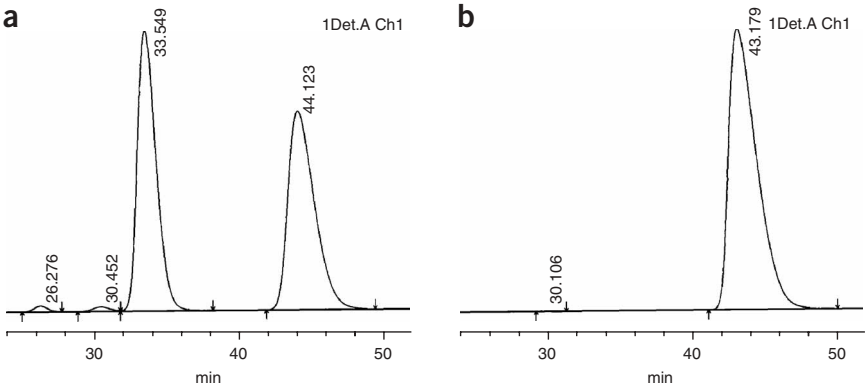
***tert*-Butyl (1*S*,2*S*)-2-formyl-3-methyl-1-phenylbutylcarbamate (3c)**
mp: 141–142 °C; $[\alpha]^{20}_D$ −70.9 ($c = 0.81$, $CHCl_3$); (ethyl acetate:hexane 15:85 vol/vol): $R_f = 0.45$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.49 (d, $J = 4.2$ Hz, 1H), 7.34-7.21 (m, 5H), 5.12 (brs, 2H), 2.53-2.47 (m, 1H), 2.14-2.08 (m, 1H), 1.40 (s, 9H), 1.13 (d, $J = 6.9$ Hz, 3H), 1.02 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 204.9, 154.9, 139.8, 128.8, 127.8, 127.2, 79.8, 65.8, 53.4, 28.3, 27.0, 21.2, 19.0; HRMS (ESI) (*m/z*) [M+Na$^+$] calcd for $C_{17}H_{25}NO_3Na$ 314.172600, found 314.172661. The enantiomeric ratio was determined to be >99:1 by chiral HPLC (Chiralpak AS-H column, 2% *i*-PrOH/heptane, 0.50 ml min^{-1}, 220 nm, tR (minor 33.4 min), tR (major 54.7 min).

***tert*-Butyl (1S,2S)-2-formyl-1-(4-methoxyphenyl)-3-methylbutylcarbamate (3d)**
mp: 151–152 °C; $[\alpha]^{20}_D$ −95.2 ($c = 1.01$, $CHCl_3$); (ethyl acetate:hexane 15:85 vol/vol): $R_f = 0.30$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.49 (d, $J = 4.2$ Hz, 1H), 7.15 (d, $J = 8.6$ Hz, 2H), 6.83 (d, $J = 8.6$ Hz, 2H), 5.06 (m, 2H), 3.77 (s, 1H), 2.50-2.44 (m, 1H), 2.13-2.07 (m, 1H), 1.40 (s, 9H), 1.11 (d, $J = 6.9$ Hz, 3H), 1.02 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 205.0, 159.1, 154.9, 131.9, 128.4, 114.1, 79.7, 62.1, 55.2, 52.8, 28.3, 27.1, 21.2, 18.9; HRMS (ESI) (*m/z*) [M+Na$^+$] calcd for $C_{18}H_{27}NO_4Na$ 344.183209, found 344.183224.

The enantiomeric ratio was determined to be >99:1 by chiral HPLC (Chiralpak AS-H column, 5% *i*-PrOH/heptane, 0.50 ml min^{-1}, 220 nm, tR (minor 28.2 min), tR (major 58.4 min).

tert-Butyl (1S,2S)-1-(4-chlorophenyl)-2-formyl-3-methylbutylcarbamate (3e)

mp: 137–140 °C; $[\alpha]^{20}_D$ −90.5 (c = 1.04, $CHCl_3$); (ethyl acetate:hexane 15:85 vol/vol): R_f = 0.42; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (d, J = 3.9 Hz, 1H), 7.23-7.09 (m, 4H), 5.02-4.98 (m, 2H), 2.44-2.39 (m, 1H), 2.04-2.02 (m, 1H), 1.32 (s, 9H), 1.06 (d, J = 6.9 Hz, 3H), 0.94 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.2, 154.4, 138.2, 133.2, 128.5, 128.2, 61.4, 52.5, 27.9, 26.6, 20.8, 18.7; HRMS (ESI) (m/z) [M+Na^+] calcd for $C_{17}H_{24}ClNO_3Na$ 348.133388, found 348.133693. The enantiomeric ratio was determined to be 98.5:1.5 by chiral HPLC (Chiralpak AS-H column, 7% *i*-PrOH/heptane, 0.50 ml min^{-1}, 220 nm, tR (minor 16.1 min), tR (major 28.7 min).



Detector A Ch1 220 nm

Peak #	Ret. time	Area %
1	26.276	0.733
2	30.452	0.722
3	33.549	49.207
4	44.123	49.338
Total		100.000

Detector A Ch1 220 nm

Peak #	Ret. time	Area %
1	30.106	0.060
2	43.179	99.940
Total		100.000

Figure 4 | HPLC chromatograms. (**a**) The racemic compound and (**b**) the enantiopure compound (Chiralpak AS-H column, 2% *i*-PrOH/heptane, 0.50 ml min^{-1}, 220 nm).

tert-Butyl (1S,2S)-2-formyl-3-methyl-1-(naphthalen-2-yl)butylcarbamate (3f)

mp: 177–180 °C (decomp.); $[\alpha]^{20}_D$ −81.8 (c = 1.02, $CHCl_3$); (ethyl acetate:hexane 25:75 vol/vol) R_f = 0.36; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.54 (d, J = 4.1 Hz, 1H), 7.84-7.77 (m, 3H), 7.70 (brs, 1H), 7.51-7.43 (m, 2H), 7.35 (dd, J = 8.3, 1.5 Hz, 1H), 5.35-5.10 (m, 2H), 2.65-2.55 (m, 1H), 2.25-2.10 (m, 1H), 1.40 (s, 9H), 1.17 (d, J = 6.9 Hz), 1.04 (d, J = 6.9 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 204.9, 155.0, 137.3, 133.2, 132.9, 128.8, 128.0, 127.6, 126.4, 126.3, 126.2, 125.0, 79.9, 62.0, 53.6, 28.3, 27.1, 21.3, 19.1; HRMS (ESI) (m/z) [M+Na^+] calcd for $C_{21}H_{27}NO_3Na$ 364.188025, found 364.188315. The enantiomeric ratio was determined to be >99:1 by chiral HPLC (Chiralpak AS-H column, 2% *i*-PrOH/heptane, 0.50 ml min^{-1}, 220 nm, tR (minor 37.5 min), tR (major 73.8 min).

tert-Butyl (1S,2S)-2-formyl-1-(furan-2-yl)-3-methylbutylcarbamate (3g)

mp: 62–64 °C; $[\alpha]^{20}_D$ −104.1 (c = 1.01, $CHCl_3$); (ethyl acetate:hexane 25:75 vol/vol) R_f = 0.40; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.60 (d, J = 3.9 Hz, 1H), 7.32 (dd, J = 1.9, 0.8 Hz, 1H), 6.29 (dd, 3.4, 1.9 Hz, 1H), 6.25-6.21 (m, 1H), 5.24-5.06 (m, 2H), 2.50-2.39 (m, 1H), 2.07-1.90 (m, 1H), 1.43 (s, 9H), 1.06 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 205.0, 155.1, 152.4, 142.5, 110.8, 108.2, 80.4, 61.4, 47.9, 28.7, 26.9, 20.8, 20.3; HRMS (ESI) (m/z) [M+Na^+] calcd for $C_{15}H_{23}NO_4Na$ 304.151806, found 304.151928. The enantiomeric ratio was determined to be 99:1 by chiral HPLC (Chiralpak AS-H column, 3% *i*-PrOH/heptane, 0.50 ml min^{-1}, 220 nm, tR (minor 22.4 min), tR (major 39.7 min).

(*S*)-*tert*-Butyl 3-oxo-1-phenylbutylcarbamate (3h)

mp: 106–107 °C; $[\alpha]^{20}_D$ −23.8 (c = 1.02, $CHCl_3$); (15:85 ethyl acetate:hexane vol/vol) R_f = 0.20; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.22 (m, 5H), 5.42 (m, 1H), 5.07 (m, 1H), 5.06 (m, 2H), 3.03 (dd, J = 14.9, 3.2 Hz, 1H), 2.90 (dd, J = 16.2, 4.5 Hz, 1H), 2.08 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 206.5, 154.7, 141.1, 128.2, 127.0, 125.8, 79.3, 50.7, 48.9, 30.2, 27.9; HRMS (ESI) (m/z) [M+Na^+] calcd for $C_{15}H_{21}NO_3Na$ 286.141260, found 286.141359. The enantiomeric ratio was determined to be >99:1 by chiral HPLC (Chiralpak AS-H column, 10% *i*-PrOH/heptane, 0.50 ml min^{-1}, 220 nm, tR (minor 20.5 min), tR (major 27.1 min).

HPLC data

Analytical data for racemic and enantiopure compounds **3a** are given in **Figure 4**.

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