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Asymmetric amination of α,α -dialkyl substituted aldehydes catalyzed by a simple chiral primary amino acid and its application to the preparation of a S1P₁ agonist†

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The chiral catalytic amination of an α,α -dialkyl substituted aldehyde usually proceeds with low enantioselectivity. We selected naphthyl-L-alanine as the catalyst and observed improved enantioselectivity for the amination. Using this method, racemic α -methyl- α -benzyloxypropanal was aminated to give chiral serine derivatives in 74% ee, which was further increased to >99% ee after recrystallization. Moreover, we also successfully synthesized a chiral phosphonium salt **9** for the preparation of one α -substituted alaninol compound **14** as an S1P₁ agonist in high overall yield.

Introduction

α,α -Disubstituted amino alcohols, aldehydes and acids are important chiral building blocks in organic synthesis. They are routinely found in a number of peptides,^{1–5} natural products^{6,7} and pharmaceuticals.^{8,9} Due to this importance, their synthesis has attracted sustained interest from the synthetic community. Existing methods for the asymmetric approach to scaffolds include classical Seebach's method,^{10,11} auxiliary Strecker synthesis,¹² and a variety of asymmetric phase transfer catalysis reactions.¹³

Recently, several methods have been reported describing the asymmetric Michael α -amination of achiral aldehydes *via* proline catalysis, resulting in the products being obtained in good yields and excellent enantioselectivities.^{14–17} However, these proline catalysts do not imbue high enantioselectivities in the amination of branched aldehydes. Wang *et al.* reported that 3-(1-naphthyl)-L-alanine (**1d**) successfully promoted the enantioselective α -amination of branched aldehydes with azidocarboxylates to give α -alkyl- α -aryl disubstituted aldehydes in up to 99% ee.¹⁸ However, low enantioselectivities only 4–28% ee were obtained with α -alkyl- α -alkyl disubstituted, potentially owing to poor stereo-differentiation between the two α -substituents.¹⁴ To some extent, the application of this kind of reaction is limited. In 2005, Barbas *et al.* reported higher

stereoselectivities were possible utilizing proline derived tetrazole catalyst (**1b**) for the amination of α -alkyl- α -benzyl disubstituted aldehydes.¹⁹ In addition, no further progress about the asymmetric amination of α -alkyl- α -alkyl disubstituted aldehydes had been reported.

Results and discussion

Herein, we report the asymmetric Machel α -amination of α -methyl- α -protected hydroxymethyl aldehydes and their subsequent reduction and cyclisation to afford oxazolidinones in good ee. We initially chose 3-(benzyloxy)-2-methylpropanal and dibenzyl azodicarboxylate (DBAD) as a model substrate to determine to optimal reaction conditions. When L-proline (**1a**) (30 mol%) was used,¹⁴ the reaction was complete in 48 hours at room temperature and provided the amino aldehyde in 56% yield, however we obtained poor enantioselectivities (32% ee). To improve the enantioselectivity, we screened a number of catalysts (Fig. 1). For example, tetrazole catalyst (**1b**) (15 mol%) in CH₃CN provided 42% ee with 68% yield (Table 1, entry 2).¹⁷ 3-(1-Naphthyl)-L-alanine catalyst (**1d**) (15 mol%) in CH₃CN gave the amino aldehyde in 70% yield with 46% ee (Table 1, entry 4).¹⁸

We then turned our attention to the effects of solvents on both yield and enantioselectivities (Table 2). Among them, dioxane, MeOH, MTBE and THF (entries 9, 10, 7 and 8) were all tolerated and produce the desired oxazolidinones in moderate

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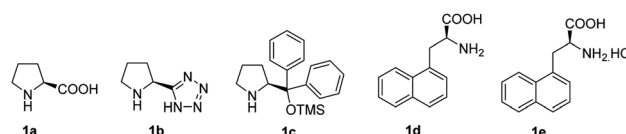
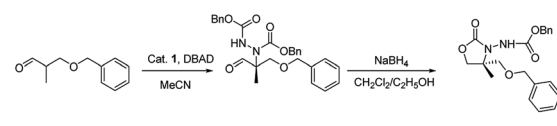


Fig. 1 Chiral catalysts.



Table 1 Screening of chiral catalysts^a


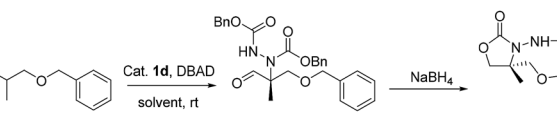
| Entry | Catalyst | Time (h) | Yield ^b (%) | ee ^c (%) |
|-------|-----------|----------|------------------------|---------------------|
| 1 | 1a | 48 | 56 | 32 |
| 2 | 1b | 12 | 68 | 42 |
| 3 | 1c | 24 | 45 | 34 ^d |
| 4 | 1d | 24 | 70 | 46 |
| 5 | 1e | 24 | 53 | 44 |

^a All reactions were carried out with aldehyde (0.75 mmol), DBAD (0.5 mmol), catalyst (15 mol%) in THF solvent (4 mL) at rt under argon, subsequent reduction and cyclisation to the oxazolidinone. ^b Isolated yield. ^c Determined by HPLC with a Chiralpak-OD column. ^d With the opposite enantiomer.

to good enantioselectivities. Of particular note, THF delivered the highest enantioselectivity (69% ee) in synthetically useful yields.

Furthermore, when lowering temperature to 0 °C, we observed no improvement in enantioselectivity, however the reaction became notably more sluggish. Increasing catalyst loading up to 30 mol% did not improve either enantioselectivity or reaction time.

With these optimized conditions in hand, we probed the substrate scope of the reaction (Table 3). In general, various oxazolidinones **5** were obtained in moderate to good yields (54–89%) and enantioselectivities (24–73% ee). The reactions showed poor enantioselectivities for α -methyl- α -ethyl and α -methyl- α -carbomethoxy disubstituted aldehydes, but not for α -

Table 2 Screening of solvents^a


| Entry | Solvent | Time | Yield ^b (%) | ee ^c (%) |
|-------|---|------|------------------------|---------------------|
| 1 | <i>n</i> -Hexane | 24 | 52 | 48 |
| 2 | Toluene | 72 | 49 | 45 |
| 3 | CH ₂ Cl ₂ | 72 | 41 | 30 |
| 4 | EtOAc | 24 | 67 | 54 |
| 5 | CH ₃ OCH ₂ CH ₂ OCH ₃ | 36 | 47 | 40 |
| 7 | MTBE | 36 | 84 | 49 |
| 8 | THF | 36 | 81 | 69 |
| 9 | Dioxane | 36 | 76 | 57 |
| 10 | MeOH | 24 | 69 | 57 |
| 11 | Ethylene glycol | 24 | 42 | 57 |

^a Reaction conditions: the azodicarboxylate (1 equiv.) was added to the aldehyde (1.5 equiv.), with catalyst (15 mol%) in THF at rt for the stated period of time under argon. Reaction without isolation of intermediate. ^b Isolated yield. ^c Determined by chiral HPLC.

methyl- α -protected hydroxymethyl substituted aldehydes with aromatic ring. The results also showed that electron-withdrawing groups were more successful than electron-donating groups. Moreover, *p*-F and *p*-CF₃ substituents both showed similar enantioselectivities. We then investigated differing azodicarboxylates and observed that di-*p*-chlorobenzyl azodicarboxylate (DCAD) provided the desired products in excellent yields (90%) and good enantioselectivities (up to ee 74%) while lower enantioselectivities were obtained with diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD). We also observed good enantioselective control with catalysts bearing naphthalene rings. This may be due to the π - π interaction between the aromatic ring of substrate and naphthalene ring limiting the conformation of the intermediate, thus improving the level of stereo-differentiation between the two α -substituents. Additionally, when the azo reagent contained an aromatic ring this π - π interaction may be further enhanced, resulting in the observed improvement of stereoselectivity.

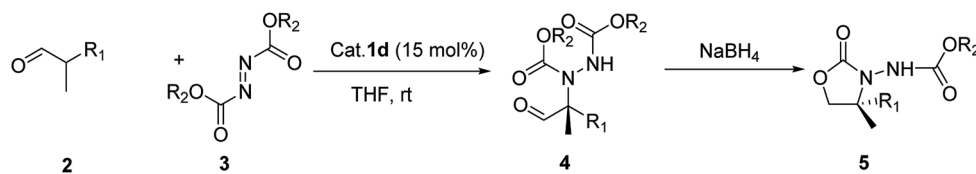
Upon recrystallization from 90% ethanol, the aldehyde **4a-p-ClBn** was obtained in 97% ee (60% yield) and **4h-p-ClBn** was obtained in 97% ee (65% yield), which was subsequently converted to oxazolidinone **5a-p-ClBn** in >99% ee and **5h-p-ClBn** was obtained in 98% ee respectively. The absolute configuration of **5-R** was determined to be (*R*) on CD spectrum. Under ambient pressure, hydrogenation using 10% Pd/C in methanol/acetic acid, the benzyloxycarbonyl group was removed. Cleavage of the hydrazine moiety, **7** was accomplished by treating with NaNO₂ (ref. 14) (Scheme 1). Alcohol **7** was treated with *p*-TsCl in pyridine, and the resulting tosylate was successively converted to iodide **8** with NaI in acetone under a reflux condition.²⁰ **8** with triphenylphosphine in DMF provided the desired phosphonium salt **9** in moderate yield as a stable white solid.²⁰

Then we applied the chiral phosphonium salt **9** to the synthesis of biological active compound as S1P₁ agonist **14**. These types of compounds possessing a chiral 2-methyl-2-aminoethanol have shown promise in recent years as the immunosuppressant.^{21,22} This compound is an analogue of SYL930, an immunosuppressant we have been reported before.²³ SYL930 is currently in phase I clinical stage. The synthesis of **14** started from the aldehyde **11** in only a three step manipulation.²⁴ Aldehyde **11** was synthesized in good yield from 4-bromobenzaldehyde and binary pinacol borate ester **10** via Suzuki reaction with Pd-dimer (dibromobis(tri-*tert*-butylphosphine)dipalladium) as the catalyst.²⁴ The Wittig reaction of **9** with **11** in dry THF at –78 °C for 3 h furnished the alkenes **12** in good yield. Subsequently reducing with 10% Pd/C in MeOH for 1 h afforded compound **13** in virtually quantitative yield after a flash-filtration. Finally, hydrolysis of the oxazolidinone part and then acidification with 1 M HCl in Et₂O produced the chiral α -substituted alaninol compound **14**.

Conclusions

In this study, we presented an efficient asymmetric amination of branched racemic aldehydes catalyzed by the commercially available amino acid (3-(1-naphthyl)-L-alanine). Under the



Table 3 Substrate scope^a

| Entry | R ₁ | R ₂ | Product | Time (h) | Yield ^b (%) | ee ^c (%) | ee ^e (%) |
|-------|--|----------------|-------------------------|----------|------------------------|---------------------|---------------------|
| 1 | BnOCH ₂ | Et | 5a-Et | 38 | 79 | 57 | — |
| 2 | BnOCH ₂ | Bn | 5a-Bn | 36 | 81 | 69 | — |
| 3 | BnOCH ₂ | <i>p</i> -ClBn | 4a-<i>p</i>-ClBn | 48 | 80 | 71 ^d | 97% |
| 4 | BnOCH ₂ | <i>p</i> -ClBn | 5a-<i>p</i>-ClBn | 1 | 94 | 72 | >99% |
| 5 | <i>p</i> -CH ₃ BnOCH ₂ | Bn | 5b-Bn | 38 | 54 | 48 | — |
| 6 | <i>p</i> -CH ₃ BnOCH ₂ | <i>p</i> -ClBn | 5b-<i>p</i>-ClBn | 36 | 56 | 54 | — |
| 7 | 3,4-DiMeOBnOCH ₂ | Et | 5c-Et | 38 | 78 | 38 | — |
| 8 | 3,4-DiMeOBnOCH ₂ | Bn | 5c-Bn | 36 | 67 | 45 | — |
| 9 | <i>p</i> -FBnOCH ₂ | Et | 5d-Et | 37 | 75 | 56 | — |
| 10 | <i>p</i> -FBnOCH ₂ | Bn | 5d-Bn | 36 | 80 | 68 | — |
| 11 | <i>p</i> -FBnOCH ₂ | <i>p</i> -ClBn | 5d-<i>p</i>-ClBn | 48 | 89 | 70 | — |
| 12 | <i>p</i> -ClBnOCH ₂ | Et | 5e-Et | 39 | 70 | 57 | — |
| 13 | <i>p</i> -ClBnOCH ₂ | Bn | 5e-Bn | 36 | 63 | 59 | — |
| 14 | <i>p</i> -BrBnOCH ₂ | Bn | 5f-Bn | 38 | 79 | 59 | — |
| 15 | <i>p</i> -BrBnOCH ₂ | <i>p</i> -ClBn | 5f-<i>p</i>-ClBn | 48 | 75 | 52 | — |
| 16 | <i>p</i> -CNBnOCH ₂ | Et | 5g-Et | 28 | 81 | 57 | — |
| 17 | <i>p</i> -CNBnOCH ₂ | Bn | 5g-Bn | 24 | 71 | 65 | — |
| 18 | <i>p</i> -CNBnOCH ₂ | <i>p</i> -ClBn | 5g-<i>p</i>-ClBn | 48 | 73 | 62 | — |
| 19 | <i>p</i> -CF ₃ BnOCH ₂ | Et | 5h-Et | 39 | 76 | 56 | — |
| 20 | <i>p</i> -CF ₃ BnOCH ₂ | Bn | 5h-Bn | 36 | 89 | 67 | — |
| 21 | <i>p</i> -CF ₃ BnOCH ₂ | <i>p</i> -ClBn | 4h-<i>p</i>-ClBn | 48 | 90 | 74 ^d | 97% |
| 22 | <i>p</i> -CF ₃ BnOCH ₂ | <i>p</i> -ClBn | 5h-<i>p</i>-ClBn | 1 | 95 | 73 | 98% |
| 23 | <i>p</i> -NO ₂ BnOCH ₂ | Bn | 5i-Bn | 48 | 77 | 55 | — |
| 24 | THPOCH ₂ | Bn | 5j-Bn | 48 | 70 | 57 | — |
| 25 | TrtOCH ₂ | Bn | 5k-Bn | 48 | — | — | — |
| 26 | Et | Bn | 5l-Bn | 48 | 78 | 37 | — |
| 27 | CO ₂ Et | Bn | 4m-Bn | 48 | 76 | 24 | — |

^a Reaction conditions: the azodicarboxylate (1 equiv.) was added to the aldehyde (1.5 equiv.), with catalyst (15 mol%) in THF at rt for the stated period of time under argon. Reaction performed without isolating the intermediate. ^b Isolated yield. ^c Isolated by silica gel column chromatography. ^d Determined by chiral HPLC. ^e ee determined by chiral HPLC after recrystallization. Absolute configuration of **5-R** to determined be (*R*) on CD spectrum.

optimized conditions, we obtained α -methyl- α -protected hydroxymethyl substituted aldehydes in high ee. Importantly, we developed an efficient catalytic method for synthesizing the Wittig reagent involving a chiral 2-methyl-2-aminoethanol structure that could be applied to other syntheses. Further, a new S1P₁ agonist **14** has been obtained by this method in high overall yield.

Experimental

General procedure for the synthesis of 4,4-disubstituted 3-alkoxycarbonylamino-oxazolidin-2-ones (**5-R**) by one pot method

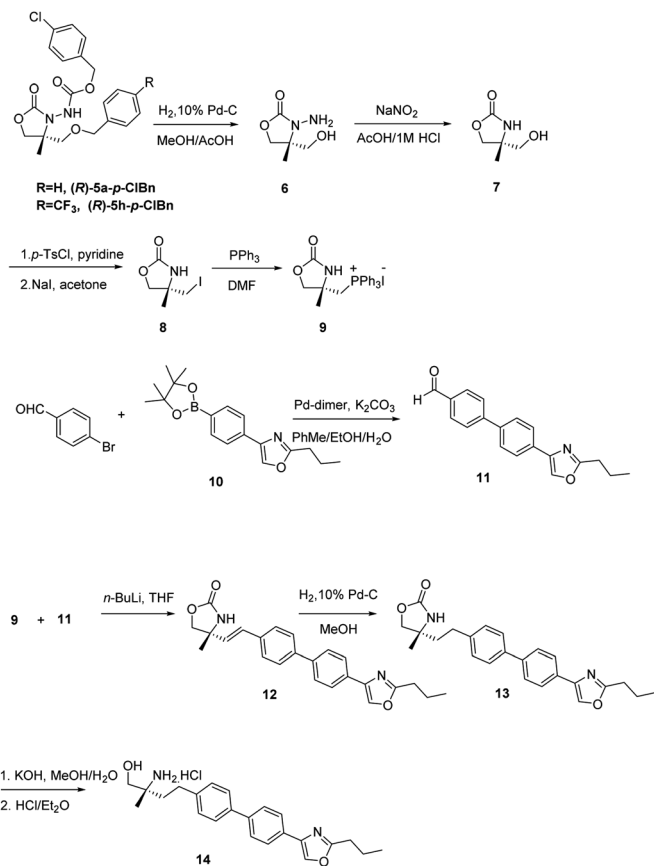
Catalyst **1d** (15 mol% in respect to the azodicarboxylate) was added to a suspension of aldehydes (**2**, 1.5 eq. in respect to the azodicarboxylate) and azodicarboxylate (**3**) in THF. The mixture stirred at rt under argon until the colour of the azodicarboxylate

had disappeared. NaBH₄ (3 eq. in respect to the azodicarboxylate) was added in portions at room temperature. The reaction mixture was stirred for 1 h, and then it was quenched by adding 1 M HCl aq. until the mixture reached pH 7, and it was extracted with CH₂Cl₂. The combined organic phases were dried over Na₂SO₄, and the solvent was evaporated under reduced pressure. The resulting crude was purified by flash chromatography on silica gel eluted with light petroleum ether–ethyl acetate mixture (4 : 1 v/v) to afford products **5-R** as oil or solid.

3-Ethoxycarbonylamino-4-methyl-4-benzyloxy-oxazolidin-2-one (**5a-Et**)

White solid, yield 79%; mp 50–55 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.24 (m, 6H, 2CH₃), 3.27 (d, 1H, *J* = 8.0 Hz, CH), 3.47 (d, 1H, *J* = 12.0 Hz, CH), 4.05 (d, 1H, *J* = 12.0 Hz, CH), 4.14 (q, 2H, *J* = 4.0 Hz, CH₂), 4.33 (d, 1H, *J* = 8.0 Hz, CH), 4.51 (s, 2H, CH₂), 6.33 (bs, 1H, NH), 7.27–7.38 (m, 5H, H_{ar}); ¹³C NMR (100 MHz, CDCl₃) δ 14.3, 19.8,





Scheme 1 Synthesis of the α -substituted alaninol compound as S1P₁ agonist.

29.7, 61.2, 62.5, 71.4, 71.8, 73.2, 127.8, 128.1, 128.7, 137.4, 156.3, 156.7; HRMS calcd for C₁₅H₂₁N₂O₅ [M + H]⁺ 309.1445, found 309.1442; HPLC (Daicel Chiralpak OD-H, hexane/isopropanol = 90 : 10, flow rate 1.0 mL min⁻¹, λ = 254 nm): t_R = 16.37 min (major), t_R = 20.63 min (minor), 57% ee.

3-Benzoyloxycarbonylamino-4-methyl-4-benzyloxy-oxazolidin-2-one (5a-Bn)

Oil, yield 81%; ¹H NMR (400 MHz, CDCl₃) δ 1.26 (s, 3H, CH₃), 3.27 (d, 1H, *J* = 12.0 Hz, CH), 3.44 (d, 1H, *J* = 12.0 Hz, CH), 4.06 (d, 1H, *J* = 12.0 Hz, CH), 4.32 (d, 1H, *J* = 12.0 Hz, CH), 4.46 (s, 2H, CH₂), 5.14 (s, 2H, CH₂), 6.38 (bs, 1H, NH), 7.24–7.35 (m, 10H, H_{ar}); ¹³C NMR (100 MHz, CDCl₃) δ 19.8, 61.2, 68.1, 71.4, 71.7, 73.2, 127.8, 128.2, 128.3, 128.5, 128.6, 128.7, 135.3, 127.3, 156.1, 156.7; HRMS calcd for C₂₀H₂₃N₂O₅ [M + H]⁺ 371.1602, found 371.1591; HPLC (Daicel Chiralpak OD, hexane/isopropanol = 90 : 10, flow rate 1.0 mL min⁻¹, λ = 254 nm): t_R = 17.15 min (major), t_R = 25.28 min (minor) 69% ee.

3-(4-Chloro)benzyloxycarbonylamino-4-methyl-4-benzyloxy-oxazolidin-2-one (5a-*p*-ClBn)

Catalyst **1d** (64 mg, 15 mol% in respect to the azodicarboxylate) was added to a suspension of 3-(benzyloxy)-2-methylpropanal (1.15 g, 6.46 mmol) and di-*p*-chlorobenzyl azodicarboxylate (1.58 g, 4.31

mmol) in THF (40 mL). The mixture stirred at rt under argon until the colour of the azodicarboxylate had disappeared and quenched by the addition H₂O, then extracted three times with Et₂O (50 mL \times 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. The resulting crude was purified by flash chromatography on silica gel, eluting with light petroleum ether–ethyl acetate mixture (4 : 1 v/v) to afford **4a-*p*-ClBn** (1.87 g) as solid in 80% yield with 71% ee. Recrystallization from 90% ethanol, the aldehyde **4a-*p*-ClBn** (930 mg) was obtained in 97% ee (50% yield). [α]_D²⁰ 9.72 (*c* 0.29, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 1.34 (s, 3H, CH₃), 3.60–3.77 (m, 2H, CH₂), 4.42 (s, 2H, CH₂), 5.01–5.15 (m, 4H, 2CH₂), 6.70 (s, 1H, NH), 7.16–7.30 (m, 13H, H_{ar}), 9.55 (s, 1H, CHO); HRMS calcd for C₂₇H₂₇N₂O₆Cl₂ [M + H]⁺ 545.12407, found 545.12390; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 85 : 15, flow rate 1.0 mL min⁻¹, λ = 213 nm): t_R = 21.62 min (major), t_R = 23.77 min (minor).

NaBH₄ (190 mg, 5.0 mmol) was added to a solution of **4a-*p*-ClBn** (900 mg, 1.65 mmol) in CH₂Cl₂/C₂H₅OH (4 mL). The reaction mixture was stirred for 1 h, and then it was quenched by adding 1 M HCl aq. until the mixture reached pH 7, and it was extracted with CH₂Cl₂. The combined organic phases were dried over Na₂SO₄, and the solvent was evaporated under reduced pressure. The resulting crude was purified by flash chromatography on silica gel eluted with light petroleum ether–ethyl acetate mixture (4 : 1 v/v) to afford **5a-*p*-ClBn** (650 mg) in 94% yield with >99% ee. As oil; [α]_D²⁰ -12.3 (*c* 0.13, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 1.24 (s, 3H, CH₃), 3.26 (d, 1H, *J* = 8.0 Hz, CH), 3.43 (d, 1H, *J* = 12.0 Hz, CH), 4.05 (d, 1H, *J* = 8.0 Hz, CH), 4.32 (d, 1H, *J* = 8.0 Hz, CH), 4.49 (s, 2H, CH₂), 5.06 (s, 2H, CH₂), 6.49 (bs, 1H, NH), 7.24–7.36 (m, 10H, H_{ar}); ¹³C NMR (100 MHz, CDCl₃) δ 19.8, 61.2, 67.2, 71.4, 71.7, 73.2, 127.8, 128.2, 128.5, 128.7, 128.8, 129.6, 134.0, 134.3, 137.3, 156.0, 156.7; HRMS calcd for C₂₀H₂₂N₂O₅Cl [M + H]⁺ 405.1212, found 405.1204; HPLC (Daicel Chiralpak OD-H, hexane/isopropanol = 90 : 10, flow rate 1.0 mL min⁻¹, λ = 213 nm): t_R = 27.77 min (major), t_R = 35.0 min (minor).

3-(4-Chloro)benzyloxycarbonylamino-4-methyl-4-(4-methyl)benzyloxy-oxazolidin-2-one (5b-Bn)

Oil, yield 54%; ¹H NMR (400 MHz, CDCl₃) δ 1.24 (s, 3H, CH₃), 2.29 (s, 3H, CH₃), 3.24 (d, 1H, *J* = 12.0 Hz, CH), 3.40 (d, 1H, *J* = 12.0 Hz, CH), 3.99 (d, 1H, *J* = 8.0 Hz, CH), 4.31 (d, 1H, *J* = 8.0 Hz, CH), 4.40–4.48 (m, 2H, CH₂), 5.12 (s, 2H, CH₂), 6.39 (bs, 1H, NH), 7.13–7.18 (m, 4H, H_{ar}), 7.31–7.37 (m, 5H, H_{ar}); ¹³C NMR (100 MHz, CDCl₃) δ 19.8, 21.2, 61.2, 68.0, 71.3, 71.4, 73.0, 73.1, 128.1, 128.2, 128.5, 128.6, 129.2, 129.4, 134.3, 135.4, 138.0, 156.2, 156.7; HRMS calcd for C₂₁H₂₅N₂O₅ [M + H]⁺ 385.1758, found 385.1738; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 90 : 10, flow rate 1.0 mL min⁻¹, λ = 254 nm): t_R = 22.42 min (major), t_R = 25.10 min (minor), 48% ee.

3-(4-Chloro)benzyloxycarbonylamino-4-methyl-4-(4-methyl)benzyloxy-oxazolidin-2-one (5b-*p*-ClBn)

Oil, yield 56%; ¹H NMR (400 MHz, CDCl₃) δ 1.23 (s, 3H, CH₃), 2.30 (s, 3H, CH₃), 3.24 (d, 1H, *J* = 12.0 Hz, CH), 3.39 (d, 1H, *J* = 12.0 Hz, CH), 4.04 (d, 1H, *J* = 8.0 Hz, CH), 4.31 (d, 1H, *J* = 12.0 Hz, CH), 4.39–4.49 (m, 2H, CH₂), 5.08 (s, 2H, CH₂), 6.22 (bs, 1H, NH), 7.13–7.16 (m,



4H, H_{ar}), 7.26 (d, 2H, *J* = 8.0 Hz, H_{ar}), 7.32 (d, 2H, *J* = 8.0 Hz, H_{ar}); ¹³C NMR (100 MHz, CDCl₃) δ 19.8, 21.2, 61.2, 67.2, 71.2, 71.4, 73.0, 128.1, 128.8, 129.4, 129.6, 133.9, 134.2, 134.4, 138.1, 156.0, 156.7; HRMS calcd for C₂₁H₂₄N₂O₅Cl [M + H]⁺ 419.1368, found 419.1359; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 90 : 10, flow rate 1.0 mL min⁻¹, λ = 254 nm): *t*_R = 23.38 min (major), *t*_R = 26.35 min (minor), 54% ee.

3-Benzylloxycarbonylamino-4-methyl-4-(3,4-dimethoxy)benzyloxy-oxazolidin-2-one (5c-Et)

Oil, yield 78%; ¹H NMR (400 MHz, CDCl₃) δ 1.20 (m, 6H, 2 CH₃), 3.21 (d, 1H, *J* = 8.0 Hz, CH), 3.40 (d, 1H, *J* = 8.0 Hz, CH), 3.82 (s, 3H, CH₃), 3.84 (s, 3H, CH₃), 4.01 (d, 1H, *J* = 8.0 Hz, CH), 4.08–4.13 (m, 2H, CH₂), 4.28 (d, 1H, *J* = 8.0 Hz, CH), 4.37–4.44 (m, 2H, CH₂), 6.45 (bs, 1H, NH), 6.76–6.80 (m, 3H, H_{ar}); ¹³C NMR (100 MHz, CDCl₃) δ 14.3, 14.5, 19.7, 55.8, 55.9, 61.2, 62.4, 71.3, 71.4, 72.9, 110.9, 111.0, 120.3, 130.0, 148.9, 149.3, 156.3, 156.9; HRMS calcd for C₁₇H₂₄N₂O₇Na [M + Na]⁺ 391.1476, found 391.1471; HPLC (Daicel Chiralpak OD-H, hexane/isopropanol = 90 : 10, flow rate 1.0 mL min⁻¹, λ = 254 nm): *t*_R = 21.88 min (major), *t*_R = 27.05 min (minor), 38% ee.

3-Benzylloxycarbonylamino-4-methyl-4-(3,4-dimethoxy)benzyloxy-oxazolidin-2-one (5c-Bn)

Oil, yield 67%; ¹H NMR (400 MHz, CDCl₃) δ 1.22 (s, 3H, CH₃), 3.22 (d, 1H, *J* = 8.0 Hz, CH₂), 3.40 (d, 1H, *J* = 12.0 Hz, CH₂), 3.80 (s, 3H, CH₃), 3.84 (s, 3H, CH₃), 4.03 (d, 1H, *J* = 8.0 Hz, CH), 4.30 (d, 1H, *J* = 8.0 Hz, CH), 4.41 (m, 2H, CH₂), 5.11 (s, 2H, CH₂), 6.347 (bs, 1H, NH), 6.79–6.82 (m, 3H, H_{ar}), 7.25–7.35 (m, 5H, H_{ar}); ¹³C NMR (100 MHz, CDCl₃) δ 19.7, 55.9, 61.3, 68.0, 71.3, 71.4, 72.9, 111.0, 120.3, 128.2, 128.4, 128.6, 129.9, 135.4, 148.9, 149.3, 156.2, 156.9; HRMS calcd for C₂₂H₂₆N₂O₇Na [M + H]⁺ 453.1632, found 453.1638; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 85 : 15, flow rate 1.0 mL min⁻¹, λ = 254 nm): *t*_R = 26.31 min (major), *t*_R = 32.42 min (minor), 45% ee.

3-Ethylloxycarbonylamino-4-methyl-4-(4-trifluoro)benzyloxy-oxazolidin-2-one (5d-Et)

White solid, yield 75%; ¹H NMR (400 MHz, CDCl₃) δ 1.21–1.26 (m, 6H, 2 CH₃), 3.26 (d, 1H, *J* = 12.0 Hz, CH), 3.46 (d, 1H, *J* = 8.0 Hz, CH), 4.04 (d, 1H, *J* = 8.0 Hz, CH), 4.13 (m, 2H, CH₂), 4.30 (d, 1H, *J* = 12.0 Hz, CH), 4.43–4.50 (m, 2H, CH₂), 6.61 (bs, 1H, NH), 6.70–7.04 (m, 2H, H_{ar}), 7.22–7.26 (m, 2H, H_{ar}); ¹³C NMR (100 MHz, CDCl₃) δ 14.3, 19.7, 61.2, 62.5, 71.4, 71.9, 72.5, 115.4, 115.6, 129.4, 129.5, 133.2, 156.4, 156.8, 161.3, 163.7; HRMS calcd for C₁₅H₂₀N₂O₅F [M + H]⁺ 327.1351, found 327.1341; HPLC (Daicel Chiralpak AS-H, hexane/isopropanol = 80 : 20, flow rate 1.0 mL min⁻¹, λ = 254 nm): *t*_R = 51.09 min (major), *t*_R = 76.63 min (minor), 56% ee.

3-Benzylloxycarbonylamino-4-methyl-4-(4-fluoro)benzyloxy-oxazolidin-2-one (5d-Bn)

Oil, yield 80%; ¹H NMR (400 MHz, CDCl₃) δ 1.33 (s, 3H, CH₃), 3.32 (d, 1H, *J* = 8.0 Hz, CH), 3.51 (d, 1H, *J* = 8.0 Hz, CH), 4.12 (d, 1H, *J* = 4.0 Hz, CH), 4.37 (d, 1H, *J* = 8.0 Hz, CH), 4.51 (s, 2H, CH₂), 5.21 (s, 2H, CH₂), 6.42 (bs, 1H, NH), 7.08 (t, *J* = 4.0 Hz, 2H,

H_{ar}), 7.30 (d, 2H, *J* = 8.0 Hz, H_{ar}), 7.40 (bs, 5H, H_{ar}); ¹³C NMR (100 MHz, CDCl₃) δ 19.8, 60.4, 68.1, 71.4, 71.9, 72.5, 115.7, 128.2, 128.5, 128.6, 129.4, 129.5, 132.5, 133.2, 135.2, 156.2, 156.7; HRMS calcd for C₂₀H₂₂N₂O₅F [M + H]⁺ 389.1507, found 389.1502; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 90 : 10, flow rate 1.0 mL min⁻¹, λ = 254 nm): *t*_R = 22.44 min (major), *t*_R = 24.32 min (minor), 68% ee.

3-(4-Chloro)benzyloxy-carbonylamino-4-methyl-4-(4-fluoro)benzyloxy-oxazolidin-2-one (5d-p-ClBn)

Oil, yield 89%; ¹H NMR (400 MHz, CDCl₃) δ 1.24 (s, 3H, CH₃), 3.24 (d, 1H, *J* = 8.0 Hz, CH), 3.43 (d, 1H, *J* = 12.0 Hz, CH), 4.04 (d, 1H, *J* = 8.0 Hz, CH), 4.30 (d, 1H, *J* = 8.0 Hz, CH), 4.40–4.48 (m, 2H, CH₂), 5.07 (s, 2H, CH₂), 6.84 (bs, 1H, NH), 7.00 (t, 2H, *J* = 8.0 Hz, H_{ar}), 7.21–7.25 (m, 2H, H_{ar}), 7.30 (d, 2H, *J* = 12.0 Hz, H_{ar}); ¹³C NMR (100 MHz, CDCl₃) δ 19.7, 61.2, 67.3, 71.4, 71.8, 72.5, 115.4, 115.7, 128.8, 129.0, 129.4, 129.5, 133.1, 133.2, 134.0, 134.2, 156.1, 156.8, 161.3, 163.7; HRMS calcd for C₂₀H₂₁N₂O₅ClF [M + H]⁺ 423.1118, found 423.1104; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 90 : 10, flow rate 1.0 mL min⁻¹, λ = 254 nm): *t*_R = 36.19 min (major), *t*_R = 45.33 min (minor), 70% ee.

3-Ethylloxycarbonylamino-4-methyl-4-(4-chloro)benzyloxy-oxazolidin-2-one (5e-Et)

White solid, yield 78%, mp 80–85 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.25 (m, 6H, 2CH₃), 3.27 (d, 1H, *J* = 8.0 Hz, CH), 3.48 (d, 1H, *J* = 12.0 Hz, CH), 4.06 (d, 1H, *J* = 8.0 Hz, CH), 4.17 (q, 2H, *J* = 16 Hz, 8 Hz, CH₂), 4.32 (d, 1H, *J* = 8.0 Hz, CH), 4.47–4.48 (m, 2H, CH₂), 6.39 (bs, 1H, NH), 6.76–6.80 (m, 4H, H_{ar}); ¹³C NMR (100 MHz, CDCl₃) δ 14.3, 19.8, 61.2, 62.6, 71.4, 72.1, 72.5, 128.8, 129.0, 133.9, 135.9, 156.3, 156.7; HRMS calcd for C₁₅H₂₀N₂O₅Cl [M + H]⁺ 343.1055, found 343.1048; HPLC (Daicel Chiralpak OJ-H, hexane/isopropanol = 90 : 10, flow rate 1.0 mL min⁻¹, λ = 254 nm): *t*_R = 32.27 min (major), *t*_R = 37.97 min (minor), 57% ee.

3-Benzylloxycarbonylamino-4-methyl-4-(4-chloro)benzyloxy-oxazolidin-2-one (5e-Bn)

White solid, yield 63%; mp 75–80 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.26 (s, 3H, CH₃), 3.25 (d, 1H, *J* = 8.0 Hz, CH), 3.45 (d, 1H, *J* = 8.0 Hz, CH), 4.06 (d, 1H, *J* = 8.0 Hz, CH), 4.31 (d, 1H, *J* = 8.0 Hz, CH), 4.41–4.49 (m, 2H, CH₂), 5.13 (s, 2H, CH₂), 6.60 (bs, 1H, NH), 7.19 (d, 2H, *J* = 8.0 Hz, H_{ar}), 7.29–7.37 (m, 7H, H_{ar}); ¹³C NMR (100 MHz, CDCl₃) δ 19.8, 60.4, 61.2, 68.1, 71.4, 71.7, 72.1, 72.5, 127.8, 128.2, 128.5, 128.7, 128.8, 129.0, 133.9, 135.3, 135.9, 156.2, 156.7; HRMS calcd for C₂₀H₂₂N₂O₅Cl [M + H]⁺ 405.1212, found 405.1201; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 90 : 10, flow rate 1.0 mL min⁻¹, λ = 254 nm): *t*_R = 16.12 min (major), *t*_R = 17.62 min (minor), 59% ee.

3-Benzylloxycarbonylamino-4-methyl-4-(4-bromo)benzyloxy-oxazolidin-2-one (5f-Bn)

White solid, yield 79%; mp 80–84 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.33 (s, 3H, CH₃), 3.32 (d, 1H, *J* = 8.0 Hz, CH), 3.52 (d, 1H, *J* = 8.0 Hz, CH), 4.12 (d, 1H, *J* = 8.0 Hz, CH), 4.37 (d, 1H, *J* = 8.0 Hz, CH), 4.49–4.50 (m, 2H, CH₂), 5.20 (s, 2H, CH₂), 6.49 (bs, 1H, NH),



7.19 (d, 2H, $J = 4.0$ Hz, H_{ar}), 7.40 (m, 5H, H_{ar}), 7.52 (d, 2H, $J = 8.0$ Hz, H_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 61.2, 68.1, 71.4, 72.2, 72.5, 121.9, 128.2, 128.5, 128.7, 129.3, 131.7, 135.4, 136.5, 156.3, 156.7; HRMS calcd for $C_{20}H_{22}N_2O_5Br$ $[M + H]^+$ 449.0707, found 449.0710; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 85 : 15, flow rate 1.0 mL min^{-1} , $\lambda = 254$ nm): $t_R = 19.46$ min (major), $t_R = 21.85$ min (minor), 59% ee.

4-Chlorobenzyl(4-(((4-bromobenzyl)oxy)methyl)-4-methyl-2-oxooxazolidin-3-yl)carbamate (5f-*p*-ClBn)

Oil, yield 75%; 1H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 3H, CH_3), 3.27 (d, 1H, $J = 10$ Hz, CH), 3.45 (d, 1H, $J = 10$ Hz, CH), 4.08 (d, 1H, $J = 8.0$ Hz, CH), 4.32 (d, 1H, $J = 8.0$ Hz, CH), 4.45 (s, 2H, CH_2), 5.11 (s, 2H, CH_2), 6.27 (bs, 1H, NH), 7.14 (d, 2H, $J = 8.0$ Hz, H_{ar}), 7.27 (d, 2H, $J = 8.0$ Hz, H_{ar}), 7.33 (d, 2H, $J = 8.0$ Hz, H_{ar}), 7.47 (d, 2H, $J = 8.0$ Hz, H_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 61.2, 68.1, 71.4, 72.2, 72.5, 121.9, 128.2, 128.5, 128.7, 129.3, 131.7, 135.4, 136.5, 156.3, 156.7; HRMS calcd for $C_{20}H_{21}N_2O_5ClBr$ $[M + H]^+$ 483.0317, found 483.0315; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 85 : 15, flow rate 1.0 mL min^{-1} , $\lambda = 254$ nm): $t_R = 22.65$ min (major), $t_R = 27.78$ min (minor), 59% ee.

3-Ethyloxycarbonylamino-4-methyl-4-(4-cyano)benzyloxy-oxazolidin-2-one (5g-Et)

Oil, yield 81%; 1H NMR (400 MHz, $CDCl_3$) δ 1.22 (m, 6H, 2 CH_3), 3.33 (d, 1H, $J = 8.0$ Hz, CH), 3.55 (d, 1H, $J = 8.0$ Hz, CH), 4.06 (d, 1H, $J = 4.0$ Hz, CH), 4.11–4.16 (m, 2H, CH_2), 4.34 (d, 1H, $J = 12.0$ Hz, CH), 4.51–4.62 (m, 2H, CH_2), 6.892 (bs, 1H, NH), 7.36 (d, 2H, $J = 8.0$ Hz, H_{ar}), 7.58 (d, 2H, $J = 8.0$ Hz, H_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 19.6, 61.2, 62.5, 70.8, 71.3, 72.3, 72.8, 111.4, 118.8, 127.6, 130.3, 132.3, 132.4, 143.1, 156.5, 156.7; HRMS calcd for $C_{16}H_{20}N_3O_5$ $[M + H]^+$ 334.1398, found 334.1416; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 90 : 10, flow rate 1.0 mL min^{-1} , $\lambda = 254$ nm): $t_R = 43.74$ min (minor), $t_R = 48.41$ min (major), 57% ee.

3-Benzyloxycarbonylamino-4-methyl-4-(4-cyano)benzyloxy-oxazolidin-2-one (5g-Bn)

Oil, yield 71%; 1H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 3H, CH_3), 3.31 (d, 1H, $J = 8.0$ Hz, CH), 3.52 (d, 1H, $J = 8.0$ Hz, CH), 4.05 (d, 1H, $J = 8.0$ Hz, CH), 4.33 (d, 1H, $J = 8.0$ Hz, CH), 4.48–4.58 (m, 2H, CH_2), 5.10 (s, 2H, CH_2), 7.09 (bs, 1H, NH), 7.25–7.35 (m, 7H, H_{ar}), 7.55 (d, 2H, $J = 8.0$ Hz, H_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 61.2, 68.1, 71.4, 72.3, 72.9, 111.5, 118.7, 127.5, 128.2, 128.5, 128.7, 132.4, 135.3, 143.0, 156.3, 156.7; HRMS calcd for $C_{21}H_{22}N_3O_5$ $[M + H]^+$ 396.1554, found 396.1573; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 90 : 10, flow rate 1.0 mL min^{-1} , $\lambda = 254$ nm): $t_R = 65.86$ min (major), $t_R = 69.48$ min (minor), 65% ee.

3-(4-Chloro)benzyloxycarbonylamino-4-methyl-4-(4-cyano)benzyloxy-oxazolidin-2-one (5g-*p*-ClBn)

Oil, yield 73%; 1H NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 3H, CH_3), 3.31 (d, 1H, $J = 8.0$ Hz, CH), 3.50 (d, 1H, $J = 12.0$ Hz, CH), 4.08

(d, 1H, $J = 8.0$ Hz, CH), 4.34 (d, 1H, $J = 8.0$ Hz, CH), 4.51–4.60 (m, 2H, CH_2), 5.09 (s, 2H, CH_2), 6.62 (bs, 1H, NH), 7.25 (d, 2H, $J = 4.0$ Hz, H_{ar}), 7.31 (d, 2H, $J = 8.0$ Hz, H_{ar}), 7.37 (d, 2H, $J = 8.0$ Hz, H_{ar}), 7.59 (d, 2H, $J = 8.0$ Hz, H_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 61.2, 67.3, 71.4, 72.5, 120.0, 122.7, 125.4, 125.5, 125.6, 125.7, 127.5, 128.9, 133.8, 134.5, 141.4, 156.1, 156.7; HRMS calcd for $C_{21}H_{21}N_3O_5Cl$ $[M + H]^+$ 430.1164, found 430.1159; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 85 : 15, flow rate 1.0 mL min^{-1} , $\lambda = 254$ nm): $t_R = 50.46$ min (major), $t_R = 57.77$ min (minor), 62% ee.

3-Ethyloxycarbonylamino-4-methyl-4-(4-trifluoro)benzyloxy-oxazolidin-2-one (5h-Et)

White solid, yield 76%; 1H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, 3H, $J = 8.0$ Hz, CH_3), 1.29 (s, 3H, CH_3), 3.31 (d, 1H, $J = 12.0$ Hz, CH), 3.52 (d, 1H, $J = 12.0$ Hz, CH), 4.06 (d, 1H, $J = 8.0$ Hz, CH), 4.14 (q, 2H, $J = 12.0$ Hz, 4 Hz, CH_2), 4.34 (d, 1H, $J = 8.0$ Hz, CH), 4.52–4.62 (m, 2H, CH_2), 6.78 (bs, 1H, NH), 7.38 (d, 2H, $J = 8.0$ Hz, H_{ar}), 7.58 (d, 2H, $J = 8.0$ Hz, H_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 19.6, 61.2, 62.5, 71.3, 72.4, 72.5, 125.5, 127.5, 141.7, 156.4, 156.8; HRMS calcd for $C_{16}H_{20}N_2O_5F_3$ $[M + H]^+$ 377.1319, found 377.1315; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 90 : 10, flow rate 1.0 mL min^{-1} , $\lambda = 254$ nm): $t_R = 13.40$ min (minor), $t_R = 15.24$ min (major), 56% ee.

3-Benzyloxycarbonylamino-4-methyl-4-(4-trifluoro)benzyloxy-oxazolidin-2-one (5h-Bn)

Oil, yield 89%; 1H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 3H, CH_3), 3.30 (d, 1H, $J = 12.0$ Hz, CH), 3.51 (d, 1H, $J = 8.0$ Hz, CH), 4.05 (d, 1H, $J = 8.0$ Hz, CH), 4.33 (d, 1H, $J = 8.0$ Hz, CH), 4.49–4.59 (m, 2H, CH_2), 5.12 (s, 2H, CH_2), 6.87 (bs, 1H, NH), 7.25–7.38 (m, 7H, H_{ar}), 7.58 (d, 2H, $J = 4.0$ Hz, H_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 61.2, 68.1, 71.4, 72.5, 72.6, 125.5, 125.6, 127.4, 128.2, 128.5, 128.6, 135.3, 141.6, 156.3, 156.8; HRMS calcd for $C_{21}H_{22}N_2O_5F_3$ $[M + H]^+$ 439.1475, found 439.1470; HPLC (Daicel Chiralpak AS-H, hexane/isopropanol = 80 : 20, flow rate 1.0 mL min^{-1} , $\lambda = 254$ nm): $t_R = 29.18$ min (major), $t_R = 61.72$ min (minor), 67% ee.

3-(4-Chloro)benzyloxycarbonylamino-4-methyl-4-(4-trifluoro)benzyloxy-oxazolidin-2-one (5h-*p*-ClBn)

Catalyst **1d** (191 mg, 15 mol% in respect to the azodicarboxylate) was added to a suspension of 2-methyl-3-((4-(trifluoromethyl)benzyl)oxy)propanal (2.2 g, 8.93 mmol) and di-*p*-chlorobenzyl azodicarboxylate (2.17 g, 5.93 mmol) in THF (50 mL). The mixture stirred at rt under argon until the colour of the azodicarboxylate had disappeared and quenched by the addition H_2O , then extracted three times with Et_2O (50 mL $\times 3$). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated. The resulting crude was purified by flash chromatography on silica gel, eluting with light petroleum ether-ethyl acetate mixture (4 : 1 v/v) to afford **4h-*p*-ClBn** (3.27 g) as solid in 90% yield with 74% ee. Mp 145–149 °C; 1H NMR (400 MHz, $CDCl_3$) δ 1.32 (s, 3H, CH_3), 3.71–3.87 (m, 2H, CH_2), 4.54 (s, 2H, CH_2), 5.10–5.20 (m, 4H, 2 CH_2), 6.71 (s, 1H, NH), 7.22–7.38 (m, 10H, H_{ar}), 7.62 (d, 2H, $J = 4.0$ Hz, H_{ar}), 9.62 (s, 1H, CHO);



HRMS calcd for $C_{28}H_{26}N_2O_6Cl_2F_3$ $[M + H]^+$ 613.1115, found 613.1110; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 85 : 15, flow rate 1.0 mL min⁻¹, λ = 254 nm): t_R = 18.00 min (major), t_R = 20.29 min (minor).

Upon recrystallization from 90% ethanol, the aldehyde **4h-p-ClBn** (2.1 g) was obtained in 98% ee (65% yield). After reduction and cyclization with NaBH₄ (380 mg, 10 mmol), **5h-p-ClBn** (1.53 g) was obtained in 95% yield with 98% ee. $[\alpha]_D^{20}$ -17.84 (*c* 0.7, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 1.34 (s, 3H, CH₃), 3.36 (d, 1H, *J* = 8.0 Hz, CH), 3.56 (d, 1H, *J* = 8.0 Hz, CH), 4.12 (d, 1H, *J* = 4.0 Hz, CH), 4.38 (d, 1H, *J* = 4.0 Hz, CH), 4.56–4.46 (m, 2H, CH₂), 5.18 (s, 2H, CH₂), 6.84 (bs, 1H, NH), 7.38–7.43 (m, 6H, H_{ar}), 7.63 (d, 2H, *J* = 4.0 Hz, H_{ar}); ¹³C NMR (100 MHz, CDCl₃) δ 19.7, 61.2, 67.3, 71.4, 72.5, 125.4, 122.7, 125.5, 125.6, 127.5, 128.8, 129.6, 133.8, 134.4, 141.4, 156.1, 156.7; HRMS calcd for $C_{21}H_{21}N_2O_5-ClF_3$ $[M + H]^+$ 473.1084, found 473.1086; HPLC (Daicel Chiralpak AS-H, hexane/isopropanol = 70 : 30, flow rate 1.0 mL min⁻¹, λ = 254 nm): t_R = 34.57 min (major), t_R = 56.49 min (minor).

3-Benzyloxycarbonylamino-4-methyl-4-(4-nitro)benzyloxyoxazolidin-2-one (5i-Bn)

Oil, yield 77%; ¹H NMR (400 MHz, CDCl₃) δ 1.30 (s, 3H, CH₃), 3.35 (d, 1H, *J* = 12.0 Hz, CH), 3.56 (d, 1H, *J* = 12.0 Hz, CH), 4.10 (d, 1H, *J* = 4.0 Hz, CH), 4.36 (d, 1H, *J* = 8.0 Hz, CH), 4.54–4.64 (m, 2H, CH₂), 5.13 (s, 2H, CH₂), 6.82 (bs, 1H, NH), 7.25–7.35 (m, 5H, H_{ar}), 7.41 (d, 2H, *J* = 8.0 Hz, H_{ar}), 8.15 (d, 2H, *J* = 12.0 Hz, H_{ar}); ¹³C NMR (100 MHz, CDCl₃) δ 18.4, 19.8, 29.7, 30.9, 61.2, 68.2, 71.4, 72.1, 73.0, 76.7, 77.1, 77.2, 77.4, 123.8, 127.7, 128.2, 128.6, 128.7, 136.2, 144.8, 147.6, 164.2, 164.6, 207.2; HRMS calcd for $C_{20}H_{22}N_3O_7$ $[M + H]^+$ 416.1452, found 416.1435; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 90 : 10, flow rate 1.0 mL min⁻¹, λ = 254 nm): t_R = 72.96 min (major), t_R = 76.57 min (minor), 55% ee.

4-Chlorobenzyl((4R)-4-methyl-2-oxo-4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)oxazolidin-3-yl)carbamate (5j-Bn)

Oil, yield 70%; ¹H NMR (400 MHz, CDCl₃) δ 1.26 (s, 3H, CH₃), 1.41–1.56 (m, 4H, 2 CH₂), 1.60–1.74 (m, 4H, CH₂), 3.34–3.84 (m, 4H, CH₂), 4.05–4.11 (m, 1H, CH), 4.33–4.38 (m, 1H, CH), 4.43–4.55 (m, 1H, CH), 5.14 (s, 2H, CH₂), 6.93 (bs, 1H, NH), 7.26–7.33 (m, 5H, H_{ar}); HRMS calcd for $C_{18}H_{24}N_2O_6Na$ $[M + Na]^+$ 387.1527, found 387.1508; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 90 : 10, flow rate 1.0 mL min⁻¹, λ = 254 nm): t_R = 26.0 min (major), t_R = 34.5 min (minor), 60% ee.

Benzy(4-ethyl-4-methyl-2-oxooxazolidin-3-yl)carbamate (5l-Bn)

Oil, yield 78%; ¹H-NMR (600 MHz, CDCl₃) δ 0.86–0.96 (m, 3H, CH₃), 1.24–1.33 (s, 3H, CH₃), 1.55–1.70 (m, 2H, CH₂), 4.06 (d, *J* = 6.0 Hz, 1H, CH), 4.20 (d, *J* = 6.0 Hz, 1H, CH), 5.19 (s, 2H, CH₂), 6.53 (bs, 1H, NH), 7.26–7.38 (m, 5H, H_{ar}); ¹³C NMR (150 MHz, CDCl₃) δ 7.7, 22.1, 29.8, 53.4, 61.8, 68.2, 72.1, 128.3, 128.5, 128.6, 135.3, 156.0, 156.3; HRMS calcd for $C_{14}H_{18}N_2O_4Na$ $[M + Na]^+$ 301.1159, found 301.1154; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 90 : 10, flow rate 1.0 mL min⁻¹, λ = 254 nm): t_R = 21.53 min (major), t_R = 23.23 min (minor), 37% ee.

Dibenzyl 1-(1-ethoxy-2-methyl-1,3-dioxopropan-2-yl)hydrazine-1,2-dicarboxylate (4m-Bn)

Oil, yield 76%; ¹H-NMR (300 MHz, CDCl₃): δ 1.26 (t, *J* = 6.0 Hz, 3H, CH₃), 1.56 (s, 3H, CH₃), 4.18–4.22 (m, 2H, CH₂), 5.16 (s, 4H, 2 CH₂), 6.60 (brs, 1H, NH), 7.25–7.32 (m, 10H, H_{ar}), 9.60 (s, 1H, CHO); HRMS calcd for $C_{22}H_{25}N_2O_7$ $[M + H]^+$ 429.1653, found 429.1656; HPLC (Daicel Chiralpak OD-H, hexane/isopropanol = 90 : 10, flow rate 1.0 mL min⁻¹, λ = 254 nm): t_R = 20.65 min (major), t_R = 22.78 min (minor), 24% ee.

(R)-3-Amino-4-(hydroxymethyl)-4-methyloxazolidin-2-one (6)

To a solution of **5h-p-ClBn** (670 mg, 1.42 mmol) in 8 ml of methanol and acetic acid (4 mL). 360 mg of 10% palladium on charcoal was added. The mixture hydrogenated at ambient pressure for 12 h and filtered. The filtrate was evaporated to dryness under reduced pressure. Column chromatography on silica gel (dichloromethane/methanol, 20 : 1 to 10 : 1) delivered 152 mg (1.03 mmol, 73%) of a colourless solid. Mp 113–115 °C; $[\alpha]_D^{20}$ -3.86 (*c* 0.9, CH₃OH); ¹H NMR (400 MHz, CDCl₃) δ 1.20 (s, 3H, CH₃), 3.31 (dd, 1H, *J* = 12.0 Hz, 1 Hz, CH), 3.55 (bs, 3H, NH₂ and OH), 3.76–3.79 (m, 1H, CH), 3.96 (d, 1H, *J* = 8.0 Hz, CH), 4.40 (d, 1H, *J* = 8.0 Hz, CH); HRMS calcd for $C_5H_{11}N_2O_3$ $[M + H]^+$ 147.0762, found 147.0764.

(R)-4-(Hydroxymethyl)-4-methyloxazolidin-2-one (7)

146 mg (1 mmol) of NaNO₂ was added dropwise to a solution of 45.0 mg (0.234 mmol) of **6** in 18 ml of acetic acid and 6 ml of 1 M HCl. The mixture was refluxed for 1 h. The solvent was evaporated to dryness under reduced pressure. Column chromatography on silica gel (dichloromethane/methanol, 20 : 1 to 10 : 1) delivered 79 mg (0.6 mmol, 60%) of a white solid. $[\alpha]_D^{20}$ -8.8 (*c* 0.5, CH₃OH); ¹H NMR (400 MHz, CDCl₃) δ 1.34 (s, 3H, CH₃), 3.55 (dd, 1H, *J* = 12.0 Hz, 4 Hz, CH₂), 4.04 (d, 1H, *J* = 8.0 Hz, CH), 4.33 (d, 1H, *J* = 8.0 Hz, CH), 5.59 (bs, 1H, NH); ¹³C NMR (150 MHz, CDCl₃) δ 22.6, 58.9, 67.5, 72.8, 159.4; HRMS calcd for $C_5H_{10}NO_3$ $[M + H]^+$ 132.0654, found 132.0655.

4'-(2-Propyloxazol-4-yl)-[1,1'-biphenyl]-4-carbaldehyde (11)

Catalyst Pd-dimer (2.5 mg, 1 mol% in respect to 4-bromobenzaldehyde) was added to a suspension of 4-bromobenzaldehyde (101 mg, 0.55 mmol), K₂CO₃ (207 mg, 1.5 mmol) and **10** (157 mg, 0.5 mmol) in toluene : EtOH : H₂O = 1 : 1 : 1 (v/v/v). The mixture was refluxed for 4 h. Then the solvent was removed under vacuum. The crude material was extracted with Et₂O and washed with brine. The organic phase was dried (Na₂SO₄) and the solvent was evaporated under reduced pressure. The crude product was chromatographed (silica gel, light petroleum ether/ethyl acetate = 20 : 1) to afford the aldehyde (116 mg, 80%) as a white solid. Mp 100 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.04 (t, 3H, *J* = 8.0 Hz, CH₃), 1.84–1.89 (m, 2H, CH₂), 2.83 (m, 2H, CH₂), 7.69 (m, 2H, H_{ar}), 7.78–7.85 (m, 4H, H_{ar}), 7.89 (s, 1H, H_{ar}), 7.95–8.01 (m, 4H, H_{ar}), 10.06 (s, 1H, CHO); HRMS calcd for $C_{19}H_{18}NO_2$ $[M + H]^+$ 292.1332, found 292.1335.



(*R,E*)-4-Methyl-4-(2-(4'-(2-propyloxazol-4-yl)-[1,1'-biphenyl]-4-yl)vinyl)oxazolidin-2-one (12)

To a suspension of the phosphonium salt (235 mg, 0.48 mmol) in THF was added *n*-butyllithium (2.5 M in hexane, 0.37 mL, 0.937 mmol) at $-78\text{ }^{\circ}\text{C}$ and then the solution was stirred for 30 min at the same temperature. After the addition of benzaldehyde (70 mg, 0.24 mmol) at $-78\text{ }^{\circ}\text{C}$, the reaction mixture was warmed to ambient temperature and stirred for 3 h. After quenching with saturated aq. NH_4Cl , the resulting biphasic mixture was extracted with AcOEt. The combined organic layer was washed with water and brine, dried over Na_2SO_4 , filtered, and evaporated. Purification by silica gel column chromatography (hexane : AcOEt = 4 : 1 to 1 : 1) provided **12** (131 mg, 73%) as a white solid. Mp $235\text{ }^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{20} -17.8$ (*c* 0.1, CH_3OH); ^1H NMR (400 MHz, CDCl_3) δ 1.03 (t, 3H, $J = 8.0\text{ Hz}$, CH_3), 1.81–1.90 (m, 2H, CH_2), 2.82 (t, 2H, $J = 8.0\text{ Hz}$, CH_2), 4.17–4.21 (m, 1H, CH), 4.58–4.65 (m, 2H, CH_2), 5.12 (s, 1H, NH), 6.16–6.22 (m, 1H, CH), 6.66 (d, 1H, $J = 16.0\text{ Hz}$, CH), 7.46 (d, 2H, $J = 8.0\text{ Hz}$, H_{ar}), 7.59–7.65 (m, 4H, H_{ar}), 7.80 (d, 2H, $J = 8.0\text{ Hz}$, H_{ar}), 7.87 (s, 1H, H_{ar}); ^{13}C NMR (100 MHz, CDCl_3) δ 13.7, 20.7, 30.2, 56.2, 70.2, 125.9, 126.3, 127.2, 127.3, 130.6, 133.2, 133.7, 134.3, 139.6, 140.1, 140.9, 158.9, 165.5; HRMS calcd for $\text{C}_{24}\text{H}_{25}\text{N}_2\text{O}_3$ $[\text{M} + \text{H}]^+$ 389.1860, found 389.1882.

(*R*)-4-Methyl-4-(2-(4'-(2-propyloxazol-4-yl)-[1,1'-biphenyl]-4-yl)ethyl)oxazolidin-2-one (13)

To a solution of **12** (120 mg, 0.32 mmol) in methanol was added 10% Pd/C (30 mg), and then the suspension was stirred for 2 h under a hydrogen atmosphere at ambient temperature. The reaction mixture was filtered and evaporated *in vacuo*, providing the product **13** (112 mg, 92%) as a white solid. Mp $185\text{ }^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{20} 14.4$ (*c* 0.5, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 1.04 (t, 3H, $J = 8.0\text{ Hz}$, CH_3), 1.44 (s, 3H, CH_3), 1.84–1.89 (m, 2H, CH_2), 1.93–1.97 (m, 2H, CH_2), 2.70–2.74 (m, 2H, CH_2), 2.75–2.86 (m, 2H, CH_2), 4.10 (d, 1H, $J = 8.0\text{ Hz}$, CH), 4.22 (d, 1H, $J = 8.0\text{ Hz}$, CH), 5.42 (bs, 1H, NH), 7.25 (d, 1H, $J = 8.0\text{ Hz}$, CH), 7.55 (d, 1H, $J = 8.0\text{ Hz}$, CH), 7.61 (d, 2H, $J = 8.0\text{ Hz}$, H_{ar}), 7.79 (m, 2H, $J = 8.0\text{ Hz}$, H_{ar}), 7.86 (s, 1H, H_{ar}); ^{13}C NMR (100 MHz, CDCl_3) δ 13.7, 20.6, 26.0, 30.0, 30.1, 42.2, 57.6, 75.6, 125.9, 127.2, 127.3, 128.7, 129.8, 133.2, 138.8, 139.8, 139.9, 140.3, 158.7, 165.6; HRMS calcd for $\text{C}_{24}\text{H}_{27}\text{N}_2\text{O}_3$ $[\text{M} + \text{H}]^+$ 391.2016, found 391.2011.

(*R*)-2-Amino-2-methyl-4-(4'-(2-propyloxazol-4-yl)-[1,1'-biphenyl]-4-yl)butan-1-ol hydrochloride (14)

Compound **13** (100 mg, 0.26 mmol) was diluted with methanol : $\text{H}_2\text{O} = 10 : 1$ (v/v), then potassium hydroxide (146 mg, 2.6 mmol) was added, which was refluxed for 18 h. After cooling to room temperature, water was added to the reaction mixture and extracted with CH_2Cl_2 . The combined organic layer was washed with water and brine, dried over Na_2SO_4 , filtered, and evaporated. The crude product was chromatographed (silica gel, dichloromethane/methanol = 10 : 1), then added 1 M HCl in Et_2O (2 mL) to afford the product **14** (82 mg, 80%) as a white solid. Mp $214\text{ }^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{20} -1.61$ (*c* 0.2, CH_3OH); ^1H NMR (400 MHz, CDCl_3) δ 1.01 (t, 3H, $J = 8.0\text{ Hz}$,

CH_3), 1.34 (s, 3H, CH_3), 1.81–1.92 (m, 2H, CH_2), 2.68–2.72 (m, 2H, CH_2), 2.83–2.86 (m, 2H, CH_2), 3.52–3.57 (m, 2H, CH_2), 3.62–3.65 (m, 2H, CH_2), 7.31 (d, 2H, $J = 8.0\text{ Hz}$, H_{ar}), 7.58 (d, 2H, $J = 8.0\text{ Hz}$, H_{ar}), 7.65 (d, 2H, $J = 8.0\text{ Hz}$, H_{ar}), 7.77 (d, 2H, $J = 8.0\text{ Hz}$, H_{ar}), 8.23 (s, 1H, H_{ar}); ^{13}C NMR (100 MHz, CDCl_3) δ 14.0, 20.4, 21.6, 30.2, 30.8, 38.7, 58.8, 66.3, 127.2, 128.2, 128.3, 130.0, 136.0, 139.9, 140.7, 141.9, 142.1, 167.8; HRMS calcd for $\text{C}_{23}\text{H}_{29}\text{N}_2\text{O}_2$ $[\text{M} + \text{H}]^+$ 365.2224, found 365.2212.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- 1 E. Katz, H. Schmitt, M. Aydin, W. A. König and G. Jung, *Liebigs Ann. Chem.*, 1985, 365.
- 2 C. Auvin-Guette, S. Rebuffat, I. Vuidepot, M. Massias and B. Bodo, *J. Chem. Soc., Perkin Trans. 1*, 1993, 249.
- 3 I. Augeven-Bour, S. Rebuffat, C. Auvin, C. Goulard, Y. Prigent and B. Bodo, *J. Chem. Soc., Perkin Trans. 1*, 1997, 1587.
- 4 M. Ahrend, *Angew. Chem.*, 1999, **111**, 3047; *Angew. Chem., Int. Ed.*, 1999, **38**, 2873.
- 5 K. L. Reddy and K. B. Sharpless, *J. Am. Chem. Soc.*, 1998, **120**, 1207.
- 6 H. F. Wang, G. H. Ma, S. B. Yang, R. G. Han and P. F. Xu, *Tetrahedron: Asymmetry*, 2008, **19**, 1630.
- 7 G. P. Miley, J. C. Rote, R. B. Silverman, N. L. Kelleher and R. J. Thomson, *Org. Lett.*, 2018, **20**, 2369.
- 8 T. Tsuji, K. Suzuki, T. Nakamura and T. Nishi, *Tetrahedron*, 2014, **70**, 5234.
- 9 M. A. Jones, A. D. Hislop and J. S. Snaith, *Org. Biomol. Chem.*, 2006, **4**, 3769.
- 10 D. Seebach, J. D. Aebi, M. Gander-Coquoz and R. Naef, *Helv. Chim. Acta*, 1987, **70**, 1194.
- 11 M. Di Giacomo, V. Vinci, M. Serra and L. Colombo, *Tetrahedron: Asymmetry*, 2008, **19**, 247.
- 12 P. Vachal and E. N. Jacobsen, *Org. Lett.*, 2000, **2**, 867.
- 13 K. Maruoka and T. Ooi, *Chem. Rev.*, 2003, **103**, 3013.
- 14 H. Vogt, S. Vanderheiden and S. Bräse, *Chem. Commun.*, 2003, **19**, 2448.
- 15 N. Kumaragurubaran, K. Juhl, W. Zhuang, A. Bøgevig and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2002, **124**, 6254.
- 16 C. E. Hartmann, T. Baumann, M. Bächle and S. Bräse, *Tetrahedron: Asymmetry*, 2010, **21**, 1341.
- 17 J. Ferreira, S. C. Rees-Jones, V. Ramaotsoa and R. Hunter, *Org. Biomol. Chem.*, 2016, **14**, 1545.
- 18 J. Y. Fu, Q. C. Yang, Q. L. Wang, J. N. Ming, F. Y. Wang, X. Y. Xu and L. X. Wang, *J. Org. Chem.*, 2011, **76**, 4661.
- 19 N. S. Chowdari and C. F. Barbas, *Org. Lett.*, 2005, **7**, 867.



- 20 T. Tsuji, K. Suzuki, T. Nakamura and T. Nishi, *Tetrahedron*, 2014, **70**, 5234.
- 21 H. Deng, S. G. Bernier, E. Doyle, J. Lorusso, B. A. Morgan, W. F. Westlin and G. Evindar, *ACS Med. Chem. Lett.*, 2013, **4**, 942.
- 22 T. Nishi, S. Miyazaki, T. Takemoto, K. Suzuki, Y. Iio, K. Nakajima, T. Ohnuki, Y. Kawase, F. Nara, S. Inaba, T. Izumi, H. Yuita, K. Ohshima, H. Doi, R. Inoue, W. Tomisato, T. Kagari and T. Shimozato, *ACS Med. Chem. Lett.*, 2011, **2**, 368.
- 23 J. Jin, J. P. Hu, W. Q. Zhou, X. J. Wang, Q. Xiao, N. N. Xue, D. L. Yin and X. G. Chen, *Biochem. Pharmacol.*, 2014, **90**, 50.
- 24 S. Chen, *et al.*, under review.

