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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 azadicarboxylates 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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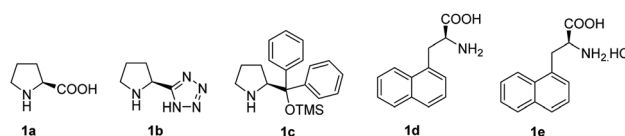
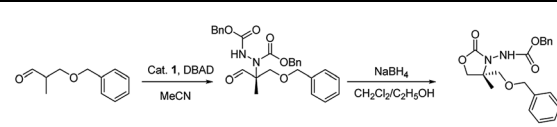


Fig. 1 Chiral catalysts.



Table 1 Screening of chiral catalysts^a


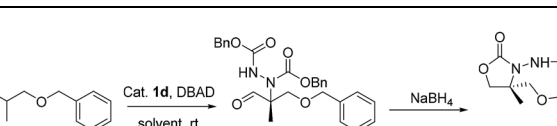
Entry	Catalyst	Time (h)	Yield ^b (%)	ee ^c (%)
1	1a	48	56	32
2	1b	12	68	42
3	1c	24	45	34 ^d
4	1d	24	70	46
5	1e	24	53	44

^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 -carbethoxy 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.

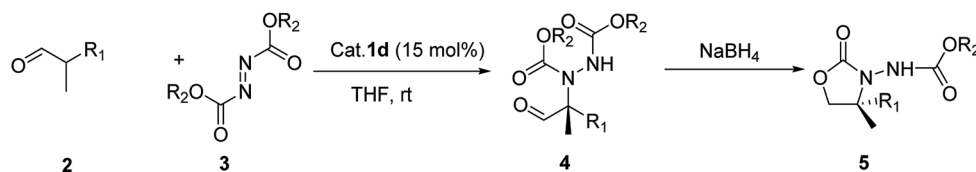
Upon recrystallization from 90% ethanol, the aldehyde **4a-p-ClBn** was obtained in 97% ee (60% yield) and **4h-p-ClBn** was obtained in 97% ee (65% yield), which was subsequently converted to oxazolidinone **5a-p-ClBn** in >99% ee and **5h-p-ClBn** was obtained in 98% ee respectively. The absolute configuration 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

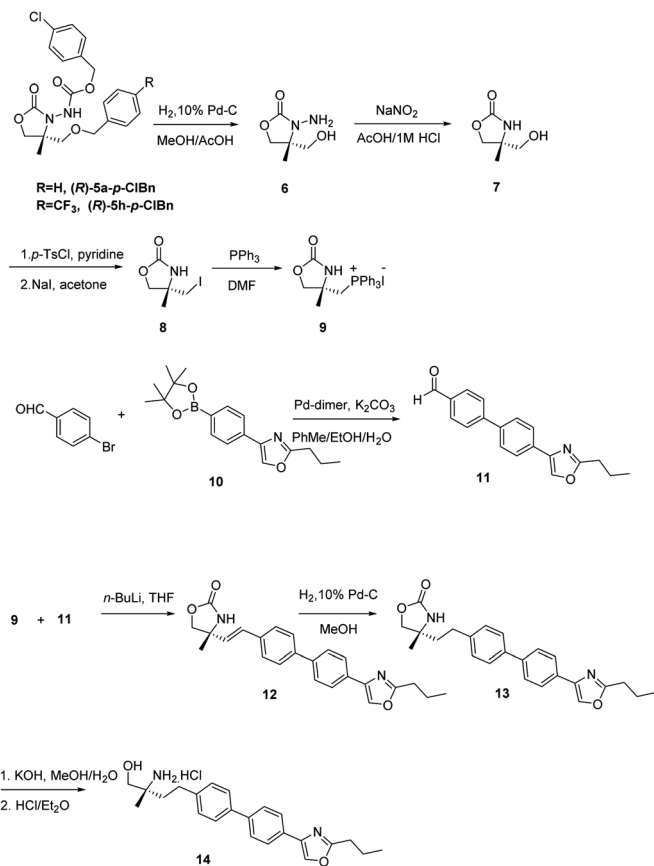
Catalyst **1d** (15 mol% in respect to the azodicarboxylate) was added to a suspension of aldehydes (**2**, 1.5 eq. in respect to the azodicarboxylate) and azodicarboxylate (**3**) in THF. The mixture stirred at rt under argon until the colour of the azodicarboxylate

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-Benzyloxycarbonylamino-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-Benzyloxycarbonylamino-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-Ethyloxycarbonylamino-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-Benzyloxycarbonylamino-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)benzyloxycarbonylamino-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-Ethyloxycarbonylamino-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-Benzyloxycarbonylamino-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-Benzyloxycarbonylamino-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 $C_{20}H_{21}N_2O_5-ClBr$ $[M + H]^+$ 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-Benzoyloxycarbonylamino-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.

Benzyl(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.



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