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-benzylxypropanal 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 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, natural products and pharmaceuticals. 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, auxiliary Strecker synthesis, and a variety of asymmetric phase transfer catalysis reactions.

Recently, several methods have been reported describing the asymmetric Michael amination of achiral aldehydes via proline catalysis, resulting in the products being obtained in good yields and excellent enantioselectivities. 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 amination of branched aldehydes with azadi- carboxylates to give α-alkyl-α-aryl disubstituted aldehydes in up to 99% ee. 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. 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. 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 amination of α-methyl-α-protected hydroxymethyl aldehydes and their subsequent reduction and cyclisation to afford oxazolidinones in good ee. We initially chose 3-(benzoxyl)-2-methylpropanal and dibenzyl azodicarboxylate (DBAD) as a model substrate to determine to optimal reaction conditions. When l-proline (1a) (30 mol%) was used, 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). 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).

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 Yields at 96% ee.
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 were obtained in moderate to good yields (54–89%) and enantioselectivities (24–73% ee). The reactions showed poor enantioselectivities for 5-ethyl-2-carbethoxy disubstituted aldehydes, but not for 5-methyl-2-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 dietyl 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-CIBn was obtained in 97% ee (60% yield) and 4h-p-CIBn was obtained in 97% ee (65% yield), which was subsequently converted to oxazolidinone 5a-p-CIBn in >99% ee and 5h-p-CIBn 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 benzylxycarbonyl 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.28 8 with triphenylphosphine in DMF provided the desired phosphonium salt 9 in moderate yield as a stable white solid.29

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.30,31 This compound is an analogue of SYL930, an immunosuppressant we have been reported before.32 SYL930 is currently in phase 1 clinical stage. The synthesis of 14 started from the aldehyde 11 in only a three step manipulation.33 Aldehyde 11 was synthesized in good yield from 4-bromobenzaldehyde and dinary pinacol borate ester 10 via Suzuki reaction with Pd-dimer (dibromobis(tri-tert-butylphosphine)dipalladium) as the catalyst.34 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
optimized conditions, we obtained $\alpha$-methyl-$\alpha$-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.

| Entry | R₁ | R₂ | Product | Time (h) | Yield (%) | ee (%) | ee (%) |
|-------|----|----|---------|----------|-----------|--------|--------|
| 1     | BnOCH₂ | Et | 5a-Et    | 38       | 79        | 57     | —      |
| 2     | BnOCH₂ | Bn | 5a-Bn    | 36       | 81        | 69     | —      |
| 3     | BnOCH₂ | p-ClBn | 4a-p-ClBn | 48       | 80        | 71%   | 97%     |
| 4     | BnOCH₂ | p-ClBn | 5a-p-ClBn | 1        | 94        | 72     | >99%    |
| 5     | p-CH₃BnOCH₂ | Bn | 5b-Bn    | 38       | 54        | 48     | —      |
| 6     | p-CH₃BnOCH₂ | p-ClBn | 5b-p-ClBn | 36       | 56        | 54     | —      |
| 7     | 3,4-DiMeOBnOCH₂ | Et | 5c-Et    | 38       | 73        | 35     | —      |
| 8     | 3,4-DiMeOBnOCH₂ | Bn | 5d-Bn    | 36       | 67        | 45     | —      |
| 9     | p-FBnOCH₂ | Et | 5d-Et    | 37       | 75        | 56     | —      |
| 10    | p-FBnOCH₂ | Bn | 5d-Bn    | 36       | 80        | 68     | —      |
| 11    | p-FBnOCH₂ | p-ClBn | 5d-p-ClBn | 48       | 89        | 70     | —      |
| 12    | p-ClBnOCH₂ | Et | 5e-Et    | 39       | 70        | 57     | —      |
| 13    | p-ClBnOCH₂ | Bn | 5e-Bn    | 36       | 63        | 59     | —      |
| 14    | p-BrBnOCH₂ | Bn | 5f-Bn    | 38       | 79        | 59     | —      |
| 15    | p-BrBnOCH₂ | p-ClBn | 5f-p-ClBn | 48       | 75        | 52     | —      |
| 16    | p-CNBnOCH₂ | Et | 5g-Et    | 28       | 81        | 57     | —      |
| 17    | p-CNBnOCH₂ | Bn | 5g-Bn    | 24       | 71        | 65     | —      |
| 18    | p-CNBnOCH₂ | p-ClBn | 5g-p-ClBn | 48       | 73        | 62     | —      |
| 19    | p-CF₃BnOCH₂ | Et | 5h-Et    | 39       | 75        | 65     | —      |
| 20    | p-CF₃BnOCH₂ | Bn | 5h-Bn    | 36       | 89        | 67     | —      |
| 21    | p-CF₃BnOCH₂ | p-ClBn | 4h-p-ClBn | 48       | 90        | 74%   | 97%     |
| 22    | p-CF₃BnOCH₂ | p-ClBn | 4h-p-ClBn | 1        | 95        | 73     | 98%     |
| 23    | p-NO₂BnOCH₂ | Bn | 5i-Bn    | 48       | 77        | 55     | —      |
| 24    | THPOCH₂ | Bn | 5j-Bn    | 48       | 70        | 57     | —      |
| 25    | TrtOCH₂ | Bn | 5k-Bn    | 48       | —         | —      | —      |
| 26    | Et | Bn | 5l-Bn    | 48       | 75        | 37     | —      |
| 27    | CO₂Et | Bn | 4m-Bn    | 48       | 76        | 24     | —      |

* 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. * Isolated yield. * Isolated by silica gel column chromatography. * Determined by chiral HPLC. * ee determined by chiral HPLC after recrystallization. Absolute configuration of 5-R to determined be $(R)$ on CD spectrum.
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 C_{20}H_{23}N_{2}O_{5} [M + H]^+ 371.1602, found 371.1591; HPLC (Daicel Chiralpak OD, hexane/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]_{22}^{D} 9.72 (c 0.29, CHCl_{3}). \(^{1}\)H NMR (400 MHz, CDCl_{3}) δ 1.34 (s, 3H, CH_{3}), 3.60–3.77 (m, 2H, CH_{2}), 4.42 (s, 2H, CH_{2}), 5.01–5.15 (m, 4H, 2CH_{2}), 6.70 (s, 1H, NH), 7.16–7.30 (m, 13H, H_{ar}), 9.55 (s, 1H, CHO); HRMS calced for C_{22}H_{29}N_{2}O_{5}Cl [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).

NaBH\(_{4}\) (190 mg, 5.0 mmol) was added to a solution of 4a-p-ClBn (900 mg, 1.65 mmol) in CH\(_{2}\)Cl\(_{2}\)/CH\(_{3}\)OH (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 CH\(_{2}\)Cl\(_{2}\). The combined organic phases were dried over Na\(_{2}\)SO\(_{4}\), 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]_{22}^{D} = +12.3 (c 0.13, CHCl_{3}). \(^{1}\)H NMR (400 MHz, CDCl_{3}) δ 1.24 (s, 3H, CH_{3}), 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, CH_{2}), 5.06 (s, 2H, CH_{2}), 6.49 (bs, 1H, NH), 7.24–7.36 (m, 10H, H_{ar})\(^{13}\)C NMR (100 MHz, CDCl_{3}) δ 19.8, 61.2, 67.2, 71.4, 71.7, 73.2, 127.8, 128.2, 128.5, 128.6, 128.7, 135.3, 137.3, 156.0, 156.7; HRMS calcd for C_{20}H_{19}NO_{5}Cl [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)benzoxycarbonylaminoo-4-methyl-4-(4-methyl) benzoxo-oxazolidin-2-one (5b-Bn)

Oil, yield 54%; \(^{1}\)H NMR (400 MHz, CDCl_{3}) δ 1.24 (s, 3H, CH_{3}), 2.29 (s, 3H, CH_{3}), 3.24 (d, 1H, J = 12.0 Hz, CH), 3.40 (d, 1H, J = 12.0 Hz, CH), 3.99 (s, 1H, J = 8.0 Hz, CH), 4.04–4.48 (m, 2H, CH_{2}), 5.12 (s, 2H, CH_{2}), 6.39 (bs, 1H, NH), 7.13–7.18 (m, 4H, H_{ar}), 7.31–7.37 (m, 5H, H_{ar}); \(^{13}\)C NMR (100 MHz, CDCl_{3}) 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 C_{20}H_{19}NO_{5}Cl [M + H]^+ 385.1758, found 385.1758; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 90 : 10, flow rate 1.0 mL min\(^{-1}\), λ = 213 nm): \(t_{R}= 22.42\) min (major), \(t_{R}= 25.10\) min (minor), 48% ee.

3-(4-Chloro)benzoxycarbonylaminoo-4-methyl-4-(4-methyl) benzoxo-oxazolidin-2-one (5b-p-ClBn)

Oil, yield 56%; \(^{1}\)H NMR (400 MHz, CDCl_{3}) δ 1.23 (s, 3H, CH_{3}), 2.30 (s, 3H, CH_{3}), 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, CH_{2}), 5.08 (s, 2H, CH_{2}), 6.22 (bs, 1H, NH), 7.13–7.16 (m, 10H, H_{ar}).

Scheme 1 Synthesis of the \(\alpha\)-substituted alanol compound as S1P\(_{1}\) agonist.
3-Benzoxycarbonylaminobenzylhydroxamic acid (4Mc-Bn) 2

Oil, yield 78%; 1H NMR (400 MHz, CDCl3) δ 1.22 (s, 3H, CH3), 3.22 (d, 1H, J = 12.0 Hz, CH2), 3.40 (d, 1H, J = 12.0 Hz, CH3), 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, CH2), 4.41 (m, 2H, CH2), 5.11 (s, 2H, CH2), 6.347 (bs, 1H, NH), 6.79-6.8 2 (m, 3H, Har), 7.25-7.35 (m, 5H, Har), 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, 129.9, 135.4, 148.9, 149.3, 156.2, 156.9; HRMS calcd for C17H20N2O5Na [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): tf = 26.31 min (major), tf = 32.42 min (minor), 45% ee.

3-Benzoxycarbonylaminobenzylhydroxamic acid (4Br-Bn) 2

White solid, yield 69%; 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, 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, Har); 13C NMR (100 MHz, CDCl3) δ 14.3, 19.8, 61.2, 62.6, 71.4, 72.1, 72.5, 128.8, 129.0, 129.4, 133.1, 133.2, 134.0, 134.2, 156.1, 156.8, 161.3, 163.7; HRMS calcd for C20H25N2O6Cl [M + H⁺] 423.1118, found 423.1104; HPLC (Daicel Chiralpak OD-H, hexane/isopropanol = 90 : 10, flow rate 1.0 mL min⁻¹, λ = 254 nm): tf = 36.19 min (major), tf = 45.33 min (minor), 70% ee.

3-Benzoxycarbonylaminobenzylhydroxamic acid (4Cl-Bn) 2

White solid, yield 79%; 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, 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, Har); 13C NMR (100 MHz, CDCl3) δ 14.3, 19.8, 61.2, 62.6, 71.4, 72.1, 72.5, 128.8, 129.0, 129.4, 133.1, 133.2, 134.0, 134.2, 156.1, 156.8, 161.3, 163.7; HRMS calcd for C17H20N2O5Cl [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): tf = 37.97 min (minor), 57% ee.
4-Chlorobenzyl-4-(((4-bromobenzoyl)oxy)methyl)-4-methyl-2-oxoazolidin-3-yl carbonate (5f-p-CBr)

Oil, yield 75%; 1H NMR (400 MHz, CDCl3) δ 1.27 (s, 3H, CH3), 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, CH2), 5.11 (s, 2H, CH2), 6.27 (bs, 1H, NH), 7.14 (d, 2H, J = 8.0 Hz, Har), 7.27 (d, 2H, J = 8.0 Hz, Har), 7.32 (d, 1H, J = 8.0 Hz, Har), 7.47 (d, 2H, J = 8.0 Hz, Har); 13C NMR (100 MHz, CDCl3) 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 C20H21N2O5-CIBr [M + H]+ 483.0317, found 483.0315; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 85 : 15, flow rate 1.0 mL min⁻¹, λ = 254 nm): tR = 20.69 min (major), tR = 21.85 min (minor), 59% ee.

3-Ethylcarbonylamino-4-methyl-4-(4-cyano)benzoyloxyazolidin-2-one (5g-Br)

White solid, yield 76%; 1H NMR (400 MHz, CDCl3) δ 1.23 (t, 3H, J = 8.0 Hz, CH3), 1.29 (s, 3H, CH3), 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 = 8.0 Hz, CH2), 4.34 (d, 1H, J = 8.0 Hz, CH), 4.52-4.62 (m, 2H, CH2), 6.78 (bs, 1H, NH), 7.38 (d, 2H, J = 8.0 Hz, Har), 7.58 (d, 2H, J = 8.0 Hz, Har); 13C NMR (100 MHz, CDCl3) δ 14.3, 19.6, 61.2, 62.5, 71.3, 72.4, 72.5, 125.7, 127.5, 141.7, 156.4, 156.8; HRMS calcd for C18H17N2O4F2 [M + H]+ 377.1319, found 377.1315; HPLC (Daicel Chiralpak AS-H, hexane/isopropanol = 90 : 10, flow rate 1.0 mL min⁻¹, λ = 254 nm): tR = 13.40 min (minor), tR = 15.24 min (major), 56% ee.

3-Benzylcarbonylamino-4-methyl-4-(4-cyano)benzoyloxyazolidin-2-one (5g-Bn)

Oil, yield 89%; 1H NMR (400 MHz, CDCl3) δ 1.27 (s, 3H, CH3), 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, CH2), 5.12 (s, 2H, CH2), 6.87 (bs, 1H, NH), 7.25-7.38 (m, 7H, Har), 7.58 (d, 2H, J = 4.0 Hz, Har); 13C NMR (100 MHz, CDCl3) δ 19.7, 61.2, 68.1, 71.4, 72.5, 72.6, 125.6, 127.4, 128.2, 128.5, 128.7, 132.6, 132.9, 141.6, 156.3, 158.9; HRMS calcd for C21H19N3O5Cl [M + H]+ 430.1164, found 430.1159; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 85 : 15, flow rate 1.0 mL min⁻¹, λ = 254 nm): tR = 44.81 min (major), 67% ee.
HRMS calcd for C_{28}H_{26}N_{2}O_{6}Cl_{2}F_{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-CBn (2.1 g) was obtained in 98% ee (65% yield). After reduction and cyclization with NaBH₄ (380 mg, 10 mmol), 5H-p-CBn (1.53 g) was obtained in 95% yield with 98% ee. [δ]D° = −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 = 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), 7.29–7.35 (m, 5H, Har), 7.41 (d, 2H, J = 8.0 Hz, Har, 8.15 (d, 2H, J = 12.0 Hz, Har); ¹³C NMR (100 MHz, CDCl₃) δ 19.7, 61.2, 67.3, 71.4, 72.5, 124.4, 125.7, 125.8, 127.5, 127.6, 128.6, 128.7, 128.9, 133.4, 141.4, 156.1, 156.7; HRMS calcd for C_{18}H_{24}N₂O₆Na [M + Na]^+ 387.1527, found 387.1508; HPLC (Daicel Chiralpak AS-H, hexane/isopropanol = 70 : 30, flow rate 1.0 mL min⁻¹, λ = 254 nm): t_R = 34.5 min (major), t_R = 56.49 min (minor).

3-Benzylcarbonylamino-4-methyl-4-(4-nitro)benzoxazolin-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), 7.29–7.35 (m, 5H, Har), 7.41 (d, 2H, J = 8.0 Hz, Har, 8.15 (d, 2H, J = 12.0 Hz, Har); 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, 144.8, 147.6, 164.2, 164.6, 207.2; HRMS calcd for C_{20}H_{22}N₂O₅ [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)oxazolin-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), 4.38–4.38 (m, 1H, CH), 5.14 (s, 2H, CH₂), 6.93 (bs, 1H, NH), 7.26–7.33 (m, 5H, Har); HRMS calcd for C_{18}H_{18}N₂O₄Na [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-oxoazoxazolin-3-yl)carbamate (5k-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, Har); ¹³C NMR (150 MHz, CDCl₃) δ 7.7, 22.1, 29.8, 53.4, 61.8, 68.2, 72.1, 128.3, 128.8, 128.6, 135.3, 156.0, 1563; HRMS calcd for C_{14}H_{14}N₂O₂Na [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.
(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 °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 °C, the reaction mixture was warmed to ambient temperature and stirred for 3 h. After quenching with saturated aq. NH₄Cl, the resulting biphasic mixture was extracted with AcOEt. The combined organic layer was washed with water and brine, dried over Na₂SO₄, 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 °C; [α]D 20 = −17.8 (c 0.1, CH₃OH); 1H NMR (400 MHz, CDCl₃) δ 1.03 (t, 3H, J = 8.0 Hz, CH₃), 1.81–1.90 (m, 2H, CH), 2.82 (t, 2H, J = 8.0 Hz, CH₂), 4.17–4.21 (m, 1H, CH₄), 4.58–4.65 (m, 2H, CH₂), 5.12 (s, 1H, NH), 6.16–6.22 (m, 1H, CH), 7.66 (d, 1H, J = 16.0 Hz, CH), 7.46 (d, 2H, J = 8.0 Hz, H₃a), 7.59–7.65 (m, 4H, H₄a), 7.80 (d, 2H, J = 8.0 Hz, H₄b), 8.07 (s, 1H, H₂a); 13C NMR (100 MHz, CDCl₃) δ 13.7, 20.7, 56.2, 70.2, 125.9, 126.3, 127.2, 130.6, 132.3, 133.7, 134.3, 139.6, 140.1, 140.9, 158.9, 165.5; HRMS calcd for C₂₃H₂₉N₂O₂ [M + H]⁺ 389.1860, found 389.1882.

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