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# Asymmetric amination of $\alpha,\alpha$ -dialkyl substituted aldehydes catalyzed by a simple chiral primary amino acid and its application to the preparation of a S1P<sub>1</sub> agonist†

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The chiral catalytic amination of an  $\alpha,\alpha$ -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  $\alpha$ -methyl- $\alpha$ -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  $\alpha$ -substituted alaninol compound **14** as an S1P<sub>1</sub> agonist in high overall yield.

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## Introduction

$\alpha,\alpha$ -Disubstituted amino alcohols, aldehydes and acids are important chiral building blocks in organic synthesis. They are routinely found in a number of peptides,<sup>1–5</sup> natural products<sup>6,7</sup> and pharmaceuticals.<sup>8,9</sup> 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,<sup>10,11</sup> auxiliary Strecker synthesis,<sup>12</sup> and a variety of asymmetric phase transfer catalysis reactions.<sup>13</sup>

Recently, several methods have been reported describing the asymmetric Michael  $\alpha$ -amination of achiral aldehydes *via* proline catalysis, resulting in the products being obtained in good yields and excellent enantioselectivities.<sup>14–17</sup> 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  $\alpha$ -amination of branched aldehydes with azidocarboxylates to give  $\alpha$ -alkyl- $\alpha$ -aryl disubstituted aldehydes in up to 99% ee.<sup>18</sup> However, low enantioselectivities only 4–28% ee were obtained with  $\alpha$ -alkyl- $\alpha$ -alkyl disubstituted, potentially owing to poor stereo-differentiation between the two  $\alpha$ -substituents.<sup>14</sup> 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  $\alpha$ -alkyl- $\alpha$ -benzyl disubstituted aldehydes.<sup>19</sup> In addition, no further progress about the asymmetric amination of  $\alpha$ -alkyl- $\alpha$ -alkyl disubstituted aldehydes had been reported.

## Results and discussion

Herein, we report the asymmetric Machel  $\alpha$ -amination of  $\alpha$ -methyl- $\alpha$ -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,<sup>14</sup> 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 CH<sub>3</sub>CN provided 42% ee with 68% yield (Table 1, entry 2).<sup>17</sup> 3-(1-Naphthyl)-L-alanine catalyst (**1d**) (15 mol%) in CH<sub>3</sub>CN gave the amino aldehyde in 70% yield with 46% ee (Table 1, entry 4).<sup>18</sup>

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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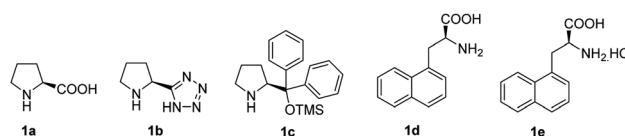
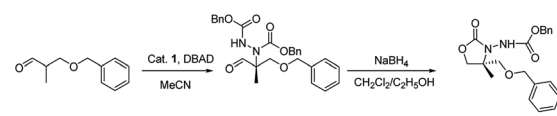


Fig. 1 Chiral catalysts.



Table 1 Screening of chiral catalysts<sup>a</sup>


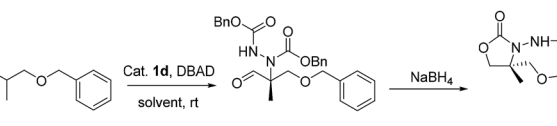
Entry	Catalyst	Time (h)	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	<b>1a</b>	48	56	32
2	<b>1b</b>	12	68	42
3	<b>1c</b>	24	45	34 <sup>d</sup>
4	<b>1d</b>	24	70	46
5	<b>1e</b>	24	53	44

<sup>a</sup> 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. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by HPLC with a Chiralpak-OD column. <sup>d</sup> 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  $\alpha$ -methyl- $\alpha$ -ethyl and  $\alpha$ -methyl- $\alpha$ -carbethoxy disubstituted aldehydes, but not for  $\alpha$ -

Table 2 Screening of solvents<sup>a</sup>


Entry	Solvent	Time	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	<i>n</i> -Hexane	24	52	48
2	Toluene	72	49	45
3	CH <sub>2</sub> Cl <sub>2</sub>	72	41	30
4	EtOAc	24	67	54
5	CH <sub>3</sub> OCH <sub>2</sub> CH <sub>2</sub> OCH <sub>3</sub>	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

<sup>a</sup> 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. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by chiral HPLC.

methyl- $\alpha$ -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*-CF<sub>3</sub> 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  $\pi$ - $\pi$  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  $\alpha$ -substituents. Additionally, when the azo reagent contained an aromatic ring this  $\pi$ - $\pi$  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 NaNO<sub>2</sub> (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.<sup>20</sup> **8** with triphenylphosphine in DMF provided the desired phosphonium salt **9** in moderate yield as a stable white solid.<sup>20</sup>

Then we applied the chiral phosphonium salt **9** to the synthesis of biological active compound as S1P<sub>1</sub> agonist **14**. These types of compounds possessing a chiral 2-methyl-2-aminoethanol have shown promise in recent years as the immunosuppressant.<sup>21,22</sup> This compound is an analogue of SYL930, an immunosuppressant we have been reported before.<sup>23</sup> SYL930 is currently in phase I clinical stage. The synthesis of **14** started from the aldehyde **11** in only a three step manipulation.<sup>24</sup> 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.<sup>24</sup> 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 Et<sub>2</sub>O produced the chiral  $\alpha$ -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<sup>a</sup>

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

<sup>a</sup> 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. <sup>b</sup> Isolated yield. <sup>c</sup> Isolated by silica gel column chromatography. <sup>d</sup> Determined by chiral HPLC. <sup>e</sup> ee determined by chiral HPLC after recrystallization. Absolute configuration of 5-*R* to determined be (*R*) on CD spectrum.

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 S1P<sub>1</sub> agonist **14** has been obtained by this method in high overall yield.

## Experimental

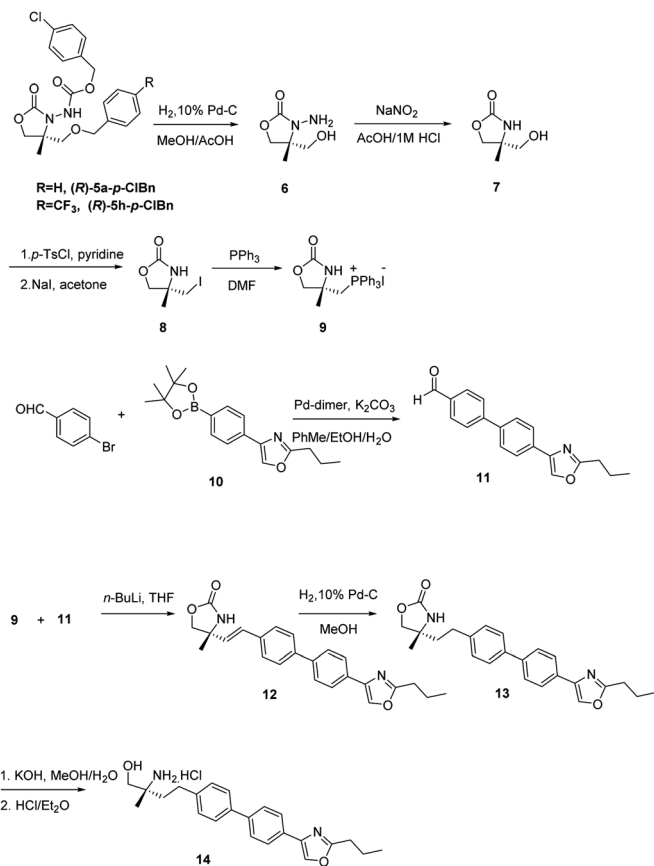
### General procedure for the synthesis of 4,4-disubstituted 3-alkoxycarbonylamino-oxazolidin-2-ones (5-*R*) by one pot method

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. NaBH<sub>4</sub> (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 CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, 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; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.24 (m, 6H, 2CH<sub>3</sub>), 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, CH<sub>2</sub>), 4.33 (d, 1H, *J* = 8.0 Hz, CH), 4.51 (s, 2H, CH<sub>2</sub>), 6.33 (bs, 1H, NH), 7.27–7.38 (m, 5H, H<sub>ar</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  14.3, 19.8,



Scheme 1 Synthesis of the  $\alpha$ -substituted alaninol compound as S1P<sub>1</sub> 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 C<sub>15</sub>H<sub>21</sub>N<sub>2</sub>O<sub>5</sub> [M + H]<sup>+</sup> 309.1445, found 309.1442; HPLC (Daicel Chiralpak OD-H, hexane/isopropanol = 90 : 10, flow rate 1.0 mL min<sup>-1</sup>,  $\lambda$  = 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%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.26 (s, 3H, CH<sub>3</sub>), 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, CH<sub>2</sub>), 5.14 (s, 2H, CH<sub>2</sub>), 6.38 (bs, 1H, NH), 7.24–7.35 (m, 10H, H<sub>ar</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  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 C<sub>20</sub>H<sub>23</sub>N<sub>2</sub>O<sub>5</sub> [M + H]<sup>+</sup> 371.1602, found 371.1591; HPLC (Daicel Chiralpak OD, hexane/isopropanol = 90 : 10, flow rate 1.0 mL min<sup>-1</sup>,  $\lambda$  = 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 H<sub>2</sub>O, then extracted three times with Et<sub>2</sub>O (50 mL  $\times$  3). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, 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). [ $\alpha$ ]<sub>D</sub><sup>20</sup> 9.72 (*c* 0.29, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.34 (s, 3H, CH<sub>3</sub>), 3.60–3.77 (m, 2H, CH<sub>2</sub>), 4.42 (s, 2H, CH<sub>2</sub>), 5.01–5.15 (m, 4H, 2CH<sub>2</sub>), 6.70 (s, 1H, NH), 7.16–7.30 (m, 13H, H<sub>ar</sub>), 9.55 (s, 1H, CHO); HRMS calcd for C<sub>27</sub>H<sub>27</sub>N<sub>2</sub>O<sub>6</sub>Cl<sub>2</sub> [M + H]<sup>+</sup> 545.12407, found 545.12390; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 85 : 15, flow rate 1.0 mL min<sup>-1</sup>,  $\lambda$  = 213 nm):  $t_R$  = 21.62 min (major),  $t_R$  = 23.77 min (minor).

NaBH<sub>4</sub> (190 mg, 5.0 mmol) was added to a solution of **4a-*p*-ClBn** (900 mg, 1.65 mmol) in CH<sub>2</sub>Cl<sub>2</sub>/C<sub>2</sub>H<sub>5</sub>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<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, 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; [ $\alpha$ ]<sub>D</sub><sup>20</sup> -12.3 (*c* 0.13, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.24 (s, 3H, CH<sub>3</sub>), 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<sub>2</sub>), 5.06 (s, 2H, CH<sub>2</sub>), 6.49 (bs, 1H, NH), 7.24–7.36 (m, 10H, H<sub>ar</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  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 C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>5</sub>Cl [M + H]<sup>+</sup> 405.1212, found 405.1204; HPLC (Daicel Chiralpak OD-H, hexane/isopropanol = 90 : 10, flow rate 1.0 mL min<sup>-1</sup>,  $\lambda$  = 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%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.24 (s, 3H, CH<sub>3</sub>), 2.29 (s, 3H, CH<sub>3</sub>), 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, CH<sub>2</sub>), 5.12 (s, 2H, CH<sub>2</sub>), 6.39 (bs, 1H, NH), 7.13–7.18 (m, 4H, H<sub>ar</sub>), 7.31–7.37 (m, 5H, H<sub>ar</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  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<sub>21</sub>H<sub>25</sub>N<sub>2</sub>O<sub>5</sub> [M + H]<sup>+</sup> 385.1758, found 385.1738; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 90 : 10, flow rate 1.0 mL min<sup>-1</sup>,  $\lambda$  = 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%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.23 (s, 3H, CH<sub>3</sub>), 2.30 (s, 3H, CH<sub>3</sub>), 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<sub>2</sub>), 5.08 (s, 2H, CH<sub>2</sub>), 6.22 (bs, 1H, NH), 7.13–7.16 (m,

4H, H<sub>ar</sub>), 7.26 (d, 2H, *J* = 8.0 Hz, H<sub>ar</sub>), 7.32 (d, 2H, *J* = 8.0 Hz, H<sub>ar</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) 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 C<sub>21</sub>H<sub>24</sub>N<sub>2</sub>O<sub>5</sub>Cl [M + H]<sup>+</sup> 419.1368, found 419.1359; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 90 : 10, flow rate 1.0 mL min<sup>-1</sup>, λ = 254 nm): t<sub>R</sub> = 23.38 min (major), t<sub>R</sub> = 26.35 min (minor), 54% ee.

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

Oil, yield 78%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.20 (m, 6H, 2 CH<sub>3</sub>), 3.21 (d, 1H, *J* = 8.0 Hz, CH), 3.40 (d, 1H, *J* = 8.0 Hz, CH), 3.82 (s, 3H, CH<sub>3</sub>), 3.84 (s, 3H, CH<sub>3</sub>), 4.01 (d, 1H, *J* = 8.0 Hz, CH), 4.08–4.13 (m, 2H, CH<sub>2</sub>), 4.28 (d, 1H, *J* = 8.0 Hz, CH), 4.37–4.44 (m, 2H, CH<sub>2</sub>), 6.45 (bs, 1H, NH), 6.76–6.80 (m, 3H, H<sub>ar</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) 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 C<sub>17</sub>H<sub>24</sub>N<sub>2</sub>O<sub>7</sub>Na [M + Na]<sup>+</sup> 391.1476, found 391.1471; HPLC (Daicel Chiralpak OD-H, hexane/isopropanol = 90 : 10, flow rate 1.0 mL min<sup>-1</sup>, λ = 254 nm): t<sub>R</sub> = 21.88 min (major), t<sub>R</sub> = 27.05 min (minor), 38% ee.

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

Oil, yield 67%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.22 (s, 3H, CH<sub>3</sub>), 3.22 (d, 1H, *J* = 8.0 Hz, CH<sub>2</sub>), 3.40 (d, 1H, *J* = 12.0 Hz, CH<sub>2</sub>), 3.80 (s, 3H, CH<sub>3</sub>), 3.84 (s, 3H, CH<sub>3</sub>), 4.03 (d, 1H, *J* = 8.0 Hz, CH), 4.30 (d, 1H, *J* = 8.0 Hz, CH), 4.41 (m, 2H, CH<sub>2</sub>), 5.11 (s, 2H, CH<sub>2</sub>), 6.347 (bs, 1H, NH), 6.79–6.82 (m, 3H, H<sub>ar</sub>), 7.25–7.35 (m, 5H, H<sub>ar</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) 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 C<sub>22</sub>H<sub>26</sub>N<sub>2</sub>O<sub>7</sub>Na [M + H]<sup>+</sup> 453.1632, found 453.1638; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 85 : 15, flow rate 1.0 mL min<sup>-1</sup>, λ = 254 nm): t<sub>R</sub> = 26.31 min (major), t<sub>R</sub> = 32.42 min (minor), 45% ee.

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

White solid, yield 75%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.21–1.26 (m, 6H, 2 CH<sub>3</sub>), 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, CH<sub>2</sub>), 4.30 (d, 1H, *J* = 12.0 Hz, CH), 4.43–4.50 (m, 2H, CH<sub>2</sub>), 6.61 (bs, 1H, NH), 6.70–7.04 (m, 2H, H<sub>ar</sub>), 7.22–7.26 (m, 2H, H<sub>ar</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) 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 C<sub>15</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub>F [M + H]<sup>+</sup> 327.1351, found 327.1341; HPLC (Daicel Chiralpak AS-H, hexane/isopropanol = 80 : 20, flow rate 1.0 mL min<sup>-1</sup>, λ = 254 nm): t<sub>R</sub> = 51.09 min (major), t<sub>R</sub> = 76.63 min (minor), 56% ee.

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

Oil, yield 80%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.33 (s, 3H, CH<sub>3</sub>), 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, CH<sub>2</sub>), 5.21 (s, 2H, CH<sub>2</sub>), 6.42 (bs, 1H, NH), 7.08 (t, *J* = 4.0 Hz, 2H,

H<sub>ar</sub>), 7.30 (d, 2H, *J* = 8.0 Hz, H<sub>ar</sub>), 7.40 (bs, 5H, H<sub>ar</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) 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 C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>5</sub>F [M + H]<sup>+</sup> 389.1507, found 389.1502; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 90 : 10, flow rate 1.0 mL min<sup>-1</sup>, λ = 254 nm): t<sub>R</sub> = 22.44 min (major), t<sub>R</sub> = 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%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.24 (s, 3H, CH<sub>3</sub>), 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, CH<sub>2</sub>), 5.07 (s, 2H, CH<sub>2</sub>), 6.84 (bs, 1H, NH), 7.00 (t, 2H, *J* = 8.0 Hz, H<sub>ar</sub>), 7.21–7.25 (m, 2H, H<sub>ar</sub>), 7.30 (d, 2H, *J* = 12.0 Hz, H<sub>ar</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) 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 C<sub>20</sub>H<sub>21</sub>N<sub>2</sub>O<sub>5</sub>ClF [M + H]<sup>+</sup> 423.1118, found 423.1104; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 90 : 10, flow rate 1.0 mL min<sup>-1</sup>, λ = 254 nm): t<sub>R</sub> = 36.19 min (major), t<sub>R</sub> = 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; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.25 (m, 6H, 2CH<sub>3</sub>), 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, CH<sub>2</sub>), 4.32 (d, 1H, *J* = 8.0 Hz, CH), 4.47–4.48 (m, 2H, CH<sub>2</sub>), 6.39 (bs, 1H, NH), 6.76–6.80 (m, 4H, H<sub>ar</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) 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 C<sub>15</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub>Cl [M + H]<sup>+</sup> 343.1055, found 343.1048; HPLC (Daicel Chiralpak OJ-H, hexane/isopropanol = 90 : 10, flow rate 1.0 mL min<sup>-1</sup>, λ = 254 nm): t<sub>R</sub> = 32.27 min (major), t<sub>R</sub> = 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; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.26 (s, 3H, CH<sub>3</sub>), 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, CH<sub>2</sub>), 5.13 (s, 2H, CH<sub>2</sub>), 6.60 (bs, 1H, NH), 7.19 (d, 2H, *J* = 8.0 Hz, H<sub>ar</sub>), 7.29–7.37 (m, 7H, H<sub>ar</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) 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 C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>5</sub>Cl [M + H]<sup>+</sup> 405.1212, found 405.1201; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 90 : 10, flow rate 1.0 mL min<sup>-1</sup>, λ = 254 nm): t<sub>R</sub> = 16.12 min (major), t<sub>R</sub> = 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; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.33 (s, 3H, CH<sub>3</sub>), 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, CH<sub>2</sub>), 5.20 (s, 2H, CH<sub>2</sub>), 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,  $CDCl_3$ )  $\delta$  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,  $CDCl_3$ )  $\delta$  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,  $CDCl_3$ )  $\delta$  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,  $CDCl_3$ )  $\delta$  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,  $CDCl_3$ )  $\delta$  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,  $CDCl_3$ )  $\delta$  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,  $CDCl_3$ )  $\delta$  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,  $CDCl_3$ )  $\delta$  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,  $CDCl_3$ )  $\delta$  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,  $CDCl_3$ )  $\delta$  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,  $CDCl_3$ )  $\delta$  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,  $CDCl_3$ )  $\delta$  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,  $CDCl_3$ )  $\delta$  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,  $CDCl_3$ )  $\delta$  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<sup>-1</sup>,  $\lambda$  = 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 NaBH<sub>4</sub> (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, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.34 (s, 3H, CH<sub>3</sub>), 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, CH<sub>2</sub>), 5.18 (s, 2H, CH<sub>2</sub>), 6.84 (bs, 1H, NH), 7.38–7.43 (m, 6H, H<sub>ar</sub>), 7.63 (d, 2H, *J* = 4.0 Hz, H<sub>ar</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  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  $C_{21}H_{21}N_2O_5ClF_3$   $[M + H]^+$  473.1084, found 473.1086; HPLC (Daicel Chiralpak AS-H, hexane/isopropanol = 70 : 30, flow rate 1.0 mL min<sup>-1</sup>,  $\lambda$  = 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%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.30 (s, 3H, CH<sub>3</sub>), 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, CH<sub>2</sub>), 5.13 (s, 2H, CH<sub>2</sub>), 6.82 (bs, 1H, NH), 7.25–7.35 (m, 5H, H<sub>ar</sub>), 7.41 (d, 2H, *J* = 8.0 Hz, H<sub>ar</sub>), 8.15 (d, 2H, *J* = 12.0 Hz, H<sub>ar</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  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<sup>-1</sup>,  $\lambda$  = 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%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.26 (s, 3H, CH<sub>3</sub>), 1.41–1.56 (m, 4H, 2 CH<sub>2</sub>), 1.60–1.74 (m, 4H, CH<sub>2</sub>), 3.34–3.84 (m, 4H, CH<sub>2</sub>), 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, CH<sub>2</sub>), 6.93 (bs, 1H, NH), 7.26–7.33 (m, 5H, H<sub>ar</sub>); 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<sup>-1</sup>,  $\lambda$  = 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%; <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$  0.86–0.96 (m, 3H, CH<sub>3</sub>), 1.24–1.33 (s, 3H, CH<sub>3</sub>), 1.55–1.70 (m, 2H, CH<sub>2</sub>), 4.06 (d, *J* = 6.0 Hz, 1H, CH), 4.20 (d, *J* = 6.0 Hz, 1H, CH), 5.19 (s, 2H, CH<sub>2</sub>), 6.53 (bs, 1H, NH), 7.26–7.38 (m, 5H, H<sub>ar</sub>); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$  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<sup>-1</sup>,  $\lambda$  = 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%; <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  1.26 (t, *J* = 6.0 Hz, 3H, CH<sub>3</sub>), 1.56 (s, 3H, CH<sub>3</sub>), 4.18–4.22 (m, 2H, CH<sub>2</sub>), 5.16 (s, 4H, 2 CH<sub>2</sub>), 6.60 (brs, 1H, NH), 7.25–7.32 (m, 10H, H<sub>ar</sub>), 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<sup>-1</sup>,  $\lambda$  = 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, CH<sub>3</sub>OH); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.20 (s, 3H, CH<sub>3</sub>), 3.31 (dd, 1H, *J* = 12.0 Hz, 1 Hz, CH), 3.55 (bs, 3H, NH<sub>2</sub> 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 NaNO<sub>2</sub> 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, CH<sub>3</sub>OH); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.34 (s, 3H, CH<sub>3</sub>), 3.55 (dd, 1H, *J* = 12.0 Hz, 4 Hz, CH<sub>2</sub>), 4.04 (d, 1H, *J* = 8.0 Hz, CH), 4.33 (d, 1H, *J* = 8.0 Hz, CH), 5.59 (bs, 1H, NH); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$  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), K<sub>2</sub>CO<sub>3</sub> (207 mg, 1.5 mmol) and **10** (157 mg, 0.5 mmol) in toluene : EtOH : H<sub>2</sub>O = 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 Et<sub>2</sub>O and washed with brine. The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) 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; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.04 (t, 3H, *J* = 8.0 Hz, CH<sub>3</sub>), 1.84–1.89 (m, 2H, CH<sub>2</sub>), 2.83 (m, 2H, CH<sub>2</sub>), 7.69 (m, 2H, H<sub>ar</sub>), 7.78–7.85 (m, 4H, H<sub>ar</sub>), 7.89 (s, 1H, H<sub>ar</sub>), 7.95–8.01 (m, 4H, H<sub>ar</sub>), 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)vinyloxadolidin-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.  $\text{NH}_4\text{Cl}$ , the resulting biphasic mixture was extracted with AcOEt. The combined organic layer was washed with water and brine, dried over  $\text{Na}_2\text{SO}_4$ , 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,  $\text{CH}_3\text{OH}$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.03 (t, 3H,  $J = 8.0$  Hz,  $\text{CH}_3$ ), 1.81–1.90 (m, 2H,  $\text{CH}_2$ ), 2.82 (t, 2H,  $J = 8.0$  Hz,  $\text{CH}_2$ ), 4.17–4.21 (m, 1H, CH), 4.58–4.65 (m, 2H,  $\text{CH}_2$ ), 5.12 (s, 1H, NH), 6.16–6.22 (m, 1H, CH), 6.66 (d, 1H,  $J = 16.0$  Hz, CH), 7.46 (d, 2H,  $J = 8.0$  Hz,  $\text{H}_{\text{ar}}$ ), 7.59–7.65 (m, 4H,  $\text{H}_{\text{ar}}$ ), 7.80 (d, 2H,  $J = 8.0$  Hz,  $\text{H}_{\text{ar}}$ ), 7.87 (s, 1H,  $\text{H}_{\text{ar}}$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  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,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.04 (t, 3H,  $J = 8.0$  Hz,  $\text{CH}_3$ ), 1.44 (s, 3H,  $\text{CH}_3$ ), 1.84–1.89 (m, 2H,  $\text{CH}_2$ ), 1.93–1.97 (m, 2H,  $\text{CH}_2$ ), 2.70–2.74 (m, 2H,  $\text{CH}_2$ ), 2.75–2.86 (m, 2H,  $\text{CH}_2$ ), 4.10 (d, 1H,  $J = 8.0$  Hz, CH), 4.22 (d, 1H,  $J = 8.0$  Hz, CH), 5.42 (bs, 1H, NH), 7.25 (d, 1H,  $J = 8.0$  Hz, CH), 7.55 (d, 1H,  $J = 8.0$  Hz, CH), 7.61 (d, 2H,  $J = 8.0$  Hz,  $\text{H}_{\text{ar}}$ ), 7.79 (m, 2H,  $J = 8.0$  Hz,  $\text{H}_{\text{ar}}$ ), 7.86 (s, 1H,  $\text{H}_{\text{ar}}$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{CH}_2\text{Cl}_2$ . The combined organic layer was washed with water and brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated. The crude product was chromatographed (silica gel, dichloromethane/methanol = 10 : 1), then added 1 M HCl in  $\text{Et}_2\text{O}$  (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,  $\text{CH}_3\text{OH}$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.01 (t, 3H,  $J = 8.0$  Hz,

$\text{CH}_3$ ), 1.34 (s, 3H,  $\text{CH}_3$ ), 1.81–1.92 (m, 2H,  $\text{CH}_2$ ), 2.68–2.72 (m, 2H,  $\text{CH}_2$ ), 2.83–2.86 (m, 2H,  $\text{CH}_2$ ), 3.52–3.57 (m, 2H,  $\text{CH}_2$ ), 3.62–3.65 (m, 2H,  $\text{CH}_2$ ), 7.31 (d, 2H,  $J = 8.0$  Hz,  $\text{H}_{\text{ar}}$ ), 7.58 (d, 2H,  $J = 8.0$  Hz,  $\text{H}_{\text{ar}}$ ), 7.65 (d, 2H,  $J = 8.0$  Hz,  $\text{H}_{\text{ar}}$ ), 7.77 (d, 2H,  $J = 8.0$  Hz,  $\text{H}_{\text{ar}}$ ), 8.23 (s, 1H,  $\text{H}_{\text{ar}}$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  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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