#### **RSC Advances**



#### **PAPER**

View Article Online
View Journal | View Issue



Cite this: RSC Adv., 2019, 9, 33497

# 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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Received 9th August 2019 Accepted 24th September 2019

DOI: 10.1039/c9ra06210f

rsc li/rsc-advances

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.

#### 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, 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  $\alpha$ -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  $\alpha$ -amination of branched aldehydes with azadicarboxylates to give  $\alpha$ -alkyl- $\alpha$ -aryl disubstituted aldehydes in up to 99% ee. 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. 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 α-amination of α-methylα-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 enantio-selectivities (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

Fig. 1 Chiral catalysts.

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<sup>†</sup> Electronic supplementary information (ESI) available. See DOI: 10.1039/c9ra06210f

COOH COOH
NH2 NH2 HCI
NH2 NH2 HCI
NH2

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

Entry	Catalyst	Time (h)	$Yield^{b}$ (%)	ee <sup>c</sup> (%)
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

 $<sup>^</sup>a$  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  $\alpha$ -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	$CH_2Cl_2$	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>&</sup>lt;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-α-protected hydroxymethyl substituted aldehydes with aromatic ring. The results also showed that electronwithdrawing groups were more successful than electrondonating 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 azadicarboxylate (DEAD) or diisopropyl azadicarboxylate (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 α-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-2aminoethanol 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.<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.24 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.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 Et<sub>2</sub>O 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<sup>a</sup>

$$O \nearrow R_1 \qquad + \bigvee_{R_2O \nearrow N} O \qquad Cat. 1d (15 \text{ mol}\%) \qquad OR_2 \\ \downarrow R_1 \qquad \qquad NaBH_4 \qquad OR_2 \\ \downarrow R_1 \qquad \qquad \downarrow N_1 \\ \downarrow R_1 \qquad \qquad \downarrow N_2 \\ \downarrow R_1 \qquad \qquad \downarrow N_1 \\ \downarrow R_1 \qquad \qquad \downarrow N_2 \\ \downarrow R_1 \qquad \qquad \downarrow N_2 \\ \downarrow R_1 \qquad \qquad \downarrow N_1 \\ \downarrow R_1 \qquad \qquad \downarrow N_2 \\ \downarrow R_1 \qquad \qquad \downarrow N_3 \\ \downarrow R_1 \qquad \qquad \downarrow N_2 \\ \downarrow R_1 \qquad \qquad \downarrow N_3 \\ \downarrow R_1 \qquad \qquad \downarrow N_2 \\ \downarrow R_1 \qquad \qquad \downarrow N_3 \\ \downarrow R_1 \qquad \qquad \downarrow N_3 \\ \downarrow R_1 \qquad \qquad \downarrow N_2 \\ \downarrow R_1 \qquad \qquad \downarrow N_3 \\ \downarrow R_2 \qquad \qquad \downarrow N_3 \\ \downarrow R_1 \qquad \qquad \downarrow N_3 \\ \downarrow R_2 \qquad \qquad \downarrow N_3 \\ \downarrow R_3 \qquad \qquad \downarrow N_$$

Entry	R <sub>1</sub>	$R_2$	Product	Time (h)	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)	ee <sup>e</sup> (%)
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-p-ClBn	48	80	$71^d$	97%
4	$BnOCH_2$	<i>p</i> -ClBn	5a-p-ClBn	1	94	72	>99%
5	p-CH <sub>3</sub> BnOCH <sub>2</sub>	Bn	5b-Bn	38	54	48	_
6	p-CH <sub>3</sub> BnOCH <sub>2</sub>	<i>p</i> -ClBn	5b-p-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	p-FBnOCH <sub>2</sub>	Et	5d-Et	37	75	56	_
10	p-FBnOCH <sub>2</sub>	Bn	5d-Bn	36	80	68	_
11	p-FBnOCH <sub>2</sub>	<i>p</i> -ClBn	5d-p-ClBn	48	89	70	_
12	p-ClBnOCH <sub>2</sub>	Et	5e-Et	39	70	57	_
13	p-ClBnOCH <sub>2</sub>	Bn	5e-Bn	36	63	59	_
14	$p ext{-BrBnOCH}_2$	Bn	5f-Bn	38	79	59	_
15	$p$ -BrBnOCH $_2$	<i>p</i> -ClBn	5f-p-ClBn	48	75	52	_
16	$p$ -CNBnOCH $_2$	Et	5g-Et	28	81	57	_
17	$p$ -CNBnOCH $_2$	Bn	5g-Bn	24	71	65	_
18	$p$ -CNBnOCH $_2$	<i>p</i> -ClBn	5g-p-ClBn	48	73	62	_
19	p-CF <sub>3</sub> BnOCH <sub>2</sub>	Et	5h-Et	39	76	56	_
20	p-CF <sub>3</sub> BnOCH <sub>2</sub>	Bn	5h-Bn	36	89	67	_
21	$p$ -CF $_3$ BnOCH $_2$	<i>p</i> -ClBn	4h-p-ClBn	48	90	$74^d$	97%
22	p-CF <sub>3</sub> BnOCH <sub>2</sub>	<i>p</i> -ClBn	5h- <i>p</i> -ClBn	1	95	73	98%
23	p-NO <sub>2</sub> BnOCH <sub>2</sub>	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 <sub>2</sub> Et	Bn	4m-Bn	48	76	24	

 $<sup>^</sup>a$  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  $\alpha$ -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  $\text{CH}_2\text{Cl}_2$ . The combined organic phases were dried over  $\text{Na}_2\text{SO}_4$ , 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 products 5-R as oil or solid.

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

White solid, yield 79%; mp 50–55 °C;  $^1$ 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>);  $^{13}$ C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  14.3, 19.8,

Scheme 1 Synthesis of the  $\alpha\text{-substituted}$  alaninol compound as  $\text{S1P}_1$  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  $C_{15}H_{21}N_2O_5$  [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.

### ${\it 3-} Benzyloxy carbonylamino-4-methyl-4-benzyloxy-oxazolidin-2-one \\ (5a-Bn)$

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 guenched by the addition H2O, then extracted three times with Et2O (50 ml ×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).  $[\alpha]_D^{20}$  9.72 (c 0.29, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 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  $C_{27}H_{27}N_2O_6Cl_2$  [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 ag, 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;  $[\alpha]_D^{20} - 12.3$  (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, I = 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,  $CDCl_3$ )  $\delta$  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  $C_{20}H_{22}N_2O_5Cl [M + H]^+$  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 (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>);  $^{13}$ C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  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>,  $\lambda=254$  nm):  $t_{\rm R}=23.38$  min (major),  $t_{\rm R}=26.35$  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>)  $\delta$  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>)  $\delta$  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>,  $\lambda$  = 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%;  $^1\mathrm{H}$  NMR (400 MHz, CDCl $_3$ )  $\delta$  1.22 (s, 3H, CH $_3$ ), 3.22 (d, 1H, J=8.0 Hz, CH $_2$ ), 3.40 (d, 1H, J=12.0 Hz, CH $_2$ ), 3.80 (s, 3H, CH $_3$ ), 3.84 (s, 3H, CH $_3$ ), 4.03 (d, 1H, J=8.0 Hz, CH), 4.30 (d, 1H, J=8.0 Hz, CH), 4.30 (d, 1H, J=8.0 Hz, CH), 4.41 (m, 2H, CH $_2$ ), 5.11 (s, 2H, CH $_2$ ), 6.347 (bs, 1H, NH), 6.79–6.82 (m, 3H, H $_3$ ), 7.25–7.35 (m, 5H, H $_3$ );  $^{13}\mathrm{C}$  NMR (100 MHz, CDCl $_3$ )  $\delta$  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 $_{22}\mathrm{H}_{26}\mathrm{N}_2\mathrm{O}_7\mathrm{Na}$  [M + H]  $^+$  453.1632, found 453.1638; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 85 : 15, flow rate 1.0 mL min  $^{-1}$ ,  $\lambda$  = 254 nm):  $t_\mathrm{R}$  = 26.31 min (major),  $t_\mathrm{R}$  = 32.42 min (minor), 45% ee.

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

White solid, yield 75%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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>)  $\delta$  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>,  $\lambda$  = 254 nm):  $t_R$  = 51.09 min (major),  $t_R$  = 76.63 min (minor), 56% ee.

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

Oil, yield 80%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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,

 $\rm H_{ar}$ ), 7.30 (d, 2H, J=8.0 Hz,  $\rm H_{ar}$ ), 7.40 (bs, 5H,  $\rm H_{ar}$ ); <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  $\rm C_{20}H_{22}N_2O_5F$  [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>,  $\lambda=254$  nm):  $t_{\rm R}=22.44$  min (major),  $t_{\rm R}=24.32$  min (minor), 68% ee.

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

Oil, yield 89%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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>)  $\delta$  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>,  $\lambda$  = 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)benzyloxyoxazolidin-2-one (5e-Et)

White solid, yield 78%, mp 80–85 °C; ¹H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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>); ¹³C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  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>,  $\lambda$  = 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)benzyloxyoxazolidin-2-one (5e-Bn)

White solid, yield 63%; mp 75–80 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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>)  $\delta$  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>,  $\lambda$  = 254 nm):  $t_R$  = 16.12 min (major),  $t_R$  = 17.62 min (minor), 59% ee.

### 3-Benzyloxycarbonylamino-4-methyl-4-(4-bromo)benzyloxyoxazolidin-2-one (5f-Bn)

White solid, yield 79%; mp 80–84 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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),

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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<sub>3</sub>)  $\delta$  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]<sup>+</sup> 449.0707, found 449.0710; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 85:15, flow rate 1.0 mL min<sup>-1</sup>,  $\lambda=254$  nm):  $t_R=19.46$  min

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

(major),  $t_R = 21.85 \text{ min (minor)}$ , 59% ee.

Oil, yield 75%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.27 (s, 3H, CH<sub>3</sub>), 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<sub>2</sub>), 5.11 (s, 2H, CH<sub>2</sub>), 6.27 (bs, 1H, NH), 7.14 (d, 2H, J=8.0 Hz, H<sub>ar</sub>), 7.27 (d, 2H, J=8.0 Hz, H<sub>ar</sub>), 7.33 (d, 2H, J=8.0 Hz, H<sub>ar</sub>), 7.47 (d, 2H, J=8.0 Hz, H<sub>ar</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  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<sub>20</sub>H<sub>21</sub>N<sub>2</sub>O<sub>5</sub>-ClBr [M + H]<sup>+</sup> 483.0317, found 483.0315; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 85:15, flow rate 1.0 mL min<sup>-1</sup>,  $\lambda$  = 254 nm):  $t_R$  = 22.65 min (major),  $t_R$  = 27.78 min (minor), 59% ee.

### 3-Ethyloxycarbonylamino-4-methyl-4-(4-cyano)benzyloxyoxazolidin-2-one (5g-Et)

Oil, yield 81%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.22 (m, 6H, 2 CH<sub>3</sub>), 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<sub>2</sub>), 4.34 (d, 1H, J = 12.0 Hz, CH), 4.51–4.62 (m, 2H, CH<sub>2</sub>), 6.892 (bs, 1H, NH), 7.36 (d, 2H, J = 8.0 Hz, H<sub>ar</sub>), 7.58 (d, 2H, J = 8.0 Hz, H<sub>ar</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  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<sub>16</sub>H<sub>20</sub>N<sub>3</sub>O<sub>5</sub> [M + H]<sup>+</sup> 334.1398, found 334.1416; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 90 : 10, flow rate 1.0 mL min <sup>-1</sup>,  $\lambda$  = 254 nm): t<sub>R</sub> = 43.74 min (minor), t<sub>R</sub> = 48.41 min (major), 57% ee.

### 3-Benzyloxycarbonylamino-4-methyl-4-(4-cyano)benzyloxyoxazolidin-2-one (5g-Bn)

Oil, yield 71%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.27 (s, 3H, CH<sub>3</sub>), 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<sub>2</sub>), 5.10 (s, 2H, CH<sub>2</sub>), 7.09 (bs, 1H, NH), 7.25–7.35 (m, 7H, H<sub>ar</sub>), 7.55 (d, 2H, J = 8.0 Hz, H<sub>ar</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  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<sub>21</sub>H<sub>22</sub>N<sub>3</sub>O<sub>5</sub> [M + H]<sup>+</sup> 396.1554, found 396.1573; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 90 : 10, flow rate 1.0 mL min<sup>-1</sup>,  $\lambda$  = 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%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.28 (s, 3H, CH<sub>3</sub>), 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<sub>2</sub>), 5.09 (s, 2H, CH<sub>2</sub>), 6.62 (bs, 1H, NH), 7.25 (d, 2H, J=4.0 Hz, H<sub>ar</sub>), 7.31 (d, 2H, J=8.0 Hz, H<sub>ar</sub>), 7.37 (d, 2H, J=8.0 Hz, H<sub>ar</sub>), 7.59 (d, 2H, J=8.0 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, 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<sub>21</sub>H<sub>21</sub>N<sub>3</sub>O<sub>5</sub>Cl [M + H]<sup>+</sup> 430.1164, found 430.1159; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 85 : 15, flow rate 1.0 mL min<sup>-1</sup>,  $\lambda=254$  nm):  $t_{\rm R}=50.46$  min (major),  $t_{\rm R}=57.77$  min (minor), 62% ee.

### 3-Ethyloxycarbonylamino-4-methyl-4-(4-trifluoro)benzyloxyoxazolidin-2-one (5h-Et)

White solid, yield 76%;  $^{1}$ H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.23 (t, 3H, J = 8.0 Hz, CH<sub>3</sub>), 1.29 (s, 3H, CH<sub>3</sub>), 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<sub>2</sub>), 4.34 (d, 1H, J = 8.0 Hz, CH), 4.52–4.62 (m, 2H, CH<sub>2</sub>), 6.78 (bs, 1H, NH), 7.38 (d, 2H, J = 8.0 Hz, H<sub>ar</sub>), 7.58 (d, 2H, J = 8.0 Hz, H<sub>ar</sub>);  $^{13}$ C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  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<sub>16</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub>F<sub>3</sub> [M + H]<sup>+</sup> 377.1319, found 377.1315; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 90 : 10, flow rate 1.0 mL min<sup>-1</sup>,  $\lambda$  = 254 nm):  $t_R$  = 13.40 min (minor),  $t_R$  = 15.24 min (major), 56% ee.

### 3-Benzyloxycarbonylamino-4-methyl-4-(4-trifluoro)benzyloxyoxazolidin-2-one (5h-Bn)

Oil, yield 89%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.27 (s, 3H, CH<sub>3</sub>), 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<sub>2</sub>), 5.12 (s, 2H, CH<sub>2</sub>), 6.87 (bs, 1H, NH), 7.25–7.38 (m, 7H, H<sub>ar</sub>), 7.58 (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, 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<sub>21</sub>H<sub>22</sub>N<sub>2</sub>O<sub>5</sub>F<sub>3</sub> [M + H]<sup>+</sup> 439.1475, found 439.1470; HPLC (Daicel Chiralpak AS-H, hexane/isopropanol = 80 : 20, flow rate 1.0 mL min<sup>-1</sup>,  $\lambda$  = 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  $\rm H_2O$ , then extracted three times with  $\rm Et_2O$  (50 mL  $\times$ 3). The combined organic layers were dried over  $\rm Na_2SO_4$ , filtered, and concentrated. The resulting crude was purified by flash chromatography on silica gel, eluting with light petroleum etherethyl 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; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.32 (s, 3H, CH<sub>3</sub>), 3.71–3.87 (m, 2H, CH<sub>2</sub>), 4.54 (s, 2H, CH<sub>2</sub>), 5.10–5.20 (m, 4H, 2CH<sub>2</sub>), 6.71 (s, 1H, NH), 7.22–7.38 (m, 10H,  $\rm H_{ar}$ ), 7.62 (d, 2H,  $\it J$  = 4.0 Hz,  $\rm H_{ar}$ ), 9.62 (s, 1H, CHO);

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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),  $t_R = 20.29 \text{ min (minor)}$ .

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.  $\left[\alpha\right]_{D}^{20}$  -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 = 8.0 Hz, CH)4.0 Hz, CH), 4.38 (d, 1H, J = 4.0 Hz, CH),  $4.56-4.46 \text{ (m, 2H, CH}_2 \text{)}$ , 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<sub>21</sub>H<sub>21</sub>N<sub>2</sub>O<sub>5</sub>-ClF<sub>3</sub> [M + H]<sup>+</sup> 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,  $H_{ar}$ ), 7.41 (d, 2H, J = 8.0 Hz,  $H_{ar}$ ), 8.15 (d, 2H, J = 12.0 Hz,  $H_{ar}$ ); <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  $(m, 5H, H_{ar})$ ; 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<sup>-1</sup>,  $\lambda$  = 254 nm):  $t_{\rm R} = 26.0 \, \text{min}$  (major),  $t_{\rm R} = 34.5 \, \text{min}$  (minor), 60% ee.

#### Benzyl(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>): δ 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,  $H_{ar}$ ); <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-1,2dicarboxylate (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),  $t_R = 22.78 \text{ min (minor)}$ , 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;  $[\alpha]_{\rm D}^{20}$  -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);  $^{13}$ 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 :  $H_2O = 1 : 1 : 1 \text{ (v/v/v)}$ . 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,  $H_{ar}$ ), 10.06 (s, 1H, CHO); HRMS calcd for  $C_{19}H_{18}NO_2$  [M + H]<sup>+</sup> 292.1332, found 292.1335.

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#### (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. NH<sub>4</sub>Cl, 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;  $[\alpha]_D^{20}$  –17.8 (c 0.1, CH<sub>3</sub>OH); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.03 (t, 3H, J = 8.0 Hz, CH<sub>3</sub>), 1.81–1.90 (m, 2H,  $CH_2$ ), 2.82 (t, 2H, J = 8.0 Hz,  $CH_2$ ), 4.17-4.21 (m, 1H, CH), 4.58-4.65 (m, 2H, CH<sub>2</sub>), 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,  $H_{ar}$ ), 7.59–7.65 (m, 4H,  $H_{ar}$ ), 7.80 (d, 2H, J = 8.0 Hz,  $H_{ar}$ ), 7.87 (s, 1H,  $H_{ar}$ ); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  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  $C_{24}H_{25}N_2O_3 [M + H]^{\dagger}$ 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 °C;  $[\alpha]_{D}^{20}$  14.4 (c 0.5, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.04 (t, 3H,  $J = 8.0 \text{ Hz}, \text{CH}_3$ , 1.44 (s, 3H, CH<sub>3</sub>), 1.84–1.89 (m, 2H, CH<sub>2</sub>), 1.93– 1.97 (m, 2H, CH<sub>2</sub>), 2.70-2.74 (m, 2H, CH<sub>2</sub>), 2.75-2.86 (m, 2H,  $CH_2$ , 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,  $H_{ar}$ ), 7.79 (m, 2H, J = 8.0 Hz,  $H_{ar}$ ), 7.86 (s, 1H,  $H_{ar}$ ); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  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  $C_{24}H_{27}N_2O_3 [M + H]^+$  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:  $H_2O = 10:1$  (v/v), then potassium hydroxide (146 mg, 2.6 mmol) was added, which was refluxed for 18 h. After cooling to room temperature, water was added to the reaction mixture and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layer was washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated. The crude product was chromatographed (silica gel, dichloromethane/methanol = 10:1), then added 1 M HCl in Et<sub>2</sub>O (2 mL) to afford the product 14 (82 mg, 80%) as a white solid. Mp 214 °C;  $[\alpha]_D^{20}$  -1.61 (c 0.2, CH<sub>3</sub>OH); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.01 (t, 3H, J = 8.0 Hz,

CH<sub>3</sub>), 1.34 (s, 3H, CH<sub>3</sub>), 1.81-1.92 (m, 2H, CH<sub>2</sub>), 2.68-2.72 (m, 2H, CH<sub>2</sub>), 2.83-2.86 (m, 2H, CH<sub>2</sub>), 3.52-3.57 (m, 2H, CH<sub>2</sub>), 3.62-3.65 (m, 2H, CH<sub>2</sub>), 7.31 (d, 2H, J = 8.0 Hz, H<sub>ar</sub>), 7.58 (d, 2H, J =8.0 Hz,  $H_{ar}$ ), 7.65 (d, 2H, J = 8.0 Hz,  $H_{ar}$ ), 7.77 (d, 2H, J = 8.0 Hz,  $H_{ar}$ ), 8.23 (s, 1H,  $H_{ar}$ ); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  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  $C_{23}H_{29}N_2O_2$  [M + H]<sup>+</sup> 365.2224, found 365.2212.

#### Conflicts of interest

There are no conflicts to declare.

#### Acknowledgements

This work was financially supported by the Drug Innovation Major Project (No. 2018ZX09711001-005-012), National Key R&D Program of China (No. 2018YFC1706403) and CAMS Innovation Fund for Medical Sciences (No. 2016-I2M-2-002).

#### Notes and references

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

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