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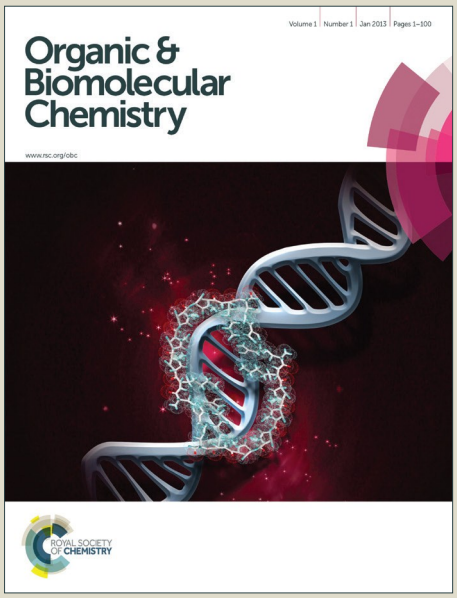

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ARTICLE

From Racemic Precursors to Fully Stereocontrolled Products: One-Pot Synthesis of Chiral α-Amino Lactones and Lactams

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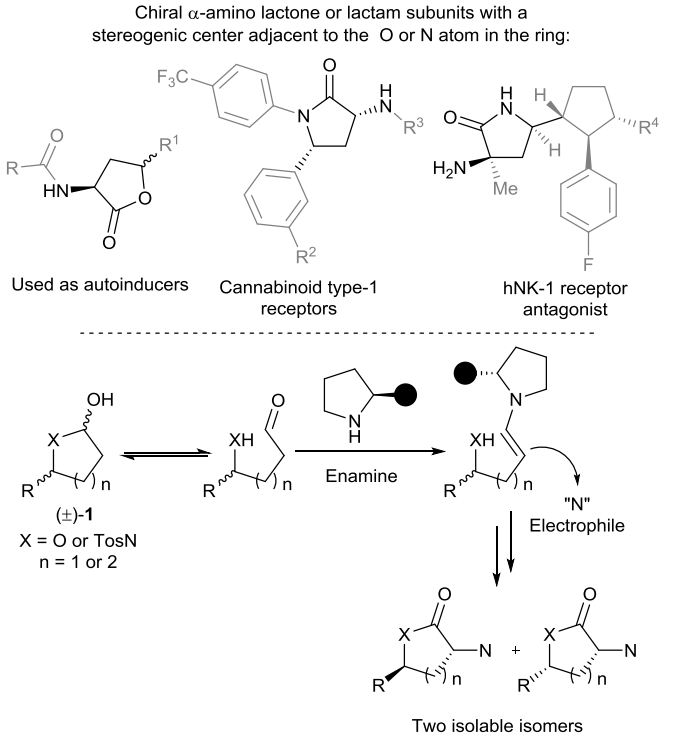
Substituted racemic lactols or cyclic hemiaminals were directly used as nucleophiles in enamine-based asymmetric amination reaction to access enantioenriched α-amino lactones or lactams via one-pot sequence. The desired products, which are very important building blocks in organic synthesis but difficult to be prepared optically enriched, could be afforded with two stereogenic centers in high yields with excellent enantioselectivities. Moreover, starting from the racemic precursors and catalyzed by the enantiomeric pair of the catalyst, all possible stereoisomeric products were discretely provided only after simple column chromatography. Additionally, this protocol provides facile access to several novel bicyclic carbamates, and such drug-like heterocyclic compounds should be potentially useful in medicinal chemistry.

Introduction

Currently, the design and synthesis of polyfunctionalized heterocyclic synthons which contain multiple stereogenic centers have become an active topic of research. Along this line, there was a challenging issue in the field of asymmetric synthesis, establishing practical and efficient access to useful chiral heterocyclic building blocks. Particularly, it is highly desirable from a synthetic point of view that, when starting from racemic materials, diastereo- and enantiomerically pure compounds are finally obtained only after simple work up, such as column chromatography, which makes the overall process more atom-efficient and attractive.[1]

Chiral α-amino lactones or lactams, especially containing a stereogenic center adjacent to the O or N atom in the ring, are the structural feature of numerous biologically active natural products and pharmaceuticals (Scheme 1, upper structures).[2,3] Moreover, functionalized chiral α-amino γ-lactones are also the crucial precursors for the preparation of α-amino acids with a hydroxyl group in γ position which are an important class of naturally occurring products.[4] In spite of their promising biological activities, the stereocontrolled synthesis of chiral α-amino lactones or lactams with multiple stereogenic centers has remained a challenging issue. Indeed, among the documented examples, stepwise process is generally involved in the formation of all chiral centers on the ring system of lactones or lactams, and relies mainly on the application of enzymatic resolution,[5] chiral auxiliaries,[6] or chiral starting materials.[7] In addition, most cases still suffered from several related drawbacks, including low efficiency,[8] costly transition metal catalysis,[9] or scope restrictions.[10] Accordingly, the development of new, flexible, and expedient protocols for the preparation of these valuable heterocycles is of significant importance.

As part of our continuous research efforts toward the chemistry of lactols and cyclic hemiaminals,[11,12] we have been interested in exploring a rapid access, which could meet the



Scheme 1. Selected biologically active compounds and our projected novel synthetic strategy.

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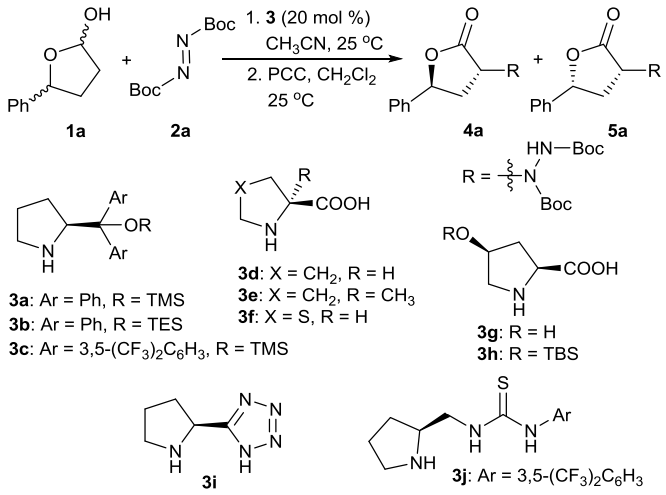
requirements of atom economy and provide chiral α-amino lactones and lactams with excellent enantio- and diastereoselectivities. In the stereodivergent reaction process (Scheme 1, lower equation),[1c] substituted racemic lactols or cyclic hemiaminals were directly used as nucleophiles in the asymmetric catalytic amination reaction under enamine-based activation,[13,14] and the subsequent oxidation step afforded the desired chiral α-amino lactones or lactams with multiple stereogenic centers as a single diastereoisomer only after simple column chromatography workup.

Results and discussion

To prove the viability of the direct enantioselective amination of lactol, we conducted the reaction of racemic lactol **1a** and di-*tert*-butyl azodicarboxylate **2a** in CH_3CN at room temperature in the presence of organocatalyst **3**, and after the amination step, a subsequent pyridine chlorochromate (PCC)-mediated oxidation reaction finished the desired products **4a** and **5a** as two isolable diastereoisomers in one-pot sequence (Table 1). According to the results in Table 1, we could rationalize the structure features of catalysts applied in these reactions, which exhibited significantly different catalytic activity and enantioselectivity toward the amination process, as the following: (1) diarylprolinol derivatives normally resulted with moderate to good enantiomeric excess (ee) for both of the diastereomeric products **4a** and **5a**.[15] It should be noted that the increased steric hindrance of silyl substituents of the catalyst would benefit to improve the stereoselectivity (Table 1, entries 1-3). (2) Proline type catalysts, which contained a carboxylic acid group, are much more efficient and showed very good catalytic activity and enantioselectivity.[16] However, it is unclear for us why no reaction occurs when **3f** is applied in the reaction. Moreover, it is worth mentioning that the unprotected hydroxyl group in *cis*-4-hydroxy-L-proline played a crucial role in the catalytic activity, since the reaction completely shut down when **3g** was used as the catalyst (Table 1, entries 4-8). (3) Catalysts with dual-activation via stronger H-bonding interaction proved to be promising catalysts.[17] Indeed, prolinetetrazole **3i** showed the best result in this asymmetric transformation (Table 1, entries 9-10).[18] Since catalysts **3d** and **3i** gave similar results, however, compared with the preparation of **3i**,[19] and also from the atom-economy standpoint, L-proline **3d** was finally chosen as the optimal catalyst. Moreover, to our delight, the amount of the catalyst **3d** had almost no effect on the process, decreasing the amount of catalyst to 10 mol % and 5 mol%, respectively, caused only a slightly longer reaction time while both the yield and enantioselectivity remained unchanged (Table 1, entries 11-12).

Given the established ability of **3d** promoting the stereoselective conjugate addition of **1a** and **2a**, various substituted racemic lactols **1** and azodicarboxylates **2** were studied under the optimized conditions, and the results are summarized in Table 2. Aromatic (Table 2, entries 1–9), heteroaromatic (Table 2, entry 10), and aliphatic (Table 2, entries 11–12) substituted racemic lactols were all converted to **4a**-**l** and **5a**-**l** with high to excellent level of enantiomeric excess in moderate to high yields. The reactivity of azodicarboxylate compounds **2** were also investigated for the direct α-amination of **1**, and the corresponding products were obtained with slightly lower enantioselectivities while in good isolated yields (Table 2, entries 13 and 14). Moreover, the lactol containing a six-membered ring was also well tolerated, and gave the aminated product **4o** and **5o** in high yield and with excellent enantioselectivity (Table 2, entry 15). Surprisingly, in several selected cases, a drastic increase in the enantioselectivity was obtained when prolinetetrazole **3i** was applied as the catalyst (Table 2, entries 1, 2, 7, 13 and 14). It should be noted that, in all the cases, both **4** and **5** were obtained as a single diastereoisomer, respectively. Finally, the possibility to easily isolate the two diastereoisomers for all of adducts **4** and **5** by column chromatography testifies to the synthetic utility of this process.

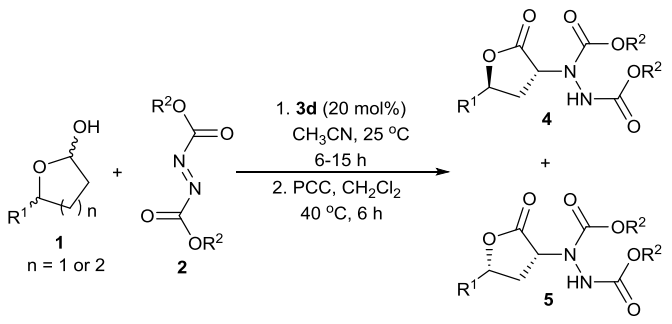
Table 1. Selected Optimization Studies[a]



Entry	3	Time (h)	Yield (%) 4a/5a	ee (%) 4a/5a
1[b]	**3a**	3	37/43	65/49
2[b]	**3b**	2.5	38/44	81/66
3[b]	**3c**	>13	27/23	39/43
4	**3d**	12	37/46	95/93
5	**3e**	>96	28/30	96/92
6	**3f**	-	-	-
7	**3g**	-	-	-
8	**3h**	5	39/45	94/91
9	**3i**	5	37/44	98/95
10[b]	**3j**	12	25/32	88/84
11[c]	**3d**	16	40/46	95/93
12[d]	**3d**	30	38/40	95/93

[a]See the Supporting Information for more details. Yields are of the isolated diastereomerically pure compounds **4a** and **5a**. The ee values are determined by HPLC analysis of isolated compounds **4a** and **5a** on chiral stationary phases. [b]20 mol % *p*-NO_2PhCOOH was used as the co-catalyst. [c]10 mol % **3d** was used. [d]5 mol % **3d** was used. PCC = pyridine chlorochromate, Boc = *tert*-butoxycarbonyl, TMS = trimethylsilyl, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl.

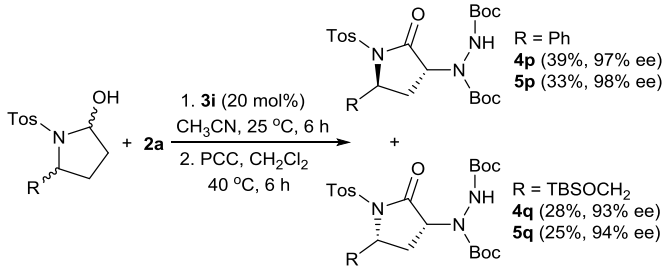
Table 2. Substrate Scope[a]



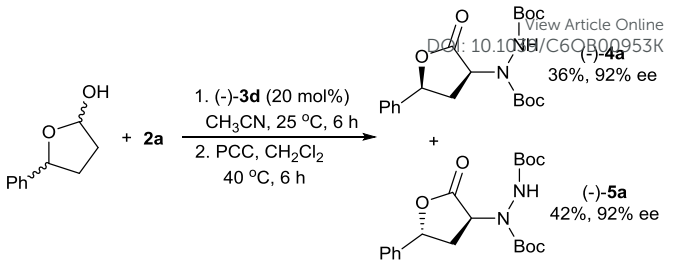
Entry	n	R^1/R^2	4/5	Yield (%) total (4/5)	ee (%) 4/5
1	1	Ph/*t*-Bu	**4a/5a**	76 (34/42)	95/93
				71 (31/40)	98/97[b]
2	1	4-MePh/*t*-Bu	**4b/5b**	76 (35/41)	89/89
				70 (32/38)	94/98[b]
3	1	4-MeOPh/*t*-Bu	**4c/5c**	77 (37/40)	93/91
4	1	4-FPh/*t*-Bu	**4d/5d**	82 (36/46)	93/92
5	1	4-ClPh/*t*-Bu	**4e/5e**	82 (37/45)	95/92
6	1	4-BrPh/*t*-Bu	**4f/5f**	86 (42/44)	94/91
7	1	3-NO_2Ph/*t*-Bu	**4g/5g**	77 (38/39)	88/90
				74 (33/41)	98/97[b]
8	1	2-FPh/*t*-Bu	**4h/5h**	79 (37/42)	95/94
9	1	2-naphthyl/*t*-Bu	**4i/5i**	75 (34/41)	94/92
10	1	2-thienyl/*t*-Bu	**4j/5j**	61 (30/31)	94/92
11	1	Bn/*t*-Bu	**4k/5k**	57 (29/28)	94/89
12	1	Me/*t*-Bu	**4l/5l**	83 (38/45)	96/93
13	1	Ph/Et	**4m/5m**	83 (39/44)	87/84
				86 (41/45)	89/88[b]
14	1	Ph/*i*-Pr	**4n/5n**	85 (41/44)	90/86
				81 (41/40)	94/93[b]
15	2	Ph/*t*-Bu	**4o/5o**	53 (24/29)	93/95

[a]Unless otherwise specified, all reactions were carried out using **1** (0.30 mmol, 1.0 equiv), **2** (0.36 mmol, 1.2 equiv) in solvent (0.6 mL) with **3d** (20 mol %) at 25 °C. After workup, the crude product was oxidized by PCC to afford **4** and **5** after purified by flash chromatography on silica gel. The total yield is reported, the values in brackets refer to the yield of isolated diastereomerically pure compounds **4** and **5**, which could be easily separated by column chromatograph on silica gel. The *ee* values are determined by HPLC analysis of isolated compounds **4** and **5** on chiral stationary phases. [b]**3i** (20 mol%) was used as the catalyst.

We noticed that, except for the lactols, substituted racemic cyclic hemiaminals, with both aromatic and aliphatic substituents, were also successfully applied in this one-pot reaction and provided α-amino lactams **4p-q** and **5p-q** with excellent enantioselectivity (Scheme 2).



Scheme 2. The synthesis of α-amino lactams.



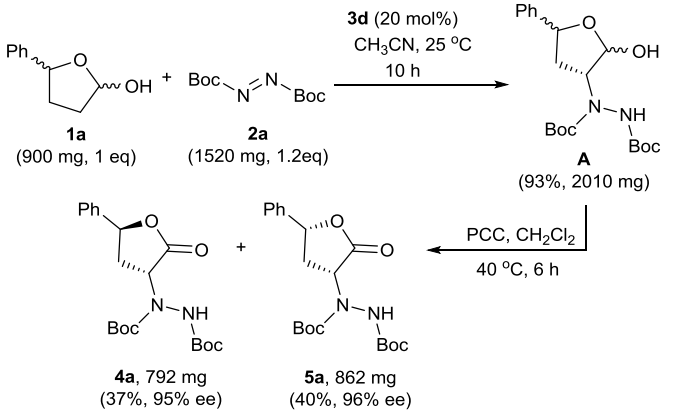
Scheme 3. The synthesis of another two stereoisomers (-)-**4a** and (-)-**5a**.

To our delight, the catalyst (-)-**3d** showed similar good catalytic activity, and the process proceeded in good reaction yield and with high enantioselectivity (Scheme 3). Thus, starting from the racemic precursors and catalyzed by the enantiomeric pair of the catalyst, we can obtained all possible stereoisomeric products only after simple column chromatography.

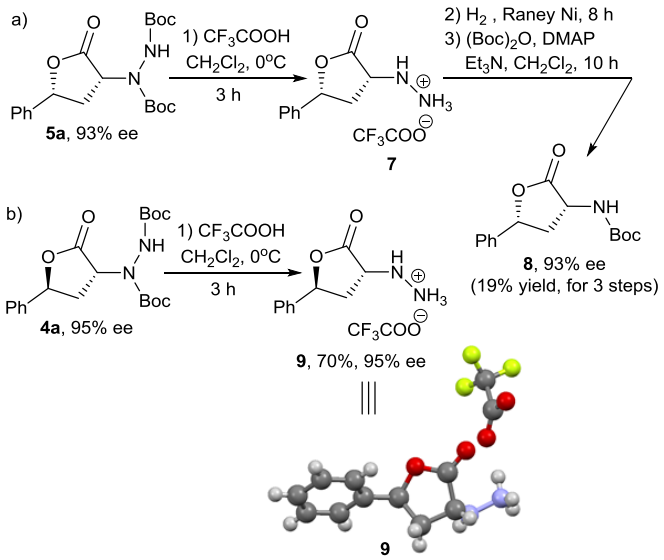
Additionally, to demonstrate the practicality of the catalytic system, the sequential amination and oxidation reactions were enlarged to a gram scale. When racemic lactol **1a** and di-*tert*-butyl azodicarboxylate **2a** were reacted under the optimal reaction conditions, the reaction proceed smoothly to afford the substituted lactol **A** in 93% yield, followed by the PCC-mediated oxidation reaction to provide the desired lactone **4a** and **5a** in good yield and excellent enantionselectivity (Scheme 4).

The most attractive application of this direct amination reaction is to provide facial access to optically active α-amino lactones. Deprotection of **5a** in the presence of CF_3COOH afforded hydrazine **7** as a CF_3COOH salt, and the reduction of **7** with H_2/Raney Ni followed by a N-Boc protection gives the N-Boc protected α-amino lactone **8** with maintained enantioselectivity (Scheme 5, a). Gratifyingly, **4a**, the diastereoisomer of **5a**, could also undergo deprotection leading to CF_3COOH salt **9** (Scheme 5, b). The absolute configuration of the amination product **9** was determined unambiguously by X-ray crystal structure analysis, and those of others were assigned by analogy.[20]

Notably, except the readily formation of α-amino lactones, when catalyzed by $BF_3•Et_2O$ instead of CF_3COOH in CH_2Cl_2,



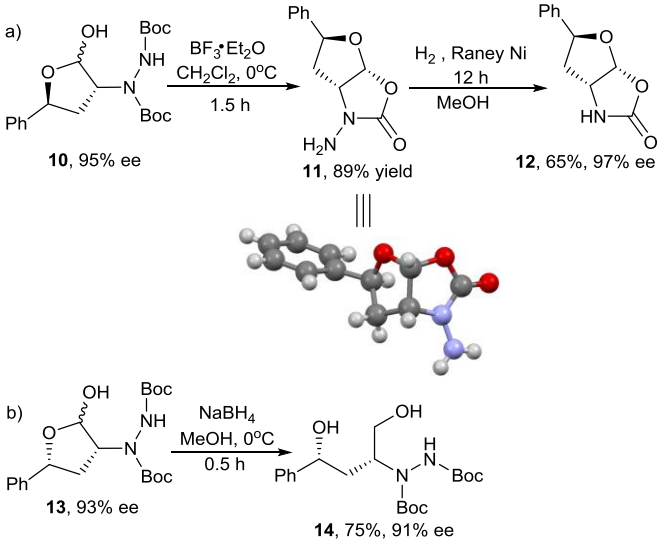
Scheme 4. The gram-scale synthesis of **4a** and **5a**.



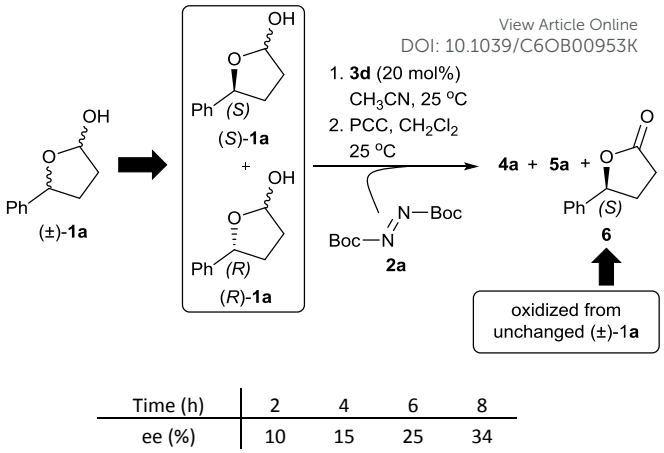
Scheme 5. The synthesis of target α-amino lactone derivatives.

lactol **10** underwent Boc-deprotection and transesterification sequence to give bicyclic carbamate **11**, and the subsequent cleavage of the N-N bond gave a novel bicyclic oxazolidinone derivative **12** as a single diastereoisomer, which might be potentionally used as chiral auxiliary (Scheme 6, a).[21] The absolute configuration of **11** was determined unambiguously by X-ray crystal structure analysis.[20] Reduction of the aminated lactol **13** with $NaBH_4$ gave the corresponding functionalized amino alcohol **14** (Scheme 6, b). All these interesting backbones might be suitable for further medicinal chemistry exploration.

Experimentally, racemic lactols were directly used in this asymmetric C-N bond formation reaction. Thus, to gain more insight into the reaction mechanism, some control experiments were performed under the optimized conditions. Several parallel reactions between **1a** and **2a** were carried out



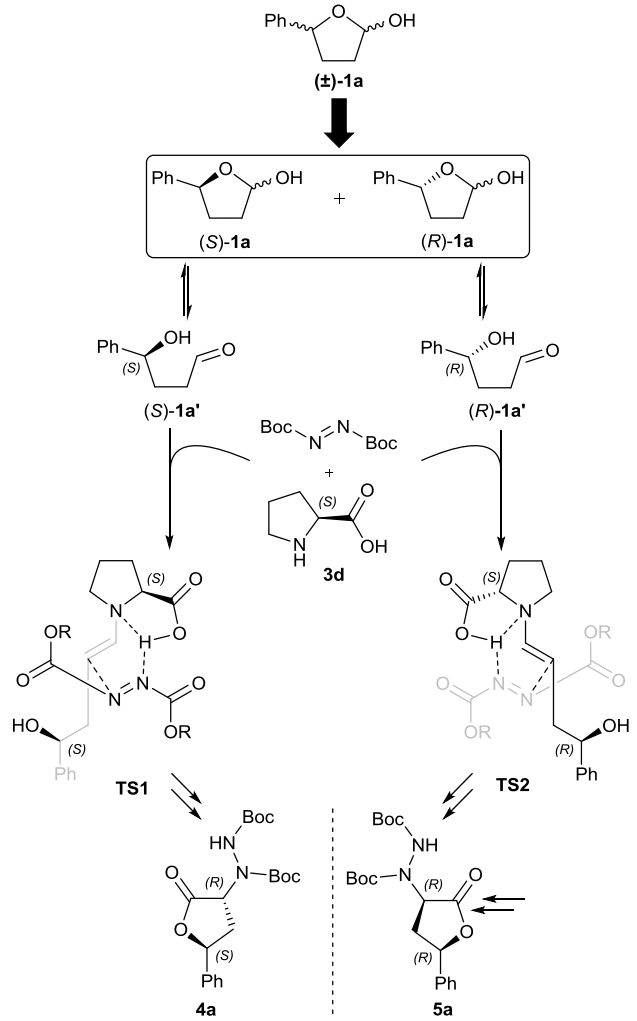
Scheme 6. The synthesis of bicyclic oxazolidinone and amino alcohol.



Time (h)	2	4	6	8
ee (%)	10	15	25	34

Scheme 7. Control experiment for mechanism studies.

under the optimized conditions. These reactions were then quenched after 2 h, 4 h, 6 h, and 8 h, respectively, and the unreacted **1a** was isolated and directly oxidized into lactone **6**, the enantiomeric excess of **6** are analyzed by chiral HPLC



Scheme 8. Proposed transition state.

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analysis.[22] Surprisingly, we found that the enantiomeric excess of **6** was increased along with the reaction time until the reaction was complete, which showed different reaction behavior from our previous studies (Scheme 7).[11e] We view this to be a very significant control experiment, suggesting that (*R*)-**1a**, as the benzylic stereogenic center showing *R* configuration, worked faster with **2a** than its isomer (*S*)-**1a**, and thus some of (*S*)-**1a** remained unchanged in the reaction process, which was then isolated and further oxidized into lactone **6**. All these results showed that there might be a kinetic resolution of lactol **1** in the reaction process of the amination step.

Based on these observations, we proposed two transition states, **TS1** and **TS2**, to rationalize the possible reaction mechanisms of the formation of **4a** and **5a** (Scheme 8).[23] In both **TS1** and **TS2**, the azodicarboxylate **2** might be directed by the proton of the carboxylic acid from the conbination of the substrate–catalyst.

Conclusions

In summary, we have developed a novel strategy that involves the first organocatalyzed directly asymmetric α-amination of lactols or cyclic hemiaminals, and a subsequent oxidation reaction providing easy access to optically active α-amino lactones or lactams. These reactions are operationally simple and proceed smoothly under mild reaction conditions. Notably, starting from racemic lactols or cyclic hemiaminals, catalyzed by the enantiomeric pair of the catalyst, all possible stereoisomeric products, which are very useful building blocks for the synthesis of complex molecules but difficult to prepare optically enriched, were discretely provided only after simple column chromatography workup. Furthermore, the reactions could be performed on a gram scale under the optimized conditions. Additionally, α-aminated products can be easily transformed into other more useful chiral building blocks. Further studies based on the reactivity of substituted racemic lactols or cyclic hemiaminals and its application are in progress.

Experimental

General methods

The ^{1}H and ^{13}C NMR spectra were recorded at 500 or 600 MHz for ^{1}H and at 125 or 150 MHz for ^{13}C, respectively. The chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvents ($CDCl_3$@ 7.24 ppm ^{1}H NMR, 77.23 ppm ^{13}C NMR). Coupling constants are given in Hz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High-resolution mass spectra (HRMS) were obtained from the Waters Q-Tof Ultima Global. X-ray data were obtained from Zhongke chemical technology service center. Optical rotations are reported as follows: $[\alpha]_D^{20}$(c in g per 100 mL, solvent). All the reactions were set up under air and using freshly distilled solvents, without any precautions to exclude moisture, unless otherwise noted, open air chemistry on the benchtop. Chromatographic purification of products was accomplished using force-flow chromatography (FC) on silica gel (200−400 mesh). For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm) were used, using UV light as the visualizing agent and Phosphomolybdic acid as stain developing solutions. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. HPLC analyses on chiral stationary phase were performed on an Hitachi Chromaste. Daicel Chiralpak IA, IB or IC columns with *i*-PrOH/*n*-hexane as the eluent were used. HPLC traces were compared to racemic samples catalyzed by DL-Proline. All catalysts and azodiformates were commercial reagents. All cyclic hemiacetals were synthesized from corresponding Weinreb amide reduced by $LiAlH_4$ or corresponding lactone reduced by DIBAL-H (1.5M solution in toluene).

General procedure

A glass vial equipped with a magnetic stirring bar was charged with cyclic hemiacetal **1** (0.3 mmol), azodicarboxylate **2** (0.36 mol) and **3d** (7 mg, 20 mol%) in acetonitrile (0.6 mL) at 25 °C. Until the starting material cyclic hemiacetal **1** was completely consumed by TLC monitor, the solvent was removed under vacuum and the crude product was dissolved in dichloromethane (3 mL). Then PCC (194 mg, 0.3 mmol) and Celite (194 mg) were added before stirred at 40 °C for 6h. Then the reaction mixture was filtered, and the filtrate was purified by flash chromatography on silica gel to give products **4** and **5**. For the synthesis of compound (-)-**4a** and (-)-**5a**, D-Proline was added instead of the **3d**.

di-*tert*-butyl 1-((3*R*,5*S*)-2-oxo-5-phenyltetrahydrofuran-3-yl)hydrazine-1,2-dicarboxylate (4a) was obtained as a white solid (40 mg) in 34% yield (36 mg; 31% yield by cat. **3i**) for two steps; mp = 115−117 °C; TLC: R_f = 0.75 (petroleum ether/EtOAc = 4:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.30 – 7.41 (m, 5H), 6.50 (s, 1H), 5.35 (dd, *J* = 11.0, 5.5 Hz, 1H), 5.15 (d, *J* = 156.3 Hz, 1H), 2.75 - 2.99 (m, 1H), 2.28 - 2.57 (m, 1H), 1.44 (d, *J* = 17.8 Hz, 18H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 173.8, 155.7, 154.4, 139.4, 129.0, 128.5, 125.0, 82.7, 81.9, 78.5, 56.8, 33.2, 28.3, 28.2 ppm; **HRMS:** $[M+Na]^+$ *calcd*. For $C_{20}H_{28}N_2O_6Na$ 415.1845, found: 415.1849; $[\alpha]_D^{20}$ = +14.77 (c = 0.52 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IC column [*n*-hexane/*i*-PrOH = 80/20, 1mL/min], λ = 210 nm, t_{minor} = 6.22 min, t_{major} = 7.26 min, ee = 95%. (by cat. **3i**: t_{minor} = 6.25 min, t_{major} = 7.25 min, ee = 98%)

di-*tert*-butyl 1-((3*R*,5*R*)-2-oxo-5-phenyltetrahydrofuran-3-yl)hydrazine-1,2-dicarboxylate (5a) was obtained as a white solid (49 mg) in 42% yield (47 mg, 40% yield by cat. **3i**) for two steps; mp = 89−91 °C; TLC: R_f = 0.60 (petroleum ether/EtOAc = 4:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.30 - 7.40 (m, 5H), 6.51 (s, 1H), 4.90 – 5.42 (m, 2H), 2.74 - 2.98 (m, 1H), 2.30 - 2.55 (m, 1H), 1.44 (d, *J* = 17.5 Hz, 18H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.3, 155.8, 154.6, 138.4, 129.1, 129.0, 126.0, 82.8, 81.9, 78.7, 59.0, 34.4, 28.3 ppm; **HRMS:** $[M+Na]^+$ *calcd*. For $C_{20}H_{28}N_2O_6Na$ 415.1845, found: 415.1848; $[\alpha]_D^{20}$ = -29.53 (c = 1.00 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IC column [*n*-hexane/*i*-PrOH

= 80/20, 1mL/min], λ = 210 nm, t_{minor} = 7.19 min, t_{major} = 12.53 min, ee = 93%. (by cat. **3i**: t_{minor} = 7.20 min, t_{major} = 12.36 min, ee = 97%)

di-*tert*-butyl 1-((3*R*,5*S*)-2-oxo-5-(p-tolyl)tetrahydrofuran-3-yl)hydrazine-1,2-dicarboxylate (4b) was obtained as a white solid (43 mg) in 35% yield (39 mg, 32% yield by cat. **3i**) for two steps; mp = 76−78 °C; TLC: R_f = 0.75 (petroleum ether/EtOAc = 4:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.10 - 7.19 (m, 4H), 6.52 (s, 1H), 5.56 - 5.66 (m, 1H), 4.90 (d, *J* = 163.4 Hz, 1H), 2.79 - 3.03 (m, 1H), 2.51 - 2.63 (m, 1H), 2.32 (s, 3H), 1.44 (d, *J* = 10.9 Hz, 18H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.6, 155.9, 154.5, 138.4, 136.6, 129.7, 125.1, 82.5, 82.0, 78.7,56.6, 33.2, 28.3, 28.3, 21.4 ppm; **HRMS:** $[M+Na]^+$ *calcd*. For $C_{21}H_{30}N_2O_6Na$ 429.2002, found: 429.2003; $[\alpha]_D^{20}$ = +24.93 (c = 0.61 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IC column [*n*-hexane/*i*-PrOH = 80/20, 1mL/min], λ = 210 nm, t_{minor} = 6.82 min, t_{major} = 7.73 min, ee = 89%. (by cat. **3i**: t_{minor} = 6.95 min, t_{major} = 7.80 min, ee = 94%)

di-*tert*-butyl 1-((3*R*,5*R*)-2-oxo-5-(p-tolyl)tetrahydrofuran-3-yl)hydrazine-1,2-dicarboxylate (5b) was obtained as a colorless gum (50 mg) in 41% yield (46 mg, 38% yield by cat. **3i**) for two steps; TLC: R_f = 0.62 (petroleum ether/EtOAc = 4:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.19 – 7.30 (m, 4H), 6.55 (s, 1H), 4.94 - 5.43 (m, 2H), 2.77 - 2.99 (m, 1H), 2.41 - 2.60 (m, 1H), 2.38 (s, 3H), 1.49 (d, *J* = 14.8 Hz, 18H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.4, 155.7, 154.7, 138.8, 135.3, 129.7, 126.2, 125.5, 82.8, 81.5, 78.8, 59.0, 34.8, 28.3, 21.4 ppm; **HRMS:** $[M+Na]^+$ *calcd*. For $C_{21}H_{30}N_2O_6Na$ 429.2002, found: 429.2004, $[\alpha]_D^{20}$ = -24.97 (c = 1.00 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IC column [*n*-hexane/*i*-PrOH = 80/20, 1mL/min], λ = 210 nm, t_{minor} = 7.72 min, t_{major} = 14.41 min, ee = 89%. (by cat. **3i**: t_{minor} = 7.81 min, t_{major} = 14.51 min, ee = 98%)

di-*tert*-butyl 1-((3*R*,5*S*)-5-(4-methoxyphenyl)-2-oxotetrahydrofuran-3-yl)hydrazine-1,2-dicarboxylate (4c) was obtained as a colorless gum (47 mg) in 37% yield for two steps; TLC: R_f = 0.76 (petroleum ether/EtOAc = 4:1 v/v). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.0 Hz, 2H), 6.51 (s, 1H), 5.55 - 5.65 (m, 1H), 4.92 (d, *J* = 169.2 Hz, 1H), 3.78 (s, 3H), 2.75 - 3.03 (m, 1H), 2.46 - 2.66 (m, 1H), 1.45 (d, *J* = 7.7 Hz, 18H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.9, 159.9, 155.8, 154.6, 131.3, 126.7, 114.5, 82.8, 82.0, 78.6, 57.1, 55.7, 33.1, 28.3, 28.3 ppm; **HRMS:** $[M+Na]^+$ *calcd*. For $C_{21}H_{30}N_2O_7Na$ 445.1951, found: 445.1952; $[\alpha]_D^{20}$ = +29.80 (c = 0.51 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IC column [*n*-hexane/*i*-PrOH = 80/20, 1mL/min], λ = 210 nm, t_{minor} = 8.79 min, t_{major} = 10.37 min, ee = 93%.

di-*tert*-butyl 1-((3*R*,5*R*)-5-(4-methoxyphenyl)-2-oxotetrahydrofuran-3-yl)hydrazine-1,2-dicarboxylate (5c) was obtained as a colorless gum (51 mg) in 40% yield for two steps; TLC: R_f = 0.63 (petroleum ether/EtOAc = 4:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.23 – 7.30 (m, 2H), 6.90 (dd, *J* = 8.6, 2.8 Hz, 2H), 6.53 (s, 1H), 4.90 –5.36 (m, 2H), 3.80 (s, 3H), 2.71 - 2.93 (m, 1H), 2.32 - 2.55 (m, 1H), 1.45 (d, *J* = 11.6 Hz, 18H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.2, 160.2, 155.7, 154.5, 130.4, 127.8, 127.3, 114.2, 82.8, 81.3, 78.7, 59.4, 55.5, 34.7, 28.3 ppm; **HRMS:** $[M+Na]^+$ *calcd*. For $C_{21}H_{30}N_2O_7Na$ 445.1951, found: 445.1955; $[\alpha]_D^{20}$ = -31.99 (c =1.00 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IC column [*n*-hexane/*i*-PrOH = 80/20, 1mL/min], λ = 210 nm, t_{minor} = 10.10 min, t_{major} = 19.03 min, ee = 91%.

di-*tert*-butyl 1-((3*R*,5*S*)-5-(4-fluorophenyl)-2-oxotetrahydrofuran-3-yl)hydrazine-1,2-dicarboxylate (4d) was obtained as a colorless gum (44 mg) in 36% yield for two steps; TLC: R_f = 0.74 (petroleum ether/EtOAc = 4:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.21 - 7.27 (m, 2H), 7.02 - 7.09 (m, 2H), 6.50 (s, 1H), 5.58 - 5.66 (m, 1H), 4.87 (d, *J* = 155.7 Hz, 1H), 2.78 - 3.09 (m, 1H), 2.41 - 2.63 (m, 1H), 1.45 (d, *J* = 10.6 Hz, 18H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 173.7, 162.8 (d, J_{CF} = 248 Hz), 155.6, 154.5, 135.3, 127.7, 116.2, 116.0, 83.0, 82.2, 78.2, 57.2, 33.6, 28.3, 28.3 ppm; **HRMS:** $[M+Na]^+$ *calcd*. For $C_{20}H_{27}FN_2O_6Na$ 433.1751, found: 433.1755; $[\alpha]_D^{20}$ = +9.24 (c = 0.67 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IC column [*n*-hexane/*i*-PrOH = 80/20, 1mL/min], λ = 210 nm, t_{minor} = 5.64 min, t_{major} = 6.53 min, ee = 93%.

di-*tert*-butyl 1-((3*R*,5*R*)-5-(4-fluorophenyl)-2-oxotetrahydrofuran-3-yl)hydrazine-1,2-dicarboxylate (5d) was obtained as a colorless gum (57 mg) in 46% yield for two steps; TLC: R_f = 0.62 (petroleum ether/EtOAc = 4:1 v/v). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.27 – 7.35 (m, 2H), 7.01 - 7.10 (m, 2H), 6.52 (s, 1H), 5.32 (dd, *J* = 10.8, 5.4 Hz, 1H), 5.13 (d, *J* = 138.5 Hz, 1H), 2.75 - 2.97 (m, 1H), 2.26 - 2.53 (m, 1H), 1.44 (d, *J* = 15.0 Hz, 18H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.1, 163.1 (d, J_{CF} = 248 Hz), 155.7, 154.1, 134.0, 128.0, 127.4, 116.2, 115.9, 82.8, 80.2, 78.1, 59.2, 34.2, 28.3 ppm; **HRMS:** $[M+Na]^+$ *calcd*. For $C_{20}H_{27}FN_2O_6Na$ 433.1751, found: 433.1752; $[\alpha]_D^{20}$ = -26.04 (c = 1.02 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IC column [*n*-hexane/*i*-PrOH = 80/20, 1mL/min], λ = 210 nm, t_{minor} = 6.26 min, t_{major} = 11.22 min, ee = 92%.

di-*tert*-butyl 1-((3*R*,5*S*)-5-(4-chlorophenyl)-2-oxotetrahydrofuran-3-yl)hydrazine-1,2-dicarboxylate (4e) was obtained as a white solid (47 mg) in 37% yield for two steps; mp = 105-107 °C; TLC: R_f = 0.76 (petroleum ether/EtOAc = 4:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 7.7 Hz, 2H), 7.19 (d, *J* = 8.2 Hz, 2H), 6.50 (s, 1H), 5.55 - 5.66 (m, 1H), 4.85 (d, *J* = 149.5 Hz, 1H), 2.83 - 3.05 (m, 1H), 2.45 - 2.60 (m, 1H), 1.45 (d, *J* = 11.1 Hz, 18H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.6, 155.8, 154.5, 138.0, 134.5, 129.3, 126.5, 83.0, 82.1, 78.0, 57.0, 33.3, 28.3, 28.3 ppm; **HRMS:** $[M+Na]^+$ *calcd*. For $C_{20}H_{27}ClN_2O_6Na$ 449.1455, found: 449.1457; $[\alpha]_D^{20}$ = +27.01 (c = 1.00 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IC column [*n*-hexane/*i*-PrOH = 80/20, 1mL/min], λ = 210 nm, t_{minor} = 5.73 min, t_{major} = 6.65 min, ee = 95%.

di-*tert*-butyl 1-((3*R*,5*R*)-5-(4-chlorophenyl)-2-oxotetrahydrofuran-3-yl)hydrazine-1,2-dicarboxylate (5e) was obtained as a colorless gum (57 mg) in 45% yield for two steps; mp = 59-61 °C; TLC: R_f = 0.63 (petroleum ether/EtOAc = 4:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 7.4 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 6.51 (s, 1H), 5.32 (dd, *J* = 10.6, 5.3 Hz, 1H), 5.13 (d, *J* = 146.1 Hz, 1H), 2.74 - 2.98 (m, 1H), 2.26 - 2.49

(m, 1H), 1.44 (d, *J* = 16.2 Hz, 18H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) *δ* 173.1, 155.6, 154.5, 137.0, 135.0, 129.2, 127.5, 82.9, 82.1, 77.9, 59.1, 34.6, 28.3 ppm; **HRMS:** $[M+Na]^+$ *calcd*. For $C_{20}H_{27}ClN_2O_6Na$ 449.1455, found: 449.1457; $[\alpha]_D^{20}$ = -26.77 (c = 0.80 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IC column [*n*-hexane/*i*-PrOH = 80/20, 1mL/min], λ = 210 nm, t_{minor} = 6.39 min, t_{major} = 11.15 min, ee = 92%.

di-*tert*-butyl 1-((3*R*,5*S*)-5-(4-bromophenyl)-2-oxotetrahydrofuran-3-yl)hydrazine-1,2-dicarboxylate (4f) was obtained as a colorless gum (59 mg) in 42% yield for two steps; TLC: R_f = 0.77 (petroleum ether/EtOAc = 4:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) *δ* 7.49 (d, *J* = 7.8 Hz, 2H), 7.13 (d, *J* = 8.2 Hz, 2H), 6.51 (s, 1H), 5.51 - 5.66 (m, 1H), 4.84 (d, *J* = 146.7 Hz, 1H), 2.78 - 3.09 (m, 1H), 2.42 - 2.62 (m, 1H), 1.45 (d, *J* = 10.9 Hz, 18H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) *δ* 173.3, 155.8, 154.4, 138.5, 132.5, 126.8, 122.5, 83.0, 82.1, 78.4, 56.9, 33.4, 28.3, 28.3 ppm; **HRMS:** $[M+Na]^+$ *calcd*. For $C_{20}H_{27}BrN_2O_6Na$ 493.0950, found: 493.0951; $[\alpha]_D^{20}$ = +23.93 (c = 0.82 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IC column [*n*-hexane/*i*-PrOH = 80/20, 1mL/min], λ = 210 nm, t_{minor} = 5.91 min, t_{major} = 6.83 min, ee = 94%.

di-*tert*-butyl 1-((3*R*,5*R*)-5-(4-bromophenyl)-2-oxotetrahydrofuran-3-yl)hydrazine-1,2-dicarboxylate (5f) was obtained as a colorless gum (62 mg) in 44% yield for two steps; TLC: R_f = 0.63 (petroleum ether/EtOAc = 4:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) *δ* 7.50 (d, *J* = 7.6 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 6.51 (s, 1H), 4.89 – 5.40 (m, 2H), 2.76 - 2.99 (m, 1H), 2.24 - 2.49 (m, 1H), 1.44 (d, *J* = 16.2 Hz, 18H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) *δ* 172.9, 155.7, 154.5, 137.5, 132.2, 127.7, 123.0, 82.9, 82.0, 77.7, 59.0, 34.2, 28.3 ppm; **HRMS:** $[M+Na]^+$ *calcd*. For $C_{20}H_{27}BrN_2O_6Na$ 493.0950, found: 493.0952; $[\alpha]_D^{20}$ = -30.18 (c = 1.00 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IC column [*n*-hexane/*i*-PrOH = 80/20, 1mL/min], λ = 210 nm, t_{minor} = 6.59 min, t_{major} = 11.53 min, ee = 91%.

di-*tert*-butyl 1-((3*R*,5*S*)-5-(3-nitrophenyl)-2-oxotetrahydrofuran-3-yl)hydrazine-1,2-dicarboxylate (4g) was obtained as a yellow solid (50 mg) in 38% yield (43 mg, 33% yield by cat. **3i**) for two steps; mp = 80-82 °C; TLC: R_f = 0.69 (petroleum ether/EtOAc = 4:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) *δ* 8.19 (d, *J* = 7.6 Hz, 1H), 8.15 (s, 1H), 7.53 – 7.66 (m, 2H), 6.55 (s, 1H), 5.61-5.81 (m, 1H), 4.82 (d, *J* = 106.0 Hz, 1H), 2.90 - 3.21 (m, 1H), 2.49 – 2.64 (m, 1H), 1.46 (d, *J* = 12.8 Hz, 18H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) *δ* 173.1, 155.6, 154.4, 148.9, 141.5, 131.3, 130.5, 123.6, 120.4, 83.3, 82.3, 57.2, 33.6, 28.3, 28.3 ppm; **HRMS:** $[M+Na]^+$ *calcd*. For $C_{20}H_{27}N_3O_8Na$ 460.1696, found: 460.1695; $[\alpha]_D^{20}$ = +11.51 (c = 1.47 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IC column [*n*-hexane/*i*-PrOH = 80/20, 1mL/min], λ = 210 nm, t_{minor} = 15.93 min, t_{major} = 20.79 min, ee = 88%. (by cat. **3i**: t_{minor} = 15.93 min, t_{major} = 20.78 min, ee = 98%)

di-*tert*-butyl 1-((3*R*,5*S*)-5-(3-nitrophenyl)-2-oxotetrahydrofuran-3-yl)hydrazine-1,2-dicarboxylate (5g) was obtained as a yellow gum (51 mg) in 39% yield (54 mg, 41% yield by cat. **3i**) for two steps; mp = 52-53 °C; TLC: R_f = 0.60 (petroleum ether/EtOAc = 4:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) *δ* 8.17 - 8.26 (m, 2H), 7.69 (d, *J* = 5.8 Hz, 1H), 7.57 (t, *J* = 7.0 Hz, 1H), 6.55 (s, 1H), 5.44 (dd, *J* = 10.8, 5.8 Hz, 1H), 5.13 (d, *J* = 128.3 Hz, 1H), 2.90 - 3.09 (m, 1H), 2.31 - 2.55 (m, 1H), 1.43 (d, *J* = 20.1 Hz, 18H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) *δ* 172.5, 155.8, 154.4, 148.8, 140.4, 132.1, 130.5, 124.0, 121.1, 83.2, 82.4, 59.1, 34.4, 28.3 ppm; **HRMS:** $[M+Na]^+$ *calcd*. For $C_{20}H_{27}N_3O_8Na$ 460.1696, found: 460.1698; $[\alpha]_D^{20}$ = -27.13 (c = 1.30 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IC column [*n*-hexane/*i*-PrOH = 80/20, 1mL/min], λ = 210 nm, t_{minor} = 19.61 min, t_{major} = 21.69 min, ee = 90%. (by cat. **3i**: t_{minor} = 19.71 min, t_{major} = 21.83 min, ee = 97%)

di-*tert*-butyl 1-((3*R*,5*S*)-5-(2-fluorophenyl)-2-oxotetrahydrofuran-3-yl)hydrazine-1,2-dicarboxylate (4h) was obtained as a white solid (45 mg) in 37% yield for two steps; mp = 92-94 °C; TLC: R_f = 0.72 (petroleum ether/EtOAc = 4:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) *δ* 7.28 - 7.35 (m,1H), 7.24 - 7.28(m, 1H), 7.13 (t, *J* = 7.0 Hz, 1H), 7.07 (t, *J* = 9.2 Hz, 1H), 6.50 (s, 1H), 5.74 - 5.87 (m, 1H), 4.92 (d, *J* = 158.1 Hz, 1H), 2.82 - 3.10 (m, 1H), 2.47 - 2.66 (m, 1H), 1.45 (d, *J* = 10.8 Hz, 18H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) *δ* 174.0, 159.8 (d, J_{CF} = 245 Hz), 155.7, 154.5, 130.5, 126.3, 124.7, 116.2, 116.1, 82.9, 82.0, 74.6, 57.0, 32.6, 28.4, 28.3 ppm; **HRMS:** $[M+Na]^+$ *calcd*. For $C_{20}H_{27}FN_2O_6Na$ 433.1751, found: 433.1752; $[\alpha]_D^{20}$ = +17.61 (c = 0.80 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IC column [*n*-hexane/*i*-PrOH = 80/20, 1mL/min], λ = 210 nm, t_{minor} = 6.37 min, t_{major} = 7.83 min, ee = 95%.

di-*tert*-butyl 1-((3*R*,5*R*)-5-(2-fluorophenyl)-2-oxotetrahydrofuran-3-yl)hydrazine-1,2-dicarboxylate (5h) was obtained as a white solid (52 mg) in 42% yield for two steps; mp = 120-122 °C; TLC: R_f = 0.64 (petroleum ether/EtOAc = 4:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) *δ* 7.42 (t, *J* = 7.2 Hz, 1H), 7.28 - 7.36 (m, 1H), 7.16 (t, *J* = 6.5 Hz, 1H), 7.05 (t, *J* = 9.1 Hz, 1H), 6.50 (s, 1H), 5.61 (dd, *J* = 10.6, 5.6 Hz, 1H), 5.16 (d, *J* = 139.1 Hz, 1H), 2.86 - 3.04 (m, 1H), 2.26 - 2.54 (m, 1H), 1.44 (d, *J* = 17.9 Hz, 18H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) *δ* 173.1, 161.1, 155.7, 154.5, 130.7, 127.3, 124.7, 116.0, 82.9, 82.0, 73.5, 58.9, 33.7, 28.3 ppm; **HRMS:** $[M+Na]^+$ *calcd*. For $C_{20}H_{27}FN_2O_6Na$ 433.1751, found: 433.1750; $[\alpha]_D^{20}$ = -25.30 (c = 0.99 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IC column [*n*-hexane/*i*-PrOH = 80/20, 1mL/min], λ = 210 nm, t_{minor} = 7.40 min, t_{major} = 9.99 min, ee = 94%.

di-*tert*-butyl 1-((3*R*,5*S*)-5-(naphthalen-2-yl)-2-oxotetrahydrofuran-3-yl)hydrazine-1,2-dicarboxylate (4i) was obtained as a white solid (45 mg) in 34% yield for two steps; mp = 129-131 °C; TLC: R_f = 0.66 (petroleum ether/EtOAc = 4:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) *δ* 7.79 - 7.89 (m, 3H), 7.73 (s, 1H), 7.46 – 7.53 (m, 2H), 7.32 (d, *J* = 8.5 Hz, 1H), 6.52 (s,1H), 5.75 - 5.87 (m, 1H), 4.94 (d, *J* = 157.6 Hz, 1H), 2.89 - 3.16 (m, 1H), 2.57 - 2.76 (m, 1H), 1.46 (d, *J* = 16.4 Hz, 18H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) *δ* 174.0, 155.8, 154.6, 136.8, 133.3, 129.2, 128.3, 127.9, 126.9, 126.7, 123.8, 123.0, 82.9, 82.1, 78.7, 57.0, 33.3, 28.4, 28.3 ppm; **HRMS:** $[M+Na]^+$ *calcd*. For $C_{24}H_{30}N_2O_6Na$ 465.2002, found: 465.2001; $[\alpha]_D^{20}$ = +54.29 (c =

0.99 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IC column [*n*-hexane/*i*-PrOH = 80/20, 1mL/min], λ = 210 nm, t_{minor} = 7.26 min, t_{major} = 8.06 min, ee = 94%.

di-*tert*-butyl 1-((3*R*,5*R*)-5-(naphthalen-2-yl)-2-oxotetrahydrofuran-3-yl)hydrazine-1,2-dicarboxylate (5i) was obtained as a colorless gum (55 mg) in 41% yield for two steps; TLC: R_f = 0.56 (petroleum ether/EtOAc = 4:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) *δ* 7.78 - 7.89 (m, 4H), 7.46 - 7.54 (m, 2H), 7.42 (d, *J* = 8.4 Hz, 1H), 6.53 (s, 1H), 5.53 (dd, *J* = 10.9, 5.5 Hz, 1H), 5.21 (d, *J* = 161.5 Hz, 1H), 2.92 - 3.09 (m, 1H), 2.40 - 2.67 (m, 1H), 1.44 (d, *J* = 28.2 Hz, 18H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) *δ* 173.5, 155.7, 154.5, 135.7, 133.5, 133.2, 129.0, 128.3, 128.0, 126.8, 125.3, 123.3, 82.8, 81.9, 78.5, 59.0, 34.3, 28.3 ppm; **HRMS**: $[M+Na]^+$ *calcd*. For $C_{24}H_{30}N_2O_6Na$ 465.2002, found: 465.2004; $[\alpha]_D^{20}$ = -37.75 (c = 1.00 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IC column [*n*-hexane/*i*-PrOH = 80/20, 1mL/min], λ = 210 nm, t_{minor} = 8.35 min, t_{major} = 15.47 min, ee = 92%.

di-*tert*-butyl 1-((3*R*,5*S*)-2-oxo-5-(thiophen-2-yl)tetrahydrofuran-3-yl)hydrazine-1,2-dicarboxylate (4j) was obtained as a white solid (36 mg) in 30% yield for two steps; mp = 117-118 °C; TLC: R_f = 0.77 (petroleum ether/EtOAc = 4:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) *δ* 7.31 (s, 1H), 7.04 (s, 1H), 6.98 (s, 1H), 6.48 (s, 1H), 5.76 - 5.88 (m, 1H), 5.06 (d, *J* = 134.5 Hz, 1H), 2.83 - 3.06 (m, 1H), 2.69 – 2.81 (m, 1H), 1.46 (s, 18H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) *δ* 173.3, 155.6, 154.5, 142.1, 127.7, 126.5, 125.6, 83.0, 82.1, 75.7, 57.3, 33.7, 28.4, 28.3 ppm; **HRMS:** $[M+Na]^+$ *calcd*. For $C_{18}H_{26}N_2O_6SNa$ 421.1409, found: 421.1408; $[\alpha]_D^{20}$ = +21.71 (c = 0.21 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IC column [*n*-hexane/*i*-PrOH = 80/20, 1mL/min], λ = 210 nm, t_{minor} = 7.50 min, t_{major} = 9.01 min, ee = 94%.

di-*tert*-butyl 1-((3*R*,5*R*)-2-oxo-5-(thiophen-2-yl)tetrahydrofuran-3-yl)hydrazine-1,2-dicarboxylate (5j) was obtained as a white solid (37 mg) in 31% yield for two steps; mp = 132-134 °C; TLC: R_f = 0.64 (petroleum ether/EtOAc = 4:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) *δ* 7.36 (s, 1H), 7.12 (d, *J* = 2.6 Hz, 1H), 7.00 (s, 1H), 6.49 (s, 1H), 5.57 (dd, *J* = 11.0, 5.5 Hz, 1H), 5.13 (d, *J* = 199.2 Hz, 1H), 2.90 – 3.03 (m, 1H), 2.45 - 2.65 (m, 1H), 1.46 (s, 18H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) *δ* 172.6, 155.8, 154.5, 140.6, 127.4, 82.9, 82.0, 74.4, 58.8, 34.7, 28.3 ppm; **HRMS:** $[M+Na]^+$ *calcd*. For $C_{18}H_{26}N_2O_6SNa$ 421.1409, found: 421.1409; $[\alpha]_D^{20}$ = -54.47 (c = 0.45 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IC column [*n*-hexane/*i*-PrOH = 80/20, 1mL/min], λ = 210 nm, t_{minor} = 8.39 min, t_{major} = 14.13 min, ee = 92%.

di-*tert*-butyl 1-((3*R*,5*R*)-5-benzyl-2-oxotetrahydrofuran-3-yl)hydrazine-1,2-dicarboxylate (4k) was obtained as a white solid (35 mg) in 29% yield for two steps; mp = 104-106 °C; TLC: R_f = 0.69 (petroleum ether/EtOAc = 4:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) *δ* 7.30 (t, *J* = 7.3 Hz, 2H), 7.25 (d, *J* = 7.2 Hz, 1H), 7.19 (d, *J* = 7.2 Hz, 2H), 6.37 (s, 1H), 4.64 - 5.05 (m, 2H), 2.95 - 3.07 (m, 1H), 2.85 - 2.95 (m, 1H), 2.43 - 2.60 (m, 1H), 2.30 – 2.41 (m, 1H), 1.42 (s, 18H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) *δ* 173.5, 155.6, 154.4, 135.6, 130.0, 129.7, 129.5, 127.4, 82.8, 81.5, 78.8, 57.2, 41.6, 30.0, 28.3 ppm; **HRMS:** $[M+Na]^+$ *calcd*. For $C_{21}H_{30}N_2O_6Na$ 429.2002, found: 429.2003; $[\alpha]_D^{20}$ = +7.25 (c = 0.48 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IB column [*n*-hexane/*i*-PrOH = 85/15, 1mL/min], λ = 210 nm, t_{major} = 7.65 min, t_{minor} = 9.21 min, ee = 94%.

di-*tert*-butyl 1-((3*R*,5*S*)-5-benzyl-2-oxotetrahydrofuran-3-yl)hydrazine-1,2-dicarboxylate (5k) was obtained as a colorless gum (34 mg) in 28% yield for two steps; TLC: R_f = 0.64 (petroleum ether/EtOAc = 4:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) *δ* 7.25 - 7.33 (m, 2H), 7.21 - 7.24 (m, 1H), 7.19 (d, *J* = 7.0 Hz, 2H), 6.40 (s, 1H), 4.97 (d, *J* = 173.5 Hz, 1H), 4.49 - 4.62 (m, 1H), 3.07 (dd, *J* = 13.6, 5.8 Hz, 1H), 2.92 (dd, *J* = 13.4, 4.8 Hz, 1H), 2.45 - 2.60 (m, 1H), 1.94 - 2.28 (m, 1H), 1.44 (s, 18H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) *δ* 174.0, 155.7, 154.6, 135.8, 129.6, 129.0, 127.3, 82.9, 81.9, 78.3,58.5, 42.0, 31.9, 28.3 ppm; **HRMS:** $[M+Na]^+$ *calcd*. For $C_{21}H_{30}N_2O_6Na$ 429.2002, found: 429.2005; $[\alpha]_D^{20}$ = -18.09 (c = 0.42 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IB column [*n*-hexane/*i*-PrOH = 85/15, 1mL/min], λ = 210 nm, t_{minor} = 12.47 min, t_{major} = 18.74 min, ee = 89%.

di-*tert*-butyl 1-((3*R*,5*R*)-5-methyl-2-oxotetrahydrofuran-3-yl)hydrazine-1,2-dicarboxylate (4l) was obtained as a white solid (38 mg) in 38% yield for two steps; mp = 94-96 °C; TLC: R_f = 0.72 (petroleum ether/EtOAc = 4:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) *δ* 6.42 (s, 1H), 5.99 – 5.26 (m, 1H), 4.68 – 4.80 (m, 1H), 2.48 - 2.73 (m, 1H), 2.12 - 2.25 (m, 1H), 1.45 (s, 18H), 1.37 (d, *J* = 6.5 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) *δ* 173.8, 155.7, 154.6, 82.8, 82.0, 75.1, 57.1, 32.1, 28.3, 21.8 ppm; **HRMS:** $[M+Na]^+$ *calcd*. For $C_{15}H_{26}N_2O_6Na$ 353.1689, found: 353.1688; $[\alpha]_D^{20}$ = +2.31 (c = 0.59 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IC column [*n*-hexane/*i*-PrOH = 80/20, 1mL/min], λ = 230 nm, t_{minor} = 7.65 min, t_{major} = 9.21 min, ee = 96%.

di-*tert*-butyl 1-((3*R*,5*S*)-5-methyl-2-oxotetrahydrofuran-3-yl)hydrazine-1,2-dicarboxylate (5l) was obtained as a white solid (45 mg) in 45% yield for two steps; mp = 48-49 °C; TLC: R_f = 0.68 (petroleum ether/EtOAc = 4:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) *δ* 6.43 (s, 1H), 5.00 (d, *J* = 185.3 Hz, 1H), 4.42 – 4.53 (m, 1H), 2.45 - 2.70 (m, 1H), 1.89 - 2.17 (m, 1H), 1.45 (s, 18H), 1.42 (d, *J* = 6.4 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) *δ* 173.6, 155.8, 154.6, 82.7, 81.9, 74.6, 58.9, 33.5, 28.3, 21.1 ppm; **HRMS:** $[M+Na]^+$ *calcd*. For $C_{15}H_{26}N_2O_6Na$ 353.1689, found: 353.1689; $[\alpha]_D^{20}$ = -17.61 (c = 1.07 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IC column [*n*-hexane/*i*-PrOH = 80/20, 1mL/min], λ = 210 nm, t_{minor} = 7.62 min, t_{major} = 12.23 min, ee = 93%.

diethyl 1-((3*R*,5*S*)-2-oxo-5-phenyltetrahydrofuran-3-yl)hydrazine-1,2-dicarboxylate (4m) was obtained as a colorless gum (39 mg) in 39% yield (41 mg, 41% yield by cat. **3i**) for two steps; TLC: R_f = 0.74 (petroleum ether/EtOAc = 3:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) *δ* 7.38 (t, *J* = 7.2 Hz, 2H), 7.30 – 7.35 (m, 1H), 7.26 (d, *J* = 7.5 Hz, 2H), 6.74 (s, 1H), 5.60 - 5.73 (m, 1H), 5.00 (d, *J* = 64.1 Hz, 1H), 4.15 - 4.26 (m, 4H), 2.89 - 3.03 (m, 1H), 2.56 – 2.69 (m, 1H), 1.26 (dt, *J* = 14.1, 7.2 Hz, 6H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) *δ* 173.3, 156.7, 155.6, 139.3, 129.1, 128.7, 125.1, 78.6, 63.6, 62.7, 57.8, 33.2, 14.7 ppm; **HRMS:**

$[M+Na]^+$ *calcd*. For $C_{16}H_{20}N_2O_6Na$ 359.1219, found: 359.1217; $[\alpha]_D^{20}$ = +19.32 (c = 1.00 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IC column [*n*-hexane/*i*-PrOH = 80/20, 1mL/min], λ = 210 nm, t_{minor} = 20.01 min, t_{major} = 21.39 min, ee = 87%. (by cat. **3i**: t_{minor} = 19.67 min, t_{major} = 20.90 min, ee = 89%)

diethyl 1-((3*R*,5*R*)-2-oxo-5-phenyltetrahydrofuran-3-yl)hydrazine-1,2-dicarboxylate (5m) was obtained as a white solid (44 mg) 44% yield (45 mg, 45% yield by cat. **3i**) for two steps; mp = 108-109 °C; TLC: R_f = 0.65 (petroleum ether/EtOAc = 3:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.30 - 7.41 (m, 5H), 6.74 (s, 1H), 5.38 (dd, *J* = 11.1, 5.5 Hz, 1H), 5.26 (d, *J* = 86.0 Hz, 1H), 4.06 – 4.29 (m, 4H), 2.85 - 3.02 (m, 1H), 2.32 - 2.51 (m, 1H), 1.21 - 1.27 (m, 6H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.0, 156.6, 155.7, 138.1, 129.1, 129.0, 126.0, 78.7, 63.6, 62.7, 59.6, 34.6, 14.6 ppm; **HRMS:** $[M+Na]^+$ *calcd*. For $C_{16}H_{20}N_2O_6Na$ 359.1219, found: 359.1218; $[\alpha]_D^{20}$ = -26.42 (c = 1.00 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IB column [*n*-hexane/*i*-PrOH = 80/20, 1mL/min], λ = 210 nm, t_{minor} = 8.07 min, t_{major} = 16.69 min, ee = 84%. (by cat. **3i**: t_{minor} = 7.93 min, t_{major} = 15.80 min, ee = 88%)

diisopropyl 1-((3*R*,5*S*)-2-oxo-5-phenyltetrahydrofuran-3-yl)hydrazine-1,2-dicarboxylate (4n) was obtained as a colorless gum (45 mg) in 41% yield (45 mg, 41% yield by cat. **3i**) for two steps; TLC: R_f = 0.70 (petroleum ether/EtOAc = 4:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35 - 7.41 (m, 2H), 7.29 - 7.35 (m, 1H), 7.26 (d, *J* = 7.5 Hz, 2H), 6.63 (s, 1H), 5.61 - 5.71 (m, 1H), 4.79 – 5.17 (m, 3H), 2.89 - 3.04 (m, 1H), 2.56 – 2.67 (m, 1H), 1.22 – 1.29 (m, 12H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 173.6, 156.5, 155.1, 139.4, 129.2, 128.6, 125.1, 78.7, 71.6, 70.7, 57.4, 33.6, 22.2, 22.1 ppm; **HRMS:** $[M+Na]^+$ *calcd*. For $C_{18}H_{24}N_2O_6Na$ 387.1532, found: 387.1534; $[\alpha]_D^{20}$ = +19.56 (c = 1.00 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IC column [*n*-hexane/*i*-PrOH = 80/20, 1mL/min], λ = 210 nm, t_{minor} = 9.82 min, t_{major} = 11.38 min, ee = 90%. (by cat. **3i**: t_{minor} = 9.73 min, t_{major} = 11.23 min, ee = 94%.)

diisopropyl 1-((3*R*,5*R*)-2-oxo-5-phenyltetrahydrofuran-3-yl)hydrazine-1,2-dicarboxylate (5n) was obtained as a white solid (48 mg) in 44% yield (44 mg, 40% yield by cat. **3i**) for two steps; mp = 147-148 °C; TLC: R_f = 0.62 (petroleum ether/EtOAc = 4:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.30 – 7.40 (m, 5H), 6.61 (s, 1H), 5.06 - 5.43 (m, 2H), 4.83 - 5.01 (m, 2H), 2.78 - 2.99 (m, 1H), 2.27 - 2.52 (m, 1H), 1.18 - 1.31 (m, 12H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.1, 156.6, 155.2, 138.2, 129.1, 126.0, 78.7, 71.5, 70.6, 59.4, 34.7, 22.2, 22.2 ppm; **HRMS:** $[M+Na]^+$ *calcd*. For $C_{18}H_{24}N_2O_6Na$ 387.1532, found: 387.1535; $[\alpha]_D^{20}$ = -24.83 (c = 1.00 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IC column [*n*-hexane/*i*-PrOH = 80/20, 1mL/min], λ = 210 nm, t_{minor} = 10.83 min, t_{major} = 23.17 min, ee = 86%. (by cat. **3i**: t_{minor} = 10.79 min, t_{major} = 22.95 min, ee = 93%.)

di-*tert*-butyl 1-((3*R*,6*S*)-2-oxo-6-phenyltetrahydro-2H-pyran-3-yl)hydrazine-1,2-dicarboxylate (4o) was obtained as a white solid (29 mg) in 24% yield for two steps; mp = 105-107 °C; TLC: R_f = 0.73 (petroleum ether/EtOAc = 4:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.29 – 7.39 (m, 5H), 6.62 (s, 1H), 5.37 (dd, *J* = 9.9, 2.7 Hz, 1H), 4.88 - 5.34 (m, 1H), 2.33 - 2.48 (m, 1H), 2.22 - 2.30 (m, 1H), 1.96 – 2.10 (m, 2H), 1.45 (d, *J* = 9.5 Hz, 18H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 171.8, 155.5, 155.2, 138.6, 128.9, 128.7, 126.7, 82.5, 81.2, 79.4, 54.8, 29. 9, 29.7, 28.4, 28.2 ppm; **HRMS:** $[M+Na]^+$ *calcd*. For $C_{21}H_{30}N_2O_6Na$ 429.2002, found: 429.2005; $[\alpha]_D^{20}$ = -20.14 (c = 0.50 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IA column [*n*-hexane/*i*-PrOH = 80/20, 1mL/min], λ = 210 nm, t_{major} = 8.47 min, t_{minor} = 11.11 min, ee = 93%.

di-*tert*-butyl 1-((3*R*,6*R*)-2-oxo-6-phenyltetrahydro-2H-pyran-3-yl)hydrazine-1,2-dicarboxylate (5o) was obtained as a white solid (35 mg) in 29% yield for two steps; mp = 110-111 °C; TLC: R_f = 0.70 (petroleum ether/EtOAc = 4:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.27 – 7.39 (m, 5H), 6.49 (s, 1H), 5.30 – 5.42 (m, 1H), 4.71 (d, *J* = 166.7 Hz, 1H), 2.34 - 2.50 (m, 1H), 2.20 – 2.32 (m, 2H), 2.03 – 2.11 (m, 1H), 1.46 (s, 18H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 169.5, 155.7, 154.9, 139.4, 129.0, 128.9, 128.7, 125.9, 125.8, 83.5, 82.5, 81.5, 58.7, 31.1, 29.9, 28.3 ppm; **HRMS:** $[M+Na]^+$ *calcd*. For $C_{21}H_{30}N_2O_6Na$ 429.2002, found: 429.2003; $[\alpha]_D^{20}$ = -2.88 (c = 0.78 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IC column [*n*-hexane/*i*-PrOH = 80/20, 1mL/min], λ = 210 nm, t_{minor} = 7.70 min, t_{major} = 9.06 min, ee = 95%.

di-*tert*-butyl 1-((3*R*,5*S*)-2-oxo-5-phenyl-1-tosylpyrrolidin-3-yl)hydrazine-1,2-dicarboxylate (4p) was obtained as a white solid (59 mg, 36% yield by cat. 3i) for two steps; mp = 84-85 °C; TLC: R_f = 0.20 (petroleum ether/EtOAc = 6:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.51 - 7.59 (m, 2H), 7.25 – 7.31 (m, 3H), 7.13 – 7.19 (m, 2H), 6.98 – 7.12 (m, 2H), 6.31 (s, 1H), 5.44 (d, J = 8.4 Hz, 1H), 5.36 (d, J = 63.1 Hz, 1H), 2.65 (ddd, J = 31.1, 19.1, 9.1 Hz, 1H), 2.38 (s, 3H), 2.32 (dd, J = 12.2, 5.7 Hz, 1H), 1.42 (d, J = 26.8 Hz, 18H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.3, 155.7, 154.7, 145.5, 139.7, 135.2, 129.4, 129.1, 128.8, 128.4, 126.2, 82.8, 81.8, 60.1, 58.4, 53.7, 32.6, 28.2, 21.9 ppm; **HRMS:** $[M+Na]^+$ *calcd*. For $C_{27}H_{35}N_3O_7SNa$ 568.2093, found: 568.2095; $[\alpha]_D^{20}$ = -43.55 (c = 1.00 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IC column [*n*-hexane/*i*-PrOH = 80/20, 1mL/min], λ = 210 nm, t_{minor} = 11.81 min, t_{major} = 18.85 min, ee = 97%.

di-*tert*-butyl 1-((3*R*,5*R*)-2-oxo-5-phenyl-1-tosylpyrrolidin-3-yl)hydrazine-1,2-dicarboxylate (5p) was obtained as a white solid (57 mg, 35% yield by cat. 3i) for two steps; mp = 176-177 °C; TLC: R_f = 0.15 (petroleum ether/EtOAc = 6:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45 (d, J = 52.3 Hz, 2H), 7.06 – 7.32 (m, 7H), 6.41 (s, 1H), 4.83 – 5.34 (m, 2H), 2.82 (s, 1H), 2.39 (s, 3H), 2.16 (s, 1H), 1.41 (dd, J = 17.2, 13.0 Hz, 18H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.6, 155.6, 154.4, 145.2, 141.0, 135.7, 129.5, 128.8, 128.5, 127.6, 127.2, 82.6, 81.8, 60.4, 59.0, 53.6, 32.3, 28.3, 21.9 ppm; **HRMS:** $[M+Na]^+$ *calcd*. For $C_{27}H_{35}N_3O_7SNa$ 568.2093, found: 568.2096; $[\alpha]_D^{20}$ = -12.21 (c = 1.00 in $CHCl_3$); As compound *rac*-**5p** couldn't be separated by chiral HPLC, N-Boc-**5q** was obtained and the enantiomeric excess of product N-Boc-**5p** was determined by HPLC analysis on Daicel Chiralpak IC column [*n*-hexane/*i*-PrOH = 70/30, 1mL/min], λ = 210 nm, t_{minor} = 31.81 min, t_{major} = 35.97 min, ee = 98%.

di-*tert*-butyl 1-((3*R*,5*S*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-oxo-1-tosylpyrrolidin-3-

yl)hydrazine-1,2-dicarboxylate (4q) was obtained as a white solid (53 mg, 29% yield by cat. 3i) for two steps; mp = 52-53 °C; TLC: R_f = 0.20 (petroleum ether/EtOAc = 8:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 7.6 Hz, 2H), 6.21 (s, 1H), 5.08 (d, *J* = 148.9 Hz, 1H), 4.40 (d, *J* = 6.9 Hz, 1H), 3.97 – 4.12 (m, 1H), 3.69 (d, *J* = 9.3 Hz, 1H), 2.40 (s, 3H), 2.23 – 2.37 (m, 2H), 1.40 (d, *J* = 20.5 Hz, 18H), 0.78 (s, 9H), -0.00 (d, *J* = 33.1 Hz, 6H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 171.2, 155.8, 154.2, 145.2, 136.2, 129.7, 128.4, 82.1, 81.5, 65.0, 58.3, 42.2, 28.3, 27.8, 26.0, 21.8, 18.3, -5.3 ppm; **HRMS:** $[M+H]^+$ *calcd*. For $C_{28}H_{48}N_3O_8SSi$ 614.2931, found: 614.2933; $[\alpha]_D^{20}$ = -35.44 (c = 0.50 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IC column [*n*-hexane/*i*-PrOH = 80/20, 1mL/min], λ = 210 nm, t_{minor} = 6.33 min, t_{major} = 8.11 min, ee = 93%.

di-*tert*-butyl 1-((3*R*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-oxo-1-tosylpyrrolidin-3-yl)hydrazine-1,2-dicarboxylate (5q) was obtained as a white solid (52 mg, 28% yield by cat. **3i**) for two steps; mp = 67-68 °C; TLC: R_f = 0.15 (petroleum ether/EtOAc = 8:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.2 Hz, 2H), 7.29 (d, *J* = 7.6 Hz, 2H), 6.24 (s, 1H), 4.77 (d, *J* = 117.3 Hz, 1H), 3.82 – 4.21 (m, 3H), 2.35 – 2.47 (m, 4H), 2.11 – 2.22 (m, 1H), 1.41 (d, *J* = 9.9 Hz, 18H), 0.83 (s, 9H), 0.03 (s, 6H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 171.3, 155.7, 154.7, 145.5, 135.6, 129.8, 128.5, 82.5, 81.7, 64.1, 58.1, 42.3, 28.3, 28.3, 26.1, 24.9, 21.9, 18.4, -5.2, -5.3 ppm; **HRMS:** $[M+H]^+$ *calcd*. For $C_{28}H_{48}N_3O_8SSi$ 614.2931, found: 614.2935; $[\alpha]_D^{20}$ = -2.69 (c = 1.00 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IB column [*n*-hexane/*i*-PrOH = 90/10, 1mL/min], λ = 210 nm, t_{minor} = 9.53 min, t_{major} = 11.55 min, ee = 94%.

di-*tert*-butyl 1-((3*S*,5*R*)-2-oxo-5-phenyltetrahydrofuran-3-yl)hydrazine-1,2-dicarboxylate ((-)-4a) was obtained by cat. (-)-**3d** as a white solid (43 mg) in 37% yield for two steps; mp = 112-113 °C; TLC: R_f = 0.75 (petroleum ether/EtOAc = 4:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) 7.28 – 7.41 (m, 3H), 7.25 (d, *J* = 8.0 Hz, 2H), 6.47 (s, 1H), 5.59 – 5.69 (m, 1H), 4.91 (d, *J* = 164.9 Hz, 1H), 2.80 – 3.09 (m 1H), 2.48 – 2.65 (m, 1H), 1.45 (d, *J* = 12.0 Hz, 18H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 173.5, 155.8, 154.5, 139.4, 129.2, 128.6, 125.6, 82.8, 82.1, 78.6, 56.7, 33.6, 28.3, 28.3 ppm; **HRMS:** $[M+Na]^+$ *calcd*. For $C_{20}H_{28}N_2O_6Na$ 415.1845, found: 415.1846; $[\alpha]_D^{20}$ = -16.17 (c = 1.00 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IC column [*n*-hexane/*i*-PrOH = 80/20, 1mL/min], λ = 210 nm, t_{major} = 6.27 min, t_{minor} = 7.31 min, ee = -92%.

di-*tert*-butyl 1-((3*S*,5*S*)-2-oxo-5-phenyltetrahydrofuran-3-yl)hydrazine-1,2-dicarboxylate ((-)-5a) was obtained by cat. (-)-**3d** as a white solid (48 mg) in 41% yield for two steps; mp = 87-88 °C; TLC: R_f = 0.60 (PE:EA, 4:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.29 – 7.41 (m, 5H), 6.49 (s, 1H), 4.93 – 5.48 (m, 2H), 2.75 – 3.01 (m, 1H), 2.24 – 2.54 (m, 1H), 1.44 (d, *J* = 18.2 Hz, 18H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 173.9, 155.8, 154.5, 139.0, 129.0, 129.0, 126.1, 83.0, 82.0, 78.7, 59.0, 34.5, 28.3 ppm; **HRMS:** $[M+Na]^+$ *calcd*. For $C_{20}H_{28}N_2O_6Na$ 415.1845, found: 415.1845; $[\alpha]_D^{20}$ = +22.57 (c = 1.00 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IC column [*n*-hexane/*i*-PrOH = 80/20, 1mL/min], λ = 210 nm, t_{major} = 7.24 min, t_{minor} = 12.50 min, ee = -92%.

General procedure for the synthesis of α-amino lactone derivatives. To a solution of **5a** (35 mg, 0.089 mmol) in dichloromethane (1 mL) was added TFA (0.5 mL) at 0 °C. After stirring at room temperature for 3h, the mixture was concentrated and desolved in etanol/aceticacid (0.6 mL/0.2 mL), then Raney Ni (89 mg) was added and purging with H_2, the mixture was stirred overnight. Then the mixture was filtered and concentrated and dissolved in dichloromethane (1 mL), Triethylamine (10mg, 0.1 mmol), DMAP (4.4 mg, 0.036 mmol) and di-*tert*-butyl dicarbonate (21.8mg, 0.1 mmol) was added at 0 °C. After stirring for 10h at room temperature, 1M HCl solution was added into the mixture, which was then extracted with dichloromethane. The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo to give a residue which was purified by flash chromatography to give **8**. For the synthesis of compound **9**, **4a** (59 mg, 0.15 mmol) was added instead of **5a**, following the first step of the procedure above and then recrystallized from dichloromethane.

***tert*-butyl ((3*R*,5*R*)-2-oxo-5-phenyltetrahydrofuran-3-yl)carbamate (8)** was obtained as white solid (4.6 mg) in 19% yield; mp = 166-168 °C; TLC: R_f=0.55 (petroleum ether/EtOAc = 3:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32–7.41 (m, 5H), 5.38 (dd, *J*=11.2, 5.2 Hz, 1H), 5.05–5.17 (m, 1H), 4.51-4.61 (m, 1H), 3.05–3.19 (m, 1H), 2.13 (dd, *J*=23.8, 11.9 Hz, 1H), 1.44 (s, 9H) ppm; **^{13}C NMR** (125MHz, $CDCl_3$) δ 174.7, 155.6, 138.0, 129.1, 129.0, 126.0, 80.9, 78.9, 52.2, 39.6, 28.5 ppm; **HRMS:** $[M+Na]^+$ *calcd*. For $C_{15}H_{19}NO_4Na$ 300.1212, found: 300.1213; $[\alpha]_D^{20}$ -7.17 (c = 0.18 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IB column [*n*-hexane/*i*-PrOH=80/20, 1mL/min], λ=210 nm, t_{major}=7.19 min, t_{minor}=8.34 min, ee = 93%.

2-((3*R*,5*S*)-2-oxo-5-phenyltetrahydrofuran-3-yl)hydrazin-1-ium 2,2,2-trifluoroacetate (9) was obtained as white solid (45.8 mg) in 70% yield; TLC: R_f=0.35 (CH_2Cl_2:MeOH = 20:1 v/v); **^{1}H NMR** (500 MHz, d_6-DMSO) δ 9.27 (s, 3H), 7.41–7.46 (m, 2H), 7.36–7.41 (m, 3H), 6.16 (s, 1H), 5.74 (dd, *J*=7.3, 5.8 Hz, 1H), 4.07 (t, *J*=7.4 Hz, 1H), 2.60 (dt, *J*=14.1, 7.2 Hz, 1H), 2.53 (dd, *J*=8.2, 5.5 Hz, 1H) ppm; **^{13}C NMR** (125MHz, d_6-DMSO) δ 174.2, 139.0, 128.7, 128.5, 125.7, 78.9, 56.1, 34.6 ppm; **HRMS:** $[M+H]^+$ *calcd*. For $C_{10}H_{13}N_2O_2$ 193.0977, found: 193.0979; $[\alpha]_D^{20}$ = +24.43 (c = 0.30 in DMSO).

General procedure for the synthesis of bicyclic oxazolidinone 12. Compound **10** and **13** were prepared following the general procedure of the first step. **10** (39.5 mg, 0.1 mmol) was dissolved in dichloromethane (1 ml), and BF_3•OEt_2 (42.6 mg, 0.3 mmol) was added at 0 °C. After stirring at 0 °C for 1.5h, the mixture was concentrated in vacuo and purified by flash chromatography to afford compound **11**. To a solution of **11** (22 mg, 0.1 mmol) in methanol (1 mL) was added Raney Ni (100 mg) and purging with H_2. After stirring at room temperature for 12h, the mixture was filtered and concentrated in vacuo, and compound **12** was obtained after flash chromatography.

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(3a*R*,5*S*,6a*R*)-1-amino-5-phenyltetrahydrofuro[3,2-*d*]oxazol-2(3aH)-one (11) was obtained as white solid (19.5 mg) in 89% yield; mp =59-61 °C; TLC: R_f=0.20 (petroleum ether/EtOAc = 1:1 v/v); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.29–7.37 (m, 5H), 6.12 (d, *J*=5.5 Hz, 1H), 5.13 (dd, *J*=11.1, 4.6 Hz, 1H), 4.46 (t, *J*=5.7 Hz, 1H), 4.04 (s, 2H), 2.64 (dd, *J*=13.6, 4.6 Hz, 1H), 1.89 (ddd, *J*=13.7, 11.1, 5.9 Hz, 1H); **^{13}C NMR**(125MHz, $CDCl_3$) δ 157.7, 138.2, 128.8, 128.6, 126.3, 100.6, 79.9, 63.8, 38.5 ppm; **HRMS:** $[M+H]^+$ *calcd*. For $C_{11}H_{13}N_2O_3$ 221.0926, found: 221.0928; $[\alpha]_D^{20}$ = -107.43 (c=0.21 in $CHCl_3$).

(3a*R*,5*S*,6a*R*)-5-phenyltetrahydrofuro[3,2-d]oxazol-2(3a*H*)-one (12) was obtained as white solid (13.4 mg) in 65% yield; mp =159-160 °C; TLC: R_f=0.3 (petroleum ether/EtOAc = 1:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.28–7.38 (m, 5H), 6.38 (s, 1H), 6.28 (d, *J*=5.5 Hz, 1H), 5.26 (dd, *J*=11.1, 4.4 Hz, 1H), 4.57 (t, *J*=5.7 Hz, 1H), 2.37 (dd, *J*=13.4, 4.5 Hz, 1H), 1.93 (ddd, *J*=13.4, 11.2, 6.0 Hz, 1H) ppm; **^{13}C NMR**(125MHz, $CDCl_3$) δ 159.0, 138.2, 128.9, 128.6, 126.3, 104.3, 79.8, 57.9, 42.0 ppm; **HRMS:** $[M+Na]^+$ *calcd*. For $C_{11}H_{11}NO_3Na$ 228.0637, found: 228.0639; $[\alpha]_D^{20}$ -46.36 (c=0.90 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IC column [*n*-hexane/*i*-PrOH=80/20, 1mL/min], λ=210 nm, t_{minor}=10.427 min, t_{major}=11.567 min, ee = 97%.

General procedure for the synthesis of amino alcohol: Compound **13** (29.0 mg, 0.074 mmol) was dissolved in methanol (1mL), and sodium borohydride (22.7 mg, 0.6 mmol) was added at 0°C. After stirring at 0°C for 0.5h, the mixture was concentrated in vacuo and purified by flash chromatography to afford compound **14**.

di-*tert*-butyl 1-((2*R*,4*R*)-1,4-dihydroxy-4-phenylbutan-2-yl)hydrazine-1,2-dicarboxylate (14) was obtained as colorless gum (22 mg) in 75% yield; TLC: R_f=0.35 (petroleum ether/EtOAc = 3:1 v/v); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32 (s, 4H), 7.24 (s, 1H), 6.06 (d, *J*=110.5 Hz, 1H), 4. 32–4. 73 (m, 2H), 3.36–3.57 (m, 2H), 1.68–1.83 (m, 1H), 1.56–1.67 (m, 1H), 1.46 (d, *J*=7.2 Hz, 18H) ppm; **^{13}C NMR** (125MHz, $CDCl_3$) δ 157.9, 155.9, 143.9, 128.8, 128.7, 128.0, 127.7, 125.8, 82.8, 82.4, 71.4, 62.6, 56.4, 37.6, 28.4, 28.3 ppm; **HRMS:** $[M+H]^+$ *calcd*. For $C_{20}H_{33}N_2O_6$ 397.2339, found: 397.2339; $[\alpha]_D^{20}$ -7.22 (c=0.86 in $CHCl_3$); The enantiomeric excess was determined by HPLC analysis on Daicel Chiralpak IA column [*n*-hexane/*i*-PrOH=85/15, 1mL/min], λ=210 nm, t_{minor}=6.30 min, t_{major}=16.05 min, ee = 91%.

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Notes and references

1 (a) G. Bergonzini and P. Melchiorre, *Angew. Chem.* **2012**, *124*, 995-998; *Angew. Chem. Int. Ed.* **2012**, *51*, 971-974; (b) M. Retini, G. Bergonzini and P. Melchiorre, *Chem. Commun.* **2012**, *48*, 3336-3338. For review, see: (c) L. C. Miller and R. Sarpong, *Chem. Soc. Rev.* **2011**, *40*, 4550-4562.

2 For selected reviews, see: (a) M. Teplitski, U. Mathesius and K. P. Rumbaugh, *Chem. Rev.* **2011**, *111*, 100-116; (b) D. M. Stacy, M. A. Welsh, P. N. Rather and H. E. Blackwell, *ACS Chem. Biol.* **2012**, *7*, 1719-1728; (c) M. Schuster, D. J. Sexton, S. P. Diggle and E. P. Greenberg, *Annu. Rev. Microbiol.* **2013**, *67*, 43-63.

3 (a) S. R. Donohue, J. H. Krushinski, V. W. Pike, E. Chernet, L. Phebus, A. K. Chesterfield, C. C. Felder, C. Halldin and J. M. Schaus, *J. Med. Chem.* **2008**, *51*, 5833-5842; (b) K. R. Campos, A. Klapars, Y. Kohmura, D. Pollard, H. Ishibashi, S. Kato, A. Takezawa, J. H. Waldman, D. J. Wallace, C. Chen and N. Yasuda, *Org. Lett.* **2011**, *13*, 1004-1007.

4 M. Jacob, M. L. Roumestant, P. Viallefont and J. Martinez, *Synlett* **1997**, *6*, 691-692.

5 M. Venkataiah, G. Reddipalli, L. S. Jasti and N. W. Fadnavis, *Tetrahedron: Asymmetry* **2011**, *22*, 1855-1860.

6 A. R. Healy, M. Izumikawa, A. M. Z. Slawin, K. Shin-ya and N. J. Westwood, *Angew. Chem. Int. Ed.* **2015**, *54*, 4046-4050.

7 W. Li, J. Gan and D. Ma, *Angew. Chem. Int. Ed.* **2009**, *48*, 8891-8895.

8 Z. Yang, Z. Wang, S. Bai, K. Shen, D. Chen, X. Liu, L. Lin and X. Feng, *Chem.—Eur. J.* **2010**, *16*, 6632-6637.

9 N. A. Aslam and S. A. Babu, *Tetrahedron* **2014**, *70*, 6402-6419.

10 (a) S. De Lamo Marin, C. Catala, S. R. Kumar, A. Valleix, A. Wagner and C. Mioskowski, *Eur. J. Org. Chem.* **2010**, 3985–3989; (b) S. K. Ghosh, B. Somanadhan, K. S.-W. Tan, M. S. Butler and M. J. Lear, *Org. Lett.* **2012**, *14*, 1560-1563; (c) T.-Y. Yuen, S. E. Eaton, T. M. Woods, D. P. Furkert, K. W. Choi and M. A. Brimble, *Eur. J. Org. Chem.* **2014**, 1431-1437.

11 (a) Y.-K. Liu, Z.-L. Li, J.-Y. Li, H.-X. Feng and Z.-P. Tong, *Org. Lett.* **2015**, *17*, 2022-2025; (b) H.-X. Feng, R. Tan and Y.-K. Liu, *Org. Lett.* **2015**, *17*, 3794-3797; (c) X.-L. Sun, Y.-H. Chen, D.-Y. Zhu, Y. Zhang and Y.-K. Liu, *Org. Lett.* **2016**, *18*, 864-867; (d) J.-Y. Li, Z.-L. Li, W.-W. Zhao, Y.-K. Liu, Z.-P. Tong and R. Tan, *Org. Biomol. Chem.* **2016**, *14*, 2444-2453; (e) P.-W. Cai, Z.-H. You, L.-H. Xie, R. Tan, Z.-P. Tong and Y.-K. Liu, *Synthesis*, **2016**, DOI: 10.1055/s-0035-1561972; (f) Z.-L. Li, C. Liu, R. Tan, Z.-P. Tong and Y.-K. Liu, *Catalysts* **2016**, 6, 65-78.

12 (a) Y. Zhu, P. Qian, J. Yang, S. Chen, Y. Hu, P. Wu, W. Wang, W. Zhang and S. Zhang, *Org. Biomol. Chem.* **2015**, *13*, 4769-4775; (b) J. Wang, P. Qian, Y. Hua, J. Yang, J. Jiang, S. Chen, Y. Zhang and S. Zhang, *Tetrahedron Lett.* **2015**, *56*, 2875-2877.

13 B. List, R. A. Lerner and C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.

14 A. Msutu and R. Hunter, *Tetrahedron Lett.* **2014**, *55*, 2295-2298.

15 (a) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 794-797; (b) Y. Hayashi, H. Gotoh, T. Hayashi and M. Shoji, *Angew. Chem. Int. Ed.* **2005**, *44*, 4212-4215.

16 For reviews, see: (a) F. Zhou, F.-M. Liao, J.-S. Yu and J. Zhou, *Synthesis* **2014**, *46*, 2983-3003; (b) C.-B. Ji, Y.-L. Liu, X.-L. Zhao, Y.-L. Guo, H.-Y. Wang and J. Zhou, *Org. Biomol. Chem.* **2012**, *10*, 1158-1161; For selected examples, see: (c) N. Kumaragurubaran, K. Juhl, W. Zhuang, A. Bøgevig and K. A. Jørgensen, *J. Am. Chem. Soc.* **2002**, *124*, 6254-6255; (d) A. Bøgevig, K. Juhl, N. Kumaragurubaran, W. Zhuang and K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2002**, *41*, 1790-1793; (e) B. List, *J. Am. Chem. Soc.* **2002**, *124*, 5656-5657.

17 J.-Y. Fu, X.-Y. Xu, Y.-C. Li, Q.-C. Huang and L.-X. Wang, *Org. Biomol. Chem.* **2010**, *8*, 4524-4526.

18 N. S. Chowdari and C. F. Barbas III, *Org. Lett.* **2005**, *7*, 867-870.

19 (a) S. T. Tong, P. W. R. Harris, D. Barker and M. A. Brimble, *Eur. J. Org. Chem.* **2008**, 164-170; (b) Z. P. Demko and K. B.

View Article Online
DOI: 10.1039/C6OB00953K

Sharpless, *Org. Lett.* **2002**, *4*, 2525-2527; (c) A. Hartikka and P. I. Arvidsson, *Eur. J. Org. Chem.* **2005**, 4287-4295.
20 CCDC 1436994 (**9**) and CCDC 1437043 (**11**) contain the supplementary crystallographic data for these compounds. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
21 D. A. Evans, *Aldrichimica Acta* **1982**, *15*, 23-32.
22 See the ESI† for more details.
23 (a) H. Iwamura, S. P. Mathew and D. G. Blackmond, *J. Am. Chem. Soc.* **2004**, *126*, 11770-11771; (b) H. Iwamura, D. H. Wells, Jr., S. P. Mathew, M. Klussmann, A. Armstrong and D. G. Blackmond, *J. Am. Chem. Soc.* **2004**, *126*, 16312-16313; (c) J. E. Hein, A. Armstrong and D. G. Blackmond, *Org. Lett.* **2011**, *13*, 4300-4303.