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Quinim 配体的探索及其在镍催化烯烃的不对称胺甲酰基-烷基化反应的应用

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摘要 发展手性配体是不对称催化的核心任务之一. 本工作报道了镍催化 1,1-二取代烯烃衍生的胺甲酰氯与烷基碘代物的不对称还原胺甲酰基-烷基化反应, 构建了一系列对映选择性富集的 *α*,*α*-双烷基取代的吡咯烷酮化合物. 通过对 Quinim 配体的广泛探索, 发现 $^{p\text{-tol}}$Quinim 至 $^{1\text{-Nap}}$Quinim 配体的革新是该反应成功的关键, 能以高收率、高对映选择性及出色的官能团容忍性得到多样的 *α*-位含有季碳中心的 *γ*-内酰胺化合物. 此外, 研究发现, 新发展的 Ni/$^{1\text{-Nap}}$Quinim 催化体系也能提高 *α*-单烷基取代 *γ*-内酰胺的合成效率及对映选择性.

关键词 Quinim 配体; 镍催化剂; 季碳手性中心; *γ*-内酰胺

Exploration of Quinim Ligand in Ni-Catalyzed Enantioselective Reductive Carbamoyl-Alkylation of Alkene

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Abstract The development of new chiral ligand constitutes the cornerstone of asymmetric catalysis. An asymmetric synthesis of *α*,*α*-dialkylated pyrrolidinones enabled by Ni-catalyzed reductive carbamoyl-alkylation of 1,1-disubstituted alkene-tethered carbamoyl chlorides and primary alkyl iodides is presented. After extensive investigation of Quinim ligands, it is found that the evolution of chiral ligand $^{p\text{-tol}}$Quinim to $^{1\text{-Nap}}$Quinim is critical for formation of the all-carbon quaternary center in high yield and enantioselectivity and broad functional group tolerance. The newly developed catalytic system that combines nickel salts and the $^{1\text{-Nap}}$Quinim ligand also improves both the yield and enantioselectivity in the synthesis of *α*-monoalkylated *γ*-lactams.

Keywords Quinim ligand; nickel catalysis; quaternary stereocenters; *γ*-lactam

1 Introduction

The catalytic enantioselective formation of nitrogen-containing heterocycles containing all-carbon quaternary centers remains a long-standing synthetic challenge.[1] Among the various nitrogen heterocycles, the *γ*-lactam scaffold is one of the most ubiquitous substructures that can be found in natural products and pharmaceuticals (Scheme 1a).[2] Although it would be of great value, an efficient synthesis of chiral 3,3-dialkylated pyrrolidinone architectures is still lacking.[3-5] Historically, the dialkylation of *γ*-lactams through the use of stoichiometric Ender's auxiliary provided moderate diastereomeric purity. The multi-step synthetic sequence required for the incorpora-

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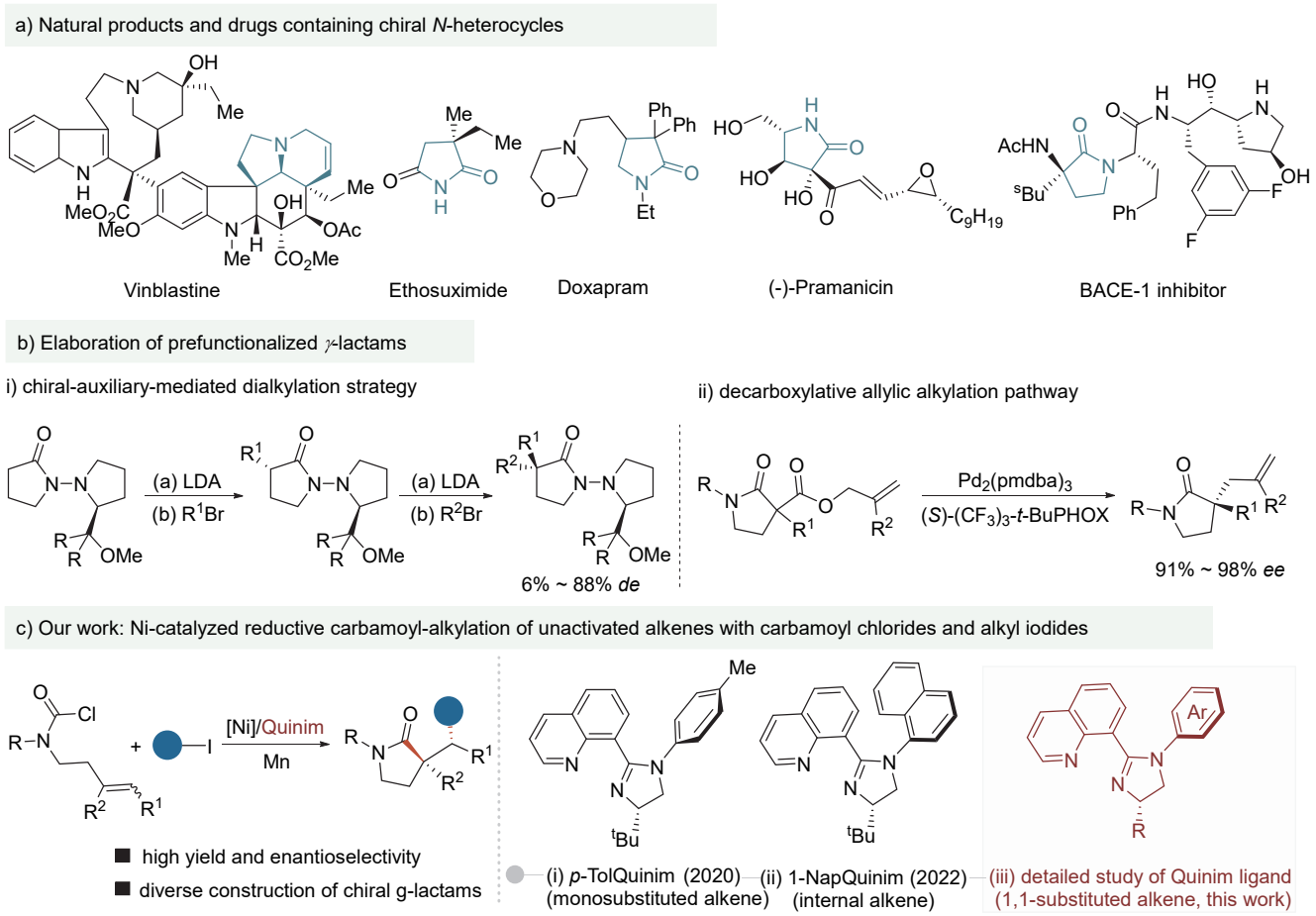


Scheme 1 Enantioselective synthesis of γ-lactams with α,α-dialkylated quaternary stereocenters

tion of the N—N bond into the lactam impeded further applications (Scheme 1b, i).[3] The catalytic asymmetric construction of 3,3-disubstituted γ-lactams with high enantiopurities had not been achieved until the elegant Pd-catalyzed decarboxylative allylic alkylation of lactams developed by the Stoltz group (Scheme 1b, ii).[4]

Recently, the transition metal-catalyzed dicarbofunctionalization of alkenes has emerged as a versatile synthetic tool in organic synthesis.[6] The transition metal-catalyzed difunctionalization of alkenes tethered to a carbamoyl electrophile is a complementary synthetic strategy for accessing the pyrrolidinone core structure.[7-11] A report by Takemoto describes the enantioselective Pd-catalyzed cyano-carbamoylation to access oxindoles, and includes a single pyrrolidinone product (15%, 27% *ee*).[9] Most recently, Ye *et al.*[10a] reported the Ni-catalyzed cascade Heck-Suzuki reaction of carbamoyl fluorides and aromatic boronic acids to access α-benzylic pyrrolidinones with high enantioselectivities. Incorporation of a more common unactivated alkyl group through this strategy to access chiral 3,3-dialkylated pyrrolidinones remains challenge. Moreover, both of these redox-neutral protocols require additional synthetic manipulations to access the carbamoyl electrophiles from the carbamoyl chloride precursors.

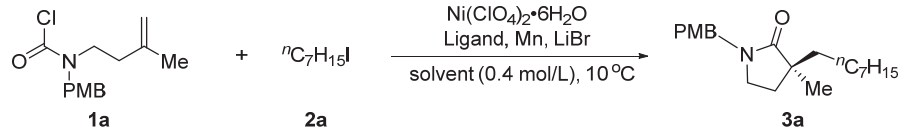
Ni-catalyzed enantioselective reductive dicarbofunctionalization of unactivated alkenes is currently undergoing rapid development to synergistically forge two consecutive carbon-carbon bonds across an alkene, which circumvents the use of prefunctionalized organometallic reagents.[12-16] We[17a] recently discovered a newly synthesized chiral 8-quinoline imidazoline ligand, named Quinim, which enabled the Ni-catalyzed reductive cross-coupling of easily accessible 3-butenyl carbamoyl chlorides with unactivated alkyl iodides to afford α-monoalkylated pyrrolidinone derivatives in high enantioselectivities (Scheme 1c, i). This represents the first asymmetric nonaromatic heterocycle synthesis via Ni-catalyzed reductive difunctionalization of alkenes. Thereafter, we realized a Ni-catalyzed enantioselective reductive dicarbofunctionalization of internal alkenes with alkyl iodides, enabling diverse construction of chiral pyrrolidinones bearing vicinal stereogenic centers. Although several preliminary mechanistic studies were carried out, the overall catalytic mechanism enabled by Ni/Quinim, especially the enantiodetermining step in the cyclization to generate the tertiary stereocenter, is still unclear. Therefore, we collaborate with Houk to carry out the DFT calculations, which reveal that the enantiodetermining step proceeds with a carbamoyl-Ni(I) intermediate that is reduced by the Mn reductant prior to intramolecular migratory insertion (Scheme 1c, ii).[17b] Driven by our

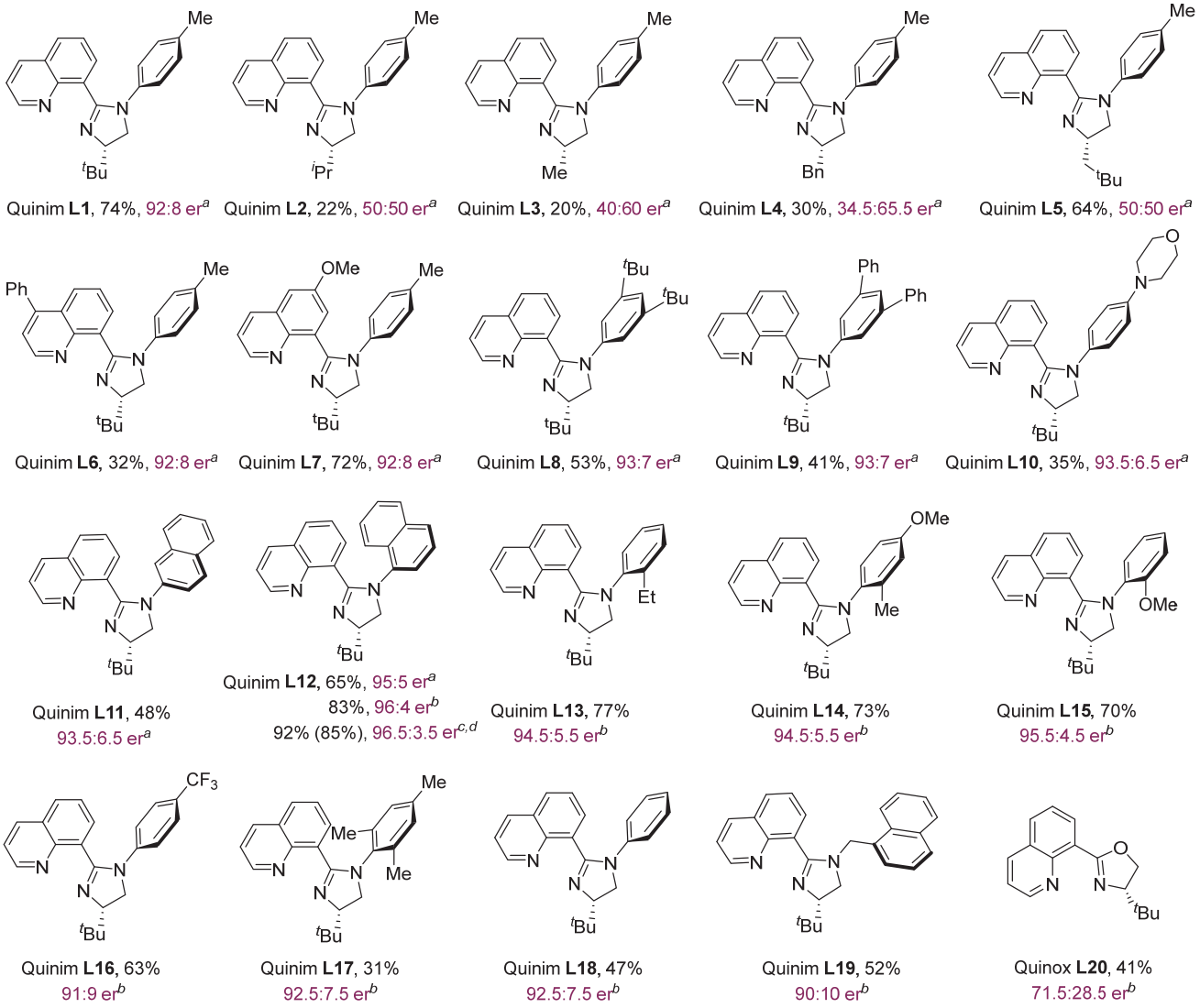
continuing interest in enantioselective difunctionalization of alkenes,[17,18] we report the detailed exploration of Quinim ligands in asymmetric Ni-catalyzed reductive carbamoyl-alkylation of 1,1-disubstituted alkene-tethered carbamoyl chlorides with a wide range of primary alkyl iodides, which enble the expedient access to the *α*,*α*-dialkylated pyrrolidinone scaffold in good enantiomeric excess under mild conditions (Scheme 1c, iii).

2 Results and discussion

We began our investigations by selecting 1,1-disubstituted alkene-tethered carbamoyl chloride **1a** as the model substrate and primary *n*-heptyl iodide **2a** as the coupling component to optimize the enantioselective synthesis of quaternary pyrrolidinone **3a** (Table 1). It was found that the combination of bench-stable $Ni(ClO_4)_2$•$6H_2O$ (15 mol%) and Quinim **L1** (18 mol%) in DMF (0.2 mol/L) with Mn (4.0 equiv) as reductant and LiBr as additive (1.0 equiv) afforded the reductive cyclized product **3a** in 74% corrected GC yield with a promising 92∶8 er (enantiomeric ratio), which revealed that the backbone of Quinim was effective in forming chiral pyrrolidinones containing

Table 1 Quinim ligand development for reaction optimization



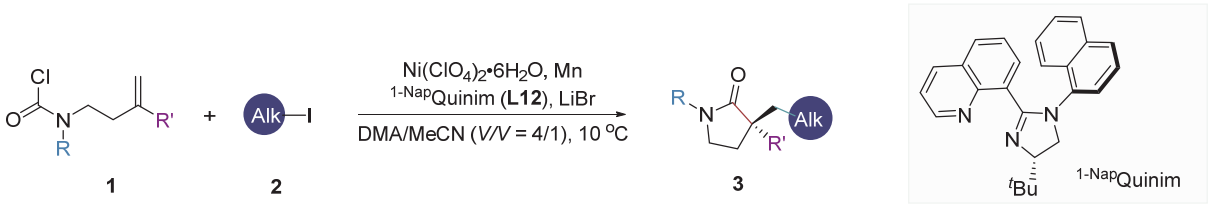


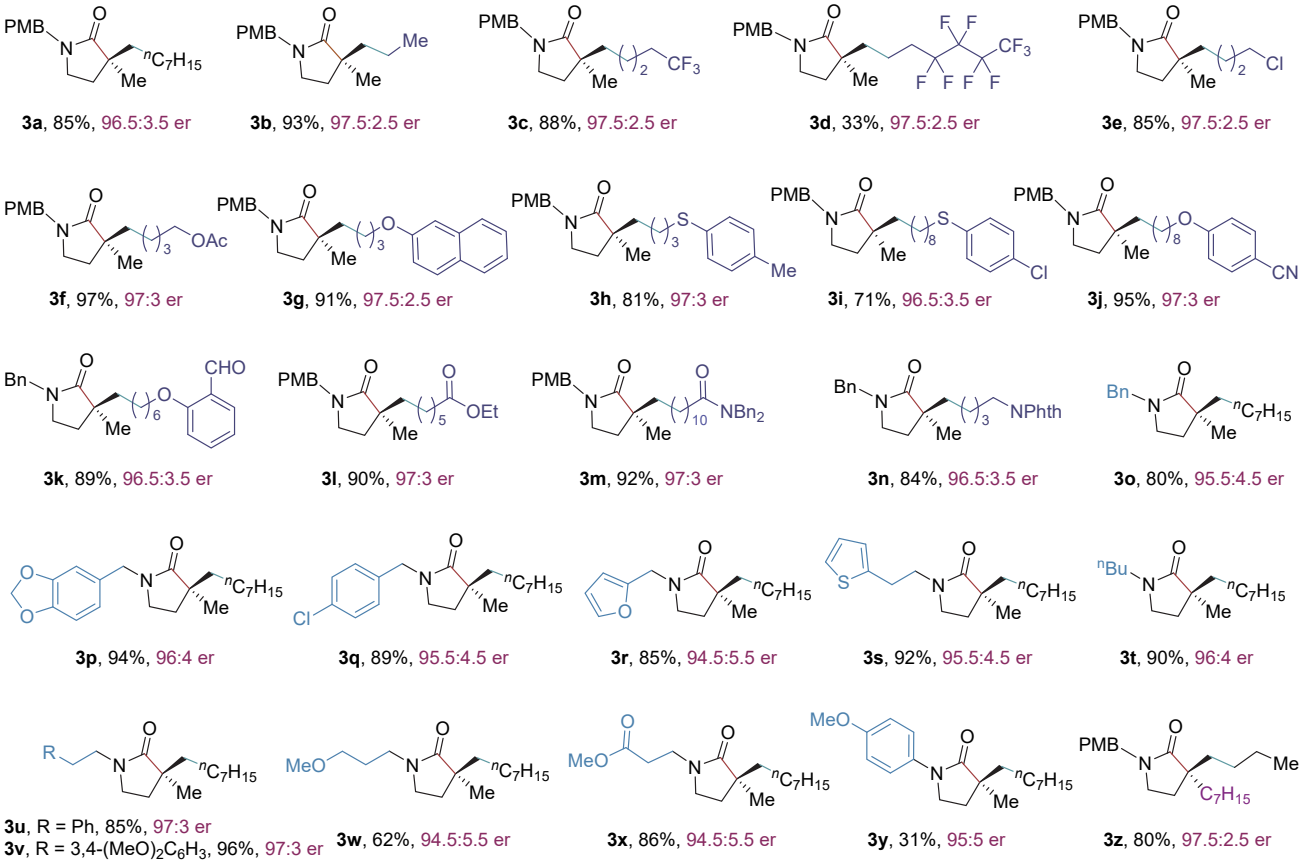
[a] Reaction conditions: **1a** (0.1 mmol), **2a** (3.0 equiv., 0.3 mmol), [Ni] (15 mol%, 0.015 mmol), ligand (18 mol%, 0.018 mmol), Mn (4.0 equiv., 0.4 mmol), LiBr (1.0 equiv., 0.1 mmol), DMF (0.5 mL) under 10 °C for 72 h. The yield was reported as corrected GC yield and the er was determined by HPLC-analysis. [b] The reaction was performed in DMF/MeCN (*V*/*V*=4/1). [c] The reaction was performed in DMA/MeCN (*V*/*V*=4/1) with 3.0 equiv. of Mn. [d] Isolated yield on 0.2 mmol scale was reported in parentheses.

α-quaternary centers. The investigation of substitution effects on the imidazoline moiety demonstrated that less bulky substituents, including ^{i}Pr (**L2**), Me (**L3**), Bn (**L4**), and $CH_2{}^{t}$Bu (**L5**) groups were detrimental for both reactivity and enantioselectivity.[19] Adding a phenyl (**L6**) or methoxy (**L7**) group at C-4 and C-6 of the quinoline ring also did not improve enantioselectivity. We then started to explore substitution effects on the aniline moiety of the imidazoline ring (**L8**～**L19**). Introducing a *tert*-butyl (**L8**) or phenyl group (**L9**) at the *meta*-position of the arene and an electron-rich morpholine group (**L10**) at the *para*-position of the arene could only slightly improve the er, while the er was improved to 93.5∶6.5 with a 2-naphthyl group (**L11**). Encouragingly, when 1-naphthyl substituted Quinim **L12** was employed, the desired product was obtained in 95∶5 er, indicating that substitution at the *ortho*-position of arenes led to high enantioselectivity. Changing the solvent to a mixture of DMF and acetonitrile (DMF/MeCN, *V*/*V*=4/1] continued to improve the er to 96∶4. Quinim ligands **L13**～**L15** with ethyl, methyl and methoxy groups at C-2 of the phenyl group indeed proved to be superior ligands than the model ligand **L1**. However, the 2,4,6-trimethyl phenyl substituted Quinim **L17** was detrimental for both reactivity and enantioselectivity, likely due to disfavored steric bulk. The er dropped to 90∶10 with the use of *N*-2-naphthyl methyl substituted Quinim **L19**. It should be noted the Quinox **L20** was not as effective as **L12** for this Ni-catalyzed reductive cyclization of carbamoyl chlorides.[20] Finally, when the reaction was performed in a DMA/MeCN mixture with Quinim **L12** as supporting ligand and 3.0 equiv. of Mn reductant, the desired γ-lactam **3a** was obtained in 85% isolated yield (92% GC yield) with 96.5∶3.5 er.

We next applied the optimal conditions to the exploration of the substrate scope of this reaction (Table 2). The commercially available alkyl iodides worked well with

Table 2 Substrate scope of Ni-catalyzed enantioselective carbamoyl-alkylation of unactivated alkenes

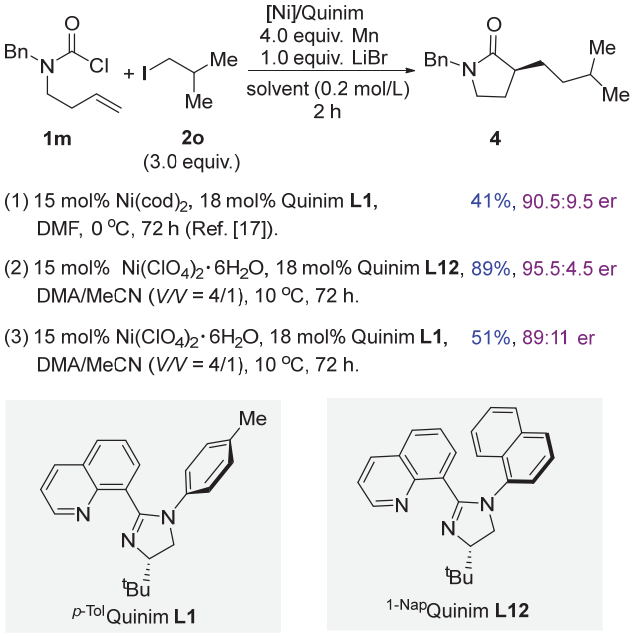




[a] Reaction conditions: **1a** (0.2 mmol), **2a** (3.0 equiv, 0.6 mmol), [Ni] (15 mol%, 0.015 mmol), Quinim **L12** (18 mol%, 0.018 mmol), Mn (3.0 equiv, 0.6 mmol), LiBr (1.0 equiv, 0.2 mmol), DMA/MeCN (*V*/*V*=4/1, 0.4 mol/L) under 10 °C for needed time.

high yield and enantioselectivity (**3a**～**3b**), including the case of short carbon chain iodoethane **3b**. Functionalized electrophilic coupling partners were then investigated. Alkyl iodides containing terminal chloride, trifluoride and polyfluoride functionalities proceeded smoothly under the standard conditions to produce products with excellent er (**3c**～**3e**), although polyfluoro-substituted alkyl electrophiles gave depreciated yields. Protected ether and thioether (**3f**～**3i**), as well as the synthetically valuable cyano group (**3j**), were all well-tolerated, furnishing the products with good isolated yield and excellent er. In addition, the reaction conditions exhibited high compatibility towards various carbonyl compounds, including aldehydes (**3k**), esters (**3l**) and amides (**3m**). Encouragingly, protected amine functionality (**3n**) was also tolerated. It should be noted that secondary and tertiary alkyl iodides were not suitable under the standard conditions. Next, our attention was turned to explore the compatibility of the carbamoyl chloride component. Benzylic groups containing both electron-donating and electron-withdrawing functional groups on nitrogen were all suitable in this reaction (**3o**～**3q**). Notably, protecting groups on the homoallylic carbamoyl chloride bearing heterocycles including furyl and thienyl were well-tolerated (**3r**, **3s**). Moreover, alkyl-substituted carbamoyl chlorides containing ether and ester functional groups all proceeded well with good yield and er (**3t**～**3x**). This protocol was also suitable for the *N*-*para*-methoxyl phenyl substituted carbamoyl chloride **3y**, albeit with decreased isolated yield. Investigation of the effects of substituents appended to the unactivated alkene moiety revealed that alkene bearing long alkyl chain (**3z**) proved to be suitable substrates for this reaction, affording the corresponding product with high yield and er. Part of substrates bearing other functional groups as well as substituents with steric hindrance or electron effect were examined in the previous work, while the configuration of the lactam product was unambiguously confirmed as *S* configuration by performing X-ray diffraction of the thioamide product derived from **3a**.[17b]

In our previous research on the synthesis of tertiary *α*-alkylated pyrrolidinones,[17a] we observed that the Ni-catalyzed reductive cross-coupling of 3-butenyl carbamoyl chlorides is susceptible to the steric properties of the primary alkyl iodide. When sterically encumbered isobutyl iodide **2o** was employed in the reaction, the desired product **4** was obtained in only 41% isolated yield and 90.5∶9.5 er (Scheme 2). Meanwhile, when isobutyl iodide was coupled with **1a** to form *α*-quaternary substituted pyrrolidinone, the product was obtained in 72% isolated yield and 95.5∶4.5 er.[17b] This inspired us to reinvestigate the reaction of mono-substituted alkene **1m** with our newly optimized ligand and reaction conditions. Importantly, these optimized conditions using Quinim **L12** allowed for the formation of tertiary *γ*-lactam **4** in 89% isolated yield and 95.5∶4.5 er. Changing $^{1\text{-Nap}}$Quinim **L12** to $^{p\text{-tol}}$Quinim **L1** with the use of $Ni(ClO_4)_2$•$6H_2O$ in a mixture of DMA and MeCN could provide **4** in only 51% yield and 89∶11 er,



Scheme 2 Comparison of Quinim ligand on tertiary pyrrolidinone formation

indicating that modification of the substructure of the Quinim ligand possesses a profound effect on both isolated yield and enantioselectivity.

3 Conclusions

In summary, we have developed an asymmetric Ni-catalyzed reductive carbamoyl-alkylation reaction to access *α*,*α*-dialkylated pyrrolidinones after extensive exploration of Quinim ligands. This protocol features broad functional group tolerance under mild reaction conditions. The modification of the Quinim ligand is the crucial factor in obtaining high enantioselectivities, which also plays a positive effect in improving both the yield and enantioselectivity in the construction of *α*-monoalkylated *γ*-lactams. Further elaboration of Quinim ligands is ongoing in our laboratory.

4 Experimental section

4.1 General information

All reactions were carried out under nitrogen atmosphere and anhydrous conditions unless otherwise indicated. All manipulations of air-sensitive or moisture-sensitive compounds were performed in a glovebox under an atmosphere of nitrogen. Unless otherwise noted, all catalytic reactions were run in dried glassware. Toluene and tetrahydrofuran (THF) were distilled from sodium/benzophenone. Dichloromethane (DCM) was distilled over CaH_2. $Ni(ClO_4)_2$•$6H_2O$ was purchased from 9dingchem. $Ni(cod)_2$ was purchased from Sinocompound. Manganese powder (325 mesh) was purchased from Alfa Aesar; LiBr and $C_7H_{15}I$ were purchased from Bidepharm and Adamas. *N*,*N*-Dimethylformamide (DMF) and *N*,*N*-dimethylacetamide (DMA) were purchased from Adamas (99.8%,

SafeDry, with molecular sieves, Water ≤50×10^{-6} (by K.F.), SafeSeal), MeCN was purchased from J&K. Other commercial reagents were purchased from Bidepharm, Energy Chemical, 9dingchem, Adamas-beta China and were used as received.

Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.20 mm Huanghai silica gel plates (HSGF 254) using UV light as the visualizing agent, iodine with H_2O, $KMnO_4$ and phosphomolybdic acid (PMA) with heat as the developing agents. All new compounds were characterized by means of GC, ^{1}H NMR, ^{13}C NMR, and HRMS. GC analysis was performed on a SHIMADZU GC-2030. GC runs were performed with the following method: GC; HP-5 column; inlet temperature 100 °C; column temperature 100 °C for 1 min, 50 °C/min to 280 °C, and then 280 °C for 6 min. HPLC was performed on a SHIMADZU LC-2030 Plus. Optical rotations were recorded on digital automatic polarimeter (WZZ-2S). X-ray analysis was performed on a Bruker D8 Venture diffractometer. NMR spectra were recorded on a Bruker AVANCE III 400 MHz NMR spectrometer. High-resolution mass spectra (HRMS) were recorded on Agilent Technologies 7250 GCQTOF (EI), JEOC AccuTOF LC-plus 4G (ESI) and Q-Exactive plus mass spectrometer (Thermo Fisher). All ^{1}H NMR data were calibrated relative to the signals for residual chloroform (δ 7.26) in deuterochloroform ($CDCl_3$). All ^{13}C NMR data are reported relative to $CDCl_3$ (δ 77.16) and were obtained with ^{1}H decoupling.

4.2 General Procedure for Ni-catalyzed reductive carbamoyl-alkylation of unactivated alkenes and characterization data for products

To a dried 8-mL vial were added ligand (18 mol%), Mn (3.0 equiv), and $Ni(ClO_4)_2$•$6H_2O$ (15 mol%). Then the vial was transferred into the glovebox. LiBr (1.0 equiv), DMA/MeCN (*V*/*V*=4/1, 0.4 mol/L), carbamoyl chloride (1.0 equiv.) and alkyl halide (3.0 equiv.) were added in sequence inside the glovebox. The vial was then taken out from the glovebox, sealed with parafilm, put into cryogenic bath (10 °C) and stirred for needed time. After completion, the reaction mixture was diluted with ethyl acetate and quenched with H_2O. Then the mixture was filtered through a pad of celite. The resulting filtrate was washed with H_2O and brine, and the combined aqueous layer was extracted with ethyl acetate two times. The combined organic phase was dried with Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was purified by silica gel flash column chromatography to afford products **3**.

(*S*)-1-(4-Methoxybenzyl)-3-methyl-3-octylpyrrolidin-2-one (**3a**): General procedure was followed on 0.2 mmol scale with a reaction time of 68 h. The reaction mixture was purified by flash column chromatography [silica gel, *V*(petroleum ether)/*V*(ethyl acetate)=5/1] to afford **3a** as a colorless oil (56.5 mg, 85% yield). R_f=0.28 [*V*(petroleum ether)/*V*(ethyl acetate)=5/1]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.13 (d, *J*=8.4 Hz, 2H), 6.83 (d, *J*=8.8 Hz, 2H), 4.36 (abq, *J*=14.4 Hz, 2H), 3.77 (s, 3H), 3.10～3.06 (m, 2H), 1.93～1.87 (m, 1H), 1.71～1.65 (m, 1H), 1.51～1.43 (m, 2H), 1.30～1.20 (m, 12H), 1.11 (s, 3H), 0.86 (t, *J*=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.1, 159.1, 129.5, 129.0, 114.0, 55.3, 46.2, 44.2, 43.3, 38.1, 32.0, 31.0, 30.2, 29.6, 29.3, 24.5, 23.3, 22.7, 14.2; HRMS (ESI) calcd for $C_{21}H_{33}NO_2Na$ $[M+Na]^+$ 354.2404, found 354.2399; HPLC (Chiralpak AD-H): *V*(*n*-Hexane)/*V*(*i*-PrOH)=90/10, flow rate 1.0 mL/min, λ=220 nm, t_{R1}=6.243 min (major), t_{R2}=6.959 min (minor); 96.5∶3.5 er; $[\alpha]_D^{25}$ −8.90 (*c* 5.57, $CHCl_3$).

(*S*)-1-(4-Methoxybenzyl)-3-methyl-3-propylpyrrolidin-2-one (**3b**): General procedure was followed on 0.2 mmol scale with a reaction time of 65 h. The reaction mixture was purified by flash column chromatography [silica gel, *V*(petroleum ether)/*V*(ethyl acetate)=5/1] to afford **3b** as a colorless oil (48.6 mg, 93% yield). R_f=0.29 [*V*(petroleum ether)/*V*(ethyl acetate)=5/1]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.13 (d, *J*=8.4 Hz, 2H), 6.83 (d, *J*=8.8 Hz, 2H), 4.36 (abq, *J*=14.4 Hz, 2H), 3.77 (s, 3H), 3.12～3.04 (m, 2H), 1.94～1.87 (m, 1H), 1.71～1.65 (m, 1H), 1.51～1.42 (m, 2H), 1.39～1.30 (m, 1H), 1.25～1.15 (m, 1H),1.11 (s, 3H), 0.89 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.1, 159.0, 129.5, 129.0, 114.0, 55.3, 46.2, 44.2, 43.3, 40.3, 31.0, 23.3, 17.8, 14.7; HRMS (ESI) calcd for $C_{16}H_{23}NO_2Na$ $[M+Na]^+$ 284.1621, found 284.1628; HPLC (Chiralpak AD-H): *V*(*n*-Hexane)/*V*(*i*-PrOH)=90/10, flow rate 1.0 mL/min, λ=220 nm, t_{R1}=8.373 min (major), t_{R2}=9.015 min (minor); 97.5∶2.5 er; $[\alpha]_D^{25}$ −1.39 (*c* 5.62, $CHCl_3$).

(*S*)-1-(4-Methoxybenzyl)-3-methyl-3-(5,5,5-trifluoropentyl)pyrrolidin-2-one (**3c**): General procedure was followed on 0.2 mmol scale with a reaction time of 83 h. The reaction mixture was purified by flash column chromatography [silica gel, *V*(petroleum ether)/*V*(ethyl acetate)=5/1] to afford **3c** as colorless oil (60.4 mg, 88% yield). R_f=0.51 [*V*(petroleum ether)/*V*(ethyl acetate)=2/1]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.12 (d, *J*=8.8 Hz, 2H), 6.82 (d, *J*=8.8 Hz, 2H), 4.35 (abq, *J*=14.4 Hz, 2H), 3.76 (s, 3H), 3.14～3.04 (m, 2H), 2.10～1.98 (m, 2H), 1.91～1.84 (m, 1H), 1.73～1.66 (m, 1H), 1.56～1.47 (m, 4H), 1.45～1.34 (m, 1H), 1.29～1.18 (m, 1H), 1.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.6, 159.1, 129.5, 128.8, 127.2 (q, J_{C-F}=274.5 Hz), 114.0, 55.3, 46.2, 44.0, 43.2, 37.5, 33.6 (q, J_{C-F}=28.2 Hz), 31.0, 23.6, 23.2, 22.4 (q, J_{C-F}=2.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −66.4; HRMS (ESI) calcd for $C_{18}H_{24}F_3NO_2Na$ $[M+Na]^+$ 366.1651, found 366.1652; HPLC (Chiralpak AD-H): *V*(*n*-Hexane)/*V*(*i*-PrOH)=90/10, flow rate 1.0 mL/min, λ=220 nm, t_{R1}=8.902 min (major), t_{R2}=9.523 min (minor); 97.5∶2.5 er; $[\alpha]_D^{25}$ −3.83 (*c* 5.79, $CHCl_3$).

(*S*)-1-(4-Methoxybenzyl)-3-methyl-3-(4,4,5,5,6,6,7,7,7-nonafluoroheptyl)pyrrolidin-2-one (**3d**): General procedure was followed on 0.2 mmol scale with a reaction time of 78 h. The reaction mixture was purified by flash column chromatography [silica gel, *V*(petroleum ether)/*V*(ethyl

acetate)=5/1] to afford **3d** as colorless oil (31.4 mg, 33% yield). R_f = 0.18 [*V*(petroleum ether)/*V*(ethyl acetate) = 2/1]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.14 (d, J=8.8 Hz, 2H), 6.85 (d, J=8.8 Hz, 2H), 4.38 (abq, J=14.4 Hz, 2H), 3.79 (s, 3H), 3.18～3.08 (m, 2H), 2.13～1.98 (m, 2H), 1.96～1.89 (m, 1H), 1.78～1.48 (m, 5H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.3, 159.2, 129.6, 128.8, 114.2, 55.4, 46.3, 44.1, 43.3, 37.5, 31.3 (t, J_{C-F}=22.0 Hz), 30.9, 23.2, 15.6 (t, J_{C-F}=3.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −81.0～−81.1 (m, 3F), −114.5 (m, 1F), −124.5 (m, 2F), −126.0～−126.1 (m, 2F); HRMS (ESI) calcd for $C_{20}H_{22}F_9NO_2Na$ $[M+Na]^+$ 502.1399, found 502.1409; HPLC (Chiralpak AD-H): *V*(*n*-Hexane)/*V*(*i*-PrOH)=90/10, flow rate 1.0 mL/min, λ=220 nm, t_{R1}=5.394 min (minor), t_{R2}=5.684 min (major); 97.5∶2.5 er; $[\alpha]_D^{25}$ −6.04 (*c* 1.69, $CHCl_3$).

(*S*)-3-(4-Chlorobutyl)-1-(4-methoxybenzyl)-3-methylpyrrolidin-2-one (**3e**): General procedure was followed on 0.2 mmol scale with a reaction time of 72 h. The reaction mixture was purified by flash column chromatography [silica gel, *V*(petroleum ether)/*V*(ethyl acetate)=5/1] to afford **3e** as colorless oil (52.7 mg, 85% yield). R_f=0.26 [*V*(petroleum ether)/*V*(ethyl acetate)=3/1]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.13 (d, J=8.0 Hz, 2H), 6.83 (d, J=8.0 Hz, 2H), 4.35 (abq, J=14.4 Hz, 2H), 3.77 (s, 3H), 3.50 (t, J=6.4 Hz, 2H), 3.14～3.05 (m, 2H), 1.94～1.87 (m, 1H), 1.77～1.67 (m, 3H), 1.53～1.42 (m, 3H), 1.35～1.23 (m, 1H), 1.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.7, 159.0, 129.5, 128.8, 114.0, 55.3, 46.2, 44.9, 44.0, 43.3, 37.1, 32.9, 30.9, 23.2, 21.8; HRMS (ESI) calcd for $C_{17}H_{24}NO_2NaCl$ $[M+Na]^+$ 332.1388, found 332.1385; HPLC (Chiralpak IC): *V*(*n*-Hexane)/*V*(*i*-PrOH) = 90/10, flow rate 1.0 mL/min, λ = 220 nm, t_{R1} = 16.174 min (major), t_{R2} = 17.944 min (minor); 97.5 ∶ 2.5 er; $[\alpha]_D^{25}$ +1.05 (*c* 4.00, $CHCl_3$).

(*S*)-5-(1-(4-Methoxybenzyl)-3-methyl-2-oxopyrrolidin-3-yl)pentyl acetate (**3f**): General procedure was followed on 0.2 mmol scale with a reaction time of 83 h. The reaction mixture was purified by flash column chromatography [silica gel, *V*(petroleum ether)/*V*(ethyl acetate)=5/1] to afford **3f** as colorless oil (67.2 mg, 97% yield). R_f=0.28 [*V*(petroleum ether)/*V*(ethyl acetate)=2/1]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.12 (d, J=8.4 Hz, 2H), 6.82 (d, J=8.8 Hz, 2H), 4.34 (abq, J=14.4 Hz, 2H), 4.00 (d, J=6.8 Hz, 2H), 3.76 (s, 3H), 3.12～3.03 (m, 2H), 2.01 (s, 3H), 1.91～1.84 (m, 1H), 1.71～1.64 (m, 1H), 1.62～1.55 (m, 2H), 1.49～1.43 (m, 2H), 1.36～1.25 (m, 3H), 1.22～1.15 (m, 1H), 1.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.9, 171.2, 159.0, 129.5, 128.9, 114.0, 64.5, 55.3, 46.2, 44.1, 43.3, 37.9, 31,0, 28.5, 26.4, 24.1, 23.2, 21.0; HRMS (ESI) calcd for $C_{20}H_{29}NO_4Na$ $[M+Na]^+$ 370.1989, found 370.1989; HPLC (Chiralpak AD-H): *V*(*n*-Hexane)/*V*(*i*-PrOH)=80/20, flow rate 1.0 mL/min, λ=254 nm, t_{R1}=7.612 min (major), t_{R2}=8.774 min (minor); 97∶3 er; $[\alpha]_D^{25}$ −6.30 (*c* 6.32, $CHCl_3$).

(*S*)-1-(4-Methoxybenzyl)-3-methyl-3-(4-(naphthalen-2-yloxy)butyl)pyrrolidin-2-one (**3g**): General procedure was followed on 0.2 mmol scale with a reaction time of 78 h. The reaction mixture was purified by flash column chromatography [silica gel, *V*(petroleum ether)/*V*(ethyl acetate)=3/1] to afford **3g** as colorless oil (76.3 mg, 91% yield). R_f = 0.18 [*V*(petroleum ether)/*V*(ethyl acetate) = 3/1]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.77～7.72 (m, 3H), 7.46～7.42 (m, 1H), 7.35～7.31 (m, 1H), 7.17～7.13 (m, 4H), 6.82 (d, J=8.8 Hz, 2H), 4.39 (abq, J=14.4 Hz, 2H), 4.06 (t, J=6.4 Hz, 2H), 3.72 (s, 3H), 3.13～3.09 (m, 2H), 1.99～1.92 (m, 1H), 1.89～1.82 (m, 2H), 1.76～1.69 (m, 1H), 1.65～1.57 (m, 3H), 1.46～1.40 (m, 1H), 1.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.8, 159.0, 157.1, 134.7, 129.5, 129.3, 128.9, 128.8, 127.6, 126.7, 126.3, 123.5, 119.0, 114.0, 106.6, 67.7, 55.2, 46.2, 44.1, 43.3, 37.8, 30.9, 29.7, 23.3, 21.2. HRMS (ESI) calcd for $C_{27}H_{31}NO_3Na$ $[M+Na]^+$ 440.2196, found 440.2190; HPLC (Chiralcel OD-H): *V*(*n*-Hexane)/*V*(*i*-PrOH)=90/10, flow rate 1.0 mL/min, λ=210 nm, t_{R1}=21.499 min (major), t_{R2}=33.198 min (minor); 97.5∶2.5 er; $[\alpha]_D^{25}$ −12.40 (*c* 7.63, $CHCl_3$).

(*S*)-1-(4-Methoxybenzyl)-3-methyl-3-(4-(*p*-tolylthio)butyl)pyrrolidin-2-one (**3h**): General procedure was followed on 0.2 mmol scale with a reaction time of 78 h. The reaction mixture was purified by flash column chromatography [silica gel, *V*(petroleum ether)/*V*(ethyl acetate)=3/1] to afford **3h** as colorless oil (64.3 mg, 81% yield). R_f=0.26 [*V*(petroleum ether)/*V*(ethyl acetate)=3/1]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.23 (d, J=8.4 Hz, 2H), 7.14 (d, J=8.4 Hz, 2H), 7.08 (d, J=8.0 Hz, 2H), 6.84 (d, J=8.8 Hz, 2H), 4.36 (abq, J=14.4 Hz, 2H), 3.77 (s, 3H), 3.13～3.04 (m, 2H), 2.85 (t, J=7.2 Hz, 2H), 2.30 (s, 3H), 1.92～1.86 (m, 1H), 1.72～1.57 (m, 3H), 1.52～1.44 (m, 3H), 1.32～1.26 (m, 1H), 1.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.8, 159.1, 136.0, 132.9, 130.0, 129.7, 129.5, 128.9, 114.1, 55.3, 46.2, 44.0, 43.3, 37.5, 34.2, 30.9, 29.7, 23.6, 23.2, 21.0. HRMS (ESI) calcd for $C_{24}H_{31}NO_2NaS$ $[M+Na]^+$ 420.1968, found 420.1957; HPLC (Chiralpak AD-H): *V*(*n*-Hexane)/*V*(*i*-PrOH)=90/10, flow rate 1.0 mL/min, λ=254 nm, t_{R1}=14.541 min (major), t_{R2}=17.795 min (minor); 97∶3 er; $[\alpha]_D^{25}$ −6.12 (*c* 6.83, $CHCl_3$).

(*S*)-3-(9-((4-Chlorophenyl)thio)nonyl)-1-(4-methoxybenzyl)-3-methylpyrrolidin-2-one (**3i**): General procedure was followed on 0.2 mmol scale with a reaction time of 69 h. The reaction mixture was purified by flash column chromatography [silica gel, *V*(petroleum ether)/*V*(ethyl acetate)=3/1] to afford **3i** as colorless oil (69.0 mg, 71% yield). R_f = 0.38 [*V*(petroleum ether)/*V*(ethyl acetate) = 3/1]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.22 (s, 4H), 7.13 (d, J=8.8 Hz, 2H), 6.83 (d, J=8.4 Hz, 2H), 4.36 (abq, J=14.4 Hz, 2H), 3.77 (s, 3H), 3.11～3.05 (m, 2H), 2.87 (t, J=7.2 Hz, 2H), 1.93～1.86 (m, 1H), 1.71～1.57 (m, 3H), 1.51～1.45 (m, 2H), 1.40～1.35 (m, 2H), 1.24 (m, 10H), 1.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.1, 159.0, 135.7, 131.6, 130.2, 129.5, 129.0, 114.0, 55.3, 46.2, 44.1, 43.3, 38.0, 33.9, 31.0, 30.1, 29.5, 29.5, 29.2, 29.1, 28.8, 24.5, 23.3. HRMS (ESI) calcd for $C_{28}H_{39}NO_2SCl$ $[M+H]^+$

488.2385, found 488.2390; HPLC (Chiralpak AD-H): *V*(*n*-Hexane)/*V*(*i*-PrOH)＝80/20, flow rate 1.0 mL/min, λ＝220 nm, t_{R1}＝8.608 min (major), t_{R2}＝10.223 min (minor); 96.5∶3.5 er; $[\alpha]_D^{25}$ −5.92 (*c* 1.69, $CHCl_3$).

(*S*)-4-((9-(1-(4-Methoxybenzyl)-3-methyl-2-oxopyrrolidin-3-yl)nonyl)oxy)benzonitrile (**3j**): General procedure was followed on 0.2 mmol scale with a reaction time of 69 h. The reaction mixture was purified by flash column chromatography [silica gel, *V*(petroleum ether)/*V*(ethyl acetate)＝3/1] to afford **3j** as colorless oil (87.8 mg, 95% yield). R_f＝0.42 [*V*(petroleum ether)/*V*(ethyl acetate)＝2/1]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.55～7.52 (m, 2H), 7.12 (d, *J*＝7.6 Hz, 2H), 6.91 (dd, *J*＝8.8, 1.2 Hz, 2H), 6.82 (dd, *J*＝8.8, 1.6 Hz, 2H), 4.35 (abq, *J*＝14.4 Hz, 2H), 3.96 (td, *J*＝6.4, 1.2 Hz, 2H), 3.76 (d, *J*＝1.6 Hz, 3H), 3.09～3.06 (m, 2H), 1.92～1.86 (m, 1H), 1.80～1.64 (m, 3H), 1.47～1.38 (m, 4H), 1.31～1.13 (m, 10H), 1.10 (d, *J*＝0.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.0, 162.5, 159.0, 133.9, 129.4, 128.9, 119.4, 115.2, 114.0, 103.6, 68.4, 55.3, 46.1, 44.1, 43.3, 38.0, 31.0, 30.1, 29.5, 29.4, 29.3, 29.0, 25.9, 24.4, 23.3; HRMS (ESI) calcd for $C_{29}H_{38}N_2O_3Na$ $[M+Na]^+$ 485.2775, found 485.2779; HPLC (Chiralpak AD-H): *V*(*n*-Hexane)/*V*(*i*-PrOH)＝80/20, flow rate 1.0 mL/min, λ＝220 nm, t_{R1}＝19.735 min (major), t_{R2}＝23.878 min (minor); 97∶3 er; $[\alpha]_D^{25}$ −8.83 (*c* 7.27, $CHCl_3$).

(*S*)-2-((7-(1-Benzyl-3-methyl-2-oxopyrrolidin-3-yl)heptyl)oxy)benzaldehyde (**3k**): General procedure was followed on 0.2 mmol scale with a reaction time of 72 h. The reaction mixture was purified by flash column chromatography [silica gel, *V*(petroleum ether)/*V*(ethyl acetate)＝3/1] to afford **3k** as colorless oil (72.9 mg, 89% yield). R_f＝0.26 [*V*(petroleum ether)/*V*(ethyl acetate)＝3/1]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.49 (s, 1H), 7.79 (dd, *J*＝7.6, 2.0 Hz, 1H), 7.52～7.48 (m, 1H), 7.31～7.18 (m, 5H), 6.99～6.94 (m, 2H), 4.41 (abq, *J*＝14.4 Hz, 2H), 4.04 (t, *J*＝6.4 Hz, 2H), 3.14～3.05 (m, 2H), 1.94～1.88 (m, 1H), 1.85～1.78 (m, 2H), 1.73～1.66 (m, 1H), 1.50～1.42 (m, 4H), 1.38～1.26 (m, 5H), 1.23～1.15 (m, 1H), 1.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 189.9, 179.1, 161.5, 136.8, 136.0, 128.6, 128.1, 128.1, 127.4, 124.8, 120.4, 112.5, 68.4, 46.7, 44.0, 43.4, 37.9, 31.0, 30.0, 29.2, 29.0, 26.0, 24.3, 23.2; HRMS (ESI) calcd for $C_{26}H_{33}NO_3Na$ $[M+Na]^+$ 430.2353, found 430.2348; HPLC (Chiralpak AD-H): *V*(*n*-Hexane)/*V*(*i*-PrOH)＝80/20, flow rate 1.0 mL/min, λ＝254 nm, t_{R1}＝10.043 min (major), t_{R2}＝14.604 min (minor); 96.5∶3.5 er; $[\alpha]_D^{25}$ −2.52 (*c* 7.05, $CHCl_3$).

Ethyl (*S*)-7-(1-(4-methoxybenzyl)-3-methyl-2-oxopyrrolidin-3-yl)heptanoate (**3l**): General procedure was followed on 0.2 mmol scale with a reaction time of 72 h. The reaction mixture was purified by flash column chromatography [silica gel, *V*(petroleum ether)/*V*(ethyl acetate)＝5/1] to afford **3l** as colorless oil (67.4 mg, 90% yield). R_f＝0.23 [*V*(petroleum ether)/*V*(ethyl acetate)＝3/1]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.11 (d, *J*＝8.4 Hz, 2H), 6.81 (d, *J*＝8.4 Hz, 2H), 4.33 (abq, *J*＝14.4 Hz, 2H), 4.08 (q, *J*＝7.2 Hz, 2H), 3.75 (s, 3H), 3.08～3.03 (m, 2H), 2.29～2.22 (m, 2H), 1.91～1.84 (m, 1H), 1.69～1.63 (m, 1H), 1.60～1.53 (m, 2H), 1.46～1.41 (m, 2H), 1.27～1.18 (m, 9H), 1.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.0, 173.9, 159.0, 129.4, 128.9, 114.0, 60.2, 55.3, 46.1, 44.1, 43.3, 37.9, 34.3, 30.9, 29.8, 29.1, 24.9, 24.3, 23.2, 14.3; HRMS (ESI) calcd for $C_{22}H_{33}NO_4Na$ $[M+Na]^+$ 398.2302, found 398.2311; HPLC (Chiralpak AD-H): *V*(*n*-Hexane)/*V*(*i*-PrOH)＝90/10, flow rate 1.0 mL/min, λ＝220 nm, t_{R1}＝13.199 min (major), t_{R2}＝15.721 min (minor); 97∶3 er; $[\alpha]_D^{25}$ −8.18 (*c* 6.31, $CHCl_3$).

(*S*)-*N*,*N*-Dibenzyl-12-(1-(4-methoxybenzyl)-3-methyl-2-oxopyrrolidin-3-yl)dodecanamide (**3m**): General procedure was followed on 0.2 mmol scale with a reaction time of 69 h. The reaction mixture was purified by flash column chromatography [silica gel, *V*(petroleum ether)/*V*(ethyl acetate)＝2/1] to afford **3m** as colorless oil (109.4 mg, 92% yield). R_f＝0.32 [*V*(petroleum ether)/*V*(ethyl acetate)＝2/1]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37～7.24 (m, 6H), 7.20 (d, *J*＝7.2 Hz, 2H), 7.14 (d, *J*＝7.6 Hz, 4H), 6.83 (d, *J*＝7.2 Hz, 2H), 4.59 (s, 2H), 4.44 (s, 2H), 4.36 (abq, *J*＝14.4 Hz, 2H), 3.76 (s, 3H), 3.08 (t, *J*＝7.2 Hz, 2H), 2.41 (t, *J*＝7.2 Hz, 2H), 1.94～1.87 (m, 1H), 1.74～1.65 (m, 3H), 1.52～1.44 (m, 2H), 1.31～1.24 (m, 16H), 1.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.0, 173.7, 159.0, 137.6, 136.7, 129.4, 128.9, 128.9, 128.6, 128.3, 127.6, 127.3, 126.4, 114.0, 55.2, 49.9, 48.1, 46.1, 44.1, 43.3, 38.0, 33.3, 31.0, 30.1, 29.6, 29.5, 29.5, 29.4, 25.5, 24.4, 23.2; HRMS (ESI) calcd for $C_{39}H_{53}N_2O_3$ $[M+H]^+$ 597.4051, found 597.4044; HPLC (Chiralpak AD-H): *V*(*n*-Hexane)/*V*(*i*-PrOH)＝80/20, flow rate 1.0 mL/min, λ＝220 nm, t_{R1}＝26.653 min (major), t_{R2}＝31.841 min (minor); 97∶3 er; $[\alpha]_D^{25}$ −3.29 (*c* 10.51, $CHCl_3$).

(*S*)-2-(5-(1-Benzyl-3-methyl-2-oxopyrrolidin-3-yl)pentyl)isoindoline-1,3-dione (**3n**): General procedure was followed on 0.2 mmol scale with a reaction time of 92 h. The reaction mixture was purified by flash column chromatography [silica gel, *V*(petroleum ether)/*V*(ethyl acetate)＝2/1] to afford **3n** as colorless oil (68.2 mg, 84% yield). R_f＝0.35 [*V*(petroleum ether)/*V*(ethyl acetate)＝2/1]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.83～7.80 (m, 2H), 7.71～7.68 (m, 2H), 7.32～7.19 (m, 5H), 4.41 (s, 2H), 3.66 (t, *J*＝7.2 Hz, 2H), 3.12～3.09 (m, 2H), 1.95～1.88 (m, 1H), 1.73～1.63 (m, 3H), 1.53～1.45 (m, 2H), 1.38～1.22 (m, 4H), 1.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.0, 168.4, 136.7, 133.9, 132.1, 128.6, 128.1, 127.5, 123.1, 46.7, 44.0, 43.4, 37.9, 37.8, 30.9, 28.5, 27.3, 24.0, 23.2; HRMS (ESI) calcd for $C_{25}H_{28}N_2O_3Na$ $[M+Na]^+$ 427.1992, found 427.1995; HPLC (Chiralpak AD-H): *V*(*n*-Hexane)/*V*(*i*-PrOH)＝80/20, flow rate 1.0 mL/min, λ＝254 nm, t_{R1}＝15.156 min (major), t_{R2}＝18.983 min (minor); 96.5∶3.5 er; $[\alpha]_D^{25}$ −1.30 (*c* 7.55, $CHCl_3$).

(*S*)-1-Benzyl-3-methyl-3-octylpyrrolidin-2-one (**3o**): General procedure was followed on 0.2 mmol scale with a reaction time of 68 h. The reaction mixture was purified by flash column chromatography [silica gel, *V*(petroleum ether)/*V*(ethyl acetate)＝5/1] to afford **3o** as colorless oil

(48.3 mg, 80% yield). R_f = 0.38 [*V*(petroleum ether)/*V*(ethyl acetate)=5/1]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33～7.20 (m, 5H), 4.43 (abq, *J*=14.4 Hz, 2H), 3.15～3.06 (m, 2H), 1.96～1.89 (m, 1H), 1.74～1.67 (m, 1H), 1.54～1.46 (m, 2H), 1.31～1.18 (m, 12H), 1.13 (s, 3H), 0.87 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.3, 136.9, 128.7, 128.2, 127.5, 46.8, 44.1, 43.5, 38.1, 32.0, 31.1, 30.2, 29.6, 29.4, 24.5, 23.3, 22.7, 14.2; HRMS (ESI) calcd for $C_{20}H_{32}NO$ $[M+H]^+$ 302.2478, found 302.2479; HPLC (Chiralpak AD-H): *V*(*n*-Hexane)/*V*(*i*-PrOH)=90/10, flow rate 1.0 mL/min, λ=220 nm, t_{R1}=5.120 min (major), t_{R2}=5.793 min (minor); 95.5∶4.5 er; $[\alpha]_D^{25}$ −7.32 (*c* 4.40, $CHCl_3$).

(*S*)-1-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-3-methyl-3-octylpyrrolidin-2-one (**3p**): General procedure was followed on 0.2 mmol scale with a reaction time of 72 h. The reaction mixture was purified by flash column chromatography [silica gel, *V*(petroleum ether)/*V*(ethyl acetate)=3/1] to afford **3p** as colorless oil (65.1 mg, 94% yield). R_f=0.41 [*V*(petroleum ether)/*V*(ethyl acetate)=3/1]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.73～6.65 (m, 3H), 5.92 (s, 2H), 4.32 (abq, *J*=14.4 Hz, 2H), 3.14～3.05 (m, 2H), 1.94～1.88 (m, 1H), 1.72～1.66 (m, 1H), 1.51～1.43 (m, 2H), 1.27～1.14 (m, 12H), 1.11 (s, 3H), 0.86 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.2, 148.0, 147.0, 130.8, 121.5, 108.6, 108.2, 101.1, 46.6, 44.1, 43.4, 38.1, 32.0, 31.1, 30.2, 29.6, 29.4, 24.5, 23.3, 22.7, 14.2; HRMS (ESI) calcd for $C_{21}H_{31}NO_3Na$ $[M+Na]^+$ 368.2196, found 368.2200; HPLC (Chiralpak AD-H): *V*(*n*-Hexane)/*V*(*i*-PrOH)=90/10, flow rate 1.0 mL/min, λ=220 nm, t_{R1}=6.938 min (major), t_{R2}=7.783 min (minor); 96∶4 er; $[\alpha]_D^{25}$ −5.48 (*c* 5.88, $CHCl_3$).

(*S*)-1-(4-Chlorobenzyl)-3-methyl-3-octylpyrrolidin-2-one (**3q**): General procedure was followed on 0.2 mmol scale with a reaction time of 72 h. The reaction mixture was purified by flash column chromatography [silica gel, *V*(petroleum ether)/*V*(ethyl acetate)=7/1] to afford **3q** as colorless oil (59.9 mg, 89% yield). R_f=0.44 [*V*(petroleum ether)/*V*(ethyl acetate)=5/1]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27 (d, *J*=8.4 Hz, 2H), 7.14 (d, *J*=8.0 Hz, 2H), 4.38 (abq, *J*=14.8 Hz, 2H), 3.13～3.05 (m, 2H), 1.96～1.89 (m, 1H), 1.74～1.67 (m, 1H), 1.51～1.44 (m, 2H), 1.30～1.14 (m, 12H), 1.12 (s, 3H), 0.86 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.34, 135.5, 133.4, 129.6, 128.9, 46.2, 44.0, 43.5, 38.0, 32.0, 31.1, 30.2, 29.6, 29.4, 24.5, 23.3, 22.7, 14.2; HRMS (ESI) calcd for calcd for $C_{20}H_{31}NOCl$ $[M+H]^+$ 336.2089, found 336.2096; HPLC (Chiralpak AD-H): *V*(*n*-Hexane)/*V*(*i*-PrOH)=90/10, flow rate 1.0 mL/min, λ=210 nm, t_{R1}=5.298 min (major), t_{R2}=6.050 min (minor); 95.5∶4.5 er; $[\alpha]_D^{25}$ −7.78 (*c* 5.35, $CHCl_3$).

(*S*)-1-(Furan-2-ylmethyl)-3-methyl-3-octylpyrrolidin-2-one (**3r**): General procedure was followed on 0.2 mmol scale with a reaction time of 72 h. The reaction mixture was purified by flash column chromatography [silica gel, *V*(petroleum ether)/*V*(ethyl acetate)=7/1] to afford **3r** as colorless oil (49.5 mg, 85% yield). R_f=0.37 [*V*(petroleum ether)/*V*(ethyl acetate)=5/1]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31 (d, *J*=0.8 Hz, 1H), 6.29～6.27 (m, 1H), 6.19 (d, *J*=3.2 Hz, 1H), 4.41 (abq, *J*=15.6 Hz, 2H), 3.18 (t, *J*=7.2 Hz, 2H), 1.95～1.88 (m, 1H), 1.74～1.67 (m, 1H), 1.49～1.40 (m, 2H), 1.26～1.22 (m, 12H), 1.09 (s, 3H), 0.85 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.1, 150.5, 142.3, 110.4, 108.2, 44.0, 43.8, 39.5, 38.1, 31.9, 31.1, 30.2, 29.6, 29.3, 24.4, 23.3, 22.7, 14.2; HRMS (ESI) calcd for $C_{18}H_{29}NO_2Na$ $[M+Na]^+$ 314.2091, found 314.2095; HPLC (Chiralpak AD-H): *V*(*n*-Hexane)/*V*(*i*-PrOH)=90/10, flow rate 1.0 mL/min, λ=210 nm, t_{R1}=5.110 min (major), t_{R2}=5.640 min (minor); 94.5∶5.5 er; $[\alpha]_D^{25}$ −4.77 (*c* 4.40, $CHCl_3$).

(*S*)-3-Methyl-3-octyl-1-(2-(thiophen-2-yl)ethyl)pyrrolidin-2-one (**3s**): General procedure was followed on 0.2 mmol scale with a reaction time of 72 h. The reaction mixture was purified by flash column chromatography [silica gel, *V*(petroleum ether)/*V*(ethyl acetate)=5/1] to afford **3s** as colorless oil (59.4 mg, 92% yield). R_f=0.41 [*V*(petroleum ether)/*V*(ethyl acetate)=3/1]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.11 (dd, *J*=5.2, 1.2 Hz, 2H), 6.90 (dd, *J*=5.2, 3.6 Hz, 1H), 6.83 (d, *J*=3.2 Hz, 1H), 3.61～3.47 (m, 2H), 3.14 (t, *J*=6.8 Hz, 2H), 3.04 (t, *J*=7.2 Hz, 2H), 1.89 (dt, *J*=12.8, 7.2 Hz, 1H), 1.67 (dt, *J*=12.8, 6.8 Hz, 1H), 1.43～1.37 (m, 2H), 1.30～1.09 (m, 12H), 1.05 (s, 3H), 0.86 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.3, 141.2, 127.0, 125.3, 123.8, 44.5, 44.3, 44.0, 38.0, 31.9, 31.3, 30.2, 29.6, 29.4, 28.0, 24.4, 23.2, 22.7, 14.2; HRMS (ESI) calcd for $C_{19}H_{31}NOSNa$ $[M+Na]^+$ 344.2019, found 344.2020; HPLC (Chiralpak AD-H): *V*(*n*-Hexane)/*V*(*i*-PrOH)=90/10, flow rate 1.0 mL/min, λ=220 nm, t_{R1}=4.932 min (major), t_{R2}=6.003 min (minor); 95.5∶4.5 er; $[\alpha]_D^{25}$ +3.66 (*c* 6.29, $CHCl_3$).

(*S*)-1-Butyl-3-methyl-3-octylpyrrolidin-2-one (**3t**): General procedure was followed on 0.2 mmol scale with a reaction time of 78 h. The reaction mixture was purified by flash column chromatography [silica gel, *V*(petroleum ether)/*V*(ethyl acetate)=5/1] to afford **3t** as colorless oil (48.4 mg, 90% yield). R_f = 0.45 [*V*(petroleum ether)/*V*(ethyl acetate)=5/1]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.30～3.17 (m, 4H), 1.93 (dt, *J*=12.8, 7.6 Hz, 1H), 1.74～1.68 (m, 1H), 1.50～1.39 (m, 4H), 1.33～1.13 (m, 14H), 1.08 (s, 3H), 0.90 (t, *J*=7.2 Hz, 3H), 0.85 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.1, 44.2, 44.0, 42.4, 38.1, 32.0, 31.2, 30.3, 29.6, 29.4, 29.4, 24.5, 23.4, 22.7, 20.1, 14.2, 13.9. HRMS (ESI) calcd for $C_{17}H_{34}NO$ $[M+H]^+$ 268.2635, found 268.2637; HPLC (Chiralpak AD-H): *V*(*n*-Hexane)/*V*(*i*-PrOH) = 90/10, flow rate 1.0 mL/min, λ=210 nm, t_{R1}=3.923 min (major), t_{R2}=4.209 min (minor); 96∶4 er; $[\alpha]_D^{25}$ +7.36 (*c* 4.59, $CHCl_3$).

(*S*)-3-Methyl-3-octyl-1-phenethylpyrrolidin-2-one (**3u**): General procedure was followed on 0.2 mmol scale with a reaction time of 72 h. The reaction mixture was purified by flash column chromatography [silica gel, *V*(petroleum ether)/*V*(ethyl acetate)=5/1] to afford **3u** as colorless oil (53.6 mg, 85% yield). R_f = 0.53 [*V*(petroleum ether)/*V*(ethyl acetate)=3/1]. ^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.30～7.18 (m, 5H), 3.61～3.46 (m, 2H), 3.11 (t, J=6.8 Hz, 2H), 2.84 (t, J=7.2 Hz, 2H), 1.87 (dt, J=12.8, 7.2 Hz, 1H), 1.65 (dt, J=12.8, 6.4 Hz, 1H), 1.41～1.38 (m, 2H), 1.31～1.25 (m, 11H), 1.14～1.04 (m, 4H), 0.88 (t, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.1, 138.9, 128.8, 128.5, 126.4, 44.5, 44.0, 43.9, 37.9, 33.8, 31.9, 31.3, 30.2, 29.6, 29.4, 24.4, 23.2, 22.7, 14.2; HRMS (ESI) calcd for $C_{21}H_{34}NO$ $[M+H]^+$ 316.2635, found 316.2635; HPLC (Chiralpak AD-H): V(*n*-Hexane)/V(*i*-PrOH)=90/10, flow rate 1.0 mL/min, λ=210 nm, t_{R1}=4.662 min (major), t_{R2}=5.574 min (minor); 97∶3 er; $[\alpha]_D^{25}$ +2.86 (*c* 4.89, $CHCl_3$).

(*S*)-1-(3,4-Dimethoxyphenethyl)-3-methyl-3-octylpyrrolidin-2-one (**3v**): General procedure was followed on 0.2 mmol scale with a reaction time of 72 h. The reaction mixture was purified by flash column chromatography [silica gel, V(petroleum ether)/V(ethyl acetate)=3/1] to afford **3v** as colorless oil (72.0 mg, 96% yield). R_f=0.25 [V(petroleum ether)/V(ethyl acetate)=3/1]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.76～6.70 (m, 3H), 3.84 (s, 3H), 3.81 (s, 3H), 3.55～3.42 (m, 2H), 3.10 (t, J=7.2 Hz, 2H), 2.76 (t, J=7.2 Hz, 2H), 1.88～1.82 (m, 1H), 1.66～1.59 (m, 1H), 1.39～1.35 (m, 2H), 1.27～1.06 (m, 12H), 1.01 (s, 3H), 0.84 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.1, 148.9, 147.6, 131.3, 120.7, 111.9, 111.2, 55.9, 44.4, 44.0, 43.9, 37.9, 33.3, 31.9, 31.2, 30.2, 29.5, 29.3, 24.4, 23.2, 22.7, 14.1; HRMS (ESI) calcd for $C_{23}H_{38}NO_3$ $[M+H]^+$ 376.2846, found 376.2839; HPLC (Chiralpak AD-H): V(*n*-Hexane)/V(*i*-PrOH)=90/10, flow rate 1.0 mL/min, λ=220 nm, t_{R1}=8.519 min (major), t_{R2}=11.180 min (minor); 97∶3 er; $[\alpha]_D^{25}$ +5.66 (*c* 6.25, $CHCl_3$).

(*S*)-1-(3-Methoxypropyl)-3-methyl-3-octylpyrrolidin-2-one (**3w**): General procedure was followed on 0.2 mmol scale with a reaction time of 72 h. The reaction mixture was purified by flash column chromatography [silica gel, V(petroleum ether)/V(ethyl acetate)=3/1] to afford **3w** as a yellow oil (35.4 mg, 62% yield). R_f=0.25 [V(petroleum ether)/V(ethyl acetate)=3/1]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.37～3.23 (m, 9H), 1.97～1.91 (m, 1H), 1.80～1.71 (m, 3H), 1.45～1.40 (m, 2H), 1.23～1.14 (m, 12H), 1.08 (s, 3H), 0.85 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.3, 70.4, 58.8, 44.3, 44.2, 40.1, 38.1, 32.0, 31.3, 30.3, 29.6, 29.4, 27.6, 24.5, 23.3, 22.7, 14.2; HRMS (ESI) calcd for $C_{17}H_{33}NO_2Na$ $[M+Na]^+$ 306.2404, found 306.2406; HPLC (Chiralpak AD-H): V(*n*-Hexane)/V(*i*-PrOH)=90/10, flow rate 1.0 mL/min, λ=220 nm, t_{R1}=4.699 min (major), t_{R2}=5.273 min (minor); 94.5∶5.5 er; $[\alpha]_D^{25}$ +6.21 (*c* 3.77, $CHCl_3$).

Methyl (*S*)-3-(3-methyl-3-octyl-2-oxopyrrolidin-1-yl)-propanoate (**3x**): General procedure was followed on 0.2 mmol scale with a reaction time of 92 h. The reaction mixture was purified by flash column chromatography [silica gel, V(petroleum ether)/V(ethyl acetate)=3/1] to afford **3x** as a yellow oil (50.9 mg, 86% yield). R_f=0.21 [V(petroleum ether)/V(ethyl acetate)=3/1]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.64 (s, 3H), 3.56～3.48 (m, 2H), 3.25 (t, J=7.2 Hz, 2H), 2.52 (t, J=6.8 Hz, 2H), 1.95～1.88 (m, 1H), 1.73～1.67 (m, 1H), 1.44～1.37 (m, 2H), 1.26～1.08 (m, 12H), 1.05 (s, 3H), 0.83 (t, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.4, 172.3, 51.8, 44.5, 44.0, 38.8, 38.0, 32.5, 31.9, 31.3, 30.2, 29.6, 29.3, 24.4, 23.2, 22.7, 14.1; HRMS (ESI) calcd for $C_{17}H_{31}NO_3Na$ $[M+Na]^+$ 320.2196, found 320.2194; HPLC (Chiralpak AD-H): V(*n*-Hexane)/V(*i*-PrOH)=90/10, flow rate 1.0 mL/min, λ=210 nm, t_{R1}=5.527 min (major), t_{R2}=6.371 min (minor); 94.5∶5.5 er; $[\alpha]_D^{25}$ +8.41 (*c* 4.92, $CHCl_3$).

(*S*)-1-(4-Methoxyphenyl)-3-methyl-3-octylpyrrolidin-2-one (**3y**): General procedure was followed on 0.2 mmol scale with a reaction time of 65 h. The reaction mixture was purified by flash column chromatography [silica gel, V(petroleum ether)/V(ethyl acetate)=3/1] to afford **3y** as colorless oil (20.0 mg, 31% yield). R_f=0.25 [V(petroleum ether)/V(ethyl acetate)=3/1]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.55 (d, J=8.8 Hz, 2H), 6.89 (d, J=8.8 Hz, 2H), 3.80 (s, 3H), 3.74～3.68 (m, 2H), 2.13～2.06 (m, 1H), 1.91～1.85 (m, 1H), 1.58～1.54 (m, 2H), 1.42～1.26 (m, 12H), 1.21 (s, 3H), 0.87 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.4, 156.5, 133.2, 121.6, 114.1, 55.6, 45.7, 45.3, 38.2, 32.0, 30.9, 30.3, 29.7, 29.4, 24.6, 23.3, 22.8, 14.2. HPLC (Chiralpak AD-H): V(*n*-Hexane)/V(*i*-PrOH)=90/10, flow rate 1.0 mL/min, λ=220 nm, t_{R1}=9.798 min (major), t_{R2}=14.700 min (minor); 95∶5 er; $[\alpha]_D^{25}$ 25.4 (*c* 0.97, $CHCl_3$).

(*R*)-3-Butyl-3-heptyl-1-(4-methoxybenzyl)pyrrolidin-2-one (**3z**): General procedure was followed on 0.2 mmol scale with a reaction time of 70 h. The reaction mixture was purified by flash column chromatography [silica gel, V(petroleum ether)/V(ethyl acetate)=7/1] to afford **3z** as colorless oil (57.8 mg, 80% yield). R_f=0.41 [V(petroleum ether)/V(ethyl acetate)=5/1]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.14 (d, J=8.8 Hz, 2H), 6.82 (d, J=8.8 Hz, 2H), 4.36 (abq, J=14.4 Hz, 2H), 3.77 (s, 3H), 3.07 (t, J=7.2 Hz, 2H), 1.82 (t, J=7.2 Hz, 2H), 1.52～1.42 (m, 4H), 1.26～1.11 (m, 14H), 0.86 (t, J=6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.3, 159.1, 129.6, 129.0, 114.0, 55.3, 47.8, 46.1, 43.8, 37.6, 37.3, 31.9, 30.3, 29.3, 28.1, 26.6, 24.4, 23.4, 22.7, 14.2, 14.1; HRMS (ESI) calcd for $C_{23}H_{37}NO_2Na$ $[M+Na]^+$ 382.2717, found 382.2708; HPLC (Chiralcel OD-H): V(*n*-Hexane)/V(*i*-PrOH)=95/5, flow rate 1.0 mL/min, λ=220 nm, t_{R1}=5.821 min (major), t_{R2}=6.216 min (minor); 97.5∶2.5 er; $[\alpha]_D^{25}$ +8.20 (*c* 5.17, $CHCl_3$).

Supporting Information General procedure and NMR data for substrates and ligand synthesis, conditions screening, as well as all copies of NMR spectra for all unknown compounds and HPLC chromatograms for the γ-lactams products. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn/.

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