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Article

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Stereoselective Synthesis of Diazabicyclic *β*-Lactams through Intramolecular Amination of Unactivated C(sp^3)-H Bonds of Carboxamides by Palladium Catalysis

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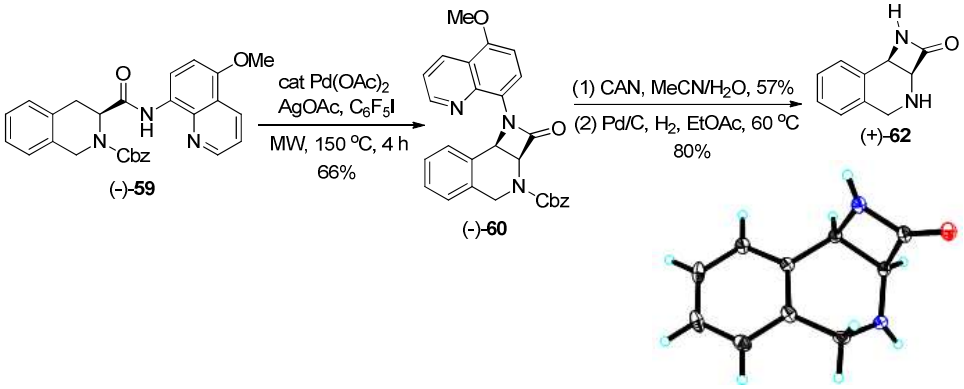


ABSTRACT: An efficient C(sp^3)-H bonds activation and intramolecular amination reaction via Palladium catalysis at the β-position of carboxyamides to make *β*-lactams was described. The investigation of the substrate scope showed that the current reaction conditions favored to activate the β-methylene group. Short sequences were developed for preparation of various diazabicyclic *β*-lactam compounds with this method as key step from chiral proline and piperidine derivatives.

INTRODUCTION

The searching for new kinds of β-lactamase inhibitors is one of effective solutions to β-lactamase-mediated resistance problem in modern medicine and pharmaceutical area.[1] The unnatural diazabicyclic β-lactam skeletons **1** and **2** in Figure 1 are important structure motifs existing in some important bioactive molecules such as compounds **3** to **7**, which have been found to be potent inhibitors of class C β-lactamase.[2] For example, based on structure of R048-1256, MK-8712 was made and screened to be best for enzymatic inhibition against pseudomonal class C β-lactamase AmpC in combination with imipenem.[3] BAL29880 (**5**) was one of important components of BAL30376, which overcomes a variety of Gram-negative bacteria.[4] Moreover, compound **8** was the key intermediate for the synthesis of the tetrahydroisoquinoline family of alkaloids such as saframycins and bioxalomycins, which are antitumor antibiotics, and ecteinascidine-743, which is a highly potent antitumor agent currently in phase II/III human clinical trials.[5]

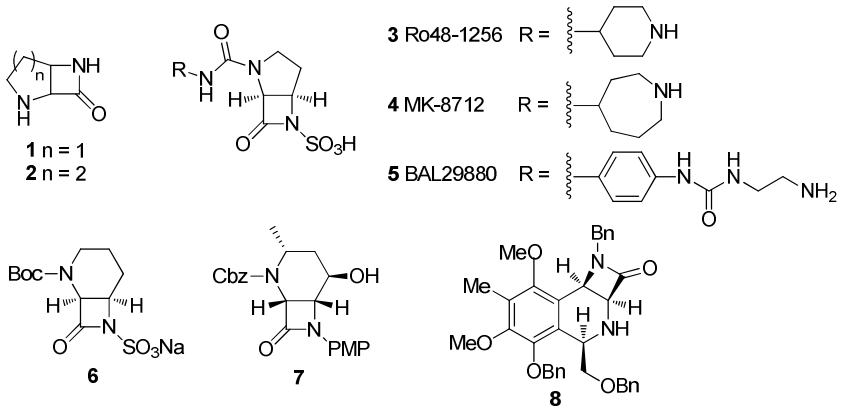


Figure 1. Biologically active compounds with diazabicyclic β-lactam skeletons.

To achieve the above mentioned diazabicyclic β-lactam skeletons, Mitsunobu reaction and intramolecular or intermolecular Staudinge ketene-imine cycloaddition reactions were used to form the second ring based on the highly strained monocyclic β-lactams.[6] However, these kinds of typical procedures suffered from some limitations such as expensive starting materials, long steps,

some toxic reagents and the removal of phosphine oxide and hydrazinodicarboxylate as by-products.

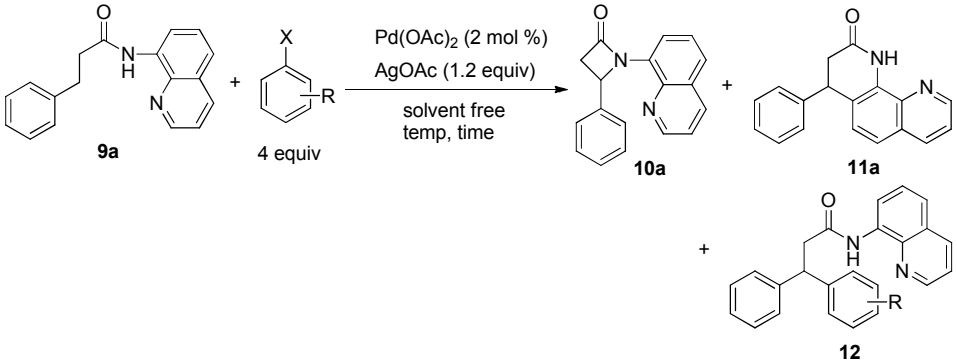
Transition-metal-catalyzed intramolecular amination reaction of the C-H bonds is an effective approach for the construction of N-heterocyclic compounds, and has attracted much attention from synthetic chemists in the past decade.[7] Several approaches for the synthesis of various lactams including β-lactams via Pd,[8a-d] Ni,[8e] Cu[8f-g] and Co[8h] catalysis have been reported. After the successful construction of simple β-lactams in initial studies utilizing the 8-amino-quinoline (AQ) as the directing group,[9] we want to extend our previous methodology on the construction of various diazabicyclic β-lactam compounds. It may provide good opportunity for the study of structure-activity relationship of β-lactamase inhibitors.

RESULTS AND DISCUSSION

We began this project initially during our study at oxidative phosphonation at β-C(sp^3)-H of substrate **9a** with diphenylphosphine oxide in the presence of 10 mol% $Pd(OAc)_2$ and 1 equiv of AgOAc in toluene at 130 ^oC for 24 h. Actually, we did not get the desired compound. Only very small amount of γ-lactam compound **11a** was formed. The use of 4'-iodoacetophenone instead of diphenylphosphine oxide in the same reaction condition led to the formation of cross-coupling product **12** and β-lactam compound **10a** (entry 1, Table 1). The structure of **10a** was further confirmed by the X-ray single-crystal analysis.[10] Compared with the research work in Daugulis' group,[11] the major difference came from the use of phenyl iodides bearing different substituents. In his paper, aryl iodides bearing electron-donating group were used in most cases, and the major products were cross-coupling compounds. We screened a set of aryl iodides with electron-withdrawing group and found this reaction led to a mixture with three kinds of products

10a-12 in the presence of Ac, CF_3, NO_2-substituted aryl iodides. *p*-$NO_2C_6H_4I$ gave the better 64% yield favoring the *β*-lactam product **10a** (entries 1-7, Table 1). Pentafluoroiodobenzene was usually employed as special fluorinated substrate in various cross-coupling reaction and worked as building blocks in material science.[12] To our delight, when pentafluoroiodobenzene was used, the reaction proceeded with high regioselectivity to afford **10a** in moderate yield, and **11a** was not detected (entry 9, Table 1). Increasing temperature led to high yield of product **10a**. And heating by means of microwave is an efficient way for this reaction (entries 10-12, Table 1). Controlled experiments showed the reaction did not occur without either $Pd(OAc)_2$ or AgOAc. In addition to AgOAc, Ag_2CO_3, AgF and AgF_2 were also found to be effective in this reaction to give *β*-lactam product **10a** in 82%, 73% and 45% yield, respectively. Other silver salts such as Ag_2O and $AgCO_2CF_3$ failed to afford the typical product **10a**. Finally, a combination of $Pd(OAc)_2$ (5 mol%), AgOAc (1.2 equiv), and pentafluoroiodobenzene (5.5 equiv) under microwave at 160 ^oC for 1.5 h was the best system for palladium-catalyzed intramolecular amination reaction of **9** to afford *β*-lactam compounds.

Table 1. Optimization of the reaction conditions.



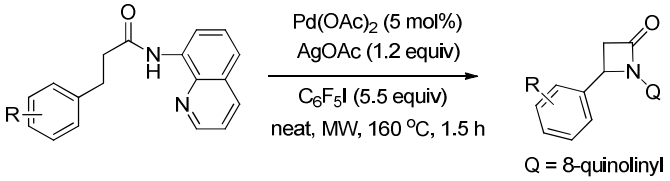
Entry	R-C_6H_4X	Temp (^oC), Time	Yield [a] (%) of **10a**/**11a**/**12**
1	*p*-AcC_6H_4I	120 ^oC, 20 min	28 / - / 58 [b]
2	*o*-CF_3 C_6H_4I	120 ^oC, 24 h	4 / 4 / - [b, e]

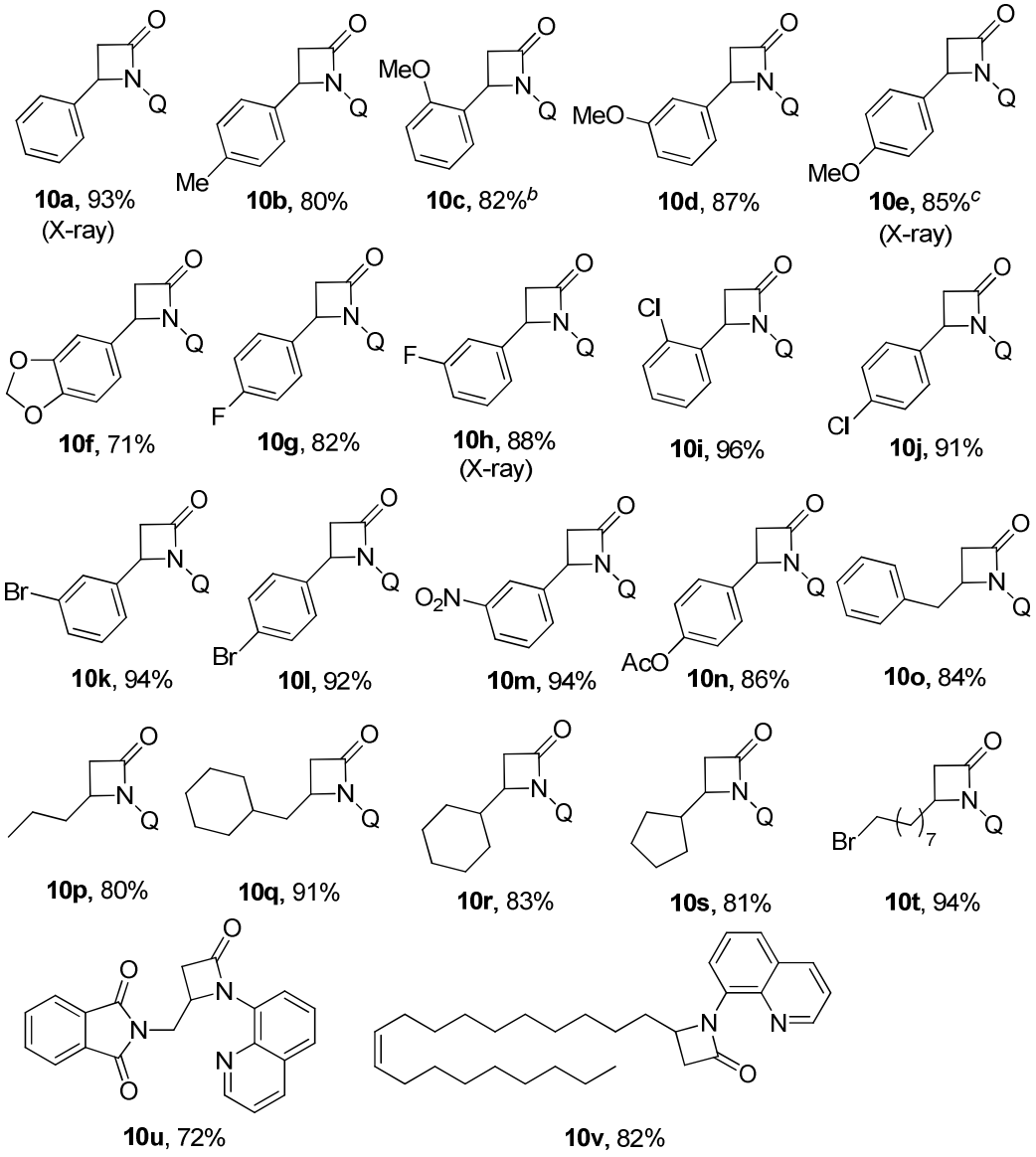
3	*p*-CF_3 C_6H_4I	120 °C, 19 h	24 / 6 / - [b, e]
4	*o*-NO_2 C_6H_4I	120 °C, 19 h	25 / 3 / 1 [b, e]
5	*p*-NO_2 C_6H_4I	THF, 120 °C, 24 h	64 / 5 / 20 [b]
6	*p*-NO_2 C_6H_4I	toluene, 120 °C, 24 h	53 / 8 / 26 [b]
7	*p*-NO_2 C_6H_4I	170 °C, 15 h	65 / - / 15 [b]
8	*p*-NO_2 C_6H_4Br	120 °C, 24 h	- / 5 / - [b, e]
9	C_6F_5I	130 °C, 24 h	49 / - / - [b, d, f]
10	C_6F_5I	130 °C, 2 h	49 / - / - [c, d, f]
11	C_6F_5I	160 °C, 1 h	83 / - / - [c, g]
12	C_6F_5I	160 °C, 1.5 h	93 / - / - [c,d]

[a] Isolated yield. [b] The reaction was conducted in seal tube. [c] The reaction was conducted with microwave machine and C_6F_5I (5.5 equiv) was used. [d] $Pd(OAc)_2$ (5 mol%) was used. [e] Most of **9a** was recovered. [f] 40% of **9a** was recovered. [g] $Pd(OAc)_2$ (2.5 mol%) was used, and 13% of **9a** was recovered.

The substrate scope was subsequently investigated (Table 2). A variety of methylene C-H bonds at the β-position of carboxamides can be efficiently activated and aminated to make the *β*-lactam compounds. Aromatic rings with electron-donating or -withdrawing groups were compatible. Many function groups on the phenyl rings, such as ethers (**10c-10f**), halides (**10g-10l**), nitroarenes (**10m**), esters (**10n**) remained untouched. Moreover, substrates with alkyl groups at the β-position of carboxamides underwent reactions to afford the corresponding *β*-lactam products (**10o-10v**) with good to excellent yields, including the sterically demanding cyclohexyl, cyclopentyl moieties and alkyl bromide, which theoretically provides potent way to make the bicyclic fused *β*-lactam compound via S_N2-type reaction at the α-position of monocyclic *β*-lactam compound **10t**.

Table 2. Substrate scope.



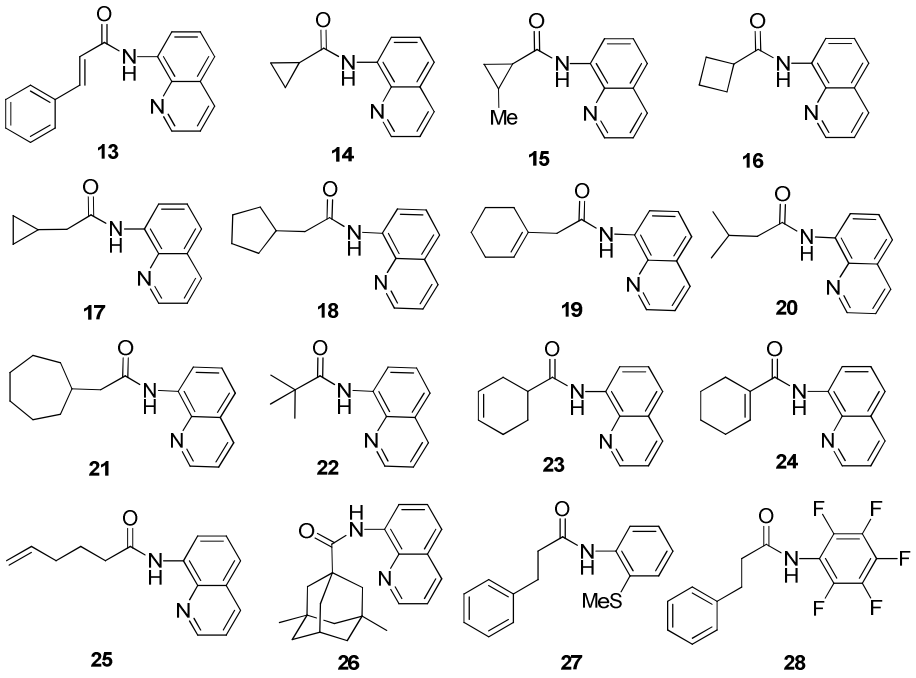


[a] Typical reaction conditions: substrate (0.10 mmol), $Pd(OAc)_2$ (0.005 mmol, 5 mol%), AgOAc (0.12 mmol, 1.2 equiv), C_5F_5I (0.55 mmol, 5.5 equiv), microwave, 160 °C, 1.5h. Isolated yields. [b] $Pd(OAc)_2$ (7 mol%) was used. [c] $Pd(OAc)_2$ (10 mol%) was used. Reaction time was 5h.

Further investigation demonstrated the limitation of this reaction. Under the current reaction conditions, β-C(sp^2)-H, β-tertiary C(sp^3)-H bonds of carboxamides **13** and **17**-**21** (Table 3) could not be activated. It showed that the position of C-C double bonds played an important effect on the reaction. In case of substrate **9v** (Table 2), which has a C-C double bond far away from the reaction center, the β-lactam product **10v** was obtained in 82% yield successfully. In contrast,

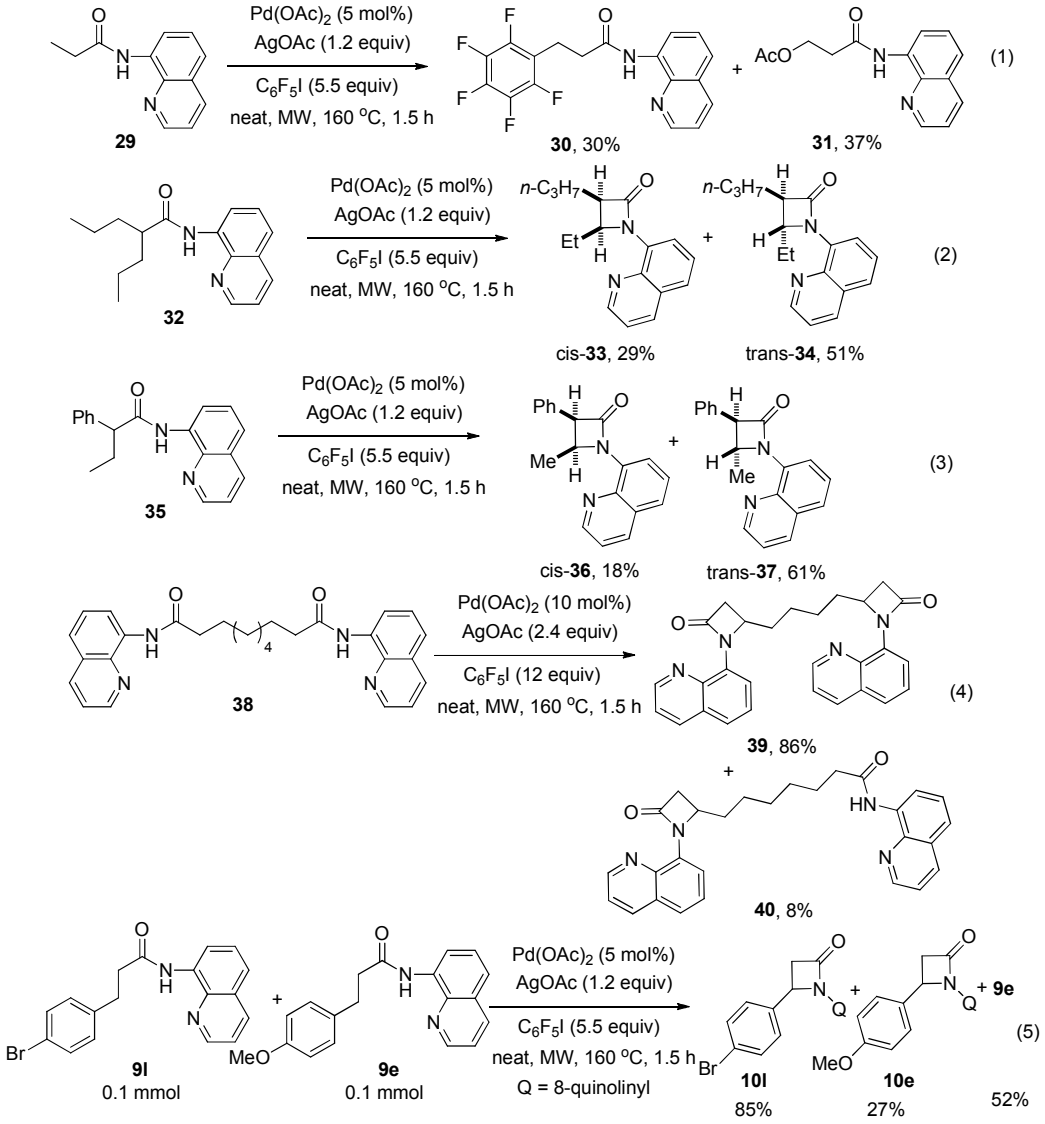
substrates **23**-**25** (Table 3), which have C-C double bonds close to reaction center probably acting as a ligand to coordinate to metal to inhibit the reaction.[13] Due to the high ring strain, cyclopropyl, cyclobutyl substrates **14**-**16** and **26** (Table 3) did not produce bicyclic fused *β*-lactam products. No reaction occurred when the auxiliary groups were changed to substrates **27** and **28**. The primary methyl C-H bonds of **29** can be activated and cross-coupled with C_6F_5I to afford **30** and **31** in 30% and 37% yield, respectively (eq 1).

Table 3. Typical unreactive substrates:



The reaction proceeded well with different *α*-substituted aminoquinoline carboxamides. For example, to *α*-disubstitued substrates **41g**, the reaction gave 6/4 fused *β*-lactam product *cis*-**42g** with the angular methyl group intact (entry7, Table 4). To *α*-monosubstitued substrates **32** and **35**, the reactions gave two diastereoisomers favoring *trans*-**34** and *trans*-**37,** respectively (eq 2 and 3). 1,10-Decanediamide **38** underwent double cyclization to afford di-*β*-lactam **39** in 86% yield, accompanied with mono-*β*-lactam **40** in 8% yield (eq 4). A controlled reaction with substrate **9e**

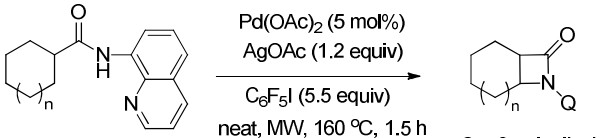
and **9l** in one pot was carried out to give *β*-lactam products **10e** and **10l** in 27% and 85% yield, along with 52% yield of recovered substrate **9e**. It indicated that the reaction rate with electron-withdrawing group on the phenyl ring was 3 times than that of electron-donating group (eq 5).

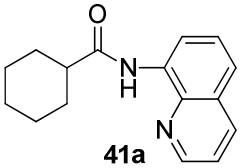
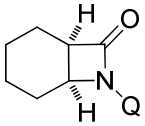
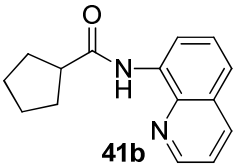
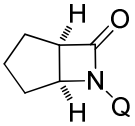
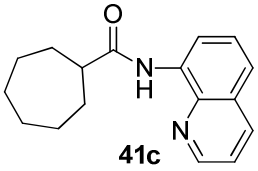
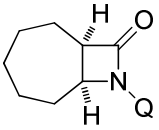


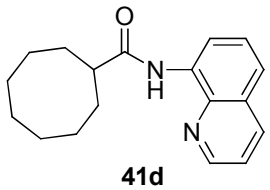
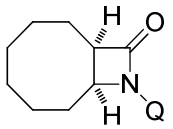
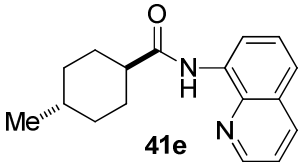
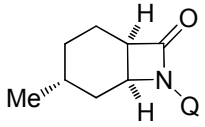
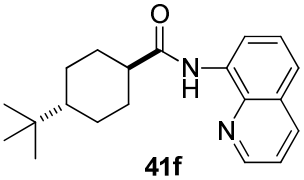
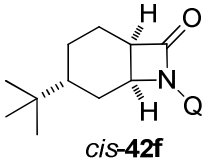
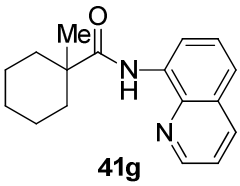
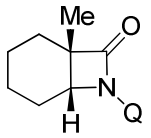
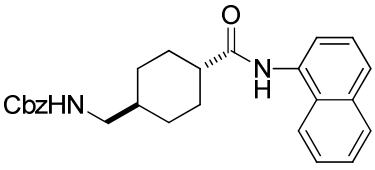
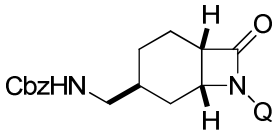
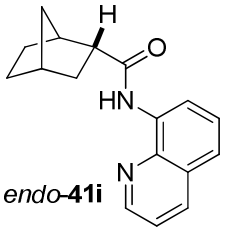
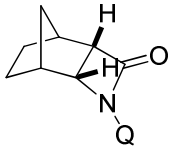
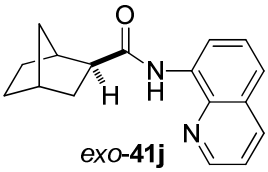
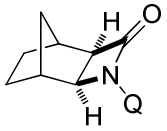
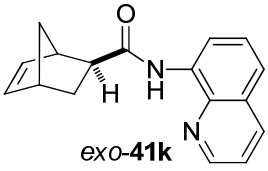
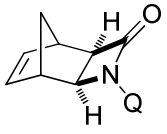
The skeletons of bicyclic or polycyclic fused *β*-lactams are widespread in pharmaceutical such as various *β*-lactam antibiotics.[1] It is much more challenge to make these kinds of skeletons based on aliphatic C-H bonds activation. Inspired by our experiments, we next screened the carboxamides with different-sized aliphatic rings. We found that the substrates with five, six, seven,

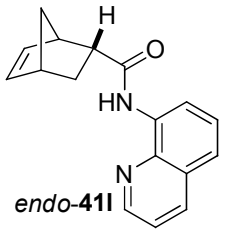
eight-membered and bridged ring fragments were suitable for this conversion to finish the relative cis-fused *β*-lactam products with good to excellent yields. The results are summarized in Table 4. It showed that the configuration of the substrates played a key effect on the efficiency of the reaction. For example, the *endo*-**41i** and *exo*-**41j** gave the corresponding relative cis-fused products *cis*-*endo*-**42i** and *cis*-*exo*-**42j** in 87% and 82% yield, respectively. Because of different orientation of C-C double bonds and carboxamides group in substrates *exo*-**41k** and *endo*-**41l**, the reaction of the *exo*-**41k** afforded the product *cis*-*exo*-**42k** in 48% yield, while the *endo*-**41l** did not work at all, probably due to the C-C double bond acting as a ligand coordinating to the metal to inhibit the reaction.[13] Interestingly, Cbz protected NH group did not affect the outcome of product *cis*-**42h** (entry 8, Table 4).

Table 4. Production of *cis*-fused *β*-lactams[a]



Entry	Substrate	Product	Yield (%)
1	 **41a**	 *cis*-**42a**	93
2	 **41b**	 *cis*-**42b**	93
3	 **41c**	 *cis*-**42c**	88

4	 **41d**	 *cis*-**42d**	83
5	 **41e**	 *cis*-**42e**	98
6	 **41f**	 *cis*-**42f**	73[b]
7	 **41g**	 *cis*-**42g**	85
8	 **41h**	 *cis*-**42h**	75
9	 *endo*-**41i**	 *cis-endo*-**42i**	87
10	 *exo*-**41j**	 *cis-exo*-**42j**	82
11	 *exo*-**41k**	 *cis-exo*-**42k**	48

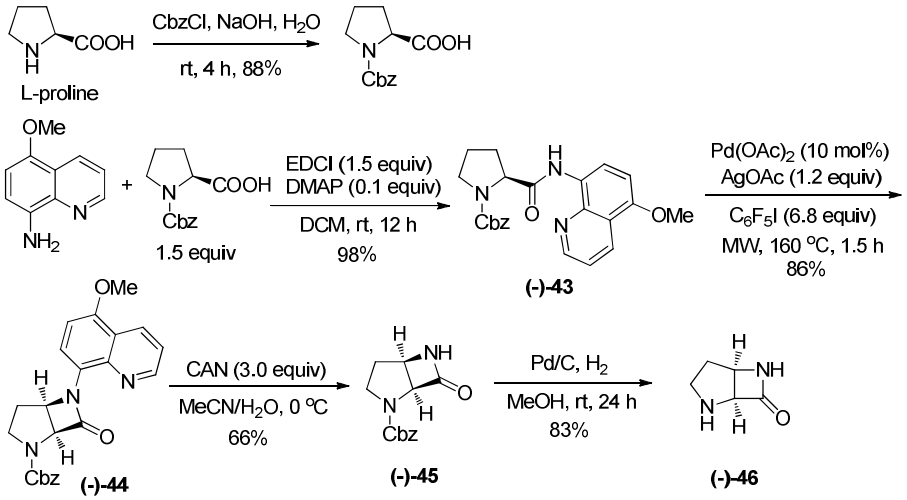
12	 *endo*-**41l**	-	-	[c]

[a] Typical reaction condition. [b] $Pd(OAc)_2$ (10 mol%) was used. [c] No reaction.

Application of the methodology on the preparation of various diazabicyclic *β*-lactam compounds[14]

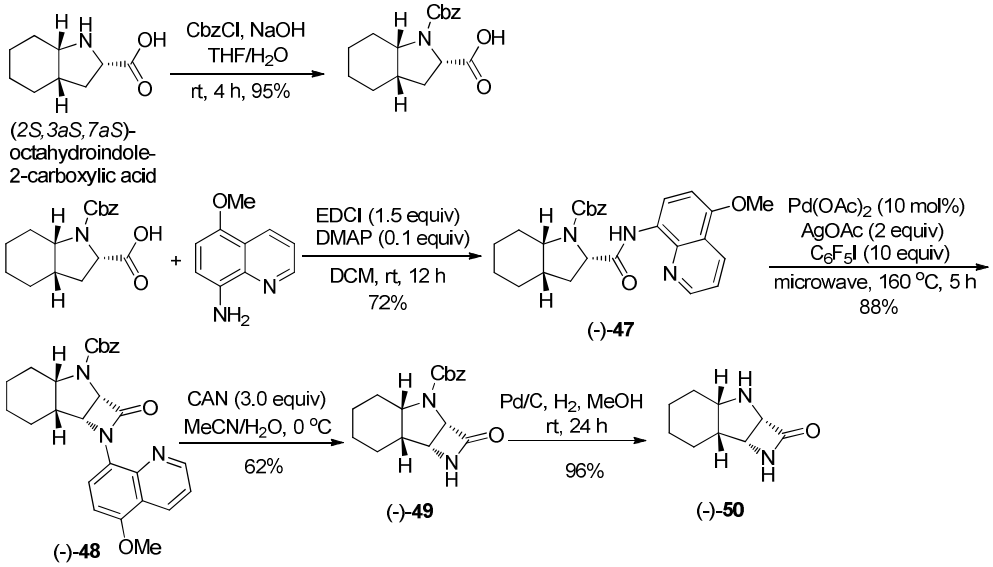
As we mentioned earlier, the core structures of Ro48-1256, MK-8712 and their derivatives are diazabicyclic *β*-lactams. MK-8712, developed by Merk company, provided an important therapeutic option for the treatment of carbapenem resistance in *Pseudomonas*. We want to apply our reaction conditions to make the key intermediates for the synthesis of MK-8712 and their derivatives. Compound (-)-**43** was easily obtained through protection with benzyl chloroformate, and coupling with 5-methoxyquinolin-8-amine under the reagents of EDCI and DMAP from the commercial available L-proline. The intramolecular amination reaction of (-)-**43** was performed under the standard conditions by combining $Pd(OAc)_2$, AgOAc, together with pentafluoroiodobenzene, and gave the desired product (-)-**44** in 86% yield. The 5-MeO-quinoline (MQ) group of (-)-**44** was readily removed upon treatment with ceric ammonium nitrate (CAN), and removal of Cbz group by hydrogenation reaction provided the cis-fused compound (-)-**46**, which is the key intermediate for the synthesis of MK-8712 (Scheme 1).

Scheme 1. Synthesis of diazabicyclic *β*-lactam (-)-46 from L-proline.



We next examined the more challenge substrate octahydro-1H-indole, which has three chiral centers. Compound (-)-**47** was prepared according the general procedure involving protection and amidation reactions from (*2S, 3aS, 7aS*)-octahydroindole-2-carboxylic acid. Then (-)-**47** was subjected to the standard reaction conditions to afford the product (-)-**48** in 88% yield. After two deprotection steps, (-)-**50**, which has four contiguous chiral centers, was successfully obtained in high yield (Scheme 2).

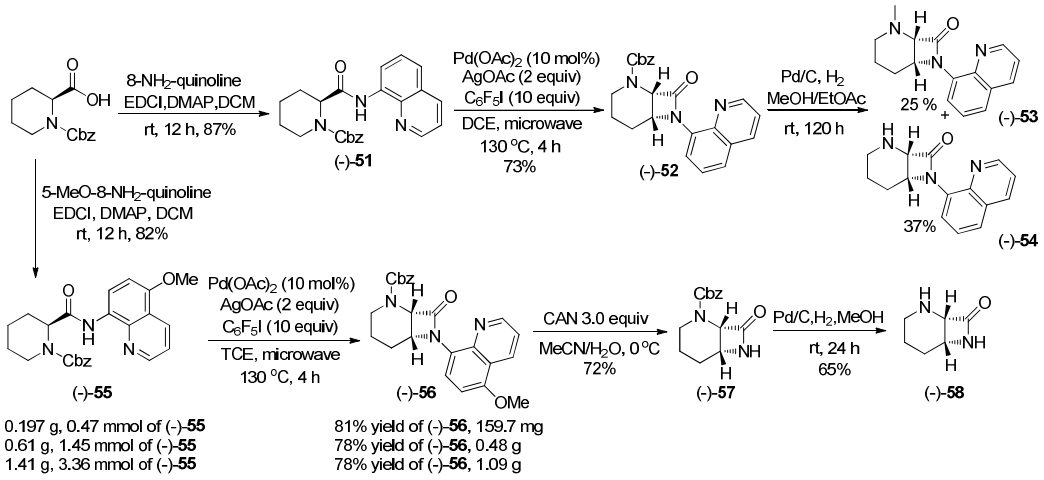
Scheme 2. Synthesis of diazabicyclic *β*-lactam (-)-50.



Piperidines bearing substituents at C3 positions are important structural motifs widely existing in natural products and pharmaceuticals with various biological activities. We envisioned to

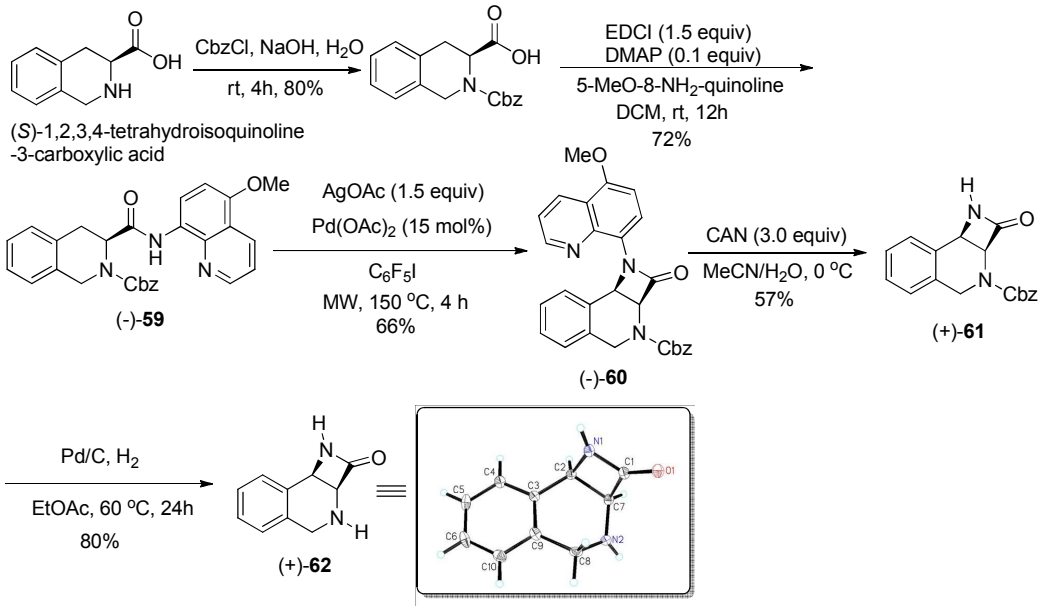
functionalize at C3 of piperidine derivatives under the current reaction conditions to make the key building blocks for the synthesis of **6** and **7** (Figure 1). Compound (-)-**55** was easily prepared, and then subjected to standard conditions to form the diazabicyclic *β*-lactam (-)-**56** with a gram scale in 78% yield, which was readily undergone deprotection step and hydrogenation reaction to get compound (-)-**58**. Compound (-)-**57** was right intermediate for preparation of **6** and **7** (Scheme 3).

Scheme 3. Synthesis of diazabicyclic *β*-lactam (-)-58.



To our delight, compound (-)-**59**, prepared from (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, was smoothly cyclized under our reaction conditions to form (-)-**60**. After two deprotection steps, (+)-**62** was obtained in high yield, whose structure was confirmed by X-ray single crystal analysis (Scheme 4).[15]

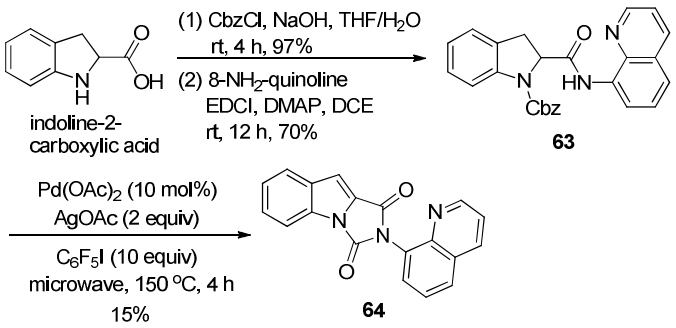
Scheme 4. Synthesis of diazabicyclic *β*-lactam (+)-62.

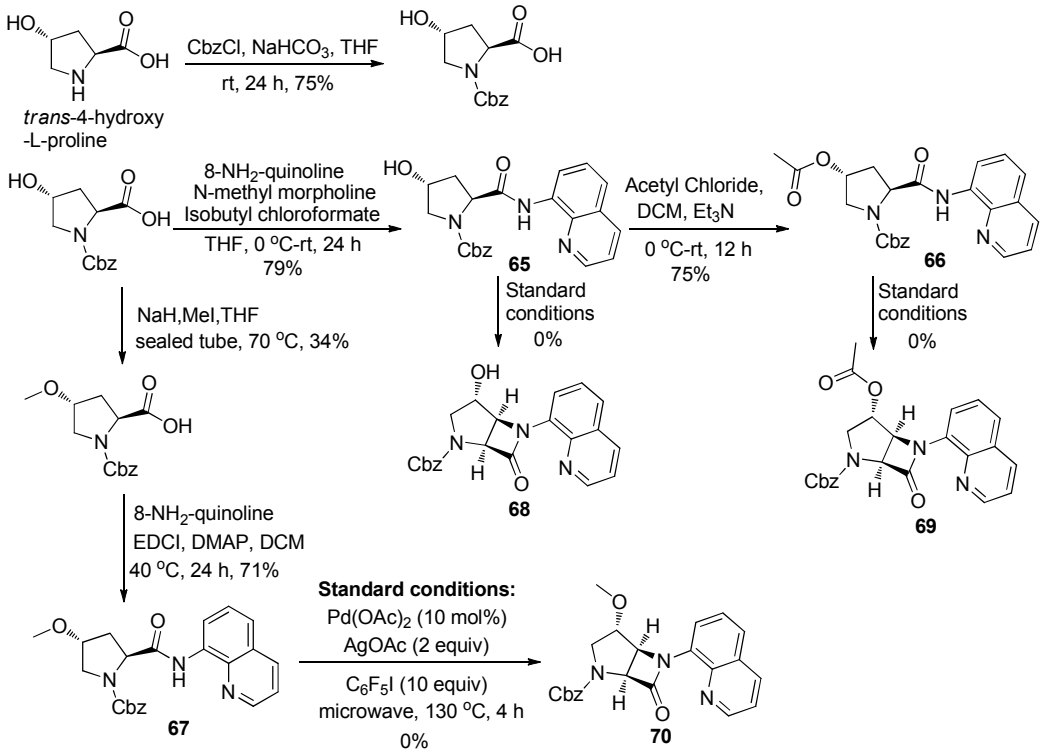


Encouraged by the success with the above substrates, it was thought worthwhile to investigate the cyclization reaction of some different types of substrates. Compound **63**, prepared from (±)-indoline-2-carboxylic acid, was selected as substrate for this reaction. Unfortunately, the reaction failed to produce diazatricyclic *β*-lactam compound, but to give **64** in 15% yield (Scheme 5).

trans-4-Hydroxy-L-proline is a very useful chiral resource for organic synthesis. We next tested this kind of substrates. Three different amide substrates **65-67** bearing free hydroxyl, ester and ether group at C4 position of L-proline were made. Disappointingly, none of these three substrates led to form the corresponding diazabicyclic *β*-lactams under the standard conditions (Scheme 5).

Scheme 5. Unsuccessful examples.





CONCLUSION

In conclusion, an efficient Pd-catalyzed C(sp^3)-H bonds activation and intramolecular amination reaction at the β-position of carboxyamides to make various *β*-lactams was described. The substrate scope of the reaction was fully investigated, which indicated that the current reaction conditions favored to activate the methylene group over methyl and tertiary CH group at the β-position of carboxamides. This method is especially very useful for making *β*-lactams with 5/4, 6/4, 7/4, 8/4 cis-fused ring system, which would otherwise require lengthy synthetic sequences. In consideration of important biological activities of diazabicyclic *β*-lactam compounds, short sequences were developed for preparation of various diazabicyclic *β*-lactam compounds with this method as key step from chiral proline and piperidine derivatives.

EXPERIMENTAL SECTION

General Techniques. All melting points are uncorrected. Microwave irradiation reactions were

carried out in a CEM Discover SP system with a floor mounted infrared temperature sensor. Reactions were performed in glass vessels (capacity 10 mL or 30 mL) sealed with a septum. Preparative chromatographic separations were performed on silica gel (300-400 mesh). Reactions were followed by TLC analysis using silica plates with a fluorescent indicator (254 nm) and visualized with a UV lamp, $KMnO_4$ or phosphomolybdic acid. Optical rotations were measured on a digital polarimeter. ^1H and ^{13}C NMR spectra were recorded in Fourier transform mode at the field strength specified on a 400, 500, or 600 MHz spectrometer. Spectra were obtained on $CDCl_3$ or C_5D_5N solutions in 5 mm diameter tubes, and chemical shifts in ppm (part per million) are quoted relative to the residual signals of chloroform (δ_H 7.26 ppm, or δ_C 77.16 ppm) and pyridine (δ_H 7.20 ppm, or δ_C 135.43 ppm). *J* values are given in hertz. IR spectra were measured for samples as KBr pellets in a FT-IR spectrophotometer. High resolution mass spectra (HRMS) were measured at 70 eV using a double focusing magnetic sector mass analyzer with an EI source. Crystallographic data were collected using graphite monochromated Mo Kα radiation (λ = 0.71073 Å) for the compounds **10a**, **10e** and **10h**, and graphite monochromated Cu Kα radiation (λ = 1.54178 Å) for the compound (+)**-62** in the ϕ and ω scans mode.

General Procedure for the Preparation of aminoquinoline carboxamides 13-28: To a solution of acid (1.0 mmol), 8-aminoquinoline (173.0 mg, 1.2 mmol) in anhydrous CH_2Cl_2 (5 mL) were added EDCI (230.0 mg, 1.2 mmol) and DMAP (11 mg, 0.2 mmol). The reaction mixture was stirred at room temperature for 24 h, then diluted with CH_2Cl_2 (30 mL), washed with aq. HCl (1 M, 2 x 30mL) and brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. Purification by flash chromatography (Silica gel, CH_2Cl_2 as eluent) gave the corresponding aminoquinoline carboxamide compound.

2-Methyl-*N*-(quinolin-8-yl)cyclopropane carboxamide (15): Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1H), 8.87–8.62 (m, 2H), 8.14 (dd, *J* = 8.2 and 1.3 Hz, 1H), 7.55–7.37 (m, 3H), 1.55–1.49 (m, 1H), 1.37–1.30 (m, 1H), 1.26 (d, *J* = 6.0 Hz, 1H), 1.18 (d, *J* = 5.6 Hz, 3H), 0.79–0.67 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 148.1, 138.3, 136.5, 134.9, 128.1, 127.6, 121.6, 121.2, 116.4, 25.1, 18.1, 17.0, 16.7; HRMS(EI) Calcd for $C_{14}H_{14}N_2O$ [M^+]: 226.1106, Found 226.1109; IR (KBr) V(cm^{-1}) : 1679, 1528, 1486, 1426, 1384, 1329, 1164.

2-Cyclopropyl-*N*-(quinolin-8-yl)acetamide (17): White solid; mp 32-34℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.29 (brs, 1H), 8.87–8.72 (m, 2H), 8.25–7.97 (m, 1H), 7.61–7.34 (m, 3H), 2.53–2.42 (m, 2H), 1.31–1.14 (m, 1H), 0.84–0.70 (m, 2H), 0.36 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 148.3, 138.7, 136.4, 134.8, 128.1, 127.5, 121.7, 121.5, 116.5, 43.3, 7.5, 5.0; HRMS(EI) Calcd for $C_{14}H_{14}N_2O$ [M^+]: 226.1106, Found 226.1108; IR (KBr) V(cm^{-1}) : 1684, 1529, 1486, 1425, 1385, 1328, 827, 792.

2-Cyclopentyl-*N*-(quinolin-8-yl)acetamide (18): White solid; mp 40-42℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (brs, 1H), 8.90–8.70 (m, 2H), 8.21–8.05 (m, 1H), 7.61–7.36 (m, 3H), 2.61–2.52 (m, 2H), 2.50–2.36 (m, 1H), 2.04–1.86 (m, 2H), 1.76–1.51 (m, 4H), 1.38–1.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 148.2, 138.5, 136.5, 134.8, 128.1, 127.6, 121.7, 121.4, 116.5, 44.6, 37.4, 32.8, 25.2; HRMS(EI) Calcd for $C_{16}H_{18}N_2O$ [M^+]: 254.1419, Found 254.1424; IR (KBr) V(cm^{-1}) : 1686, 1526, 1485, 1425, 1386, 1326, 827, 792.

2-Cyclohexenyl-*N*-(quinolin-8-yl)acetamide (19): White solid; mp 65-67℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.22 (brs, 1H), 8.88–8.59 (m, 2H), 8.20–8.06 (m, 1H), 7.60–7.35 (m, 3H), 5.86 (s, 1H), 3.19 (s, 2H), 2.25–2.15 (m, 2H), 2.15–2.05 (m, 2H), 1.80–1.60 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 148.4, 138.8, 136.4, 134.7, 132.6, 128.14, 128.06, 127.5, 121.7, 121.5, 116.3,

48.0, 28.8, 25.8, 23.0, 22.1; HRMS(EI) Calcd for $C_{17}H_{18}N_2O$ [M^+]: 266.1419, Found 266.1423; IR (KBr) V(cm^{-1}) : 1684, 1525, 1485, 1425, 1385, 1327, 827, 792.

3-Methyl-*N*-(quinolin-8-yl)butanamide (20): White solid; mp 53-55℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (brs, 1H), 8.90–8.70 (m, 2H), 8.14 (d, *J* = 7.3 Hz, 1H), 7.60–7.36 (m, 3H), 2.43 (d, *J* = 7.1 Hz, 2H), 2.38–2.23 (m, 1H), 1.07 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 148.2, 138.5, 136.5, 134.7, 128.0, 127.5, 121.7, 121.5, 116.5, 47.7, 26.4, 22.7; HRMS(EI) Calcd for $C_{14}H_{16}N_2O$ [M^+]: 228.1263, Found 228.1266; IR (KBr) V(cm^{-1}) : 1687, 1527, 1485, 1385, 793.

2-Cycloheptyl-*N*-(quinolin-8-yl)acetamide (21): White solid; mp 71-72℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (brs, 1H), 8.85–8.75 (m, 2H), 8.20–8.05 (m, 1H), 7.58–7.36 (m, 3H), 2.52–2.42 (m, 2H), 2.28–2.14 (m, 1H), 1.92–1.79 (m, 2H), 1.74–1.58 (m, 4H), 1.58–1.42 (m, 4H), 1.40–1.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 148.2, 138.5, 136.5, 134.7, 128.1, 127.6, 121.7, 121.4, 116.5, 47.0, 37.2, 34.8, 28.4, 26.4; HRMS(EI) Calcd for $C_{18}H_{22}N_2O$ [M^+]: 282.1732, Found 282.1738; IR (KBr) V(cm^{-1}) : 1681, 1525, 1485, 1385, 831.

***N*-(Quinolin-8-yl)cyclohex-3-ene carboxamide (23):** White solid; mp 95-96℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.95 (brs, 1H), 8.85–8.75 (m, 2H), 8.19–8.06 (m, 1H), 7.57–7.37 (m, 3H), 5.84–5.68 (m, 2H), 2.84–2.65 (m, 1H), 2.55–2.33 (m, 2H), 2.27–2.08 (m, 3H), 1.99–1.81 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 148.2, 138.6, 136.5, 134.7, 128.1, 127.5, 126.9, 125.5, 121.7, 121.5, 116.6, 42.9, 28.4, 26.0, 24.9; HRMS(EI) Calcd for $C_{16}H_{16}N_2O$ [M^+]: 252.1263, Found 252.1259; IR (KBr) V(cm^{-1}) : 1679, 1527, 1485, 1423, 1379, 792.

***N*-(Quinolin-8-yl)hex-5-enamide (25):** Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (brs, 1H), 8.85–8.70 (m, 2H), 8.10 (dd, *J* = 8.1 and 1.7 Hz, 1H), 7.55–7.35 (m, 3H), 5.92–5.72 (m, 1H),

5.15–4.95 (m, 2H), 2.55 (t, *J* = 7.4 Hz, 2H), 2.19 (q, *J* = 6.9 Hz, 2H), 1.97–1.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 148.1, 138.3, 137.9, 136.4, 134.6, 127.9, 127.4, 121.6, 121.4, 116.4, 115.5, 37.4, 33.2, 24.7; HRMS(EI) Calcd for $C_{15}H_{16}N_2O$ [M^+]: 240.1263, Found 240.1263; IR (KBr) V(cm^{-1}) : 1688, 1527, 1485, 1425, 1386, 1326, 792.

***N*-(Quinolin-8-yl)-3,5-dimethyladamantane-1-carboxamide (26):** White solid; mp 65-66℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.21 (brs, 1H), 8.90–8.75 (m, 2H), 8.15 (d, *J* = 8.2 Hz, 1H), 7.60–7.37 (m, 3H), 2.28–2.20 (m, 1H), 1.95 (d, *J* = 2.2 Hz, 2H), 1.78–1.66 (m, 4H), 1.52–1.36 (m, 4H), 1.25 (s, 2H), 0.93 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 148.4, 139.0, 136.5, 134.8, 128.1, 127.6, 121.6, 121.3, 116.5, 50.9, 45.7, 44.4, 43.0, 38.2, 31.4, 30.6, 29.6； HRMS(EI) Calcd for $C_{22}H_{26}N_2O$ [M^+]: 334.2045, Found 334.2037; IR (KBr) V(cm^{-1}) : 1673, 1527, 1486, 1326, 792.

(-)-(2*S*,3a*S*,7a*S*)-Benzyl 2-(5-methoxyquinolin-8-ylcarbamoyl)octahydro-1*H*- indole-1-Carboxylate (47): To a 25 ml of round-bottom flask equipped with magnetic stirrer were added N-Carbobenzyloxy-L-octahydroindole-2-carboxylic acid (274 mg, 0.9 mmol), 5-methoxyquinolin-8-amine (131 mg, 0.75 mmol), EDCI (188 mg, 1.0 mmol), DMAP (9.2 mg, 0.08 mmol) and anhydrous CH_2Cl_2(10 mL). The mixture was stirred at room temperature for 12 h, then diluted with CH_2Cl_2(50 mL), and washed with aq. HCl (1 M, 2 x 50 mL) and brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. Purification by flash chromatography (Silica gel, CH_2Cl_2 as eluent) gave the product (-)-**47** (407 mg, 72 % yield) as a white solid: mp 156-157 ^oC; $[\alpha]^{22}_D$ -41.8 (*c* 1.10, $CHCl_3$); ^{1}H NMR (400 MHz, C_5D_5N, 70°C) δ 10.54 (s, 1H), 9.09 (d, *J* = 8.5 Hz, 1H), 8.80 (s, 1H), 8.59 (d, *J* = 8.2 Hz, 1H), 7.40 (s, 3H), 7.13 (s, 3H), 6.90 (d, *J* = 8.6 Hz, 1H), 5.32 (s, 2H), 4.81 (t, *J* = 8.1 Hz, 1H), 4.16 (s, 1H), 3.85 (s, 3H), 2.42–2.21 (m, 4H), 2.18–1.80 (m, 1H), 1.75–1.48 (m, 3H), 1.46–0.98 (m, 3H); ^{13}C NMR (100 MHz, C_5D_5N, 70°C) δ

171.0, 155.6, 150.9, 149.3, 140.1, 137.8, 131.4, 129.1, 128.7, 128.0, 121.2, 121.1, 117.2, 105.4, 67.2, 63.2, 59.0, 56.1, 37.4, 33.4, 29.0, 26.3, 24.0, 21.1; HRMS(EI) Calcd for $C_{27}H_{29}N_3O_4$ [M^+]: 459.2158, Found 459.2155; IR (KBr) V(cm^{-1}): 3348, 1717, 1695, 1531, 1419, 1092.

(-)-(2a*S*,3a*S*,7a*R*,7b*R*)-Benzyl 1-(5-methoxyquinolin-8-yl)-2-oxooctahydro-1*H*- azeto[3,2-*b*] indole-3(7b*H*)-carboxylate (48): In a 10 mL of glass tube were placed substrate (-)-**47** (116 mg, 0.25 mmol), $Pd(OAc)_2$ (5.7 mg, 0.025 mmol), AgOAc (84.5 mg, 0.51 mmol), and iodoperfluorobenzene (735 mg 2.5 mmol). After the reaction mixture was mixed well with stirring at room temperature for about 5 min, the glass tube was placed into the CEM microwave reactor and sealed with a pressure lock. Use step-by-step program to increase the reaction temperature as following: first, increase the temperature from room temperature to 50 ^oC with 20 W irradiation and keep it at 50 ^oC for 1 min; then increase the temperature from 50 ^oC to 120 ^oC with 50 W irradiation and keep it at 120 ^oC for 3 min; after that, increase the temperature from 120 ^oC to 160 ^oC with 100 W irradiation; finally, start the reaction with stirring at 160 ^oC for 5 h. After the reaction mixture was cooled down below 50 °C, the pressure lock was opened. Purification by flash chromatography (Silica gel, petroleum ether : ethyl acetate = 2 : 1 as eluent) gave the product (-)-**48** (99.9 mg, 88 % yield) as a brown solid: mp 73-74 ^oC; $[\alpha]^{22}_D$ -131.7 (*c* 1.10, $CHCl_3$); ^1H NMR (400 MHz, C_5D_5N, 70°C) δ 8.95 (dd, *J* = 4.1 and 1.8 Hz, 1H), 8.59 (dd, *J* = 8.5 and 1.8 Hz, 1H), 8.36 (d, *J* = 8.4 Hz, 1H), 7.57 (s, 2H), 7.44–7.25 (m, 4H), 6.91 (d, *J* = 8.5 Hz, 1H), 6.20 (t, *J* = 5.2 Hz, 1H), 5.60 (s, 1H), 5.40 (s, 2H), 4.37–4.22 (m, 1H), 3.86 (s, 3H), 2.48–2.27 (m, 2H), 1.86 (d, *J* = 14.4 Hz, 1H), 1.75–1.60 (m, 1H), 1.54–1.36 (m, 2H), 1.10–0.85 (m, 2H), 0.79–0.60 (m, 1H); ^{13}C NMR (100 MHz, C_5D_5N, 70°C) δ166.5, 154.1, 152.7, 149.8, 142.3, 137.9, 131.2, 128.9, 128.5, 128.24, 128.16, 122.7, 121.6, 121.1, 105.1, 69.3, 67.2, 66.3, 59.3, 56.1, 39.4, 30.0 23.5,

23.3, 22.2; HRMS(EI) Calcd for $C_{27}H_{27}N_3O_4$ [M^+]: 457.2002, Found 457.2008; IR (KBr) V(cm^{-1}): 1748, 1703, 1593, 1411, 1093.

(-)-(2a*S*,3a*S*,7a*S*,7b*R*)-Benzyl 2-oxooctahydro-1*H*-azeto[3,2-*b*]indole-3(7b*H*)-carboxylate (49): To a solution of (-)-**48** (71 mg, 0.16 mmol) in CH_3CN (5 mL) was added ceric ammonium nitrate (256 mg, 0.48 mmol) in H_2O (2 mL) at room temperature. The mixture was stirred at room temperature for 5 h. Then purification by preparative TLC plate ($CHCl_3$: MeOH = 10 : 1 as eluent) gave the product (-)-**49** (29.2 mg, 62%) as a brown oil. $[\alpha]^{21}_D$ -129.1 (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, C_5D_5N, 70°C) δ 8.89 (s, 1H), 7.59–7.22 (m, 5H), 5.43–5.22 (m, 3H), 4.41–4.16 (m, 2H), 2.44–2.12 (m, 1H), 2.10–1.85 (m, 2H), 1.80–1.30 (m, 5H), 1.20–1.0 (m, 1H); ^{13}C NMR (100 MHz, C_5D_5N, 70°C) δ 167.7, 137.9, 128.9, 128.2, 128.1, 70.0, 67.1, 61.3, 58.9, 37.6, 26.2, 24.2, 23.4, 22.3; HRMS(EI) Calcd for $C_{17}H_{20}N_2O_3$ [M^+]: 300.1474, Found 300.1468; IR (KBr) V(cm^{-1}): 1759,1726,1422,1294,1098.

(-)-(2a*S*,3a*S*,7a*R*,7b*R*)-Octahydro-1*H*-azeto[3,2-*b*]indol-2(7b*H*)-one (50): To a solution of (-)-**49** (15 mg, 0.05 mmol) in MeOH (2 mL) was added (10%) Pd/C (3 mg). The reaction mixture was stirred at room temperature for 24 hours under H_2 (balloon). The reaction mixture was filtered through celite and then washed with MeOH. The solution was condensed under vacuum. Purification by preparative TLC plate ($CHCl_3$: MeOH = 10 : 1 as eluent) gave the product (-)-**50** (8 mg, 96%) as a brown solid: mp 150-151 °C; $[\alpha]^{16}_D$ -54.2 (*c* 0.20, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.04 (s, 1H), 4.46 (t, *J* = 3.2 Hz, 1H), 4.17 (t, *J* = 4.7 Hz, 1H), 3.46–3.38 (m, 1H), 2.07–1.99 (m, 2H), 1.80–1.72 (m, 2H), 1.60–1.48 (m, 2H), 1.37–1.14 (m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.3, 72.0, 60.0, 59.5, 38.0, 31.7, 24.1, 24.0, 23.2. HRMS(EI) Calcd for $C_9H_{14}N_2O$ [M^+]: 166.1106, Found 166.1108;IR (KBr) V(cm^{-1}): 2932,1743,1639,1418,582.

(-)-(*S*)-Benzyl 2-(quinolin-8-ylcarbamoyl)piperidine-1-carboxylate (51): To a 25 ml of round-bottom flask equipped with magnetic stirrer were added N-Carbobenzyloxy-L-Pipecolic acid (1.1g, 4.19 mmol), 8-amine -quinoline (725 mg, 5 mmol), EDCI (1.2 g, 6.3 mmol), DMAP (51 mg, 0.4 mmol) and anhydrous CH_2Cl_2 (50 mL). The mixture was stirred at room temperature for 12 h, then diluted with CH_2Cl_2 (50 mL), and washed with aq. HCl (1 M, 2 x 100 mL) and brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. Purification by flash chromatography (Silica gel, CH_2Cl_2 as eluent) gave the product (-)-**51 (**1.4 g, 87 % yield) as a yellow oil. $[\alpha]^{24}_D$ -107.7 (*c* 0.78, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.44 (s, 1H), 8.78 (dd, *J* = 7.0 and 1.8 Hz, 1H), 8.71 (brs, 1H), 8.13 (dd, *J* = 8.2 and 1.2 Hz, 1H), 7.59–7.12 (m, 8H), 5.45–5.02 (m, 3H), 4.30 (brs, 1H), 3.16 (brs, 1H), 2.51 (d, *J* = 11.6 Hz, 1H), 1.81–1.44 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 148.5, 138.7, 136.6, 136.2, 134.2, 128.5, 128.1, 128.0, 127.9, 127.3, 121.8, 121.7, 116.4, 67.7, 56.2, 42.5, 26.0, 25.0, 20.6; HRMS(EI) Calcd for $C_{23}H_{23}N_3O_3$ [M^+]: 389.1739, Found 389.1735; IR (KBr) V(cm^{-1}): 2942, 1693, 1528, 1422, 1258.

(-)-(1*S*,6*R*)-Benzyl 8-oxo-7-(quinolin-8-yl)-2,7-diazabicyclo[4.2.0]octane-2- carboxylate (52): In a 10 mL of glass tube were placed substrate (-)-**51** (113mg, 0.29 mmol), $Pd(OAc)_2$ (6.5 mg, 0.029 mmol), AgOAc (97 mg, 0.58 mmol), iodoperfluorobenzene (852 mg, 2.9 mmol) and $ClCH_2CH_2Cl$ (1 ml). After the reaction mixture was mixed well with stirring at room temperature for about 5 min, the glass tube was placed into the CEM microwave reactor and sealed with a pressure lock. Use step-by-step program to increase the reaction temperature as following: first, increase the temperature from room temperature to 50 ^{o}C with 20 W irradiation and keep it at 50 ^{o}C for 1 min; then increase the temperature from 50 ^{o}C to 120 ^{o}C with 50 W irradiation and keep it at 120 ^{o}C for 3 min; after that, increase the temperature from 120 ^{o}C to 130 ^{o}C with 100 W

irradiation; finally, start the reaction with stirring at 130 ^{o}C for 4 h. After the reaction mixture was cooled down below 50 °C, the pressure lock was opened. Purification by flash chromatography (Silica gel, petroleum ether : ethyl acetate = 4 : 1 as eluent) gave the product (-)-**52** (82.3 mg, 73 % yield) as a brown solid: mp 56-58 ^{o}C; $[\alpha]^{24}_{D}$ -186.3 (*c* 0.26, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) two rotamers δ 8.88–8.79 (m, 1H), 8.52 (d, *J* = 7.5 Hz, 0.48H), 8.47 (d, *J* = 7.4 Hz, 0.52H), 8.13 (d, *J* = 8.2 Hz, 1H), 7.62–7.56 (m, 1H), 7.52 (td, *J* = 7.8 and 2.4 Hz, 1H), 7.47–7.27 (m, 6H), 5.76–5.64 (m, 1.51H), 5.55 (d, *J* = 6.2 Hz, 0.49H), 5.31–5.12 (m, 2H), 3.76–3.61 (m, 1H), 3.59–3.46 (m, 1H), 2.18–2.03 (m, 1H), 1.87–1.73 (m, 2H), 1.72–1.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) two rotamers δ 168. 6, 168.1, 156.3, 155.5, 149.10, 149.08, 140.2, 140.1, 136.53, 136.51, 136.23, 136.21, 134.1, 133.8, 129.1, 128.6, 128.2, 128.14, 128.11, 128.05, 126.93, 126.91, 124.4, 124.2, 121.53, 121.50, 121.4, 121.2, 67.7, 67.6, 60.0, 57.7, 57.5, 43.2, 24.63, 24.58, 16.7, 16.4; HRMS(EI) Calcd for $C_{23}H_{21}N_3O_3$ [M^+]: 387.1583, Found 387.1579; IR (KBr) V(cm^{-1}): 1749, 1702, 1503, 1474, 1406, 1307, 1117.

(-)-(1*S*,6*R*)-2-Methyl-7-(1,2,3,4-tetrahydroquinolin-8-yl)-2,7-diazabicyclo[4.2.0]octan-8-one (53): To a solution of (-)-**52** (120 mg, 0.31 mmol) in 20 mL of EtOAc/MeOH (1:1, v/v) was added (10%) Pd/C (12 mg). The reaction mixture was stirred at room temperature for 120 hours under H_2 (balloon). The reaction mixture was filtered through celite and washed with MeOH. The solution was condensed under vacuum. Purification by preparative TLC plate ($CHCl_3$: MeOH = 30 : 1 as eluent) gave the product (-)-**53** (21 mg, 25%) and the product (-)-**54** (29 mg, 37%). Data of (-)-**53**: white solid, mp 134-135 ^{o}C; $[\alpha]^{23}_{D}$ -301.4 (*c* 0.21, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (d, *J* = 7.3 Hz, 1H), 6.68 (d, *J* = 7.7 Hz, 1H), 6.52 (t, *J* = 7.6 Hz, 1H), 5.57 (s, 1H), 4.43–4.37 (m, 1H), 3.93 (d, *J* = 5.8 Hz, 1H), 3.47–3.26 (m, 2H), 2.88–2.67 (m, 4H), 2.59 (s, 3H), 1.94–

1.84 (m, 4H), 1.79–1.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 139.2, 127.4, 123.8, 123.0, 118.5, 115.7, 66.8, 52.9, 48.3, 44.0, 42.0, 27.9, 21.6, 20.2, 16.7; HRMS(EI) Calcd for $C_{16}H_{21}N_3O$ [M^+]: 271.1685, Found 271.1684;IR (KBr) V(cm^{-1}): 2933, 1714, 1632, 1604, 1462, 1386, 732.

(-)-(1*S*,6*R*)-7-(1,2,3,4-Tetrahydroquinolin-8-yl)-2,7-diazabicyclo[4.2.0]octan-8-one (54): Data of (-)-**54** (29 mg, 37%): yellow solid, mp 82-83 ^{o}C; $[\alpha]^{23}_{D}$ -212.9 (*c* 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (d, *J* = 7.3 Hz, 1H), 6.69 (d, *J* = 7.8 Hz, 1H), 6.52 (t, *J* = 7.6 Hz, 1H), 5.63 (brs, 1H), 4.43–4.31 (m, 1H), 4.23 (d, *J* = 5.7 Hz, 1H), 3.45–3.28 (m, 2H), 3.19–3.06 (m, 1H), 3.03–2.89 (m, 1H), 2.88–2.67 (m, 2H), 2.07 (brs, 1H), 2.00–1.80 (m, 4H), 1.75–1.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167. 7, 139.1, 127. 5, 123.8, 123.0, 118. 6, 115.7, 60.4, 52.5, 42.0, 39.5, 27. 9, 21.5, 21.3, 17.0; HRMS(EI) Calcd for $C_{15}H_{19}N_3O$ [M^+]: 257.1528, Found 257.1535;IR (KBr) V(cm^{-1}): 2941, 2926, 1714, 1606, 1463, 1385, 1304, 1191, 731.

(-)-(*S*)-Benzyl 2-(5-methoxyquinolin-8-yl carbamoyl)piperidine-1-carboxylate (55): To a 25 ml of round-bottom flask equipped with magnetic stirrer were added N-Carbobenzyloxy-L-Pipecolic acid (263 mg, 1 mmol), 5-methoxyquinolin-8-amine (209 mg,1.2 mmol), EDCI (287.6 mg, 1.5 mmol), DMAP (12.2 mg, 0.1 mmol) and anhydrous CH_2Cl_2 (10 mL). The mixture was stirred at room temperature for 12 h, then diluted with CH_2Cl_2 (50 mL), and washed with aq. HCl (1 M, 2 x 50 mL) and brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. Purification by flash chromatography (Silica gel, CH_2Cl_2 as eluent) gave the product (-)-**55** (343mg, 82 % yield) as a yellow oil. $[\alpha]^{24}_{D}$ -138.0 (*c* 0.14, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.18 (s, 1H), 8.71 (s, 1H), 8.68 (d, *J* = 8.5 Hz, 1H), 8.55 (dd, *J* = 8.4 and 1.6 Hz, 1H), 7.52–7.12 (m, 6H), 6.83 (d, *J* = 8.5 Hz, 1H), 5.44–4.99 (m, 3H), 4.29 (brs, 1H), 3.98 (s, 3H), 3.17 (brs, 1H), 2.50 (d, *J* = 11.3 Hz, 1H), 1.80–1.44 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

168.9, 150.5, 149.0, 139.4, 136.8, 131.2, 128.6, 128.1, 127.9, 127.7, 120.8, 120.5, 116.5, 104.3, 67.7, 56.3, 55.9, 42.5, 26.1, 25.0, 20.6; HRMS(EI) Calcd for $C_{24}H_{25}N_3O_4$ [M^+]: 419.1845, Found 419.1849; IR (KBr) V(cm^{-1}): 2942, 1686, 1531, 1462, 1271.

(-)-(1*S*,6*R*)-Benzyl 7-(5-methoxyquinolin-8-yl)-8-oxo-2,7-diazabicyclo[4.2.0]octane-2-carboxylate (56): In a 10 mL of glass tube were placed substrate (-)-**55** (197 mg, 0.47 mmol), $Pd(OAc)_2$ (10.8 mg, 0.048 mmol), AgOAc (160.4 mg, 0.95 mmol), iodoperfluorobenzene (705.6 mg, 2.4 mmol) and 1,1,2,2-tetrachloroethane (2 ml). After the reaction mixture was mixed well with stirring at room temperature for about 5 min, the glass tube was placed into the CEM microwave reactor and sealed with a pressure lock. Use step-by-step program to increase the reaction temperature as following: first, increase the temperature from room temperature to 50 ^oC with 20 W irradiation and keep it at 50 ^oC for 1 min; then increase the temperature from 50 ^oC to 120 ^oC with 50 W irradiation and keep it at 120 ^oC for 3 min; after that, increase the temperature from 120 ^oC to 130 ^oC with 100 W irradiation; finally, start the reaction with stirring at 130 ^oC for 4 h. After the reaction mixture was cooled down below 50 °C, the pressure lock was opened. Purification by flash chromatography (Silica gel, petroleum ether : ethyl acetate = 4 : 1 as eluent) gave the product (-)-**56** (159.7 mg, 81 % yield) as a brown solid: mp 134-135 ^oC; $[\alpha]^{24}_D$ -156.6 (*c* 0.13, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) two rotamers δ 8.88–8.79(m, 1H), 8.55 (d, *J* = 8.5 Hz, 1H), 8.32 (d, *J* = 8.4 Hz, 0.48H), 8.26 (d, *J* = 8.4 Hz, 0.52H), 7.48–7.28 (m, 6H), 6.84 (d, *J* = 8.4 Hz, 1H), 5.71 (d, *J* = 6.1 Hz, 0.48H), 5.61–5.50 (m, 1.54H), 5.30–5.12 (m, 2H), 3.98 (s, 3H), 3.75–3.63 (m, 1H), 3.57–3.44 (m, 1H), 2.07–1.95 (m, 1H), 1.93–1.52 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) two rotamers δ 168.2, 167.7, 156.3, 155.5, 152.7, 152.5, 149.69, 149.65, 141.6, 141.4, 136.57, 136.56, 131.0, 130.9, 128.60, 128.59, 128.2, 128.1, 128.0, 126.9, 126.5, 122.6,

122.1, 121.1, 121.0, 120.69, 120.67, 104.33, 104.30, 67.7, 67.6, 59.8, 57.1, 56.9, 56.0, 43.2, 24.3, 16.6, 16.3; HRMS(EI) Calcd for $C_{24}H_{23}N_3O_4$ [M^+]: 417.1689, Found 417.1696; IR (KBr) V(cm^{-1}): 1743, 1692, 1471, 1413, 1266, 1112.

Compound (-)-**56** was also characterized in C_5D_5N at 77 ^oC. Data shown as following indicated (-)-**56** was a pure chemical compound. ^1H NMR (400 MHz, C_5D_5N, 77°C) δ 8.95–8.88(m, 1H), 8.58 (d, *J* = 8.5 Hz, 1H), 8.52 (d, *J* = 8.4 Hz, 1H), 7.60–7.47 (m, 2H), 7.45–7.25 (m 4H), 6.91 (d, *J* = 8.4 Hz, 1H), 5.80 (brs, 1H), 5.57–5.50 (m, 1H), 5.43–5.27 (m, 2H), 3.90 (s, 3H), 3.78–3.67 (m, 1H), 3.67–3.51 (m, 1H), 2.06 (d, *J* = 14.4 Hz, 1H), 1.97–1.82 (m, 1H), 1.79–1.65 (m, 1H), 1.60–1.45 (m, 1H); ^{13}C NMR (100 MHz, C_5D_5N, 77°C) δ 168.0, 156.1, 153.0, 150.0, 142.1, 137.8, 131.1, 128.9, 128.32, 128.27, 127.8, 122.7, 121.6, 121.1, 105.3, 67.7, 60.7, 57.2, 56.2, 43.4, 24.8, 17.3.

(-)-(1*S*,6*R*)-Benzyl 8-oxo-2,7-diazabicyclo[4.2.0]octane-2-carboxylate (57): To a solution of (-)-**56** (100 mg, 0.24 mmol) in CH_3CN (5 mL) was added ceric ammonium nitrate (394 mg, 0.72 mmol) in H_2O (2 mL) at room temperature. The mixture was stirred at room temperature for 5 h, then diluted with CH_2Cl_2 (15 mL), and washed with H_2O (2 x 15 mL) and brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. Purification by flash chromatography (Silica gel, $CHCl_3$: MeOH = 50 : 1 as eluent) gave the product (-)-**57** (44.8 mg, 72%) as a brown oil. $[\alpha]^{25}_D$ -75.3 (*c* 0.84, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) two rotamers δ 7.45–7.25 (m, 5H), 6.39 (s, 1H), 5.36 (d, *J* = 5.7 Hz, 0.53H), 5.24–5.05 (m, 2.63H), 4.19–4.06 (m, 1H), 3.68–3.55 (m, 1H), 3.40 (td, *J* = 12.2 and 5.7 Hz, 1H), 2.03–1.87 (m, 2H), 1.78–1.58 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) two rotamers δ 170.5, 170.0, 156.2, 155.4, 136.40, 136.36, 128.6, 128.20, 128.16, 128.1,

67.7, 67.6, 59.8, 59.7, 49.1, 49.0, 43.10, 43.07, 26.0, 16.0, 15.7; HRMS(EI) Calcd for $C_{14}H_{16}N_2O_3$ [M^+]: 260.1161, Found 260.1156; IR (KBr) V(cm^{-1}): 1754, 1700, 1417, 1312, 1112.

(-)-(1*S*,6*R*)-2,7-Diazabicyclo[4.2.0]octan-8-one (58): To a solution of (-)-**57** (81 mg, 0.31 mmol) in MeOH (5 mL) was added (10%) Pd/C (8 mg). The reaction mixture was stirred at room temperature for 24 hours under H_2 (balloon). The reaction mixture was filtered through celite and washed with MeOH. The solution was condensed under vacuum. Purification by flash chromatography (Silica gel, $CHCl_3$: MeOH = 50 : 1 as eluent) gave the product (-)-**58** (25.5 mg, 65%) as a yellow solid: mp 143-145 ^oC; $[\alpha]^{23}_D$ -6.0 (*c* 1.1, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 6.46 (s, 1H), 4.15 (d, *J* = 5.1 Hz, 1H), 3.86 (dd, *J* = 7.7 and 4.7 Hz, 1H), 3.06–2.94 (m, 1H), 2.92–2.84 (m, 1H), 2.14 (s, 1H), 2.00–1.90 (m, 1H), 1.86–1.79 (m, 1H), 1.73–1.64 (m, 1H), 1.61–1.52 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.3, 64.0, 47.8, 39.7, 24.1, 16.8; HRMS(EI) Calcd for $C_6H_{10}N_2O$ [M^+]: 126.0793, Found 126.0797;IR (KBr) V(cm^{-1}): 2929, 1733, 1643, 1455, 592.

(-)-(*S*)-Benzyl 3-(5-methoxyquinolin-8-ylcarbamoyl)-3,4-dihydroisoquinoline-2(1 *H*)-carboxylate (59): To a 25 ml of round-bottom flask equipped with magnetic stirrer were added (*S*)-2-(benzyloxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (600 mg, 1.9 mmol), 5-methoxyquinolin-8-amine (403 mg, 2.3 mmol), EDCI (665 mg, 3.5 mmol), DMAP (24.4 mg, 0.2 mmol) and anhydrous CH_2Cl_2(20 mL). The mixture was stirred at room temperature for 12 h, then diluted with DCM (50 mL), and washed with aq. HCl (1 M, 2 x 50 mL) and brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. Purification by flash chromatography (Silica gel, CH_2Cl_2 as eluent) gave the product (-)-**59** (649 mg, 72 % yield) as a yellow oil. $[\alpha]^{25}_D$ -5.0 (*c* 0.72, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) two rotamers δ 10.17 (s, 0.45H), 10.01 (s, 0.55H), 8.71 (dd, *J* = 4.1 and 1.4 Hz, 1H), 8.61–8.46 (m, 2H), 7.54–6.95 (m, 10H), 6.79–6.71 (m, 1H), 5.46–

4.99 (m, 3H), 4.96 (d, *J* = 16.0 Hz, 1H), 4.79 (d, *J* = 16.0 Hz, 1H), 3.99–3.89 (m, 3H), 3.55 (d, *J* = 15.3 Hz, 0.48H), 3.43 (dd, *J* = 15.1 and 3.5 Hz, 0.58H), 3.26 (d, *J* = 6.0 Hz, 0.64H), 3.22 (d, *J* = 6.0 Hz, 0.47H); ^{13}C NMR (100 MHz, $CDCl_3$) two rotamers δ 169.3, 168.7, 156.5, 155.9, 150. 6, 148.9, 139.32, 139.29, 136.6, 136.2, 133.5, 133.2, 132.9, 132.5, 131.13, 131.07, 128.7, 128.3, 128.1, 128.0, 127.9, 127.5, 127.4, 127.3, 127.0, 126.76, 126.75, 126.4, 126.18, 126.16, 120.7, 120.4, 116.6, 116.5, 104.2, 67.9, 56.9, 55.8, 55.7, 45.2, 45.0, 31. 8, 30.8; HRMS(EI) Calcd for $C_{28}H_{25}N_3O_4$ [M^+]: 467.1845, Found 467.1853; IR (KBr) V(cm^{-1}): 1704, 1532, 1495, 1402, 1270, 1091.

(-)-(2a*S*,8b*R*)-Benzyl 1-(5-methoxyquinolin-8-yl)-2-oxo-1,2,2a,8b-tetrahydroazeto [3,2-*c*] isoquinoline-3(4*H*)-carboxylate (60): In a 10 mL of glass tube were placed substrate (-)-**59** (46.8 mg, 0.1 mmol), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), AgOAc (25 mg, 0.15 mmol), and iodoperfluorobenzene (0.5 mL). After the reaction mixture was mixed well with stirring at room temperature for about 5 min, the glass tube was placed into the CEM microwave reactor and sealed with a pressure lock. Use step-by-step program to increase the reaction temperature as following: first, increase the temperature from room temperature to 50 ^{o}C with 20 W irradiation and keep it at 50 ^{o}C for 1 min; then increase the temperature from 50 ^{o}C to 120 ^{o}C with 50 W irradiation and keep it at 120 ^{o}C for 3 min; after that, increase the temperature from 120 ^{o}C to 150 ^{o}C with 100 W irradiation; finally, start the reaction with stirring at 150 ^{o}C for 4 h. After the reaction mixture was cooled down below 50 °C, the pressure lock was opened. The crude H^1 NMR was checked directly. Purification by preparative TLC plate (petroleum ether : ethyl acetate = 2 : 1 as eluent) gave the product (-)-**60** (30.8 mg, 66 % yield) as a yellow solid: mp 66-67 ^{o}C; $[\alpha]^{25}_D$ -153.6 (*c* 1.07, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) two rotamers δ 9.00 (brs, 1H), 8.55 (d, *J* =

8.3 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 0.46H), 7.70 (d, *J* = 8.3 Hz, 0.60H), 7.50–7.11 (m, 9H), 7.04–6.96 (m, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 6.37 (d, *J* = 5.1 Hz, 0.48H), 6.31 (d, *J* = 5.3 Hz, 0.65H), 6.24 (d, *J* = 4.0 Hz, 0.42H), 6.10 (d, *J* = 4.6 Hz, 0.58H), 5.34–5.07 (m, 3H), 4.49 (d, *J* = 16.0 Hz, 0.46H), 4.41 (d, *J* = 15.9 Hz, 0.62H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) two rotamers δ 166.5, 166.3, 154.9, 154.7, 153.7, 153.6, 149.9, 142.8, 142.7, 136.3, 136.2, 134.9, 131.9, 131.5, 131.31, 131.30, 131.16, 131.0, 128.9, 128.6, 128.3, 128.1, 127.5, 127.2, 126.8, 125.1, 125.0, 124.7, 121.2, 120.9, 103.9, 68.1, 63.2, 63.0, 57.9, 55.9, 44.7, 44.1; HRMS(EI) Calcd for $C_{28}H_{23}N_3O_4$ [M^+]: 465.1689, Found 465.1694; IR (KBr) V(cm^{-1}): 1750, 1706, 1591, 1480, 1427, 1271, 1211, 1092.

(+)-(2a*S*,8b*R*)-Benzyl 2-oxo-1,2,2a,8b-tetrahydroazeto[3,2-*c*]isoquinoline-3(4*H*)-carboxylate (61): To a solution of (-)-**60** (75 mg, 0.16 mmol) in CH_3CN (3 mL) was added ceric ammonium nitrate (263 mg, 0.48 mmol) in H_2O (0.5 mL) at room temperature. The mixture was stirred at room temperature for 4 h, then diluted with CH_2Cl_2 (15 mL), and washed with H_2O (2 x 15 mL) and brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. Purification by flash chromatography (Silica gel, $CHCl_3$: MeOH = 50 : 1 as eluent) gave the product (+)-**61** (28.2 mg, 57%) as a brown solid: mp 55-56 ^{o}C; $[\alpha]^{25}_{D}$ +125.7 (*c* 0.25, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) two rotamers δ 7.42–7.27 (m, 9H), 6.24 (s, 0.46H), 6.21 (s, 0.54H), 5.96 (d, *J* = 4.4 Hz, 0.46H), 5.80 (d, *J* = 4.7 Hz, 0.54H), 5.26–5.01 (m, 3H), 4.85 (d, *J* = 5.1 Hz, 0.47H), 4.82 (d, *J* = 5.2 Hz, 0.56H), 4.26 (d, *J* = 16.0 Hz, 0.47H), 4.18 (d, *J* = 16.0 Hz, 0.55H); ^{13}C NMR (100 MHz, $CDCl_3$) two rotamers 167.7, 167.4, 154.8, 154.5, 136.1, 136.0, 134.7, 134.6, 132.8, 132.5, 130.2, 130.0, 129.0, 128.7, 128.3, 128.1, 128.0, 127.6, 127.2, 68.2, 64.0, 63.8, 50.4, 50.2, 44.4, 43.8; HRMS(EI) Calcd for $C_{18}H_{16}N_2O_3$ [M^+]: 308.1161, Found 308.1159; IR (KBr) V(cm^{-1}): 1761, 1703, 1429,

1304, 1214, 1121.

(+)-(2a*S*,8b*R*)-1,3,4,8b-Tetrahydroazeto[3,2-*c*]isoquinolin-2(2a*H*)-one(62): To a solution of (+)-**61** (25 mg, 0.08 mmol) in EtOAc (3 mL) was added (10%) Pd/C (5 mg). The reaction mixture was stirred at 60 ^{o}C for 24 hours under H_2 (balloon). The reaction mixture was filtered through celite and washed with MeOH. The solution was condensed in vacuum. Purification by flash chromatography (Silica gel, $CHCl_3$: MeOH = 50 : 1 as eluent) gave the product (+)-**62** (11.2 mg, 80%) as a yellow solid: mp 162-164 ^{o}C; $[\alpha]^{26}_{D}$ +366.1 (*c* 0.56, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.26 (m, 3H), 7.19 (d, *J* = 7.3 Hz, 1H), 6.27 (brs, 1H), 4.74–4.70 (m, 1H), 4.68 (d, *J* = 4.8 Hz, 1H), 3.96 (d, *J* = 15.6 Hz, 1H), 3.89 (d, *J* = 15.5 Hz, 1H), 1.94 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 137.7, 133.3, 130.4, 128.7, 127.5, 127.1, 67.4, 49.7, 45.4; HRMS(EI) Calcd for $C_{10}H_{10}N_2O$ [M^+]: 174.0793, Found 174.0796;IR (KBr) V(cm^{-1}): 3298, 1743, 1701, 1456, 1348, 754.

Benzyl 2-(quinolin-8-ylcarbamoyl)indoline-1-carboxylate (63): To a 25 ml of round-bottom flask equipped with magnetic stirrer were added N-Carbobenzyloxy- Indoline-2-carboxylic acid (565 mg,1.9 mmol), 8-amine-quinoline (332 mg,2.3 mmol), EDCI (546 mg, 2.9 mmol), DMAP (23 mg, 0.2 mmol) and anhydrous CH_2Cl_2 (20 mL). The mixture was stirred at room temperature for 12 h, then diluted with CH_2Cl_2 (40 mL), and washed with aq. HCl (1 M, 2 x 50 mL) and brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. Purification by flash chromatography (Silica gel, CH_2Cl_2 as eluent) gave the product **63** (561 mg, 70 % yield) as a white solid: mp 160-161 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.37 (brs, 1H), 8.73 (dd, *J* = 5.7 and 3.0 Hz, 1H), 8.68 (d, *J* = 3.0 Hz, 1H), 8.12 (dd, *J* = 8.3 and 1.6 Hz, 1H), 8.03 (brs, 1H), 7.57–7.48 (m, 2H), 7.40 (dd, *J* = 8.3 and 4.2 Hz, 1H), 7.37–7.13 (m, 5H), 7.03 (t, *J* = 7.4 Hz, 2H), 6.98 (s,

1H), 5.41–5.09 (m, 3H), 3.66 (dd, *J* = 16.4 and 11.1 Hz, 1H), 3.46 (dd, *J* = 16.4 and 2.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 148.5, 138.6, 136.2, 135.8, 134.0, 128.32, 128.28, 128.1, 128.0, 127.9, 127.3, 124.9, 123.7, 122.0, 121.7, 116.7, 115.6, 67.9, 63.1, 33.5; HRMS(EI) Calcd for $C_{26}H_{21}N_3O_3$ [M^+]: 423.1583, Found 423.1573; IR (KBr) V(cm^{-1}): 3316, 1710, 1677, 1533, 1485, 1398.

2-(Quinolin-8-yl)-1H-imidazo[1,5-*a*]indole-1,3(2*H*)-dione (64): In a 10 mL of glass tube were placed substrate **63** (42.4 mg, 0.1 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), AgOAc (33.4 mg, 0.2 mmol), and iodoperfluorobenzene (294 mg 1 mmol). After the reaction mixture was mixed well with stirring at room temperature for about 5 min, the glass tube was placed into the CEM microwave reactor and sealed with a pressure lock. Use step-by-step program to increase the reaction temperature as following: first, increase the temperature from room temperature to 50 ^{o}C with 20 W irradiation and keep it at 50 ^{o}C for 1 min; then increase the temperature from 50 ^{o}C to 120 ^{o}C with 50 W irradiation and keep it at 120 ^{o}C for 3 min; after that, increase the temperature from 120 ^{o}C to 150 ^{o}C with 100 W irradiation; finally, start the reaction with stirring at 150 ^{o}C for 4 h. After the reaction mixture was cooled down below 50 °C, the pressure lock was opened. Purification by preparative TLC plate (petroleum ether : ethyl acetate = 2 : 1 as eluent) gave the product **64** (4.8 mg, 15 % yield) as a white solid: mp 223-224 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (dd, *J* = 4.1 and 1.5 Hz, 1H), 8.22 (dd, *J* = 8.3 and 1.5 Hz, 1H), 8.01–7.93 (m, 2H), 7.81 (dd, *J* = 7.3 and 1.1 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.67 (t, *J* = 7.8 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 1H), 7.45 (dd, *J* = 8.3 and 4.2 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.26 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 151.3, 148.5, 144.3, 136.4, 133.4, 132.6, 130.6, 130.3, 129.5, 129.2, 129.0, 128.6, 126.3, 124.34, 124.30, 122.3, 113.9, 109.6; HRMS(EI) Calcd for $C_{19}H_{11}N_3O_2$ [M^+]: 313.0851,

Found 313.0850; IR (KBr) V(cm^{-1}): 1787, 1735, 1613, 1475, 1397.

(-)-(2*S*,4*R*)-Benzyl 4-hydroxy-2-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate(65): According to the procedure of literature,[16] to a solution of N-carbobenzyloxy-trans-4-hydroxy-L-proline (444 mg, 1.67 mmol) in 10 mL of dry THF was added N-methyl morpholine (184 μL, 1.67 mmol) at 0^{o}C. A solution of isobutyl chloroformate (220 μL, 1.67 mmol) in 2 mL of dry THF was added to reaction mixture dropwise. After 3 hour at 0 ^{o}C, the reaction was complete indicated by TLC (CH_2Cl_2/MeOH = 5:1 as eluent). Then 8-aminoquinoline (481.6 mg, 3.3 mmol) in 5 mL of dry THF were added to reaction mixture slowly. The reaction was allowed to warm to room temperature for 24 h, then diluted with 50 mL of ethyl acetate, and extracted 3 x with 30 mL of 5% aqueous sodium bicarbonate. In order to regain the desired product, combined aqueous layers were extracted 3 x with 30 mL of ethyl acetate and all organic layers were dried with anhydrous Na_2SO_4. Concentration in vacuum gave the product **65** (514.9 mg, 79% yield) as a yellow oil. $[\alpha]^{14}_{D}$ -55.8 (*c* 1.90, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) two rotamers δ 10.29 (s, 0.4H), 10.09 (s, 0.6H), 8.71–8.49 (m, 2H), 8.06–7.91 (m, 1H), 7.47–7.08 (m, 5H), 6.95 (d, *J* = 6.8 Hz, 1H), 6.78–6.57 (m, 2H), 5.06 (d, *J* = 10.8 Hz, 1.4H), 4.86 (d, *J* = 12.2 Hz, 0.6H), 4.75–4.55 (m, 1H), 4.44 (s, 1H), 3.84–3.45 (m, 3H), 2.46–2.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) two rotamers δ 170.9, 170.6, 155.9, 155.4, 148.4, 138.5, 138.4, 136.5, 136.2, 135.8, 134.1, 133.8, 128.5, 128.0, 127.9, 127.8, 127.6, 127.5, 127.2, 122.0, 121.6, 116.8, 116.6, 70.0, 69.4, 67.6, 67.4, 61.0, 55.8, 55.0, 39.9, 38.7. HRMS(EI) Calcd for $C_{22}H_{21}N_3O_4$ [M^{+}]: 391.1532, Found 391.1528; IR (KBr) V(cm^{-1}): 3431, 3345, 1696, 1533, 1423, 1355, 1325, 1121, 792.

(-)-(2*S*,4*R*)-Benzyl 4-acetoxy-2-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate (66):

Compound **65** (514.9 mg, 1.3 mmol) and triethylamine (263.1 mg, 2.6 mmol) were dissolved in 30 mL of CH_2Cl_2 and then cooled down to 0 ^oC. Acetyl chloride (183 μL, 2.6 mmol) in 10 mL of CH_2Cl_2 was added to reaction mixture dropwise by syringe at 0 ^oC. The reaction mixture was allowed to warm to room temperature for 12 h, then diluted with 40 mL of CH_2Cl_2, and washed with aq. HCl (1 M, 2 x 50 mL) and brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. Purification by flash chromatography (Silica gel, CH_2Cl_2 as eluent) gave the product **66** (422 mg, 75 % yield) as a yellow oil. $[\alpha]^{24}_D$ -31.9 (*c* 0.79, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) two rotamers δ 10.41 (s, 0.43H), 10.18 (s, 0.57H), 8.81–8.60 (m, 2H), 8.11 (d, *J* = 6.4 Hz, 1H), 7.50 (s, 2H), 7.44–7.27 (m, 3H), 7.07 (d, *J* = 6.7 Hz, 1H), 6.91–6.70 (m, 2H), 5.36 (s, 1H), 5.17 (d, *J* = 12.2 Hz, 1.54H), 5.02 (d, *J* = 12.2 Hz, 0.58H), 4.79–4.60 (m, 1H), 4.01–3.77 (m, 2H), 2.62–2.40 (m, 2H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) two rotamers δ 170.3, 170.0, 169.6, 155.5, 154.8, 148.3, 138.6, 138.4, 136.3, 136.2, 135.7, 134.1, 133.8, 128.5, 128.1, 127.9, 127.8, 127.6, 127.2, 122.0, 121.6, 116.8, 116.5, 72.9, 72.2, 67.6, 67.5, 60.8, 60.7, 53.2, 52.6, 37.1, 35.5, 21.0; HRMS(EI) Calcd for $C_{24}H_{23}N_3O_5$ [M^+]: 433.1638, Found 433.1654; IR (KBr) V(cm^{-1}): 3341, 1740, 1708, 1532, 1424, 1241.

(-)-(2*S*,4*R*)-Benzyl 4-methoxy-2-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate (67): To a 35 ml of sealed tube equipped with magnetic stirrer were added (2*S*,4*R*)-1-(benzyloxycarbonyl)-4-methoxypyrrolidine-2-carboxylic acid (172 mg, 0.62 mmol), 8-aminoquinoline (106.6 mg,0.74 mmol), EDCI (178.3 mg, 0.93 mmol), DMAP (7.6 mg, 0.062 mmol) and anhydrous CH_2Cl_2 (15 mL). The reaction mixture was stirred at 40 ^oC for 24 h, then diluted with CH_2Cl_2 (10 mL), and washed with aq. HCl (1 M, 2 x 30 mL) and brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. Purification by flash chromatography (Silica

gel, CH_2Cl_2 as eluent) gave the product **67** (561 mg, 71 % yield) as a brown oil. $[\alpha]^{23}_D$ -51.3 (*c* 0.26, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) two rotamers δ 10.43 (s, 0.42H), 10.21 (s, 0.58H), 8.82–8.65 (m, 2H), 8.13 (d, *J* = 8.2 Hz, 1H), 7.51 (s, 2H), 7.42 (dd, *J* = 8.3 and 4.2 Hz, 1H), 7.39–7.27 (m, 2H), 7.09 (d, *J* = 7.1 Hz, 1H), 6.92–6.74 (m, 2H), 5.18 (d, *J* = 12.5 Hz, 1.50H), 5.02 (d, *J* = 12.2 Hz, 0.59H), 4.73 (t, *J* = 6.8 Hz, 0.44H), 4.62 (t, *J* = 7.8 Hz, 0.59H), 4.17–4.03 (m, 1H), 3.94 (d, *J* = 11.5 Hz, 0.65H), 3.85–3.64 (m, 1.64H), 3.34 (s, 3H), 2.58–2.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) two rotamers δ 170.7, 170.3, 155.8, 155.2, 148.5, 138.7, 138.5, 136.6, 136.3, 136.0, 134.3, 134.0, 128.6, 128.1, 127.9, 127.8, 127.6, 127.3, 122.0, 121.7, 116.8, 116.6, 79.0, 78.4, 67.6, 67.5, 61.0, 60.9, 56.9, 56.8, 52.2, 51.9, 37.0, 35.3; HRMS(EI) Calcd for $C_{23}H_{23}N_3O_4$ $[M^+]$: 405.1689, Found 405.1696; IR (KBr) V(cm^{-1}):1703, 1532, 1424, 1354, 1119, 1097.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

X-ray crystallographic analysis, ^1H and ^{13}C NMR spectra of new compounds (PDF).

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Notes

The authors declare no competing financial interest.

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