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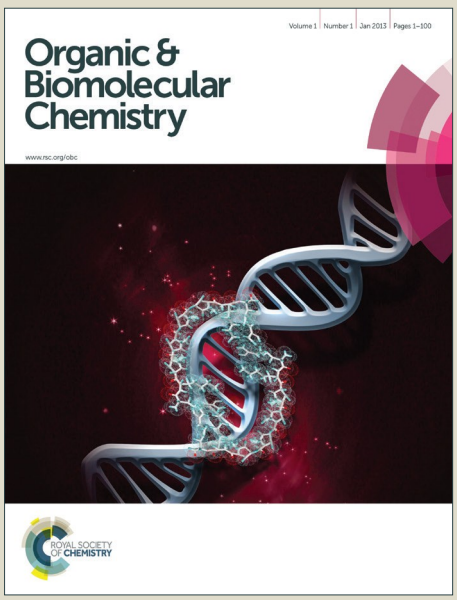

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PAPER

Catalytic Asymmetric [3+2]-Cycloaddition for Stereodivergent Synthesis of Chiral Indolyl-pyrrolidines†

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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Stereochemically divergent synthesis of indolyl-pyrrolidines was accomplished using an imidazolidine-aminophenol (IAP)-Ni(OAc)$_2$ complex and a bis(imidazolidine)pyridine (PyBidine)-Cu(OTf)$_2$ complex. The former catalyzed *exo*'-selective asymmetric [3+2] cyclization of iminoesters with indolyl nitroalkenes, and the later catalyzed the reaction in an *endo*-selective manner. These catalysts are tolerant toward the highly functional substrates that supply the chiral indolyl-pyrrolidine hybrids.

Introduction

Indoles and pyrrolidines are ubiquitous molecules in biologically important natural products. The bisindoles and relating indolyl-pyrrolidines shown in Figure 1 are representative of molecules containing both skeletons in their structure.[1]

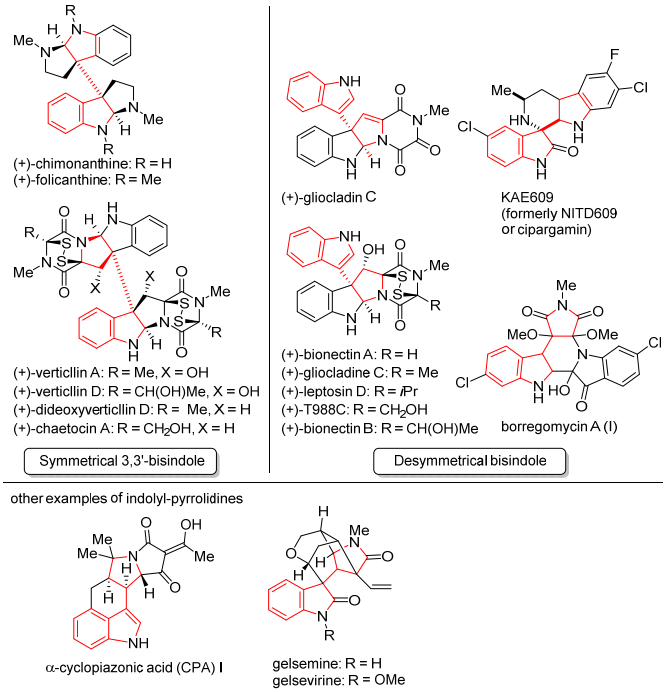
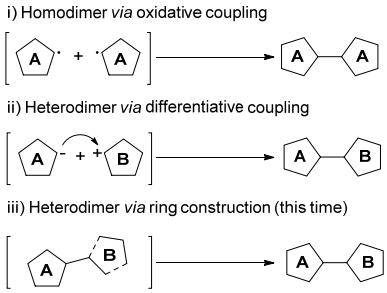


Fig. 1 Examples of natural products containing indole and pyrrolidine motifs.

The total synthesis of symmetrical bisindoles (*e.g.*, chimonantine and chaetocin A) has been achieved through radical coupling of indole substrates (Scheme 1-i).[2,3] In contrast, unsymmetrical molecules (*e.g.*, gliocladin C) require differentiative coupling involving two types of substrates (Scheme 1-ii).[4] In the total synthesis of (+)-gliocladin C, Overman[5] and Trost[6] employed 3-indol-3'-yloxindoles, which were synthesized through Rh-catalyzed coupling of indoles with an isatin-derived diazo compound. Stephenson developed the visible-light photoredox catalytic unsymmetrical coupling of pyrroloindolines with indoles for the total synthesis of (+)-gliocladin C; however, the success of the differentiative radical coupling of two *N*-heterocyclic substrates was rather limited.[7] Wang and Li reported the organocatalytic synthesis of 3-indolyl-3-hydroxy-2-oxindoles using enantioselective Friedel-Crafts reaction of indoles with isatins.[8] Guo and Peng constructed a chiral quaternary carbon center from racemic 3-indolyl-3-hydroxy-2-oxindoles *via* asymmetric α alkylation of ketones.[9] The catalytic asymmetric synthesis of mixed indoles also has been reported using an asymmetric Friedel-Crafts coupling reaction of indoles with isatin-derived nitroalkenes.[10,11]



Scheme 1 Classification for approaching homo- and hetero-bicyclic compounds.

Compared to the differentiative coupling approach (Scheme 1-ii), the puwerful catalytic asymmetric synthesis of *N*-heterocycle unit **B** (*e.g.*, pyrrolidine) using the *N*-heterocycle-containing substrate **A** (*e.g.*, indolyl nitroalkene) would provide an alternative method for accessing the hybrid molecules of **A**-**B**

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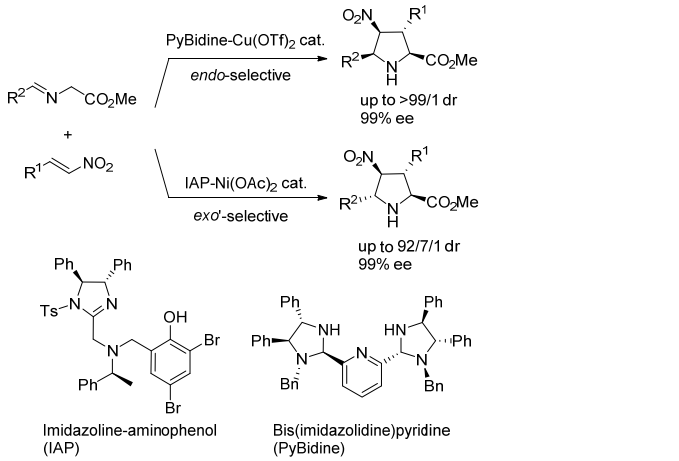
†Electronic Supplementary Information (ESI) available. See DOI: 10.1039/x0xx00000x

(*i.e.*, indolyl-pyrrolidine) (Scheme 1-iii).[12] Here, with considering the structure of α-cyclopiazoic acid (CPA) I,[13] gelsemine,[14] and gelsevirine,[15] the catalytic asymmetric [3+2] cyclization of iminoesters with an indolyl nitroalkene is successfully conducted to supply a unique family of chiral indolyl-pyrrolidine hybrid molecules.

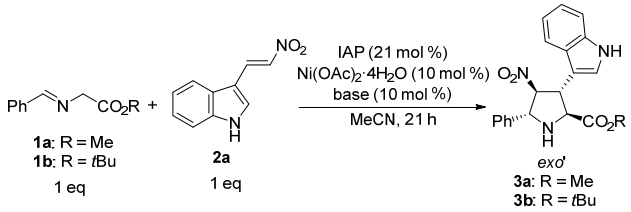
Results and discussion

An imidazolidine-aminophenol ligand (IAP)[16] and a bis(imidazolidine)pyridine ligand (PyBidine)[17] have been developed to achieve metal-catalyzed [3+2] cyclization of nitroalkenes with iminoesters. The IAP-Ni(OAc)$_2$ complex was the first general asymmetric catalyst to provide [3+2]-cycloadducts of iminoesters with nitroalkenes in an *exo*'-selective manner,[16d,e] while the PyBidine-Cu(OTf)$_2$ catalyst gave the *endo*-product in a highly enantioselective manner.[17a,f]



Scheme 1 PyBidine-Ni(OAc)$_2$ catalyzed *endo*-selective [3+2]-cycloaddition and IAP-Ni(OAc)$_2$ catalyzed *exo*'-selective [3+2]-cycloaddition.

Table 1 Optimization of IAP-Ni(OAc)$_2$ catalyzed [3+2] cyclization.

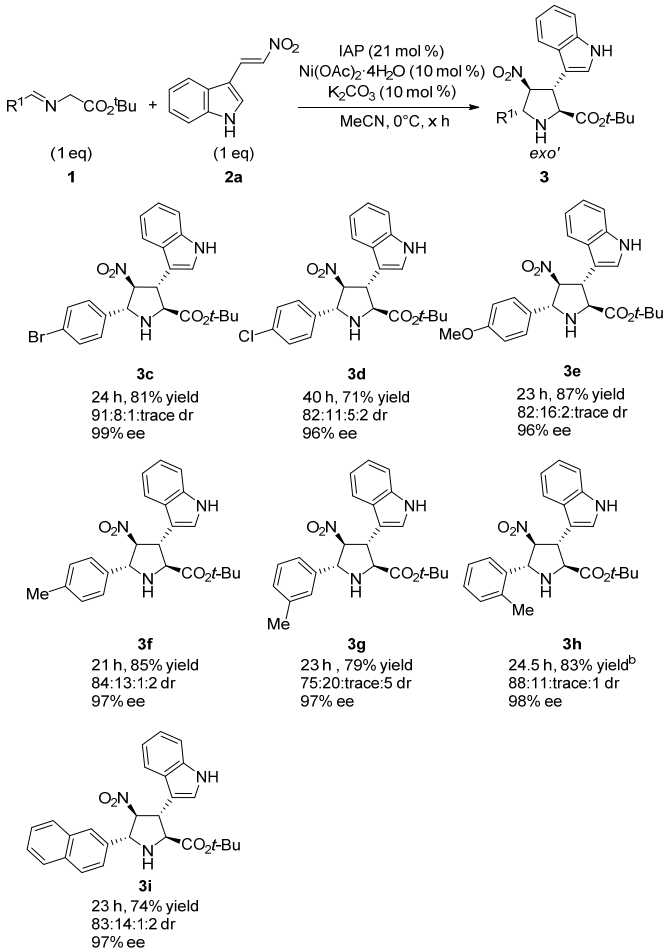


Entry	R	Base	Temp (°C)	Yield (%)	dr (*exo*':*endo*: *exo*: *endo*')	ee of *exo*' (%)
1	Me	NEt_3	25	76	75:14:8:3	89
2	Me	DIPEA	25	78	81:14:4:1	91
3	Me	K_2CO_3	25	71	62:18:13:7	96
4[a]	Me	K_2CO_3	25	<72	53:26:13:8	91
5	*t*Bu	K_2CO_3	25	81	84:8:5:3	95
6	*t*Bu	K_2CO_3	0	74	82:14:2:2	98

[a] 11 mol% IAP

Diversity-oriented asymmetric catalysis (DOAC)[16g,17f] for constructing the stereochemically variegated indolyl-pyrrolidines began with application of the IAP-Ni(OAc)$_2$ catalyst for *exo*'-selective [3+2]-cycloaddition of iminoesters with indolyl nitroalkenes. Reaction conditions for the IAP-Ni(OAc)$_2$ catalysis were optimized using test substrates of benzaldehyde-derived iminoesters (**1a** or **1b**) with indolyl nitroalkene (**2a**) (Table 1). For imino methylester **1a** (entries 1-3), the use of K_2CO_3 as the base provided the *exo*'-adduct with 96% ee, although *exo*'-selectivity was slightly lower than those achieved using NEt_3 and DIPEA. For reaction using indolyl nitroalkene, increasing the IAP to Ni(OAc)$_2$ ratio to 2 : 1 was effective for improving the diastereo- and enantioselectivity.[16f] Using the imino *t*-butylester **1b**, *exo*'-selectivity was improved, and reaction at 0 °C provided the *exo*'-adduct with 98% ee.

Table 2 IAP-Ni(OAc)$_2$ catalyzed *exo*'-selective [3+2] cyclization of iminoesters **1** with indolyl nitroalkenes **2a**.[a]

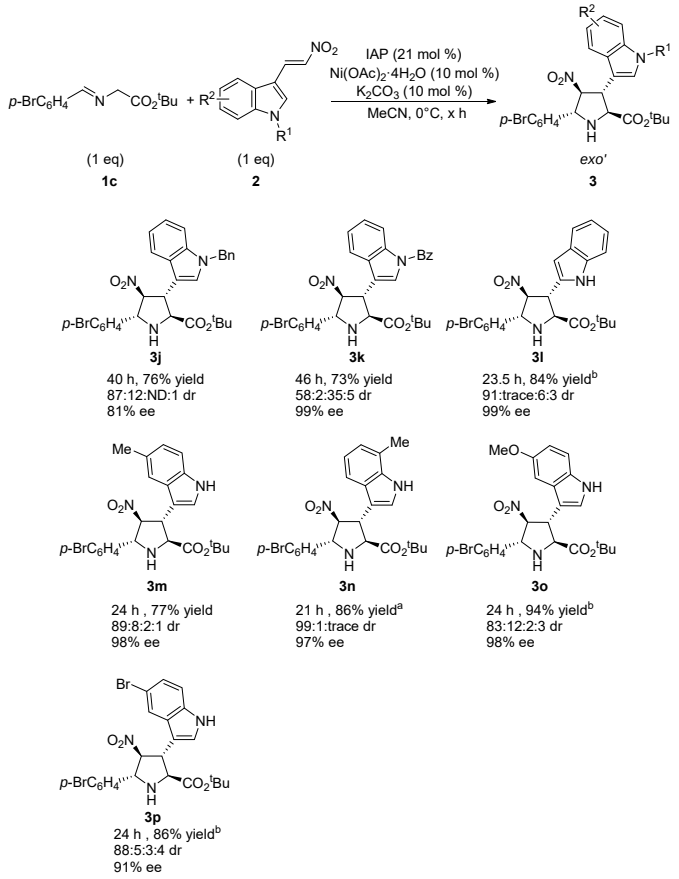


a) The absolute configuration was assigned by analogy with the previous report using nitrostyrene. b) 1.2 eq of iminoester

Under optimized reaction conditions, generality of the iminoesters was examined (Table 2). Various substituents on the benzene ring of iminoesters can be designed for highly *exo*'-selective [3+2]-cycloaddition ranging from 96% ee to 99% ee. The iminoester derived from 2-naphthoaldehyde also was applicable to give product **3i** with 97% ee.

The general applicability of indolyl nitroalkenes **2** is shown in Table 3 using *p*-bromobenzaldehyde-derived imino *t*-butylester (**1c**). The *N*-benzyl-protected indolyl nitroalkene was converted effectively to product **3j** in a manner similar to the results using NH indolyl nitroalkenes, although the reaction using *N*-benzoated indolyl nitroalkene resulted in low *exo*'-selectivity (**3k**). In contrast, both electron-donating and -withdrawing substituents on the benzene ring of the indole resulted in highly *exo*'-selective [3+2]-cycloaddition. These results demonstrate that IAP-Ni(OAc)$_2$ catalysis can be applied to highly functional substrates for *exo*'-selective [3+2]-cycloaddition reactions.

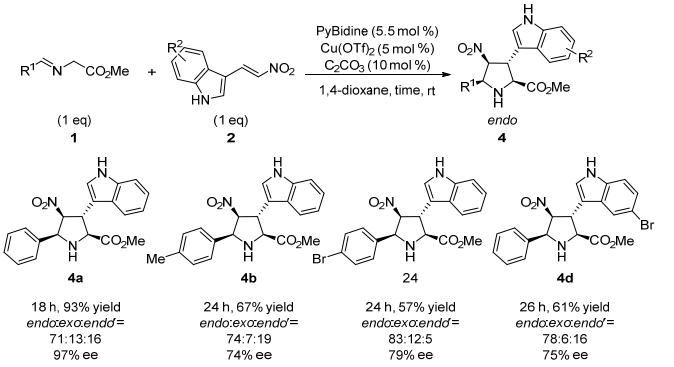
Table 3. IAP-Ni(OAc)$_2$-catalyzed *exo*'-selective [3+2] cyclization of iminoester (**1c**) with various indolyl nitroalkenes.[a]



a) The absolute configuration was assigned by analogy with the previous report using nitrostyrene. b) 1.2 eq of iminoester

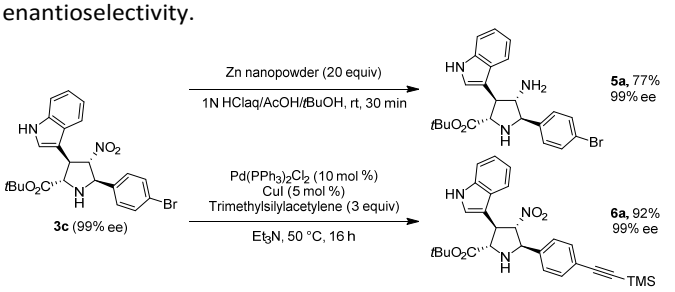
The bis(imidazolidine)pyridine (PyBidine)-Cu(OTf)$_2$-catalyzed *endo*-selective [3+2] cyclization[17a,f] was also adapted for reaction of iminoesters with indolyl nitroalkenes. The PyBidine-Cu(OTf)$_2$ possessed greater catalytic activity for iminoester **1a** than for **1b**. For reaction of indolyl nitroalkene (**2a**) with **1a**, PyBidine-Cu(OTf)$_2$ gave the [3+2]- cycloadduct **4a** in 93% yield with good endo-selectivity (*endo*:*exo*:*endo'* = 71:13:16), although the reaction using **1b** resulted in 26% yield with low diastereoselectivity (*endo*:exo=*56*:44).

Table 4. Cu-(OTf)$_2$-catalyzed *endo*-selective [3+2] cyclization of iminoesters with nitroalkenes.[a)]



a) The absolute configuration was assigned by analogy with the previous report using nitrostyrene.

Because *endo*-**4a** was obtained with 97% ee, the original reaction conditions (Cs_2CO_3 as the base in 1,4-dioxane at rt) were applied to examine the generality of the PyBidine-Cu(OTf)$_2$-catalyzed *endo*-selective [3+2] cyclization (Table 4). Although the (PyBidine)-Cu(OTf)$_2$ catalyst appeared to be more sensitive to highly functional substrates and products compared to the IAP-Ni(OAc)$_2$ catalyst, *endo*-selective adducts were obtained as the major isomers with moderate to good enantioselectivity.



Scheme 2 Chemical transformation of *exo*'-cycloadduct **3c**.

The synthetic application of the catalytically prepared chiral indolyl-pyrrolidines is demonstrated in Scheme 2. From the *exo*'-adduct **3c** (99% ee), a reduction using zinc nanopowder in acidic media gave the indolyl-4-amino pyrrolidine **5a** in 77% yield. A palladium-catalyzed Sonogashira coupling reaction with trimethylsilylacetylene gave 92% yield of **6a**. In both cases, the diastereo- and enantiopurity were maintained.

Conclusions

Stereochemically divergent indolyl-pyrrolidines were obtained by the imidazolidine-aminophenol (IAP)-Ni(OAc)$_2$-catalyzed *exo*'-selective asymmetric [3+2] cyclization of iminoesters with indolyl nitroalkenes, while a bis(imidazolidine)pyridine (PyBidine)-Cu(OTf)$_2$ complex catalyzed *endo*-selective [3+2] cyclization. The products, which contained *N*-heterocycles, have potential as building blocks for biologically active molecules, and the chemical library generated by diversity-oriented asymmetric catalysis (DOAC) could provide drug candidates with enhanced biological activity and target specificity. Extension of DOAC to create novel hydride molecules and

studies on the biological activity of chiral indolyl-pyrrolidines are in progress.

Experimental

General information

Dry solvents were purchased from commercial suppliers and used without further purification. Analytical thin-layer chromatography (TLC) was performed on glass plates coated with 0.25 mm 230-400 mesh silica gel containing a fluorescent indicator (Merck, #1.05715.0009). Silica gel column chromatography was performed on Kanto silica gel 60 (spherical, 100-210 μm). IR spectra were recorded on JASCO FT/IR-4100 using ATR. ^{1}H-NMR spectra were recorded on JEOL ECS-400 (400MHz), ECA-500 (500MHz), ECX-400 (400MHz) spectrometers. Chemical shifts of ^{1}H-NMR spectra were reported relative to tetramethyl silane (δ 0). ^{13}C-NMR spectra were recorded on JEOL ECS-400 (100MHz), ECA-500 (125MHz), ECX-400 (100MHz) spectrometers. Chemical shifts of ^{13}C-NMR spectra were reported relative to $CDCl_3$ (δ 77.0). Splitting patterns were reported as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

General procedure for *exo'*-selective [3+2] cycloaddition.

IAP (24 mg, 0.0315 mmol) and $Ni(OAc)_2$•$4H_2O$ (3.7 mg, 0.015 mmol) were added to a two-necked round flask containing a stir bar under Ar. MeCN (0.75 ml) was added to the flask and the mixture was stirred for 2 hours. To the resulting yellow solution, indolylnitroalkene 2 (0.15 mmol) and K_2CO_3 (3.5 mg, 0.015 mmol) were added subsequently at rt, and then iminoester 1 (0.15 mmol) was added at indicated temperature. After being stirred for appropriate time, the reaction mixture was quenched by water. The aqueous layer was extracted with ethyl acetate; the collected organic layer was dried over Na_2SO_4. After removal of the solvent under reduced pressure, the diastereomeric ratio was determined by crude ^{1}H NMR. The resulting crude mixture was purified by silica gel column chromatography to afford cycloadduct. The enantiomeric excesses of the products were determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H, OJ-H, Chiralpak AD-H, AS-H, IA, and Chiralpak IC-3 column.

***tert*-butyl (2S, 3R, 4S, 5R)-3-(1*H*-indol-3-yl)-4-nitro-5-phenylpyrrolidine-2-carboxylate (3b)**

According to the general procedure, the title compound was obtained by silica gel column chromatography (Hexane: AcOEt=3:1) as a yellow solid; ^{1}H NMR (500MHz, $CDCl_3$) δ 8.13 (br, 1H), 7.78 (d, *J*=7.85, 1H), 7.71 (dd, *J*=3.37, 5.61, 1H), 7.54-7.51 (m, 2H), 7.40-7.33 (m, 3H), 7.22 (t, 2H), 7.17 (t, 1H), 7.07 (d, *J*=2.24 Hz, 1H), 5.06 (t, 1H), 4.95 (d, *J*=7.63 Hz, 1H), 4.44 (t, 1H), 4.20 (d, *J*=5.61 Hz, 1H), 1.50 (s, 9H); ^{13}C NMR (125MHz, $CDCl_3$) δ 172.7, 139.1, 136.7, 128.8, 128.5, 126.7, 125.4, 122.6, 122.3, 120.1, 118.8, 114.2, 111.6, 97.5, 82.4, 67.1, 65.2, 47.1, 28.0; HRMS calcd for $C_{23}H_{24}N_3O_4$ $(M-H)^-$: 406.1772, found: *m/z* 406.1791; Enantiomeric excess was determined by HPLC with a Chiralpack AD-H column (90:10 hexane: 2-propanol, 1.0 mL/min, 254 nm); major enantiomer t_r =27.2 min, minor enantiomer t_r = 37.3 min; 97% ee; $[\alpha]_D^{25.5}$=-20.8 (c=1.0, $CHCl_3$, 97% ee); IR (neat) 3246, 2969, 2899, 1732, 1550, 1440, 749 cm^{-1}.

***tert*-butyl (2S, 3R, 4S, 5R) -5-(4-bromophenyl)-3-(1*H*-indol-3-yl)-4-nitro pyrrolidine-2-carboxylate (3c)**

According to the general procedure, the title compound was obtained by silica gel column chromatography (Hexane: AcOEt=3:1) as a yellow solid; ^{1}H NMR (500MHz, $CDCl_3$) ^{1}H NMR (500MHz, $CDCl_3$) δ 8.09 (br, 1H), 7.77 (d, *J*=7.85 Hz, 1H), 7.50 (d, *J*=8.53 Hz, 2H), 7.40 (d, *J*=8.53 Hz, 2H), 7.27-7.16 (m, 2H), 7.09 (d, *J*=2.47 Hz, 1H), 4.98 (t, 1H), 4.91 (d, *J*=7.63 Hz, 1H), 4.43 (t, 1H), 4.20 (d, *J*=5.16 Hz, 1H), 3.00 (s, 1H) 1.50 (s, 9H); ^{13}C NMR (125MHz, $CDCl_3$)
δ 172.8, 138.4, 136.8, 132.1, 128.6, 125.4, 122.8, 122.5, 122.4, 120.2, 118.8, 1114.0, 111.8, 97.4, 82.7, 66.5, 65.1, 47.0, 28.1; HRMS calcd for $C_{23}H_{25}BrN_3O_4$ $(M+H)^+$: 486.0846, found: *m/z* 486.0878; Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (95:5 hexane: 2-propanol, 1.0 mL/min, 254 nm); major enantiomer t_r = 47.7 min, minor enantiomer t_r = 53.1 min; 99% ee; $[\alpha]_D^{25.0}$= -5.5 (c=1.0, $CHCl_3$, 99% ee); IR (neat) 3415, 1726, 1550, 1487, 1369 cm^{-1}.

***tert*-butyl (2S, 3R, 4S, 5R) -5-(4-chloroophenyl)-3-(1*H*-indol-3-yl)-4-nitro pyrrolidine-2-carboxylate (3d)**

According to the general procedure, the title compound was obtained by silica gel column chromatography (Hexane: AcOEt=3:1) as a yellow solid; ^{1}H NMR (500MHz, $CDCl_3$) δ 8.12 (br, 1H), 7.77 (d, *J*=7.85 Hz, 1H), 7.46 (d, 8.53 Hz, 1H), 7.40-7.33 (m, 3H), 7.27-7.23 (m, 1H), 7.18 (t, 1H), 7.08 (d, *J*=2.47 Hz, 1H), 4.99 (t, 1H), 4.93 (d, *J*=7.63 Hz, 1H), 4.43 (t, 1H), 4.21 (d, J=5.16 Hz, 1H), 3.02 (br, 1H), 1.48 (s, 9H); ^{3}C NMR (125MHz, $CDCl_3$)
δ 172.7, 137.7, 136.7, 134.3, 129.0, 128.1, 125.3, 122.7, 122.3, 120.1, 118.7, 114.0, 111.6, 97.3, 82.5, 66.3, 65.0, 46.9, 28.0; HRMS calcd for $C_{23}H_{25}ClN_3O_4$ $(M+H)^+$: 440.1383, found: *m/z* 440.1404; Enantiomeric excess was determined by HPLC with a Chiralpack IC-3 column (90:10 hexane: 2-propanol, 1.0 mL/min, 254 nm); major enantiomer t_r = 6.9 min, minor enantiomer t_r = 5.9 min; 96% ee; $[\alpha]_D^{24.8}$= -13.5 (c=0.5, $CHCl_3$, 96% ee); IR (neat) 3416, 2919, 1726, 1550, 1458, 1369, 798, 747 cm^{-1}.

***tert*-butyl (2S, 3R, 4S, 5R) -3- (1*H*-indol-3-yl)-5-(4-methoxylphenyl)-4-nitro pyrrolidine-2-carboxylate (3e)**

According to the general procedure, the title compound was obtained by silica gel column chromatography (Hexane: AcOEt=3:1) as a yellow solid; ^{1}H NMR (500MHz, $CDCl_3$) δ 8.11 (br, 1H), 7.81 (d, *J*=7.70 Hz, 1H), 7.41 (dd, *J*=16.08, 8.04 Hz, 2H), 7.39 (d, 1H), 7.27-7.16 (m, 2H), 7.09 (d, *J*=2.27 Hz, 1H), 6.90 (d, *J*=8.61 Hz, 1H), 5.03 (t, 1H), 4.88 (d, *J*=7.70 Hz, 1H), 4.43(t, 1H), 4.19 (d, *J*=5.21 Hz, 1H), 3.81 (s, 3H), 2.95 (br, 1H), 1.49(s, 9H); ^{13}C NMR (125MHz, $CDCl_3$)
δ 172.8, 159.8. 136.8, 131.0, 128.1, 125.5, 122.8, 122.4, 120.2, 119.0, 114.4, 114.3, 111.7, 97.6, 82.4, 66.9, 65.1, 55.4, 46.9, 28.1; HRMS calcd for $C_{27}H_{26}N_3O_4$ $(M-H)^-$: 436.1878, found: *m/z* 436.1897; Enantiomeric excess was determined by HPLC with a Chiralpack AS-H column (80:20 hexane: 2-propanol, 1.0 mL/min, 254 nm); major enantiomer t_r = 19.9 min, minor enantiomer t_r = 10.2 min;

96% ee; $[\alpha]_D^{25.6}$=+0.43 (c=0.25 , $CHCl_3$, 99% ee); IR (neat) 3400, 2918, 1725, 1613, 1550, 1514, 1458, 1368, 874 cm^{-1}.

tert-butyl (2S, 3R, 4S, 5R)-3-(1_H_-indol-3-yl)-4-nitro-5-(_p_-tolyl)pyrrolidine-2-carboxylate (3f)

According to the general procedure, the title compound was obtained by silica gel column chromatography (Hexane: AcOEt=3:1) as a yellow solid; ^{1}H NMR (500MHz, $CDCl_3$) δ 8.14 (br, 1H), 7.79 (d, _J_=7.85 Hz, 1H), 7.40-7.35 (m, 3H), 7.23-7.14 (m, 4H), 7.05 (d, _J_=2.02 Hz, 1H), 5.05 (t, 1H), 4.91 (d, _J_=7.85 Hz, 1H), 4.44 (t, 1H), 4.19 (d, _J_=5.39 Hz, 1H), 2.96 (br, 1H), 2.34 (s, 3H), 1.48 (s, 9H); ^{13}C NMR(125MHz,$CDCl_3$)
δ 172.2, 139.1, 136.7, 128.8, 128.5, 126.7, 125.4, 122.6, 122.3, 120.1, 118.8, 114.2, 111.6, 97.5, 82.4, 67.1, 65.2, 47.1, 28.0; HRMS calcd for $C_{24}H_{26}N_3O_4$ (M-H)$^-$: 420.1929, found: _m/z_ 420.1951; Enantiomeric excess was determined by HPLC with a Chiralpack AD-H column (90:10 hexane: 2-propanol, 1.0 mL/min, 254 nm); major enantiomer t_r =16.7 min, minor enantiomer t_r = 45.7 min; 97% ee; $[\alpha]_D^{25.6}$= -15.5 (c=1.0, $CHCl_3$, 97% ee) ;IR (neat) 3415, 2919, 1725, 1550, 1457 cm^{-1}.

tert-butyl (2S, 3R, 4S, 5R)-3-(1_H_-indol-3-yl)-4-nitro-5-(_m_-tolyl)pyrrolidine-2-carboxylate (3g)

According to the general procedure, the title compound was obtained by silica gel column chromatography (Hexane: AcOEt=3:1) as a yellow solid; ^{1}H NMR (500MHz, $CDCl_3$) δ 8.12 (br, 1H), 7.79 (d, _J_=7.85 Hz, 1H), 7.38 (d, _J_=7.85 Hz, 1H), 7.31 (s, 2H), 7.28-7.22 (m, 2H), 7.19-7.13 (m, 2H), 7.07 (d, _J_=1.80, 1H), 5.07 (t, 1H), 4.92 (d, _J_=4.92 Hz, 1H), 4.44 (t, 1H), 4.20 (d, _J_=5.39, 1H); ^{13}C NMR (125MHz, $CDCl_3$)
δ 172.7, 138.9, 138.5, 136.6, 129.3, 128.7, 127.4, 123.7, 122.6, 122.3, 120.0, 118.8, 114.1, 111.6, 97.4, 82.3, 67.1, 65.2, 47.1, 28.0, 21.4; HRMS calcd for $C_{24}H_{26}N_3O_4$ (M-H)$^-$: 420.1929, found: _m/z_ 420.1951; Enantiomeric excess was determined by HPLC with a Chiralpack AD-H column (80:20 hexane: 2-propanol, 1.0 mL/min, 254 nm); major enantiomer t_r =8.75 min, minor enantiomer t_r = 11.5 min; 97% ee; $[\alpha]_D^{20.6}$= -14.9 (c=1.0, $CHCl_3$, 97% ee); IR (neat) 3420, 2918, 1726, 1550, 1458, 1369, 748, 701 cm^{-1}.

tert-butyl (2S, 3R, 4S, 5R)-3-(1_H_-indol-3-yl)-4-nitro-5-(_o_-tolyl)pyrrolidine-2-carboxylate (3h)

According to the general procedure, the title compound was obtained by silica gel column chromatography (Hexane: AcOEt=3:1) as a yellow solid; ^{1}H NMR (500MHz, $CDCl_3$) δ 8.09 (br, 1H), 7.80 (d, _J_= 8.08 Hz, 1H), 7.73 (d, _J_=7.41, 2H), 7.40 (d, _J_=8.08, 1H), 7.27-7.15 (m, 5H), 7.10 (d, _J_=2.47, 1H), 5.26 (d, _J_=7.41, 1H), 5.12 (t, 1H), 4.45 (t, 1H), 4.25 (d, 4.24, 1H), 3.00 (br, 1H), 2.34(s, 3H), 1.50 (s, 9H); ^{13}C NMR (125MHz, $CDCl_3$)
δ 172.7, 136.9, 136.7, 136..5, 130.8, 128.1, 126.5, 126.3, 125.4, 122.6, 122.3, 120.1, 1118.9, 114.3, 111.6, 96.8, 82.3, 65.4, 63.3, 47.6, 28.0, 19.2; HRMS calcd for $C_{24}H_{26}N_3O_4$ (M+H)$^-$: 420.1918, found: _m/z_ 420.1946; Enantiomeric excess was determined by HPLC with a Chiralpack AD-H column (80:20 hexane: 2-propanol, 1.0 mL/min, 254 nm); major enantiomer t_r = 7.75 min, minor enantiomer t_r = 9.30 min; 98% ee; $[\alpha]_D^{24.6}$= -23.8 (c=1.0, $CHCl_3$, 98% ee)); IR (neat) 3279, 2971, 1721, 1544, 1457, 1366 cm^{-1}.

tert-butyl (2S, 3R, 4S, 5R) -3- (1_H_-indol-3-yl)-5-(naphthalene-2-yl)-4-nitro pyrrolidine-2-carboxylate (3i)

According to the general procedure, the title compound was obtained by silica gel column chromatography (Hexane: AcOEt=3:1) as a yellow solid; ^{1}H NMR (500MHz, $CDCl_3$) δ 8.11 (br, 1H), 7.96 (s, 1H), 7.87-7.80 (m, 2H), 7.64 (dd, _J_=8.61 Hz, 1.59 Hz, 1H), 7.50-7.47 (m, 1H), 7.37-7.35 (d, _J_=8.15 Hz, 1H), 7.23-7.15 (m, 2H), 7.05 (d, _J_=2.04 Hz, 1H), 5.16 (m, 2H), 4.50 (t, 1H), 4.27 (d, _J_=5.44 Hz, 1H), 3.15 (s, 1H), 1.50 (s, 9H); ^{13}C NMR (125MHz, $CDCl_3$) δ 172.7, 136.5, 133.3, 128.8, 128.1, 127.7, 126.3, 126.2, 126.1, 125.4, 124.1, 122.6, 122.3, 120.1, 118.8, 114.1, 111.6, 97.4, 82.4, 67.3, 65.3, 47.2, 28.0; HRMS calcd for $C_{27}H_{26}N_3O_4$ (M-H)$^-$: 456.1918, found: _m/z_ 456.1947; Enantiomeric excess was determined by HPLC with a Chiralpack AD-H column (80:20 hexane: 2-propanol, 1.0 mL/min, 254 nm); major enantiomer t_r = 13.7 min, minor enantiomer t_r = 17.3 min; 97% ee; $[\alpha]_D^{25.4}$= -1.1 (c=1.0, $CHCl_3$, 97% ee); IR (neat) 2919, 1722, 1548, 1367 cm^{-1}.

tert-butyl (2S, 3R, 4S, 5R) -3-(1-benzyl-1_H_-indol-3-yl)-5-(4-bromophenyl)-4-nitro pyrrolidine-2-carboxylate (3j)

According to the general procedure, the title compound was obtained by silica gel column chromatography (Hexane: AcOEt=5:1) as a yellow solid; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.74 (d, _J_=7.63 Hz, 1H), 7.48 (d, _J_=8.30 Hz, 2H), 7.38 (d, _J_=8.53 Hz, 2H), 7.31-7.27 (m, 5H), 7.24-7.14 (m, 1H), 7.08 (m, 2H), 7.0 (s, 1H), 5.27 (d, _J_=7.18 Hz, 2H), 4.98 (t, 1H), 4.92 (d, _J_=7.41 Hz 1H), 4.41 (t, 1H), 4.21 (d, _J_=5.16 z, 1H), 3.00 (br, 1H), 1.46(s, 9H); ^{13}C NMR (125MHz, $CDCl_3$) δ 172.7, 138.4, 137.1, 137.0, 131.9, 128.8, 128.4, 127.8, 126.8, 126.3, 126.0, 122.4, 122.4, 119.9, 118.9, 112.9, 110.2, 97.3, 82.5, 66.3, 65.0, 50.0, 46.9, 28.0; HRMS calcd for $C_{27}H_{26}N_3O_4$ (M-H)$^-$: 574.1347, found: _m/z_ 574.1377; Enantiomeric excess was determined by HPLC with a Chiralpack AD-H column (80:20 hexane: 2-propanol, 1.0 mL/min, 254 nm); major enantiomer t_r =10.7 min, minor enantiomer t_r = 13.4 min; 81% ee; $[\alpha]_D^{25.5}$= -1.2 (c=0.5, $CHCl_3$, 81% ee); IR (neat) 3288, 2972, 1723, 1547, 1365, 821, 1 cm^{-1}.

tert-butyl (2S, 3R, 4S, 5R) -3-(1-benzoyl-1_H_-indol-3-yl)-5-(4-bromophenyl)-4-nitro

pyrrolidine-2-carboxylate (3k)

According to the general procedure, the title compound was obtained by silica gel column chromatography (Hexane: AcOEt=5:1) as a yellow solid; ^{1}H NMR (500MHz, $CDCl_3$) δ 8.41 (d, _J_=8.08 Hz, 1H), 7.79 (d, _J_=7.41 Hz, 1H), 7.69-7.64 (m, 3H), 7.54 (t, 2H), 7.48-7.35 (m, 6H), 7.17 (s, 1H), 4.90 (d, _J_=5.16 Hz, 2H), 4.36 (t, 1H), 4.13 (d, 1H), 2.96 (br, 1H), 1.50 (s, 9H); ^{13}C NMR (125MHz, $CDCl_3$) δ 172.2, 168.4, 137.9, 136.9, 134.2, 132.3, 132.1, 129.2, 128.8, 128.5, 128.4, 125.9, 125.3, 124.4, 122.7, 119.8, 119.0, 117.1, 96.1, 83.0, 66.3, 64.6, 45.8, 28.1; HRMS calcd for $C_{27}H_{26}N_3O_4$ (M-H)$^-$: 588.1140, found: _m/z_ 588.1166; Enantiomeric excess was determined by HPLC with a Chiralpack AD-H column (80:20

hexane: 2-propanol, 1.0 mL/min, 254 nm); major enantiomer t_r =12.1 min, minor enantiomer t_r = 15.3 min; 99% ee; $[\alpha]_D^{25.5}$= +21.0 (c=1.0, $CHCl_3$, 99% ee); IR (neat) 2969, 1728, 1550, 1452, 1363 cm^{-1}.

tert-butyl (2S,3R,4S,5R)-5-(4-bromophenyl)-3-(1*H*-indol-2-yl)-4-nitro pyrrolidine-2-carboxylate(3l)

According to the general procedure, the title compound was obtained by silica gel column chromatography (Hexane: AcOEt=3:1) as a yellow solid; ^{1}H NMR (500MHz, $CDCl_3$) δ 8.65 (br, 1H), 7.56-7.49 (m, 3H), 7.38-7.31 (m, 4H), 7.24-7.16 (m, 1H), 7.17-7.08 (m, 1H), 6.39 (d, *J*=2.21 Hz, 1H), 4.97 (t, 1H), 4.88 (d, *J*=6.96 Hz, 1H), 4.43 (t, 1H), 4.11 (d, *J*=4.94 Hz, 1H), 3.03 (br, 1H), 1.59 (br, 1H); ^{13}C NMR (125MHz, $CDCl_3$) δ 202.6, 168.4, 167.2, 166.7, 163.1, 159.3, 158.8, 153.7, 153.4, 151.5, 151.2; HRMS calc for $C_{27}H_{26}N_3O_4$ $(M-H)^-$: 484.0877, found: *m/z* 484.0905; Enantiomeric excess was determined by HPLC with a Chiralpack AD-H column (95:5 hexane: 2-propanol, 0.7 mL/min, 254 nm); major enantiomer t_r =13.0 min, minor enantiomer t_r = 17.8 min; 99% ee; $[\alpha]_D^{25.3}$= -12.9 (c=1.0, $CHCl_3$,99% ee); IR (neat) 1725, 1551, 1456, 1341, 819 cm^{-1}.

tert-butyl (2S, 3R, 4S, 5R) -5- (4-bromophenyl)-3-(5-methoxy-1*H*-indol-3-yl)-4-nitro pyrrolidine-2-carboxylate (3m)

According to the general procedure, the title compound was obtained by silica gel column chromatography (Hexane: AcOEt=3:1) as a yellow solid; ^{1}H NMR (500MHz, $CDCl_3$) δ 8.21 (br, 1H), 7.88 (d, *J*=1.57 Hz, 1H), 7.51 (d, *J*=8.53 Hz, 2H), 7.39 (d, *J*= 8.30 Hz, 2H), 7.30 (dd, *J*=8.53, 1.80 Hz, 1H), 7.18 (d. *J*=3.59 Hz, 1H), 6.96 (d, *J*=2.24 Hz, 1H), 4.85 (d, *J*=5.39 Hz, 2H), 4.31 (t, 1H), 4.03 (d, *J*=4.94 Hz, 1H), 2.93 (br, 1H), 1.43 (s, 9H), ^{13}C NMR (125MHz, $CDCl_3$) δ 172.5, 154.3, 138.4, 131.9, 131.7, 128.3, 125.6, 122.9, 122.4, 113.6, 112.8, 112.4, 100.4, 97.3, 82.5, 66.3, 65.0, 55.8, 47.2, 28.0, HRMS calcd for $C_{27}H_{26}N_3O_4$ $(M-H)^-$: 514.0983 , found: *m/z* 514.1006; Enantiomeric excess was determined by HPLC with a Chiralpack AD-H column (80:20 hexane: 2-propanol, 1.0 mL/min, 254 nm); major enantiomer t_r =14.1 min, minor enantiomer t_r = 26.4 min; 98% ee; $[\alpha]_D^{25.4}$= -12.5 (c=0.5, $CHCl_3$, 98% ee); IR (neat) 1721, 1546, 1485, 1367, 626 cm^{-1}.

tert-butyl (2S, 3R, 4S, 5R) -5-(4-bromophenyl)-3-(7-methyl-1*H*-indol-3-yl)-4-nitro pyrrolidine-2-carboxylate (3n)

According to the general procedure, the title compound was obtained by silica gel column chromatography (Hexane: AcOEt=3:1) as a yellow solid; ^{1}H NMR (500MHz, $CDCl_3$) δ 8.04 (br, 1H), 7.61 (d, *J*=7.85 Hz, 1H), 7.49 (d, *J*=8.53 Hz, 2H), 7.39 (d, *J*=8.30 Hz, 2H), 7.12-7.04 (m, 3H), 4.98 (t, 1H), 4.91 (d, *J*=7.63 Hz, 1H), 4.41 (t, 1H), 4.20 (d, *J*=4.94 Hz, 1H), 2.98 (br, 1H), 2.48 (3H), 1.48 (s, 9H) ; ^{13}C NMR (125MHz, $CDCl_3$) δ 172.7, 138.2, 131.9, 128.5, 124.7, 123.2, 122.0, 120.9, 120.4, 116.4, 114.4, 97.2, 82.5, 66.4, 64.9, 47.0, 28.0, 16.6; HRMS calcd for $C_{27}H_{26}N_3O_4$ $(M-H)^-$: 498.1023, found: *m/z* 498.1056; Enantiomeric excess was determined by HPLC with a Chiralpack AD-H column (80:20 hexane: 2-propanol, 1.0 mL/min, 254 nm); major enantiomer t_r =9.4 min, minor enantiomer t_r = 30.0 min; 97% ee; $[\alpha]_D^{25.1}$= -8.8 (c=1.0, $CHCl_3$, 97% ee); IR (neat) 2918, 1725, 1549, 1487, 1368, 627 cm^{-1}.

tert-butyl (2S, 3R, 4S, 5R) -5- (4-bromophenyl)-3-(5-methyl-1*H*-indol-3-yl)-4-nitro pyrrolidine-2-carboxylate (3o)

According to the general procedure, the title compound was obtained by silica gel column chromatography (Hexane: AcOEt=3:1) as a yellow solid; ^{1}H NMR (500MHz, $CDCl_3$) δ 8.02 (br, 1H), 7.51 (d, *J*=8.61 Hz, 2H), 7.43 (m, 1H), 7.41 (d, *J*=8.61 Hz, 2H), 7.27 (m, 1H), 7.05 (d, 1H), 7.01 (d, *J*=7.82 Hz, 1H), 5.01 (t, 1H), 4.93 (d, *J*=7.25, 1H), 4.40 (t, 1H), 4.17 (d, *J*=5.44 Hz, 1H), 3.00 (br, 1H), 2.45 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (125MHz, $CDCl_3$) δ 172.6, 138.5, 135.0, 132.0, 129.4, 128.4, 125.5, 124.3, 122.4, 122.3, 118.3, 113.4, 111.3, 97.4, 82.5, 66.4, 65.2, 47.2, 28.0, 21.6; HRMS calcd for $C_{27}H_{26}N_3O_4$ $(M-H)^-$: 498.1034, found: *m/z* 498.1061; Enantiomeric excess was determined by HPLC with a Chiralpack OD-H column (80:20 hexane: 2-propanol, 1.0 mL/min, 254 nm); major enantiomer t_r =9.65 min, minor enantiomer t_r =11.5 min; 98% ee; $[\alpha]_D^{25.7}$= -8.6 (c=1.0, $CHCl_3$, 98% ee); IR (neat) 3412, 1724, 1549, 1487, 1368, 627 cm^{-1}.

tert-butyl (2S, 3R, 4S, 5R) -3-(5-bromo-1*H*-indol-3-yl)-5-(4-bromopheny)-4-nitro pyrrolidine-2-carboxylate (3p)

According to the gener.lal procedure, the title compound was obtained by silica gel column chromatography (Hexane: AcOEt=3:1) as a yellow solid; ^{1}H NMR (500MHz, $CDCl_3$) δ 8.14 (br, 1H), 7.81 (d, *J*=1.57 Hz, 1H), 7.44 (d, *J*=8.53 Hz, 2H), 7.32 (d, *J*=8.30 Hz, 2H), 7.24 (dd, *J*=8.53 Hz, 1.80 Hz, 1H), 7.17 (d, *J*=3.59 Hz, 1H), 6.74 (d, *J*=2.24Hz , 1H), 4.85 (d, *J*=7.63, 2H), 4.31 (t, 1H), 4.04 (d, *J*=4.94, 1H), 2.94 (br, 1H), 1.43 (s, 9H); ^{13}C NMR (125MHz, $CDCl_3$) δ 172.3, 138.1, 135.2, 132.0, 128.3, 127.0, 125.6, 123.3, 122.5, 121.4, 113.9, 113.4, 113.1, 97.2, 82.8, 66.3, 65.3, 46.6, 28.0, HRMS calcd for $C_{27}H_{28}N_3O_4$ $(M-H)^+$: 563.9962, found: *m/z* 563.9984; Enantiomeric excess was determined by HPLC with a Chiralpack OD-H column (80:20 hexane: 2-propanol, 1.0 mL/min, 254 nm); major enantiomer t_r =10.2 min, minor enantiomer t_r = 16.2 min; 91% ee; $[\alpha]_D^{24.5}$= -4.6 (c=1.0, $CHCl_3$, 91% ee); IR (neat) 2974, 1729, 1547, 1453, 1365 cm^{-1}.

General procedure for *endo*-selective [3+2] cycloaddition

PyBidine (7.7 mg, 0.011 mmol) and $Cu(OTf)_2$ (3.6 mg, 0.01 mmol) were added to a two-necked round flask containing a stir bar under Ar. CH_2Cl_2 (1.0 ml) was added to the flask and the mixture was stirred for 2 hours. After removal of the solvent under reduced pressure, anhydrous 1,4-dioxane (1 mL) was added. To the resulting solution, indolylnitroalkene **2** (0.2 mmol), Cs_2CO_3 (6.5 mg, 0.02 mmol), and iminoester **1** (0.22 mmol) were added subsequently at rt. After being stirred for appropriate time, the reaction mixture was quenched by water. The aqueous layer was extracted with ethyl acetate; the collected organic layer was dried over Na_2SO_4. After removal of the solvent under reduced pressure, the diastereomeric ratio was determined by crude ^{1}H NMR. The resulting crude mixture was purified by silica gel column chromatography to afford cycloadduct. The enantiomeric excesses of the products were determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column.

Methyl (2*S*,3*R*,4*S*,5*S*)-3-(1*H*-indol-3-yl)-4-nitro-5-phenylpyrrolidine-2-carboxylate (4a)

According to the general procedure, the title compound was obtained by silica gel column chromatography (Hexane: AcOEt=2:1) as a yellow solid; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.29 (br, 1H), 7.59 (d, *J*=7.70 Hz, 1H), 7.42 (d, *J*=8.15 Hz, 1H), 7.35-7.33 (m, 5H), 7.29 (d, *J*=8.15 Hz, 1H), 7.21-7.17 (m, 2H), 5.36 (dd, *J*=2.72, 6.12 Hz, 1H), 4.91 (d, *J*=5.56 Hz, 1H), 4.53 (dd, *J*=2.49, 6.68 Hz, 1H), 4.39 (d, *J*=6.57 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 172.2, 136.6, 134.2, 128.7, 128.6, 126.3, 125.8, 123.0, 121.9, 120.3, 118.4, 113.3, 111.7, 96.1, 67.2, 65.4, 52.7, 48.1; HRMS calcd for $C_{20}H_{20}O_4N_3$ $(M+H)^+$: 366.1448 found: *m/z* 406.1444; Enantiomeric excess was determined by HPLC with a Chiralpack OD-H column (80:20 hexane: 2-propanol, 1.0 mL/min, 254 nm); major enantiomer t_r =20.7 min, minor enantiomer t_r = 46.2 min; 97% ee; $[\alpha]_D^{24.0}$=-4.76 (c=0.1, $CHCl_3$, 97% ee); IR (neat) 3411, 1729, 1547,1458, 1371, 744 cm^{-1}.

Methyl (2*S*,3*R*,4*S*,5*S*)-3-(1*H*-indol-3-yl)-4-nitro-5-(*p*-tolyl)pyrrolidine-2-carboxylate (4b)

According to the general procedure, the title compound was obtained by silica gel column chromatography (Hexane: AcOEt=2:1) as a yellow solid; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.29 (br, 1H), 7.59 (d, *J*=7.70 Hz, 1H), 7.42 (d, *J*=8.15 Hz 1H), 7.28 (d, *J*=7.14 Hz 1H), 7.21 (m, 4H), 7.15 (d, *J*=8.15 Hz, 2H), 5.33 (dd, *J*=2.72, 6.12 Hz, 1H), 4.83 (s, 1H), 4.52 (dd, *J*=2.49, 6.80 Hz 1H), 4.38 (s, 1H), 3.81 (s,3H), 3.47 (br,1H), 2.32 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 172.2, 138.4, 136.6, 131.1, 129.4, 126.1, 125.8, 123.0, 121.9, 120.3, 118.5, 113.4, 111.7, 96.2, 67.1, 65.4, 52.7, 48.1, 21.1; HRMS calcd for $C_{21}H_{21}N_3O_4$ $(M+H)^+$: 380.1605, found: *m/z* 380.16; Enantiomeric excess was determined by HPLC with a Chiralpack OD-H column (70:30 hexane: 2-propanol, 0.7 mL/min, 254 nm); major enantiomer t_r =21.5 min, minor enantiomer t_r = 26.2 min; 74% ee; $[\alpha]_D^{24.2}$=-9.91 (c=0.2, $CHCl_3$, 74% ee); IR (neat) 3413, 1739, 1549, 1457, 1339, 1212 743 cm^{-1}.

Methyl (2*S*,3*R*,4*S*,5*S*)-5-(4-bromophenyl)-3-(1*H*-indol-3-yl)-4-nitropyrrolidine-2-carboxylate (4c)

According to the general procedure, the title compound was obtained by silica gel column chromatography (Hexane: AcOEt=2:1) as a yellow solid; ^{1}H NMR (500MHz, $CDCl_3$) δ 8.26 (br, 1H), 7.58 (d, *J*=7.93 Hz, 1H), 7.48 (d, *J*=8.61 Hz, 2H), 7.43 (d, *J*=8.15 Hz, 1H), 7.31-7.27 (m, 1H), 7.25-7.17 (m, 4H), 5.35 (dd, *J*=2.94, 6.12 Hz, 1H), 4.86 (t, *J*=4.53 Hz, 1H), 4.53 (dd, *J*=2.49, 6.80 Hz, 1H), 4.38 (t, *J*=5.21 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (125MHz, $CDCl_3$) δ 172.0, 136.6, 133.5, 131.9, 128.1, 125.7, 123.1, 122.7, 121.9, 120.4, 118.4, 113.1, 111.8, 95.7 66.5, 65.2, 52.8, 47.9; HRMS calcd for $C_{20}H_{18}N_3O_4Br$ $(M-H)^-$: 442.0408, found: *m/z* 442.0425; Enantiomeric excess was determined by HPLC with a Chiralpack OD-H column (70:30 hexane: 2-propanol, 1.0 mL/min, 254 nm); major enantiomer t_r =13.6 min, minor enantiomer t_r = 17.0 min; 79% ee; $[\alpha]_D^{24.3}$=-9.83 (c=0.1, $CHCl_3$, 79% ee); IR (neat) 2951, 1737, 1543, 1437, 1257, 1088, 887, 741 cm^{-1}.

Methyl (2*S*,3*R*,4*S*,5*S*)-3-(5-bromo-1*H*-indol-3-yl)-4-nitro-5-phenylpyrrolidine-2-carboxylate (4d)

According to the general procedure, the title compound was obtained by silica gel column chromatography (Hexane: AcOEt=2:1) as a yellow solid; ^{1}H NMR (500MHz, $CDCl_3$) δ 8.34 (br, 1H), 7.72 (d, *J*=1.59, 1H), 7.39-7.32 (m, 6H), 7.29 (d, *J*=8.83 Hz, 1H), 7.22 (d, *J*=2.27 Hz, 1H), 5.32 (dd, *J*=3.40, 6.23 Hz, 1H), 4.92 (d, *J*=6.12 Hz, 1H), 4.48 (dd, *J*=3.17, 6.68 Hz, 1H), 4.32 (d, *J*=6.80 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (125MHz, $CDCl_3$) δ 172.0, 135.2, 134.2, 128.8, 128.7, 127.6, 127.5, 126.4, 126.0, 123.1, 121.1, 113.6, 113.1, 95.8, 67.2, 65.6, 52.8, 47.5; HRMS calcd for $C_{20}H_{18}N_3O_4Br$ $(M-H)^-$: 442.0408, found: *m/z* 442.0428; Enantiomeric excess was determined by HPLC with a Chiralpack OD-H column (80:20 hexane: 2-propanol, 1.0 mL/min, 254 nm); major enantiomer t_r =25.6 min, minor enantiomer t_r = 49.7 min; 75% ee; $[\alpha]_D^{24.4}$=-9.84 (c=0.1, $CHCl_3$, 75% ee); IR (neat) 2953, 1739, 1544, 1457, 1435, 1371, 1258, 1211, 892, 861, 698 cm^{-1}.

***tert*-butyl (2*S*,3*S*,4*S*,5*R*)-4-amino-5-(4-bromophenyl)-3-(1*H*-indol-3-yl)pyrrolidine-2-carboxylate (5a)**

3c (48.6mg, 0.1 mmol) and *t*BuOH (0.9 mL) was added to flask. To the solution, 2 mmol of Zn (nanopowder, purchased from Sigma Aldrich) was added at room temperature. A mixture of 1N aq. HCl (600 μL) and AcOH (300 μL) was added to the solution and stirred for 30 minutes. After removal of insoluble residue by a filtration, the filtrate was concentrated by rotary evaporator. $CHCl_3$ was added to the flask and neutralized by aq. $NaHCO_3$. The mixture was extracted with $CHCl_3$ (10 mL x 3) and combined organic layer was dried over Na_2SO_4. The combined organic layers were concentrated in vacuo to give crude mixture. The crude mixture was purified by flash silica gel column chromatography ($CHCl_3$: MeOH =50 : 1) to afford **5a** (35mg, 77%) as white powder.; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.25 (br, 1H), 7.84 (d, *J*=7.70, 1H), 7.48 (dd, *J*=7.70, 8.38, 4H), 7.37 (d, *J*=7.93, 1H), 7.22 (t, *J*=7.02, 1H), 7.15 (t, *J*=7.02, 1H), 7.11 (s, 1H), 4.18 (d, *J*=7.70, 1H), 4.04 (d, *J*=8.83, 1H), 3.45 (t, *J*=9.01, 1H), 4.19 (q, *J*=7.70, 1H), 1.72 (br, 2H), 1.37 (s, 9H); ^{13}C NMR (125MHz, $CDCl_3$) δ 174.7, 141.2, 136.8, 131.6, 128.8, 126.0, 122.23, 122.16, 121.2, 119.4, 119.3, 115.0, 111.5, 81.3, 69.0, 65.9, 63.9, 50.8, 28.0; HRMS calcd for $C_{23}H_{27}N_3O_2Br$ $(M+H)^+$: 456.1281, found: *m/z* 456.1271; Enantiomeric excess was determined by HPLC with a Chiralpack AD-H column (70:30 hexane: 2-propanol, 1.0 mL/min, 254 nm); major enantiomer t_r =6.3 min, minor enantiomer t_r = 11.6 min; 99% ee; $[\alpha]_D^{21.6}$=-13.1 (c=0.5, CH_2Cl_2, 99% ee); IR (neat) 3402, 2977, 2925, 1716, 1155, 740 cm^{-1}.

***tert*-butyl (2*S*,3*R*,4*S*,5*R*)-3-(1*H*-indol-3-yl)-4-nitro-5-(4-((trimethylsilyl)ethynyl)phenyl) pyrrolidine-2-carboxylate (6a)**

To a suspension of **3c** (20 mg, 0.041 mmol), $Pd(PPh_3)_2Cl_2$ (2.9 mg, 0.0041 mmol), and CuI (0.4 mg, 0.0021 mmol) in Et_3N (0.2 mL), trimethylsilylacetylene (9 μL, 0.062 mmol) was added under Ar. The reaction mixture was stirred for 10 hours at 50 °C under Ar. Additional trimethylsilylacetylene (9 μL, 0.062 mmol) was added and the mixture was stirred for 6 hours at 50 °C. The resulting mixture was cooled to room temperature, quenched with water, and the organic layer was separated. The aqueous layer was extracted

twice with $CHCl_3$. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated in vacuo to give crude mixture. The mixture was purified by column chromatography (Hexane: AcOEt=10:1 to 4:1) to afford **6a** (19 mg, 92%) as a orange oil.; ^{1}H NMR (500MHz, $CDCl_3$) δ 8.12 (br, 1H), 7.75 (d, *J*=7.76, 1H), 7.47 (d, *J*=9.16, 1H), 7.44 (d, *J*=8.92, 1H), 7.37 (d, *J*=8.24, 1H), 7.15-7.26 (m, 2H), 7.02 (d, *J*=2.52, 1H), 5.01 (t, *J*=7.32, 1H), 4.94 (d, *J*=7.32, 1H), 4.43 (t, *J*=6.64, 1H), 4.19 (d, *J*=5.28, 1H), 3.06 (br, 1H), 1.48 (s, 9H), 0.25 (s, 9H); ^{13}C NMR (125MHz, $CDCl_3$) δ 172.6, 139.6, 136.6, 132.4, 126.6, 125.3, 123.3, 122.7, 122.2, 120.1, 118.7, 114.0, 111.6, 104.6, 97.3, 94.8, 82.5, 66.7, 65.2, 47.2, 28.0, -0.1; HRMS calcd for $C_{28}H_{34}N_3O_4Si$ $(M+H)^+$: 504.2313, found: *m/z* 504.2311; Enantiomeric excess was determined by HPLC with a Chiralpack AD-H column (80:20 hexane: 2-propanol, 1.0 mL/min, 254 nm); major enantiomer t_r =6.1 min, minor enantiomer t_r = 15.9 min; 99% ee; $[\alpha]_D^{21.6}$=+2.2 (c=0.5, CH_2Cl_2, 99% ee); IR (neat) 3415, 2958, 2931, 2156, 1725, 1550, 1158, 841, 740 cm^{-1}.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology (Japan), and by the Workshop on Chirality in Chiba University (WCCU).

Notes and references

‡ Footnotes relating to the main text should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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