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Synthesis of Highly Functionalized Chiral Benzopyrano[3,4-*c*]pyrrolidines Bearing Five Contiguous Stereogenic Centers

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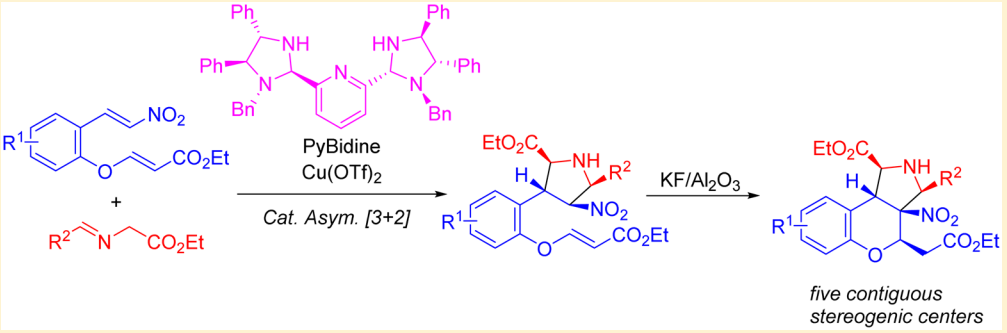
Supporting Information



ABSTRACT: A chiral bis(imidazolidine)pyridine-Cu complex smoothly catalyzed the asymmetric [3 + 2] cycloaddition reaction of α,β-unsaturated ester-containing nitroalkenes with imino esters to give *endo*-pyrrolidine products in a highly enantioselective manner while maintaining the α,β-unsaturated ester functionality. Subsequent intramolecular diastereoselective cyclizations of the obtained pyrrolidine products were accomplished by treatment with KF/Al_2O_3 in toluene/EtOH (4:1) to give highly functionalized benzopyrano[3,4-*c*]pyrrolidines bearing five contiguous stereogenic centers.

Benzopyrano[3,4-*c*]pyrrolidine is a unique and important core structure in medicinal chemistry (Figure 1). For example, S33138, a dopamine-D3-receptor antagonist, has a *trans*-benzopyrano[3,4-*c*]pyrrolidine framework as the pharmacophore.[1] Abbott Corporation, Ltd., adopted the *cis*-benzopyrano[3,4-*c*]pyrrolidine framework to develop Fiduxosin as an α1-adrenoceptor antagonist.[2]

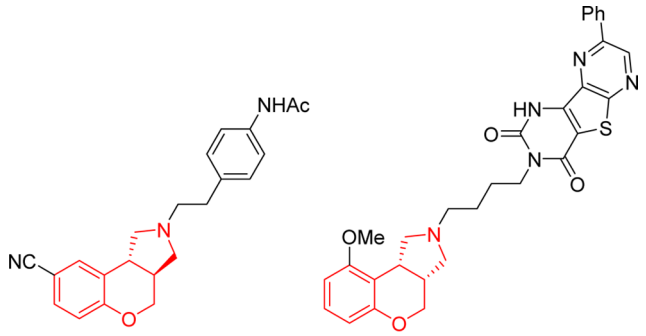


Figure 1. Biologically important chiral benzopyrano[3,4-*c*]pyrrolidine derivatives.

Despite the crucial role of benzopyrano[3,4-*c*]pyrrolidines in medicinal chemistry, there are a limited number of catalytic asymmetric synthetic methods to prepare benzopyrano[3,4-*c*]pyrrolidine derivatives.[1b,2b] For example, in 2012, Enders et al. reported a short and highly stereoselective synthesis of a decyano derivative of S33138 via a catalytic asymmetric domino oxa-Michael/Michael reaction of nitrovinylphenol with acrolein.[3] Considering their fascinating structure and bioactivity, further diversified benzopyrano[3,4-*c*]pyrrolidine derivatives with multiple arrays of stereogenic centers are important for investigating unsolved biological phenomena and for enhancing the biological selectivity of drug candidates.[4,5] Because [3 + 2] cycloaddition is a powerful tool for the construction of highly functionalized chiral five-membered pyrrolidines, here, we present a concise synthesis of benzopyrano[3,4-*c*]pyrrolidines bearing five contiguous stereogenic centers via the catalytic asymmetric [3 + 2] cycloaddition of imino esters with nitroalkenes.[6,7]

We previously succeeded in the development of a chiral *N,N,N*-tridentate bis(imidazolidine)pyridine (PyBidine)-Cu complex[8] for catalytic asymmetric [3 + 2] cycloaddition using imino esters. The PyBidine-Cu$(OTf)_2$ complex catalyzed the asymmetric [3 + 2] cycloaddition of imino esters with

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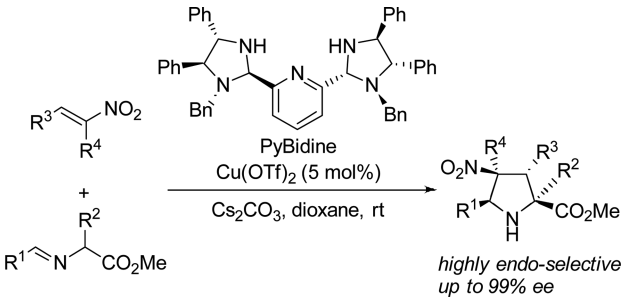
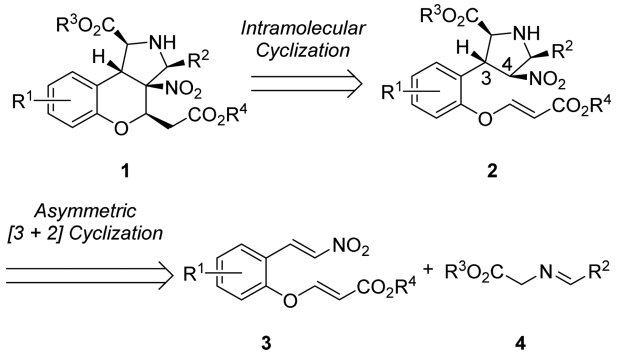
nitroalkenes in a highly *endo*-selective manner to give the chiral pyrrolidines with up to 99% ee (Scheme 1).[8a]

Scheme 1. PyBidine-Cu-catalyzed Asymmetric *endo*-Selective [3 + 2] Cycloaddition



The chiral benzopyrano[3,4-*c*]pyrrolidine derivatives (**1**) bearing five contiguous stereogenic centers were designed as shown in Scheme 2. Because the PyBidine-Cu(OTf)$_2$-catalyzed

Scheme 2. Retrosynthesis of Highly Functionalized Chiral Benzopyrano[3,4-*c*]pyrrolidines

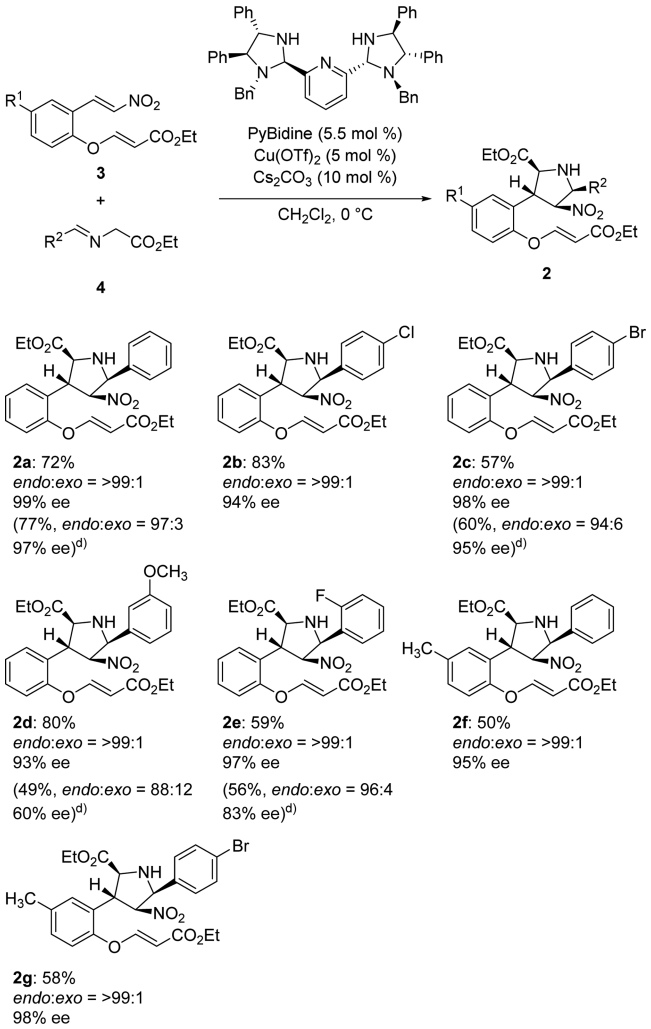


[3 + 2] cycloaddition of imino esters with nitrostyrenes can provide 3-aryl-4-nitropyrrolidines, the construction of a chroman ring was planned by diastereoselective cyclization using conjugate addition at the 4-position of pyrrolidine to the *β*-oxo-*α*,*β*-unsaturated ester side chain in intermediate **2**. The 3-phenyl-4-nitropyrrolidine intermediates **2** having the *β*-oxo-*α*,*β*-unsaturated ester at the ortho position of the benzene ring would be provided by the *endo*-selective [3 + 2] cycloaddition of imino esters (**4**) with *o*-nitrovinyl phenoxyacrylates (**3**).

The *o*-nitrovinyl phenoxyacrylate (**3a**: R^1 = H, R^4 = Et) was prepared from salicylaldehyde according to a known procedure (see Experimental Section).[9] Under the original conditions, the PyBidine-Cu complex smoothly catalyzed the asymmetric [3 + 2] cycloaddition reaction of **3a** with imino ester (**4a**: R^2 = Ph, R^3 = Et) in dioxane to give the pyrrolidine product (**2a**) with the phenoxyacrylate functionality intact in 77% yield in an *endo*-selective manner (*endo*:*exo* =97:3). The enantioselectivity of the *endo* adduct was 97% ee. When the reaction was carried out in CH_2Cl_2 at 0 °C, 72% of *endo*-**2a** was obtained in excellent diastereoselectivity (*endo*:*exo* = >99:1) with 99% ee.

The scope of the PyBidine-Cu(OTf)$_2$-catalyzed *endo*-selective asymmetric [3 + 2] cycloaddition reaction of *o*-nitrovinyl phenoxyacrylates (**3**) with imino esters (**4**) is summarized in Scheme 3. Both electron-deficient and -donating aryl functionalities were successfully employed as the R^2 substituents of the imino esters to provide the *endo* products

Scheme 3. *endo*-Selective Asymmetric [3 + 2] Reaction of *o*-Nitrovinyl Phenoxyacrylate with Imino Esters Catalyzed by PyBidine-Cu(OTf)$_2$ Complex[a−c]



[a]Isolated yield. [b]Diastereoselectivity (dr) was determined by evaluation of ^{1}H NMR spectra of the crude products. [c]Enantiomeric excess (ee) was determined by chiral HPLC analysis of the product using a Daicel Chiralcel OD-H and Chiralpak AD-H columns (hexane/2-propanol). The absolute configuration is presented by analogy with the product synthesized from nitroalkene without *α*,*β*-unsaturated ester.[8a] [d]Values in parentheses are the results carried in dioxane.

in 94−99% ee, though the introduction of an electron-deficient substituent reduced the chemical yields. An *o*-fluorinated phenyl substrate was also compatible in the PyBidine-Cu(OTf)$_2$-catalyzed asymmetric [3 + 2] cycloaddition to give the product *endo*-**2e** in 59% yield with 97% ee. For the *o*-nitrovinyl phenoxyacrylates, the substrates having additional alkyl substituents on the benzene ring were converted to the *endo*-products **2f** and **2g** with 95 and 98% ee, respectively.

Next, we focused on the cyclization of *endo*-[3 + 2] cycloaddition adducts **2** by conjugate addition of pyrrolidine at the 4-position to a *β*-oxo-*α*,*β*-unsaturated ester side chain. The cyclization was examined using **2a** (*endo*:*exo* = 97:3) as the test sample, and the results are shown in Table 1. DBU and KO^{t}Bu as the base resulted in the formation of a complex mixture. TBAF did not promote the reaction at all.

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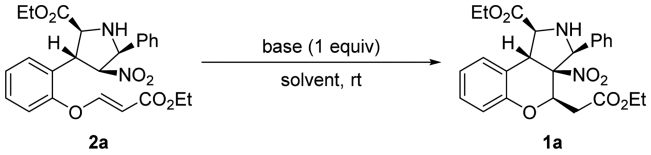
Table 1. Optimization of Cyclization of *endo*-[3 + 2] Cycloaddition Adducts 2



2a
dr 97 : 3 (*endo*/*exo*)
97% ee

1a

entry	base	solvent	time (h)	yield[a] (%)	dr[b]
1	DBU	EtOH	2	*c*	
2	KO^{t}Bu	EtOH	2	*c*	
3	TBAF	EtOH	5.5	nr[d]	
4	K_2CO_3	EtOH	5.5	<82	75:25
5	KF/Al_2O_3	EtOH	5.5	>99	75:25
6	KF/Al_2O_3	CH_2Cl_2-EtOH (4:1)	17	89	91:9
7	KF/Al_2O_3	toluene-EtOH (4:1)	17	>99	94:6
8	KF/Al_2O_3	toluene-EtOH (9:1)	18	96	96:4
9	KF/Al_2O_3	toluene-EtOH (19:1)	18	76	97:3

[a]Determined by ^{1}H NMR spectra of crude products. [b]Determined by ^{1}H NMR spectra. [c]Complex mixture was obtained. [d]No reaction proceeded.

When pyrrolidine product **2a** was treated with KF/Al_2O_3 in EtOH, desired benzopyrano[3,4-*c*]pyrrolidine **1a** was obtained in 99% yield in a diastereoselective manner at a ratio of 75:25. Fortunately, **1a** retained the 97% ee from starting material **2a**. To improve the diastereoselectivity, we conducted a detailed examination of the solvent effects for the KF/Al_2O_3 promoted cyclization. The combined use of an aprotic solvent with EtOH was effective for improving the diastereoselectivity, although increasing the ratio of the aprotic solvent prolonged the reaction time. Finally, the toluene-EtOH (4:1) solvent system was selected as the best choice for producing **1a** in >99% yield with 94:6 diastereoselectivity.

Under the optimized conditions, a series of chiral benzopyrano[3,4-*c*]pyrrolidines **1** was synthesized from the *endo*-[3 + 2] cycloaddition adducts **2** obtained in Scheme 3 (Scheme 4). A simple filtering out of KF/Al_2O_3 gave **1** with satisfying purities, and further purification was not effective. After concentration of the filtrate, the isolated yield of **1** was reported with the purity shown in Scheme 4. All substrates (**2a**−**g**) were successfully converted to benzopyrano[3,4-*c*]pyrrolidines (**1a**−**g**) with high diastereoselectivities while maintaining their enantiomeric purities.

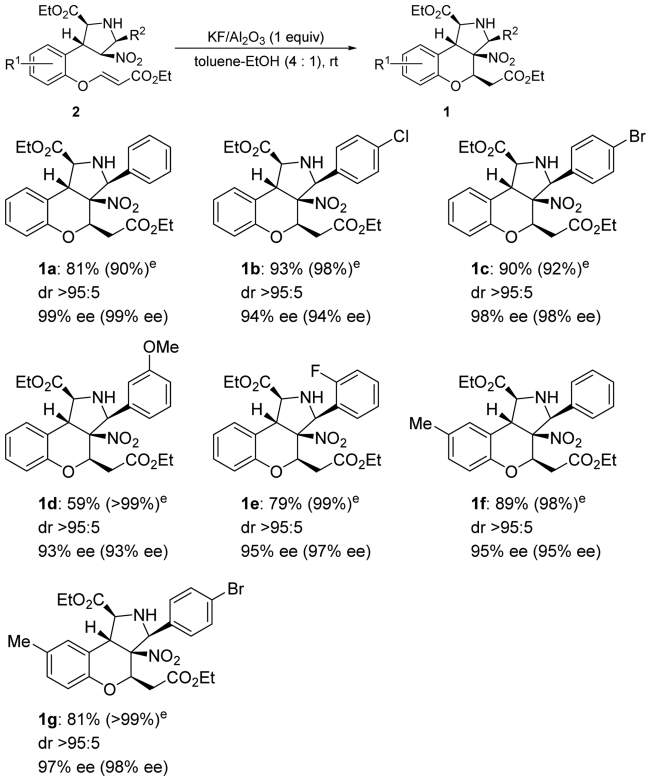
The stereochemistry of the *cis*-benzopyrano[3,4-*c*]pyrrolidine product was determined by 2D ^{1}H−^{1}H NOESY experiments on **1b** (Figure 2). Because all substituents on the benzopyrano-[3,4-*c*]pyrrolidine ring system were present on the convex phase, the benzopyrano[3,4-*c*]pyrrolidines (**1a**−**g**) were obtained as thermodynamically stable compounds.

In conclusion, the PyBidine-Cu(OTf)$_2$-catalyzed highly *endo*-selective asymmetric [3 + 2] cycloaddition of nitroalkenes with imino esters was applied to the synthesis of novel chiral benzopyrano[3,4-*c*]pyrrolidines bearing five contiguous stereogenic centers. The biological activity of these unique molecules is being examined by our group.[10]

EXPERIMENTAL SECTION

General Information. Dry solvents were purchased from commercial suppliers and used without further purification. Analytical thin-layer chromatography (TLC) was performed on glass plates

Scheme 4. Synthesis of Chiral Benzopyrano[3,4-*c*]pyrrolidines Having Five Contiguous Stereogenic Centers[a−d]



[a]Values in parentheses are ee of **2**. [b]Isolated yield. [c]Diastereoselectivity (dr) was determined by evaluation of ^{1}H NMR spectra of the crude products. [d]Enantiomeric excess (ee) was determined by chiral HPLC analysis of the product using Daicel Chiralcel OD-H and Chiralpak AD-H columns. [e]Purity of products was evaluated by ^{1}H NMR spectra.

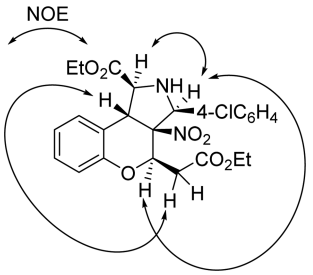


Figure 2. NOE connectivities of benzopyrano[3,4-*c*]pyrrolidine product **1b**.

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 using ATR. Chemical shifts of ^{1}H NMR spectra were reported relative to tetramethyl silane (δ 0). 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; and br, broad. Ethyl (*E*)-3-{2-[(*E*)-2-nitrovinyl]phenoxy}-prop-2-enoate was synthesized according to a known procedure.[9] Iminoesters were synthesized according to a known procedure.[11]

Synthesis of Substrates. *General Synthetic Routes of Substrate 3.* Substrates (**3**) were prepared by the following procedures.

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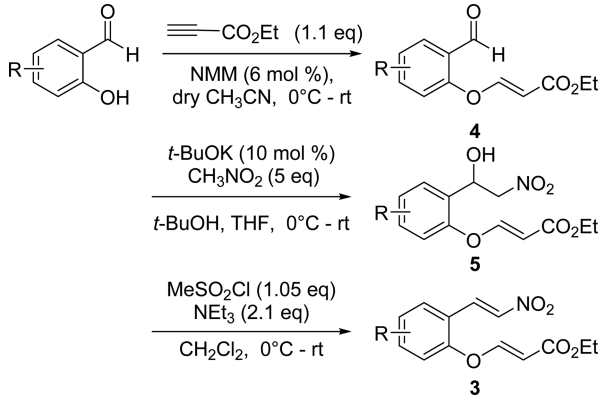

General Procedure for the Synthesis of Intermediate ***4****.* To a solution of salicylaldehydes (26 mmol) in dry MeCN (130 mL) were added ethyl propiolate (1.1 equiv) and *N*-methylmorpholine (6 mol %) at 0 °C, and the resultant mixture was stirred at rt for 24 h. After evaporation, the residue was purified by silica-gel column chromatography (hexane/ethyl acetate = 6:1) to afford ethyl (*E*)-3-{2-[(*E*)-2-formyl]phenoxy}prop-2-enoates (**4**).

*Analytical Data of Ethyl (E)-3-(2-Formylphenoxy)prop-enoate (**4a**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.38 (s, 1H), 7.93 (dd, J = 7.8, 1.7 Hz, 1H), 7.85 (d, J = 12.2 Hz, 1H), 7.67−7.63 (m, 1H), 7.32 (t, J = 7.7, 7.5 Hz, 1H), 7.16 (d, J = 8.3 Hz, 1H), 5.64 (d, J = 12.2 Hz, 1H), 4.21 (q = J = 7.1 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.1, 166.5, 157.9, 157.5, 136.0, 128.9, 126.5, 125.3, 118.3, 104.2, 60.4, 14.3; FTMS (ESI) calcd for $C_{12}H_{12}O_4^-$ [M − H]$^-$ 221.0808, found 221.0804; FTIR (neat) 1715, 1697, 1228, 934, 824 cm^{-1}.

General Procedure for the Synthesis of Intermediate ***5****.* To a solution of ethyl (*E*)-3-{2-[(*E*)-2-formyl]phenoxy}prop-2-enoates (24 mmol) in *t*-BuOH (24 mL) and THF (24 mL) were added CH_3NO_2 (5 equiv) and *t*-BuOK (10 mol %) at 0 °C. The resulting solution was stirred at rt for 16 h. The reaction mixture was diluted with H_2O and extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica-gel column chromatography (hexane/ethyl acetate = 5:1) to afford the nitroaldols (**5**).

*Analytical Data of Ethyl (E)-3-[2-(1-Hydroxy-2-nitroethyl)-phenoxy]prop-enoate (**5a**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 12.2 Hz, 1H), 7.63 (d, J = 7.7 Hz, 1H), 7.40 (t, J = 7.81 Hz, 1H), 7.23 (t, J = 7.48 1H), 7.07 (d, J = 8.2 Hz, 1H), 5.73−5.69 (m, 1H), 5.60 (d, J = 12.2 Hz, 1H), 4.62−4.5 (m, 2H), 4.20 (t J = 7.1 Hz 2H), 3.16 (J = 4.8 Hz), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 157.9, 152.0, 130.2, 128.4, 127.6, 125.7, 117.5, 103.5, 65.8, 60.4, 30.9, 14.2; FTMS (ESI) calcd for $C_{13}H_{14}NO_6^-$ [M − H]$^-$ 280.0827, found 280.0846; FTIR (neat) 3450, 1709, 1557, 1322, 932, 854 cm^{-1}.

General Procedure for the Synthesis of Substrate ***3****.* To a solution of nitroaldols (14 mmol) and NEt_3 (2.1 equiv) in CH_2Cl_2 (14 mL) was added $MeSO_2Cl$ (1.05 equiv) dropwise at 0 °C. The resultant solution was stirred at rt for 1 h. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica-gel column chromatography (hexane/ethyl acetate = 6:1). The resulting residue was washed with hexane to afford substrate **3**.

*Analytical Data of Ethyl (E)-3-{2-[(E)-2-Nitrovinyl]phenoxy}prop-2-enoate (**3a**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 13.7 Hz, 1H), 7.77 (d, J = 12.2 Hz, 1H), 7.69 (d, J = 13.7 Hz, 1H), 7.59−7.51 (m, 2H), 7.29 (dd, J = 7.5, 0.9 Hz, 1H), 7.16 (dd, J = 8.4, 0.9 Hz, 1H), 5.69 (d, J = 12.2 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 157.2, 155.0, 139.0, 133.5, 133.1, 130.7, 125.5, 121.1, 118.3, 104.6, 60.4, 14.3; FTMS (ESI) calcd for $C_{13}H_{12}NO_5^-$ [M − H]$^-$ 262.0721, found 262.0734; FTIR (neat) 2986, 1715, 1577, 1346, 1126, 976, 852, 824 cm^{-1}.

*Analytical Data of Ethyl (E)-3-{4-Methyl-2-[(E)-2-nitrovinyl]-phenoxy}prop-2-enoate (**3b**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 13.8 Hz, 1H), 7.75 (d, J = 12.2 Hz, 1H), 7.67 (d, J = 13.8 Hz, 1H), 7.36 (d, J = 1.6 Hz, 1H), 7.32 (dd, J = 8.4, 1.6 Hz, 1H), 7.16 (d, J = 8.4 Hz, 1H), 5.63 (d, J = 12.2 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 2.38 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 157.8, 153.0, 138.8, 133.4, 134.2, 133.3, 130.9, 120.8, 118.4, 104.0, 60.4, 20.6, 14.3; FTMS (ESI) calcd for $C_{14}H_{14}NO_5^-$ [M − H]$^-$ 276.0877, found 276.0896; FTIR (neat) 2923, 1708, 1582, 1517, 1369, 1236, 970, 843 cm^{-1}.

General Procedure of PyBidine-Cu(OTf)$_2$-Catalyzed Asymmetric [3 + 2] Cycloaddition. PyBidine (0.011 mmol) and $Cu(OTf)_2$ (0.01 mmol) were added to a round flask containing a stir bar under Ar. CH_2Cl_2 (1 mL) was added to the flask, and the mixture was stirred for 1 h. To the resulting solution were added ethyl (*E*)-3-{2-[(*E*)-2-nitrovinyl]phenoxy}prop-2-enoate (0.2 mmol) and Cs_2CO_3 (0.02 mmol) at rt. After cooling to 0 °C, to the mixture was added iminoester (0.22 mmol). After stirring for an appropriate amount of time, the reaction mixture was diluted with satd $NaHCO_3$(aq) and extracted with AcOEt. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica-gel column chromatography (hexane/ethyl acetate = 3:1) to afford pyrrolidine product **2**.

General Procedure of Intramolecular Diastreoselective Cyclization of Pyrrolidine Product ***2****.* To a solution of pyrrolidine product **2** (0.18 mmol) in toluene/EtOH (4:1) was added KF/Al_2O_3 (0.18 mmol, Aldrich). After stirring at rt for an appropriate amount of time, the reaction mixture was filtered and concentrated in vacuo to afford benzopyrano[3,4-*c*]pyrrolidine **1**. (A simple filtering out of KF/Al_2O_3 gave **1** with satisfying purities. Further purification (e.g., silica-gel column chromatography, alumina column chromatography, and preparative TLC) was not effective. After concentration of the filtrate, the isolated yield of **1** was reported with the purity in Scheme 4.)

*Ethyl (2S,3R,4S,5S)-3-{2-[(E)-2-Carbethoxy-eth-1-enoxy]phenyl}-4-nitro-5-phenyl-pyrrolidine-2-carboxylate (**2a**).* Sixty seven milligrams, 72% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 12.1 Hz, 1H), 7.42−7.31 (m, 7H), 7.22 (dd, J = 7.5, 0.9 Hz, 1H), 7.13 (d, J = 8.2 Hz, 1H), 5.66 (d, J = 12.1 Hz, 1H), 5.36 (dd, J = 6.7, 3.6 Hz, 1H), 4.92 (dd, J = 10.3, 6.7 Hz, 1H), 4.29−4.18 (m, 5H), 4.13 (t, J = 7.9 Hz, 1H), 3.36 (t, J = 10.3 Hz, 1H), 1.30 (t, J = 7.3 Hz, 3H), 1.23 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 166.5, 157.4, 153.7, 134.1, 130.4, 129.9, 128.7, 128.0, 126.4, 125.4, 117.6, 104.0, 96.4, 67.6, 65.6, 61.7, 60.4, 53.4, 52.4, 14.2, 14.1; FTMS (ESI) calcd for $C_{24}H_{25}N_2O_7^-$ [M − H]$^-$ 453.1667, found 453.1683; enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (70:30 hexane/2-propanol, 1.0 mL/min, 254 nm); minor enantiomer t_r = 16.9 min, major enantiomer t_r = 25.2 min; $[\alpha]_D^{21}$ −89.4 (*c* 1.0, $CHCl_3$, 99% ee); FTIR (neat) 3774, 3663, 1710, 1550, 1223, 1124, 756, 699 cm^{-1}.

*Ethyl (2S,3R,4S,5S)-5-(4-Chlorophenyl)-3-{2-[(E)-2-carbethoxy-eth-1-enoxy]phenyl}-4-nitro-pyrrolidine-2-carboxylate (**2b**).* Eighty one milligrams, 83% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 12.2 Hz, 1H), 7.40 (td, J = 8.1, 1.4 Hz, 1H), 7.36−7.27 (m, 5H), 7.21 (t, J = 7.5 Hz, 1H), 7.12 (d, J = 8.1 Hz, 1H), 5.65 (d, J = 12.2 Hz, 1H), 5.34 (dd, J = 6.7, 4.0 Hz, 1H), 4.88 (dd, J = 9.9, 4.0 Hz, 1H), 4.30−4.18 (m, 5H), 4.12 (t, J = 8.1 Hz, 1H), 3.26 (t, J = 9.9 Hz, 1H), 1.29 (t, J = 7.2 Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 166.4, 157.3, 153.6, 134.5, 132.8, 130.4, 130.0, 128.9, 127.8, 127.7, 125.4, 117.6, 104.0, 96.1, 66.7, 65.3, 61.7, 60.4, 52.0, 14.2, 14.0; FTMS (ESI) calcd for $C_{24}H_{26}ClN_2O_7^+$ [M + H]$^+$ 489.1423, found 489.1409; calcd for $C_{24}H_{26}Cl^{37}N_2O_7^+$ [M + H]$^+$ 491.1394, found 491.1380; enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (70:30 hexane/2-propanol, 1.0 mL/min, 254 nm); minor enantiomer t_r = 26.1 min, major enantiomer t_r = 53.2 min; $[\alpha]_D^{20}$ −72.8 (*c* 1.0, $CHCl_3$, 94% ee); FTIR (neat) 3774, 3663, 1709, 1549, 1224, 1122, 758 cm^{-1}.

*Ethyl (2S,3R,4S,5S)-5-(4-Bromophenyl)-3-{2-[(E)-2-carbethoxy-eth-1-enoxy]phenyl}-4-nitro-pyrrolidine-2-carboxylate (**2c**).* Sixty two milligrams, 57% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 12.2 Hz, 1H), 7.49 (d, J = 8.3 Hz, 2H), 7.40 (td, J = 7.7, 1.5 Hz, 1H), 7.31 (dd, J = 7.7, 1.5 Hz, 1H), 7.24−7.19 (m, 3H), 7.12 (d, J = 8.3 Hz, 1H), 5.65 (d, J = 12.2 Hz, 1H), 5.33 (dd, J = 6.6, 3.9 Hz, 1H),

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4.86 (dd, J = 6.6 Hz, 1H), 4.29−4.17 (m, 5H), 4.12 (d, J = 8.6 Hz, 1H), 3.26 (br, 1H), 1.29 (t, J = 7.0 Hz, 3H), 1.22 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 166.4, 157.3, 153.6, 133.3, 131.8, 130.4, 130.0, 128.1, 127.7, 125.4, 122.7, 117.6, 104.0, 96.0, 66.7, 65.3, 61.7, 60.4, 52.0, 14.2, 14.0; FTMS (ESI) calcd for $C_{24}H_{26}BrN_2O_7^+$ $[M + H]^+$ 533.0918, found 533.0901; calcd for $C_{24}H_{26}Br^{81}N_2O_7^+$ $[M + H]^+$ 535.0897, found 535.0883; enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (70:30 hexane/2-propanol, 1.0 mL/min, 254 nm); minor enantiomer t_r = 18.5 min, major enantiomer t_r = 30.8 min; $[\alpha]_D^{20}$ −119.5 (c 0.50, $CHCl_3$, 98% ee); FTIR (neat) 2982, 1706, 1548, 1121, 757 cm^{-1}.

*Ethyl (2S,3R,4S,5S)-3-{2-[(E)-2-Carbethoxy-eth-1-enoxy]phenyl}-5-(3-methoxyphenyl)-4-nitro-pyrrolidine-2-carboxylate (**2d**).* Seventy eight milligrams, 80% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 12.1 Hz, 1H), 7.40 (td, J = 7.7, 1.6 Hz, 1H), 7.32 (dd, J = 7.7, 1.6 Hz, 1H), 7.27 (t, J = 7.7 z, 1H), 7.22 (td, J = 7.5, 0.9 Hz, 1H), 7.12 (d, J = 8.0 Hz), 6.92−6.84 (m, 3H), 5.65 (d, J = 12.1 Hz, 1H), 5.35 (dd, J = 6.6, 4.0 Hz, 1H), 4.89 (dd, J = 10.9, 6.6 Hz, 1H), 4.30−4.17 (m, 5H), 4.12 (t, J = 8.9 Hz, 1H), 3.80 (s, 3H), 3.34 (t, J = 10.9 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 166.5, 159.7, 157.4, 153.6, 135.7, 130.4, 129.4, 129.7, 128.0, 125.4, 118.6, 117.6, 114.0, 112.2, 104.0, 96.2, 67.5, 65.6, 61.7, 60.4, 55.2, 52.3, 14.2, 14.0; FTMS (ESI) calcd for $C_{25}H_{29}N_2O_8^+$ $[M + H]^+$ 485.1918, found 485.1901; enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (70:30 hexane/2-propanol, 1.0 mL/min, 254 nm); minor enantiomer t_r = 13.5 min, major enantiomer t_r = 26.7 min; $[\alpha]_D^{20}$ −77.8 (c 0.50, $CHCl_3$, 96% ee); FTIR (neat) 2982, 1709, 1550, 1123, 756 cm^{-1}.

*Ethyl (2S,3R,4S,5S)-3-{2-[(E)-2-Carbethoxy-eth-1-enoxy]phenyl}-5-(2-fluorophenyl)-4-nitro-pyrrolidine-2-carboxylate (**2e**).* Fifty six milligrams, 59% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 12.2 Hz, 1H), 7.43−7.36 (m, 2H), 7.35−7.29 (m, 2H), 7.23−7.18 (m, 2H), 7.14−7.06 (m, 2H), 5.71 (d, J = 12.1 Hz, 1H), 5.52 (ddd, J = 6.3, 3.4, 1.4 Hz, 1H), 5.13 (dd, J = 12.6, 6.3 Hz, 1H), 4.32−4.19 (m, 5H), 4.07 (dd, J = 10.4, 8.6 Hz, 1H), 3.38 (dd, J = 12.1, 11.1 Hz, 1H), 1.30 (t, J = 7.2 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 166.5, 159.9, 157.0, 153.6, 130.8, 130.2, 129.9, 127.8, 126.7, 125.2, 124.5, 121.4, 117.3, 115.1, 104.2, 95.2, 65.8, 61.9, 61.8, 61.7, 60.3, 53.0, 14.2, 14.1; FTMS (ESI) calcd for $C_{24}H_{26}FN_2O_7^+$ $[M + H]^+$ 473.1719, found 473.1702; enantiomeric excess was determined by HPLC with a Chiralcel AS-H column (70:30 hexane/2-propanol, 1.0 mL/min, 254 nm); major enantiomer t_r = 15.7 min, minor enantiomer t_r = 22.6 min; $[\alpha]_D^{21}$ −109.2 (c 0.50, $CHCl_3$, 97% ee); FTIR (neat) 2983, 1710, 1549, 1123, 756 cm^{-1}.

*Ethyl (2S,3R,4S,5S)-3-{2-[(E)-2-Carbethoxy-eth-1-enoxy]-5-methyl-phenyl}-4-nitro-5-phenyl-pyrrolidine-2-carboxylate (**2f**).* Forty seven milligrams, 50% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 12.2 Hz, 1H), 7.39−7.30 (m, 5H), 7.18 (dd, J = 8.2, 1.6 Hz, 1H), 7.10 (d, J = 1.6 Hz, 1H), 7.00 (d, J = 8.2 Hz, 1H), 5.61 (d, J = 10.6 Hz, 1H), 5.34 (dd, J = 6.6, 3.9 Hz, 1H), 4.92 (dd, J = 11.0, 6.6 Hz, 1H), 4.33−4.18 (m, 5H), 4.10 (t, J = 8.7 Hz, 1H), 3.35 (t, J = 10.6 Hz, 1H), 2.35 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 166.6, 158.0, 151.5, 135.2, 134.2, 131.0, 130.3, 128.7 (2C), 127.8, 126.4, 117.7, 103.5, 96.5, 67.6, 65.8, 61.7, 60.3, 52.4, 20.7, 14.3, 14.1; FTMS (ESI) calcd for $C_{25}H_{29}N_2O_7^+$ $[M + H]^+$ 469.1969, found 469.1952; enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (95:5 hexane/2-propanol, 1.0 mL/min, 254 nm); minor enantiomer t_r = 36.0 min, major enantiomer t_r = 49.0 min; $[\alpha]_D^{17}$ −71.5 (c 1.0, $CHCl_3$, 95% ee); FTIR (neat) 3734, 1709, 1548, 1126, 1028, 697 cm^{-1}.

*Ethyl (2S,3R,4S,5S)-5-(4-Bromophenyl)-3-{2-[(E)-2-carbethoxy-eth-1-enoxy]-5-methyl-phenyl}-4-nitro-pyrrolidine-2-carboxylate (**2g**).* Sixty three milligrams, 58% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 12.2 Hz, 1H), 7.49 (d, J = 8.5 Hz, 2H), 7.23 (d, J = 8.5 Hz, 1H), 7.18 (dd, J = 8.3, 1.8 Hz, 1H), 7.09 (d, J = 1.8 Hz, 1H), 7.00 (d, J = 8.3 Hz, 1H), 5.60 (d, J = 12.2 Hz, 1H), 5.32 (dd, J = 6.7, 4.0 Hz, 1H), 4.86 (t, J = 7.9 Hz, 1H), 4.32−4.17 (m, 5H), 4.09 (t, J = 7.9 Hz, 1H), 3.35 (t, J = 7.9 Hz, 1H), 2.35 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 166.6, 157.9, 151.5, 135.3, 133.4, 131.9, 131.0, 130.4, 128.1, 127.5, 122.8, 117.8, 103.5, 96.1, 66.8, 65.5, 61.8, 60.4, 52.2, 20.7, 14.3, 14.1; FTMS (ESI) calcd for $C_{25}H_{28}BrN_2O_7^+$ $[M + H]^+$ 547.1074, found 547.1057; calcd for $C_{25}H_{28}Br^{81}N_2O_7^+$ $[M + H]^+$ 549.1054, found 549.1038; enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 hexane/2-propanol, 1.0 mL/min, 254 nm); minor enantiomer t_r = 19.9 min, major enantiomer t_r = 23.7 min; $[\alpha]_D^{17}$ −73.5 (c 0.13, $CHCl_3$, 98% ee); FTIR (neat) 3734, 1709, 1548, 1126, 1028, 697 cm^{-1}; mp 60−62 °C.

*Ethyl (1S,3S,3aS,4R,9bR)-4-Carbethoxy-3a-nitro-3-phenyl-2,3,4,9b-tetrahydro-1H-chromeno[3,4-c]pyrrole-1-carboxylate (**1a**).* Sixty six milligrams, 81% yield (90% purity); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 7.6 Hz, 1H), 7.42−7.29 (m, 5H), 7.23 (d, J = 7.0 Hz, 1H), 7.12 (td, J = 7.6, 0.9 Hz, 1H), 6.95 (dd, J = 8.1, 0.9 Hz, 1H), 5.14 (dd, J = 9.9, 2.5 Hz, 1H), 4.84 (d, J = 10.7 Hz, 1H), 4.54−4.42 (m, 2H), 4.38 (d, J = 3.4 Hz, 1H), 4.16−4.07 (m, 2H), 4.04−4.02 (m, 1H), 3.17 (dd, J = 10.7, 8.0 Hz, 1H), 2.59 (dd, J = 15.7, 9.9 Hz), 2.42 (dd, J = 15.7, 2.5 Hz, 1H), 1.46 (t, J = 7.2 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 169.2, 148.8, 133.4, 129.6, 129.1 (2C), 129.0, 126.5, 124.2, 123.5, 118.4, 96.8, 69.8, 69.2, 68.7, 62.1, 61.0, 46.0, 34.2, 14.3, 14.1; FTMS (ESI) calcd for $C_{24}H_{25}N_2O_7^-$ $[M - H]^-$ 453.1667, found 453.1685; enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (70:30 hexane/2-propanol, 1.0 mL/min, 254 nm); minor enantiomer t_r = 15.4 min, major enantiomer t_r = 20.4 min; $[\alpha]_D^{23}$ +9.5 (c 0.1, $CHCl_3$, 99% ee); FTIR (neat) 3774, 3663, 1710, 1550, 1223, 1124, 756, 699 cm^{-1}; mp 52−55 °C.

*Ethyl (1S,3S,3aS,4R,9bR)-3-(4-Chlorophenyl)-4-carbethoxy-3a-nitro-2,3,4,9b-tetrahydro-1H-chromeno[3,4-c]pyrrole-1-carboxylate (**1b**).* Eighty two milligrams, 93% yield (98% purity); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 7.6 Hz, 1H), 7.41−7.38 (m, 2H), 7.30−7.26 (m, 2H), 7.25−7.22 (m, 1H), 7.12 (td, J = 7.6, 1.1 Hz, 1H), 6.94 (dd, J = 8.2, 1.1 Hz, 1H), 5.10 (dd, J = 9.9, 2.7 Hz, 1H), 4.82 (d, J = 10.5 Hz, 2H), 4.51−4.42 (m, 2H), 4.39 (d, J = 3.6 Hz, 1H), 4.12−4.08 (m, 2H), 4.02 (dd, J = 7.4, 3.6 Hz, 1H), 3.02 (dd, J = 10.5, 7.5 Hz, 1H), 2.58 (dd, J = 15.7, 9.9 Hz), 2.40 (dd, J = 15.7, 2.7 Hz, 1H), 1.46 (t, J = 7.2 Hz, 3H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 169.1, 148.7, 135.5, 132.2, 129.3, 129.1, 128.7, 128.0, 124.0, 123.6, 118.5, 96.6, 69.7, 68.3, 68.2, 62.2, 61.1, 45.6, 34.2, 14.3, 14.1; FTMS (ESI) calcd for $C_{24}H_{26}ClN_2O_7^+$ $[M + H]^+$ 489.1423, found 489.1419; calcd for $C_{24}H_{26}Cl^{37}N_2O_7^+$ $[M + H]^+$ 491.1394, found 491.1378; enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (95:5 hexane/2-propanol, 1.0 mL/min, 254 nm); major enantiomer t_r = 23.8 min, minor enantiomer t_r = 34.4 min; $[\alpha]_D^{23}$ +19.3 (c 0.1, $CHCl_3$, 94% ee); FTIR (neat) 3847, 2981, 1710, 1549, 1225, 1125, 836, 760 cm^{-1}.

*Ethyl (1S,3S,3aS,4R,9bR)-3-(4-Bromophenyl)-4-carbethoxy-3a-nitro-2,3,4,9b-tetrahydro-1H-chromeno[3,4-c]pyrrole-1-carboxylate (**1c**).* Eighty six milligrams, 90% yield (92% purity); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 7.5 Hz, 1H), 7.25−7.21 (m, 3H), 7.12 (td, J = 7.5, 1.1 Hz, 1H), 6.94 (dd, J = 8.2, 1.1 Hz, 1H), 5.10 (td, J = 10.1, 2.6 Hz, 1H), 4.81 (d, J = 10.3 Hz, 1H), 4.53−4.42 (m, 2H), 4.39 (d, J = 3.6 Hz, 1H), 4.17−4.08 (m, 2H), 4.01 (dd, J = 7.5, 3.6 Hz, 1H), 3.01 (dd, J = 10.3, 7.5 Hz, 1H), 2.58 (dd, J = 15.7, 10.1 Hz), 2.40 (dd, J = 15.7, 2.6 Hz, 1H), 1.46 (t, J = 7.2 Hz, 3H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 169.1, 148.7, 132.7, 132.2, 129.1, 128.3, 124.0, 123.7, 123.6, 118.5, 96.6, 69.7, 68.3 (2C), 62.2, 61.1, 45.6, 34.2, 14.3, 14.1; FTMS (ESI) calcd for $C_{24}H_{26}BrN_2O_7^+$ $[M + H]^+$ 533.0918, found 533.0920; calcd for $C_{24}H_{26}Br^{81}N_2O_7^+$ $[M + H]^+$ 535.0897, found 535.0899; enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (95:5 hexane/2-propanol, 1.0 mL/min, 254 nm); major enantiomer t_r = 35.7 min, minor enantiomer t_r = 52.1 min; $[\alpha]_D^{23}$ +0.8 (c 0.1, $CHCl_3$, 98% ee); FTIR (neat) 2981, 1733, 1540, 1190, 1010, 735 cm^{-1}.

*Ethyl (1S,3S,3aS,4R,9bR)-4-Carbethoxy-3-(3-methoxyphenyl)-3a-nitro-2,3,4,9b-tetrahydro-1H-chromeno[3,4-c]pyrrole-1-carboxylate (**1d**).* Fifty two milligrams, 59% yield (>99% purity); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 7.6 Hz, 1H), 7.33 (t, J = 8.0 Hz, 1H), 7.24−7.22 (m, 1H), 7.11 (td, J = 8.0, 1.1 Hz, 1H), 7.00−6.86 (m, 4H), 5.17 (dd, J = 10.0, 2.6 Hz, 1H), 4.80 (d, J = 11.0 Hz, 1H), 4.51−4.42

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(m, 2H), 4.38 (d, J = 3.6 Hz, 1H), 4.16−4.08 (m, 2H), 4.02 (dd, J = 7.5, 3.6 Hz, 1H), 3.83 (s, 3H), 3.12 (dd, J = 11.0, 7.6 Hz, 1H), 2.59 (dd, J = 15.7, 10.0 Hz), 2.44 (dd, J = 15.7, 2.6 Hz, 1H), 1.46 (t, J = 7.1 Hz, 3H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 169.2, 159.9, 148.8, 135.0, 130.1, 129.1, 129.0, 124.2, 123.5, 118.6, 118.4, 114.8, 112.4, 96.7, 69.8, 69.1, 68.6, 62.1, 61.0, 55.3, 46.0, 34.3, 14.3, 14.1; FTMS (ESI) calcd for $C_{25}H_{27}N_2O_8^-$ $[M - H]^-$ 483.1773, found 483.1787; enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (95:5 hexane/2-propanol, 1.0 mL/min, 254 nm); major enantiomer t_r = 29.2 min, minor enantiomer t_r = 36.4 min; $[\alpha]_D^{23}$ +10.3 (c 0.1, $CHCl_3$, 93% ee); FTIR (neat) 2980, 1735, 1541, 1236, 1191, 1091, 893, 736 cm^{-1}; mp 45−45 °C.

*Ethyl (1S,3S,3aS,4R,9bR)-4-Carbethoxy-3-(2-fluorophenyl)-3a-nitro-2,3,4,9b-tetrahydro-1H-chromeno[3,4-c]pyrrole-1-carboxylate (**1e**).* Sixty seven milligrams, 79% yield (99% purity); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 7.7 Hz, 1H), 7.41−7.35 (m, 2H), 7.24−7.08 (m, 4H), 6.96 (dd, J = 8.2, 0.9 Hz, 1H), 5.18−5.13 (m, 2H), 4.52−4.37 (m, 3H), 4.20−4.09 (m, 2H), 4.02 (dd, J = 7.7, 4.5 Hz, 1H), 3.24 (t, J = 9.3 Hz, 1H), 2.66−2.45 (m, 2H), 1.45 (t, J = 7.1 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 169.3, 149.3, 130.9, 129.0, 127.6, 124.8, 123.4 (C), 121.4, 118.4, 115.9, 97.1, 70.4, 68.4, 62.9, 62.2, 61.1, 45.9, 34.6, 14.3, 14.1; FTMS (ESI) calcd for $C_{24}H_{26}FN_2O_7^-$ $[M + H]^+$ 473.1724, found 473.1713; enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (95:5 hexane/2-propanol, 0.7 mL/min, 254 nm); major enantiomer t_r = 30.5 min, minor enantiomer t_r = 34.3 min; $[\alpha]_D^{23}$ +9.0 (c 0.1, $CHCl_3$, 95% ee); FTIR (neat) 2982, 1735, 1542, 1192, 1028 cm^{-1}; mp 62−66 °C.

*Ethyl (1S,3S,3aS,4R,9bR)-4-Carbethoxy-8-methyl-3a-nitro-3-phenyl-2,3,4,9b-tetrahydro-1H-chromeno[3,4-c]pyrrole-1-carboxylate (**1f**).* Seventy five milligrams, 89% yield (98% purity); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.31 (m, 6H), 7.03 (dd, J = 8.4, 2.0 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 5.11 (dd, J = 10.1, 2.6 Hz, 1H), 4.84 (d, J = 11.1 Hz, 1H), 4.54−4.41 (m, 2H), 4.33 (d, J = 3.6 Hz, 1H), 4.16−4.07 (m, 2H), 4.03 (dd, J = 7.6, 3.6 Hz, 1H), 3.13 (dd, J = 11.1, 7.6 Hz, 1H), 2.58 (dd, J = 15.6, 10.1 Hz), 2.40 (dd, J = 15.7, 2.6 Hz, 1H), 2,34 (s, 3H), 1.47 (t, J = 7.1 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 169.3, 146.5, 133.5, 133.0, 129.8, 129.6, 129.2, 129.0, 126.5, 123.8, 118.1, 97.0, 69.7, 69.2, 68.7, 62.1, 61.0, 46.1, 34.2, 20.8, 14.3, 14.1; FTMS (ESI) calcd for $C_{25}H_{28}KN_2O_7^+$ $[M + K]^+$ 507.1534, found 507.1508; enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (95:5 hexane/2-propanol, 1.0 mL/min, 254 nm); major enantiomer t_r = 14.4 min, minor enantiomer t_r = 18.5 min; $[\alpha]_D^{17}$ +2.1 (c 0.67, $CHCl_3$, 95% ee); FTIR (neat) 3734, 3032, 2938, 2828, 1735, 1540, 1180, 1029, 698 cm^{-1}; mp 52−54 °C.

*Ethyl (1S,3S,3aS,4R,9bR)-3-(4-Bromophenyl)-4-carbethoxy-8-methyl-3a-nitro-2,3,4,9b-tetrahydro-1H-chromeno[3,4-c]pyrrole-1-carboxylate (**1g**).* Eighty milligrams, 81% yield (>99% purity); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 1.8 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 7.03 (dd, J = 8.2, 1.8 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 5.07 (dd, J = 10.0, 2.5 Hz, 1H), 4.80 (d, J = 10.4 Hz, 1H), 4.53−4.39 (m, 2H), 4.35 (d, J = 3.5 Hz, 1H), 4.16−4.08 (m, 2H), 4.01 (dd, J = 7.5, 3.5 Hz, 1H), 2.99 (dd, J = 10.4, 7.5 Hz, 1H), 2.57 (dd, J = 15.6, 10.0 Hz), 2.37 (dd, J = 15.6, 2.5 Hz, 1H), 2.34 (s, 3H), 1.46 (t, J = 7.1 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 169.1, 146.4, 133.1, 132.8, 132.2, 129.9, 129.2, 128.3, 123.6, 118.2, 96.7, 69.7, 68.3, 68.2, 62.1, 61.1, 45.6, 34.1, 20.8, 14.3, 14.1; FTMS (ESI) calcd for $C_{25}H_{28}BrN_2O_7^+$ $[M + H]^+$ 547.1074, found 547.1063; calcd for $C_{25}H_{28}Br^{81}N_2O_7^+$ $[M + H]^+$ 549.1054, found 549.1042; enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (95:5 hexane/2-propanol, 1.0 mL/min, 254 nm); major enantiomer t_r = 22.2 min, minor enantiomer t_r = 31.3 min; $[\alpha]_D^{17}$ +10.5 (c 0.51, $CHCl_3$, 97% ee); FTIR (neat) 2981, 1735, 1541, 1212, 1010, 753 cm^{-1}.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01445.

Optimization of [3 + 2] cycloaddition and copies of ^{1}H and ^{13}C spectra (PDF)

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Notes

The authors declare no competing financial interest.

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