Construction of the Pyrrolo[2,3-*d*]carbazole Core of Spiroindoline Alkaloids by Gold-Catalyzed Cascade Cyclization of Ynamide

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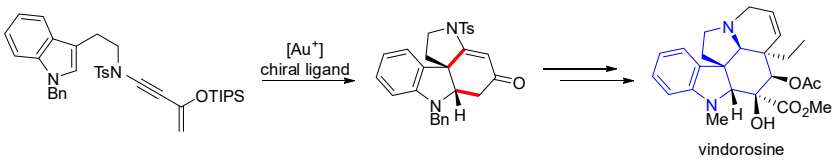
Supporting Information Placeholder



ABSTRACT: We achieved direct construction of the common pyrrolo[2,3-*d*]carbazole core of aspidosperma and malagasy alkaloids by a gold-catalyzed cascade cyclization of ynamide. This reaction involves intramolecular cyclization from indole to ynamide followed by trapping of the resulting iminium intermediate. Through the use of chiral gold complexes, an enantiomerically enriched pyrrolo[2,3-*d*]carbazole was obtained in up to 74% *ee*. This methodology was successfully applied to the asymmetric formal synthesis of vindorosine.

Terpene indole alkaloids are a large family of nitrogen-containing metabolic compounds derived from various plants. Among them, aspidosperma-type alkaloids, including more than 250 members, constitute the largest family of terpene indole alkaloids.[1] These alkaloids have important biological activities: for example, vinblastine and vincristine are used clinically as anticancer therapeutics.[2] Vindorosine and vindoline (Figure 1), isolated from *Cantharanthus Roseus*,[3] share features of the structure of vinblastine. Malagasy alkaloids, including malagashanol, were isolated from the stem bark of the Madagascan shrub *Strychnos myrtoides* in 1994.[4] They were reported to have potentials for a chloroquine-enhancing action. The common structural feature of these alkaloids is the pyrrolo[2,3-*d*]carbazole, where a highly substituted spirocyclic indoline is fused with a cyclohexane ring bearing continuous stereocenters (A-C & E ring system of aspidosperma alkaloids (Figure 1).

The structural complexity and biological activities of vindorosine have inspired the synthetic community. Since the first total synthesis of vindorosine reported by the Büchi group in 1971,[5] various efficient total syntheses have been reported including Kuehne's first asymmetric total synthesis in 1987.[6] Recently, the groups of Boger[7] and Zhang[8] reported their asymmetric total syntheses via tandem intermolecular Diels–Alder/1,3-dipolar cycloaddition of 1,3,4-oxadiazoles or intramolecular Heathcock/aza-Prins cyclization, respectively. However, to the best of our knowledge, the asymmetric syntheses reported to date have relied on chiral pool strategies or diastereoselective reactions with the use of chiral auxiliaries. Thus, the total synthesis of vindorosine based on a catalytic asymmetric reaction remains challenging. We expected gold catalysis would provide an efficient approach to vindorosine and related alkaloids in an enantioselective manner.

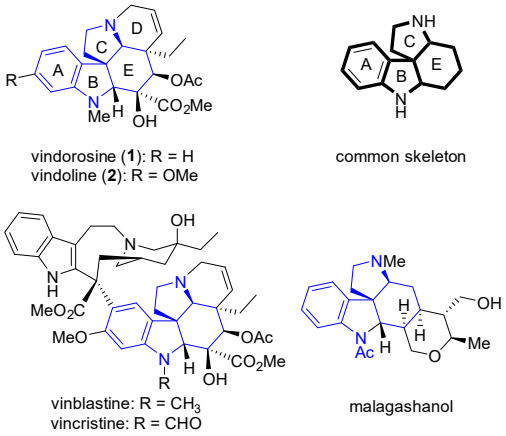
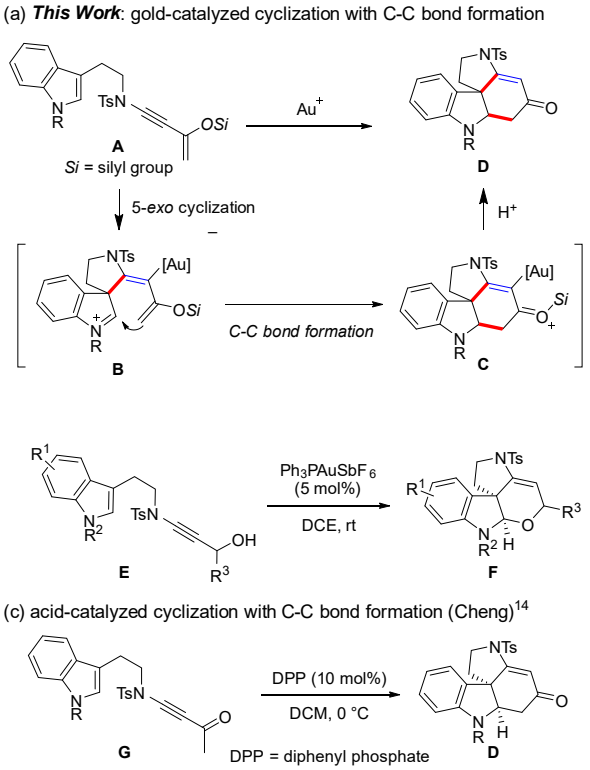


Figure 1. Polycyclic spiroindoline alkaloids.

Gold-catalyzed annulation of ynamides has emerged as a useful strategy for the construction of polycyclic nitrogen heterocycles.[9-12] Following Dankwardt's report, a number of effective synthetic approaches to the construction of cyclic structures based on a gold-catalyzed cyclization of alkyne and silyl enol ether have been developed.[13] We envision that a gold-catalyzed annulation of ynamides bearing a silyl enol ether moiety would provide direct access to pyrrolo[2,3-*d*]carbazole, the common tetracyclic indoline core of aspidosperma and malagasy alkaloids. Our working hypothesis is shown in Scheme 1a. Activation of the triple bond of ynamide **A** would promote nucleophilic attack at the indole 3 position to generate the spiroindoline intermediate **B**. The subsequent addition of silyl enol ether to the resulting iminium moiety

leads to the formation of intermediate **C**, followed by deauration and cleavage of the silyl group to produce pyrrolo[2,3-*d*]carbazole **D**. During the course of this study, a related gold-catalyzed cascade cyclization was reported by Yang and coworkers,[12] where the iminium intermediate was trapped by intramolecular nucleophilic attack of hydroxy group (Scheme 1b). Quite recently, the Cheng and Liu group[14] reported an acid-catalyzed cascade reaction of ynamide for the racemic synthesis of pyrrolo[2,3-*d*]carbazole **D** using methyl ketone derivative **G** (Scheme 1c). Herein, we describe a gold-catalyzed cascade reaction of ynamide with silyl enol ether, leading to pyrrolo[2,3-*d*]carbazole **D**. A catalytic enantioselective version of the reaction and its application to formal synthesis of vindorosine are also presented.

Scheme 1. Intramolecular Cascade Reaction of Indole-Ynamides



The preparation of silyl enol ether **7** is shown in Scheme 2. The protected tryptamine **3**, prepared by tosylation and benzylation of tryptamine, was treated with trichloroethene (TCE) and Cs_2CO_3 to give dichloroenamine **4** in 99% yield. Dehydrochlorination–lithiation of **4** with PhLi and subsequent addition to acetaldehyde resulted in ynamide **5** bearing a secondary hydroxy group in 98% yield.[15] Silyl enol ether **7** was then formed through a two-step sequence involving oxidation of **5** with MnO_2 and subsequent silylation of ketone **6**. Note that ketone **6** was not isolated because of its instability on silica gel.[16]

We then explored the optimal conditions for the gold-catalyzed cascade cyclization (Table 1). The treatment of methyl ketone **6** with JohnPhosAuSbF$_6$ led to recovery of the unreacted starting material without providing the desired product (entry 1). We next performed the reaction of silyl enol ether **7** with JohnPhosAuSbF$_6$. Rewardingly, the expected cascade cyclization proceeded smoothly to afford the desired tetracyclic indoline **8** in 74% yield (entry 2). Considering that the demetalation of the vinylgold intermediate of type **C** requires protonation,[13] we next evaluated the influence of additional proton sources. Among *i*-PrOH, AcOH, and TFA (entries 3–5), only *i*-PrOH had a positive effect on the yield of the desired product **8** (79%, entry 3). Finally, optimization of the ligands (entries 6–8) revealed that IPr was most effective in terms of the yield of the desired product (91%, entry 8).

Scheme 2. Synthesis of Indole-Ynamide Having a Silyl Enol Ether

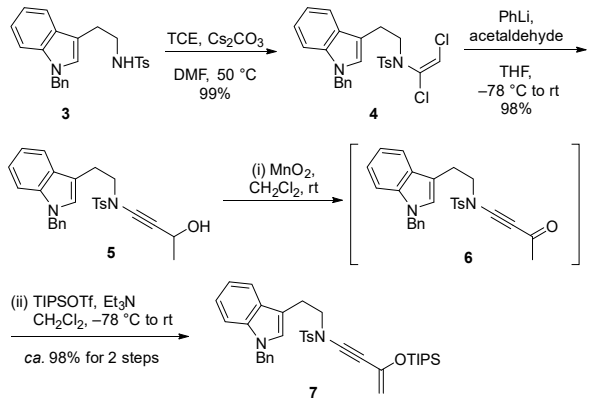
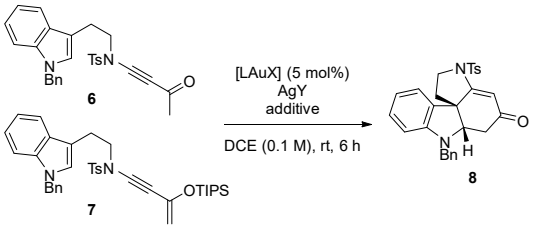


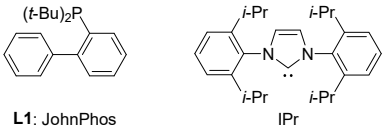
Table 1. Optimization of the Racemic Reaction[a]



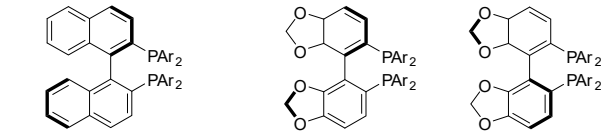
entry	substrate	LAuX[b]	AgY	additive	yield (%)[f]
1[c]	**6**[d]	**L1**AuSbF$_6$	-	-	ND
2	**7**[e]	**L1**AuSbF$_6$	-	-	74
3	**7**[e]	**L1**AuSbF$_6$	-	*i*-PrOH	79
4	**7**[e]	**L1**AuSbF$_6$	-	AcOH	61
5	**7**[e]	**L1**AuSbF$_6$	-	TFA	68
6	**7**[e]	**L1**AuCl	AgSbF$_6$	*i*-PrOH	63
7	**7**[e]	Ph$_3$PAuCl	AgSbF$_6$	*i*-PrOH	69
8	**7**[e]	IPrAuCl	AgSbF$_6$	*i*-PrOH	91

[a] Reaction condition: substrate (**6** or **7**, 1 equiv), Au(I)·ligand (5 mol %), AgY (5 mol %), 1,2-dichloroethane (DCE), additive (10 equiv where applicable) rt. [b] Catalysts were prepared *in situ* by mixing AuCl·ligand with AgY, except for JohnPhosAu(MeCN)SbF$_6$ (prepared in advance). The ligand structures are shown below. [c] Reaction was performed for 24 h. [d] Crude substrate was used owing to the instability of **6** on silica gel. [e] Includ-

ing TIPSOH (9–15%). [f] Isolated yields based on the purity of **7** (85–91%).



L1: JohnPhos IPr

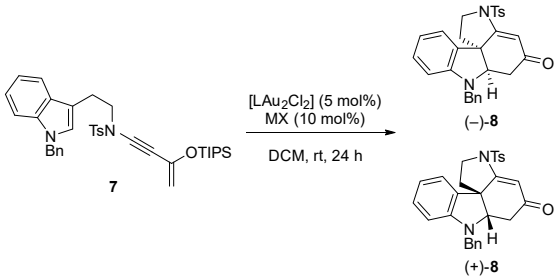


L2: Ar = Ph
L3: Ar = C_6H_2[3,5-(*t*-Bu)$_2$](4-OMe)
L4: Ar = C_6H_2(3,5-Me_2)(4-NMe_2)

(*R*)-**L5** (*S*)-**L5**
Ar = C_6H_2[3,5-(*t*-Bu)$_2$](4-OMe)

Next we proceeded to investigate the asymmetric gold-catalyzed cascade reaction. We focused on the biaryl-type chiral ligands, which are known to act as efficient ligands for gold-catalyzed asymmetric reactions in the previous reports (Table 2).[12,17-19] We tested cationic binuclear gold complexes derived from chiral C_2-symmetrical bis-phosphine ligands **L2**–**5** in the cascade reaction (entries 1–4) and found that DTBM-BINAP (**L3**, entry 2) gave the most promising result (58% yield, 50% *ee*). Evaluation of the counterions using **L3** (entries 5–7) revealed that sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) improved the enantioselectivity to 72% but decreased the yield of (–)-**8** to 38% (entry 7). A slight increase in enantioselectivity was observed when using a DTBM-SEGPHOS complex, **L5**Au_2Cl_2/NaBARF, (38% yield, 74% *ee*, entry 8). Unfortunately, further investigations on the reaction temperature and catalyst loading did not further improve the yield (see Supporting Information).

Table 2. Optimization of the Asymmetric Reaction[a]

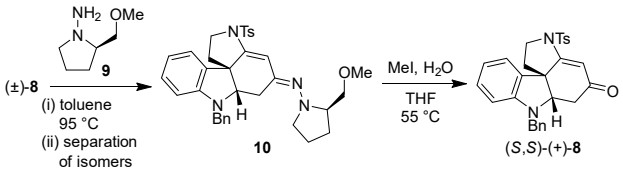


entry	LAu_2Cl_2[b]	MX	yield (%)[c]	% *ee*[d]
1	**L2**Au_2Cl_2	$AgBF_4$	trace	2 (–)
2	**L3**Au_2Cl_2	$AgBF_4$	58	50 (–)
3	**L4**Au_2Cl_2	$AgBF_4$	23	12 (–)
4	(*R*)-**L5**Au_2Cl_2	$AgBF_4$	30	52 (–)
5	**L3**Au_2Cl_2	$AgSbF_6$	32	54 (–)
6	**L3**Au_2Cl_2	$LiB(C_6F_5)_4$	17	38 (–)
7	**L3**Au_2Cl_2	NaBARF	38	72 (–)
8	(*R*)-**L5**Au_2Cl_2	NaBARF	38	74 (–)
9	(*S*)-**L5**Au_2Cl_2	NaBARF	33	72 (+)

[a] Reaction condition: **7** (including 9–15% TIPSOH, 1 equiv), Au(I)·ligand (5 mol %), MX (10 mol %), dichloromethane (DCM). [b] Unless otherwise noted the catalysts were prepared *in situ* by mixing AuCl·ligand with MX. Ligand structures are shown below. [c] Isolated yields based on the purity of **7** (85–91%). [d] Determined by chiral HPLC analysis.

To reveal the absolute configuration of optically active **8** prepared by the reaction of **7** and a chiral gold catalyst, we synthesized hydrazone **10** bearing a chiral hydrazine **9** from racemic **8** (Scheme 3). After separation of diastereomers by column chromatography, the absolute configuration of **10** was confirmed by X-ray analysis (Figure 2). Then we obtained the authentic sample of (*S*,*S*)-(+)-**8** by the reaction of **10** with MeI and H_2O. This experiment has revealed that (–)-**8** has the opposite configuration to that of natural vindorosine. Thus, we prepared (+)-**8** by the reaction using (*S*)-**L5**$AuCl_2$ (Table 2, entry 9).

Scheme 3. Determination of Absolute Configuration of 8



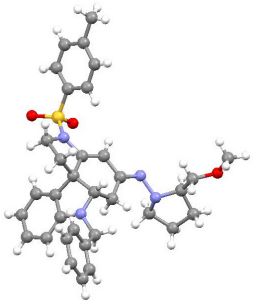
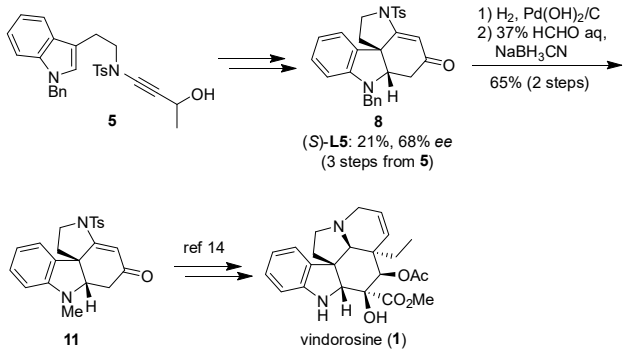


Figure 2. X-ray structure of **10**. There are two crystallographically independent molecules in the single crystal lattices, one of which is shown for clarity.

We finally applied the catalytic asymmetric synthesis of pyrrolo[2,3-*d*]carbazole **8** to formal total synthesis of vindorosine (Scheme 4). The annulation of **7** was carried out on a 1.3 mmol scale to produce (+)-**8** in 68% *ee* (21% isolated yield in three steps from **5**). The subsequent removal of the benzyl group and *N*-methylation afforded the known precursor **11** in 65% yield, which can be converted to vindorosine (**1**) as reported by Cheng.[14]

Scheme 4. Formal Synthesis of Vindorosine



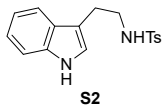
In conclusion, we have developed a new method for the construction of the pyrrolo[2,3-*d*]carbazole core of aspidosperma alkaloids based on a gold-catalyzed cascade reaction of ynamide with silyl enol ether. Notably, enantioselective synthesis of the pyrrolo[2,3-*d*]carbazole was also achieved in up to 74% *ee*. The developed reaction provides ready access to the synthetic intermediate of vindorosine.

Experimental Section

1. General Methods

IR spectra were determined on a JASCO FT/IR-4100 spectrometer. Exact mass (HRMS) spectra were recorded on JMS-HX mass spectrometer or Shimadzu LC-ESI-IT-TOF-MS equipment. ^{1}H NMR spectra were recorded using a JEOL ECA-400 or JEOL ECA-500 spectrometer at a 500 MHz frequency. Chemical shifts are reported in δ (ppm) relative to Me_4Si (in $CDCl_3$) as an internal standard. ^{13}C NMR spectra were recorded using a JEOL ECA-500 unit and referenced to the residual solvent signal. Melting points were measured by a hot stage melting point apparatus (uncorrected). For column chromatography, silica gel (Wakogel C-200E: Wako Pure Chemical Industries, Ltd) or amine silica gel (CHROMATOREX NH-DM1020: Fuji Silysia Chemical Ltd.) was employed. Chiral chromatography was performed with a Cosmosil CHiRAL 5B column (4.6 mm × 250 mm, Nacalai Tesque Inc.) or CHIRALCEL OD-H column (4.6 mm × 250 mm, Daicel Inc.) with using *n*-hexane/*i*-PrOH as an eluent. The gold complexes (*R*)-DTBM-SEGPHOS(AuCl)$_2$, (*S*)-DTBM-SEGPHOS(AuCl)$_2$, (*R*)-DTBM-BINOL(AuCl)$_2$, and (*R*)-DADMP-BINOL(AuCl)$_2$ were prepared according to the literature.[18,19]

2. Preparation of the Cyclization Precursor



***N*-[2-(1*H*-Indol-3-yl)ethyl]-4-methylbenzenesulfonamide (S2).** To a solution of tryptamine (**S1**) (9.61 g, 60.0 mmol) and Et_3N (9.20 mL, 66.0 mmol) in CH_2Cl_2 (90 mL) at 0 °C was added *p*-TsCl (13.7 g, 72.0 mmol) in one portion. After the mixture was stirred for 2 h at room temperature, the reaction was quenched with 1 M HCl and neutralized with 1 M NaOH. The resulting mixture was extracted with CH_2Cl_2 twice. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was filtered through a short pad of NH_2 silica gel with $CHCl_3$ to afford **S2** (18.9 g, 60.0 mmol, 100%) as a white solid. This material was recrystallized from $CHCl_3$ to afford pure **S2** as colorless needles: mp 112–114 °C; IR ($CDCl_3$) 3406 (N−H), 1319 (O=S=O), 1152 (O=S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.37 (s, 3H), 2.90 (t, J = 6.6 Hz, 2H), 3.24 (td, J = 6.6, 6.0 Hz, 2H), 4.58 (t, J = 6.0 Hz, 1H), 6.92 (d, J = 2.3 Hz, 1H), 7.04 (dd, J = 7.4, 7.4 Hz, 1H), 7.15-7.19 (m, 3H), 7.32 (d, J = 8.6 Hz, 1H), 7.39 (d, J = 7.4 Hz, 1H), 7.62 (d, J = 8.0 Hz, 2H), 8.12 (br s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.4, 25.4, 43.0, 111.3, 111.4, 118.4, 119.4, 122.1, 122.6, 126.8, 127.0 (2C), 129.6 (2C), 136.3, 136.6, 143.3; HRMS (ESI) calcd for $C_{17}H_{18}N_2NaO_2S^+$ [M + Na]$^+$ 337.0981, found 337.0982.

***N*-[2-(1-Benzyl-1*H*-indol-3-yl)ethyl]-4-methylbenzenesulfonamide (3).** To a solution of **S2** (18.9 g, 60.0 mmol) in dry DMF (200 mL) was slowly added NaH (60% dispersion in mineral oil, 8.40 g, 210 mmol) at room temperature under argon, and stirring continued at this temperature for 30 min. The solution was cooled to 0 °C, and BnBr (7.09 mL, 60.0 mmol) was added dropwise. After being stirred for 2 h, the reaction mixture was allowed to warm up to room temperature and stirred overnight. The reaction mixture was diluted with sat. NH_4Cl and extracted with EtOAc. The combined organic layer was washed with water and brine and dried over $MgSO_4$. After concentration *in vacuo*, the residue was purified by flash chromatography on silica gel (hexane/EtOAc = 4/1 → 3/1) to afford **3** (19.2 g, 47.5 mmol, 79%) as a pale yellow solid: mp 90–93 °C; IR ($CDCl_3$) 3278 (N−H), 1323 (O=S=O), 1154 (O=S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.38 (s, 3H), 2.91 (t, J = 6.9 Hz, 2H), 3.26 (td, J = 6.9, 5.7 Hz, 2H), 4.48 (d, J = 5.7 Hz, 1H), 5.23 (s, 2H), 6.85 (s, 1H), 7.04 (dd, J = 7.7, 7.7 Hz, 1H), 7.09 (d, J = 6.9 Hz, 2H), 7.14-7.19 (m, 3H), 7.24-7.31 (m, 4H), 7.41 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 8.0 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.5, 25.4, 43.1, 49.9, 109.8, 110.7, 118.7, 119.2, 122.0, 126.5, 126.8 (2C), 127.0 (2C), 127.5, 127.7, 128.8 (2C), 129.6 (2C), 136.76, 136.78, 137.3, 143.2. *Anal*. calcd for $C_{24}H_{24}N_2O_2S$: C, 71.26; H, 5.98; N, 6.93. Found: C, 71.18; H, 6.00; N, 6.89.

(*E*)-*N*-[2-(1-Benzyl-1*H*-indol-3-yl)ethyl]-*N*-(1,2-dichlorovinyl)-4-methylbenzenesulfonamide (4). To a solution of **3** (19.2 g, 47.4 mmol) and Cs_2CO_3 (23.2 g 52.1 mmol) in dry DMF (47 mL) was added dropwise trichloroethylene (4.69 mL, 52.1 mmol) over 10 min at room temperature under argon. The reaction mixture was allowed to warm up to 50 °C and stirred for 1.5 h. Upon cooling to room temperature, the reaction mixture was diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was filtered through a short pad of silica gel (EtOAc) to afford **4** (23.4 g, 46.9 mmol, 99%) as a pale yellow solid. This material was recrystallized from EtOAc to afford pure **4** as colorless needles: mp 103–107 °C; IR ($CDCl_3$) 1357 (O=S=O), 1164 (O=S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.37 (s, 3H), 3.03 (t, J = 7.7 Hz, 2H), 3.53 (br s, 2H), 5.20 (s, 2H), 6.51 (s, 1H), 6.93 (s, 1H), 7.07-7.09 (m, 3H), 7.15 (dd, J = 7.7, 7.7 Hz, 3H), 7.18-7.28 (m, 4H), 7.51 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.5, 24.0, 48.3, 49.8, 109.7, 110.6, 118.6, 119.2, 121.4, 121.8, 126.3, 126.8 (2C), 127.5, 127.7, 128.2 (2C), 128.7 (2C), 129.6 (3C), 135.0, 136.5, 137.3, 144.4. *Anal*. calcd for $C_{26}H_{24}Cl_2N_2O_2S$: C, 62.53; H, 4.84; N, 5.61. Found: C, 62.32; H, 4.77; N, 5.66.

***N*-[2-(1-Benzyl-1*H*-indol-3-yl)ethyl]-*N*-(3-hydroxybut-1-yn-1-yl)-4-methylbenzenesulfonamide (5).** To a solution of **4** (2.50 g, 5.01 mmol) in dry THF (50 mL) was added PhLi (*ca*. 1.6 M in dibutyl ether, 6.88 mL, 11.0 mmol) dropwise at −78 °C under argon, and stirring was continued at this temperature for 2 h. After complete conversion to the intermediate (confirmed by TLC), acetaldehyde (0.34 mL, 6.0 mmol) was added at −78 °C and the reaction mixture was allowed to warm up to room temperature. After being stirred for 1 h, the reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with water and brine and dried over $MgSO_4$. After concentration *in vacuo*, the residue was purified by flash chromatography on silica gel (hexane/EtOAc = 2/1) to afford **5** (2.31 g, 4.89 mmol, 98%) as an orange amorphous: IR ($CDCl_3$) 3407 (O–H), 2240 (C≡C), 1357 (O=S=O), 1165 (O=S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (d, J = 6.9 Hz, 3H), 2.00 (d, J = 5.2 Hz, 1H), 2.40 (s, 3H), 3.08 (t, J = 7.7 Hz, 2H), 3.57-3.66 (m, 2H), 4.57-4.62 (m, 1H), 5.21 (s, 2H), 6.89 (s, 1H), 7.09 (m, 3H), 7.16 (t, J = 7.7 Hz, 1H), 7.23-7.29 (m, 6H), 7.54 (d, J = 7.4 Hz, 1H), 7.71 (d, J = 8.0 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.6, 24.2, 24.3,

49.8, 51.7, 58.4, 73.0, 77.5, 109.7, 110.6, 118.7, 119.2, 121.8, 126.6, 126.8 (2C), 127.5 (2C), 127.6, 127.8, 128.7 (2C), 129.6 (2C), 134.6, 136.5, 137.7, 144.5; HRMS (ESI) calcd for $C_{28}H_{29}N_2O_3S^+$ $[M + H]^+$ 473.1893, found 473.1887.

***N*-[2-(1-Benzyl-1*H*-indol-3-yl)ethyl]-4-methyl-*N*-{3-[(triisopropylsilyl)oxy]but-3-en-1-yn-1-yl}benzenesulfonamide (7).** To a solution of **5** (5.57 g, 11.8 mmol) in dry CH_2Cl_2 (118 mL) was added MgO (30.5 g, 353 mmol) at room temperature. After being stirred for 6 h, the reaction mixture was filtered through Celite. The filtrate was concentrated *in vacuo* to afford the corresponding ketone **6**. This material was used for the next reaction without further purification because of its instability toward silica gel. To a solution of the crude **6** and Et_3N (4.11 mL, 29.5 mmol) in dry CH_2Cl_2 (118 mL) was added TIPSOTf (3.96 mL, 14.7 mmol) dropwise at −78 °C under argon, and the reaction mixture was allowed to warm up to room temperature. After being stirred for 2 h, the reaction mixture was diluted with sat. NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash chromatography on NH_2 silica gel (hexane/EtOAc = 12/1) to afford **7** (7.21 g, 11.5 mmol, *ca*. 98%; including a small amount of TIPSOH) as a pale yellow oil; IR ($CDCl_3$) 2229 (C≡C), 1369 (O=S=O), 1167 (O=S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09 (d, J = 7.5 Hz, 18H), 1.18-1.26 (m, 3H), 2.41 (s, 3H), 3.10 (t, J = 8.1 Hz, 2H), 3.64 (t, J = 7.8 Hz, 2H), 4.63 (s, 1H), 4.72 (s, 1H), 5.24 (s, 2H), 6.92 (s, 1H), 7.08-7.12 (m, 3H), 7.17 (t, J = 7.0 Hz, 1H), 7.23-7.31 (m, 6H), 7.55 (d, J = 7.5 Hz, 1H), 7.71 (d, J = 8.1 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 12.5 (3C), 17.9 (6C), 21.6, 24.3, 49.9, 52.0, 69.1, 79.8, 102.6, 109.7, 110.6, 118.7, 119.2, 121.9, 126.4, 126.8 (2C), 127.5 (2C), 127.6, 127.8, 128.7 (2C), 129.7 (2C), 134.7, 136.5, 137.4, 139.6, 144.5; HRMS (ESI) calcd for $C_{37}H_{47}N_2O_3SSi^+$ $[M + H]^+$ 627.3071, found 627.3071.

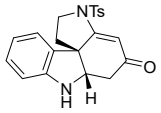
3. Gold-Catalyzed Cascade Cyclization

(6a*R,11b*R**)-7-Benzyl-3-tosyl-2,3,6a,7-tetrahydro-1*H*-pyrrolo[2,3-*d*]carbazol-5(6*H*)-one (8) (Table 1, Entry 8).** To a solution of **7** (62.7 mg, 0.1 mmol) in DCE (1 mL) was added IPrAuCl (3.1 mg, 5 mol%), $AgSbF_6$ (1.7 mg, 5 mol%), and *i*-PrOH (77 µL, 1.0 mmol) at room temperature. After the mixture was stirred for 6 h, TBAF (*ca*. 1 M in THF, 150 µL, 0.15 mmol) was added. After being stirred for 30 min at room temperature, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (hexane/EtOAc = 3/1) to afford (+)-**8** (43.0 mg, 0.091 mmol, 91%) as a yellow solid: mp 180–182 °C; IR ($CDCl_3$) 1620 (C=O), 1360 (O=S=O), 1168 (O=S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.98 (ddd, J = 11.7, 11.7, 8.2 Hz, 1H), 2.10-2.15 (m, 2H), 2.49 (s, 3H), 2.51 (dd, J = 16.6, 6.3 Hz, 1H), 3.76 (dd, J = 10.3, 5.7 Hz, 1H), 3.80 (td, J = 10.9, 5.3 Hz, 1H), 3.96 (d, J = 14.9 Hz, 1H), 4.04 (dd, J = 10.0, 8.3 Hz, 1H), 4.43 (d, J = 14.9 Hz, 1H), 6.02 (d, J = 6.9 Hz, 1H), 6.29 (s, 1H), 6.46 (m, 2H), 7.06-7.10 (m, 1H), 7.27-7.30 (m, 1H), 7.32-7.37 (m, 4H), 7.41 (d, J = 8.0 Hz, 2H), 7.88 (d, J = 8.6 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.6, 35.2, 35.4, 48.7, 48.9, 53.8, 67.4, 106.5, 109.1, 118.7, 122.0, 127.2 (2C), 127.6, 127.8 (2C), 128.7 (2C), 129.1, 130.3 (2C), 130.5, 134.6, 136.9, 145.5, 148.1, 159.4, 196.4; HRMS (ESI) calcd for $C_{28}H_{27}N_2O_3S^+$ $[M + H]^+$ 471.1737, found 471.1738.

Asymmetric Reaction Using DTBM-SEGPHOS(AuCl)$_2$ (Table 2, Entry 9)

To a solution of **7** (62.7 mg, 0.1 mmol) in DCM (1.0 mL) was added (*S*)-DTBM-SEGPHOS(AuCl)$_2$ (8.2 mg, 5 mol%) and NaBARF (8.9 mg, 10 mol%) at room temperature. After being stirred for 24 h, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (hexane/EtOAc = 3/1) to afford **8** (18.0 mg, 0.038 mmol 33%, 72% *ee*) as a yellow amorphous solid [HPLC, Chiralcel-OD-H column eluting with 65% *i*-PrOH/*n*-hexane over 30 min at 0.80 mL/min, t_1 = 17.66 min (minor isomer), t_2 = 25.44 min (major isomer)].

4. Formal Synthesis of Vindorosine



S3

(6a*S*,11b*S*)-3-Tosyl-2,3,6a,7-tetrahydro-1*H*-pyrrolo[2,3-*d*]carbazol-5(6*H*)-one (S3). A mixture of **8** (91.0 mg, 0.193 mmol) and $Pd(OH)_2$/C (ca. 50 wt % on carbon, 53 mg) in *i*-PrOH (1.0 mL) was stirred under a hydrogen atmosphere at rt for 12 h. The resulting suspension was filtered through a celite pad, and the pad was washed with EtOAc. The filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel ($CHCl_3$/MeOH = 20/1) to afford **S3** (21 mg, 0.055 mmol, 29%, 65% brsm) as a white solid: mp 232–237 °C; IR ($CDCl_3$) 1612 (C=O), 1360 (O=S=O), 1166 (O=S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.98-2.07 (m, 2H), 2.23 (dd, J = 16.0, 10.0 Hz, 1H), 2.50 (s, 3H), 2.54 (dd, J = 16.5, 6.5 Hz, 1H), 3.76-3.82 (m, 2H), 3.93 (dd, J = 9.5, 6.5 Hz, 1H), 4.03-4.06 (m, 1H), 6.02 (d, J = 7.5 Hz, 1H), 6.33 (s, 1H), 6.49-6.52 (m, 1H), 6.72 (d, J = 8.0 Hz, 1H), 7.07 (ddd, J = 7.5, 7.5, 1.5 Hz, 1H), 7.43 (d, J = 8.0 Hz, 2H), 7.90 (d, J = 8.0 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.7, 35.4, 40.8, 48.6, 54.8, 63.8, 106.5, 111.7, 119.7, 122.3, 127.3 (2C), 129.1, 129.8, 130.3 (2C), 134.7, 145.5, 147.5, 159.2, 196.2; HRMS (ESI) calcd for $C_{21}H_{21}N_2O_3S^+$ $[M + H]^+$ 381.1267, found 381.1266.

(6a*S*,11b*S*)-7-Methyl-3-tosyl-2,3,6a,7-tetrahydro-1*H*-pyrrolo[2,3-*d*]carbazol-5(6*H*)-one (11). A mixture of **S3** (21.0 mg, 0.055 mmol) and 37% HCHO aq (170 µL) in CH_2Cl_2 : MeOH (10 : 1) was added to $NaBH_3CN$ (14 mg, 0.221 mmol) at 0 °C. The reaction mixture was adjusted to pH 3 and stirred for 1.5 h. The reaction mixture was diluted with $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash chromatography on silica gel ($CHCl_3$/MeOH = 40/1) to afford **11** (22 mg, 0.055 mmol, quant., 74% *ee*) as a white solid: [HPLC, Cosmosil CHiRAL 5B column eluting with 55% *i*-PrOH/*n*-hexane over 30 min at 0.80 mL/min, t_1 = 17.84 min (minor isomer), t_2 = 19.18 min (major isomer)]: mp 174–177 °C; IR ($CDCl_3$) 1616 (C=O), 1357 (O=S=O), 1168 (O=S=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.75 (dd, J = 17.0, 9.5 Hz, 1H), 1.86 (dd, J = 12.0, 5.0 Hz, 1H), 2.10-2.28 (m, 1H), 2.45-2.48 (m, 4H), 2.67 (s, 3H), 3.70-3.76 (m, 1H), 4.01 (dd, J = 10.0, 6.0 Hz, 1H), 4.07 (dd, J = 10.0, 8.0 Hz, 1H), 5.85 (d, J = 7.5 Hz, 1H), 5.93 (s, 1H), 6.40 (ddd, J = 7.0, 7.0, 1.0 Hz, 1H), 6.56 (d, J = 8.0 Hz, 1H), 7.08 (ddd, J = 7.5, 7.5, 1.0 Hz, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.96 (d, J = 8.5 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 21.1, 31.4, 34.59, 34.62, 48.8, 53.4, 68.3, 105.5, 108.7, 117.9, 121.2, 127.2 (2C), 129.0, 130.6 (3C), 134.1, 145.8, 149.0, 159.4, 195.2; HRMS (ESI) calcd for $C_{22}H_{23}N_2O_3S^+$ $[M + H]^+$ 395.1424, found 395.1425. The spectral data were in good agreement with those previously reported.[14]

(6a*S*,11b*S*,*E*)-7-Benzyl-*N*-[(*R*)-2-(methoxymethyl)pyrrolidin-1-yl]-3-tosyl-2,3,6a,7-tetrahydro-1*H*-pyrrolo[2,3-*d*]carbazol-5(6*H*)-imine (10). A mixture of racemic **8** (100.0 mg, 0.21 mmol) and (*R*)-1-amino-2-(methoxymethyl)pyrrolidine **9** (56 µL, 0.043 mmol) in toluene (1.0 mL) was stirred at 95 °C for 24 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by flash chromatography on amine silica gel (hexane/EtOAc = 4/1) to afford **10** (9.6 mg, 0.016 mmol, 8%) as a white solid. This material was recrystallized from MeCN: mp 88–92 °C; $[\alpha]^{26}_D$ -206.2 (c 0.48, $CHCl_3$); IR ($CDCl_3$) 1643, 1600 (C=N), 1355 (O=S=O), 1166 (O=S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.64-1.73 (m, 2H), 1.78-1.84 (m, 2H), 1.90-2.06 (m, 3H), 2.29-2.34 (m, 1H), 2.48 (s, 3H), 3.07-3.11 (m, 1H), 3.20-3.27 (m, 2H), 3.33-3.36 (m, 4H), 3.41-3.43 (dd, J =9.0, 4.0 Hz, 1H), 3.57-3.65 (m, 2H), 3.95 (t, J = 8.0 Hz, 1H), 4.23 (d, J = 15.0 Hz, 1H), 4.36 (d, J = 15.0 Hz, 1H), 5.65 (d, J = 7.0 Hz, 1H), 6.31-6.35 (m, 2H), 6.54 (s, 1H), 6.98 (t, J = 8.0 Hz, 1H), 7.27-7.37 (m, 5H), 7.40 (d, J = 8.0 Hz, 2H), 7.90 (d, J = 8.0 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ

21.6, 22.5, 25.7, 26.6, 36.1, 47.7, 49.2, 53.3, 54.4, 59.2, 66.6, 67.8, 75.4, 107.8, 108.7, 117.9, 122.2, 127.27 (2C), 127.30 (3C), 128.4, 128.6 (2C), 130.0 (2C), 132.4, 135.3, 137.9, 144.3, 144.5, 148.2, 158.3; HRMS (ESI) calcd for $C_{34}H_{39}N_4O_3S^+$ $[M + H]^+$ 583.2737, found 583.2735.

(6a*S*,11b*S*)-7-Benzyl-3-tosyl-2,3,6a,7-tetrahydro-1*H*-pyrrolo[2,3-*d*]carbazol-5(6*H*)-one [(*S*,*S*)-(+)-8]. A mixture of **10** (5.8 mg, 0.010 mmol) and MeI (6.2 μL, 0.10 mmol) in THF (0.2 mL) was stirred at 55 °C for 48 h. The reaction mixture was concentrated *in vacuo*. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash chromatography on silica gel (hexane/EtOAc = 2/1) to afford **8** (2.0 mg, 0.0043 mmol, 43%): $[\alpha]^{25}_D$ +84.3 (c 0.13, $CHCl_3$).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org.
Optimization of the Asymmetric Reaction, X-ray crystal structure and crystal data of compound **10**, HPLC chromatograms, and ^1H and $^{13}C\{^1H\}$ NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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