Total Synthesis of (+)-Conolidine by the Gold(I)-Catalyzed Cascade Cyclization of a Conjugated Enyne

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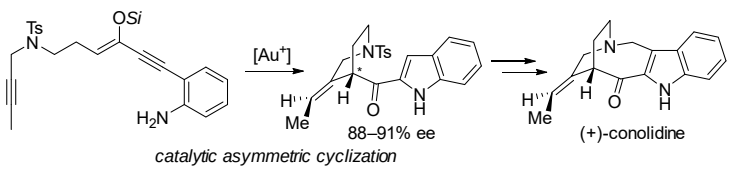


Abstract: A total synthesis of (+)-conolidine has been achieved via the gold(I)-catalyzed cascade cyclization of a conjugated enyne. Remarkably, this strategy allowed for the simultaneous formation of the indole ring and the ethylidene-substituted piperidine moiety of (+)-conolidine under homogenous gold catalysis in an enantioselective manner (88–91% ee).

Conolidine (**1**), which belongs to the C5-nor stemmadenine family of alkaloids, was first isolated from *Tabernaemonta divaricata* by Kam *et al.* in 2004 (Figure 1).[1] This group only managed to isolate 0.0013 g of conolidine from the stem bark of this small flowering plant. Since Bohn, Micalizio, and co-workers accomplished the first asymmetric total synthesis of conolidine (**1**) in 2011, there has been considerable interest in its unique analgesic activity, which differs from that of many common opioids, including morphine.[2] Although several efficient methods have been reported for the synthesis of C5-nor stemmadenine-type indoles,[2-4] the development of a diversity-oriented route suitable for evaluating the structure-activity relationships of these compounds is still highly desired.

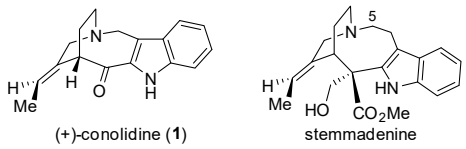


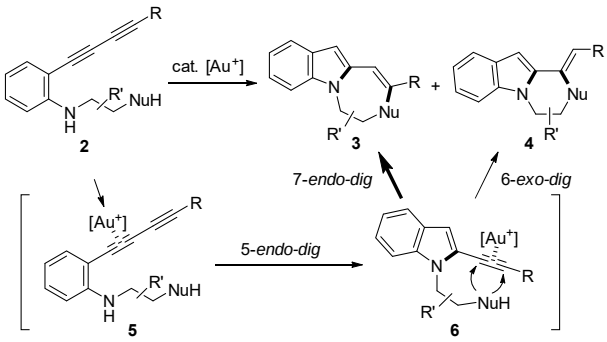
Figure 1. Stemmadenine-based alkaloids

Homogeneous gold catalysis has attracted considerable attention because of the strong π-acidity of gold, as well as its potential to stabilize cationic reaction intermediates.[5] The versatile reactivity of gold catalysts has allowed for the design of several eloquent cascade reactions for the direct step- and atom-economical synthesis of complex molecules.[6] Nowadays, homogeneous gold catalysis is recognized as one of the most effective strategies for the electrophilic activation of alkynes for the synthesis of natural products.[6f]

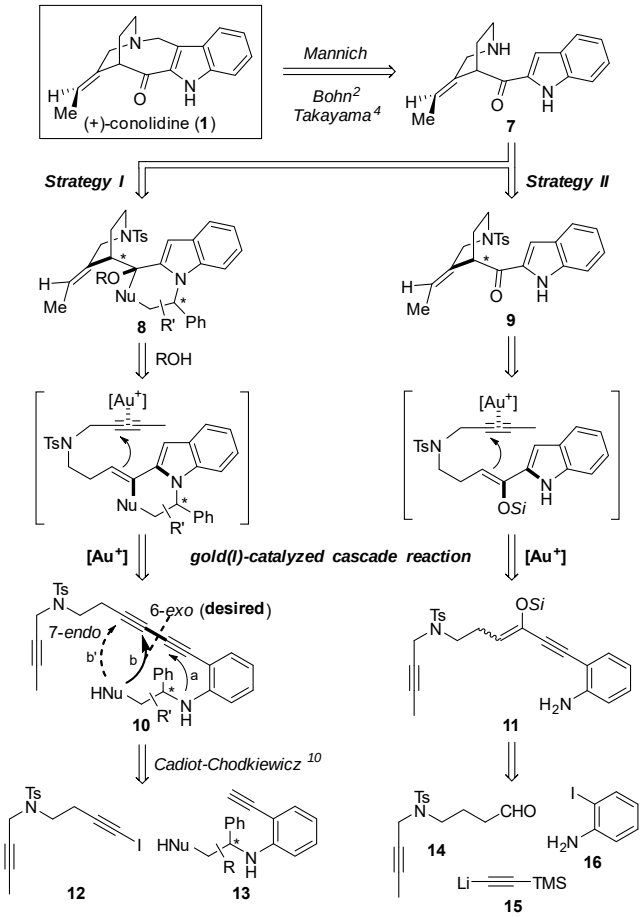
We recently reported the gold(I)-catalyzed bis-cyclization of conjugated diynes **2** (R' = H, –NuH = CH_2OH) as an efficient strategy for the construction of fused indoles **3** and **4** (Scheme 1).[7] In this reaction, the initial indole formation occurred via a 5-*endo-dig* cyclization, which was followed by a 7-*endo-dig* cyclization to give the fused indole **3** as the major product. Based on this reaction, we designed a strategy for the synthesis of (+)-conolidine (**1**) (Scheme 2, strategy I). It was envisaged that the known conolidine precursor **7**[2,4] could be prepared by the gold(I)-catalyzed cascade cyclization of conjugated diyne **10**. In this sense, the bis-cyclization reaction would allow for the formation of a fused indole (path a and b), which would be followed by a third cyclization to give the piperidine moiety. One of the potential issues with this strategy would be controlling the regioselectivity of the second cyclization step. In particular, the 6-*exo-dig* cyclization (path b) would need to be favored over the 7-*endo-dig* pathway (path b') to allow for the introduction of the oxygen atom at the appropriate carbon of the product. We also designed a second strategy (strategy II) using a conjugated enyne **11** bearing a silyl enol ether.[8] Notably, this strategy would avoid the need to control the regioselectivity of the second cyclization described in strategy I by introducing the oxygen atom of the conolidine as a silyl ether. It was also envisaged that the nucleophilicity of

the enol ether would be increased following the formation of the indole, leaving it better equipped to promote the subsequent formation of the piperidine ring. Furthermore, the use of a chiral auxiliary (in strategy I) or chiral gold complex would allow for the asymmetric induction of these key steps. Both of these strategies involve the use of readily accessible synthons **12**–**16**, and can therefore be considered as diversity-oriented convergent syntheses. Herein, we report the total synthesis of (+)-conolidine (**1**) based on the catalytic asymmetric cyclization of the enol ether-type substrate **11** (strategy II).

Scheme 1. Previous Work: Gold(I)-Catalyzed Intra-molecular Consecutive Cyclizations of a Conjugated Diyne

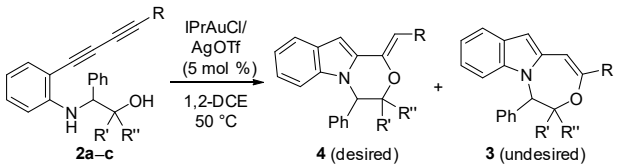


Scheme 2. Retrosynthetic Analysis of Conolidine Based on the Gold(I)-Catalyzed Cascade Reaction of Conjugated Alkynes



Strategy I. We initially conducted a series of model experiments using conjugated diynes **2a**–**c** to evaluate the possibility of controlling the regioselectivity in strategy I (Scheme 3). The reaction of **2a** bearing a phenylglycinol moiety gave the desired isomer **4a** as a minor product (**4a**/**3a** = 29:71). In contrast, substrate **2b** bearing a vicinal phenyl group and substrate **2c** bearing a carboxylic acid preferentially afforded the corresponding 6-*exo*-products (**4**/**3** = 71:29–80:20). Based on these results, we prepared the corresponding alcohol and carboxylic acid substrates **10a** and **10b** as the most suitable candidates for the synthesis of conolidine.

Scheme 3. Model Experiment for Control of the Regioselectivity in the Second Cyclization

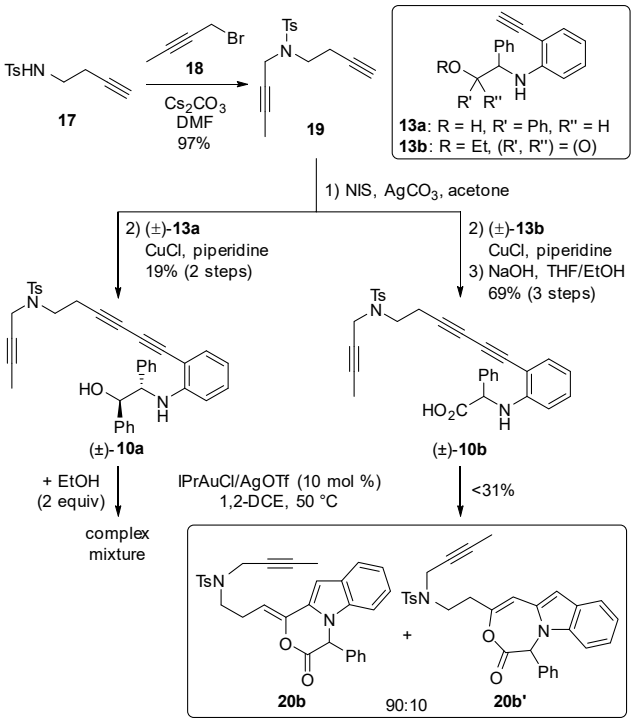


	R	R', R''	time (h)	yield (%)	ratio (**4**:**3**)
(*R*)-**2a**	Ph	H, H	5	86	29:71
(±)-**2b**	Ph	Ph, H[a]	2.5	92	71:29
(±)-**2c**	*n*-Pr	=O	3	<35	80:20

[a] The *erythro*-isomer of (±)-**2b** was used.

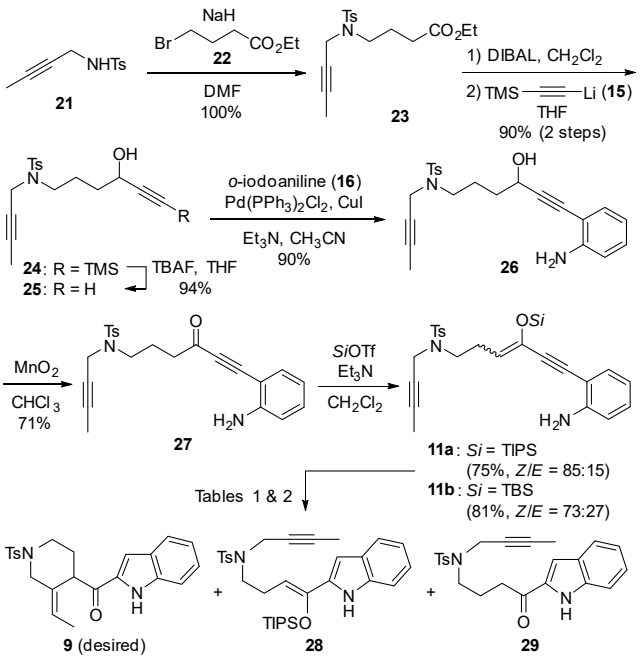
Our initial efforts towards the preparation and subsequent gold(I)-catalyzed cyclization of the conjugated diynes **10a** and **10b** are shown in Scheme 4. The alkylation of tosylamide **17**[9] with 1-bromobut-2-yne (**18**) gave diyne **19**. The iodination of the terminal alkyne moiety in **19** with NIS and $AgNO_3$, followed by the subsequent Cadiot–Chodkiewicz coupling[10] of the resulting iodoalkyne with **13a** or **13b** gave the amino alcohol- and amino acid-type substrates (±)-**10a** and **10b** (after hydrolysis), respectively. Unfortunately, however, the subsequent reaction of **10a** with IPrAuCl/AgOTf (10 mol %) and EtOH (2 equiv) in 1,2-DCE at 50 °C for 2 h gave a complex mixture of unidentified products. In contrast, the reaction of **10b** under the same conditions led to the formation of the bis-cyclization products **20b** and **20b'** with good regioselectivity for the former of these two products (**20b**/**20b'** = 90/10). It is noteworthy, however, that these compounds were formed in low yields (<31%) because of their poor stability. Disappointingly, all of our other attempts to promote the formation of the piperidine using **10b** and **20b/20b'** resulted in failure, most likely because of the poor nucleophilicity of the enol ether moiety of **20b** bearing an electron-withdrawing group. Based on these results, we discarded strategy I and focused our efforts on strategy II using the conjugated enynes **11a** and **11b**.

Scheme 4. Unsuccessful Attempts at the Gold(I)-Catalyzed Cyclization of the Conjugated Diynes **10a** and **10b** (Strategy I)



Strategy II. Conjugated enynes **11a** and **11b** bearing different silyl enol ether moieties were prepared according to route shown in Scheme 5. The alkylation of tosylamide **21**[11] with ethyl 4-bromobutanoate (**22**) gave ester **23**, which was reduced with DIBAL to give the corresponding aldehyde. The subsequent 1,2-addition of lithium (trimethylsilyl)acetylide (**15**) to this aldehyde, followed by the removal of the TMS group with TBAF afforded the terminal alkyne **25** in excellent yield. The Sonogashira coupling reaction of alkyne **25** with *o*-iodoaniline (**16**) provided alkynylaniline **26** in 90% yield. The oxidation of **26** with MnO_2 gave the corresponding ketone **27** in 71% yield, which was treated with TIPSOTf or TBSOTf in the presence of Et_3N to give the conjugated enyne-type silyl enol ethers **11a** and **11b** in 75 and 81% yields, respectively. It is noteworthy that the (*E*)- and (*Z*)-isomers[12] of **11** could be separated, as necessary, by column chromatography over silica gel followed by PTLC (see Supporting Information).

Scheme 5. Preparation and Gold-Catalyzed Cyclization of the Conjugated Enynes **11a** and **11b**



We then investigated the gold(I)-catalyzed cascade reaction of the enol ether-type conjugated enynes **11a** and **11b** (Table 1). The treatment of enyne **11a** with **L1**Au(MeCN)SbF_6 (5 mol %) (Figure 2) in toluene-d_8 at room temperature afforded the desired product **9** (16%), as well as the two monocyclization products **28**[13] (34%) and **29** (14%). To drive the reaction to completion, we investigated the use of an additive as a proton source as well as silyl scavenger. Fortunately, the addition of H_2O[4] improved the yields of **9** to 38% (entry 2), In contrast, the use of MeOH was less efficient (entry 3). The use of an IPr ligand was found to be unsuitable for this reaction (entry 4). Similarly, several other experiments using NaBARF[8h] (Figure 2) as the counter anion (entry 5), CD_2Cl_2 as a solvent (entry 6) or the TBS ether **11b** as a substrate (entry 7) did not improve the yield.

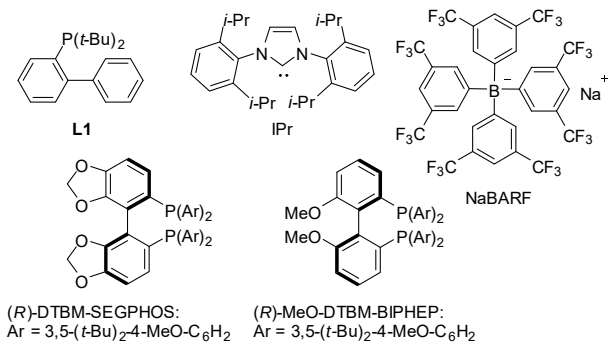
Table 1. Optimization of the Reaction Conditions[a]

entry	Ligand	additive	R	time (h)	yield(%)[b]		
					9	**28**	**29**
1	**L1**	–	TIPS	24	16	34	14
2	**L1**	**H_2O**	**TIPS**	**24**	**38**	**–**	**2**
3	**L1**	MeOH	TIPS	19	29	–	2
4	IPr	H_2O	TIPS	24	3	45	10

5	**L1**[c]	H_2O	TIPS	24	15	5	45
6[d]	**L1**	H_2O	TIPS	24	16	–	43
7	**L1**	H_2O	TBS	24	33	–	-

[a] Unless otherwise noted, all of these reactions were carried out using **11a** (*Z*/*E* = 79:21) or **11b** (*Z*/*E* = 71:29) with **L1**Au(MeCN)SbF_6 or IPrAuCl (5 mol %)/$AgSbF_6$ (5 mol %) in toluene-d_8 (0.2 M) at room temperature in the presence of an additive (1.5 equiv). [b] NMR yields were evaluated using mesitylene as an internal standard. [c] Using **L1**AuCl/NaBARF. [d] Using CD_2Cl_2 as a solvent instead of toluene-d_8.

Figure 2. Ligands and co-catalysts screened in this study



We then proceeded to investigate the enantioselective gold(I)-catalyzed cascade reaction of the conjugated enyne **11a** (Table 2). Based on a related study reported by Toste and co-workers involving the asymmetric carbocyclization of a silyl enol ether,[8h] we investigated the use of biarylphosphine-type dinuclear chiral gold complexes to affect this reaction (Figure 2). The treatment of the conjugated enyne **11a** with (*R*)-DTBM-SEGPHOS$(AuCl)_2$ (5 mol %)/$AgSbF_6$ (10 mol %) resulted in the formation of the undesired ketone **29** as the major product (entry 1). The use of (*R*)-MeO-DTBM-BIPHEP gave the desired product (*S*)-**9** in 13% yield and 89% ee (entry 2). An increase in catalyst loading (10 mol % for the bimetallic gold complex) led to a slight decreased in the yield to 10%, as well as a decrease in the ee to 76% (entry 3). Expecting that the sterically less hindered (*Z*)-isomer has better reactivity, we examined the reaction of the both isomers, (*Z*)- and (*E*)-**11a**. Interestingly, the use of (*Z*)-**11a** led to an improvement in the yield of (*S*)-**9** to 32% (entry 5), whereas the reaction of (*E*)-**11a** failed to afford the desired product (entry 4). Taken together,

these results suggested that it was only possible to generate the desired product **9** from the *Z*-isomer of **11a** when a *E*/*Z* mixture of **11a** was used as the substrate (entries 1–3). The use of **11a** in conjunction with a decreased loading of H_2O (1.0 equiv) led to an improvement in the ee to 91%, although the yield dropped to 18% (entry 6).

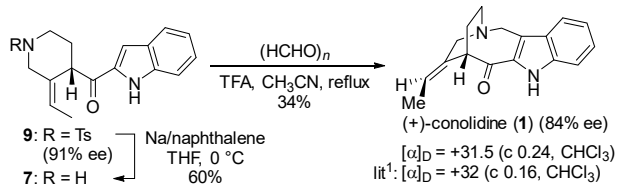
Table 2. Enantioselective Gold(I)-Catalyzed Cyclization[a]

entry	*Z*/*E* (**11**)	catalyst	time (h)	yield of **9** (%)[b]	% ee[c] [(*S*)-**9**]
1	53/47	(*R*)-DTBM-SEGPHOS$(AuCl)_2$/$AgSbF_6$	24	N.D.[d,e]	–
2	53/47	(*R*)-MeO-DTBM-BIPHEP$(AuCl)_2$/$AgSbF_6$	19	13	89
3[f]	53/47	(*R*)-MeO-DTBM-BIPHEP$(AuCl)_2$/$AgSbF_6$	19	*ca.*10	76
4	*E* only	(*R*)-MeO-DTBM-BIPHESP$(AuCl)_2$/$AgSbF_6$	20	N.D.[e]	–
5	*Z* only	**(*R*)-MeO-DTBM-BIPHEP$(AuCl)_2$**/$AgSbF_6$	**17**	**32**	**88**
6[g]	83/17	(*R*)-MeO-DTBM-BIPHEP$(AuCl)_2$/$AgSbF_6$	14	18	91

[a] Unless otherwise noted, these reactions were carried out using **11a** in toluene (0.2 M) at room temperature in the presence of H_2O (1.5 equiv) with a catalyst loading of 5 (for the bimetallic gold complex) and 10 mol % (for $AgSbF_6$). [b] Isolated yields. [c] Determined by chiral HPLC. [d] Ketone **29** was obtained as the major product. [e] N.D. = not detected. [f] The catalyst loading was increased to 10 and 20 mol %. [g] Using H_2O (1.0 equiv).

Finally, we investigated the conversion of the bis-cyclization product (*S*)-**9** (91% ee) to (+)-conolidine (**1**). The treatment of (*S*)-**9** with Na/naphthalene resulted in the cleavage of the Ts protecting group to give the known conolidine precursor **7** in 60% yield (Scheme 6). According to the procedure reported by Bohn, Micalizio, and co-workers,[2] we obtained (+)-conolidine (**1**) in 34% yield and 84% ee. The spectroscopic and specific optical rotation data for the synthetic conolidine were identical to those reported in the literature.[1,2]

Scheme 6. Total Synthesis of (+)-Conolidine



In conclusion, we have achieved the total synthesis of (+)-conolidine based on the gold(I)-catalyzed cascade cyclization of a conjugated enyne. This study has shown that the feasibility of catalytic asymmetric reactions involving chiral gold(I) complexes for the construction of stemmadenine-type scaffolds.

Experimental Section

General Methods. For open column chromatography, silica gel or NH_2 silica gel was employed. Thin layer chromatography was performed on TLC silica gel 60 F_{254} or NH_2 silica gel 60 F_{254} plate (layer thickness 0.25 mm), which were developed using standard visualizing agents: UV fluorescence (254 nm) and anisaldehyde with heating. Melting points were measured by a hot stage melting point apparatus (uncorrected). In ^{1}H NMR spectra, chemical shifts are reported in δ (ppm) relative to TMS as internal standard. In ^{13}C NMR spectra, chemical shifts are referenced to the residual solvent signal. ^{1}H NMR spectra are tabulated as follows: chemical shift, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), number of protons, and coupling constant(s).

The compounds **16**, **18**, **22**, and (*R*)-DTBM-SEGPHOS(AuCl)$_2$ were obtained commercially and used without further purification. The known compounds **S1**,[14] **S4**,[15] **S7**,[16] **17**,[9] **21**,[11] and (*R*)-MeO-BIPHES(AuCl)$_2$[17,18] were prepared according to the literature. Structures of **S1**–**S9** are shown in Schemes S1–S3 (Supporting Information).

Preparation of Starting Materials.

(*R*)-2-Phenyl-2-({2-[(trimethylsilyl)ethynyl]phenyl}amino)ethan-1-ol (S2). The coupling of

S1 and trimethylsilylacetylene was carried out according to the reported method[19] as follows: to a stirred suspension of **S1** (1.42 g, 4.86 mmol), $PdCl_2(PhCN)_2$ (112 mg, 0.29 mmol) and CuI (55.6 mg, 0.29 mmol) in dry 1,4-dioxane (10 mL) under argon were added diisopropylamine (3.4 mL, 24.2 mmol), trimethylsilylacetylene (0.7 mL, 5.06 mmol) and tri(*tert*-butyl)phosphine (0.2 mL, 0.85 mmol). After stirring at 50 °C for 12 h, the reaction mixture was diluted with EtOAc and filtered through a short pad of silica gel. The filtrate was concentrated *in vacuo* and the residue was chromatographed on silica gel (hexane/EtOAc = 5/1) to afford **S2** (976 mg, 65%) as amber oil: $[\alpha]^{29}_{D}$ 242 (*c* 0.51, $CHCl_3$); IR (neat): 3393 (OH), 2143 (C≡C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.30 (s, 9H), 1.69 (br s, 1H), 3.80-3.83 (br m, 1H), 3.96-4.00 (br m, 1H), 4.56-4.57 (br m, 1H), 5.52-5.53 (br m, 1H), 6.38 (d, *J* = 8.6 Hz, 1H), 6.57-6.58 (m, 1H), 7.00-7.04 (m, 1H), 7.25-7.35 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 0.0 (3C), 59.3, 67.3, 100.7, 101.8, 108.0, 110.9, 116.6, 126.5 (2C), 127.6, 128.7 (2C), 129.9, 131.7, 139.7, 148.4; HRMS (FAB) calcd for $C_{19}H_{24}NOSi$ (MH^+) 310.1622, found 310.1620.

(*R*)-2-[(2-Ethynylphenyl)amino]-2-phenylethan-1-ol (S3). The desilylation of **S2** was carried out according to the reported method[20] as follows: K_2CO_3 (1.08 g, 8.0 mmol) was added to the solution of **S2** (804 mg, 2.60 mmol) in MeOH (26 mL). After stirring at room temperature for 1 h, the mixture was diluted with EtOAc. The organic layer was separated, washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc = 5/1) to afford **S3** (445 mg, 72%) as pale amber powder: mp 79 °C; $[\alpha]^{26}_{D}$ 240 (*c* 1.06, $CHCl_3$); IR (neat): 3401 (OH), 3253 (C≡CH), 2089 (C≡C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.66 (dd, *J* = 7.5, 5.2 Hz, 1H), 3.50 (s, 1H), 3.82-3.87 (m, 1H), 3.97-4.03 (m, 1H), 4.60 (dd, *J* = 10.4, 6.4 Hz, 1H), 5.47-5.48 (br m, 1H), 6.39 (d, *J* = 8.7 Hz, 1H), 6.59-6.61 (m, 1H), 7.04-7.06 (m, 1H), 7.27-7.30 (m, 1H), 7.31-7.38 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 59.4, 67.3, 80.6, 83.3, 106.9, 111.1, 116.8, 126.6 (2C), 127.7, 128.9 (2C), 130.2, 132.6, 139.6, 148.4; HRMS (FAB) calcd for $C_{16}H_{16}NO$ (MH^+) 238.1226, found 238.1232.

(*R*)-2-Phenyl-2-{[2-(phenylbuta-1,3-diyn-1-yl)phenyl]amino}ethan-1-ol (2a). The coupling

of **S3** and ethynylbenzene was carried out according to the reported method[21] as follows: a mixture of **S3** (432 mg, 1.82 mmol), ethynylbenzene (1.0 mL, 9.11 mmol), $Cu(OAc)_2 \cdot H_2O$ (36.3 mg, 0.18 mmol) and piperidine (0.5 mL, 5.06 mmol) in CH_2Cl_2 (9 mL) was stirred in open atmospheric air at room temperature for 5 h. The reaction mixture was concentrated *in vacuo* and the residue was chromatographed on silica gel (hexane/EtOAc = 5/1) to afford **2a** (349 mg, 57%) as amber oil: $[\alpha]^{26}_{D}$ 470 (*c* 1.00, $CHCl_3$); IR (neat): 3391 (OH), 2208 (C≡C), 2140 (C≡C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.71-1.73 (m, 1H), 3.86-3.89 (m, 1H), 3.99-4.04 (m, 1H), 4.60-4.62 (m, 1H), 5.45-5.47 (br m, 1H), 6.38 (d, *J* = 8.1 Hz, 1H), 6.60-6.62 (m, 1H), 7.05-7.07 (m, 1H), 7.27-7.31 (m, 1H), 7.33-7.39 (m, 8H), 7.56-7.57 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 59.4, 67.2, 74.0, 78.5, 79.7, 83.0, 106.5, 111.3, 117.0, 121.8, 126.6 (2C), 127.7, 128.4 (2C), 128.8 (2C), 129.1, 130.7, 132.4 (2C), 133.4, 139.4, 149.4; HRMS (FAB) calcd for $C_{24}H_{20}NO$ (MH^+) 338.1539, found 338.1537.

(±)-(1*R*,2*S*)-2-[(2-Bromophenyl)amino]-1,2-diphenylethan-1-ol [(±)-S5]. The reaction of 2-bromoiodobenzene and (±)-**S4** was carried out according to the reported method[14] as follows: a mixture of 2-bromoiodobenzene (0.9 mL, 7.01 mmol), (±)-**S4** (1.72 g, 8.06 mmol), NaOH (600 mg, 15.0 mmol), and CuI (35.7mg, 0.19 mmol) was stirred under argon at 90 °C for 13 h. The reaction mixture was diluted with EtOAc, washed water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc = 10/1) to afford (±)-**S5** (2.06 g, 80%) as pale amber powder: mp 100 °C; IR (neat): 3398 (OH), 1321 (NH); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.37-2.39 (br m, 1H), 4.67-4.69 (m, 1H), 5.06-5.07 (m, 1H), 5.14-5.16 (br m, 1H), 6.35 (d, *J* = 8.0 Hz, 1H), 6.48 (t, *J* = 7.7 Hz, 1H), 6.93 (t, *J* = 7.7 Hz, 1H), 7.11-7.12 (m, 4H), 7.23-7.24 (m, 3H), 7.27-7.28 (m, 3H), 7.35-7.37 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 64.4, 78.0, 110.5, 112.8, 118.0, 126.5 (2C), 127.1 (2C), 127.7, 128.0, 128.2, 128.3 (2C), 128.6 (2C), 132.2, 139.6, 140.4, 143.9. *Anal.* calcd for $C_{20}H_{18}BrNO$: C, 65.23; H, 4.93; N, 3.80. Found: C, 65.48; H, 4.89; N, 3.79.

(±)-(1*R*,2*S*)-1,2-Diphenyl-2-({2-[(trimethylsilyl)ethynyl]phenyl}amino)ethan-1-ol [(±)-S6]. According to the procedure described for the preparation of **S2**, (±)-**S5** (2.95 g, 8.01 mmol) was

converted to (±)-**S6** (2.72 g, 88%). Column chromatography: silica gel (hexane/EtOAc = 10/1): dark brown oil; IR (neat): 3298 (OH), 2140 (C≡C), 1252 (NH); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.31 (s, 9H), 2.30-2.31 (br m, 1H), 4.73-4.74 (br m, 1H), 5.10-5.11 (br m, 1H), 5.57-5.58 (br m, 1H), 6.36 (d, *J* = 8.0 Hz, 1H), 6.53-6.54 (m, 1H), 6.97-6.99 (m, 1H), 7.09-7.11 (m, 4H), 7.22-7.27 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 0.0 (3C), 63.2, 76.9, 100.2, 101.7, 108.0, 110.8, 116.5, 126.3 (2C), 127.4, 127.6 (2C), 127.7, 127.96 (2C), 128.02 (2C), 129.7, 132.0, 137.9, 139.7, 147.8; HRMS (FAB) calcd for $C_{25}H_{28}NOSi$ (MH^+) 386.1935, found 386.1927.

(±)-(1*R*,2*S*)-2-[(2-Ethynylphenyl)amino]-1,2-diphenylethan-1-ol [(±)-13a]. According to the procedure described for the preparation of **S3**, (±)-**S6** (1.44 g, 3.74 mmol) was converted into (±)-**13a** (852 mg, 73%). Column chromatography: silica gel (hexane/$CHCl_3$= from 1/1 to 1/2): amber oil; IR (neat): 3396 (OH), 3292 (C≡CH), 2094 (C≡C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.54-2.55 (br m, 1H), 3.38 (s, 1H), 4.70-4.71 (br m, 1H), 5.02-5.03 (br m, 1H), 5.44-5.45 (br m, 1H), 6.30 (d, *J* = 8.6 Hz, 1H), 6.52-6.53 (m, 1H), 6.94-6.98 (m, 1H), 7.06-7.08 (m, 4H), 7.17-7.28 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 63.1, 77.2, 80.6, 83.1, 107.0, 111.1, 116.7, 126.6 (2C), 127.55, 127.63 (2C), 128.0, 128.1 (2C), 128.2 (2C), 130.1, 132.4, 138.3, 139.5, 148.2; HRMS (FAB) calcd for $C_{22}H_{20}NO$ (MH^+) 314.1539, found 314.1535.

(±)-(1*R*,2*S*)-1,2-Diphenyl-2-{[2-(phenylbuta-1,3-diyn-1-yl)phenyl]amino}ethan-1-ol [(±)-2b]. According to the procedure described for the preparation of **2a**, (±)-**13a** (430 mg, 1.37 mmol) was converted into (±)-**2b** (337 mg, 59%). Column chromatography: silica gel (hexane/$CHCl_3$= 1/1 to $CHCl_3$ only): brown powder; mp 122–124 °C; IR (neat): 3401 (OH), 2209 (C≡C), 2141 (C≡C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.43-2.43 (br m, 1H), 4.72-4.73 (br m, 1H), 5.05-5.06 (br m, 1H), 5.45-5.46 (br m, 1H), 6.29 (d, *J* = 8.6 Hz, 1H), 6.54 (t, *J* = 7.4 Hz, 1H), 6.98 (t, *J* = 7.4 Hz, 1H), 7.16 (d, *J* = 6.9 Hz, 4H), 7.26-7.30 (m, 7H), 7.36-7.41 (m, 3H), 7.59-7.60 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 63.4, 74.1, 77.5, 78.5, 79.9, 82.9, 106.6, 111.2, 116.9, 122.0, 126.6 (2C), 127.6 (2C), 127.8, 128.2, 128.4 (2C), 128.5 (2C), 128.6 (2C), 129.2, 130.7, 132.4 (2C), 132.9, 138.5, 139.2, 149.3; HRMS (FAB) calcd for $C_{30}H_{24}NO$ (MH^+) 414.1852, found 414.1860.

Ethyl 2-Phenyl-2-({2-[(trimethylsilyl)ethynyl]phenyl}amino)acetate [(±)-S8]. To a stirred suspension of (±)-**S7** (2.59 g, 6.78 mmol), $PdCl_2(PPh_3)_2$ (119 mg, 0.17 mmol) and CuI (32.3 mg, 0.17 mmol) in THF (14 mL) under argon was added trimethylsilylacetylene (1.0 mL, 7.46 mmol) and Et_3N (4.3 mL, 33.9 mmol). After stirring at rt for 3 h, the reaction mixture was diluted with EtOAc and filtered through a short pad of silica gel. The filtrate was concentrated *in vacuo* and the residue was chromatographed on silica gel (hexane/$CHCl_3$ = 3/1) to afford (±)-**S8** (2.10 g, 88%) as amber oil: IR (neat): 2145 (C≡C), 1736 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.31 (s, 9H), 1.21 (t, *J* = 7.2 Hz, 3H), 4.13-4.16 (m, 1H), 4.23-4.26 (m, 1H), 5.09 (d, *J* = 5.7 Hz, 1H), 6.04-6.05 (br m, 1H), 6.29 (d, *J* = 8.6 Hz, 1H), 6.58-6.59 (m, 1H), 7.02-7.03 (m, 1H), 7.30 (d, *J* = 6.9 Hz, 2H), 7.34-7.36 (m, 2H), 7.50 (d, *J* = 6.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 0.00 (3C), 14.0, 60.4, 61.7, 100.8, 108.1, 101.5, 110.3, 116.8, 127.0 (2C), 128.2, 128.7 (2C), 129.8, 131.8, 137.4, 147.2, 171.0; HRMS (FAB) calcd for $C_{21}H_{26}NO_2Si$ (MH^+) 352.1733, found 352.1726.

Ethyl 2-[(2-Ethynylphenyl)amino]-2-phenylacetate [(±)-13b]. According to the procedure described for the preparation of **S3**, (±)-**S8** (5.27 g, 15.0 mmol) was converted into (±)-**13b** (2.99 g, 71%). Column chromatography: silica gel (hexane/EtOAc = 20/1) The product was recrystallized from $CHCl_3$–hexane: white powder; mp 100 °C; IR (neat): 3264 (C≡CH), 2095 (C≡C), 1723 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.22 (t, *J* = 7.2 Hz, 3H), 3.51 (s, 1H), 4.15 (dq, *J* = 11.0, 7.0 Hz, 1H), 4.24 (dq, *J* = 11.0, 7.0 Hz, 1H), , 5.11 (d, *J* = 5.7 Hz, 1H), 6.03-6.04 (br m, 1H), 6.30 (d, *J* = 8.6 Hz, 1H), 6.61 (ddd, *J* = 7.4, 7.4, 1.1 Hz, 1H), 7.05-7.07 (m, 1H), 7.29-7.31 (m, 1H), 7.35-7.37 (m, 3H), 7.49-7.51 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.0, 60.3, 61.9, 80.3, 83.2, 107.1, 110.5, 117.0, 127.1 (2C), 128.3, 128.8 (2C), 130.1, 132.6, 137.3, 147.3, 171.2. *Anal*. calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.36; H, 6.11; N, 5.00.

Ethyl 2-{[2-(Hepta-1,3-diyn-1-yl)phenyl]amino}-2-phenylacetate [(±)-S9]. According to the procedure described for the preparation of **2a**, (±)-**13b** (836 mg, 3.0 mmol) was converted into **S9** (621 mg, 60%). Column chromatography: silica gel (hexane/EtOAc = 10/1): brown powder; mp 83–84 °C; IR (neat): 2236 (C≡C), 2139 (C≡C), 1733 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.04 (t,

J = 7.4 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.63 (qt, *J* = 7.4, 7.2 Hz, 2H), 2.37 (t, *J* = 7.2 Hz, 2H), 4.14-4.27 (m, 2H), 5.09 (d, *J* = 6.3 Hz, 1H), 5.99-6.00 (br m, 1H), 6.28 (d, *J* = 8.0 Hz, 1H), 6.58-6.59 (m, 1H), 7.02-7.04 (m, 1H), 7.32-7.34 (m, 4H), 7.50 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.6, 14.0, 21.7, 21.8, 60.4, 61.9, 65.2, 71.2, 80.3, 86.0, 107.1, 110.6, 117.1, 127.1 (2C), 128.3, 128.8 (2C), 130.2, 133.3, 137.2, 148.1, 171.0; HRMS (FAB) calcd for $C_{23}H_{24}NO_2$ (MH^+) 346.1802, found 346.1804.

2-{[2-(Hepta-1,3-diyn-1-yl)phenyl]amino}-2-phenylacetic acid [(±)-2c]. To a stirred suspension of (±)-**S9** (86.9 mg, 0.25 mmol) in EtOH (5 mL) was added THF until (±)-**S9** dissolved (*ca*. 2 mL), and 0.4*N* NaOH aq. (19 mL) was added to the reaction mixture. After stirring at rt for 40 min, the reaction mixture was diluted with CH_2Cl_2, washed with water, 1*N* HCl aq., and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was recrystallized from CH_2Cl_2–hexane to afford (±)-**2c** (43.3 mg, 54%): white solid; mp 164–166 °C; IR (neat): 3394 (OH), 2238 (C≡C), 2147 (C≡C), 1709 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.04 (t, *J* = 7.4 Hz, 3H), 1.63 (qt, *J* = 7.4, 6.9 Hz, 2H), 2.37 (t, *J* = 6.9 Hz, 2H), 5.14 (s, 1H), 6.30-6.32 (m, 1H), 6.61-6.63 (m, 1H), 7.04-7.08 (m, 1H), 7.35-7.37 (m, 4H), 7.51-7.52 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.5, 21.68, 21.74, 60.2, 65.1, 71.0, 80.4, 86.2, 107.3, 110.6, 117.6, 127.2 (2C), 128.8, 129.1 (2C), 130.3, 133.4, 136.4, 147.8, 175.8; HRMS (FAB) calcd for $C_{21}H_{20}NO_2$ (MH^+) 318.1489, found 318.1485.

***N*-(But-2-yn-1-yl)-*N*-(but-3-yn-1-yl)-4-methylbenzenesulfonamide (19).** A mixture of **17** (4.47 g, 20.0 mmol) and Cs_2CO_3 (16.3 g, 50.0 mmol) in dry DMF (100 mL) was stirred in open atmospheric air at 0 ºC. After stirring at the same temperature for 0.5 h, 1-bromobut-2-yne (**18**) (2.7 mL, 29.8 mmol) was added to the mixture. The mixture was stirred for 0.5 h. The mixture was diluted with Et_2O, washed with water and brine, dried over $MgSO_4$, and concentrated in *vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc = 5/1) to afford **19** (5.33 g, 97%) as colorless oil: IR (neat): 3288 (C≡CH), 2224 (C≡C), 2120 (C≡C), 1343 (S=O), 1156 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.58 (t, *J* = 2.1 Hz, 3H), 2.01 (t, *J* = 2.5 Hz, 1H), 2.42 (s, 3H), 2.51 (td, *J* = 7.4, 2.5 Hz, 2H), 3.35 (t, *J* = 7.4 Hz, 2H), 4.12 (q, *J* = 2.1 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H),

7.73 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 3.2, 18.9, 21.4, 37.7, 45.3, 70.1, 71.7, 80.8, 81.7, 127.6 (2C), 129.3 (2C), 135.9, 143.3; HRMS (FAB) calcd for $C_{15}H_{18}NO_2S$ (MH^+) 276.1058, found 276.1059.

***N*-(But-2-yn-1-yl)-*N*-[6-(2-{[(1*R*,2*S*)-2-hydroxy-1,2-diphenylethyl]amino}phenyl)hexa-3,5-diyn-1-yl]-4-methylbenzenesulfonamide [(±)-10a].** A mixture of **19** (1.10 g, 4.0 mmol), $AgNO_3$ (203 mg, 1.20 mmol), and NIS (1.26 g, 5.60 mmol) in acetone (100 mL) was stirred in open atmospheric air at room temperature under dark. After stirring at the room temperature for 1 h, the mixture was concentrated *in vacuo*. The residue was diluted with $CHCl_3$, washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. This crude iodide **12** was used for the next reaction without further purification. According to the reported method,[22] the copper-mediated coupling of (±)-**13a** and **12** was conducted as follows: **12**, (±)-**13a** (0.63 g, 2.02 mmol), and CuCl (60.0 mg, 0.60 mmol) in piperidine (7.0 mL) was stirred at room temperature under argon for 3 h. The reaction mixture was quenched with aqueous saturated NH_4Cl, diluted with Et_2O, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc =10/1) to afford (±)-**10a** (0.31 g, 19% based on (±)-**13a**) as pale amber amorphous: IR (neat): 3396 (OH), 2230 (C≡C), 2214 (C≡C), 1327 (S=O), 1157 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.58 (t, J = 2.0 Hz, 3H), 2.40 (s, 3H), 2.59 (br s, 1H), 2.77 (t, J = 7.4 Hz, 2H), 3.44 (t, J = 7.4 Hz, 2H), 4.14-4.15 (br m, 2H), 4.69-4.70 (br m, 1H), 5.07 (br s, 1H), 5.48-5.49 (br m, 1H), 6.26 (d, J = 8.6 Hz, 1H), 6.51 (t, J = 7.2 Hz, 1H), 6.94-6.97 (m, 1H), 7.11-7.11 (m, 4H), 7.24-7.28 (m, 9H), 7.75 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 3.3, 20.3, 21.4, 37.9, 45.2, 63.1, 67.0, 71.7, 72.5, 77.2, 79.8, 81.8, 81.9, 106.3, 111.1, 116.7, 126.5 (2C), 127.55, 127.58 (2C), 127.7 (2C), 128.0, 128.15 (2C), 128.22 (2C), 129.4 (2C), 130.4, 132.8, 135.6, 138.3, 139.3, 143.5, 149.3; HRMS (FAB) calcd for $C_{37}H_{35}N_2O_3S$ (MH^+) 587.2368, found 587.2363.

Ethyl 2-{[2-(6-{[*N*-(But-2-yn-1-yl)-4-methylphenyl]sulfonamide}hexa-1,3-diyn-1-yl)phenyl]amino}-2-phenylacetate [(±)-S10)]. According to the procedure described for the preparation of (±)-**10a**, (±)-**13b** (12.0 g, 3.0 mmol) was converted to (±)-**S10** (0.80 g, 73%) by the

reaction with **12** in the presence of CuCl (59.4 mg, 0.6 mmol) in piperidine (7 mL) at room temperature for 4 h. Column chromatography: silica gel (hexane/EtOAc = 3/1); yellow oil; IR (neat): 2226 (C≡C), 2146 (C≡C), 1735 (C=O), 1328 (S=O), 1158 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.22 (t, *J* = 7.2 Hz, 3H), 1.61 (t, *J* = 2.3 Hz, 3H), 2.41 (s, 3H), 2.71-2.74 (m, 2H), 3.39-3.42 (m, 2H), 4.12-4.27 (m, 4H), 5.09 (d, *J* = 5.7 Hz, 1H), 5.98 (d, *J* = 5.7 Hz, 1H), 6.28 (d, *J* = 8.6 Hz, 1H), 6.57-6.60 (m, 1H), 7.02-7.05 (m, 1H), 7.30-7.35 (m, 6H), 7.49 (d, *J* = 7.4 Hz, 2H), 7.75 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 3.3, 13.9, 20.3, 21.4, 38.0, 45.2, 60.3, 61.9, 66.8, 71.8, 72.2, 79.8, 81.8, 81.9, 106.6, 110.6, 117.1, 127.0 (2C), 127.7 (2C), 128.3, 128.8 (2C), 129.4 (2C), 130.4, 133.3, 135.8, 137.1, 143.4, 148.2, 170.9; HRMS (FAB) calcd for $C_{33}H_{33}N_2O_4S$ (MH^+) 553.2161, found 553.2155.

2-{[2-(6-{[*N*-(But-2-yn-1-yl)-4-methylphenyl]sulfonamide}hexa-1,3-diyn-1-yl)phenyl]amino}-2-phenylacetic Acid [(±)-10b]. THF (*ca*. 2 mL) was added to the mixture (±)-**S10** (0.15 g, 0.27 mmol) and 0.4*N* NaOH (2 mL) in EtOH (4 mL). After stirring at the room temperature for 0.5 h, the reaction mixture was diluted with CH_2Cl_2, washed with water, 1*N* HCl, and brine, dried over Na_2SO_4, and concentrated *in vacuo* to afford (±)-**10b** (0.14 g, 95%) as brown powder; mp 64–65 °C; IR (neat): 3386 (OH), 2309 (C≡C), 2145 (C≡C), 1715 (C=O), 1326 (S=O), 1157 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.60 (br s, 3H), 2.42 (s, 3H), 2.71-2.72 (br m, 2H), 3.39-3.41 (br m, 2H), 4.12 (br s, 2H), 5.12 (br s, 1H), 6.31-6.32 (br m, 1H), 6.61-6.63 (m, 1H), 7.06-7.07 (m, 1H), 7.29-7.37 (m, 7H), 7.50-7.52 (m, 2H), 7.75 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 3.3, 20.3, 21.5, 37.9, 45.1, 60.2, 66.8, 71.8, 72.2, 79.8, 81.9, 82.1, 106.6, 110.7, 117.4, 127.2 (2C), 127.7 (2C), 128.6, 129.0 (2C), 129.4 (2C), 130.5, 133.5, 135.7, 136.5, 143.5, 148.0, 176.0; HRMS (FAB) calcd for $C_{31}H_{29}N_2O_4S$ (MH^+) 525.1848, found 525.1849.

Ethyl 4-{[*N*-(But-2-yn-1-yl)-4-methylphenyl]sulfonamide}butanoate (23). The coupling of **21** and ethyl 4-bromobutanoate (**22**) was carried out according to the reported method[23] as follows: a mixture of **21** (448 mg, 2.0 mmol) and NaH (48.0 mg, 2.4 mmol) in dry DMF (5 mL) was stirred at room temperature for 0.5 h under argon. 4-Bromobutanoate (**22**) (0.17 mL, 2.4 mmol) was added

to the reaction mixture. The mixture was stirred for 3 h. The mixture was quenched with aqueous saturated NH_4Cl, diluted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc = 10/1) to afford **23** (0.68 g, 100%) as pale yellow oil: IR (neat): 1730 (C=O), 1345 (S=O), 1157 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.26 (t, *J* = 7.2 Hz, 3H), 1.54 (t, *J* = 2.3 Hz, 3H), 1.88 (tt, *J* = 6.6, 6.6 Hz, 2H), 2.40-2.41 (m, 5H), 3.21 (t, *J* = 6.6 Hz, 2H), 4.05 (q, *J* = 2.3 Hz, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 3.2, 14.2, 21.5, 22.7, 31.1, 36.8, 45.5, 60.5, 71.6, 81.6, 127.8 (2C), 129.2 (2C), 136.0, 143.2, 173.1; HRMS (FAB) calcd for $C_{17}H_{24}NO_4S$ (MH^+) 338.1426, found 338.1423.

***N*-(But-2-yn-1-yl)-*N*-[4-hydroxy-6-(trimethylsilyl)hex-5-yn-1-yl]-4-methylbenzenesulfonamide (24).** Alkynylation was carried out according to the reported method[24] as follows: to a mixture of **23** (2.70 g, 8.0 mmol) in dry CH_2Cl_2 (40 mL) was added 1M DIBAL in toluene (9 mL, 8.7 mmol) at –78 ºC under argon. After stirring at the same temperature for 1 h, the reaction was quenched with MeOH (1 equiv) and H_2O (6 equiv) at –78 ºC, and the resulting slurry was allowed to warm to room temperature. It was then filtered through $MgSO_4$ and Celite and the solvent was evaporated under reduced pressure to leave aldehyde **14** as a yellow liquid. This crude material was used for the next reaction without further purification. To a mixture of trimethylsilylacetylene (1 mL, 7.20 mmol) in dry THF (36 mL) at –78 ºC under argon was added *n*-BuLi in THF (2.6M solution in *n*-BuLi; 3.1 mL, 8.0 mmol) dropwise, and the mixture was stirred at –78 ºC for 0.5 h to afford a solution of lithium trimethylsilylacetylide (**15**), to which the solution of **14** in THF (18 mL) was slowly added. After stirring at –78 ºC for 2 h, the reaction mixture was cooled to room temperature, quenched with aqueous saturated NH_4Cl, diluted with Et_2O, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc =3/1) to afford **24** (2.81 g, 90%) as colorless oil: IR (neat): 3511 (OH), 2223 (C≡C), 2170 (C≡C), 1345 (S=O), 1158 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.17 (s, 9H), 1.53 (t, *J* = 2.3 Hz, 3H), 1.72-1.77 (m, 4H), 2.03-2.04 (br m, 1H), 2.42 (s, 3H), 3.20-3.21 (br m, 2H),

4.06 (q, J = 2.3 Hz, 2H), 4.42-4.43 (br m, 1H), 7.28-7.30 (m, 2H), 7.72-7.73 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 0.0 (3C), 3.4, 21.7, 23.1, 34.4, 36.6, 45.8, 62.5, 71.7, 81.7, 89.9, 106.4, 128.0 (2C), 129.4 (2C), 136.1, 143.3; HRMS (FAB) calcd for $C_{20}H_{30}NO_3SSi$ (MH^+) 392.1716, found 392.1710.

***N*-(But-2-yn-1-yl)-*N*-(4-hydroxyhex-5-yn-1-yl)-4-methylbenzenesulfonamide (25).** To a mixture of **24** (4.48 g, 11.4 mmol) in dry THF (23 mL) at 0 ºC under argon was added 1M TBAF in THF (11.5 mL, 11.4 mmol) dropwise, and the mixture was stirred at room temperature for 0.7 h. The mixture was diluted with CH_2Cl_2, washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc =5/1) to afford **25** (3.42 g, 94%) as pale amber oil: IR (neat): 3516 (OH), 3284 (C≡H), 2225 (C≡C), 2114 (C≡C), 1327 (S=O), 1156 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.54 (br s, 3H), 1.72-1.81 (m, 4H), 2.31 (br s, 1H), 2.42 (s, 3H), 2.48-2.48 (br m, 1H), 3.21 (t, J = 6.6 Hz, 2H), 4.06-4.06 (br m, 2H), 4.45 (br s, 1H), 7.29 (d, J = 8.0 Hz, 2H), 7.72 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 3.2. 21.4, 22.8, 34.1, 36.5, 45.6, 61.6, 71.5, 73.1, 81.6, 84.5, 127.8 (2C), 129.2 (2C), 135.8, 143.2; HRMS (FAB) calcd for $C_{17}H_{22}NO_3S$ (MH^+) 320.1320, found 320.1318.

***N*-[6-(2-Aminophenyl)-4-hydroxyhex-5-yn-1-yl]-*N*-(but-2-yn-1-yl)-4-methylbenzenesulfonamide (26).** Et_3N (1.5 mL, 12.0 mmol) was added to a stirred mixture of **25** (0.97 g, 3.02 mmol), 2-iodoaniline (**16**) (0.66 g, 3.03 mmol), $PdCl_2(PPh_3)_2$ (53.1 mg, 0.08 mmol) and CuI (28.8 mg, 0.15 mmol) in CH_3CN (20 mL) under argon. After stirring at room temperature for 1.5 h, the mixture was diluted with EtOAc, washed with aqueous saturated NH_4Cl and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc =2/1) to afford **26** (1.11 g, 90%) as colorless oil: IR (neat): 3379 (OH), 2301 (C≡C), 2218 (C≡C), 1328 (S=O), 1306 (NH), 1156 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.52 (t, J = 2.3 Hz, 3H), 1.78-1.90 (m, 4H), 2.40 (s, 3H), 2.49 (br s, 1H), 3.24 (t, J = 6.6 Hz, 2H), 4.06 (q, J = 2.3 Hz, 2H), 4.24 (br s, 2H), 4.70-4.72 (br m, 1H), 6.65-6.68 (m, 2H), 7.09-7.13 (m, 1H), 7.23-7.27 (m, 3H), 7.72 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 3.2, 21.4, 23.2, 34.6, 36.7, 45.8, 62.5,

71.6, 81.6, 81.7, 95.1, 107.1, 114.3, 117.8, 127.8 (2C), 129.2 (2C), 129.8, 132.2, 135.8, 143.2, 147.9; HRMS (FAB) calcd for $C_{23}H_{27}N_2O_3S$ (MH^+) 411.1742, found 411.1742.

***N*-[6-(2-Aminophenyl)-4-oxohex-5-yn-1-yl]-*N*-(but-2-yn-1-yl)-4-methylbenzenesulfonamide (27).** According to the reported method,[25] oxidation of **26** was conducted as follows: a mixture of **26** (421 mg, 1.03 mmol) and MnO_2 (882 mg, 10.3 mmol) in dry $CHCl_3$ (10 mL) was stirred under reflux for 0.5 h. The reaction mixture was cooled to room temperature, filtered through Celite, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc = 5/1) to afford **27** (297 mg, 71%) as orange amber oil: IR (neat): 2300 (C≡C), 2180 (C≡C), 1658 (C=O), 1342 (S=O), 1330 (NH), 1156 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.54 (t, *J* = 2.3 Hz, 3H), 1.99 (tt, *J* = 7.0, 7.0 Hz, 2H), 2.41 (s, 3H), 2.82 (t, *J* = 7.2 Hz, 2H), 3.22 (t, *J* = 6.6 Hz, 2H), 4.05 (q, *J* = 2.3 Hz, 2H), 4.47 (br s, 2H), 6.68-6.69 (m, 2H), 7.20-7.24 (m, 1H), 7.28 (d, *J* = 8.6 Hz, 2H), 7.36-7.37 (m, 1H), 7.72 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 3.2, 21.4, 21.9, 37.0, 42.1, 45.5, 71.5, 81.7, 89.1, 94.1, 103.4, 114.5, 117.8, 127.8 (2C), 129.2 (2C), 132.5, 133.8, 135.7, 143.3, 105.3, 186.5; HRMS (FAB) calcd for $C_{23}H_{25}N_2O_3S$ (MH^+) 409.1586, found 409.1590.

(*E*)- and (*Z*)-*N*-{6-(2-Aminophenyl)-4-[(triisopropylsilyl)oxy]hex-3-en-5-yn-1-yl}-*N*-(but-2-yn-1-yl)-4-methylbenzenesulfonamide (11a). TIPSOTf (0.9 mL, 3.24 mmol) was added dropwise to a mixture of **27** (883 mg, 2.16 mmol) and Et_3N (0.8 mL, 6.84 mmol) in dry CH_2Cl_2 (36 mL) at –78 ºC under argon, and the mixture was stirred for 2 h. The mixture allowed to warm slowly to room temperature. The mixture was diluted with EtOAc, washed with 3*N* HCl twice, water, aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in *vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc =5/1) to afford **11a** (921 mg, 75%, *Z*/*E* = 85/15, determined by ^{1}H NMR).[11] Both products were isolated by column chromatography on silica gel followed by PTLC (silica gel) with hexane/EtOAc (10/1). Compound (*Z*)-**11a** (more polar isomer): amber oil; IR (neat): 2193 (C≡C), 1616 (SiOC=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.12 (d, *J* = 7.4 Hz, 18H), 1.27-1.36 (m, 3H), 1.54 (t, *J* = 2.3 Hz, 3H), 2.41 (s, 3H), 2.47-2.53 (m, 2H), 3.22 (t, *J* =

7.4 Hz, 2H), 4.09 (q, J = 2.3 Hz, 2H), 4.19 (br s, 2H), 5.09 (t, J = 7.2 Hz, 1H), 6.67-6.69 (m, 2H), 7.11-7.14 (m, 1H), 7.21 (d, J = 6.9 Hz, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.74 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 3.2, 12.9 (3C), 18.0 (6C), 21.5, 24.4, 36.7, 45.3, 71.8, 81.4, 83.7, 92.3, 107.1, 114.3, 114.8, 117.8, 127.8 (2C), 129.2 (2C), 129.9, 131.9, 134.1, 136.1, 143.1, 148.0; HRMS (FAB) calcd for $C_{32}H_{45}N_2O_3SSi$ (MH^+) 565.2920, found 565.2919. Compound (*E*)-**11a** (less polar isomer): amber oil; IR (neat): 2191 (C≡C), 1616 (SiOC=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.13 (d, J = 7.4 Hz, 18H), 1.27 (m, 3H), 1.51 (t, J = 2.3 Hz, 3H), 2.40 (s, 3H), 2.51-2.54 (m, 2H), 3.21 (t, J = 7.4 Hz, 2H), 4.10 (q, J = 2.3 Hz, 2H), 4.27 (br s, 2H), 5.30 (t, J = 8.0 Hz, 1H), 6.67-6.70 (m, 2H), 7.11-7.14 (m, 1H), 7.26-7.27 (m, 3H), 7.72 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 3.2, 12.5 (3C), 17.9 (6C), 21.5, 27.4, 37.0, 45.9, 71.8, 81.6, 89.1, 89.8, 107.0, 114.4, 114.6, 117.7, 127.8 (2C), 129.2 (2C), 130.0, 132.1, 135.8, 136.0, 143.1, 148.0; HRMS (FAB) calcd for $C_{32}H_{45}N_2O_3SSi$ (MH^+) 565.2920, found 565.2913.

(*E*)- and (*Z*)-*N*-{6-(2-Aminophenyl)-4-[(*tert*-butyldimethylsilyl)oxy]hex-3-en-5-yn-1-yl}-*N*-(but-2-yn-1-yl)-4-methylbenzenesulfonamide (11b). TBSOTf (0.2 mL, 0.81 mmol) was added dropwise to a mixture of **27** (166 mg, 0.41 mmol) and Et_3N (0.1 mL, 0.81 mmol) in dry CH_2Cl_2 (0.8 mL) at 0 ºC under argon and the mixture was stirred at room temperature for 1 h. The mixture was diluted with EtOAc, washed with 1*N* HCl, water, aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc =5/1) to afford **11b** (171 mg, 81%, *Z*/*E* = 73/27, determined by ^{1}H NMR).[11] Both products were isolated by column chromatography on silica gel followed by PTLC (silica gel) with hexane/EtOAc (10/1). Compound (*Z*)-**11b** (more polar isomer): reddish amber oil; IR (neat): 2193 (C≡C), 1616 (SiOC=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.26 (s, 6H), 0.96 (s, 9H), 1.54 (t, J = 2.3 Hz, 3H), 2.41 (s, 3H), 2.45 (dt, J = 7.4, 7.4 Hz, 2H), 3.21 (t, J = 7.4 Hz, 2H), 4.09 (q, J = 2.3 Hz, 2H), 4.20 (br s, 2H), 5.13 (t, J = 7.4 Hz, 1H), 6.67-6.69 (m, 2H), 7.12-7.13 (m, 1H), 7.25-7.28 (m, 3H), 7.73 (d, J = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.1 (2C), 3.2, 18.1, 21.5, 24.3, 25.7 (3C), 36.7, 45.3, 71.7, 81.5, 84.3, 92.1, 107.0, 114.3, 115.2, 117.8, 127.8 (2C), 129.2 (2C), 129.9, 131.9, 133.8,

136.0, 143.1, 147.9; HRMS (FAB) calcd for $C_{29}H_{39}N_2O_3SSi$ (MH^+) 523.2451, found 523.2458. Compound (*E*)-**11b** (less polar isomer): reddish amber oil; IR (neat): 2193 (C≡C), 1616 (SiOC=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.23 (s, 6H), 0.96 (s, 9H), 1.51 (t, *J* = 2.3 Hz, 3H), 2.40 (s, 3H), 2.52 (dt, *J* = 7.6, 7.6 Hz, 2H), 3.22 (t, *J* = 7.6 Hz, 2H), 4.10 (q, *J* = 2.3 Hz, 2H), 4.27 (br s, 2H), 5.27 (t, *J* = 8.0 Hz, 1H), 6.66-6.70 (m, 2H), 7.11-7.14 (m, 1H), 7.25-7.29 (m, 3H), 7.72 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.4 (2C), 3.2, 18.1, 21.5, 25.6 (3C), 27.3, 37.0, 45.9, 71.8, 81.6, 89.4, 89.7, 107.0, 114.4, 115.1, 117.7, 127.8 (2C), 129.2 (2C), 130.1, 132.1, 135.4, 136.0, 143.1, 148.0; HRMS (FAB) calcd for $C_{29}H_{39}N_2O_3SSi$ (MH^+) 523.2451, found 523.2454.

2. Gold(I)-Catalyzed Cascade Reactions.

General Procedure A: Synthesis of (*R*)-2,5-Diphenyl-4,5-dihydro-[1,4]oxazepino[4,5-*a*]indole (3a) and (*R, Z*)-1-Benzylidene-4-phenyl-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]indole (4a). A screw-cap test tube was charged with **2a** (33.7 mg, 0.10 mmol), IPrAuCl (3.1 mg, 5.0 μmol) and AgOTf (1.3 mg, 5.0 μmol). Dry 1,2-DCE (1.5 mL) was added to the screw-cap test tube. After stirring at 50 °C for 5 h, the reaction mixture was concentrated *in vacuo* and chromatographed on NH_2 silica gel (hexane/$CHCl_3$ = 2/1), and the collected solid was rinsed with hexane to afford an inseparable mixture of **3a**/**4a** (29.0 mg, 86%, **3a**/**4a** = 71/29, determined by ^{1}H NMR): greenish gray powder; mp 198–200 °C; IR (neat) 1627 (CH_2OC=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: (Major isomer **3a**) 4.70 (dd, *J* = 12.6, 1.1 Hz, 1H), 5.00 (dd, *J* = 12.6, 3.7 Hz, 1H), 5.89 (br m, 1H), 6.47 (s, 1H), 6.55 (s, 1H), 7.04-7.08 (m, 3H), 7.11-7.17 (m, 2H), 7.19-7.35 (m, 6H), 7.58-7.58 (m, 1H), 7.63-7.64 (m, 2H); (Minor isomer **4a**): 4.57-4.61 (m, 2H), 5.50-5.50 (br m, 1H), 6.37 (s, 1H), 6.94 (s, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 7.11-7.17 (m, 5H), 7.19-7.35 (m, 6H), 7.69 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: (Major isomer **3a**): 61.3, 73.3, 96.6, 102.8, 109.1, 120.19, 120.20, 121.7, 125.5 (2C), 126.5 (2C), 127.7, 128.2 (2C), 128.3, 128.5, 128.6 (2C), 136.0, 136.6, 138.1, 138.4, 153.4; (Minor isomer **4a**): 55.3, 70.6, 97.7, 105.5, 109.6, 120.8 (2C), 122.2 (2C), 126.1 (2C),

127.8, 128.2 (2C), 128.3, 128.46, 128.47, 128.7, 128.9, 130.6, 135.7, 135.9, 138.1, 144.7; HRMS (ESI) calcd for $C_{24}H_{20}NO$ (MH^+): 338.1545; found: 338.1550.

(±)-(4*R*,5*S*)-2,4,5-Triphenyl-4,5-dihydro-[1,4]oxazepino[4,5-*a*]indole (3b) and (±)-(3*R*,4*S*)-1-[(*Z*)-Benzylidene]-3,4-diphenyl-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]indole (4b). By use of the General Procedure A, **2b** (41.4 mg, 0.10 mmol) was converted to **3b**/**4b** (37.9 mg, 92%, **3b**/**4b** = 29/71, determined by ^{1}H NMR) by the reaction in the presence of IPrAuCl (3.1 mg, 5.0 μmol) and AgOTf (1.3 mg, 5.0 μmol) in dry 1,2-DCE (1.0 mL) at 50 °C for 2.5 h. Both the products were isolated by PTLC (NH_2 silica gel) with hexane/Et_2O (3/1). Compound **3b** (less polar isomer): white solid; mp >250 °C; IR (neat): 1642 (CHOC=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.90 (d, *J* = 6.9 Hz, 2H), 6.61 (s, 1H), 6.64 (s, 1H), 6.82 (d, *J* = 6.9 Hz, 2H), 7.05-7.12 (m, 5H), 7.15-7.18 (m, 1H), 7.23-7.24 (m, 2H), 7.32-7.36 (m, 6H), 7.59-7.60 (m, 1H), 7.69-7.70 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 67.5, 83.4, 97.2, 103.0, 109.2, 120.19, 120.24, 121.8, 125.7 (2C), 126.6 (2C), 127.71 (2C), 127.73, 127.9, 128.0, 128.25 (2C), 128.34 (2C), 128.4 (2C), 128.6, 135.7, 135.9, 136.4, 138.1, 138.4, 152.7; HRMS (FAB) calcd for $C_{30}H_{24}NO$ (MH^+) 414.1852, found 414.1861. Compound **4b** (more polar isomer): pale yellow solid; mp 168–172 °C; IR (neat): 1632 (CH_2OC=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.54-5.55 (br m, 1H), 5.76-5.77 (br m, 1H), 6.48 (s, 1H), 6.70-6.70 (m, 2H), 7.00 (d, *J* = 8.6 Hz, 1H), 7.04-7.05 (m, 2H), 7.09-7.18 (m, 7H), 7.26-7.33 (m, 5H), 7.65-7.67 (m, 1H), 7.75 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 60.9, 80.3, 97.5, 105.8, 109.1, 120.82, 120.84, 122.3, 126.1, 126.5 (2C), 127.881 (2C), 127.886 (2C), 128.0, 128.17 (2C), 128.22, 128.35 (2C), 128.38, 128.8 (2C), 130.3, 134.8, 135.6, 135.7, 136.2, 144.9; HRMS (FAB) calcd for $C_{30}H_{24}NO$ (MH^+) 414.1852, found 414.1859.

5-Phenyl-2-propyl-[1,4]oxazepino[4,5-*a*]indol-4(5*H*)-one (3c) and (*Z*)-1-Butylidene-4-phenyl-1*H*-[1,4]oxazino[4,3-*a*]indol-3(4*H*)-one (4c). By use of the General Procedure A, **2c** (31.7 mg, 0.10 mmol) was converted to **3c**/**4c** (11.1 mg, <35%, **3c**/**4c** = 20/80, determined by ^{1}H NMR) by the reaction in the presence of IPrAuCl (3.1 mg, 5.0 μmol) and AgOTf (1.3 mg, 5.0 μmol) in dry 1,2-DCE (1.0 mL) at 50 °C for 3 h. The products were separated by PTLC (NH_2 silica gel) with

hexane/ Et_2O (3/1). Compound **3c** (less polar isomer): unstable pale amber oil; IR (neat): 1749 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.62 (t, *J* = 7.4 Hz, 3H), 1.10-1.19 (m, 1H), 1.33-1.43 (m, 1H), 1.95-2.01 (m, 1H), 2.11-2.17 (m, 1H), 5.96 (s, 1H), 6.55 (s, 1H), 6.67-6.69 (m, 2H), 6.76 (s, 1H), 7.19-7.29 (m, 5H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.0, 19.9, 37.0, 62.9, 102.3, 102.9, 108.7, 120.8, 121.1, 122.6, 124.6 (2C), 128.5, 128.9 (3C), 132.3, 133.0, 136.9, 149.0, 164.2; HRMS (FAB) calcd for $C_{21}H_{20}NO_2$ (MH^+) 318.1489, found 318.1484. Compound **4c** (more polar isomer): unstable yellow oil; IR (neat): 1760 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.93 (t, *J* = 7.4 Hz, 3H), 1.47-1.51 (m, 2H), 2.29-2.41 (m, 2H), 5.69 (t, *J* = 7.7 Hz, 1H), 6.24 (s, 1H), 6.82 (s, 1H), 7.04-7.06 (m, 3H), 7.10-7.17 (m, 2H), 7.28-7.28 (m, 3H), 7.63 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.7, 22.4, 26.6, 59.2, 97.5, 109.7, 112.4, 121.0, 121.4, 122.8, 126.1 (2C), 127.1, 129.0, 129.1, 129.2 (2C), 134.65, 134.74, 139.5, 163.1; HRMS (FAB) calcd for $C_{21}H_{20}NO_2$ (MH^+) 318.1489, found 318.1484.

(*Z*)-*N*-(But-2-yn-1-yl)-4-methyl-*N*-[3-(3-oxo-4-phenyl-3,4-dihydro-*1H*-[1,4]oxazino[4,3-*a*]indol-1-ylidene)propyl]benzenesulfonamide (20b). A screw-cap test tube was charged with (±)-**10b** (52.5 mg, 0.1 mmol), IPrAuCl (6.2 mg, 0.01 mmol) and AgOTf (2.6 mg, 0.01 mmol). Dry 1,2-DCE (1 mL) was added to the screw-cap test tube. After stirring at 50 °C for 27 h, the mixture was concentrated *in vacuo* and chromatographed on NH_2 silica gel (hexane/$CHCl_3$ = 3/1) to afford **20b**/**20b'** (16.3 mg, <31%, **20b**/**20b'** = 90/10, determined by ^{1}H NMR) as an isomeric mixture of unstable compounds. The major isomer **20b** was isolated by PTLC (silica gel) with hexane/Et_2O (3/1): unstable yellow oil; IR (neat): 2225 (C≡C), 1765 (C=O), 1345 (S=O), 1157 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.53 (t, *J* = 2.3 Hz, 3H), 2.40 (s, 3H), 2.61-2.65 (m, 2H), 3.33-3.34 (m, 2H), 3.99-4.10 (m, 2H), 5.73 (t, *J* = 7.4 Hz, 1H), 6.25 (s, 1H), 6.87 (s, 1H), 7.05-7.07 (m, 3H), 7.11-7.17 (m, 2H), 7.27-7.30 (m, 5H), 7.64-7.66 (m, 1H), 7.72 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 3.2, 21.5, 23.0, 36.7, 45.2, 59.2, 71.5, 81.9, 98.5, 107.6, 109.7, 121.3, 121.5, 123.06, 126.13 (2C), 126.4, 127.8 (2C), 128.9, 129.2, 129.27 (2C), 129.31 (2C), 134.65, 134.71, 135.9, 140.9, 143.3, 162.8; HRMS (FAB) calcd for $C_{31}H_{29}N_2O_4S$ (MH^+) 525.1848, found 525.1851.

Gold(I)-Catalyzed Cyclization of the Conjugated Enyne (Table 1): (*E*)-(3-Ethylidene-1-tosylpiperidin-4-yl)(1*H*-indol-2-yl)methanone [(±)-9]. The experiments shown in Table 1 were carried out as follows: **11a** (56.5 mg, 0.1 mmol; *Z*/*E* = 79:21) or **11b** (52.3 mg, 0.1 mmol; *Z*/*E* = 71:29) were treated with JohnPhosAu(MeCN)SbF_6 (3.9 mg, 5.0 μmol) or IPrAuCl (3.1 mg, 5.0/5.0 μmol; 5 mol %)/$AgSbF_6$ (1.7 mg, 5.0 μmol; 5 mol %) in toluene-d_8 (0.5 mL, 0.2 M) at room temperature in the presence of an additive (1.5 equiv) and mesitylene (1.0 equiv) as an internal standard. After completion of the reaction (monitored by TLC), the reaction mixtures were analyzed by ^{1}H NMR to determine the yields of (±)-**9**, **28**, and **29** based on the internal standard. Pure (±)-**9** was obtained as follows: a screw-cap test tube was charged with **11a** (293 mg, 0.52 mmol, *Z*/*E* = 93/7) and JohnPhosAu(MeCN)SbF_6 (20 mg, 25.9 μmol). H_2O (14 μL, 0.8 mmol) and dry toluene (2.6 mL) were added to the mixture. After stirring at room temperature for 24 h, the mixture was concentrated *in vacuo* and chromatographed on NH_2 silica gel (hexane/EtOAc = 5/1). The product was recrystallized from $CHCl_3$–hexane to afford (±)-**9** (64.1 mg, 30%) as white solid: mp 183–186 °C; IR (neat): 3343 (NH), 1643 (C=O), 1341 (S=O), 1162 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.72 (dd, *J* = 6.9, 1.7 Hz, 3H), 2.06-2.11 (m, 1H), 2.15-2.16 (m, 1H), 2.44 (s, 3H), 2.86 (ddd, *J* = 12.2, 12.0, 3.2 Hz, 1H), 3.43-3.45 (br m, 1H), 3.71-3.74 (br m, 1H), 4.09-4.11 (br m, 1H), 4.43-4.43 (br m, 1H), 5.72 (q, *J* = 6.7 Hz, 1H), 7.14-7.17 (m, 1H), 7.25 (d, *J* = 2.3 Hz, 1H), 7.33-7.36 (m, 4H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 9.2 Hz, 1H), 8.86 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.3, 21.6, 28.5, 41.2, 43.2, 52.3, 109.4, 112.0, 121.2, 123.2, 124.8, 126.7, 127.4, 127.7 (2C), 129.7 (2C), 129.9, 133.5, 133.8, 137.3, 143.5, 192.6; HRMS (FAB) calcd for $C_{23}H_{25}N_2O_3S$ (MH^+) 409.1586, found 409.1577.

(*Z*)-*N*-{4-(1*H*-Indol-2-yl)-4-[(triisopropylsilyl)oxy]but-3-en-1-yl}-*N*-(but-2-yn-1-yl)-4-methylbenzenesulfonamide (28). Amber oil: IR (neat): 3386 (NH), 2225 (C≡C), 1650 (SiOC=C), 1341 (S=O), 1157 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.09 (d, *J* = 6.9 Hz, 18H), 1.18-1.21 (m, 3H), 1.56 (t, *J* = 2.3 Hz, 3H), 2.40 (s, 3H), 2.54 (q, *J* = 7.3 Hz, 2H), 3.27 (t, *J* = 7.4 Hz, 2H), 4.11 (q, *J* = 2.3 Hz, 2H), 5.13 (t, *J* = 6.9 Hz, 1H), 6.54-6.54 (br m, 1H), 7.08-7.10 (m, 1H), 7.16-7.18 (m,

1H), 7.26 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 7.4 Hz, 1H), 7.74 (d, J = 8.6 Hz, 2H), 8.15 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 3.3, 13.6 (3C), 17.9 (6C), 21.5, 24.5, 36.8, 45.8, 71.8, 81.5, 100.1, 106.4, 110.8, 119.9, 120.6, 122.2, 127.8 (2C), 128.5, 129.2 (2C), 135.7, 136.0, 136.7, 143.2, 144.8; HRMS (FAB) calcd for $C_{32}H_{45}N_2O_3SSi$ (MH^+) 565.2920, found 565.2927.

***N*-[4-(1*H*-Indol-2-yl)-4-oxobutyl]-*N*-(but-2-yn-1-yl)-4-methylbenzenesulfonamide (29).** White powder: mp 120–121 °C; IR (neat): 3326 (NH), 2224 (C≡C), 1649 (C=O), 1340 (S=O), 1157 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.53 (t, J = 2.3 Hz, 3H), 2.01-2.07 (m, 2H), 2.41 (s, 3H), 3.08 (t, J = 7.4 Hz, 2H), 3.30 (t, J = 6.9 Hz, 2H), 4.08-4.08 (br m, 2H), 7.15-7.17 (m, 1H), 7.25-7.28 (m, 3H), 7.34-7.36 (m, 1H), 7.41-7.43 (m, 1H), 7.72-7.74 (m, 3H), 9.01 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 3.2, 21.4, 22.0, 34.9, 36.9, 45.8, 71.7, 81.7, 109.4, 112.1, 120.9, 123.1, 126.3, 127.6, 127.8 (2C), 129.3 (2C), 134.9, 135.9, 137.1, 143.3, 192.2; HRMS (FAB) calcd for $C_{23}H_{25}N_2O_3S$ (MH^+) 409.1586, found 409.1590.

Enantioselective Cyclization of Conjugated Enyne (Table 2): Synthesis of (*S*,*E*)-(3-Ethylidene-1-tosylpiperidin-4-yl)(1*H*-indol-2-yl)methanone [(*S*)-9]. (*R*)-MeO-DTBM-BIPHEP$(AuCl)_2$ (8.1 mg, 5.0 μmol; 5 mol %) and $AgSbF_6$ (3.4 mg, 0.01 mmol; 10 mol %) was dissolved in toluene (0.1 mL) and stirred for 10 min at room temperature. A solution of (*Z*)-**11a** (56.5 mg, 0.1 mmol) in toluene (0.4 mL) was transferred to the catalyst mixture. The mixture was stirred at room temperature for 17 h. The mixture was concentrated and purified on PTLC (silica gel) with hexane/EtOAc (3/1) to afford (*S*)-**9** as a white amorphous solid {13.1 mg, 32% yield, 88% ee [HPLC, Chiralcel-OD-H column eluting under condition with 40% *i*-PrOH/*n*-hexane over 30 min at 0.75 mL/min, t_1 = 12.66 min (major isomer), t_2 = 16.60 min (minor isomer)]}: $[\alpha]^{26}_D$ –2.1 (*c* 0.92, $CHCl_3$); IR (neat): 3334 (NH), 1641 (C=O), 1341 (S=O), 1159 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.71 (dd, J = 6.9, 1.7 Hz, 3H), 2.03-2.10 (m, 1H), 2.14-2.17 (m, 1H), 2.40 (s, 3H), 2.88 (ddd, J = 12.3, 12.3, 2.9 Hz, 1H), 3.47-3.49 (br m, 1H), 3.71-3.74 (br m, 1H), 4.10-4.13 (br m, 1H), 4.43-4.44 (br m, 1H), 5.71 (q, J = 6.9 Hz, 1H), 7.13-7.16 (m, 1H), 7.32-7.34 (m, 4H), 7.65 (d, J =

8.0 Hz, 2H), 7.70 (d, J = 8.0 Hz, 1H), 9.20 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.3, 21.5, 28.5, 41.1, 43.2, 52.3, 109.5, 112.1, 121.2, 123.1, 124.7, 126.7, 127.4, 127.7 (2C), 129.6 (2C), 129.9, 133.4, 133.8, 137.3, 143.4, 192.7; HRMS (FAB) calcd for $C_{23}H_{25}N_2O_3S$ (MH^+) 409.1586, found 409.1585.

3. Total Synthesis of (+)-Conolidine (Scheme 6).

(*S*,*E*)-(3-Ethylidenepiperidin-4-yl)(1*H*-indol-2-yl)methanone (7). According to the reported method,[26] removal of the tosyl group was carried out as follows: sodium (27.7 mg, 1.20 mmol) was added to a solution of naphthalene (193 mg, 1.50 mmol) in THF (1.5 mL) at room temperature and the mixture stirred for 30 min. The resulting dark green/blue solution (*ca.* 0.8 M in THF) was added dropwise to a solution of (*S*)-**9** (49.2 mg, 0.12 mmol, 91% ee) in THF (1.2 mL) at 0 °C until dark green/blue color persisted. Saturated aqueous $NaHCO_3$ was added and the solution was allowed to warm slowly to room temperature. The aqueous layer was then extracted with CH_2Cl_2 and the organic layers were washed with brine, combined, dried over K_2CO_3 and filtered. Concentration under reduced pressure and recrystallization from CH_2Cl_2–hexane afforded (+)-**7** (18.5 mg, 60%): mp 205–210 °C; $[\alpha]^{28}_D$ = +41.0 (*c* 0.26, MeOH), comparable to the report by Bohn *et. al.* (2011)[16]: $[\alpha]^{25}_D$ = +45.0 (*c* 0.24, MeOH); IR (neat): 3345 (NH), 1627 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.72 (dd, J = 6.9, 1.7 Hz, 3H), 1.87-1.95 (m, 1H), 2.20-2.22 (br m, 1H), 2.97-3.00 (br m, 1H), 3.15 (ddd, J = 12.6, 12.6, 2.9 Hz, 1H), 3.33 (d, J = 12.6 Hz, 1H), 3.49 (s, 1H), 3.72 (d, J = 12.6 Hz, 1H), 4.53-4.54 (br m, 1H), 5.54 (q, J = 6.7 Hz, 1H), 7.15-7.17 (m, 1H), 7.28 (s, 1H), 7.34-7.36 (m, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 9.16 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.0, 31.5, 43.0, 43.2, 53.1, 108.9, 112.1, 120.8, 121.0, 123.1, 126.3, 127.6, 134.4, 135.1, 137.1, 193.6; HRMS (FAB) calcd for $C_{16}H_{19}N_2O$ (MH^+) 255.1497, found 255.1490.

(+)-Conolidine (1). According to the Bohn's procedure,[2] the amine (+)-**7** (16.0 mg, 0.06 mmol), paraformaldehyde (6.8 mg, 0.23 mmol), and TFA (14.5 μL, 0.19 mmol) were dissolved in dry MeCN (1.2 mL) and the reaction mixture heated under reflux for 2 h. TFA (14.5 μL) was added and

the mixture was stirred for further 3 h. The mixture was concentrated *in vacuo* and the crude product was made basic with aqueous saturated $NaHCO_3$ (to pH 9.0) and extracted with CH_2Cl_2 three times. The resultant orange solution was dried over Na_2SO_4, concentrated *in vacuo* and chromatographed on NH_2 silica gel (MeOH/$CHCl_3$ = 99/1) to afford (+)-conolidine (**1**) (5.7 mg, 34%, 84% ee [HPLC, Chiralcel-AD-H column eluting under condition with 80% *i*-PrOH/*n*-hexane over 25 min at 0.75 mL/min, t_1 = 14.25 min (minor isomer), t_2 = 16.95 min (major isomer)]): mp 178–180 °C; $[\alpha]^{28}_D$ = +31.5 (*c* 0.24, $CHCl_3$), comparable to the report by Kam *et. al.* (2004)[1]: $[\alpha]_D$ = +32.0 (*c* 0.16, $CHCl_3$), Bohn *et. al.* (2011)[16]: $[\alpha]^{27}_D$ = +28.1 (*c* 0.16, $CHCl_3$); IR (neat): 2914 (NH), 1634 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.51-1.52 (br m, 3H), 2.04-2.06 (m, 1H), 2.10-2.18 (m, 1H), 3.06-3.13 (m, 1H), 3.30-3.33 (br m, 1H), 3.41 (ddd, *J* = 13.7, 8.6, 2.9 Hz, 1H), 3.85-3.88 (br m, 1H), 3.97-3.98 (br m, 1H), 4.29 (d, *J* = 18.3 Hz, 1H), 4.78 (d, *J* = 18.3 Hz, 1H), 5.47 (q, *J* = 6.9 Hz, 1H), 7.11 (ddd, *J* = 16.0, 8.0, 4.0 Hz, 1H), 7.32-7.37 (m, 2H), 7.57 (d, *J* = 8.0 Hz, 1H), 9.02 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 12.7, 22.9, 44.2, 48.1, 53.3, 55.0, 111.7, 120.1, 120.5, 120.8, 122.9, 126.5, 127.9, 130.1, 133.5, 136.1, 193.5; HRMS (FAB) calcd for $C_{17}H_{19}N_2O$ (MH^+) 267.1497, found 267.1494.

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Supporting Information Available.

Additional synthetic schemes (preparation of **2a**–**c**), NMR spectra, and HPLC chromatograms. This material is available freely via the Internet at http://pubs.acs.org.

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