JOC The Journal of Organic Chemistry

Note

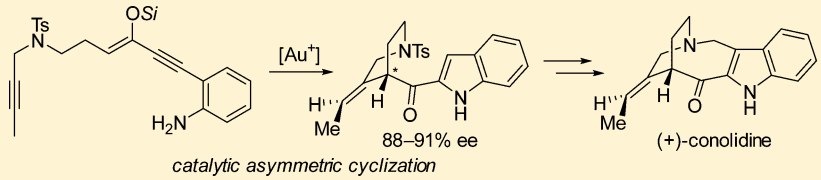
pubs.acs.org/joc

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

Saori Naoe, Yusuke Yoshida, Shinya Oishi, Nobutaka Fujii,* and Hiroaki Ohno*

Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan

Supporting Information



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 homogeneous 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]

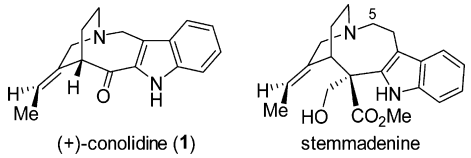


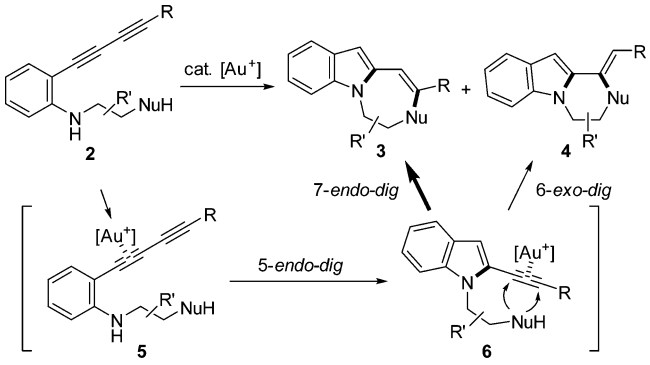
Figure 1. Stemmadenine-based alkaloids.

This group managed to isolate only 0.0013 g/kg of conolidine from the stem bark of this small flowering plant. Since 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.

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] Today, 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 = OH) 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*

Scheme 1. Gold(I)-Catalyzed Intramolecular Consecutive Cyclizations of a Conjugated Diyne (from previous work)

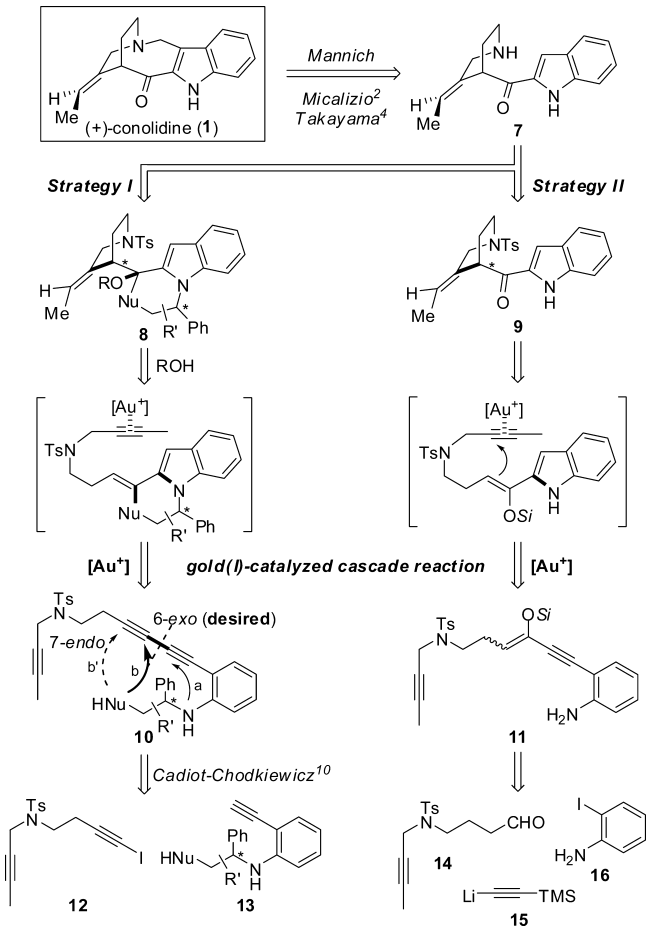


cyclization to give fused indole **3** as the major product. On the basis of this reaction, we designed a strategy for the synthesis of (+)-conolidine (**1**) (Scheme 2, strategy I). It was envisaged that known conolidine precursor **7**[2,4] could be prepared by the gold(I)-catalyzed cascade cyclization of conjugated diyne **10**. In this sense, the bis-cyclization reaction would allow for the formation of a fused indole (paths a and b), which would be followed by the 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

Received: April 4, 2016
Published: June 8, 2016

DOI: 10.1021/acs.joc.6b00720
J. Org. Chem. 2016, 81, 5690−5698

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

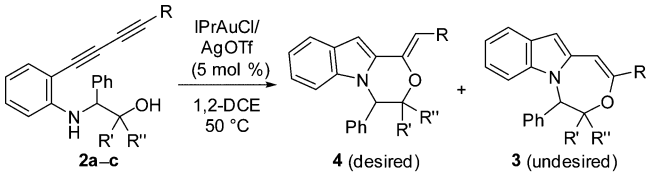


by introducing the oxygen atom of the conolidine as a silyl ether. It was also envisaged that the nucleophilicity of the enol ether would be increased following the formation of the indole, leaving it better equipped to promote the subsequent formation of the piperidine ring. Furthermore, the use of 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 enol ether-type substrate **11** (strategy II).

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 desired isomer **4a** as a minor product (29:71 **4a**:**3a** ratio). 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** ratio from 71:29 to 80:20). On the basis of these results, we prepared the corresponding alcohol and carboxylic acid substrates, **10a** and **10b**, respectively, as the most suitable candidates for the synthesis of conolidine.

Our initial efforts toward the preparation and subsequent gold(I)-catalyzed cyclization of conjugated diynes **10a** and **10b** are shown in Scheme 4. The alkylation of tosylamide **17**[9] with

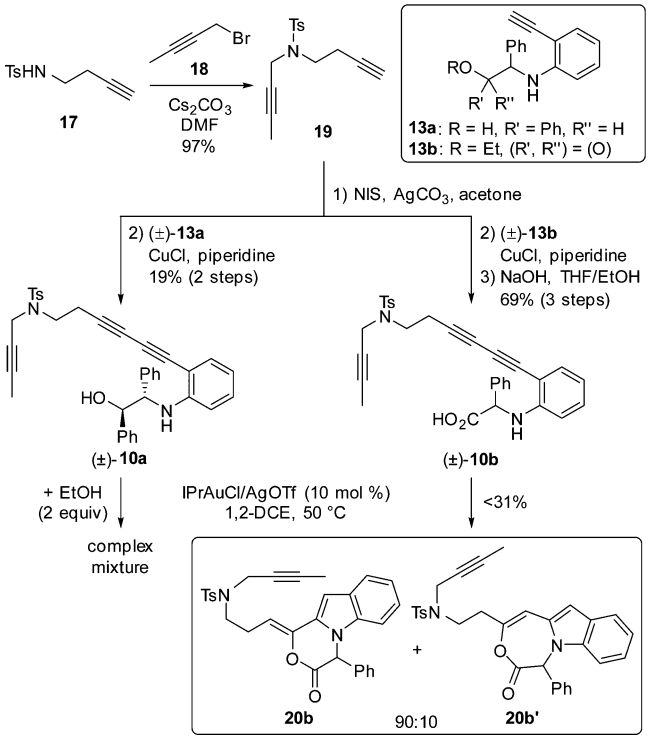
Scheme 3. Model Experiment for Control of the Regioselectivity in the Second Cyclization



	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.

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



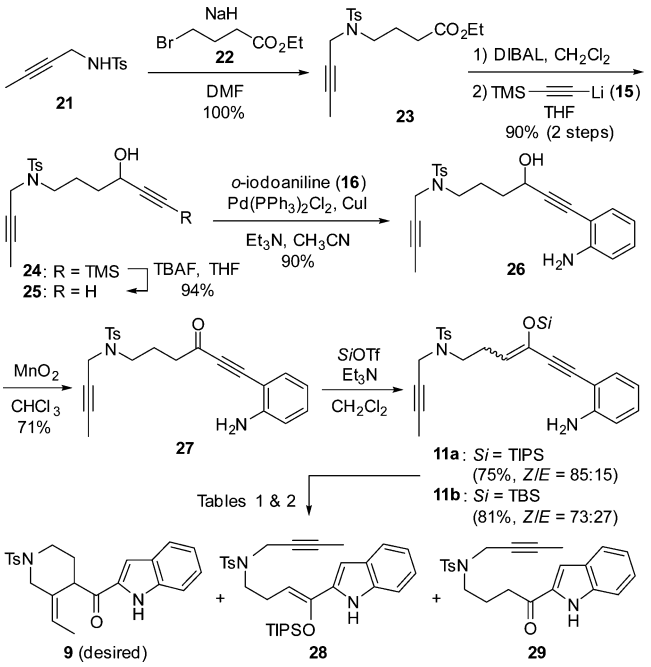
1-bromobut-2-yne (**18**) gave diyne **19**. The iodination of the terminal alkyne moiety in **19** with NIS and $AgNO_3$, followed by the subsequent Cadiot–Chodkiewicz coupling[10] of the resulting iodoalkyne with **13a** or **13b**, gave the amino alcohol- and amino acid-type substrates (±)-**10a** 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 bis-cyclization products **20b** and **20b′** with good regioselectivity for the former of these two products (90:10 **20b**:**20b′**). 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. On the

DOI: 10.1021/acs.joc.6b00720
J. Org. Chem. 2016, 81, 5690–5698

basis of these results, we discarded strategy I and focused our efforts on strategy II using conjugated enynes **11a** and **11b**.

Strategy II. Conjugated enynes **11a** and **11b** bearing different silyl enol ether moieties were prepared according to the route shown in Scheme 5. The alkylation of tosylamide

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



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 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 corresponding ketone **27** in 71% yield, which was treated with TIPSOTf or TBSOTf in the presence of Et_3N to give 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 the Supporting Information).

We then investigated the gold(I)-catalyzed cascade reaction of 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 rt 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 a 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 counteranion (entry 5), CD_2Cl_2 as a solvent (entry 6), or TBS ether **11b** as a substrate (entry 7) did not improve the yield.

We then proceeded to investigate the enantioselective gold(I)-catalyzed cascade reaction of the conjugated enyne

Table 1. Optimization of the Reaction Conditions[a]

entry	ligand	additive	R	time (h)	yield (%)[b] 9	28	29
1	**L1**	–	TIPS (**11a**)	24	16	34	14
2	**L1**	**H_2O**	**TIPS (11a)**	**24**	**38**	–	**2**
3	**L1**	MeOH	TIPS (**11a**)	19	29	–	2
4	IPr	H_2O	TIPS (**11a**)	24	3	45	10
5	**L1**[c]	H_2O	TIPS (**11a**)	24	15	5	45
6[d]	**L1**	H_2O	TIPS (**11a**)	24	16	–	43
7	**L1**	H_2O	TBS (**11b**)	24	33	–	–

[a]Unless otherwise noted, all of these reactions were conducted using **11a** (79:21 *Z*:*E*) or **11b** (71:29 *Z*:*E*) with **L1**Au(MeCN)SbF_6 (5 mol %) or IPrAuCl (5 mol %)/$AgSbF_6$ (5 mol %) in toluene-d_8 (0.2 M) at rt 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.

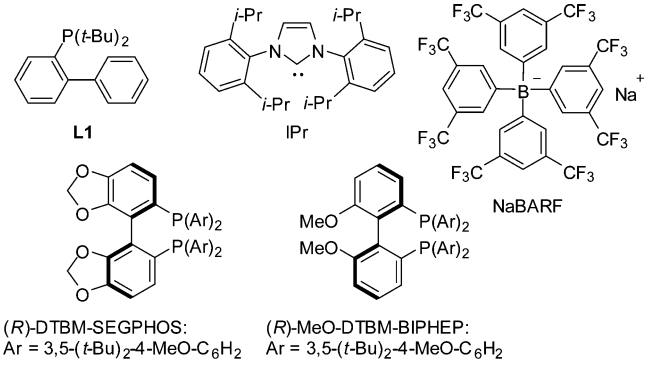


Figure 2. Ligands and cocatalysts screened in this study.

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

entry	*Z*:*E* (**11a**)	catalyst	time (h)	yield of **9** (%)[b]	% ee[c] [(*S*)-**9**]
1	53:47	(*R*)-DTBM-SEGPHOS$(AuCl)_2$/$AgSbF_6$	24	ND[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	~10	76
4	*E* only	(*R*)-MeO-DTBM-BIPHEP$(AuCl)_2$/$AgSbF_6$	20	ND[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 conducted using **11a** in toluene (0.2 M) at rt in the presence of H_2O (1.5 equiv) with a catalyst loading of 5 mol % (for the bimetallic gold complex) or 10 mol % (for $AgSbF_6$). [b]Isolated yields. [c]Determined by chiral HPLC. [d]Ketone **29** was obtained as the major product. [e]Not detected. [f]The catalyst loading was increased to 10 and 20 mol %. [g]Using H_2O (1.0 equiv).

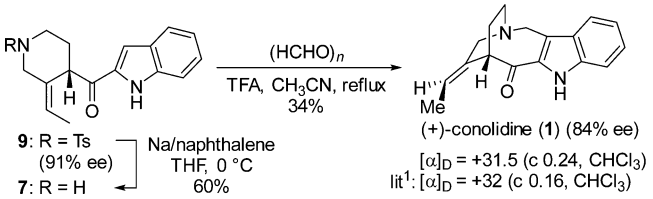
11a (Table 2). On the basis of a related study reported by Toste and co-workers involving the asymmetric carbocyclization of a silyl enol ether,[8h] we investigated the use of biarylphosphine-type dinuclear chiral gold complexes to affect this reaction (Figure 2). The treatment of conjugated enyne **11a** with (*R*)-DTBM-SEGPHOS$(AuCl)_2$ (5 mol %)/$AgSbF_6$ (10 mol %) in the presence of H_2O (1.5 equiv) resulted in the formation of undesired ketone **29** as the major product (entry

DOI: 10.1021/acs.joc.6b00720
J. Org. Chem. 2016, 81, 5690−5698

1). The use of (*R*)-MeO-DTBM-BIPHEP gave 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 decrease in the yield to 10%, as well as a decrease in ee to 76% (entry 3). Expecting that the sterically less hindered *Z* isomer has better reactivity, we examined the reaction of 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 possible to generate desired product **9** only from the *Z* isomer of **11a** when a *E*/*Z* mixture of **11a** was used as the substrate (entries 2 and 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).

Finally, we investigated the conversion of 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 known conolidine precursor **7** in 60% yield (Scheme 6). According to the procedure reported by

Scheme 6. Total Synthesis of (+)-Conolidine



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]

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 a TLC silica gel 60 F_{254} or NH_2 silica gel 60 F_{254} plate (layer thickness of 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 (parts per million) relative to TMS as an 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).

Compounds **16**, **18**, **22**, and (*R*)-DTBM-SEGPHOS$(AuCl)_2$ were obtained commercially and used without further purification. 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 methods described in the literature. Structures of **S1**−**S9** are shown in Schemes S1−S3.

Preparation of Starting Materials. *(R)-2-Phenyl-2-({2-[(trimethylsilyl)ethynyl]phenyl}amino)ethan-1-ol (**S2**).* The coupling of **S1** and trimethylsilylacetylene was conducted 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 being stirred 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 (5:1 hexane:EtOAc) 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 conducted 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 being stirred at rt 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 (5:1 hexane:EtOAc) 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 conducted 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 rt for 5 h. The reaction mixture was concentrated *in vacuo*, and the residue was chromatographed on silica gel (5:1 hexane:EtOAc) 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.

*(±)-(1R,2S)-2-[(2-Bromophenyl)amino]-1,2-diphenylethan-1-ol [(±)-**S5**].* The reaction of 2-bromoiodobenzene and (±)-**S4** was conducted 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 (35.7 mg, 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 (10:1 hexane:EtOAc) 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.

*(±)-(1R,2S)-1,2-Diphenyl-2-({2-[(trimethylsilyl)ethynyl]phenyl}-amino)ethan-1-ol [(±)-**S6**].* According to the procedure described for

DOI: 10.1021/acs.joc.6b00720
J. Org. Chem. 2016, 81, 5690−5698

the preparation of **S2**, (±)-**S5** (2.95 g, 8.01 mmol) was converted to (±)-**S6** (2.72 g, 88%): column chromatography, silica gel (10:1 hexane:EtOAc); 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.

*(±)-(1R,2S)-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 (1:1 to 1:2 hexane:$CHCl_3$); 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.

*(±)-(1R,2S)-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 (1:1 hexane/$CHCl_3$ 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 were added trimethylsilylacetylene (1.0 mL, 7.46 mmol) and Et_3N (4.3 mL, 33.9 mmol). After being stirred 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 (3:1 hexane:$CHCl_3$) 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 (20:1 hexane:EtOAc). The product was recrystallized from $CHCl_3$ and 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 (10:1 hexane:EtOAc); 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 (~2 mL), and 0.4 N aqueous NaOH (19 mL) was added to the reaction mixture. After being stirred at rt for 40 min, the reaction mixture was diluted with CH_2Cl_2, washed with water, 1 N aqueous HCl, and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was recrystallized from CH_2Cl_2 and 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 °C. After the mixture had been stirred 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 (5:1 hexane:EtOAc) 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-{[(1R,2S)-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 rt in the dark. After being stirred at rt 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) were stirred at rt under argon for 3 h. The reaction was quenched with aqueous saturated NH_4Cl and the mixture diluted with Et_2O, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed on silica gel (10:1 hexane:EtOAc) to afford (±)-**10a** [0.31 g, 19% based on (±)-**13a**] as a pale amber amorphous material: 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,

DOI: 10.1021/acs.joc.6b00720
J. Org. Chem. 2016, 81, 5690−5698

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]sulfonamido}-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 rt for 4 h: column chromatography, silica gel (3:1 hexane:EtOAc); 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]sulfonamido}hexa-1,3-diyn-1-yl)phenyl]amino}-2-phenylacetic Acid [(±)-**10b**].* THF (~2 mL) was added to the mixture of (±)-**S10** (0.15 g, 0.27 mmol) and 0.4 N NaOH (2 mL) in EtOH (4 mL). After being stirred at rt 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]sulfonamido}-butanoate (**23**).* The coupling of **21** and ethyl 4-bromobutanoate (**22**) was conducted 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 rt 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 reaction was quenched with aqueous saturated NH_4Cl and the mixture diluted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed on silica gel (10:1 hexane:EtOAc) 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 conducted 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 1 M DIBAL in toluene (9 mL, 8.7 mmol) at −78 °C under argon. After the mixture had been stirred at the same temperature for 1 h, the reaction was quenched with MeOH (1 equiv) and H_2O (6 equiv) at −78 °C, and the resulting slurry was allowed to warm to rt. 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 °C under argon was added *n*-BuLi in THF (2.6 M solution in *n*-BuLi; 3.1 mL, 8.0 mmol) dropwise, and the mixture was stirred at −78 °C 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 being stirred at −78 °C for 2 h, the reaction mixture was warmed to rt, the reaction quenched with aqueous saturated NH_4Cl, and the mixture diluted with Et_2O, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel (3:1 hexane:EtOAc) 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 °C under argon was added 1 M TBAF in THF (11.5 mL, 11.4 mmol) dropwise, and the mixture was stirred at rt 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 (5:1 hexane:EtOAc) 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 being stirred at rt 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 (2:1 hexane:EtOAc) 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 rt, filtered through Celite, and concentrated *in vacuo*. The residue was chromatographed on silica gel (5:1 hexane:EtOAc) 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,

DOI: 10.1021/acs.joc.6b00720
J. Org. Chem. 2016, 81, 5690−5698

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 °C under argon, and the mixture was stirred for 2 h. The mixture allowed to warm slowly to rt. 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 (5:1 hexane:EtOAc) to afford **11a** (921 mg, 75%, 85:15 *Z*:*E*, determined by ^{1}H NMR).[12] Both products were isolated by column chromatography on silica gel followed by PTLC (silica gel) with a 10:1 hexane/EtOAc solvent. 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 °C under argon, and the mixture was stirred at rt 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 (5:1 hexane:EtOAc) to afford **11b** (171 mg, 81%, 73:27 *Z*:*E*, determined by ^{1}H NMR).[12] Both products were isolated by column chromatography on silica gel followed by PTLC (silica gel) with a 10:1 hexane/EtOAc solvent. 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.

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-1H-[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 being stirred at 50 °C for 5 h, the reaction mixture was concentrated *in vacuo* and chromatographed on NH_2 silica gel (2:1 hexane:$CHCl_3$), and the collected solid was rinsed with hexane to afford an inseparable mixture of **3a** and **4a** (29.0 mg, 86%, 71:29 **3a**:**4a**, 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); ^{1}H NMR (500 MHz, $CDCl_3$) δ (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; ^{13}C NMR (125 MHz, $CDCl_3$) δ (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.

*(±)-(4R,5S)-2,4,5-Triphenyl-4,5-dihydro[1,4]oxazepino[4,5-a]indole (**3b**) and (±)-(3R,4S)-1-[(Z)-Benzylidene]-3,4-diphenyl-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indole (**4b**).* By using general procedure A, **2b** (41.4 mg, 0.10 mmol) was converted to **3b**/**4b** (37.9 mg, 92%, 29:71 **3b**:**4b**, 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 products were isolated by PTLC (NH_2 silica gel) with a 3:1 hexane/Et_2O solvent. 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), 127.88 (2C), 127.89 (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(5H)-one (**3c**) and (Z)-1-Butylidene-4-phenyl-1H-[1,4]oxazino[4,3-a]indol-3(4H)-one (**4c**).* By using general procedure A, **2c** (31.7 mg, 0.10 mmol) was converted to **3c**/**4c** (11.1 mg, <35%, 20:80 **3c**:**4c**, 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 a 3:1 hexane/Et_2O solvent. 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)

DOI: 10.1021/acs.joc.6b00720
J. Org. Chem. 2016, 81, 5690−5698

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 being stirred at 50 °C for 27 h, the mixture was concentrated *in vacuo* and chromatographed on NH_2 silica gel (3:1 hexane:$CHCl_3$) to afford **20b**/**20b′** (16.3 mg, <31%, 90:10 **20b**:**20b′**, determined by ^{1}H NMR) as an isomeric mixture of unstable compounds. Major isomer **20b** was isolated by PTLC (silica gel) with a 3:1 hexane/Et_2O solvent: 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)(1H-indol-2-yl)methanone [(±)-**9**].* The experiments documented in Table 1 were conducted as follows. **11a** (56.5 mg, 0.1 mmol; 79:21 *Z*:*E*) or **11b** (52.3 mg, 0.1 mmol, 71:29 *Z*:*E*) was 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 rt 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, 93:7 *Z*:*E*) 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 being stirred at rt for 24 h, the mixture was concentrated *in vacuo* and chromatographed on NH_2 silica gel (5:1 hexane:EtOAc). The product was recrystallized from $CHCl_3$ and hexane to afford (±)-**9** (64.1 mg, 30%) as a 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-(1H-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-(But-2-yn-1-yl)-N-[4-(1H-indol-2-yl)-4-oxobutyl]-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)(1H-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 %) were dissolved in toluene (0.1 mL) and stirred for 10 min at rt. 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 rt for 17 h. The mixture was concentrated and purified on PTLC (silica gel) with a 3:1 hexane/EtOAc solvent 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 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.

Total Synthesis of (+)-Conolidine (Scheme 6). *(S,E)-(3-Ethylidenepiperidin-4-yl)(1H-indol-2-yl)methanone (**7**).* According to the reported method,[26] removal of the tosyl group was conducted 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 rt and the mixture stirred for 30 min. The resulting dark green/blue solution (~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 rt. 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 and 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 Micalizio and co-workers[2] $[\alpha]^{25}_D$ = +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 Micalizio's procedure,[2] 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 was heated under reflux for 2 h. TFA (14.5 μL) was added and the mixture stirred for a 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 (99:1 MeOH:$CHCl_3$) to afford (+)-conolidine (**1**) {5.7 mg, 34%, 84% ee [HPLC, Chiralcel-AD-H column eluting under condition with 80% *i*-

DOI: 10.1021/acs.joc.6b00720
J. Org. Chem. 2016, 81, 5690−5698

PrOH/*n*-hexane 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 reports by Kam et al.,[1] $[\alpha]_D$ = +32.0 (*c* 0.16, $CHCl_3$), and Micalizio and co-workers,[2] $[\alpha]^{27}_D$ = +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.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00720.

Additional synthetic schemes (preparation of **2a**−**c**), NMR spectra, and HPLC chromatograms (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: hohno@pharm.kyoto-u.ac.jp.
*E-mail: nfujii@pharm.kyoto-u.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a Grant-in-Aid for Encouragement of Young Scientists (A) (H.O.) and the Targeted Proteins Research Program from the Ministry of Education, Culture, Sports, Science and Technology of Japan. S.N. is grateful for Research Fellowships from the JSPS for Young Scientists.

■ REFERENCES

(1) Kam, T.-S.; Pang, H.-S.; Choo, Y.-M.; Komiyama, K. *Chem. Biodiversity* **2004**, *1*, 646.

(2) Tarselli, M. A.; Raehal, K. M.; Brasher, A. K.; Streicher, J. M.; Groer, C. E.; Cameron, M. D.; Bohn, L. M.; Micalizio, G. C. *Nat. Chem.* **2011**, *3*, 449.

(3) (a) Bennasar, M.-L.; Zulaica, E.; Solé, D.; Alonso, S. *Chem. Commun.* **2009**, 3372. (b) Bennasar, M.-L.; Zulaica, E.; Solé, D.; Roca, T.; García-Díaz, D.; Alonso, S. *J. Org. Chem.* **2009**, *74*, 8359. (c) Hirose, T.; Noguchi, Y.; Furuya, Y.; Ishiyama, A.; Iwatsuki, M.; Otoguro, K.; Ōmura, S.; Sunazuka, T. *Chem. - Eur. J.* **2013**, *19*, 10741.

(4) During the course of this study, a similar approach was recently reported for construction of the ethylidene-piperidine moiety and used to synthesize (±)-conolidine and (±)-apparicine: Takanashi, N.; Suzuki, K.; Kitajima, M.; Takayama, H. *Tetrahedron Lett.* **2016**, *57*, 375.

(5) For recent reviews, see: (a) Corma, A.; Leyva-Pérez, A.; Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657. (b) Garayalde, D.; Nevado, C. *ACS Catal.* **2012**, *2*, 1462. (c) Cera, G.; Bandini, M. *Isr. J. Chem.* **2013**, *53*, 848. (d) Nunes dos Santos Comprido, L.; Hashmi, A. S. K. *Isr. J. Chem.* **2013**, *53*, 883. (e) Gatineau, D.; Goddard, J.-P.; Mouriès-Mansuy, V.; Fensterbank, L. *Isr. J. Chem.* **2013**, *53*, 892. (f) Brand, J. P.; Li, Y.; Waser, J. *Isr. J. Chem.* **2013**, *53*, 901.

(6) (a) Gorin, D. J.; Dubé, P.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 14480. (b) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994. (c) Ohno, H. *Isr. J. Chem.* **2013**, *53*, 869. (d) Qian, D.; Zhang, J. *Chem. Rec.* **2014**, *14*, 280. (e) Dorel, R.; Echavarren, A. M. *Chem. Rev.* **2015**, *115*, 9028. (f) Pflästerer, D.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2016**, *45*, 1331.

(7) Naoe, S.; Saito, T.; Uchiyama, M.; Oishi, S.; Fujii, F.; Ohno, H. *Org. Lett.* **2015**, *17*, 1774.

(8) Gold(I)-catalyzed reactions of alkyne and silyl enol ether have been reported as powerful strategies for the construction of carbocyclic structures. See: (a) Staben, S. T.; Kennedy-Smith, J. J.; Huang, D.; Corkey, B. K.; LaLonde, R. L.; Toste, F. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 5991. (b) Lee, K.; Lee, P. H. *Adv. Synth. Catal.* **2007**, *349*, 2092. (c) Minnihan, E. C.; Colletti, S. L.; Toste, F. D.; Shen, H. C. *J. Org. Chem.* **2007**, *72*, 6287. (d) Barabé, F.; Bétournay, G.; Bellavance, G.; Barriault, L. *Org. Lett.* **2009**, *11*, 4236. (e) Kusama, H.; Karibe, Y.; Onizawa, Y.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 4269. (f) Barabé, F.; Levesque, P.; Korobkov, I.; Barriault, L. *Org. Lett.* **2011**, *13*, 5580. (g) Sow, B.; Bellavance, G.; Barabé, F.; Barriault, F. *Beilstein J. Org. Chem.* **2011**, *7*, 1007. (h) Brazeau, J.-F.; Zhang, S.; Colomer, I.; Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2012**, *134*, 2742. (i) Iwai, T.; Okochi, H.; Ito, H.; Sawamura, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 4239.

(9) Teichert, J. F.; Zhang, S.; Zijl, A. W. V.; Slaa, J. W.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2010**, *12*, 4658.

(10) For a recent review, see: Sindhu, K. S.; Thankachan, A. P.; Sajitha, P. S.; Anilkumar, G. *Org. Biomol. Chem.* **2015**, *13*, 6891.

(11) Barbazanges, M.; Augé, M.; Moussa, J.; Amouri, H.; Aubert, C.; Desmarets, C.; Fensterbank, L.; Gandon, V.; Malacria, M.; Ollivier, C. *Chem. - Eur. J.* **2011**, *17*, 13789.

(12) The geometries of **11a** and **11b** were determined according to the literature: (a) Reich, H. J.; Holtan, R. C.; Borkowsky, S. L. *J. Org. Chem.* **1987**, *52*, 312. (b) Reich, H. J.; Holtan, R. C.; Bolm, C. *J. Am. Chem. Soc.* **1990**, *112*, 5609.

(13) The geometry of **28** was confirmed by an NOE between the protons at the indole 3-position and vinylic carbon.

(14) Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3703.

(15) (a) Jagtap, R. S.; Joshi, N. N. *Tetrahedron: Asymmetry* **2011**, *22*, 1861. (b) Gunderson, K. G.; Shapiro, M. J.; Doti, R. A.; Skiles, J. W. *Tetrahedron: Asymmetry* **1999**, *10*, 3263.

(16) Liu, G.; Li, J.; Qiu, L.; Liu, L.; Xu, G.; Ma, B.; Sun, J. *Org. Biomol. Chem.* **2013**, *11*, 5998.

(17) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002.

(18) Melhado, A. D.; Luparia, M.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 12638.

(19) Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729.

(20) Naoe, S.; Suzuki, Y.; Hirano, K.; Inaba, Y.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2012**, *77*, 4907.

(21) Balaraman, K.; Kesavan, V. *Synthesis* **2010**, *2010*, 3461.

(22) Alami, M.; Ferri, F. *Tetrahedron Lett.* **1996**, *37*, 2763.

(23) Kinoshita, A.; Sakakibara, N.; Mori, M. *Tetrahedron* **1999**, *55*, 8155.

(24) Jervis, P. J.; Kariuki, B. M.; Cox, L. R. *Org. Lett.* **2006**, *8*, 4649.

(25) Morita, S.; Otsubo, K.; Matsubara, J.; Ohtani, T.; Uchida, M. *Tetrahedron: Asymmetry* **1995**, *6*, 245.

(26) Craig, D.; Goldberg, F. W.; Pett, R. W.; Tholen, N. T. H.; White, A. J. P. *Chem. Commun.* **2013**, *49*, 9275.

DOI: 10.1021/acs.joc.6b00720
J. Org. Chem. 2016, 81, 5690−5698