Synthesis of Fused-Ring Compounds through Gold-Catalyzed Cascade Reaction

（金触媒連続反応を用いた縮環型化合物の合成研究）

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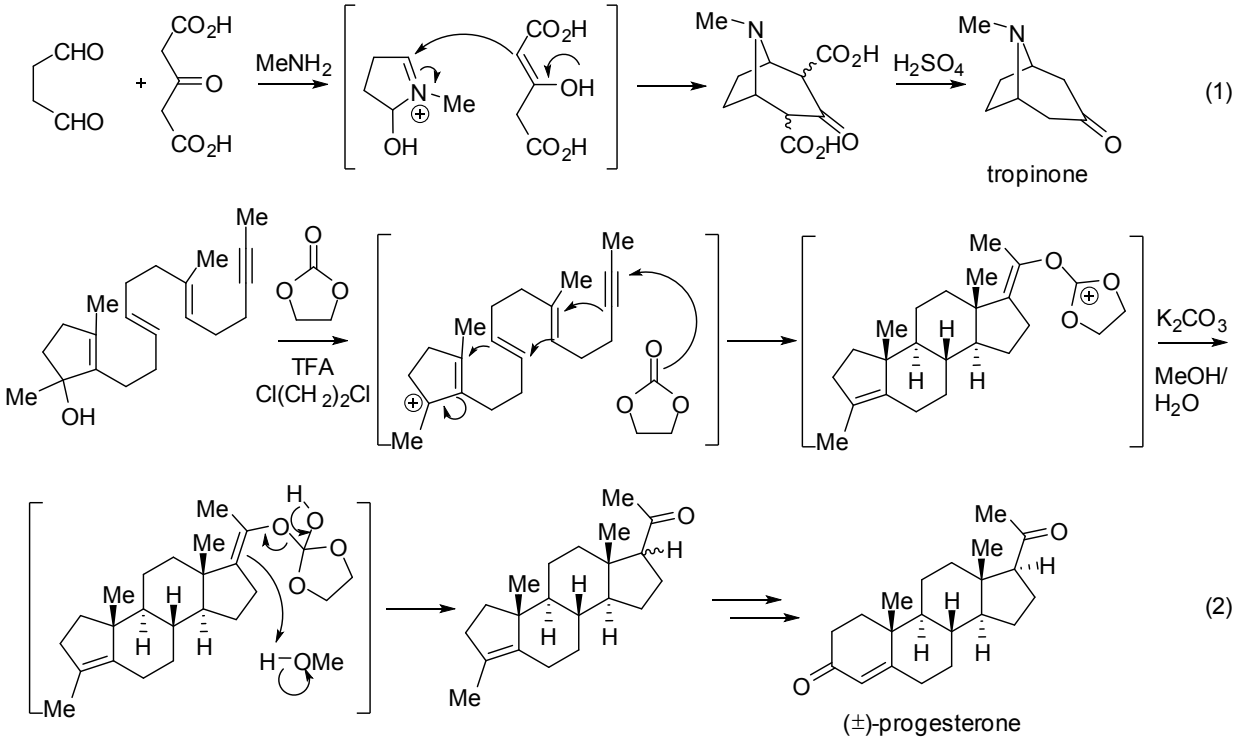
Saori Naoe

Contents

Preface

Fused-ring scaffolds are found in a wide range of natural and synthetic products exhibiting various functions and biological activities. The development of efficient methods for direct synthesis of fused-ring compounds is thus important in synthetic organic chemistry.[1] Cascade reaction is considered to be a useful approach to complex fused-ring compounds because several bonds are directly formed in one operation.[2] For example, Robinson *et al*. succeeded in constructing azabicyclo[3.2.1]octane scaffold by a three-component cascade reaction of succindialdehyde, methylamine, and acetonedicarboxylic acid to accomplish one-pot biomimetic synthesis of tropinone (Scheme 1, eq 1).[3a] Johnson *et al*. reported an elegant synthesis of progesterone, where successive carbocyclizations were exploited to assemble the entire carbon framework of this steroid in a single operation.[3b,c] From the viewpoint of green chemistry, cascade reactions can save reagents and solvent for the reactions, and reduce time and labor requirements, and waste generated during the synthesis. Such considerations have led the author to develop novel cascade reactions to form fused ring compounds which are applicable to synthesis of useful compounds in medicinal chemistry.

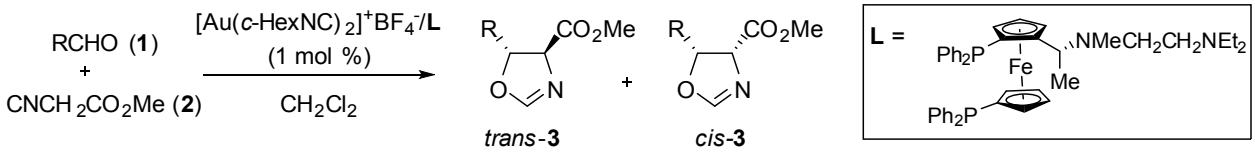


Scheme 1. Total Synthesis of Tropinone (eq 1) and (±)-Progesterone (eq 2) Based on Cascade Cyclizations

Recently, transition-metal-catalyzed cascade reactions are being widely investigated. Transition metal catalysts can activate the reactant to promote the bond-forming reaction with relatively low activation energy, producing the reactive intermediates for further transformations.[4] Within transition metals, homogeneous gold, especially gold(I), has attracted much attention in the past decades,

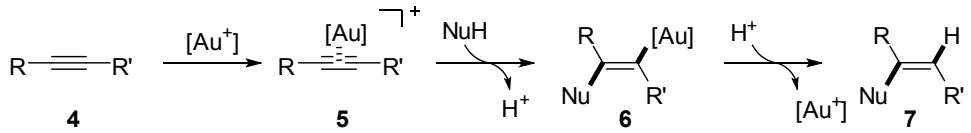
because of its strong π acidity coupled with potential to stabilize cationic reaction intermediates.[5] The versatile reactivity of gold catalysts enables design of cascade reactions for step- and atom-economical direct syntheses of complex molecules.[4b-e,g]

Gold had been considered to be catalytically inactive for a long time until 1986, when Ito and Hayashi reported the first example of a catalytic asymmetric aldol reaction using a gold(I) complex bearing a (diphenylphosphino)ferrocene-type chiral ligand (Scheme 2).[6] In 1991, the first gold(III)-catalyzed nucleophilic addition of alcohols, water and amines to alkyne was reported by Fukuda and Utimoto.[7a] Seven years later, Tales *et al*. reported the first example of gold(I) activation of alkynes.[7b] They demonstrated that cationic gold(I) species gave excellent turnover numbers (TONs) and turnover frequencies (TOFs) for the addition of alcohols to alkynes. Since then, a wide range of powerful synthetic approaches have been developed for the construction of carbon-carbon or carbon-heteroatom bonds. Nowadays, homogeneous gold is one of the most effective catalysts for the electrophilic activation of alkynes that can be applied to total synthesis of natural products.



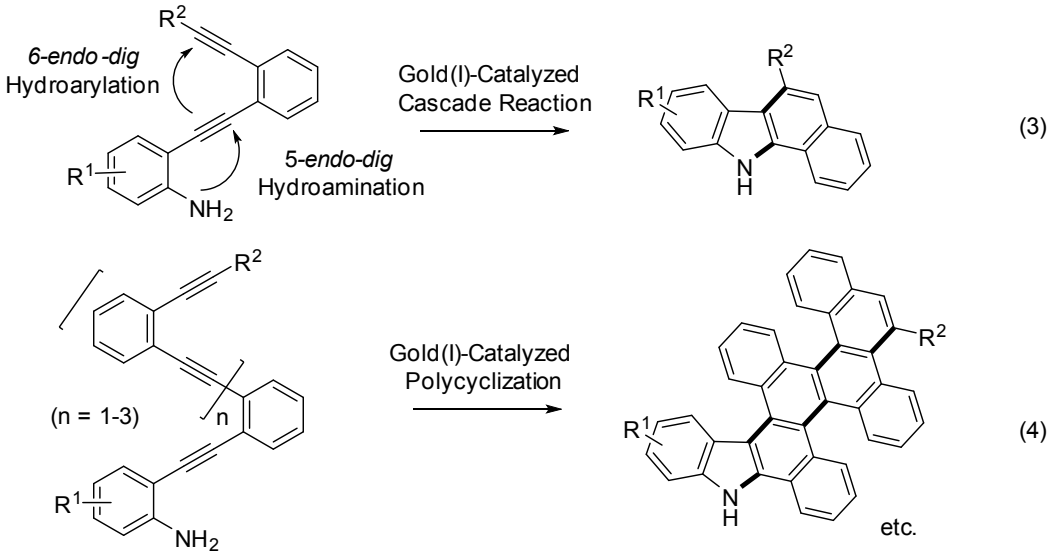
Scheme 2. Asymmetric Gold(I)-Catalyzed Aldol Reaction by Ito and Hayashi *et al*.

The general mechanism for gold(I)-catalyzed addition of a nucleophile (NuH) to an alkyne is shown in Scheme 3. The π-coordination of alkyne **4** to a cationic gold(I) complex gives η^2-$[AuL]^+$-activated alkyne **5**. The nucleophilic addition of NuH to alkyne from the *anti*-face forms alkenylgold intermediate **6**, which is followed by protodeauration to give alkene **7**. Various nucleophiles can be used for this reaction, including alcohols, amines, amides, thiols, arenes, alkenes and alkynes. Particularly notable is that the resulting alkenes **7** can be used for further transformations as nucleophilic species when Nu is electron-donating.

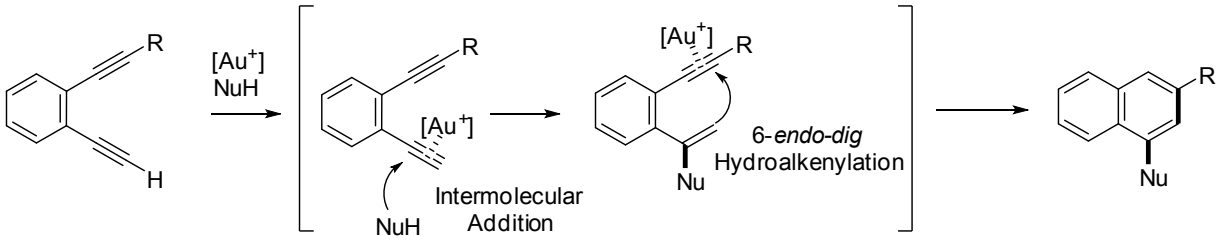


Scheme 3. Cationic Gold(I)-Catalyzed Nucleophilic Addition to Alkynes

The author's group has been involved in development of gold(I)-catalyzed reactions mostly based on addition cascades. For example, a cascade cyclization of diyne-type anilines to form carbazoles and related fused indoles through consecutive intramolecular hydroamination/hydroarylation was developed by the author's group (Scheme 4, eq 3).[8] This reaction is also applicable to synthesis of highly fused carbazoles by use of polyyne-type anilines as the cyclization precursor (Scheme 4, eq 4).[9] These successful cascade reactions prompted the author to investigate a related intermolecular reaction using external nucleophile for synthesis of 1,3-disubstituted naphthalenes (Scheme 5).

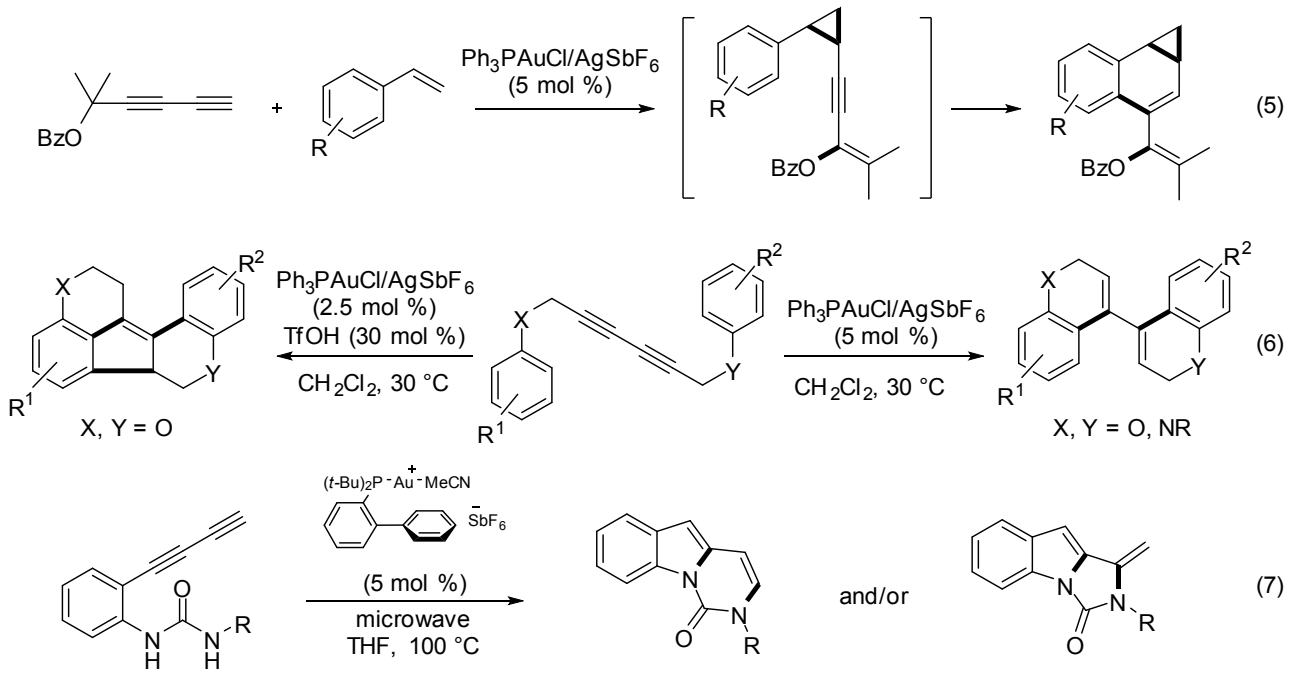


Scheme 4. Gold(I)-Catalyzed Cascade Cyclization Reaction of Polyyne-Type Anilines

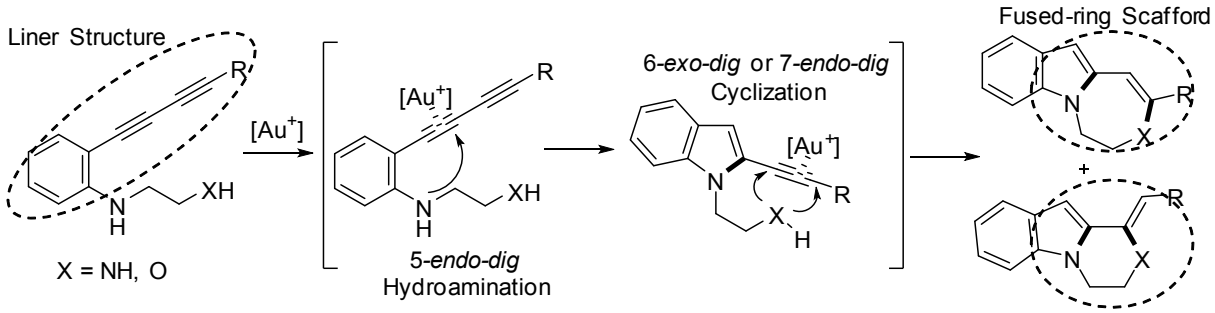


Scheme 5. The Author's Concept (1): Gold(I)-Catalyzed Addition Cascade of Dialkynylbenzenes Using External Nucleophiles

Compared to isolated alkyne, the use of conjugated diynes with gold(I) catalysis stands at the very beginning. Recently, several useful gold(I)-catalyzed reactions of conjugated diynes have been reported,[10] including [4 + 3] annulation of conjugated diynes (Scheme 6, eq 5)[10a] and double hydroarylation to form highly fused or linked rings (Scheme 6, eq 6).[10d] Banwell *et al*. reported a gold(I)-catalyzed consecutive hydroamination of phenylurea derivatives bearing a terminal conjugated diyne moiety at the ortho-position (Scheme 6, eq 7).[10f] This reaction proceeds through indole formation followed by 5-*exo*- or 6-*endo-dig* cyclization, depending on the substrate structure. The challenging issue of the gold-catalyzed reactions using conjugated diynes would be the difficulty in controlling the regioselectivity of the reaction(s) because conjugated diynes often have several reactive carbons. The author designed a novel gold(I)-catalyzed cascade cyclization of conjugated diynes (Scheme 7), featuring construction of fused indoles from linear structure. Although the indole formation of 2-dienylaniline derivatives was unprecedented when the author started this investigation, the author expected that the regioselectivity issue in this case would focus on the second ring closure (6-*exo-dig* vs. 7-*endo-dig*), because gold(I)-catalyzed indole formation of 2-alkynylaniline derivatives is generally fast.



Scheme 6. Gold(I)-Catalyzed Reactions of Conjugated Diynes



Scheme 7. The Author's Concept (2): Gold(I)-Catalyzed Addition Cascade of Conjugated Diynes

The author attempted an application of the developed gold(I)-catalyzed reaction to natural product synthesis. Conolidine, C5-nor stemmadenine-type monoterpene indole alkaloid isolated from *Tabernaemonta divaricata* species, has received much attention as non-opioid analgesic (Figure 1).[11] Bohn *et al*. have accomplished the first asymmetric total synthesis of conolidine and disclosed the unique analgesic activity unlike opioids including morphine.[12] Although several efficient methods have been reported for the synthesis of C5-nor stemmadenine-type indoles, the development of a diversity-oriented synthetic route to these alkaloids suitable for structure-activity relationship study is still desired.[13]

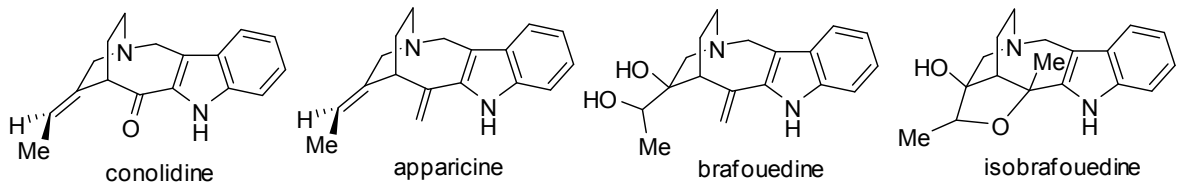
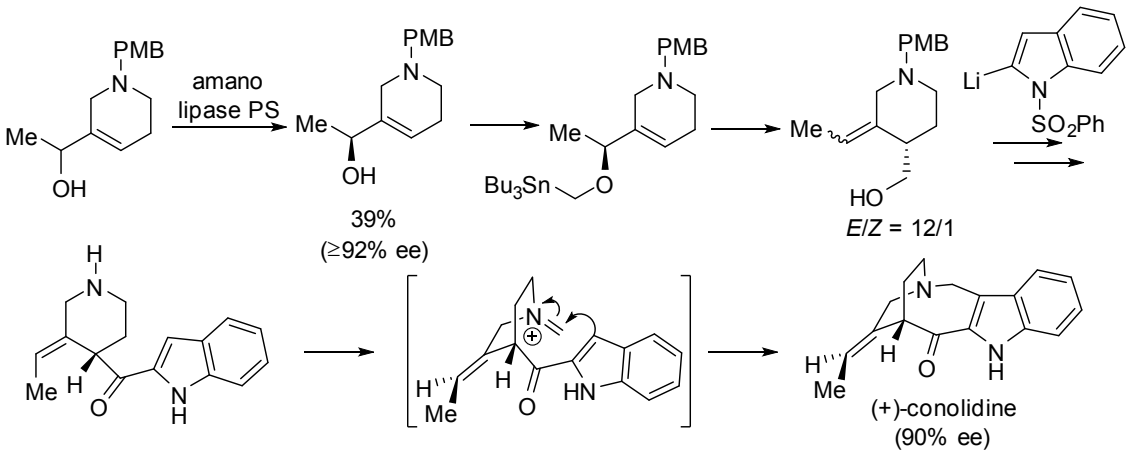


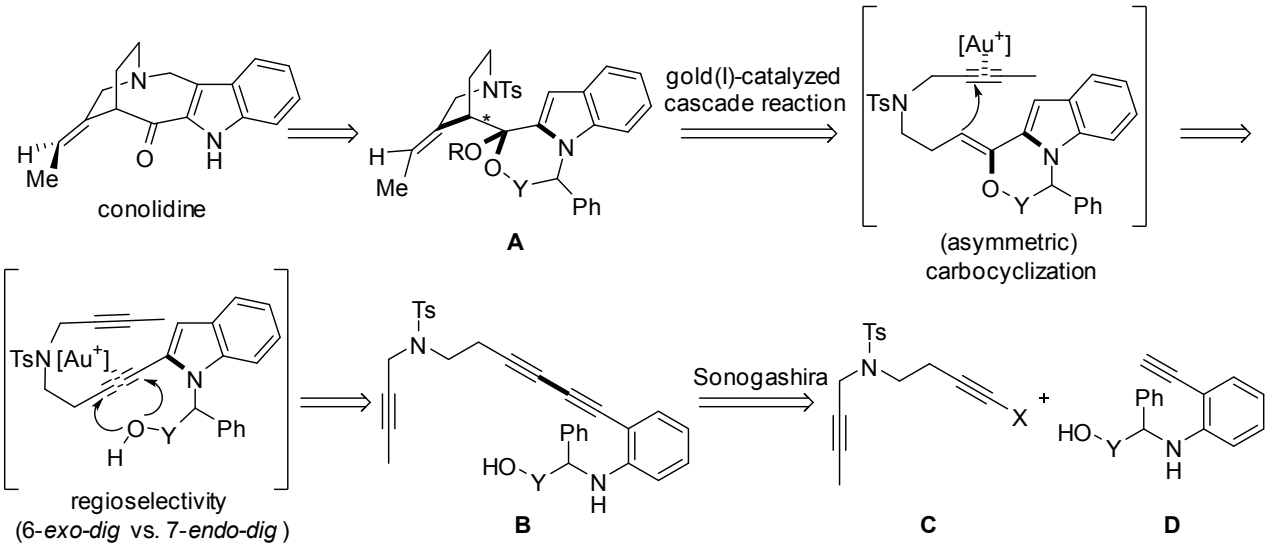
Figure 1. Structures of C5-Nor Stemmadenine-Type Indole Alkaloids

Bohn's synthetic route to conolidine is shown in Scheme 8. Based on biosynthetic pathway for conversion of stemmadenine to vallesamine reported by Scott *et al*.,[14] the eight-membered bridged ring was constructed by Mannich reaction through a conformation that minimizes 1,3-allylic strain. It should be noted that this synthetic route requires lipase-mediated optical resolution of secondary alcohol in the middle stage of the synthesis as well as stepwise construction/introduction of the rings.



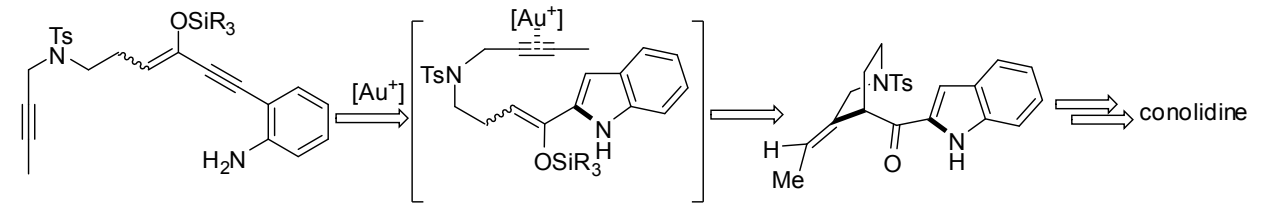
Scheme 8. Total Synthesis of (+)-Conolidine Reported by Bohn *et al*.

Based on the successful gold-catalyzed fused indole formation shown in Scheme 7, the author designed novel strategy for the synthesis of conolidine via gold(I)-catalyzed cascade reaction of conjugated alkynes (Scheme 9). This strategy uses an aniline substrate **B** bearing a conjugated diyne moiety, readily accessible from phenylglycine derivative **C** and *o*-iodoaniline derivative **D** using the Sonogashira-type coupling, for formation of the fused indole. This is followed by the subsequent cyclization to allow introduction of the oxygen atom. The carbocyclization from the resulting enol ether moiety as the final step would form piperidine ring to produce **A** in a one-pot manner. The remaining eight-membered ring can be constructed by the reported Mannich reaction.[13d] This strategy can be considered as diversity-oriented convergent synthesis based on two alkyne fragments. The author expected that the cascade reaction using chiral gold complex would lead to asymmetric total synthesis of conolidine. The potential issues associated with this strategy were regioselectivity in the cyclization for introduction of the oxygen atom (6-*exo*-*dig* vs. 7-*endo*-*dig*).



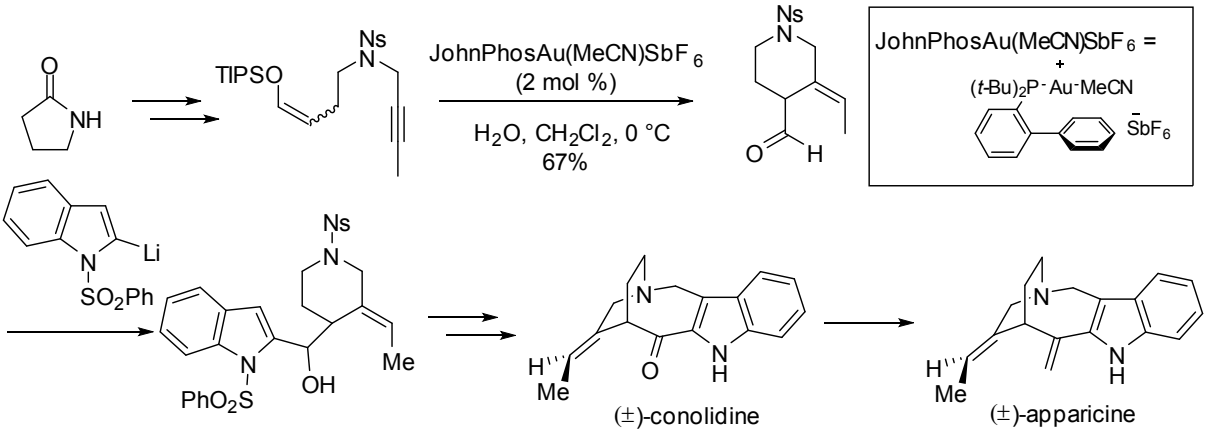
Scheme 9. The Author's Strategy (3-1): The First Strategy for the Total Synthesis of Conolidine by Cascade Cyclization of Conjugated Diyne

On the other hand, several gold(I)-catalyzed reactions of alkyne and silyl enol ether have been reported as powerful strategies for the construction of carbocyclic structures.[15] These reports led the author to design the second strategy that depends on the cascade reaction of conjugated enynes bearing a silyl enol ether moiety (Scheme 10), where the control of the regioselectivity in the second cyclization in Scheme 9 is unnecessary because the oxygen atom in conolidine is already introduced as the silyl ether. The author expected that the nucleophilicity of the silyl enol ether would be increased by indole formation to promote the subsequent formation of piperidine ring.



Scheme 10. The Author's Strategy (3-2): The Second Strategy for the Total Synthesis of Conolidine by Cascade Cyclization of Conjugated Enyne

Indeed, during the cource of this study, the total synthesis of conolidine and apparicine via gold(I)-catalyzed reaction of alkyne and silyl enol ether was reported by Takayama *et al* (Scehme 11).[13d] This report showed utility of gold(I)-catalyzed reaction using silyl enol ether for the construction of carbocyclic ring. However, application of this strategy to asymmetric total synthesis might be difficult because the asymmetric carbon at the α position in resulting aldehyde constructed in the gold(I)-catalyzed reaction is at the allylic position, which would easily lead to racemization.



Scheme 11. Total Synthesis of (±)-Conolidine and (±)-Apparicine Reported by Takayama *et al*.

In this thesis, the author has developed gold(I)-catalyzed cascade reactions for the synthesis of fused ring compounds.

Chapter 1 describes a gold(I)-catalyzed cascade intermolecular addition/intramolecular carbocyclization reaction of dialkynylbenzenes. The intermolecular addition proceeds at the terminal alkyne in a regioselective manner. The reaction using triyne-type substrate was also performed, producing disubstituted chrysenes via an addition and double cyclization cascade.

The transformations and application of conjugated alkynes have been described in Chapter 2. Section 1 presents a gold(I)-catalyzed cascade reaction of conjugated diynes, yielding 1,2-fused indoles. The regioselectivity of the second cyclization was discussed by using DFT calculation. Section 2 presents total synthesis of conolidine via the gold(I)-catalyzed cascade reaction of conjugated enynes. Remarkably, construction of bicyclic intermediate was achieved with excellent enantioselectivity under asymmetric gold(I) catalysis conditions.

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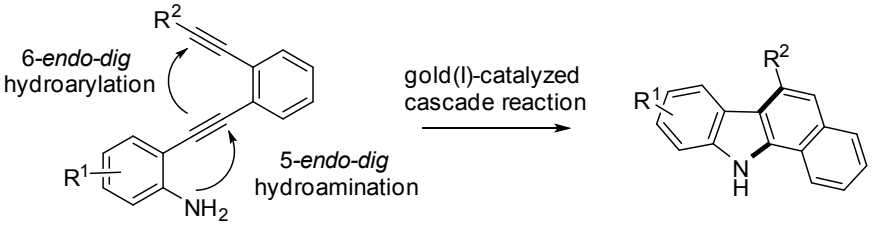
Chapter 1. Regioselective Inter-/Intramolecular Addition Cascade of Di- and Triynes for Direct Construction of Substituted Naphthalenes

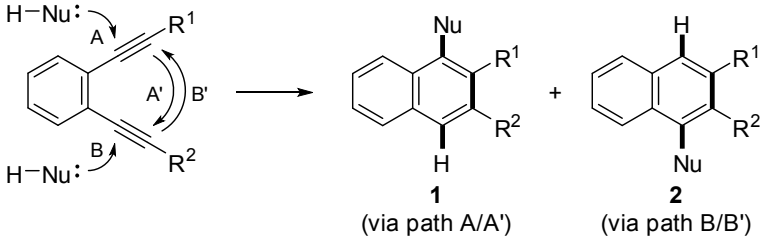
Summary

The gold-catalyzed cascade intermolecular addition−intramolecular carbocyclization reaction of dialkynylbenzenes was developed. In this reaction, regioselective addition of an external nucleophile toward the terminal alkyne and subsequent 6-endo-dig cyclization proceeded to give the 1,3-disubstituted naphthalenes in good yields. The direct synthesis of disubstituted chrysenes via a gold-catalyzed addition and double cyclization cascade using a triyne-type substrate was also achieved.

As described in preface, the author's group have been engaged in the development of gold-catalyzed intramolecular hydroamination/hydroarylation cascade of dienyne-type anilines for synthesis of aryl-annulated carbazoles[1] and successfully applied this reaction to polyyne-type anilines to produce highly fused carbazoles by consecutive hydroarylation (Scheme 1).[2] In these intramolecular reaction cascades, the alkyne that participates in the first nucleophilic addition (hydroamination) among the several alkynes can be predicted from the substrate structures. By contrast, when applying this method to intermolecular reactions using external nucleophiles, the regioselectivity issue arises, *i.e.* which of the two regioisomeric products **1** and **2** predominates (Scheme 2).

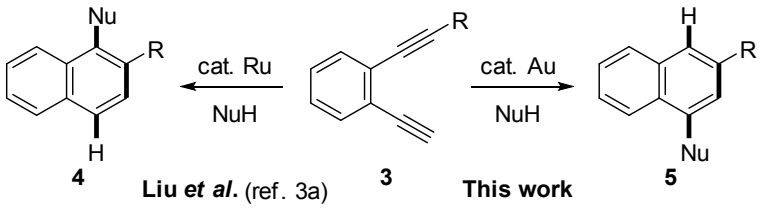


Scheme 1. Gold(I)-Catalyzed Cascade Cyclization Reaction of Polyyne-Type Anilines



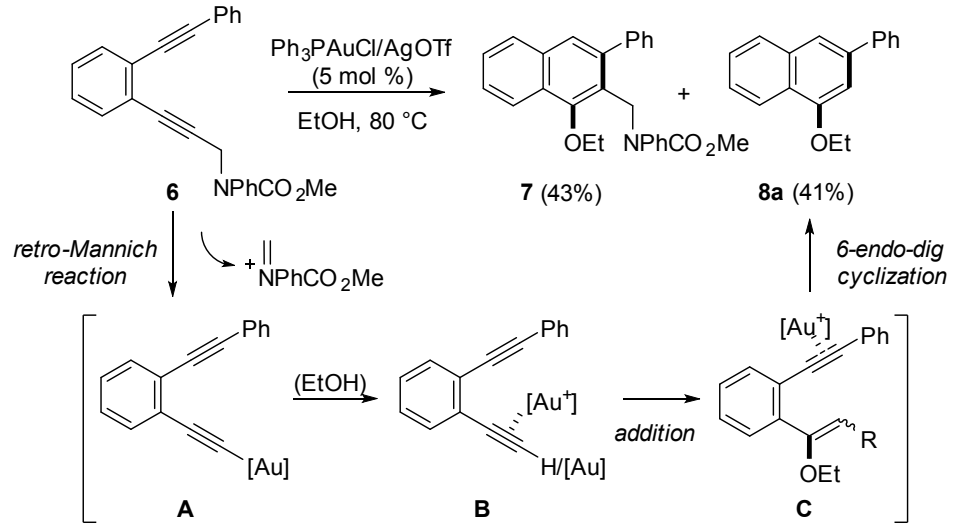
Scheme 2. The Regioselectivity Issue for Intermolecular Addition

Liu and co-workers reported ruthenium-catalyzed naphthalene formation via nucleophilic addition/insertion cascade of dialkynylbenzenes to afford 1,2-disubstituted naphthalene derivatives.[3] The nucleophilic addition of external nucleophiles to diynes **3** bearing internal and terminal alkyne moieties regioselectively proceeds at the internal alkyne to produce **4** (Scheme 3).



Scheme 3. Liu's Work and This Work

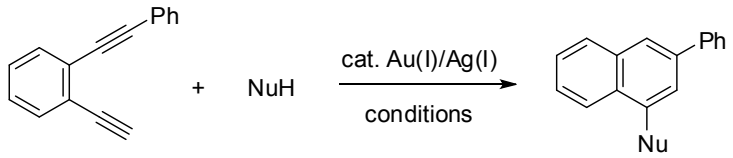
During previous studies on intramolecular reaction cascades using carbamate **6** for investigation of double hydroarylation, this reaction gave unexpected naphthalene derivatives **7** (43%) and **8a** (41%) both bearing an ethoxy group (Scheme 4). Formation of **7** can be explained by gold-catalyzed intermolecular addition of ethanol toward the propargylamine moiety of **6** followed by 6-*endo-dig* cyclization. The naphthalene **8a** lacking the aminomethyl group would be formed by a gold-catalyzed retro-Mannich reaction to furnish gold acetylide **A** followed by the same reaction sequence (ethanol addition and 6-*endo-dig* cyclization).[4] Addition of ethanol proceeded exclusively at the terminal alkyne moiety of the intermediate **B**. Hence, the author expected that diynes bearing terminal and internal alkynes would be promising substrates for a regioselective gold-catalyzed inter/intramolecular addition cascade of dialkynylbenzenes with external nucleophiles (Scheme 3).[3] In the this chapter, the cascade cyclization of di- and triyne derivatives, which provides convenient access to 1,3-disubstituted naphthalene derivatives,[5] benzofuran, benzothiophene, and chrysenes, is described.[6] Mechanistic consideration on the naphthalene formation is also presented.



Scheme 4. Unexpected Regioselective Formation of 1-Ethoxy-3-phenylnaphthalenes

Initially, the author investigated the reaction of **9a** under the conditions shown in Scheme 4. When dialkynylbenzene **9a** was treated with 5 mol % of $Ph_3PAuCl/AgOTf$ in EtOH (**10a**) at 80 °C for 1.5 h, naphthalene derivative **8a** was obtained in 36% yield (Table 1, entry 1). As expected, addition of EtOH regioselectively proceeded at the terminal alkyne of **9a**.[7] The reaction at lower temperature (rt) or use of $AgNTf_2$ instead of AgOTf was less effective (entries 2 and 3). Use of a bulky and electron-

Table 1. Optimization of Reaction Conditions[a]

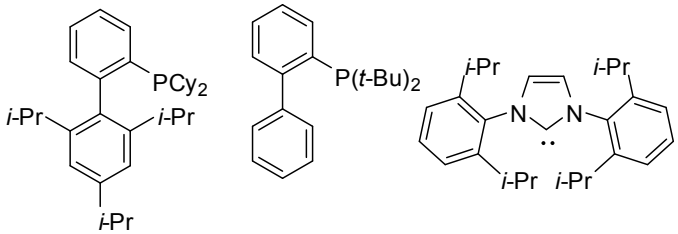


9a **10**

8a: Nu = OEt
8b: Nu = NMePh

entry	catalyst (mol %)	NuH (**10**)[b]	solvent[c]	*T* (°C)	time (h)	yield (%)[d]
1	$Ph_3PAuCl/AgOTf$ (5)	(EtOH)	EtOH	80	1.5	36
2	$Ph_3PAuCl/AgOTf$ (5)	(EtOH)	EtOH	rt	26	11
3	$Ph_3PAuCl/AgNTf_2$ (5)	(EtOH)	EtOH	80	0.5	30
4	$XphosAuCl/AgNTf_2$ (5)	(EtOH)	EtOH	rt	0.5	15
5	$JohnPhosAuCl/AgNTf_2$ (5)	(EtOH)	EtOH	rt	24	<6
6	IPrAuCl/AgOTf (5)	(EtOH)	EtOH	80	1	44
7	$IPrAuCl/AgNTf_2$ (5)	(EtOH)	EtOH	80	0.25	36
8	$IPrAuCl/AgNTf_2$ (5)	(EtOH)	EtOH	rt	2	31
9	IPrAuCl/ AgOTf (5)	(EtOH)	AcOH/EtOH	80	1	48
10	IPrAuCl/ AgOTf (5)	EtOH (**10a**)	1,2-DCE	50	4	50
11[e]	IPrAuCl/ AgOTf (2)	EtOH (**10a**)	1,2-DCE	50	2	61
12[e]	IPrAuCl/ AgOTf (2)	PhNHMe (**10b**)	1,2-DCE	50	7	93
13[e]	IPrAuCl (2)	PhNHMe (**10b**)	1,2-DCE	50	24	N.R.[f]
14[e]	AgOTf (2)	PhNHMe (**10b**)	1,2-DCE	50	24	N.R.[f]
15[e]	AuCl (2)	PhNHMe (**10b**)	1,2-DCE	50	22	5

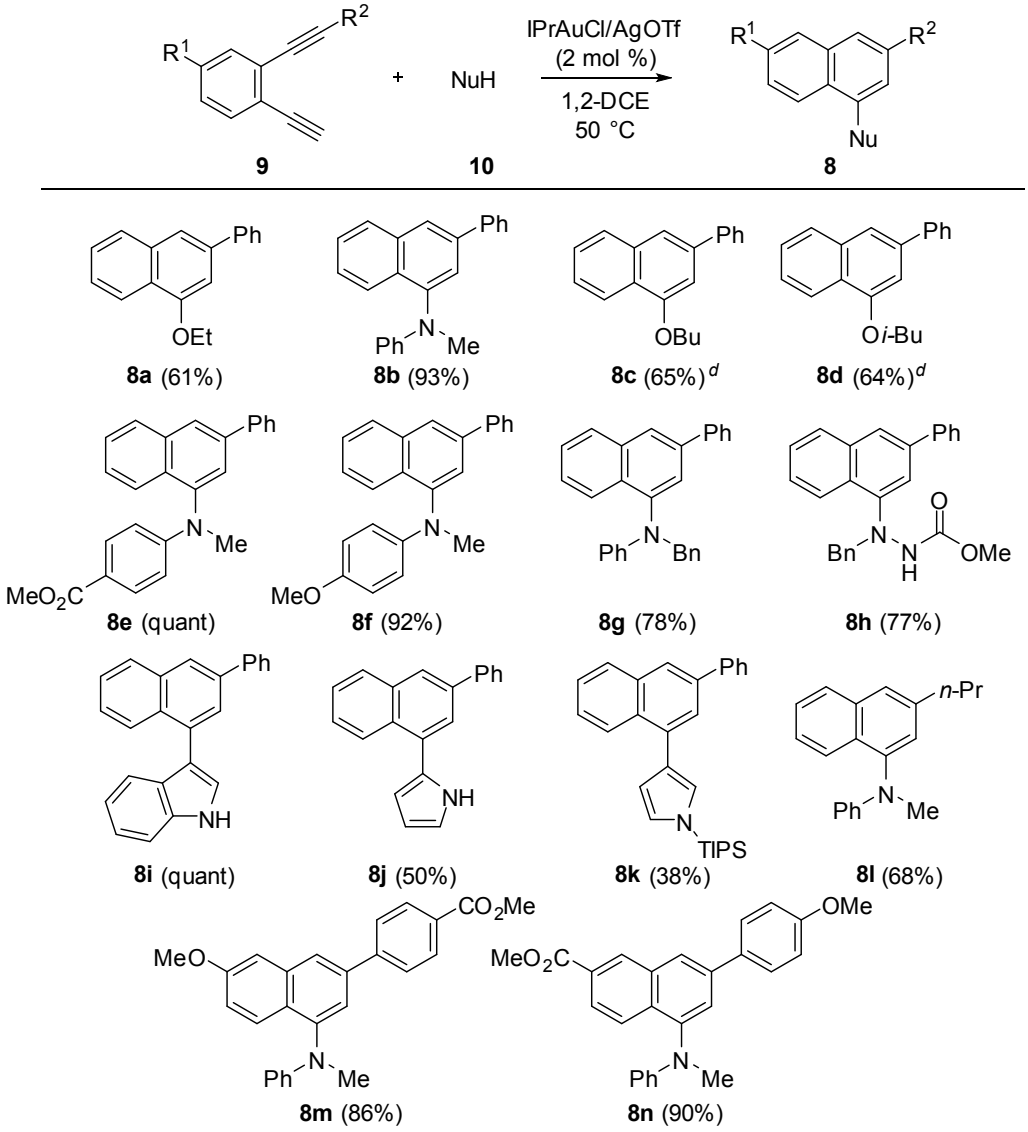
[a] Reactions were carried out using **9a** (0.1 mmol) and **10** (1.1 equiv) at 0.2 M. [b] PhNHMe = *N*-methylaniline. [c] 1,2-DCE = 1,2-dichloroethane. [d] isolated yields. [e] 0.17 mmol of **9a** was used. [f] N.R. = No reaction.



XPhos JohnPhos IPr

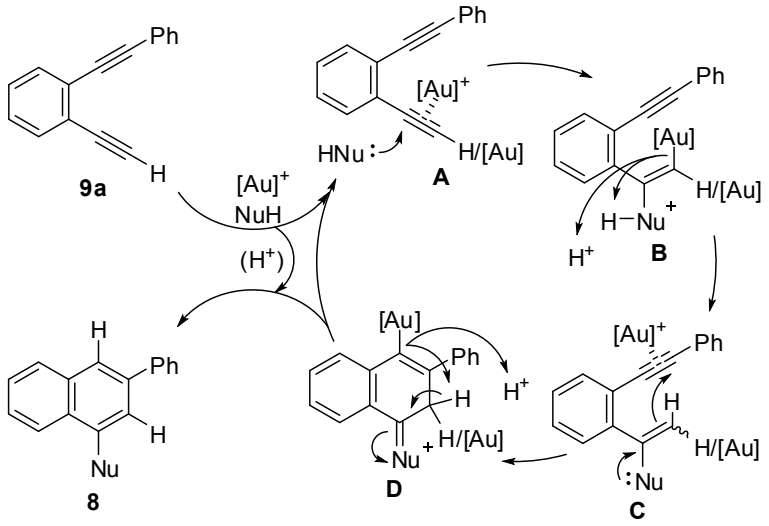
donating phosphine ligand (XPhos or JohnPhos) considerably decreased the yields (entries 4 and 5). Use of an *N*-heterocyclic carbene (NHC) ligand IPr [IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene] in place of PPh_3 exhibited more efficient conversion to **8a** (44%, entry 6). Decreasing the loading of EtOH improved the yields slightly (48−50%, entries 9 and 10), probably by suppressing side reactions with excess EtOH.[8] Interestingly, the most efficient conversion was observed by decreasing the loading of catalyst (2 mol %, entry 11). When using *N*-methylaniline (PhNHMe) as the external nucleophile, the desired product **8b** formed by nucleophilic carbon−nitrogen bond formation was obtained in an excellent yield (93%, entry 12). Use of IPrAuCl or AgOTf alone proved unsuccessful (entries 13 and 14). The reaction with AuCl bearing no ligand gave **8b** in only 5% yield (entry 15).

Table 2. Substrate Scope[a,b,c]

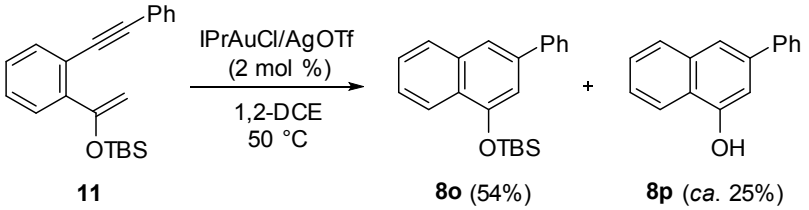


[a] Unless otherwise stated, the reaction was carried out using **9** (0.17 mmol) and **10** (1.1 equiv) at 0.2 M. [b]Isolated yields. [c] 1,2-DCE = 1,2-dichloroethane. [d] 5.0 equiv of **10c** (BuOH) or **10d** (*i*-BuOH) were used.

Using the optimized conditions described in entries 11 and 12 [2 mol % IPrAuCl/AgOTf and 1.1 equiv of NuH in 1,2-dichloroethane (1,2-DCE), Table 1], the reaction scope with various substrates and nucleophiles was investigated (Table 2). The use of aliphatic alcohols resulted in desired products **8c** and **8d** in moderate yields (65% and 64%, respectively). As the nitrogen nucleophiles, the electron density of the aniline ring had a small influence on reactivity (**8b**, **8e** and **8f**; 92%−quant). Similarly, the reaction with *N*-benzylaniline and the protected hydrazine derivative gave the desired products **8g** and **8h** in good yields (78% and 77%, respectively). Use of heteroaromatic rings such as indole and pyrrole as carbon nucleophiles afforded the desired biaryl products formed via nucleophilic C−C bond formation in moderate to good yields (**8i**−**k**).[9] For diynes, the internal alkyne bearing an alkyl group (R^2 = propyl) resulted in the desired product **8l** in 68% yield. Moreover, a range of substituents (R^1 and R^2) were tolerated, including benzene rings bearing an electron-withdrawing or -donating group (**8m** and **8n**; 86% and 90%, respectively).



Scheme 5. A Plausible Catalytic Cycle

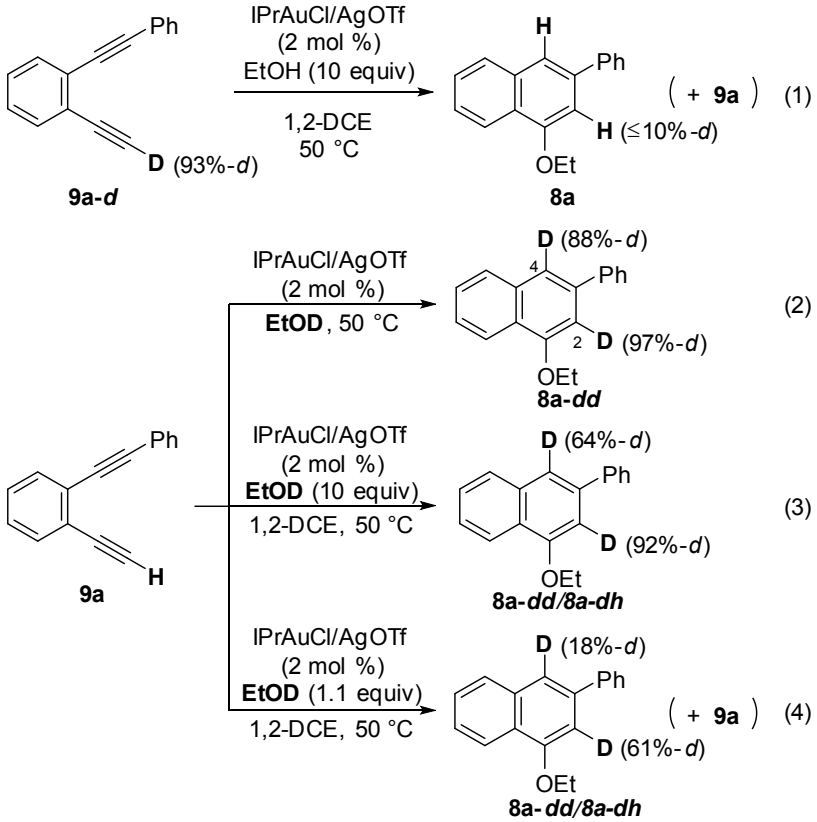


Scheme 6. Reaction of the Silyl Enol Ether **11**

A plausible catalytic cycle of the gold-catalyzed naphthalene formation is shown in Scheme 5. As described previously,[1,2] this reaction would proceed through a stepwise pathway including (1) intermolecular nucleophilic addition onto terminal alkyne or gold acetylide of **9a** as depicted in **A** by electronic and steric effects, (2) protodeauration of **B**, (3) intramolecular nucleophilic addition of the resulting enol ether/enamine-type intermediate **C**, and (4) aromatization of **D** involving protodeauration (1,3-proton shift and/or intermolecular protonation) leading to the naphthalenes **8**. To support this catalytic cycle including intermediacy of **C**, the author prepared a related silyl enol

ether **11** and subjected to the cyclization conditions (Scheme 6). As the author expected, clean conversion to the corresponding naphthol derivatives **8o** and **8p** as the silyl ether and alcohol forms, respectively, was observed.

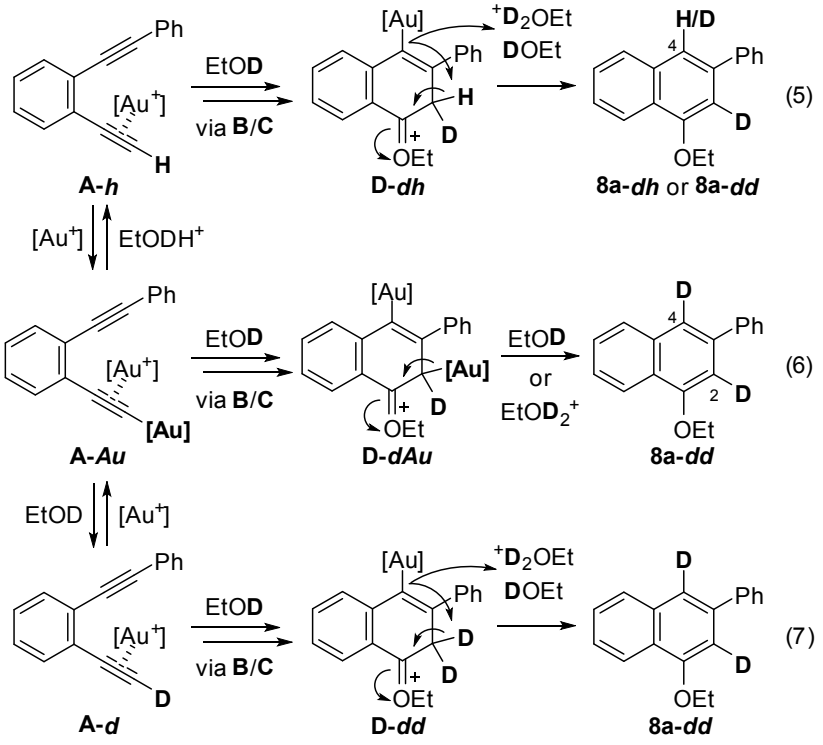
To obtain further mechanistic insights especially on the gold acetylide formation, the author next conducted deuterium-labeling experiments (Scheme 7). The reaction of the labeled substrate **9a-*d*** (93%-*d*) with EtOH (10 equiv) under the standard conditions gave the corresponding naphthalene derivative **8a** with a loss of deuterium labeling (≤10%-*d*, Scheme 7, eq 1). This suggests that gold acetylide is efficiently generated in the reaction. Isolation of the unlabeled substrate **9a** with a decreased deuterium content (<20%-*d*) from the reaction mixture before completion indicates that the D−H exchange by protonation of the gold acetylide is also promoted, presumably with cogenerated $EtODH^+$ or $EtOH_2^+$. Similarly, when the reaction of the unlabeled substrate **9a** was carried out in excess EtOD (Scheme 7, eq 2), a high deuterium incorporation (88−97%) was observed at the 2- and 4-positions of **8a**. Interestingly, in the reaction with a decreased amount of EtOH (10 equiv, Scheme 7, eq 3), the author observed a significant decrease of the deuterium incorporation at the 4-position (64%-*d*). When the reaction was conducted using 1.1 equiv of EtOD (Scheme 7, eq 4), deuterium contents at the 4- and 2-position dropped to 18% and 61%, respectively.



Scheme 7. Isotopic Labeling Experiments

The deuterium experiments using unlabeled **9a** using EtOD (Scheme 7, eqs 2−4) provide some information on the reaction mechanism (Scheme 8). Thus, the reaction of the π-complex **A-*h*** with

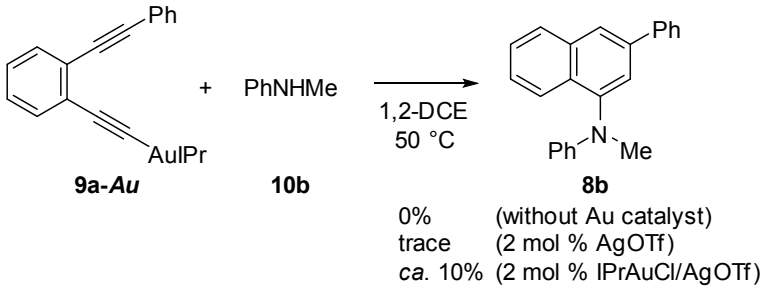
EtOD before H−D exchange would produce **8a**-***dh*** bearing a hydrogen atom at the 4-position through preferential 1,3-proton shift from **D**-***dh*** (Scheme 8, eq 5).[10] The reaction after gold acetylide formation (Scheme 8, eq 6) or deuterium incorporation (Scheme 8, eq 7) furnishes **8a**-***dd*** bearing two deuteriums at the 2- and 4-positions via deauration. Considering the lower deuterium incorporation at the 4-position when using a decreased amount of EtOD (18−64%-*d*, eqs 3 and 4 in Scheme 7) compared with the case using excess EtOD (88%-*d*, Scheme 7, eq 2), it is reasonable that both of the pathways (Scheme 8, eq 5) and (eq 6)/(eq 7) would be involved: an increased amount of EtOD accelerates the intermolecular reaction of **D**-***dh*** (eq 5) with EtOD/$EtOD_2^+$ over 1,3-shift, as well as the H−D exchange from **A**-***h*** to **A**-***d***. Relatively lower deuterium content (61%-*d*) at the 2-position in the case using 1.1 equiv of EtOD (Scheme 7, eq 4) can be rationalized by two possibilites: relatively unfavorable 1,3-deuterium shift over 1,3-proton shift from **D**-***dh*** (Scheme 8, eq 5) in the more dominated pathway and nucleophilic addition of cogenerated EtOH which should not be negligible here. Overall, interconversion between the terminal alkynes and gold acetylides would be one of the important factors for the regioselective intermolecular nucleophilic addition to the terminal alkyne moiety in addition to the steric reason.



Scheme 8. Proposed Mechanism by the Experimental Results

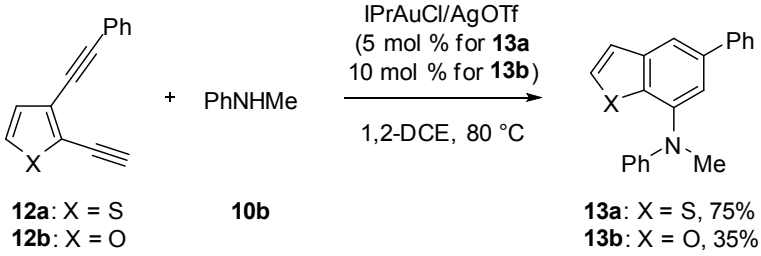
The remaining unsolved problem was the possibility of the intermolecular nucleophilic addition onto the gold acetylide **A**-***Au*** (Scheme 8, eq 6). Thus, the author prepared gold acetylide complex **9a**-***Au*** according to the reported procedure[11] and examined its reactivity. When **9a**-***Au*** was treated under the standard cyclization conditions using **10b** (1.1 equiv) without the gold catalyst, only gradual decomposition of **9a**-***Au*** was observed without producing the naphthalene **8b** (Scheme 9). The addition of the AgOTf (2 mol %) did not promote the reaction. Similarly, addition of the gold

catalyst IPrAuCl/AgOTf (2 mol %) to **9a**-Au in 1,2-DCE only partially promoted the naphthalene formation to afford **8b** in *ca.* 10% yield.[12] Thus, the gold acetylide complex **9a**-***Au*** has proven to have low reactivity toward the intermolecular nucleophilic addition.

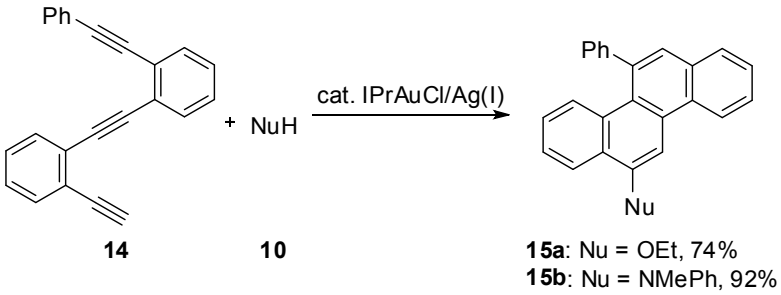


Scheme 9. Conversion of Gold Acetylide Complex **9a**-***Au***

Next, the reaction of heteroaromatic ring derivatives **12a** and **12b** was investigated (Scheme 10). When thiophene **12a** was treated with 5 mol % of IPrAuCl/AgOTf and 1.1 equiv of *N*-methylaniline (**10b**) in 1,2-DCE at 80 °C for 4 h, the benzothiophene derivative **13a** was obtained in 75% yield. A limitation of the reaction can be seen in synthesis of aminobenzofuran derivative **13b** in low yield (35%) by using an increased amount (10 mol %) of IPrAuCl/AgOTf.



Scheme 10. Reaction of Heteroaromatic Compounds



Scheme 11. Application to Consecutive Cyclization
Reaction conditions: (for **15a**) **14** (0.09 mmol), IPrAuCl/$AgNTf_2$ (5 mol %), EtOH (0.1 M), 80 °C; (for **15b**) **14** (0.11 mmol), **10b** (1.1 equiv), IPrAuCl/$AgNTf_2$ (10 mol %), 1,2-DCE (0.2 M), 80 °C.

Finally, biscyclization of triyne-type substrate **14** through intermolecular nucleophilic addition and intramolecular double carbocyclization cascade was investigated (Scheme 11). When the triyne **14** was treated with 5 mol % of IPrAuCl/$AgNTf_2$ in EtOH at 80 °C for 1 h, the chrysene derivative **15a**

was obtained in 74% yield.[13] An improved result was obtained using *N*-methylaniline as the external nucleophile (92%). From these observations, the inter-/intramolecular nucleophilic addition cascade is also useful for atom-economical syntheses of not only the 1,3-disubstituted naphthalenes but also the corresponding fused naphthalenes.

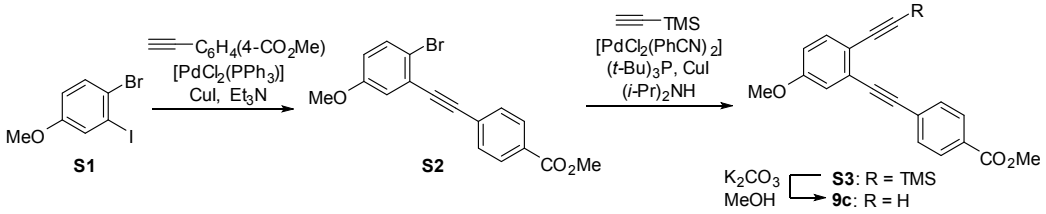
In conclusion, the author developed a novel gold-catalyzed cascade reaction for direct construction of naphthalenes. The reaction of di- and trialkynylbenzene derivatives produced the 1,3-disubstituted naphthalenes and disubstituted chrysenes, respectively, through regioselective intermolecular addition of an external nucleophile such as alcohols, amines, and heteroarenes followed by (consecutive) 6-*endo*-*dig* carbocyclization(s).

Experimental Section

General Methods. For open column chromatography, silica gel (Wakogel C-200E: Wako Pure Chemical Industries, Ltd) or NH_2 silica gel (Chromatorex NH-DM1020: Fuji Silysia Chemical Ltd.) was employed. Thin layer chromatography was performed on Merck TLC silica gel 60 F_{254} or Wako 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). ^{1}H NMR spectra were recorded using a JEOL AL-400 or a JEOL ECA-500 spectrometer, and chemical shifts are reported in δ (ppm) relative to TMS as internal standard. ^{13}C NMR spectra were recorded using a JEOL AL-400 or a JEOL ECA-500 spectrometer and 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). Exact mass (HRMS) spectra were recorded on a JMS-HX/HX 110A mass spectrometer. Infrared (IR) spectra were obtained on a JASCO FT/IR-4100 FT-IR spectrometer with JASCO ATR PRO410-S.

The compound **S8** was obtained commercially and used without further purification.
The known compounds **S1**,[14] **S4**,[15] **S6**,[2] **S12**,[2] **9a**[1a], 1-ethynyl-2-(pent-1-yn-1-yl)benzene (**9b**),[16] **9a-*Au***,[3c] **10e**,[17] **10g**,[18] **11**,[19] and **14**[20] were prepared according to the literature.

1. Preparation of Starting Materials.



Methyl 4-[(2-Bromo-5-methoxyphenyl)ethynyl]benzoate (S2)

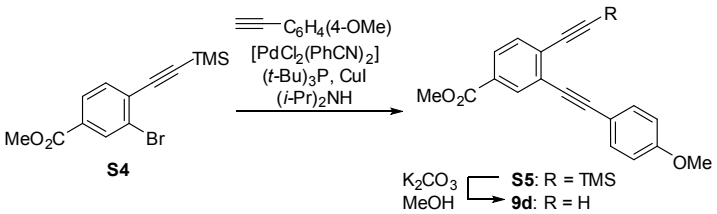
To a stirred suspension of **S1** (775 mg, 2.48 mmol), methyl 4-ethynylbenzoate (476 mg, 2.97 mmol), $PdCl_2(PPh_3)_2$ (43.5 mg, 0.06 mmol) and CuI (11.8 mg, 0.06 mmol) in THF (8 mL) under argon was added Et_3N (1.7 mL, 12.4 mmol). After stirring at rt for 4 h, the reaction mixture was diluted with EtOAc 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 = 50/1) to afford **S2** (841 mg, 98%) as colorless crystals: mp 105–106 °C; IR (neat): 2360 (C≡C), 1709 (C=O), 1274 (OCH_3); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.81 (s, 3H), 3.93 (s, 3H), 6.79 (dd, *J* = 9.2, 2.9 Hz, 1H), 7.09 (d, *J* = 2.9 Hz, 1H), 7.49 (d, *J* = 9.2 Hz, 1H), 7.63-7.65 (m, 2H), 8.03-8.04 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.3, 55.6, 90.9, 92.7, 116.5, 117.0, 117.9, 125.4, 127.5, 129.6 (2C), 129.9, 131.6 (2C), 133.2, 158.5, 166.5. *Anal*. calcd for $C_{17}H_{13}BrO_3$: C, 59.16; H, 3.68. Found: C, 59.16; H, 3.80.

Methyl 4-({5-Methoxy-2-[(trimethylsilyl)ethynyl]phenyl}ethynyl)benzoate (S3)

The coupling of **S2** and trimethylsilylacetylene was carried out according to the method reported as follows:[21] to a stirred suspension of **S2** (690 mg, 2.00 mmol), $PdCl_2(PhCN)_2$ (23.0 mg, 0.06 mmol) and CuI (7.6 mg, 0.04 mmol) in 1,4-dioxane (2 mL) under argon were added diisopropylamine (0.8 mL, 6.00 mmol), trimethylsilylacetylene (0.3 mL, 2.20 mmol) and tri(*tert*-butyl)phosphine (30 μL, 0.12 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/EtOAc = 50/1) to afford **S3** (776.7 mg, quant.) as colorless crystals: mp 73 °C; IR (neat): 2362, 2148 (C≡C), 1718 (C=O), 1308 ($SiCH_3$), 1268, 1231 (OCH_3); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.25 (s, 9H), 3.83 (s, 3H), 3.93 (s, 3H), 6.85 (dd, *J* = 8.6, 2.9 Hz, 1H), 7.03 (d, *J* = 2.9 Hz, 1H), 7.43 (d, *J* = 8.6 Hz, 1H), 7.61-7.62 (m, 2H), 8.02-8.04 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 0.0 (3C), 52.1, 55.4, 91.0, 92.3, 97.0, 103.2, 115.3, 116.2, 118.3, 126.7, 127.8, 129.4 (2C), 129.6, 131.5 (2C), 133.6, 159.2, 166.5; HRMS (FAB) calcd for $C_{22}H_{22}O_3Si$ (M^+) 362.1338, found 362.1335.

Methyl 4-[(2-Ethynyl-5-methoxyphenyl)ethynyl]benzoate (9c)

To the solution of **S3** (294.9 mg, 0.80 mmol) in MeOH (8 mL) was added K_2CO_3 (331.7 mg, 2.40 mmol). After stirring at rt for 4.5 h, the mixture was diluted with Et_2O and filtered through a short pad of silica gel. The filtrate was concentrated in *vacuo* and the residue was chromatographed on silica gel (hexane) to afford **9c** (154.9 mg, 67%) as orange crystals: mp 113–115 °C; IR (neat): 3267 (C≡CH), 2208 (C≡C), 1720 (C=O), 1275, 1232 (OCH_3); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.29 (s, 1H), 3.84 (s, 3H), 3.93 (s, 3H), 6.87 (dd, *J* = 8.5, 2.6 Hz, 1H), 7.06 (d, *J* = 2.6 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.61-7.63 (m, 2H), 8.02-8.03 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.3, 55.5, 79.9, 82.0, 90.7, 92.4, 115.5, 116.4, 117.3, 127.7, 127.0, 129.5 (2C), 129.8, 131.7 (2C), 134.0, 159.5, 166.5. *Anal*. calcd for $C_{19}H_{14}O_3$: C, 78.61; H, 4.86. Found: C, 78.42; H, 4.66.

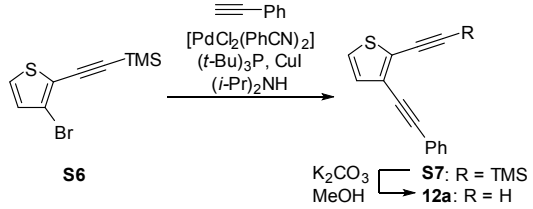


Methyl 3-[(4-Methoxyphenyl)ethynyl]-4-[(trimethylsilyl)ethynyl]benzoate (S5)

According to the procedure described for the preparation of **S3**, **S4** (636 mg, 2.00 mmol) was converted into **S5** (750.7 mg, quant.). Column chromatography: silica gel (hexane); yellow oil; IR (neat): 2252 (C≡C), 2209 (C≡C), 1723 (C=O), 1320 ($SiCH_3$), 1289, 1247 (OCH_3); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.28 (s, 9H), 3.84 (s, 3H), 3.92 (s, 3H), 6.88-6.90 (m, 2H), 7.49-7.51 (m, 2H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.88 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.16 (d, *J* = 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 0.0 (3C), 52.4, 55.4, 86.3, 94.5, 101.9, 103.0, 114.1 (2C), 115.2, 126.8, 128.3, 129.5, 129.7, 132.4, 132.7, 133.4 (2C), 160.1, 166.1; HRMS (FAB) calcd for $C_{22}H_{22}O_3Si$ (M^+) 362.1338, found 362.1337.

Methyl 4-Ethynyl-3-[(4-methoxyphenyl)ethynyl]benzoate (9d)

According to the procedure described for the preparation of **9c**, **S6** (262 mg, 0.70 mmol) was converted into **9d** (114.8 mg, 55%). Column chromatography: silica gel (hexane); colorless crystals; mp 133–134 °C; IR (neat): 3252 (C≡CH), 2209 (C≡C), 1729 (C=O), 1286, 1247 (OCH_3); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.50 (s, 1H), 3.83 (s, 3H), 3.93 (s, 3H), 6.88-6.90 (m, 2H), 7.50-7.52 (m, 2H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.90 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.18 (d, *J* = 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.4, 55.3, 81.7, 83.7, 85.9, 94.6, 114.1 (2C), 114.9, 127.0, 128.2, 128.4, 130.1, 132.58, 132.64, 133.4 (2C), 160.1, 165.9; HRMS (FAB) calcd for $C_{19}H_{14}O_3$ (M^+) 290.0943, found 290.0942.

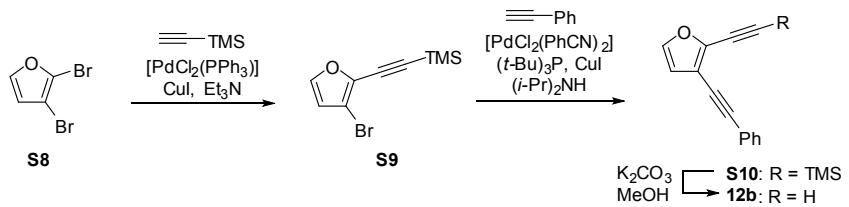


Trimethy[{3-(phenylethynyl)thiophen-2-yl}ethynyl]silane (S7)

The coupling of **S6** and ethynylbenzene was carried out according to the method reported as follows:[2] to a stirred suspension of **S6** (714 mg, 2.75 mmol), $PdCl_2(PhCN)_2$ (63.4 mg, 0.17 mmol) and CuI (31.5 mg, 0.17 mmol) in 1,4-dioxane (5.5 mL) were added diisopropylamine (1.9 mL, 13.7 mmol), ethynylbenzene (0.4 mL, 3.3 mmol) and tri(*tert*-butyl)phosphine (80 μL, 0.33 mmol). After stirring at rt for 6 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) to afford **S7** (705 mg, 91%) as a pale yellow oil; IR (neat): 2144 (C≡C); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.28 (s, 9H), 7.05 (d, *J* = 5.4 Hz, 1H), 7.16 (d, *J* = 5.4 Hz, 1H), 7.33-7.36 (m, 3H), 7.52-7.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 0.0 (3C), 83.9, 93.7, 96.6, 103.7, 123.3, 126.1, 126.2, 127.7, 128.4, 128.5 (2C), 129.3, 131.7 (2C); HRMS (FAB) calcd for $C_{17}H_{17}SSi$ (MH^+) 281.0815, found 281.0804.

2-Ethynyl-3-(phenylethynyl)thiophene (12a)

According to the procedure described for the preparation of **S3**, **S7** (671.9 mg, 2.40 mmol) was converted into **12a** (457 mg, 92%). Column chromatography: silica gel (hexane); amber oil; IR (neat): 3299 (C≡CH), 2248 (C≡C), 2102 (C≡C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.62 (s, 1H), 7.07 (d, *J* = 5.2 Hz, 1H), 7.20 (d, *J* = 5.2 Hz, 1H), 7.33-7.36 (m, 3H), 7.54-7.55 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 76.0, 83.3, 85.3, 93.5, 122.9, 124.7, 126.4, 127.9, 128.3 (2C), 128.5, 129.5, 131.7 (2C); HRMS (FAB) calcd for $C_{14}H_9S$ (MH^+) 209.0419, found 209.0416.



[(3-Bromofuran-2-yl)ethynyl]trimethylsilane (S9)

The coupling of **S8** and trimethylsilylacetylene was carried out according to the reported method as follows:[2] to a stirred suspension of **S8** (1.00 g, 4.40 mmol), $PdCl_2(PPh_3)_2$ (101 mg, 0.14 mmol) and CuI (52.7 mg, 0.28 mmol) in Et_3N (5.9 mL) under argon was added trimethylsilylacetylene (0.73 mL, 5.30 mmol). After stirring at 80 °C overnight, 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) to afford **S9** (627 mg, 58%) as an amber oil; IR (neat): 2158 (C≡C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.27 (s, 9H), 6.45 (d, *J* = 1.8 Hz, 1H), 7.28 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 0.0 (3C), 92.2, 104.5, 106.6, 114.8, 136.8, 143.9; HRMS (FAB) calcd for $C_9H_{12}BrOSi$ (MH^+) 242.9835, found 242.9826.

Trimethyl[{3-(phenylethynyl)furan-2-yl}ethynyl]silane (S10)

The coupling of **S9** and ethynylbenzene was carried out according to the method reported as follows:[20] to a stirred suspension of **S9** (355 mg, 1.46 mmol), $PdCl_2(PhCN)_2$ (33.6 mg, 0.09 mmol) and CuI (16.7 mg, 0.09 mmol) in 1,4-dioxane (3 mL) under argon were added diisopropylamine (1.0 mL, 7.30 mmol), ethynylbenzene (0.17 mL, 1.60 mmol) and tri(*tert*-butyl)phosphine (40 μL, 0.18 mmol). After stirring at rt for 6 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) to afford **S10** (313 mg, 81%) as a dark amber oil; IR (neat): 2252 (C≡C), 2157 (C≡C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.29 (s, 9H), 6.48 (d, *J* = 1.7 Hz, 1H), 7.30 (d, *J* = 1.7 Hz, 1H), 7.33-7.35 (m, 3H), 7.50-7.51 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 0.0 (3C), 80.8, 93.4, 95.1, 104.6, 113.47, 113.51, 113.7, 123.6, 128.6 (2C), 131.9 (2), 143.26, 143.29 ; HRMS (FAB) calcd for $C_{17}H_{17}OSi$ (MH^+) 265.1043, found 265.1039.

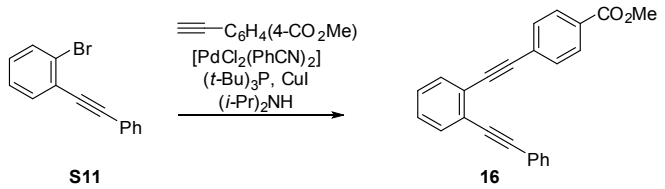
2-Ethynyl-3-(phenylethynyl)furan (12b)

According to the procedure described for the preparation of **S3**, **S10** (268 mg, 1.00 mmol) was converted into **12b** (159 mg, 81%). Column chromatography: silica gel (hexane); dark amber oil; IR (neat): 3302 (C≡CH), 2253 (C≡C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.66 (s, 1H), 6.51 (d, *J* = 1.7 Hz, 1H), 7.34-7.35 (m, 4H), 7.52-7.53 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 72.8, 79.8, 85.7, 94.7, 113.3, 113.7, 122.9, 128.3 (2C), 128.6, 131.6 (2C), 139.0, 143.4; HRMS (FAB) calcd for $C_{14}H_9O$ (MH^+) 193.0648, found 193.0646.

1-(Deuterioethynyl)-2-(phenylethynyl)benzene 9a-*d*)

1-Ethynyl-2-(phenylethynyl)benzene (**9a-*d***) was prepared according to the reported method as follows:[11] *n*-butyllithium (1.5 M in hexane, 260 μL, 0.39 mmol) was added to a mixture of 1-ethynyl-2-(phenylethynyl)benzene (**9a**) (66.1 mg, 0.33 mmol) in anhydrous diethylether (16 mL) under argon atmosphere at –78 °C. After stirring for 30 min, the reaction mixture was quenched with D_2O. The aqueous layer was extracted three times with dichloromethane. The organic layer was dried over $MgSO_4$ and filtrated. Evaporation of the solvent gave **9a-*d*** (73.0 mg, quant.) as a colorless oil.; IR (neat): 2585 (C≡CD), 2249 (C≡C), 2218 (C≡C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.36 (s, 0.07H), 7.27-7.38 (m, 5H), 7.54-7.57 (m, 4H);

^{13}C NMR (125 MHz, $CDCl_3$) δ: 81.1, 87.8, 92.1, 93.5, 123.2, 124.6, 126.3, 127.9, 128.3 (2C), 128.45, 128.48, 128.5, 131.8 (2C), 132.6; HRMS (FAB) calcd for $C_{16}H_{10}D$ (MH^+) 204.0918, found 204.0917.



S11 **16**

Methyl 4-{[2-(Phenylethynyl)phenyl]ethynyl}benzoate (16)

According to the procedure described for the preparation of **S3**, **S11** (298 mg, 1.16 mmol) was converted into **16** (203 mg, 52%). Column chromatography: silica gel (hexane/EtOAc = 5/1); pale amber solid; mp 92–95 °C; IR (neat): 2322 (C≡C), 2212 (C≡C), 1720 (C=O), 1271 (OCH_3); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.93 (s, 3H), 7.31-7.39 (m, 5H), 7.55-7.59 (m, 4H), 7.62 (dd, *J* = 6.3, 1.7 Hz, 2H), 8.01 (dd, *J* = 6.3, 1.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.2, 88.1, 91.2, 92.7, 23.8, 123.1, 125.2, 126.1, 127.96, 128.05, 128.4 (2C), 128.5, 128.6, 129.5 (2C), 129.6, 131.5 (2C), 131.6 (2C), 131.8, 131.9, 166.5; HRMS (FAB) calcd for $C_{24}H_{17}O_2$ (MH^+) 337.1223, found 337.1222.

2. Gold(I)-Catalyzed Naphthalene Formation by Intermolecular/Intramolecular Addition Cascade

General Procedure: Synthesis of 1-Ethoxy-3-phenylnaphthalene (8a) (Table 1, Entry 11)

To a stirred suspension of 1-ethynyl-2-(phenylethynyl)benzene (**9a**) (33.8 mg, 0.17 mmol), IPrAuCl (2.1 mg, 3.4 μmol) and AgOTf (0.9 mg, 3.4 μmol) in 1,2-dichloroethane (1,2-DCE) (0.9 mL) under argon was added ethanol (**10a**) (0.01 mL, 0.19 mmol), and the resulting mixture was stirred at 50 °C for 2 h. The reaction mixture was concentrated in *vacuo*. The residue was chromatographed on silica gel (hexane) to afford **8a** (25.5 mg, 61%) as pale yellow crystals: mp 78–81 °C; IR (neat): 1233 (OCH_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.58 (t, *J* = 6.9 Hz, 3H), 4.29 (q, *J* = 6.9 Hz, 2H), 7.05 (s, 1H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.46-7.49 (m, 4H), 7.61 (s, 1H), 7.70 (d, *J* = 7.4 Hz, 2H), 7.83 (d, *J* = 8.0 Hz, 1H), 8.29 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.9, 63.8, 104.6, 118.2, 122.0, 124.9, 125.1, 126.8, 127.3, 127.4 (2C), 127.7, 128.8 (2C), 134.6, 138.9, 141.7, 155.1; HRMS (FAB) calcd for $C_{18}H_{17}O$ (MH^+) 249.1274, found 249.1278.

***N*-Methyl-*N*,3-diphenylnaphthalen-1-amine (8b) (Table 1, Entry 12)**

The diyne **9a** (22.6 mg, 0.11 mmol) was converted to **8b** (31.6 mg, 93%) by the reaction with *N*-methylaniline (**10b**) (0.01 mL, 0.12 mmol) in the presence of IPrAuCl (1.4 mg, 2.2 μmol) and AgOTf (0.6 mg, 2.2 μmol) in 1,2-DCE (0.6 mL) at 50 °C for 7 h: yellow oil; IR (neat): 1397 (NAr); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.43 (s, 3H), 6.67 (d, *J* = 8.0 Hz, 2H), 6.74 (t, *J* = 7.2 Hz, 1H), 7.14-7.18 (m, 2H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.39-7.51 (m, 4H), 7.67-7.69 (m, 3H), 7.87 (d, *J* = 8.6 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.99 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 40.3, 113.6 (2C), 117.3, 123.8, 124.3, 124.9, 126.4, 126.7, 127.3 (2C), 127.5, 128.8, 128.9 (2C), 129.0 (2C), 130.4, 135.4, 139.3, 140.5, 145.9, 150.1; HRMS (FAB) calcd for $C_{23}H_{20}N$ (MH^+) 310.1590, found 310.1583.

1-Butoxy-3-phenylnaphthalene (8c) (Table 2)

The diyne **9a** (34.7 mg, 0.17 mmol) was converted to **8c** (30.8 mg, 65%) by the reaction with 1-butanol (**10c**) (0.08 mL, 0.85 mmol) in the presence of IPrAuCl (2.1 mg, 3.4 μmol) and AgOTf (0.9 mg, 3.4 μmol) in 1,2-DCE (0.9 mL) at 50 °C for 6 h: pale yellow needles: mp 49 °C; IR (neat): 1234 (OCH_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.04 (t, *J* = 7.4 Hz, 3H), 1.62 (qt, *J* = 7.4, 7.4 Hz, 2H), 1.91-1.97 (m, 2H), 4.22 (t, *J* = 6.3 Hz, 2H), 7.05 (d, *J* = 1.1 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.44-7.51 (m, 4H), 7.60 (s, 1H), 7.69-7.71 (m, 2H), 7.83 (d, *J* = 7.4 Hz, 1H), 8.28 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.9, 19.5, 31.4, 67.9, 104.6, 118.1, 122.0, 125.0, 125.1, 126.8, 127.3, 127.4 (2C), 127.7, 128.8 (2C), 134.6, 139.0, 141.7, 155.3; HRMS (FAB) calcd for $C_{20}H_{20}O$ (M^+) 276.1514, found 276.1514.

1-Isobutoxy-3-phenylnaphthalene (8d)

The diyne **9a** (33.7 mg, 0.17 mmol) was converted to **8d** (29.3 mg, 64%) by the reaction with isobutanol (**10d**) (0.08 mL, 0.83 mmol) in the presence of IPrAuCl (2.1 mg, 3.3 μmol) and AgOTf (0.9 mg, 3.3 μmol) in 1,2-DCE (0.9 mL) at 50 °C for 24.5 h: yellow oil; IR (neat): 1230 (OCH); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.07 (t, *J* = 7.4 Hz, 3H), 1.44 (d, *J* = 6.3 Hz, 3H), 1.75-1.83 (m, 1H), 1.90-1.94 (m, 1H), 4.61-4.64 (m, 1H), 7.07 (d, *J* = 1.1 Hz, 1H), 7.35-7.39 (m, 1H), 7.44-7.49 (m, 4H), 7.59 (s, 1H), 7.68-7.70 (m, 2H), 7.83 (d, *J* = 8.0 Hz, 1H), 8.29 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 9.9, 19.3, 29.4, 75.3, 106.1, 118.0, 122.3, 125.0, 125.8, 126.7, 127.3, 127.5 (2C), 127.8, 128.8 (2C), 134.9, 139.0, 141.8, 154.3; HRMS (FAB) calcd for $C_{20}H_{21}O$ (MH^+) 277.1587, found 277.1577.

Methyl 4-[Methyl(3-phenylnaphthalen-1-yl)amino]benzoate (8e)

The diyne **9a** (35.2 mg, 0.17 mmol) was converted to **8e** (71.1 mg, quant.) by the reaction with methyl 4-(methylamino)benzoate (**10e**)[17] (30.9 mg, 0.19 mmol) in the presence of IPrAuCl (2.2 mg, 3.5 μmol) and AgOTf (0.9 mg, 3.5 μmol) in 1,2-DCE (0.9 mL) at 50 °C for 6 h: yellow oil; IR (neat): 1702 (C=O), 1397 (NAr), 1278 (OCH_3); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.49 (s, 3H), 3.83 (s, 3H), 6.60 (d, *J* = 8.6 Hz, 2H), 7.41-7.51 (m, 5H), 7.70-7.72 (m, 4H), 7.84 (d, *J* = 9.2 Hz, 2H), 7.98 (d, *J* = 8.0 Hz, 1H), 8.06 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 40.2, 51.5, 112.0 (2C), 118.3, 123.2, 125.2, 125.4, 126.8, 126.9, 127.2 (2C), 127.7, 128.93, 128.94 (2C), 129.8, 131.2 (2C), 135.4, 139.3, 140.1, 144.2, 153.2, 167.3; HRMS (FAB) calcd for $C_{25}H_{22}NO_2$ (MH^+) 368.1645, found 368.1644.

***N*-(4-Methoxyphenyl)-*N*-methyl-3-phenylnaphthalen-1-amine (8f)**

The diyne **9a** (34.5 mg, 0.17 mmol) was converted to **8f** (53.0 mg, 92%) by the reaction with 4-methoxy-*N*-methylaniline (**10f**) (25.7 mg, 0.19 mmol) in the presence of IPrAuCl (2.1 mg, 3.4 μmol) and AgOTf (0.9 mg, 3.4 μmol) in 1,2-DCE (0.9 mL) at 50 °C for 24 h: yellow oil; IR (neat): 1285 (NAr), 1242 (OCH_3); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.40 (s, 3H), 3.74 (s, 3H), 6.67-6.70 (m, 2H), 6.75-6.78 (m, 2H), 7.33-7.51 (m, 5H), 7.60 (d, *J* = 1.7 Hz, 1H), 7.67-7.69 (m, 2H), 7.92-7.93 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 41.1, 55.7, 114.5 (2C), 116.1 (2C), 123.5, 123.6, 124.0, 126.1, 126.5, 127.3 (2C), 127.5, 128.7, 128.8 (2C), 130.1, 135.3, 139.2, 140.7, 144.9, 146.9, 152.4; HRMS (FAB) calcd for $C_{24}H_{21}NO$ (M^+) 339.1623, found 339.1622.

***N*-Benzyl-*N*,3-diphenylnaphthalen-1-amine (8g)**

The diyne **9a** (33.6 mg, 0.17 mmol) was converted to **8g** (50.1 mg, 78%) by the reaction with *N*-benzylaniline (**10g**)[18] (0.03 mL, 0.18 mmol) in the presence of IPrAuCl (2.0 mg, 3.3 μmol) and AgOTf (0.9 mg, 3.3 μmol) in 1,2-DCE (0.9 mL) at 50 °C for 4 h: yellow crystals; mp 128–131 °C; IR (neat): 1336 (NAr); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.07 (s, 2H), 6.64-6.66 (m, 2H), 6.70-6.74 (m, 1H), 7.08-7.13 (m, 2H), 7.22-7.24 (m, 1H), 7.30-7.53 (m, 9H), 7.62-7.64 (m, 2H), 7.73 (d, *J* = 2.0 Hz, 1H), 7.88 (d, *J* = 8.3 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.99 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 57.1, 114.1 (2C), 117.6, 123.9, 124.7, 126.2, 126.4, 126.6, 126.9, 127.0 (2C), 127.3 (2C), 127.5, 128.6 (2C), 128.87 (2C), 128.94, 128.95 (2C), 130.2, 135.6, 139.15, 139.16, 140.5, 144.5, 149.5. *Anal*. calcd for $C_{29}H_{23}N$: C, 90.35; H, 6.01; N, 3.63. Found: C, 90.56; H, 6.06; N, 3.61.

Methyl 2-Benzyl-2-(3-phenylnaphthalen-1-yl)hydrazinecarboxylate (8h)

The diyne **9a** (33.4 mg, 0.17 mmol) was converted to **8h** (48.8 mg, 77%) by the reaction with methyl 2-benzylhydrazinecarboxylate (**10h**) (32.7 mg, 0.18 mmol) in the presence of IPrAuCl (2.0 mg, 3.3 μmol) and AgOTf (0.9 mg, 3.3 μmol) in 1,2-DCE (0.8 mL) at 50 °C for 2 h: pale yellow crystals; mp 137 °C; IR (neat): 1712 (C=O), 1246 (OCH_3); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.62 (s, 3H), 4.71 (br s, 2H), 6.49 (br s, 1H), 7.31 (dd, *J* = 6.7, 1.7 Hz, 1H), 7.34-7.39 (m, 5H), 7.47 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.52-7.54 (m, 3H), 7.65 (d, *J* = 7.4 Hz, 2H), 7.83 (s, 1H), 7.89-7.90 (m, 1H), 8.41-8.43 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.3 (br), 60.0 (br), 117.1 (br), 123.2, 123.5, 126.0, 126.5, 127.36 (2C), 127.38, 127.7, 127.8 (2C), 128.46 (2C), 128.53, 128.8 (2C), 129.1 (2C), 134.9, 136.2 (br), 138.1, 141.0, 146.3 (br), 155.8 (br); HRMS (FAB) calcd for $C_{25}H_{23}N_2O_2$ (MH^+) 383.1754, found 383.1760.

3-(3-Phenylnaphthalen-1-yl)-1*H*-indole (8i)

The diyne **9a** (32.8 mg, 0.16 mmol) was converted to **8i** (52.9 mg, quant.) by the reaction with indole (**10i**) (20.6 mg, 0.18 mmol) in the presence of IPrAuCl (2.0 mg, 3.2 μmol) and AgOTf (0.8 mg, 3.2 μmol) in 1,2-DCE (0.8 mL) at 50 °C for 2 h. For column chromatography, NH_2 silica gel (hexane/EtOAc = 50/1) was employed: dark yellow oil; IR (neat): 3468 (NH); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.13-7.15 (m, 1H), 7.26-7.30 (m, 1H), 7.37-7.40 (m, 3H), 7.49-7.53 (m, 5H), 7.76-7.78 (m, 2H), 7.89 (d, *J* = 1.7 Hz, 1H), 7.97 (d, *J* = 8.6 Hz, 1H), 8.07-8.08 (m, 2H), 8.33 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 111.3, 116.6, 120.1, 120.3, 122.5, 123.6, 125.0, 125.8, 126.2, 126.4, 127.32, 127.35, 127.5 (2C), 127.7, 128.6, 128.8 (2C), 131.8, 133.5, 134.3, 136.1, 138.2, 141.1; HRMS (FAB) calcd for $C_{24}H_{18}N$ (MH^+) 320.1434, found 320.1431.

2-(3-Phenylnaphthalen-1-yl)-1*H*-pyrrole (8j)

The diyne **9a** (33.1 mg, 0.16 mmol) was converted to **8j** (21.4 mg, 50%) by the reaction with pyrrole (**10j**) (0.01 mL, 0.18 mmol) in the presence of IPrAuCl (2.1 mg, 3.3 μmol) and AgOTf (0.9 mg, 3.3 μmol) in 1,2-DCE (0.8 mL) at 50 °C for 26 h. For column chromatography, NH_2 silica gel (hexane) was employed: dark brown oil; IR (neat): 3349 (NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.44 (dd, *J* = 5.7, 2.8 Hz, 1H), 6.56-6.57 (m, 1H), 6.99-7.00 (m, 1H), 7.38-7.40 (m, 1H), 7.47-7.54 (m, 4H), 7.73-7.74 (m, 2H), 7.78 (d, *J* = 1.7 Hz, 1H),

7.93-7.94 (m, 1H), 8.00 (s, 1H), 8.29 (d, J = 8.6 Hz, 1H), 8.46 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 109.55, 109.64, 118.5, 125.3, 125.6, 125.8, 126.38, 126.38, 127.4 (2C), 127.5, 128.7, 128.9 (2C), 130.5, 130.6, 132.1, 134.4, 138.2, 140.8; HRMS (FAB) calcd for $C_{20}H_{16}N$ (MH^+) 270.1277, found 270.1276.

3-(3-Phenylnaphthalen-1-yl)-1-(triisopropylsilyl)-1*H*-pyrrole (8k)

The diyne **9a** (30.4 mg, 0.15 mmol) was converted to **8k** (24.4 mg, 38%) by the reaction with 1-(triisopropylsilyl)-1*H*-pyrrole (**10k**) (0.04 mL, 0.16 mmol) in the presence of IPrAuCl (1.9 mg, 3.0 μmol) and AgOTf (0.8 mg, 3.0 μmol) in 1,2-DCE (0.8 mL) at 50 °C for 6 h: amber oil; IR (neat): 2867, 2946 (CH); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.17 (d, J = 7.4 Hz, 18H), 1.51-1.53 (m, 3H), 6.64 (dd, J = 2.9, 1.4 Hz, 1H), 6.91-6.93 (m, 1H), 7.02-7.03 (m, 1H), 7.37 (t, J = 7.4 Hz, 1H), 7.48-7.45 (m, 4H), 7.76-7.77 (m, 3H), 7.91-7.94 (m, 2H), 8.34 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 11.8 (3C), 17.9 (6C), 112.5, 123.5, 124.2, 124.3, 125.2, 125.6, 125.9, 126.1, 126.3, 127.2, 127.5 (2C), 128.5, 128.8 (2C), 131.3, 134.3, 135.6, 138.2, 141.4; HRMS (FAB) calcd for $C_{29}H_{36}NSi$ (MH^+) 426.2612, found 426.2603.

***N*-Methyl-*N*-phenyl-3-propylnaphthalen-1-amine (8l)**

1-Ethynyl-2-(pent-1-ynyl)benzene (**9b**) (26.0 mg, 0.15 mmol) was converted to **8l** (29.1 mg, 68%) by the reaction with *N*-methylaniline (**10b**) (0.02 mL, 0.17 mmol) in the presence of IPrAuCl (1.9 mg, 3.1 μmol) and AgOTf (0.8 mg, 3.1 μmol) in 1,2-DCE (0.8 mL) at 50 °C for 10 h: yellow oil; IR (neat): 1396 (NAr); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.97 (t, J = 7.2 Hz, 3H), 1.70-1.73 (m, 2H), 2.72 (t, J = 7.4 Hz, 2H), 3.38 (s, 3H), 6.61 (d, J = 8.6 Hz, 2H), 6.71 (dd, J = 7.2, 7.2 Hz, 1H), 7.13-7.17 (m, 2H), 7.23-7.24 (m, 1H), 7.33-7.38 (m, 1H), 7.45 (dd, J = 7.2, 7.2 Hz, 1H), 7.56 (s, 1H), 7.82 (dd, J = 9.5, 8.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.8, 24.4, 38.0, 40.2, 113.4, 117.0, 123.6, 125.2, 125.4, 126.2, 126.8, 127.1, 127.9, 128.9, 129.6, 131.8, 135.2, 141.1, 145.1, 150.1; HRMS (FAB) calcd for $C_{20}H_{22}N$ (MH^+) 276.1747, found 276.1745.

Methyl 4-{7-Methoxy-4-[methyl(phenyl)amino]naphthalen-2-yl}benzoate (8m)

Methyl 4-[(2-ethynyl-5-methoxyphenyl)ethynyl]benzoate (**9c**) (49.4 mg, 0.17 mmol) was converted to **8m** (57.8 mg, 86%) by the reaction with *N*-methylaniline (**10b**) (0.02 mL, 0.19 mmol) in the presence of IPrAuCl (2.1 mg, 3.4 μmol) and AgOTf (0.9 mg, 3.4 μmol) in 1,2-DCE (0.9 mL) at 50 °C for 7 h: orange crystals; mp 150–151 °C; IR (neat): 1713 (C=O), 1391 (NAr), 1276, 1231 (OCH_3); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.43 (s, 3H), 3.94 (s, 6H), 6.66 (d, J = 8.0 Hz, 2H), 6.74 (t, J = 7.4 Hz, 1H), 7.15-7.19 (m, 2H), 7.10 (dd, J = 9.2, 2.9 Hz, 1H), 7.26 (d, J = 2.9 Hz, 1H), 7.51 (d, J = 1.7 Hz, 1H), 7.75-7.78 (m, 3H), 7.93 (d, J = 1.1 Hz, 1H), 8.12 (dd, J = 6.8, 1.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 40.3, 52.1, 55.4, 106.8, 113.7 (2C), 117.4, 119.6, 122.1, 123.7, 125.5, 126.2, 127.1 (2C), 128.97 (2C), 129.04, 130.1 (2C), 136.6, 138.7, 145.1, 146.2, 149.9, 158.4, 166.9. *Anal*. calcd for $C_{26}H_{23}NO_3$: C, 78.57; H, 5.83; N, 3.52. Found: C, 78.30; H, 5.85; N, 3.42.

Methyl 7-(4-Methoxyphenyl)-5-[methyl(phenyl)amino]-2-naphthoate (8n)

Methyl 4-ethynyl-3-[(4-methoxyphenyl)ethynyl]benzoate (**9d**) (49.8 mg, 0.17 mmol) was converted to **8n** (60.8 mg, 90%) by the reaction with *N*-methylaniline (**10b**) (0.02 mL, 0.19 mmol) in the presence of IPrAuCl

(2.1 mg, 3.4 μmol) and AgOTf (0.9 mg, 3.4 μmol) in 1,2-DCE (0.9 mL) at 50 °C for 10 h: colorless crystals; mp 133 °C; IR (neat): 1710 (C=O), 1368 (NAr), 1259, 1240 (OCH_3); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.44 (s, 3H), 3.87 (s, 3H), 3.98 (s, 3H), 6.67 (d, *J* = 8.6 Hz, 2H), 6.76 (t, *J* = 7.4 Hz, 1H), 7.00-7.03 (m, 2H), 7.16-7.19 (m, 2H), 7.62-7.63 (m, 2H), 7.73 (d, *J* = 1.7 Hz, 1H), 7.90 (d, *J* = 9.2 Hz, 1H), 7.96 (dd, *J* = 8.6, 1.7 Hz, 1H), 8.03 (s, 1H), 8.69 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 40.3, 52.2, 55.4, 113.8 (2C), 114.4 (2C), 117.7, 124.1, 124.6, 125.3, 126.9, 128.2, 128.3 (2C), 129.0 (2C), 131.7, 132.1, 132.4, 134.6, 139.8, 145.9, 149.8, 159.6, 167.1. *Anal*. calcd for $C_{26}H_{23}NO_3$: C, 78.57; H, 5.83; N, 3.52. Found: C, 78.33; H, 5.74; N, 3.48.

tert-Buthyldimethyl[(3-phenylnaphthalen-1-yl)oxy]silane (8o)

tert-Butyldimethyl[{1-(2-(phenylethynyl)phenyl)vinyl}oxy]silane (**11**) (51.2 mg, 0.15 mmol) was converted to **8o** (27.8 mg, 54%) and **8p** containing some impurities (8.4 mg, *ca*. 25%), by the reaction in the presence of IPrAuCl (1.9 mg, 3.1 μmol) and AgOTf (0.8 mg, 3.1 μmol) in 1,2-DCE (0.8 mL) at 50 °C for 24 h. The spectral data for **8p** was matched those presented in the literature.[22] Compound **8o**: orange oil; IR (neat): 1296 (Si-CH_3), 1100 (Si-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.33 (s, 6H), 1.12 (s, 9H), 7.13 (d, *J* = 1.4 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.43-7.51 (m, 5H), 7.66-7.68 (m, 3H), 7.84 (t, *J* = 4.6 Hz, 1H), 8.18 (d, *J* = 4.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.14, 18.5, 25.9, 112.4, 119.0, 122.5, 125.2, 126.6, 127.1, 127.3 (3C), 128.0, 128.8 (2C), 135.1, 138.9, 141.3, 152.1; HRMS (FAB) calcd for $C_{22}H_{26}OSi$ (M^+) 334.1753, found 334.1753.

***N*-Methyl-*N*,5-diphenylbenzo[*b*]thiophene-7-amine (13a)**

2-Ethynyl-3-(phenylethynyl)thiophene (**12a**) (34.1 mg, 0.16 mmol) was converted to **13a** (38.7 mg, 75%) by the reaction with *N*-methylaniline (**10b**) (0.02 mL, 0.18 mmol) in the presence of IPrAuCl (5.1 mg, 8.2 μmol) and AgOTf (2.1 mg, 8.2 μmol) in 1,2-DCE (0.8 mL) at 80 °C for 4 h: amber oil; IR (neat): 1366 (NAr); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.44 (s, 3H), 6.84-6.86 (m, 3H), 7.20-7.23 (m, 3H), 7.34 (t, *J* = 6.8 Hz, 1H), 7.39-7.40 (m, 2H), 7.43-7.45 (m, 3H), 7.63-7.64 (m, 2H), 7.88 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 39.7, 116.4 (2C), 118.9, 119.2, 120.6, 124.5, 124.9, 127.2, 127.4 (2C), 128.8 (2C), 129.0 (2C), 135.9, 139.4, 141.1, 142.0, 143.7, 148.4; HRMS (FAB) calcd for $C_{21}H_{18}NS$ (MH^+) 316.1154, found 316.1152.

***N*-Methyl-*N*,5-diphenylbenzofuran-7-amine (13b)**

2-Ethynyl-3-(phenylethynyl)furan (**9c**) (31.6 mg, 0.16 mmol) was converted to **13b** (17.2 mg, 35%) by the reaction with *N*-methylaniline (**10b**) (0.02 mL, 0.18 mmol) in the presence of IPrAuCl (10.2 mg, 20 μmol) and AgOTf (4.2 mg, 20 μmol) in 1,2-DCE (0.8 mL) at 80 °C for 27 h: amber oil; IR (neat): 1369 (NAr); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.49 (s, 3H), 6.81 (d, *J* = 1.7 Hz, 1H), 6.85 (t, *J* = 7.4 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 2H), 7.22-7.24 (m, 3H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.37 (d, *J* = 1.7 Hz, 1H), 7.42 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.57-7.58 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 39.7, 107.1, 115.7, 116.0 (2C), 119.2, 120.2, 127.0, 127.4 (2C), 128.7 (2C), 128.9 (2C), 129.8, 133.3, 137.5, 141.4, 145.4, 148.6, 148.9; HRMS (FAB) calcd for $C_{21}H_{18}NO$ (MH^+) 300.1383, found 300.1384.

12-Ethoxy-5-phenylchrysene (15a) (Scheme 11)

1-Ethynyl-2-{[2-(phenylethynyl)phenyl]ethynyl}benzene (**14**) (27.1 mg, 0.09 mmol) was converted to **15a** (23.2 mg, 74%) by the reaction with ethanol (**10a**) in the presence of IPrAuCl (2.8 mg, 4.5 μmol) and $AgNTf_2$ (1.8 mg, 4.5 μmol) in ethanol (0.9 mL) under reflux for 1 h: pale yellow crystals: mp 147–148 °C; IR (neat): 1230 (OCH_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.68 (t, *J* = 6.9 Hz, 3H), 4.49 (q, *J* = 6.9 Hz, 2H), 7.11-7.14 (m, 1H), 7.40-7.47 (m, 6H), 7.65-7.67 (m, 2H), 7.59-7.62 (m, 1H), 7.77 (d, *J* = 8.6 Hz, 1H), 7.92 (d, *J* = 6.3 Hz, 1H), 8.00 (s, 1H), 8.44 (dd, *J* = 8.0, 1.1 Hz, 1H), 8.66 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.9, 63.8, 98.6, 121.9, 122.5, 123.0, 125.0, 125.4, 126.1, 126.6, 126.8, 127.0, 128.42, 128.44, 128.7, 128.8 (2C), 129.0 (2C), 129.5, 130.9, 131.6, 131.7, 138.3, 145.7, 153.8; HRMS (FAB) calcd for $C_{26}H_{21}O$ (MH^+) 349.1587, found 349.1583.

***N*-Methyl-*N*,11-diphenylchrysen-6-amine (15b) (Scheme 11)**

1-Ethynyl-2-{[2-(phenylethynyl)phenyl]ethynyl}benzene (**14**) (31.9 mg, 0.11 mmol) was converted to **15b** (39.4 mg, 92%) by the reaction with *N*-methylaniline (**10b**) (0.01 mL, 0.12 mmol) in the presence of IPrAuCl (6.5 mg, 12 μmol) and $AgNTf_2$ (4.1 mg, 12 μmol) in 1,2-DCE (0.6 mL) under reflux for 24 h: pale yellow powder: mp 172–175 °C; IR (neat): 1346 (NAr); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.54 (s, 3H), 6.75-6.77 (m, 3H), 7.13 (t, *J* = 7.7 Hz, 1H), 7.20 (t, *J* = 7.7 Hz, 2H), 7.39 (t, *J* = 7.7 Hz, 1H), 7.43-7.52 (m, 5H), 7.61-7.66 (m, 2H), 7.84 (s, 1H), 7.89 (d, *J* = 9.2 Hz, 1H), 7.94 (d, *J* = 7.4 Hz, 1H), 7.98 (d, *J* = 8.6 Hz, 1H), 8.62 (d, *J* = 8.0 Hz, 1H), 8.69 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 40.3, 113.7 (2C), 117.4, 120.6, 123.1, 123.9, 124.9, 126.2, 126.5, 126.7, 126.9, 127.0, 128.4, 128.96 (2C), 129.01 (2C), 129.1 (2C), 129.4, 129.7, 130.5, 130.9, 131.2, 131.5, 132.3, 138.2, 144.6, 145.5, 150.0; HRMS (FAB) calcd for $C_{31}H_{24}N$ (MH^+) 410.1903, found 410.1901.

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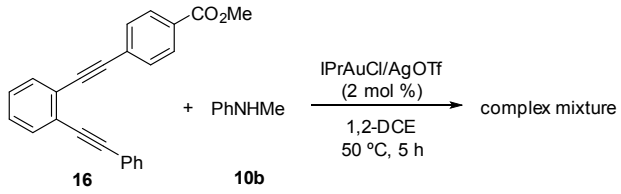
4. The author confirmed that the naphthalene derivative **7** does not undergo the retro-Mannich reaction under the conditions shown in Scheme 4.
5. 1,3-Disubstituted naphthalene derivatives are biologically and synthetically useful. For recent reviews, see: (a) Ukita, T.; Nakamura,Y.; Kubo, A.; Yamamoto, Y.; Takahashi, M.; Kotera, J.; Ikeo, T. *J. Med. Chem*. **1999**, *42*, 1293. (b) Bochkarev, M. N. *Chem. Rev.* **2002**, *108*, 2089. (c) Medarde, M.; Morgan, B. J.; Linton, E. C. J. *Enzyme Inhib. Med. Chem*. **2004**, *19,* 521. (d) Kozlowski, M. C.; Morgan, B. J.; Linton, E. C. *Chem. Soc. Rev.* **2009**, *38*, 3193. (e) Rokade, Y. B.; Sayyed, R. Z. *Rasayan J. Chem.* **2009**, *2*, 972−980. (f) Lin, C. Y.; Wheelock, A. M.; Morin, D.; Baldwin, R. M.; Lee, M. G.; Taff, A.; Plopper, C.; Buckpitt, A.; Rohde, A. *Toxicology* **2009**, *260*, 16.
6. For gold-catalyzed reactions of the related 1,2-diethynylbenzenes to form indene derivatives; see: (a) Ye, L.; Wang, Y.; Aue, D. H.; Zhang, L. *J. Am. Chem. Soc.* **2012**, *134*, 31. (b) Hashmi, A. S. K.; Braun, I.; Nösel, P.; Schädlich, J.; Wieteck, M.; Rudolph, M.; Rominger, F. *Angew. Chem., Int. Ed*. **2012**, *51*, 4456. See also, ref 11.
7. The reaction of diyne **16** without having a terminal alkyne moiety under the optimized reaction conditions (Table 1, entry 11) produced an inseparable mixture of several compounds, which contains the products with the desired mass number.



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13. In this case, $AgNTf_2$ was more effective than AgOTf. When **14** was treated using 2 mol % IPrAuCl/AgOTf in EtOH under the optimized conditions for 24 h, the reaction did not reach completion and the desired product **15a** was obtained in only 25% yield.
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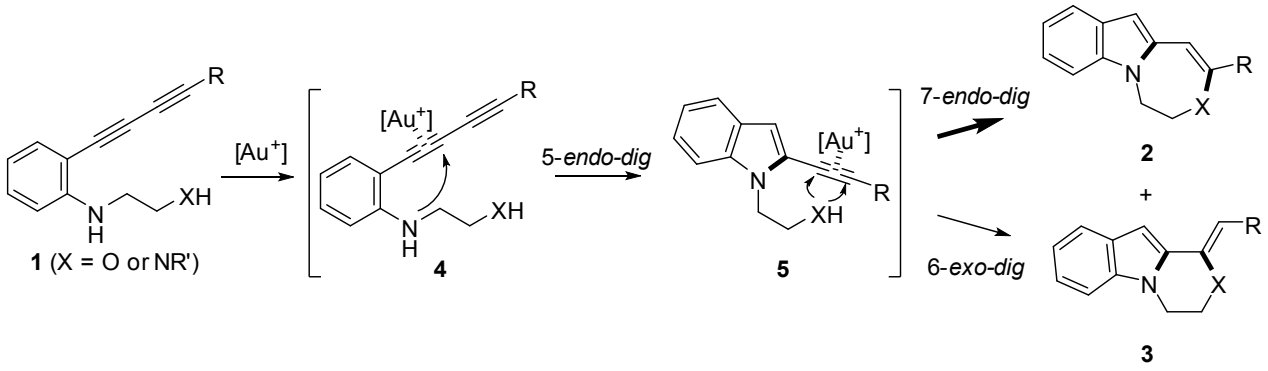
Chapter 2. Cascade Cyclization of Conjugated Alkynes

Section 1. Direct Construction of Fused Indoles by Cascade Cyclization of Conjugated Diynes

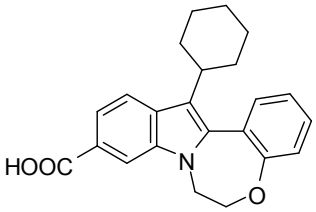
Summary

A gold-catalyzed cascade cyclization of aniline derivatives bearing a conjugated diyne moiety was developed. Following the 5-endo-dig indole formation, subsequent 7-endo-dig cyclization predominated over 6-exo-dig cyclization to give the indole fused with a seven-membered ring in good yields.

Gold-catalyzed reactions of conjugated diynes have great potential for ring construction including indoles.[1a] Recently, some useful gold-catalyzed reactions of conjugated diynes have been reported.[2] The author's group also developed a gold-catalyzed nucleophilic addition and hydroarylation cascade using unconjugated diynes for construction of fused rings such as carbazoles and naphthalenes.[1b–e] When the reactions were applied to polyyne derivatives, highly fused rings were efficiently produced.[3] Given the author's interest in the reactivity of conjugated diynes, the author designed a gold-catalyzed intramolecular consecutive cyclization of conjugated diyne **1** bearing two nucleophilic functionalities, such as an amino alcohol and diamine (Scheme 1). The potential issues associated with this reaction were regioselectivity in the second cyclization (6-*exo-dig* vs 7-*endo-dig*) and reactivity of conjugated diynes toward indole formation. It is well-known that gold-catalyzed cyclizations of alkynes usually favor 6-*exo-dig* over 7-*endo-dig*,[4] except for some limited cases using terminal[5,6] and arylated alkynes.[7] In the reaction of the intermediate **5**, the 6-*exo* cyclization might be promoted by the electron-donating nature of the indole ring, which can effectively stabilize a developing positive charge at the neighboring alkyne carbon when activated by a gold catalyst. In this section, the author describes a gold-catalyzed synthesis of oxepino- and diazepino[1,7-*a*]indole derivatives **2**, which are important structural motifs found in hepatitis C virus polymerase inhibitors[8] and dopamine receptor-binding compounds (Figure 1).[9] The reaction proceeds through regioselective 7-*endo-dig* cyclization starting from conjugated diynes **1**.



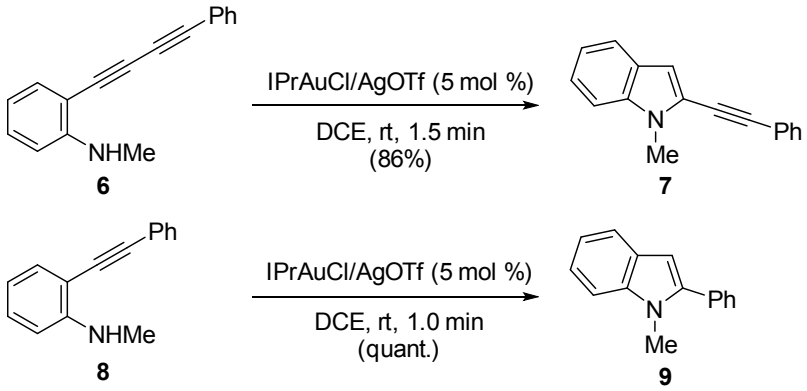
Scheme 1. Gold(I)-Catalyzed Intramolecular Consecutive Cyclization of a Conjugated Diyne



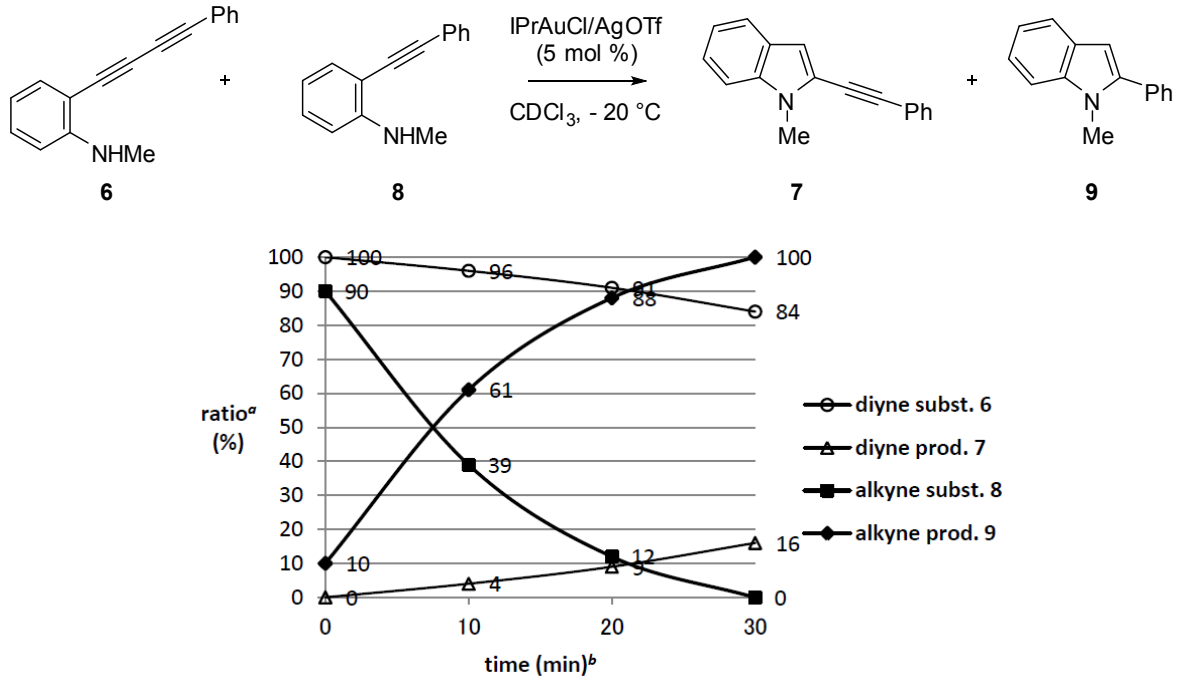
IC_{50} = 0.026 μM

Figure 1. Tetracyclic Compound as Potent Hepatitis C Virus NS5B RNA Polymerase Inhibitor

On initiation of this work, no information was available on the reactivity of conjugated diynes toward indole formation. For a feasibility study of the working hypothesis, the gold-catalyzed reaction of the conjugated diyne **6** bearing an *N*-methylamino group was examined. Indole formation proceeded smoothly to give the alkynylindole **7** in 86% yield after treatment of **6** with IPrAuCl/AgOTf (5 mol %) in 1,2-DCE at rt for 1.5 min. Interestingly, indole formation from 2-alkynylaniline **8** was faster than that from **6**, which reached completion within 1.0 min under identical conditions.[10] This is in contrast to the steric effect, where conjugated diyne derivatives would have a positive effect on the coordination to gold catalysts compared to 2-(phenylethynyl)anilines. The relatively lower reactivity of diyne **6** compared with alkyne **8** toward indole formation can be more clearly seen in the competition experiment at lower temperature shown in Scheme 2 and 3.



Scheme 2. Comparison of the Reactivities toward Indole Formation between Diynyl- and (Phenylethynyl)anilines

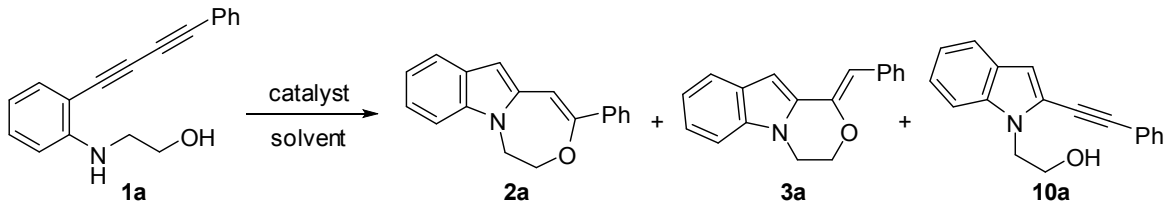


Scheme 3. NMR Analysis of Comparison of the Reactivities toward Indole Formation between Diynyl- and (Phenylethynyl)anilines

[a]Ratios were determined by ^{1}H NMR. [b]The horizontal axis indicates the time of NMR measurement.[11]

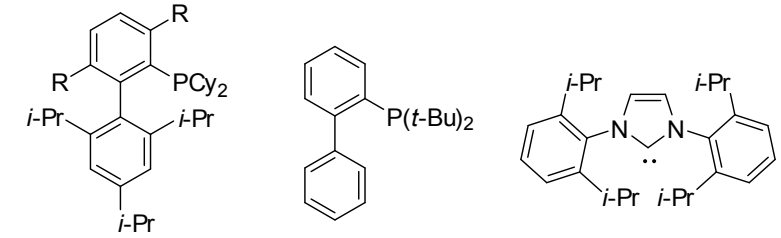
The conjugated diyne has a sufficient level of reactivity for gold-catalyzed indole formation, although it is relatively lower than one of the isolated alkyne. A search for suitable catalysts and solvents for the intramolecular consecutive cyclization of **1a** was then conducted (Table 1). When conjugated diyne **1a** was treated with Ph_3PAuCl/AgOTf (5 mol %) in 1,2-DCE at 50 °C, the desired fused indole derivatives **2a**/**3a** and alkynylindole derivative **10a** were obtained in 28% and 56% yields, respectively (entry 1). The ratio of **2a**/**3a** was determined by ^{1}H NMR after purification of **2a**/**3a** as an isomeric mixture. Surprisingly, 7-*endo-dig* cyclization preferentially proceeded in the second cyclization (**2a**/**3a** = 85/15). The reactions using XPhos (**L1**) or BrettPhos (**L2**) in place of PPh_3 gave the fused indoles **2a**/**3a** in 48% or 27% yield, respectively (entries 2 and 3). Use of JohnPhos (**L3**) resulted in efficient conversion to give a good yield of fused indoles **2a**/**3a** (76%, entry 4). The most efficient conversion was observed when an *N*-heterocyclic carbene ligand, IPr, was used (86%, entry 6). Compared with AgOTf (entry 6), other silver salts such as $AgNTf_2$, AgOTs, and $AgBF_4$ were less effective (entries 7−9). Of the four solvents tested (1,2-DCE, toluene, MeCN, and EtOH), 1,2-DCE was the best (entries 6 and 10−12). The reaction at lower temperature (rt) reduced the yield slightly (73%, entry 13). Use of AgOTf alone produced the alkynylindole **10a** in 58% yield (entry 14). The reactions using AuCl, $AuCl_3$ without any phosphine or carbene ligands, or $PtCl_4$ were unsuccessful (entries 15−17).

Table 1. Optimization of the Reaction Conditions[a]



entry	catalysts (5 mol %)	solvent (0.1 M)	*T* (°C)	time (h)	yield (%)[b]	
					2a/**3a**(ratio[c])	**10a**
1	$Ph_3PAuCl/AgOTf$	1,2-DCE	50	5	28 (85/15)	56
2	**L1**AuCl/AgOTf	1,2-DCE	50	10	48 (91/9)	14
3	**L2**AuCl/AgOTf	1,2-DCE	50	5	27 (85/15)	43
4	**L3**AuCl/AgOTf	1,2-DCE	50	2	76 (93/7)	–
5	**L3**Au(MeCN)SbF_6	1,2-DCE	50	5	3 (93/7)	39
6	**IPrAuCl/AgOTf**	**1,2-DCE**	**50**	**2**	**86 (88/12)**	–
7	IPrAuCl/$AgNTf_2$	1,2-DCE	50	8	32 (85/15)	*ca*. 33
8	IPrAuCl/AgOTs	1,2-DCE	50	6	57 (95/5)	–
9	IPrAuCl/$AgBF_4$	1,2-DCE	50	5	29 (98/2)	trace
10	IPrAuCl/AgOTf	toluene	50	2	<47 (93/7)	–
11	IPrAuCl/AgOTf	MeCN	50	6	trace	trace
12	IPrAuCl/AgOTf	EtOH	50	2	<17 (93/7)	–
13	IPrAuCl/AgOTf	1,2-DCE	rt	8	73 (92/8)	trace
14[d]	AgOTf	1,2-DCE	50	24	–	58
15[d]	AuCl	1,2-DCE	50	4	N.R.[e]	
16[d]	$AuCl_3$	1,2-DCE	50	4	N.R.[e]	
17[d]	$PtCl_4$	1,2-DCE	50	4	N.R.[e]	

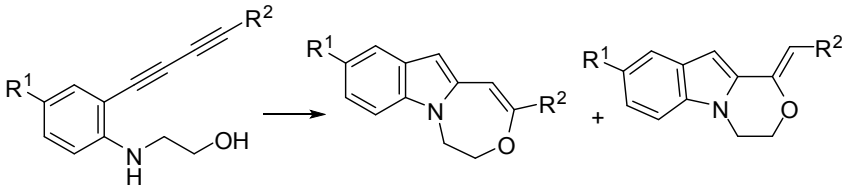
[a] Reaction was carried out using **1a** (0.15 mmol) and catalyst (5 mol %) at 0.1 M at 50 °C. [b](Combined) isolated yields. [c] Ratios were determined by ^{1}H NMR analysis. [d] 0.10 mmol of **1a** was used. [e] N.R. = No reaction.



With the conditions optimized (Table 1, entry 6), the cascade reaction was investigated using various substrates (Table 2). The reaction of **1b** and **1c** with electron-donating or -withdrawing

groups at the *para*-position of the amino group (R^1) gave the desired double cyclization products **2b**/**3b** (86%) and **2c**/**3c** (88%), respectively (entries 2 and 3). In both cases, the 7-*endo* product was obtained with good selectivities (>90/10). A range of substituents at the conjugated diyne terminus (R^2) were tolerated, including benzene rings bearing an electron-donating or -withdrawing group (entries 4 and 5). The observed low regioselectivity of the reaction of **1e** (R^2 = 4-(MeO_2C)C_6H_4) might result from the activation of 6-*exo* cyclization by the electron-deficient phenyl group. Interestingly, use of **1f** bearing an alkyl group exclusively afforded the 7-*endo*-product **2f** in 78% yield (entry 6).

Table 2. Reaction of Various Conjugated Diynes[a]



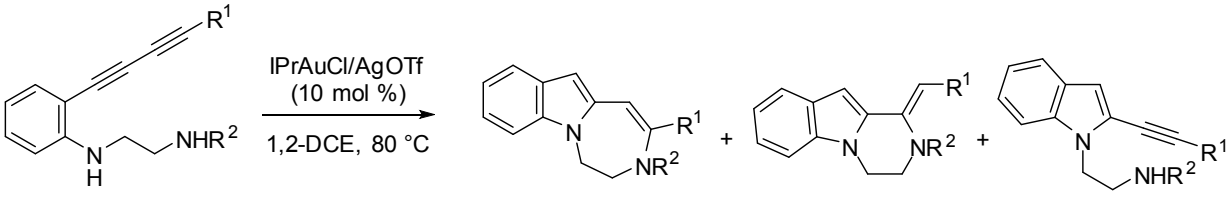
1 **2** **3**

entry	subst.	R^1	R^2	time (h)	yield (%)[b]	ratio (**2**/**3**)[c]
1	**1a**	H	Ph	2	86	88/12
2	**1b**	OCF_3	Ph	2	86	91/9
3	**1c**	CO_2Me	Ph	1.5	88	90/10
4	**1d**	H	4-(MeO)C_6H_4	2	90	94/6
5	**1e**	H	4-(MeO_2C)C_6H_4	1	71–92[d]	56-61/44-39
6	**1f**	H	*n*-Pr	1	78	100/0

[a]Reaction conditions: IPrAuCl/AgOTf (5 mol %) in 1,2-DCE (0.1 M) at 50 °C. [b]Combined isolated yields. [c]Ratios were determined by ^{1}H NMR analysis after purification of the isomeric mixture. [d]Low reproducibility due to the products instability.

Preliminary results of the reaction of diamine derivatives **11** are shown in Table 3. These reactions required an increased loading of the catalyst (10 mol %) and higher temperature (80 °C) because of the low reactivity. The reaction of **11a** bearing a free primary amino group (R^2 = H) was unsuccessful and produced a complex mixture of unidentified products (entry 1). The reaction of the corresponding carbamate derivative **11b** (R^2 = Boc) was slow to give the alkynylindoles **14b** (entry 2). Due to speculation that steric repulsion between R^1 and R^2 groups obstructs progress of the second cyclization, the reaction of the aliphatic diyne derivative **11c** was examined (R^1 = *n*-Pr). This reaction led to the desired fused indole products **12c**/**13c** in 49−73% yields (entry 3). The observed low reproducibility is because of the instability of **12c**/**13c** bearing a sterically congested enamine structure.[12] Thus, the 1,2-diamine derivatives have proven to be less suitable substrates for the present gold-catalyzed cascade cyclization.

Table 3. Reaction of Ethylenediamine-Type Substrates[a]

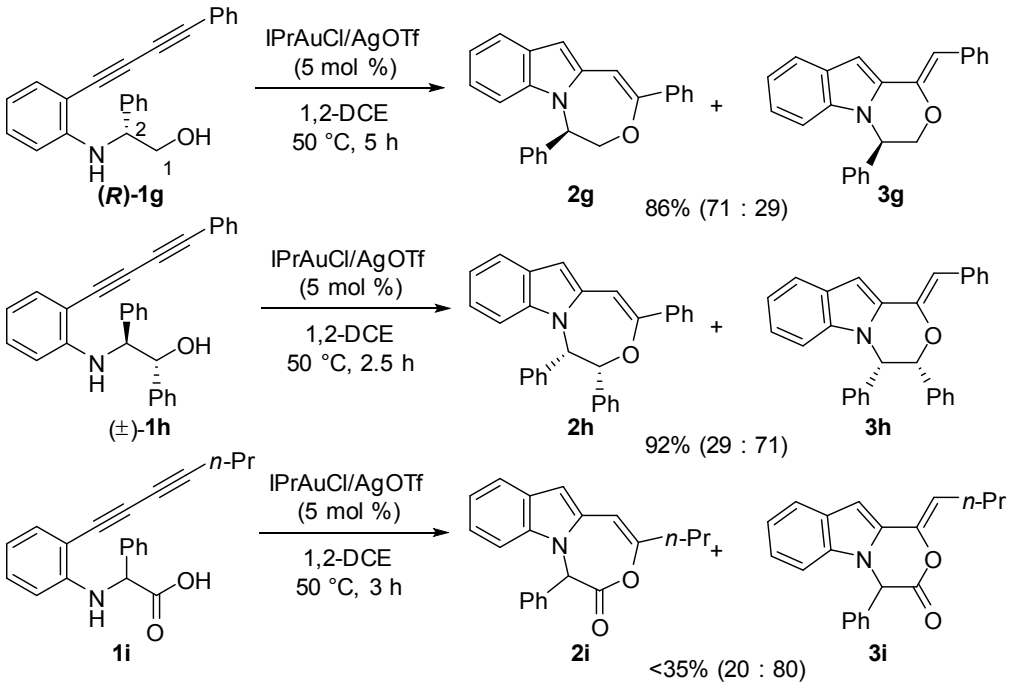


11 **12** **13** **14**

entry	subst.	R^1	R^2	time (h)	% yield[b] (ratio[c])	
					12/**13**	**14**
1	**11a**	Ph	H	24	complex mixture	
2	**11b**	Ph	Boc	24	trace	79
3	**11c**	*n*-Pr	Boc	8	49–73[d] (82-85/18-15)	-

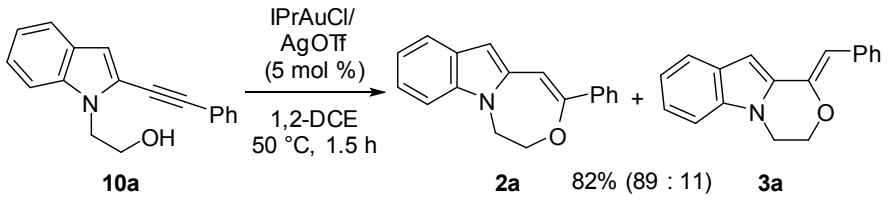
[a]Reaction conditions: IPrAuCl/AgOTf (10 mol %) in 1,2-DCE (0.1 M) at 80 °C. [b]Combined isolated yields. [c]Ratios were determined by ^{1}H NMR analysis. [d]Low reproducibility due to the products instability.

The author investigated the effect of nucleophilic moiety in the regioselectivity in the second cyclization (Scheme 4). The reaction of **1g** bearing a phenyl group at the 2-position gave the desired double cyclization products **2g**/**3g** (86%) with moderate regioselectivity (**2g**/**3g** = 71/29). Use of **1h** bearing vicinal phenyl groups preferentially afforded the 6-*exo*-product (**2h**/**3h** = 29/71) in 92% yield. Similarly, the reaction of **1i** bearing a carboxylic group as the nucleophile preferentially produced the 6-*exo*-*di*g cyclization product **3i** (**2i**/**3i**= 20/80) in low yields (<35%). These results suggested that the regioselectivity of the reaction is dependent on the subtle balance of steric and electronic factors.



Scheme 4. Investigation of the Nucleophilic Moiety.

To obtain some insight of the reaction mechanism and regioselectivity, the author's collaborator investigated the second cyclization of the possible intermediate **10a** (Scheme 5). Also in this case, the seven-membered ring formation predominated to give a mixture of **2a** and **3a** in an 89:11 ratio, essentially the same as the original reaction of diyne **1a** (entry 1, Table 2). The author then undertook a density functional theory (DFT) based exploration of the origin of the regioselectivity (Figure 2). The energy diagram clearly suggests that the kinetically and thermodynamically more favorable pathway is the 7-*endo-dig* cyclization. Both cyclizations from the starting complex **10a**·$AuPMe_3$[13] proceed smoothly, and 7-*endo-dig* cyclization requires a lower activation energy (14.0 kcal/mol) than that of 6-*exo-dig* (17.3 kcal/mol). However, the cyclizations are remarkably both highly endothermic processes and retro-cyclizations should occur very smoothly. Thus, an equilibration between **INT-1** and **INT-2** via **10a**·$AuPMe_3$ should exist and the seven-membered ring formation proceeds preferentially through **INT-2**, which is more stable than **INT-1** by 1.7 kcal/mol.



Scheme 5. Reaction of the Possible Intermediate **10a**

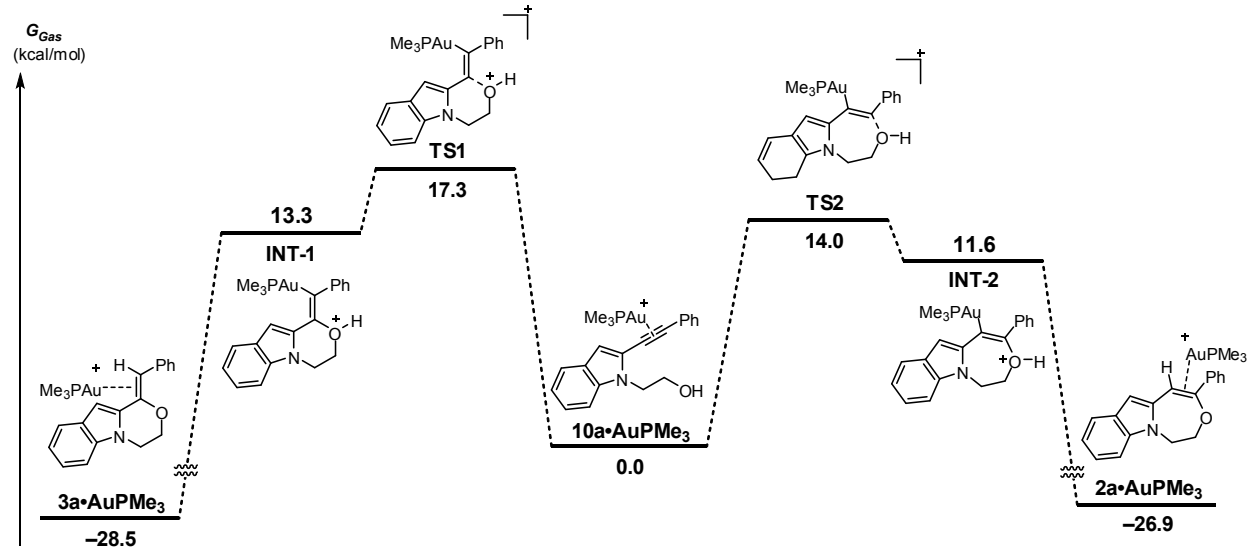
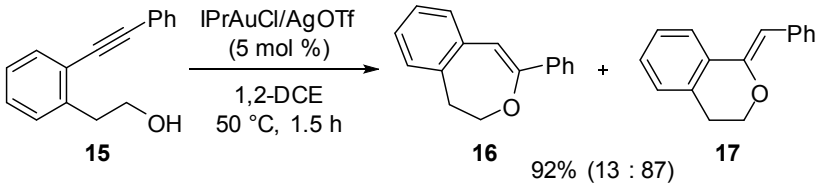


Figure 2. DFT calculations on cyclization of **10a** [M06-2X/6-31G(d,p)&SDD(Au)].

The author assumed that the thermodynamic preference for **INT-2** may result from ring strain of the six-membered ring in **INT-1** fused with the indole ring. To evaluate this possibility, the author investigated the reaction of alkynylbenzene derivative **15** (Scheme 6, a benzene congener of the alkynylindole intermediate **10a**). In this case, the ring strain for the 6-*exo* cyclization would be considerably less compared with that from **10a**. As expected, the 6-*exo-dig* cyclization product **17** was preferentially produced (**16**/**17** = 13/87) from **15**, which partially supports the assumption.

However, in order to completely understand regioselectivity of this reaction, it is necessary to take the protodeauration step into account.



15 **16** **17**

92% (13 : 87)

Scheme 6. Reaction of the Benzene Congener **15**

In summary, a novel gold-catalyzed cascade cyclization of conjugated diynes was developed. This reaction provides direct access to oxepino[1,7-*a*]indole derivatives with good functional group tolerance. The observed 7-*endo*-selectivity was well rationalized by DFT calculations: the second ring formation proceeds through a more stable intermediate.

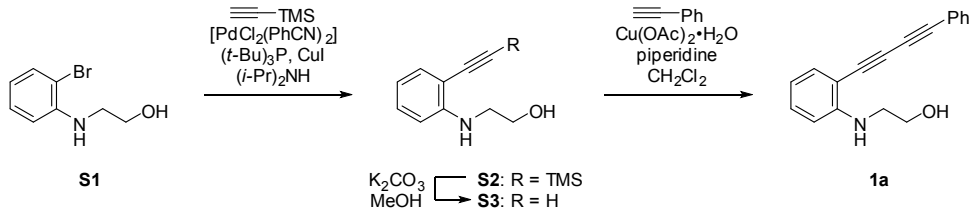
Experimental Section

General Methods. For open column chromatography, silica gel (Wakogel C-200E: Wako Pure Chemical Industries, Ltd) or NH_2 silica gel (Chromatorex NH-DM1020: Fuji Silysia Chemical Ltd.) was employed. Thin layer chromatography was performed on Merck TLC silica gel 60 F_{254} or Wako 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). ^{1}H NMR spectra were recorded using a JEOL ECA-500 spectrometer, and chemical shifts are reported in δ (ppm) relative to TMS as internal standard. ^{13}C NMR spectra were recorded using a JEOL ECA-500 spectrometer and 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). Exact mass (HRMS) spectra were recorded on a JMS-HX/HX 110A mass spectrometer. Infrared (IR) spectra were obtained on a JASCO FT/IR-4100 FT-IR spectrometer with JASCO ATR PRO410-S.

The known compounds **S1**,[14] **S8**,[15] **S12**,[16] **S15**,[17] **S19**,[18] **S26**,[3] **8**,[19] **15**[20] were prepared according to the literature. The ^{1}H NMR data of **7**[21] and **9**[22] corresponded to those reported in literature.

1. Preparation of Starting Materials

1-1. Synthesis of Amino Alcohol-Type Conjugated Diynes (1a-h)



2-({2-[(Trimethylsilyl)ethynyl]phenyl}amino)ethan-1-ol (S2)

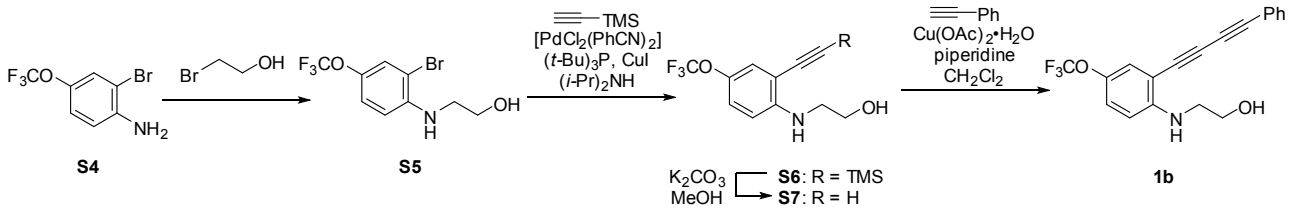
The coupling of **S1** and trimethylsilylacetylene was carried out according to the reported method as follows:[23] to a stirred suspension of **S1** (1.10 g, 5.08 mmol), $PdCl_2(PhCN)_2$ (58.4 mg, 0.15 mmol) and CuI (19.3 mg, 0.10 mmol) in dry 1,4-dioxane (5 mL) under argon were added diisopropylamine (2.1 mL, 15.2 mmol), trimethylsilylacetylene (0.8 mL, 5.59 mmol) and tri(*tert*-butyl)phosphine (72 μL, 0.30 mmol). After stirring at room temperature 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/EtOAc = 5/1) to afford **S2** (1.15 g, 97%) as amber oil: IR (neat): 2947 (OH), 2251 (C≡C), 1323 (NH); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.27 (s, 9H), 1.70 (br s, 1H), 3.37-3.38 (m, 2H), 3.85-3.86 (m, 2H), 4.93 (br s, 1H), 6.61-6.64 (m, 2H), 7.17-7.20 (m, 1H), 7.30 (dd, *J* = 8.0, 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 0.0 (3C), 45.5, 61.2, 100.4, 101.7, 107.8, 109.6, 116.5, 130.0, 132.2, 149.1; HRMS (FAB) calcd for $C_{13}H_{20}NOSi$ (MH^+) 234.1309, found 234.1301.

2-[(2-Ethynylphenyl)amino]ethan-1-ol (S3)

The desilylation of **S2** was carried out according to the reported method as follows:[24] K_2CO_3 (1.54 g, 11.2 mmol) was added to the solution of **S2** (869 mg, 3.72 mmol) in MeOH (37 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 = 3/1) to afford **S3** (540 mg, 90%) as dark amber oil: IR (neat): 2935 (OH), 2251 (C≡C), 1322 (NH); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.70-1.71 (br m, 1H), 3.37-3.41 (m, 3H), 3.85-3.86 (m, 2H), 4.91 (br s, 1H), 6.63-6.66 (m, 2H), 7.20-7.24 (m, 1H), 7.34 (dd, *J* = 8.0, 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 45.6, 61.3, 80.6, 83.0, 106.8, 109.8, 116.7, 130.4, 132.8, 149.4; HRMS (FAB) calcd for $C_{10}H_{12}NO$ (MH^+) 162.0913, found 162.0914.

2-{[2-(Phenylbuta-1,3-diyn-1-yl)phenyl]amino}ethan-1-ol (1a)

The coupling of **S3** and ethynylbenzene was carried out according to the reported method as follows:[25] a mixture of **S3** (319 mg, 1.98 mmol), ethynylbenzene (1.1 mL, 9.89 mmol), $Cu(OAc)_2 \cdot H_2O$ (39.5 mg, 0.20 mmol) and piperidine (0.6 mL, 5.93 mmol) in CH_2Cl_2 (10 mL) was stirred in open atmospheric air at room temperature for 12 h. The reaction mixture was concentrated in *vacuo* and the residue was chromatographed on silica gel (hexane/EtOAc = 5/1) to afford **1a** (327 mg, 63%) as pale brown powder: mp 94–95 °C; IR (neat): 2939 (OH), 2251, 2209 (C≡C), 1321 (NH); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.72 (br s, 1H), 3.41-3.42 (m, 2H), 3.87-3.88 (m, 2H), 4.94 (br s, 1H), 6.64-6.66 (m, 2H), 7.21-7.25 (m, 1H), 7.32-7.39 (m, 4H), 7.52-7.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 45.6, 61.2, 73.9, 78.6, 79.6, 83.0, 106.3, 109.9, 116.9, 121.9, 128.5 (2C), 129.2, 130.9, 132.4 (2C), 133.5, 150.4. *Anal*. calcd for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36. Found: C, 82.51; H, 5.75; N, 5.33.



2-{[2-Bromo-4-(trifluoromethoxy)phenyl]amino}ethan-1-ol (S5)

2-Bromo-4-(trifluoromethoxy)aniline (**S4**) was purchased from commercial vendors. The reaction of **S4** and 2-bromoethanol was carried out according to the reported method as follows:[26] a mixture of **S4** (0.3 mL, 2.1 mmol) and 2-bromoethanol (0.1 mL, 1.40 mmol) was stirred under argon at 90 °C for 4 h. The reaction mixture was diluted with EtOAc, washed with 2N NaOH aq and brine, dried over Na_2SO_4, and concentrated in *vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc = 3/1) to afford **S5** (228 mg, 54%) as reddish yellow oil: IR (neat): 2945 (OH), 1218 (CF_3); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.76 (br s, 1H), 3.346-3.352 (br m, 2H), 3.88-3.89 (m, 2H), 4.65 (br s, 1H), 6.63 (d, *J* = 9.2 Hz, 1H), 7.07-7.09 (m, 1H), 7.35 (d, *J* = 2.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 46.0, 60.9, 109.1, 110.9, 120.6 (q, *J* = 256.7 Hz), 121.7, 125.9, 139.7 (q, *J* = 2.4 Hz), 144.0; HRMS (FAB) calcd for C_9H_9NOBr (M^+) 298.9769, found 298.9777.

2-({4-(Trifluoromethoxy)-2-[(trimethylsilyl)ethynyl]phenyl}amino)ethan-1-ol (S6)

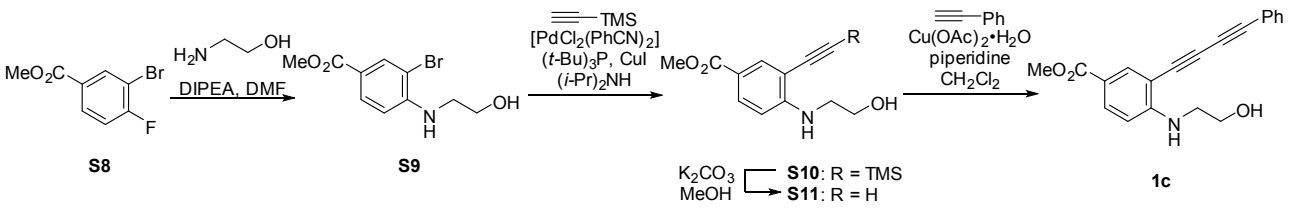
According to the procedure described for the preparation of **S2**, **S5** (2.50 g, 8.33 mmol) was converted to **S6** (2.13 g, 81%) by the reaction with diisopropylamine (5.9 mL, 41.6 mmol) and trimethylsilylacetylene (1.3 mL, 9.16 mmol) in the presence of $PdCl_2(PhCN)_2$ (192 mg, 0.50 mmol), CuI (95.2 mg, 0.50 mmol) and tri(*tert*-butyl)phosphine (0.23 mL, 1.00 mmol) in dry 1,4-dioxane (17 mL) under argon at 50 °C for 3.5 h. Column chromatography: silica gel (hexane/EtOAc = 3/1): amber oil; IR (neat): 2961 (OH), 2145 (C≡C), 1249 (CF_3); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.27 (s, 9H), 1.71 (br s, 1H), 3.35-3.36 (m, 2H), 3.86-3.37 (m, 2H), 5.00 (br s, 1H), 6.56 (d, *J* = 8.6 Hz, 1H), 7.04-7.06 (m, 1H), 7.18 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 0.0 (3C), 45.7, 61.2, 100.3, 101.9, 108.4, 110.1, 120.7 (q, *J* = 255.9 Hz), 123.7, 125.1, 139.3, 148.1; HRMS (FAB) calcd for $C_{14}H_{19}F_3NO_2Si$ (MH^+) 318.1132, found 318.1140.

2-{[2-Ethynyl-4-(trifluoromethoxy)phenyl]amino}ethan-1-ol (S7)

According to the procedure described for the preparation of **S3**, **S6** (213 mg, 0.67 mmol) was converted into **S7** (121 mg, 74%). Column chromatography: silica gel (hexane/EtOAc = 3/1): amber oil; IR (neat): 3301 (C≡CH), 2943 (OH), 2252 (C≡C), 1254 (CF_3); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.95 (br s, 1H), 3.34-3.35 (m, 2H), 3.45 (s, 1H), 3.83-3.85 (m, 2H), 4.96 (br s, 1H), 6.58 (d, *J* = 9.2 Hz, 1H), 7.07-7.08 (m, 1H), 7.21 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 45.7, 61.0, 79.2, 84.0, 107.1, 110.1, 120.6 (q, *J* = 255.9 Hz), 123.8. 125.6, 139.2 (q, *J* = 2.4 Hz), 148.1; HRMS (FAB) calcd for $C_{11}H_{11}F_3NO_2$ (MH^+) 246.0736, found 246.0739.

2-{[2-(Phenylbuta-1,3-diyn-1-yl)-4-(trifluoromethoxy)phenyl]amino}ethan-1-ol (1b)

According to the procedure described for the preparation of **1a**, **S7** (221 mg, 0.90 mmol) was converted into **1b** (185 mg, 60%). Column chromatography: silica gel (hexane/EtOAc = 3/1): light yellow powder; mp 85 °C; IR (neat): 2917 (OH), 2337, 2141 (C≡C), 1254 (CF_3); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.75 (t, *J* = 5.4 Hz, 1H), 3.39-3.40 (m, 2H), 3.87-3.88 (m, 2H), 4.99 (t, *J* = 5.4 Hz, 1H), 6.60 (d, *J* = 9.2 Hz, 1H), 7.07-7.09 (m, 1H), 7.23 (d, *J* = 2.3 Hz, 1H), 7.33-7.40 (m, 3H), 7.53-7.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 45.7, 61.1, 73.5, 76.9, 80.5, 83.6, 106.8, 110.3, 121.5, 121.6 (q, *J* = 255.9 Hz), 124.4, 126.1, 128.5 (2C), 129.4, 132.5 (2C), 139.3, 149.2. *Anal*. calcd for $C_{19}H_{14}F_3NO_2$: C, 66.09; H, 4.09; N, 4.06. Found: C, 65.81; H, 3.88; N, 3.97.



Methyl 3-Bromo-4-[(2-hydroxyethyl)amino]benzoate (S9)

The reaction of **S8** and 2-aminoethan-1-ol was carried out according to the reported method as follows:[27] to a stirred suspension of **S8** (2.34 g, 10.1 mmol) and DIPEA (2.1 mL, 12.1 mmol) in dry DMF (12.6 mL) under

argon was slowly added diisopropylamine (5.9 mL, 41.6 mmol) at the temperature below 20 °C. The reaction mixture was stirred at 1 h at room temperature and additional 50 h at 60 °C. The reaction mixture was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, and concentrated in *vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc = 3/1) to afford **S9** (1.15 g, 42%) as colorless powder: mp 93 °C; IR (neat): 2944 (OH), 1698 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.72 (t, *J* = 5.4 Hz, 1H), 3.42-3.43 (m, 2H), 3.86 (s, 3H), 3.90-3.91 (m, 2H), 5.12 (br s, 1H), 6.63 (d, *J* = 8.5 Hz, 1H), 7.85-7.87 (m, 1H), 8.13 (d, *J* = 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 45.4, 51.8, 60.9, 108.9, 109.8, 119.4, 130.6, 134.2, 148.4, 166.2. *Anal*. calcd for $C_{10}H_{12}BrNO_3$: C, 43.82; H, 4.41; N, 5.11. Found: C, 43.69; H, 4.46; N, 5.11.

Methyl 4-[(2-Hydroxyethyl)amino]-3-[(trimethylsilyl)ethynyl]benzoate (S10)

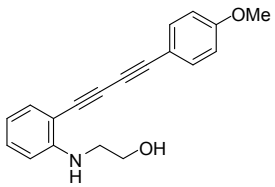
According to the procedure described for the preparation of **S2**, **S9** (959 mg, 3.50 mmol) was converted to **S10** (1.12 g, quant.). Column chromatography: silica gel (hexane/EtOAc = 3/1): amber oil; IR (neat): 2954 (OH), 2251 (C≡C), 1697 (C=O), 1292 (NH); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.27 (s, 9H), 2.20 (br s, 1H), 3.40-3.41 (m, 2H), 3.84 (s, 3H), 3.87-3.88 (m, 2H), 5.45-5.56 (br m, 1H), 6.56 (d, *J* = 8.6 Hz, 1H), 7.83-7.86 (m, 1H), 7.99 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 0.0 (3C), 45.0, 51.7, 60.9, 100.6, 101.2, 107.2, 108.5, 117.6, 132.0, 134.3, 152.3, 166.8; HRMS (FAB) calcd for $C_{15}H_{22}NO_3Si$ (MH^+) 292.1363, found 292.1366.

Methyl 3-Ethynyl-4-[(2-hydroxyethyl)amino)benzoate (S11)

According to the procedure described for the preparation of **S3**, **S10** (553 mg, 1.90 mmol) was converted into **S11** (309 mg, 66%). Column chromatography: silica gel (hexane/EtOAc = 3/1): colorless crystals; mp 67 °C; IR (neat): 3209 (C≡CH), 2927 (OH), 2323 (C≡C), 1672 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.98 (br s, 1H), 3.42-3.43 (m, 3H), 3.85 (s, 3H), 3.87-3.88 (m, 2H), 5.41 (br s, 1H), 6.60 (d, *J* = 8.6 Hz, 1H), 7.87 (dd, *J* = 8.6, 2.3 Hz, 1H), 8.02 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 45.1, 51.7, 60.9, 79.5, 83.5, 106.0, 108.6, 117.8, 132.3, 134.8, 152.4, 166.6; HRMS (FAB) calcd for $C_{12}H_{14}NO_3$ (MH^+) 220.0968, found 220.0963.

Methyl 4-[(2-Hydroxyethyl)amino]-3-(phenylbuta-1,3-diyn-1-yl)benzoate (1c)

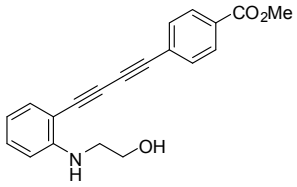
According to the procedure described for the preparation of **1a**, **S11** (527 mg, 2.40 mmol) was converted into **1c** (185 mg, 47%). Column chromatography: silica gel (hexane/EtOAc = 3/2). The product was recrystallized from $CHCl_3$–hexane: colorless crystals; mp 114 °C; IR (neat): 2947 (OH), 2210, 2142 (C≡C), 1684 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.82 (t, *J* = 5.2 Hz, 1H), 3.46-3.47 (m, 2H), 3.86 (s, 3H), 3.89-3.90 (m, 2H), 5.40-5.41 (br m, 1H), 6.62 (d, *J* = 9.2 Hz, 1H), 7.35-7.38 (m, 3H), 7.53-7.54 (m, 2H), 7.87-7.89 (m, 1H), 8.06 (d, *J* = 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 45.2, 51.8, 61.0, 73.6, 77.2, 79.9, 83.2, 105.7, 108.8, 118.2, 121.6, 128.5 (2C), 129.3, 132.4 (2C), 132.6, 135.6, 153.2, 166.4. *Anal*. calcd for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 75.08; H, 5.16; N, 4.25.



1d

2-({2-[(4-Methoxyphenyl)buta-1,3-diyn-1-yl]phenyl}amino)ethan-1-ol (1d)

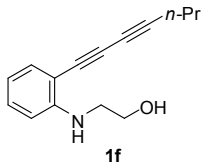
According to the procedure described for the preparation of **1a**, **S3** (342 mg, 1.95 mmol) was converted into **1d** (119 mg, 42%). Column chromatography: silica gel (hexane/$CHCl_3$ = 1/3). The product was recrystallized from $CHCl_3$–hexane: colorless powder; mp 90 °C; IR (neat): 2937 (OH), 2205, 2130 (C≡C), 1320 (NH), 1248 (OCH_3); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.71-1.72 (m, 1H), 3.41-3.42 (m, 2H), 3.83 (s, 3H), 3.86-3.87 (m, 2H), 4.93 (br s, 1H), 6.64-6.65 (m, 2H), 6.86-6.87 (m, 2H), 7.22 (t, *J* = 7.7 Hz, 1H), 7.35-7.37 (m, 1H), 7.47-7.48 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 45.6, 55.3, 61.2, 72.7, 77.9, 79.9, 83.2, 106.6, 109.9, 113.8, 114.2 (2C), 116.9, 130.7, 133.4, 134.0 (2C), 150.3, 160.4. *Anal*. calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.41; H, 5.73; N, 4.85.



1e

Methyl 4-({2-[(2-Hydroxyethyl)amino]phenyl}buta-1,3-diyn-1-yl)benzoate (1e)

According to the procedure described for the preparation of **1a**, **S3** (170 mg, 0.97 mmol) was converted into **1e** (164 mg, 53%). Column chromatography: NH_2 silica gel (hexane/$CHCl_3$ = 1/3). The product was recrystallized from $CHCl_3$–hexane: light yellow powder; mp 109 °C; IR (neat): 2951 (OH), 2206, 2142 (C≡C), 1704 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.75 (br s, 1H), 3.41-3.42 (m, 2H), 3.87-3.88 (m, 2H), 3.93 (s, 3H), 4.94 (br s, 1H), 6.64-6.67 (m, 2H), 7.22-7.24 (m, 1H), 7.36-7.38 (m, 1H), 7.57-7.58 (m, 2H), 8.00-8.11 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 45.6, 52.3, 61.2, 76.8, 79.3, 80.2, 82.0, 105.9, 110.0, 116.9, 126.6, 129.6 (2C), 130.2, 131.2, 132.2 (2C), 133.6, 150.5, 166.3. *Anal*. calcd for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 75.14; H, 5.22; N, 4.36.

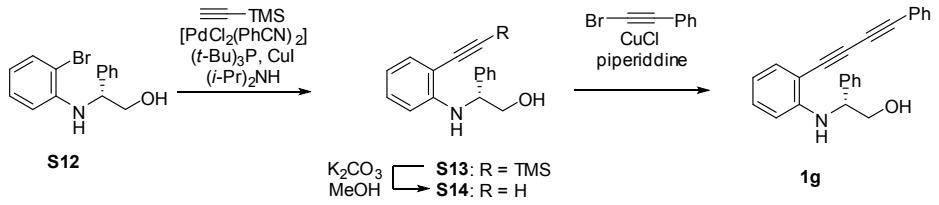


1f

2-{[2-(Hepta-1,3-diyn-1-yl)phenyl]amino}ethan-1-ol (1f)

According to the procedure described for the preparation of **1a**, **S3** (273 mg, 1.56 mmol) was converted into **1f** (70.6 mg, 20%). Column chromatography: silica gel (hexane/EtOAc = 3/1): dark amber oil; IR (neat): 2963 (OH), 2233, 2142 (C≡C), 1321 (NH); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.03 (t, *J* = 7.4 Hz, 3H), 1.60-1.63 (m, 2H), 1.69 (br s, 1H), 2.36 (t, *J* = 7.2 Hz, 2H), 3.39-3.40 (m, 2H), 3.84-3.85 (m, 2H), 4.87 (br s, 1H), 6.61-6.63 (m, 2H), 7.17-7.21 (m, 1H), 7.32-7.33 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.5, 21.6, 21.7, 45.6, 61.1,

65.1, 71.6, 80.0, 86.0, 106.6, 109.8, 116.7, 130.4, 133.4, 150.3; HRMS (FAB) calcd for $C_{15}H_{18}NO$ (MH^+) 228.1383, found 228.1383.



(*R*)-2-Phenyl-2-({2-[(trimethylsilyl)ethynyl]phenyl}amino)ethan-1-ol (S13)

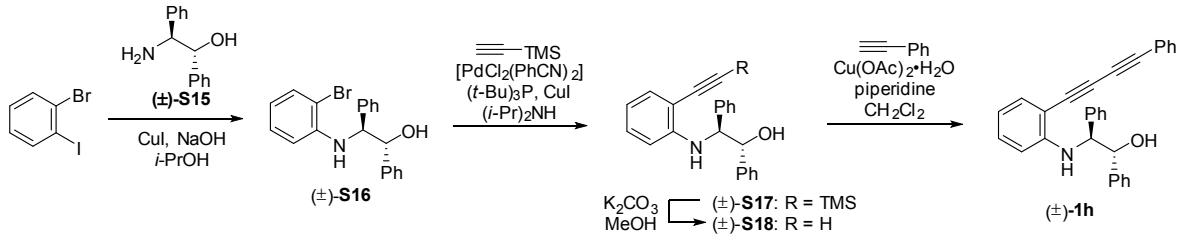
According to the procedure described for the preparation of **S2**, **S12** (1.42 g, 4.86 mmol) was converted to **S13** (976 mg, 65%). Column chromatography: silica gel (hexane/EtOAc = 5/1): amber oil; IR (neat): 3393 (OH), 2143 (C≡C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.30 (s, 9H), 1.69 (br s, 1H), 3.80-3.83 (m, 1H), 3.96-4.00 (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 (S14)

According to the procedure described for the preparation of **S3**, **S13** (804 mg, 2.63 mmol) was converted into **S14** (442 mg, 72%). Column chromatography: silica gel (hexane/EtOAc = 5/1): pale amber powder; mp 79 °C; IR (neat): 3401 (OH), 3253 (C≡CH); ^{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 (1g)

According to the procedure described for the preparation of **1a**, **S14** (432 mg, 1.82 mmol) was converted into **1g** (349 mg, 57%). Column chromatography: silica gel (hexane/EtOAc = 5/1): amber oil; 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.



***erythro*-2-[(2-Bromophenyl)amino]-1,2-diphenylethan-1-ol (S16)**

The reaction of 2-bromoiodobenzene and **S15** was carried out according to the reported method as follows:[16] a mixture of 2-bromoiodobenzene (0.9 mL, 7.01 mmol), **S15** (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 **S16** (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, 118.1, 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.

***erythro* -1,2-Diphenyl-2-({2-[(trimethylsilyl)ethynyl]phenyl}amino)ethan-1-ol (S17)**

According to the procedure described for the preparation of **S2**, **S16** (2.95 g, 8.01 mmol) was converted to **S17** (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 (t, J = 8.0 Hz, 1H), 7.09-7.11 (m, 4H), 7.22-7.27 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 0.0 (3C), 63.2, 76.9, 100.2, 101.7, 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 $C_{25}H_{27}NOSi$ (MH^+) 386.1935, found 359.1927.

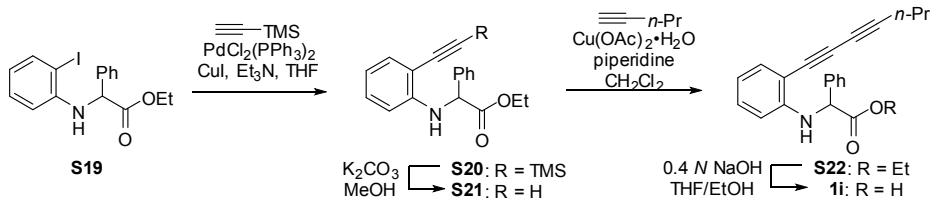
***erythro* -2-[(2-Ethynylphenyl)amino]-1,2-diphenylethan-1-ol (S18)**

According to the procedure described for the preparation of **S3**, **S17** (1.44 g, 3.74 mmol) was converted into **S18** (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), 6.31 (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, 8H); ^{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 $C_{22}H_{19}NO$ (MH^+) 314.1539, found 314.1535.

***erythro* -1,2-Diphenyl-2-{[2-(phenylbuta-1,3-diyn-1-yl)phenyl]amino}ethan-1-ol (1h)**

According to the procedure described for the preparation of **1a**, **S18** (430 mg, 1.37 mmol) was converted into **1h** (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, 2141 (C≡C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 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), 7.15-7.17 (br m, 4H), 7.26-7.30 (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, 106.2, 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.

1-3. Synthesis of Carboxylic Acid-Type Conjugated Diyne (1i)



Ethyl 2-Phenyl-2-({2-[(trimethylsilyl)ethynyl]phenyl}amino)acetate (S20)

To a stirred suspension of **S19** (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 **S20** (2.10 mg, 88%) as amber oil: IR (neat): 2145 (C≡C), 1736 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.81 (s, 3H), 3.93 (s, 3H), 6.79 (dd, *J* = 9.2, 2.9 Hz, 1H), 7.09 (d, *J* = 2.9 Hz, 1H), 7.49 (d, *J* = 9.2 Hz, 1H), 7.63-7.65 (m, 2H), 8.03-8.04 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.3, 55.6, 90.9, 92.7, 116.5, 117.0, 117.9, 125.4, 127.5, 129.6 (2C), 129.9, 131.6 (2C), 133.2, 158.5, 166.5. *Anal*. calcd for $C_{17}H_{13}BrO_3$: C, 59.16; H, 3.68. Found: C, 59.16; H, 3.80.

Ethyl 2-[(2-Ethynylphenyl)amino]-2-phenylacetate (S21)

According to the procedure described for the preparation of **S3**, **S20** (5.27 g, 15.0 mmol) was converted into **S21** (2.99 mg, 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), 1723 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.22 (t, *J* = 7.2 Hz, 3H), 3.51 (s, 1H), 4.12-4.27 (m, 2H), 5.11 (d, *J* = 5.7 Hz, 1H), 6.04 (d, *J* = 5.2 Hz, 1H), 6.30 (d, *J* = 8.6 Hz, 1H), 6.61 (td, *J* = 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, 60.4, 61.9, 80.3, 83.2, 107.1, 110.5, 117.0, 127.1 (2C), 128.3, 128.8 (2C), 130.2, 132.6, 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.

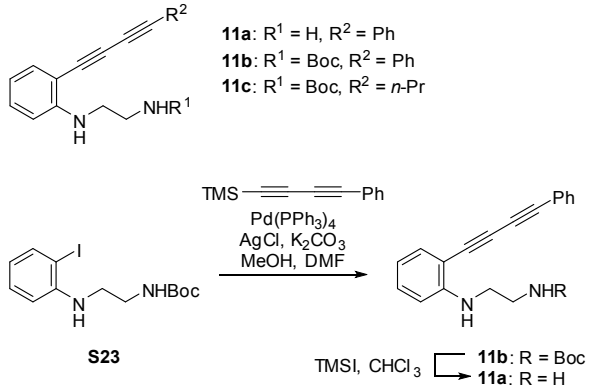
Ethyl 2-{[2-(Hepta-1,3-diyn-1-yl)phenyl]amino}-2-phenylacetate (S22)

According to the procedure described for the preparation of **1a**, **S21** (836 mg, 3.0 mmol) was converted into **S22** (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 (td, *J* = 14.6, 7.3 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, 1480.1, 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 (1i)

To a stirred suspension of **S22** (86.9 mg, 0.25 mmol) in EtOH (5 mL) was added THF until **S22** dissolved, 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 **1i** (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 (td, *J* = 14.5, 7.3 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, 128.8, 129.1, 130.3, 133.4, 136.4, 147.8, 175.8; HRMS (FAB) calcd for $C_{21}H_{20}NO_2$ (MH^+) 318.1489, found 318.148.

1-4. Synthesis of Diamine-Type Conjugated Diynes (11a–c)



***tert*-Butyl {2-[(2-Iodophenyl)amino]ethyl}carbamate (S23)**

Prepared according to the reported method as follows:[28] *tert*-butyl allylcarbamate[29] (2.95 g, 18.8 mmol) was dissolved in dry MeOH (69 mL) and the solution was cooled to –78 °C. Ozone was bubbled through the solution until it became blue. After the excess of ozone was bubbled out with oxygen, dimethyl sulfide (2.1 mL, 28.2 mmol) was added and the solution was kept at –78 °C for 5 h, and then slowly warmed to room temperature. After 1 h at room temperature, the solvent was evaporated. The residue was dissolved in $CHCl_3$,

washed with 2% HCl and aqueous saturated $NaHCO_3$, and dried with $MgSO_4$. After concentration in *vacuo*, *tert*-butyl (2-oxoethyl)carbamate was obtained as a colorless oil. This material was used for the next reaction without further purification.

According to the reported method as follows:[30] acetic acid (1.1 mL, 18.8 mmol) was added to a stirred suspension of *tert*-butyl (2-oxoethyl)carbamate, 2-iodoaniline (3.29 g, 15.0 mmol) and 3Å molecular sieve (1.50 g) in dry MeOH (30 mL) under argon. After stirring at room temperature for 20 min, $NaCNBH_3$ (1.18 g, 18.8 mmol) was added to the reaction mixture and stirred for further 3 h. The reaction mixture was diluted with EtOAc, washed with 1*N* HCl, aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in *vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc =10/1) to afford **S23** (2.23 g, 41%) as colorless needless: mp 70 °C; IR (neat): 1678 (C=O), 1297 (NH); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.46 (s, 9H), 3.29-3.30 (m, 2H), 3.40-3.41 (m, 2H), 4.42 (br s, 1H), 4.82 (br s, 1H), 6.44-6.45 (m, 1H), 6.58 (d, J = 8.6 Hz, 1H), 7.18-7.21 (m, 1H), 7.65 (dd, J = 8.0, 1.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.4 (3C), 39.7, 44.4, 79.6, 85.4, 110.5, 118.8, 129.4, 139.1, 147.1, 156.2. *Anal*. calcd for $C_{13}H_{19}IN_2O_2$: C, 43.11; H, 5.29; N, 7.44. Found: C, 42.99; H, 5.31; N, 7.57.

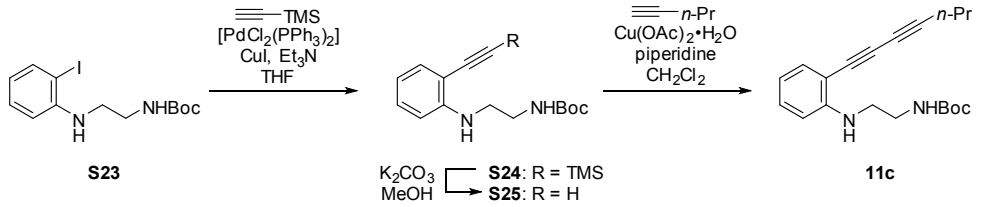
tert-Butyl (2-{[2-(Phenylbuta-1,3-diyn-1-yl)phenyl]amino}ethyl)carbamate (11b)

Prepared according to the reported method as follows:[31] a mixture of **S23** (1.09 g, 3.00 mmol), $Pd(PPh_3)_4$ (173 mg, 0.15 mmol), AgCl (86.0 mg, 0.60 mmol) and K_2CO_3 (3.32 g, 24.0 mmol) in dry DMF (7.5 mL) at room temperature under argon was stirred for 5 min, then dry MeOH (0.3 mL, 24.0 mmol) was added. Then a solution of trimethyl(phenylbuta-1,3-diyn-1-yl)silane[32] (898 mg, 4.53 mmol) in dry DMF (7.5 mL) was added to the mixture. The reaction mixture was warmed to 40 °C and stirred at the same temperature for 12 h, then quenched with aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with 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 **11b** (1.05 g, 61%) as ocher powder: mp 81–83 °C; IR (neat): 2249, 2142 (C≡C), 1699 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.46 (s, 9H), 3.35-3.40 (m, 4H), 4.82 (br s, 1H), 5.00 (br s, 1H), 6.62-6.63 (m, 2H), 7.20-7.24 (m, 1H), 7.32-7.39 (m, 4H), 7.52-7.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.4 (3C), 39.9, 43.8, 74.1, 78.6, 79.57, 79.62, 82.9, 105.9, 109.5, 116.6, 121.9, 128.4 (2C), 129.1, 130.9, 132.3 (2C), 133.4, 150.3, 156.3; HRMS (FAB) calcd for $C_{23}H_{24}N_2O_2$ (M^+) 360.1838, found 360.1838.

_N_^{1}-[2-(Phenylbuta-1,3-diyn-1-yl)phenyl]ethane-1,2-diamine (11a)

Prepared according to the reported method as follows:[33] iodotrimethylsilane (0.1 mL, 0.75 mmol) was added to the solution of **11b** (180 mg, 0.50 mmol) in dry $CHCl_3$ (5.0 mL) under argon. After stirring at room temperature for 30 min, the reaction mixture was quenched with MeOH (0.1 mL, 3.00 mmol) and triethylamine (0.1 mL, 1.00 mmol) and was stirred for 5 min. The reaction mixture was concentrated in *vacuo* and the residue was chromatographed on NH_2 silica gel (hexane/$CHCl_3$ = 3/2) to afford **11a** (131 mg, quant) as brown oil: IR (neat): 2207, 2139 (C≡C), 1318 (NH); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.38 (br s, 2H), 2.98-2.99 (m, 2H), 3.29-3.30 (m, 2H), 4.96 (br s, 1H), 6.62 (t, J = 7.4 Hz, 2H), 7.22 (t, J = 7.7 Hz, 1H), 7.34-7.37 (m, 4H), 7.53 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 41.1, 46.3, 74.0, 78.8, 79.5, 82.9, 105.9,

109.8, 116.5, 121.9, 128.4 (2C), 129.1, 130.9, 132.4 (2C), 133.4, 150.6; HRMS (FAB) calcd for $C_{18}H_{17}N_2$ (MH^+) 261.1386, found 261.1387.



***tert*-Butyl [2-({2-[(Trimethylsilyl)ethynyl]phenyl}amino)ethyl]carbamate (S24)**

The coupling of **S23** and trimethylsilylacetylene was carried out according to the reported method as follows:[24] to a stirred suspension of **S23** (1.45 g, 4.00 mmol), $PdCl_2(PPh_3)_2$ (70.2 mg, 0.10 mmol) and CuI (19.0 mg, 0.10 mmol) in dry THF (8 mL) under argon were added triethylamine (2.5 mL, 20.0 mmol) and trimethylsilylacetylene (0.6 mL, 4.40 mmol). After stirring at room temperature for 1.5 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 = 10/1) to afford **S24** (1.28 g, 96%) as amber oil: IR (neat): 2144 (C≡C), 1699 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.27 (s, 9H), 1.45 (s, 9H), 3.34-3.35 (br m, 4H), 4.77 (br s, 2H), 6.60-6.62 (m, 2H), 7.16-7.19 (m, 1H), 7.29 (dd, *J* = 8.0, 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 0.0 (3C), 28.2 (3C), 39.9, 43.1, 79.3, 100.2, 101.7, 107.5, 109.3, 116.3, 130.0, 132.2, 148.8, 155.9; HRMS (FAB) calcd for $C_{18}H_{29}N_2O_2Si$ (MH^+) 333.1993, found 333.1989.

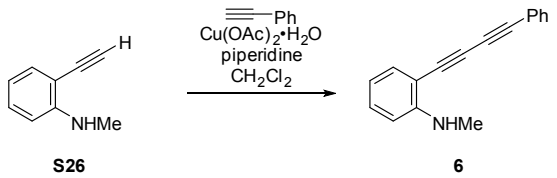
***tert*-Butyl {2-[(2-Ethynylphenyl)amino]ethyl}carbamate (S25)**

According to the procedure described for the preparation of **S3**, **S24** (1.35 mg, 4.06 mmol) was converted into **S25** (672 mg, 64%). Column chromatography: silica gel (hexane/EtOAc = 5/1); light brown crystals; mp 60 °C; IR (neat): 2096 (C≡C), 1691 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.45 (s, 9H), 3.32-3.33 (m, 2H), 3.39-3.41 (m, 3H), 4.78 (br s, 1H), 4.87 (br s, 1H), 6.62-6.64 (m, 2H), 7.19-7.23 (m, 1H), 7.33 (dd, *J* = 7.4, 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.4 (3C), 39.9, 43.7, 79.5, 80.6, 83.0, 106.4, 109.4, 116.4, 130.4, 132.7, 149.3, 156.2. *Anal*. calcd for $C_{15}H_{20}IN_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 68.93; H, 7.79; N, 10.57.

***tert*-Butyl (2-{[2-(Hepta-1,3-diyn-1-yl)phenyl]amino}ethyl)carbamate (11c)**

According to the procedure described for the preparation of **1a**, **S25** (398 mg, 1.53 mmol) was converted into **11c** (133 mg, 27%). Column chromatography: silica gel (hexane/EtOAc = 10/1); light yellow crystals; mp 86 °C; IR (neat): 2318, 2138 (C≡C), 1666 (C=O), 1365 (NH); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.03 (t, *J* = 7.4 Hz, 3H), 1.46 (s, 9H), 1.59-1.65 (m, 2H), 2.36 (t, *J* = 6.9 Hz, 2H), 3.31-3.37 (m, 4H), 4.79 (br s, 1H), 4.88 (br s, 1H), 6.59-6.61 (m, 2H), 7.17-7.20 (m, 1H), 7.30-7.32 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.6, 21.6, 21.8, 28.4 (3C), 40.0, 43.7, 65.2, 71.6, 79.6, 80.1, 85.9, 106.4, 109.4, 116.6, 130.5, 133.4, 150.2, 156.2. *Anal*. calcd for $C_{20}H_{26}N_2O_2$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.44; H, 8.08; N, 8.50.

1-5. Synthesis of Diyne (6) (Scheme 2)



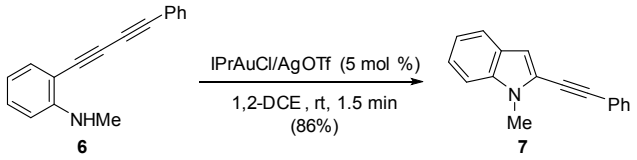
S26 6

***N*-Methyl-2-(phenylbuta-1,3-diyn-1-yl)aniline (6)**

According to the procedure described for the preparation of **1a**, **S26** (183 mg, 1.40 mmol) was converted into **6** (217 mg, 67%). Column chromatography: silica gel (hexane/EtOAc = 10/1); brown solid; mp 60 °C; IR (neat): 2236, 2139 (C≡C), 1301 (NH); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.92 (d, *J* = 5.2 Hz, 3H), 4.72 (br s, 1H), 6.58-6.64 (m, 2H), 7.23-7.27 (m, 1H), 7.33-7.37 (m, 4H), 7.51-7.53 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 30.2, 74.0, 78.9, 79.3, 82.8, 105.5, 109.1, 116.2, 121.9, 128.5 (2C), 129.1, 131.0, 132.4 (2C), 133.1, 151.5. *Anal*. calcd for $C_{17}H_{13}N$: C, 88.28; H, 5.67; N, 6.06. Found: C, 88.02; H, 5.55; N, 5.85.

2. Gold-Catalyzed Cascade Cyclization of Conjugated Diynes

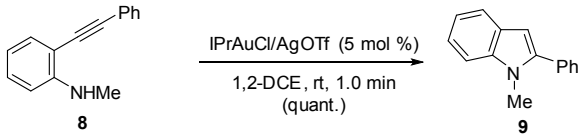
2-1. Comparison of the Reactivities toward Indole Formation between Diynyl- and (Phenylethynyl)anilines (Scheme 2)



6 7

1-Methyl-2-(phenylethynyl)-1*H*-indole (7)

A screw-cap test tube was charged with *N*-methyl-2-(phenylbuta-1,3-diyn-1-yl)aniline (**6**) (23.1 mg, 0.1 mmol), IPrAuCl (3.1 mg, 5.0 μmol) and AgOTf (1.3 mg, 5.0 μmol). Dry 1,2-dichloroethane (1,2-DCE) (1 mL) was added to the screw-cap test tube, and the resulting mixture was stirred at room temperature for 1.5 min. The reaction mixture was concentrated in *vacuo*. The residue was chromatographed on NH_2 silica gel (hexane/EtOAc = 10/1) to afford **7** (19.9 mg, 86%) as a yellow solid.

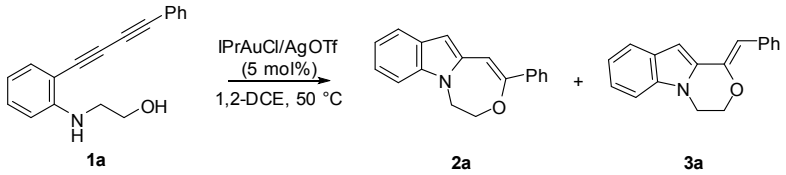


8 9

1-Methyl-2-phenyl-1*H*-indole (9)

According to the procedure described for the preparation of **7**, *N*-methyl-2-(phenylethynyl)aniline (**8**) (20.7 mg, 0.1 mmol) was converted to **9** (20.8 mg, quant) 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 mL) at room temperature for 1.0 min. Column chromatography: NH_2 silica gel (hexane/EtOAc = 10/1); colorless solid.

2-2. Reaction of Conjugated Diynes Bearing Various Substituents (Table 1 and 2)



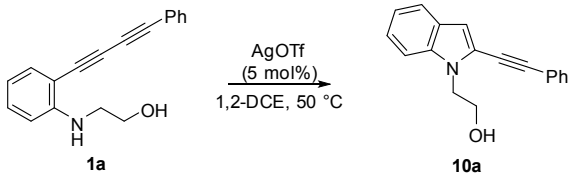
1a 2a 3a

General Procedure A: Synthesis of 2-Phenyl-4,5-dihydro[1,4]oxazepino[4,5-*a*]indole (2a) and (*Z*)-1-Benzylidene-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]indole (3a) (Table 1, Entry 6)

A screw-cap test tube was charged with **1a** (39.2 mg, 0.15 mmol), IPrAuCl (4.7 mg, 7.5 μmol) and AgOTf (1.9 mg, 7.5 μmol). Dry 1,2-DCE (1.5 mL) was added to the screw-cap test tube. After stirring at 50 °C for 2 h, the reaction mixture was concentrated in *vacuo* and chromatographed on NH_2 silica gel (hexane/$CHCl_3$ = 3/1), and the collected solid was rinsed with hexane to afford **2a**/**3a** (33.6 mg, 86%, **2a**/**3a** = 88/12, determined by ^{1}H NMR). Both products were isolated by PTLC (NH_2 silica gel) with hexane/ Et_2O (9/1).

The major product **2a**: green crystals; mp 164 °C; IR (neat): 1631 (CH_2OC=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.50-4.52 (m, 2H), 4.64-4.66 (m, 2H), 6.36 (s, 1H), 6.46 (s, 1H), 7.08-7.10 (m, 1H), 7.16-7.20 (m, 1H), 7.23 (d, *J* = 7.4 Hz, 1H), 7.32-7.35 (m, 1H), 7.37-7.40 (m, 2H), 7.56 (d, *J* = 7.4 Hz, 1H), 7.69-7.71 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 47.2, 69.7, 95.8, 102.4, 108.3, 119.9, 120.2, 121.6, 125.5 (2C), 128.3 (2C), 128.4, 128.5, 136.3, 136.4, 137.9, 152.8. *Anal*. calcd for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36. Found: C, 82.57; H, 5.74; N, 5.35.

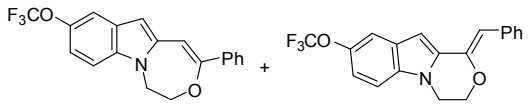
The minor product **3a**: pale brown solid; mp 135 °C; IR (neat): 1714 (CH_2OC=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.29 (t, *J* = 5.2 Hz, 2H), 4.49 (t, *J* = 5.2 Hz, 2H), 6.27 (s, 1H), 6.84 (s, 1H), 7.12-7.23 (m, 3H), 7.28-7.30 (m, 1H), 7.33-7.35 (m, 2H), 7.62 (d, *J* = 7.4 Hz, 1H), 7.73 (d, *J* = 6.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 40.9, 64.8, 97.5, 105.2, 108.5, 120.6, 120.8, 122.1, 126.0, 127.9, 128.3 (2C), 128.6 (2C), 130.4, 135.8, 136.1, 144.7; HRMS (FAB) calcd for $C_{18}H_{16}NO$ (MH^+) 262.1226, found 262.1233.



1a 10a

2-[2-(Phenylethynyl)-1*H*-indol-1-yl]ethan-1-ol (10a) (Table 1, Entry 14)

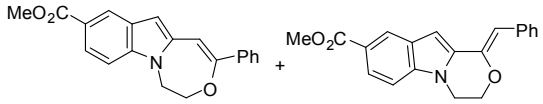
By use of the procedure A, **1a** (26.1 mg, 0.10 mmol) was converted to **10a** (15.2 mg, 56%) by the reaction with AgOTf (1.3 mg, 5.0 μmol) in the absence of a gold salt in dry 1,2-DCE (1.0 mL) at 50 °C for 24 h: colorless needless; mp 110 °C; IR (neat): 3230 (OH), 2204 (C≡C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.52 (t, *J* = 6.0 Hz, 1H), 4.04-4.06 (m, 2H), 4.49 (t, *J* = 5.4 Hz, 2H), 6.87 (s, 1H), 7.13 (t, *J* = 7.4 Hz, 1H), 7.26-7.28 (m, 1H), 7.36-7.40 (m, 4H), 5.55-5.56 (m, 2H), 7.60 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 46.8, 62.3, 80.9, 95.5, 108.2, 109.7, 120.3, 121.1, 121.4, 122.5, 123.3, 127.4, 128.5 (2C), 128.7, 131.4 (2C), 137.2; HRMS (FAB) calcd for $C_{18}H_{16}NO$ (MH^+) 262.1226, found 262.1230.



2b **3b**

2-Phenyl-9-(trifluoromethoxy)-4,5-dihydro[1,4]oxazepino[4,5-*a*]indole (2b) (Table 2, Entry 2)

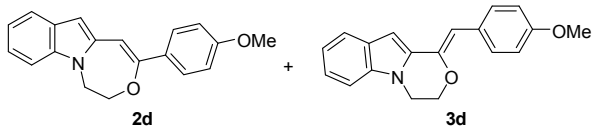
By use of the procedure A, **1b** (34.5 mg, 0.10 mmol) was converted to **2b**/**3b** (29.5 mg, 86%, **2b**/**3b** = 91/9, determined by ^{1}H NMR) by the reaction with IPrAuCl (3.1 mg, 5.0 μmol) and AgOTf (1.3 mg, 5.0 μmol) in dry 1,2-DCE (1.0 mL) at 50 °C for 1.5 h. The major product **2b** was isolated by careful column chromatography over NH_2 silica gel with hexane/EtOAc (10:1): white powder; mp 150 °C; IR (neat): 1633 (CH_2OC=C), 1150 (CF_3); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.49 (t, *J* = 3.4 Hz, 2H), 4.65 (t, *J* = 3.4 Hz, 2H), 6.33 (s, 1H), 6.44 (s, 1H), 7.03-7.04 (m, 1H), 7.18 (d, *J* = 8.6 Hz, 1H), 7.33-7.40 (m, 4H), 7.70-7.71 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 47.4, 69.5, 95.3, 102.4, 108.8, 112.4, 115.2, 120.8 (q, *J* = 255.5 Hz), 125.6 (2C), 128.4 (2C), 128.5, 128.8, 136.1, 138.1, 143.23, 143.24, 153.7. *Anal*. calcd for $C_{19}H_{14}F_3NO_2$: C, 66.09; H, 4.09; N, 4.06. Found: C, 65.81; H, 4.00; N, 3.88.



2c **3c**

Methyl 2-Phenyl-4,5-dihydro[1,4]oxazepino[4,5-*a*]indole-9-carboxylate (2c) (Table 2, Entry 3)

By use of the procedure A, **1c** (31.9 mg, 0.10 mmol) was converted to **2c**/**3c** (28.2 mg, 88%, **2c**/**3c** = 90/10, 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 1.5 h. The major product **2c** was isolated by careful column chromatography over NH_2 silica gel with hexane/EtOAc (10:1): pale yellow solid; mp 194–199 °C; IR (neat): 1705 (C=O), 1632 (CH_2OC=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.93 (s, 3H), 4.53-4.55 (m, 2H), 4.67-4.38 (m, 2H), 6.35 (s, 1H), 6.53 (s, 1H), 7.24 (d, *J* = 9.2 Hz, 1H), 7.33-7.41 (m, 3H), 7.70-7.71 (m, 2H), 7.88-7.90 (m, 1H), 8.31 (d, *J* = 1.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 47.4, 51.8, 69.5, 95.2, 103.4, 107.9, 121.9, 122.97, 123.02, 125.6 (2C), 128.0, 128.4 (2C), 128.8, 136.1, 137.8, 140.2, 153.5, 168.1; HRMS (FAB) calcd for $C_{20}H_{18}NO_3$ (MH^+) 320.1281, found 320.1277.

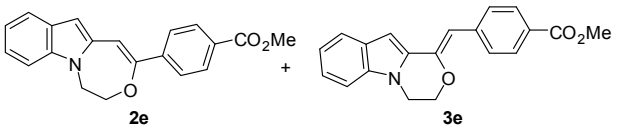


2d **3d**

2-(4-Methoxyphenyl)-4,5-dihydro[1,4]oxazepino[4,5-*a*]indole (2d) (Table 2, Entry 4)

By use of the procedure A, **1d** (29.1 mg, 0.10 mmol) was converted to **2d**/**3d** (31.6 mg, 90%, **2d**/**3d** = 94/6, determined by ^{1}H NMR) by the reaction with 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 h. The major product **2d** was isolated by careful column chromatography over NH_2 silica gel with hexane/EtOAc (10:1): green crystals; mp 200 °C; IR (neat): 1627 (CH_2OC=C), 1255 (OMe); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.84 (s, 3H), 4.50 (t, *J* = 3.7 Hz, 2H), 4.64 (t, *J* = 3.7 Hz, 2H), 6.24 (s, 1H), 6.42 (s, 1H), 6.91 (d, *J* = 8.6 Hz, 2H), 7.08-7.09 (m, 1H), 7.16-7.17 (m, 1H), 7.22-7.23 (m, 1H), 7.55 (d,

J = 7.4 Hz, 1H), 7.63-7.65 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 47.2, 55.3, 69.6, 94.3, 101.8, 108.2, 113.7 (2C), 119.8, 120.1, 121.3, 127.0 (2C), 128.5, 129.0, 136.6, 137.8, 152.9, 160.0; HRMS (FAB) calcd for $C_{19}H_{18}NO_2$ (MH^+) 292.1332, found 292.1335.



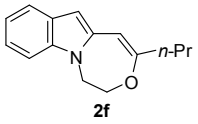
2e **3e**

Methyl 4-(4,5-Dihydro[1,4]oxazepino[4,5-*a*]indol-2-yl)benzoate (2e) and Methyl (*Z*)-4-[(3,4-Dihydro-1*H*-[1,4]oxazino[4,3-*a*]indol-1-ylidene)methyl]benzoate (3e) (Table 2, Entry 5)

By use of the procedure A, **1e** (31.9 mg, 0.11 mmol) was converted to **2e**/**3e** (22.7-29.5 mg, 71-92%, **2e**/**3e** = 56-61/44-39, 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 1 h. Both the products were isolated by PTLC (NH_2 silica gel) with hexane/ Et_2O (9/1).

The major product **2e**: yellow powder; mp 225 °C; IR (neat): 1719 (C=O), 1602 (CH_2OC=C), 1274 (OMe); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.93 (s, 3H), 4.52-4.53 (m, 2H), 4.66-4.67 (m, 2H), 6.47 (s, 1H), 6.52 (s, 1H), 7.10-7.12 (m, 1H), 7.20-7.23 (m, 2H), 7.58 (d, J = 8.0 Hz, 1H), 7.76-7.78 (m, 2H), 8.03-8.05 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 47.2, 52.1, 69.7, 97.7, 103.6, 108.4, 120.1, 120.5, 122.0, 125.2 (2C), 128.3, 129.6 (2C), 129.7, 135.7, 138.2, 140.6, 151.5, 166.8; HRMS (FAB) calcd for $C_{20}H_{18}NO_3$ (MH^+) 320.1281, found 320.1281.

The minor product **3e**: light yellow solid; mp 217 °C; IR (neat): 1714 (C=O), 1597 (CH_2OC=C), 1279 (OMe); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.91 (s, 3H), 4.31 (t, J = 5.2 Hz, 2H), 4.53 (t, J = 5.2 Hz, 2H), 6.28 (s, 1H), 6.88 (s, 1H), 7.15-7.16 (m, 1H), 7.24-7.25 (m, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 8.6 Hz, 2H), 7.99 (d, J = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 40.8, 51.9, 65.0, 98.6, 104.1, 108.6, 120.7, 121.1, 122.6, 126.8, 127.8, 128.2 (2C), 129.6 (2C), 129.8, 136.2, 140.6, 146.8, 167.1; HRMS (FAB) calcd for $C_{20}H_{18}NO_3$ (MH^+) 320.1281, found 320.1274.

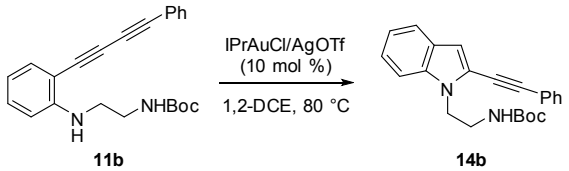


2f

2-Propyl-4,5-dihydro[1,4]oxazepino[4,5-*a*]indole (2f) (Table 2, Entry 6)

By use of the procedure A, **1f** (23.0 mg, 0.1 mmol) was converted to **2f** (18.0 mg, 78%, **2f**/**3f** = 100/0, 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 h: pale green solid; mp 164 °C; IR (neat): 1651 (CH_2OC=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.96 (t, J = 7.4 Hz, 3H), 1.60-1.62 (m, 2H), 2.22 (t, J = 7.4 Hz, 2H), 4.39-4.43 (m, 4H), 5.57 (s, 1H), 6.23 (s, 1H), 7.05-7.06 (m, 1H), 7.11-7.14 (m, 1H), 7.19 (d, J = 7.4 Hz, 1H), 7.51 (d, J = 7.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.6, 20.9, 32.3, 46.9, 69.2, 94.8, 99.8, 108.0, 119.6, 119.9, 120.8, 128.5, 136.6, 137.4, 156.6; HRMS (FAB) calcd for $C_{15}H_{18}NO$ (MH^+) 228.1383, found 228.1382.

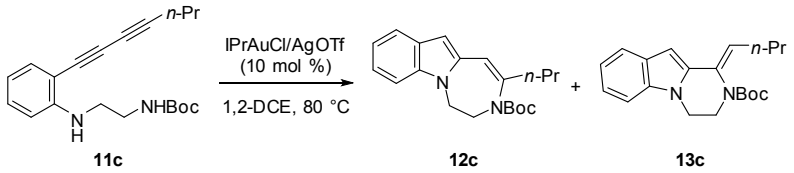
2-3. Reaction of Ethylenediamine-Type Substrates (Table 3)



11b **14b**

General Procedure B: *tert*-Butyl {2-[2-(Phenylethynyl)-1*H*-indol-1-yl]ethyl}carbamate (14b) (Table 3, Entry 2)

A screw-cap test tube was charged with **11b** (36.0 mg, 0.1 mmol), IPrAuCl (6.2 mg, 10.0 μmol) and AgOTf (2.6 mg, 10.0 μmol). Dry 1,2-DCE (1.0 mL) was added to the screw-cap test tube. After stirring at 80 °C for 24 h, the reaction mixture was concentrated in *vacuo* and chromatographed on NH_2 silica gel (hexane/EtOAc = 5/1). The collected solid was rinsed with hexane to afford **14b** (28.3 mg, 79%) as brown crystals; mp 94 °C; IR (neat): 2206 (C≡C), 1690 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.38 (s, 9H), 3.57-3.58 (m, 2H), 4.46 (t, *J* = 5.7 Hz, 2H), 4.63 (br s, 1H), 6.86 (s, 1H), 7.12-7.13 (m, 1H), 7.23-7.27 (m, 1H), 7.36-7.38 (m, 4H), 7.57-7.59 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.3 (3C), 40.8, 44.1, 79.5, 80.8, 95.5, 108.2, 109.6, 120.3, 121.0, 121.3, 122.5, 123.3, 127.3, 128.4 (2C), 128.7, 131.5 (2C), 137.1, 155.9; HRMS (FAB) calcd for $C_{23}H_{25}N_2O_2$ (MH^+) 361.1911, found 361.1907.



11c **12c** **13c**

***tert*-Butyl 2-Propyl-4,5-dihydro-3*H*-[1,4]diazepino[1,7-*a*]indole-3-carboxylate (12c) and *tert*-Butyl (*Z*)-1-Butylidene-3,4-dihydropyrazino[1,2-*a*]indole-2(1*H*)-carboxylate (13c)**

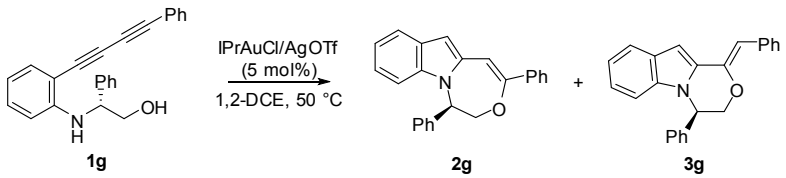
By use of the procedure B, **11c** (32.6 mg, 0.1 mmol) was converted to **12c**/**13c** (16.0-23.9 mg, 49-73%, 82-85/18-15, determined by ^{1}H NMR) by the reaction in the presence of IPrAuCl (6.2 mg, 10.0 μmol) and AgOTf (2.6 mg, 10.0 μmol) in dry 1,2-DCE (1.0 mL) at 80 °C for 5.5-8 h. Both the products were isolated by careful column chromatography over NH_2 silica gel with hexane/Et_2O (9/1).

The major product **12c**: light yellow crystals; mp 139 °C; IR (neat): 1705 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.95 (t, *J* = 7.4 Hz, 3H), 1.49 (s, 9H), 1.53-1.55 (m, 2H), 2.60 (t, *J* = 7.4 Hz, 2H), 4.00-4.01 (m, 2H), 4.32-4.33 (m, 2H), 6.02 (s, 1H), 6.39 (s, 1H), 7.09-7.11 (m, 1H), 7.18-7.19 (m, 1H), 7.24-7.25 (m, 1H), 7.56 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.8, 21.2, 28.3 (3C), 37.7, 47.0, 47.3, 81.4, 103.5, 109.0, 110.6, 120.0, 120.4, 121.8, 127.5, 136.1, 138.7, 140.8, 152.6; HRMS (FAB) calcd for $C_{20}H_{27}N_2O_2$(MH^+) 327.2067, found 327.2062.

The minor product **13c**: light yellow solid; mp 150–152 °C; IR (neat): 1692 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ: 0.94 (t, *J* = 7.2 Hz, 3H), 1.42 (s, 9H), 1.45-1.51 (m, 2H), 2.13-2.15 (m, 2H), 3.93 (br s, 2H), 4.08 (t, *J* = 5.4 Hz, 2H), 6.12 (t, *J* = 7.2 Hz, 1H), 6.67 (s, 1H), 7.01-7.02 (m, 1H), 7.07-7.10 (m, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ: 13.9, 22.2, 28.4 (3C),

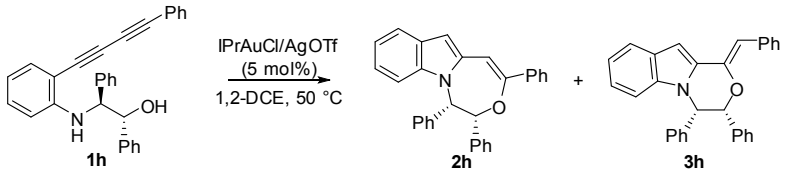
30.3, 41.2, 43.7, 81.0, 95.6, 108.6, 120.3, 120.4, 121.5, 124.20, 124.22, 128.2, 133.5, 136.3, 161.1; HRMS (FAB) calcd for $C_{20}H_{27}N_2O_2$ (MH^+) 327.2067, found 327.2065.

2-4. Reaction of Substituted Nucleophilic Part (Scheme 3)



(*R*)-2,5-Diphenyl-4,5-dihydro-[1,4]oxazepino[4,5-*a*]indole (2g) and (*R, Z*)-1-Benzylidene-4-phenyl-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]indole (3g) (2g/3g = 71/29)

By use of the procedure A, **1g** (33.7 mg, 0.10 mmol) was converted into an inseparable mixture of **2g**/**3g** (29.0 mg, 86%, **2g**/**3g** = 71/29, 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 1 h.: greenish gray powder; mp 198–200 °C; IR (neat) 1627 (CH_2OC=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: (Major isomer **2g**) 4.72 (d, *J* = 12.6 Hz, 1H), 5.02 (dd, *J* = 12.3, 3.7 Hz, 1H), 5.89 (d, *J* = 3.7 Hz, 1H), 6.48 (s, 1H), 6.55 (s, 1H), 7.08-7.09 (m, 3H), 7.15 (d, *J* = 7.4 Hz, 2H), 7.22 (d, *J* = 6.9 Hz, 1H), 7.27-7.35 (m, 5H), 7.58-7.59 (m, 1H), 7.64 (d, *J* = 8.6 Hz, 2H); (Minor isomer **3g**): 4.58-4.63 (m, 2H), 5.52-5.53 (br m, 1H), 6.38 (s, 1H), 6.94 (s, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 7.10-7.12 (m, 5H), 7.20-7.22 (m, 1H), 7.27-7.35 (m, 5H), 7.70 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: (Major isomer **2g**) 61.2, 73.3, 96.6, 102.7, 109.1, 120.2, 121.7, 125.5 (2C), 126.5 (2C), 127.7, 128.2 (2C), 128.3, 128.4, 128.5, 128.6 (2C), 136.0, 136.6, 138.1, 138.4, 153.4; (Minor isomer **3g**) 55.3, 70.5, 97.7, 105.5, 109.6, 110.7, 120.8 (2C), 122.2 (2C), 125.7, 126.1 (2C), 127.8, 128.16 (2C), 128.19, 128.7, 128.9, 130.6, 135.6, 135.9, 138.1, 144.7; HRMS (ESI) calcd for $C_{24}H_{20}NO$ (MH^+): 338.1545; found: 338.1550.



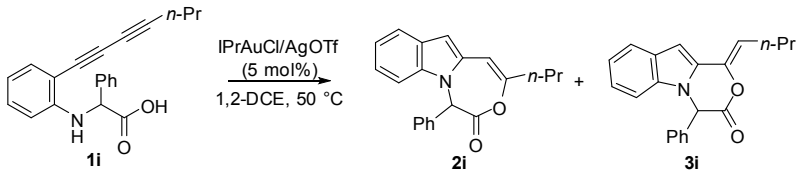
***erythro*-2,4,5-Triphenyl-4,5-dihydro-[1,4]oxazepino[4,5-*a*]indole (2h) and *erythro*-1-((*Z*)-Benzylidene)-3,4-diphenyl-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]indole (3h)**

By use of the procedure A, **1h** (41.4 mg, 0.10 mmol) was converted to **2h**/**3h** (37.9 mg, 92%, **2h**/**3h** = 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 1 h. Both the products were isolated by PTLC (NH_2 silica gel) with hexane/Et_2O (3/1).

The minor product **2h**: 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), 127.7 (2C), 127.7, 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 414.1852.

The major product **3h**: 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), 127.9 (4C), 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.



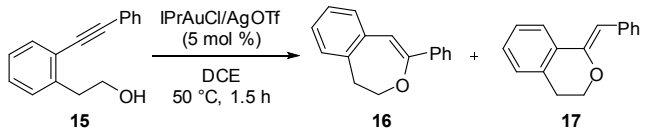
5-Phenyl-2-propyl-[1,4]oxazepino[4,5-*a*]indol-4(5*H*)-one (2i) and (*Z*)-1-Butylidene-4-phenyl-1*H*-[1,4]oxazino[4,3-*a*]indol-3(4*H*)-one (3i)

By use of the procedure A, **1i** (31.7 mg, 0.10 mmol) was converted to **2i**/**3i** (11.1 mg, <35%, **2i**/**3i** = 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 1 h. Both the products were isolated by PTLC (NH_2 silica gel) with hexane/ Et_2O (3/1).

The minor product **2i**: 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), 1.12-1.18 (m, 1H), 1.33-1.42 (m, 1H), 1.97-2.00 (m, 1H), 2.11-2.17 (m, 1H), 5.96 (s, 1H), 6.55 (s, 1H), 6.68 (dd, *J* = 6.9, 1.1 Hz, 2H), 6.76 (s, 1H), 7.20-7.28 (m, 5H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 8.0 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 (2C), 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.

The major product **3i**: 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.

2-5. Reaction of the Benzene Congener (Scheme 4)



15 16 17

4-Phenyl-1,2-dihydrobenzo[*d*]oxepine (16) and (*Z*)-1-Benzylideneisochromane (17)

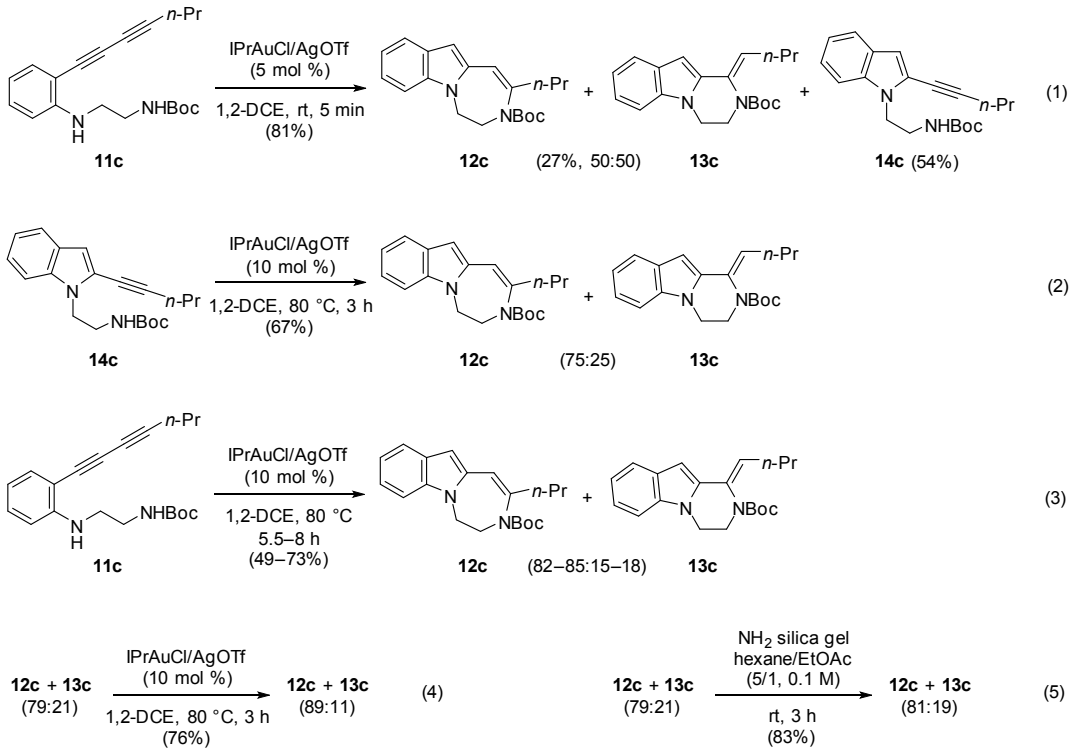
By use of the procedure A, **15** (47.5 mg, 0.21 mmol) was converted to **16**/**17** (43.9 mg, 92%, **16**/**17** = 13/87, determined by ^{1}H NMR) by the reaction with IPrAuCl (6.6 mg, 10.6 μmol) and AgOTf (2.7 mg, 10.5 μmol) in dry 1,2-DCE (2.1 mL) at 50 °C for 1.5 h. For column chromatography, silica gel (hexane/EtOAc = 20/1) was employed. Both the products were isolated by PTLC (NH_2 silica gel) with hexane/Et_2O (9/1).

The minor product **16**: white powder; mp >300 °C; IR (neat): 1624 (CH_2OC=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.21-3.22 (m, 2H), 4.48-4.51 (m, 2H), 6.14 (s, 1H), 7.05-7.10 (m, 2H), 7.17-7.19 (m, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.31-7.39 (m, 3H), 7.69-7.71 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 38.8, 69.8, 103.4, 125.1, 126.0 (2C), 126.4, 128.2 (2C), 128.3, 128.7, 130.3, 135.1, 137.9, 138.5, 154.3; HRMS (FAB) calcd for $C_{16}H_{15}O$ (MH^+) 223.1117, found 223.1115.

The major product **17**: colorless oil; IR (neat): 1627 (CH_2OC=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.95 (d, *J* = 5.4 Hz, 2H), 4.27 (d, *J* = 5.4 Hz, 2H), 6.13 (s, 1H), 7.14-7.16 (m, 2H), 7.22-7.25 (m, 2H), 7.31-7.32 (m, 2H), 7.69-7.70 (m, 1H), 7.74 (d, *J* = 7.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 29.5, 64.8, 103.3, 124.2, 125.6, 126.9, 127.8, 128.1, 128.2 (2C), 128.6 (2C), 130.7, 133.9, 136.5, 150.1; HRMS (FAB) calcd for $C_{16}H_{15}O$ (MH^+) 223.1117, found 223.1118.

2-6. Isolation and Reaction of the Possible Intermediates 14c

A possible intermediate **14c** in the reaction of diamine-type substrate **11c** was isolated by stopping the reaction before completion (eq 1). As expected, treatment of **14c** with IPrAuCl/AgOTf (10 mol %) at 80 °C gave **12c**/**13c** in 67% yield (eq 2). Interestingly, the regioselectivity of the incomplete reaction of **11c** (**12c**:**13c** = 50:50) was lower than that of the completed reaction of **14c** (**12c**:**13c** = 75:25). Taking into the consideration that the selectivity in the completed reaction of **11c** was not constant (**12c**:**13c** = 82-85:15-18; eq 3), the author suspected that the minor product **13c** is unstable under the reaction conditions. To verify this possibility, the author investigated the reaction of **12c**/**13c** under the reaction conditions [with IPrAuCl/AgOTf (10 mol %) in 1,2-DCE at 80 °C]. In this case, the ratio of **12c**/**13c** was changed from 79:21 to 89:11 (eq 4). It should be noted that treatment of the same mixture with NH_2 silica gel in hexane/EtOAc (simulated purification conditions) did not alter the product ratio significantly (eq 5).



***tert*-Butyl {2-[2-(Pent-1-yn-1-yl)-1*H*-indol-1-yl]ethyl}carbamate (14c)**

According to the procedure described for the preparation of **7**, **11c** (65.3 mg, 0.2 mmol) was converted to **14c** (35.4 mg, 54%) and **12c**/**13c** (17.8 mg, 27%, **12c**/**13c** = 50/50, determined by ^{1}H NMR) by the reaction in the presence of IPrAuCl (6.2 mg, 10.0 μmol) and AgOTf (2.6 mg, 10.0 μmol) in dry 1,2-DCE (2 mL) at room temperature for 5 min. Column chromatography: NH_2 silica gel (hexane/EtOAc = 5/1).

The major product **14c**: pale yellow solid; mp 94–98 °C; IR (neat): 2319 (C≡C), 1684 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.07 (t, *J* = 7.4 Hz, 3H), 1.42 (s, 9H), 1.67-1.70 (m, 2H), 2.48 (t, *J* = 6.9 Hz, 2H), 3.51-3.52 (br m, 2H), 4.36-4.37 (br m, 2H), 4.59 (br s, 1H), 6.68 (s, 1H), 7.09-7.10 (m, 1H), 7.20-7.22 (m, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.6, 21.6, 22.1, 28.3 (3C), 40.9, 43.8, 72.2, 79.4, 96.7, 106.9, 109.5, 120.0, 120.7, 122.0, 122.7, 127.2, 136.7, 155.9; HRMS (FAB) calcd for $C_{20}H_{27}N_2O_2$ (MH^+) 327.2067, found. 327.2067.

3. Kinetic Experiments

Comparison of the Reactivities toward Indole Formation between Diynylaniline 6 and (Phenylethynyl)aniline 8 (Scheme 2)

The anilines **6** (9.3 mg, 0.04 mmol) and **8** (8.3 mg, 0.04 mmol) were weighted in a vial, then $CDCl_3$ (0.4 mL) was added. On the other hand, a catalyst solution was prepared in another vial using IPrAuCl (2.5 mg, 4.0 μmol), AgOTf (1.0 mg, 4.0 μmol) and $CDCl_3$ (2 mL). A part of this catalyst solution (0.5 mL, 0.2 M in $CDCl_3$) was transferred to a NMR tube via pipette and cooled to -78 °C. To the catalyst solution in the NMR tube was added the substrate solution (0.1 mL, 0.2 M in $CDCl_3$) via pipette and immediately. The NMR tube was inserted to the spectromer at -78 °C. The NMR analysis (4 scan) was conducted at -20 °C every 10 min for a period of 30 min (Figure 3). It is worth noting that all the operations should be conducted quickly because this reaction completes at room temperature within 1 min.

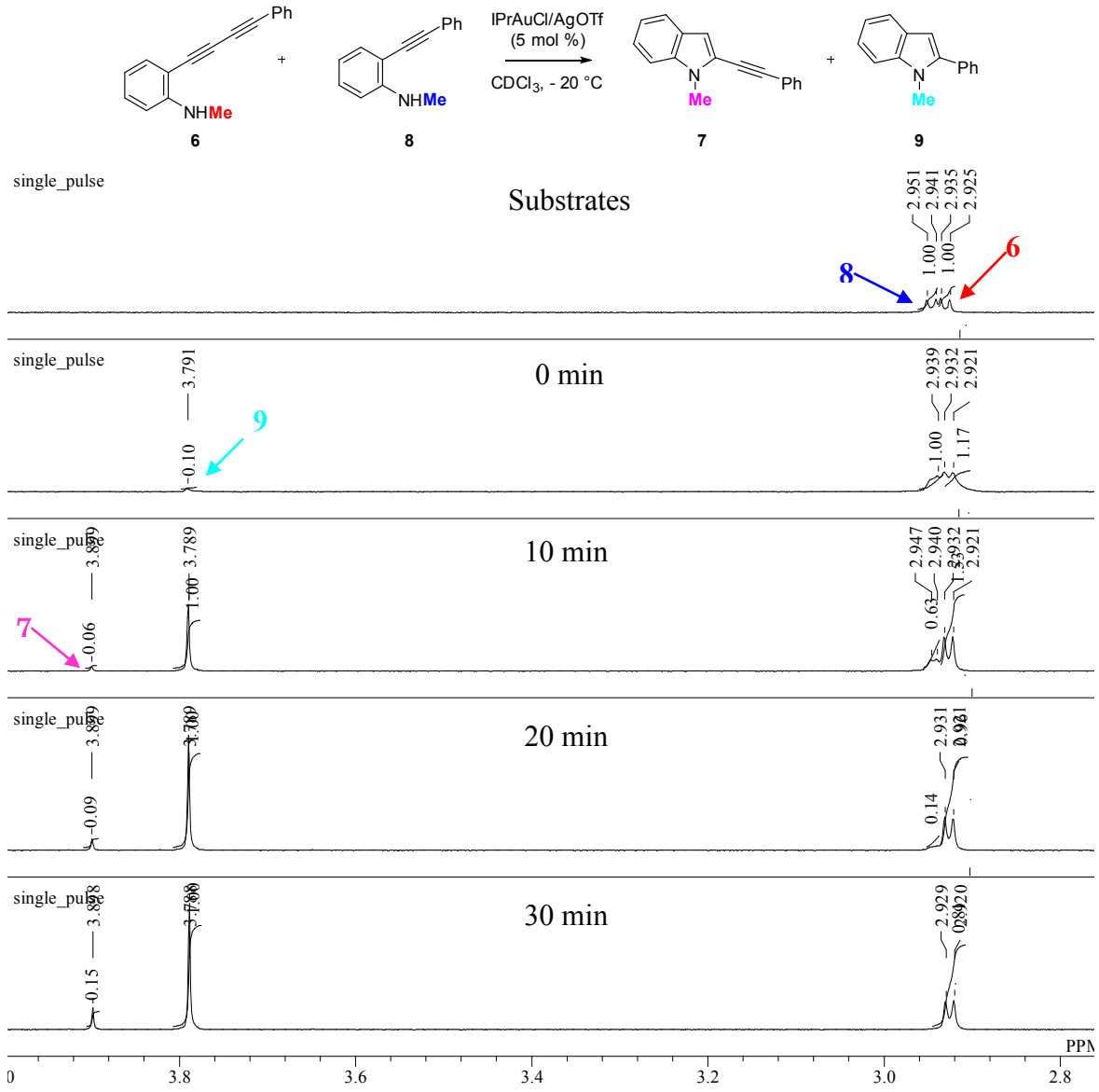
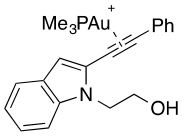


Figure 3. ^{1}HNMR Experiment Chart of Comparison of the Reactivities toward Indole Formation between Diynylaniline **6** and (Phenylethynyl)aniline **8**

4. Computational Details

All DFT calculations were performed with Gaussian 09 program.[34] The molecular structures optimizations were carried out at the M06-2X level[35] in the gas phase using the SDD basis set[36] for Au, and the 6-31G** basis set[37] for H, C, O, N, and P (keywords 5D and int (grid = ultrafine) were used in the calculations) (Figure 4). The vibrational frequencies were computed at the same level to check whether each optimized structure is an energy minimum (no imaginary frequency) or a transition state (one imaginary frequency) and to evaluate its zero-point vibrational energy (ZPVE) and thermal corrections at 298 K. Intrinsic reaction coordinate (IRC) were calculated to confirm the connection between the transition states and the correct reactants/products.[38]

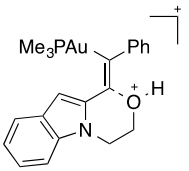
10a•AuPMe$_3$



Energy (RM062X): –1421.007253 A.U.

Gibbs Free Energy: –1420.670460 A.U.

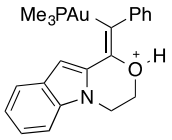
TS1



Energy (RM062X): –1420.989288 A.U.

Gibbs Free Energy: –1420.642884 A.U.

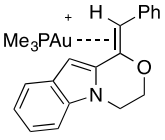
INT-1



Energy (RM062X): –1420.994923 A.U.

Gibbs Free Energy: –1420.649276 A.U.

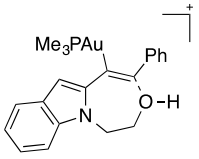
3a•AuPMe$_3$



Energy (RM062X): –1421.063769 A.U.

Gibbs Free Energy: –1420.715923 A.U.

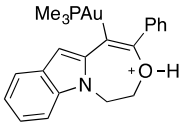
TS2



Energy (RM062X): –1420.991921 A.U.

Gibbs Free Energy: –1420.648111 A.U.

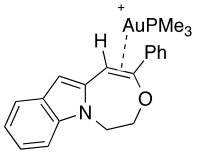
INT-2



Energy (RM062X): –1420.997254 A.U.

Gibbs Free Energy: –1420.651984 A.U.

2a•AuPMe$_3$



Energy (RM062X): –1421.062271 A.U.

Gibbs Free Energy: –1420.713330 A.U.

Figure 4. Optimized Geometries

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10. Because the reaction partially proceeds before the NMR measurement even when the catalyst was added at a low temperature, the ratio at the zero time is slightly variable for every experiment.
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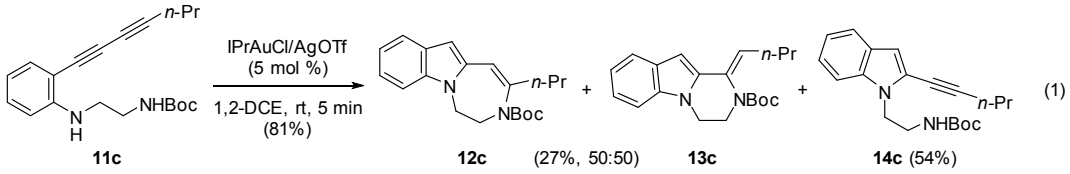
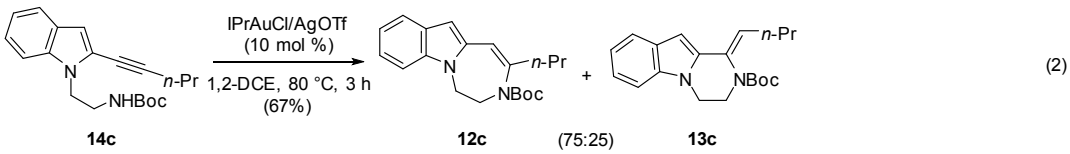
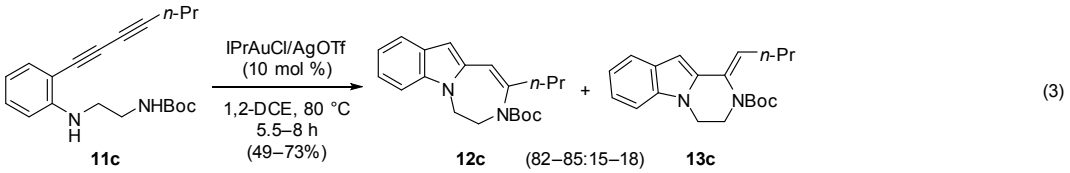
12. The reaction of a possible intermediate **14c** showed slightly low regioselectivity (**12c**:**13c** = 75:25; eq 2). Interestingly, the regioselectivity of the incomplete reaction of **11c** (**12c**:**13c** = 50:50; eq 1) was lower than that of the completed reaction of **14c** (**12c**:**13c** = 75:25; eq 2). Taking into the consideration that selectivity in the completed reaction of **11c** was not constant (**12c**:**13c** = 82-85:15-18; eq 3), the author suspected that the minor product **13c** is unstable under the reaction conditions.







13. The author confirmed that $Me_3PAuCl/AgOTf$ shows similar regioselectivity (**2a**:**3a** = 82:18) although the reactivity was considerably decreased (<6% yield of **2a**/**3a**; 45% of **10a** after 24 h at 50 °C).
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Chapter 2. Cascade Cyclization of Conjugated Alkynes

Section 2. Total Synthesis of Conolidine by Cascade Cyclization of Conjugated Enyne

Summary

The total synthesis of conolidine was accomplished via gold(I)-catalyzed cascade cyclization of conjugated enyne. In this reaction, 5-endo-dig hydroamination provided indole and subsequent 6-exo-dig carbocyclization from enol ether moiety proceeded to form piperidine ring in a one-pot manner. With the chiral biarylphosphine ligands, the desired product was obtained with good enantiomeric excess.

Conolidine, a member of the C5-nor stemmadenine family, was first isolated from *Tabernaemonta divaricata* by Kam *et al.* in 2004 as exceedingly rare component of a Malayan *T. divaricata* (Figure 1). In this report, only 0.0013 g/kg of conolidine was obtained from the stem bark of this small flowering plant.[1] Since Bohn *et al.* accomplished the first asymmetric total synthesis of conolidine in 2011, much attention has focused on the unique analgesic activity unlike opioids including morphine.[2] Although several efficient methods have been reported for the synthesis of C5-nor stemmadenine-type indoles,[2,3] the development of a diversity-oriented route suitable for structure-activity relationship study is still desired.

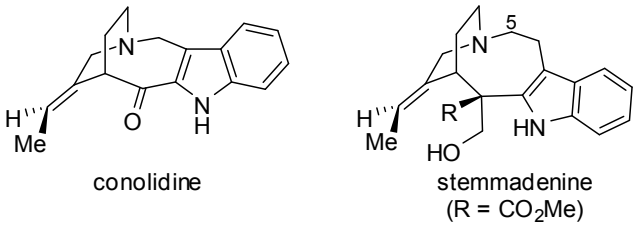
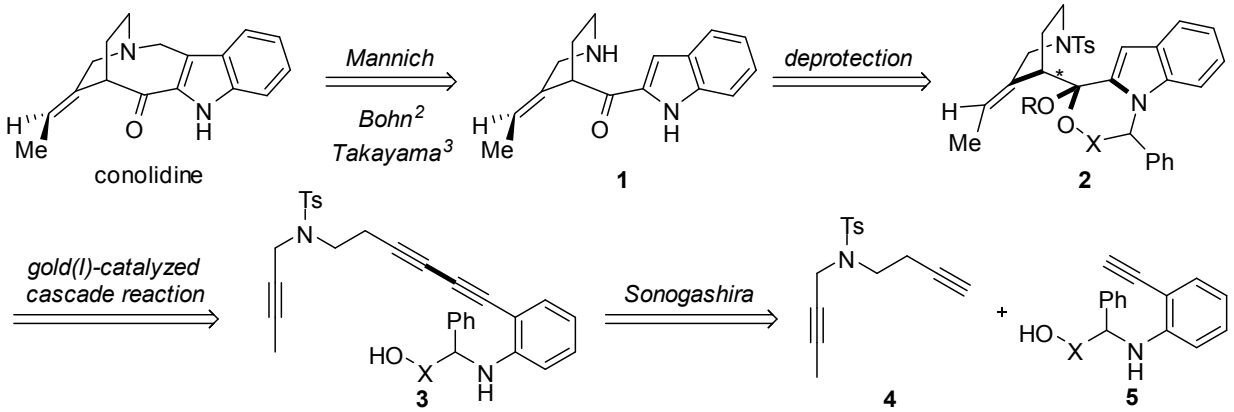
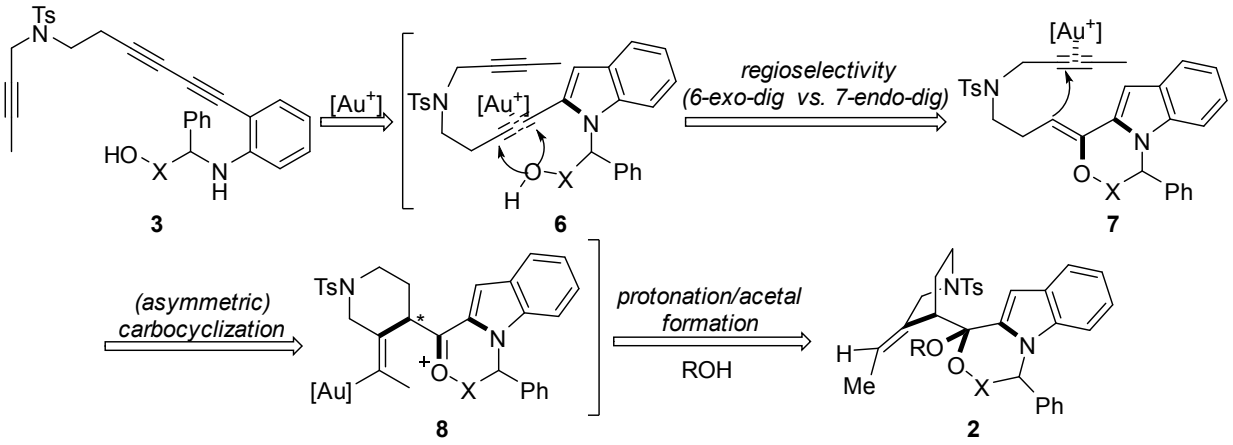


Figure 1. Stemmadenine-Based Alkaloids



Scheme 1. The Author's Strategy (1): Gold(I)-Catalyzed Cascade Reaction of Conjugated Diynes

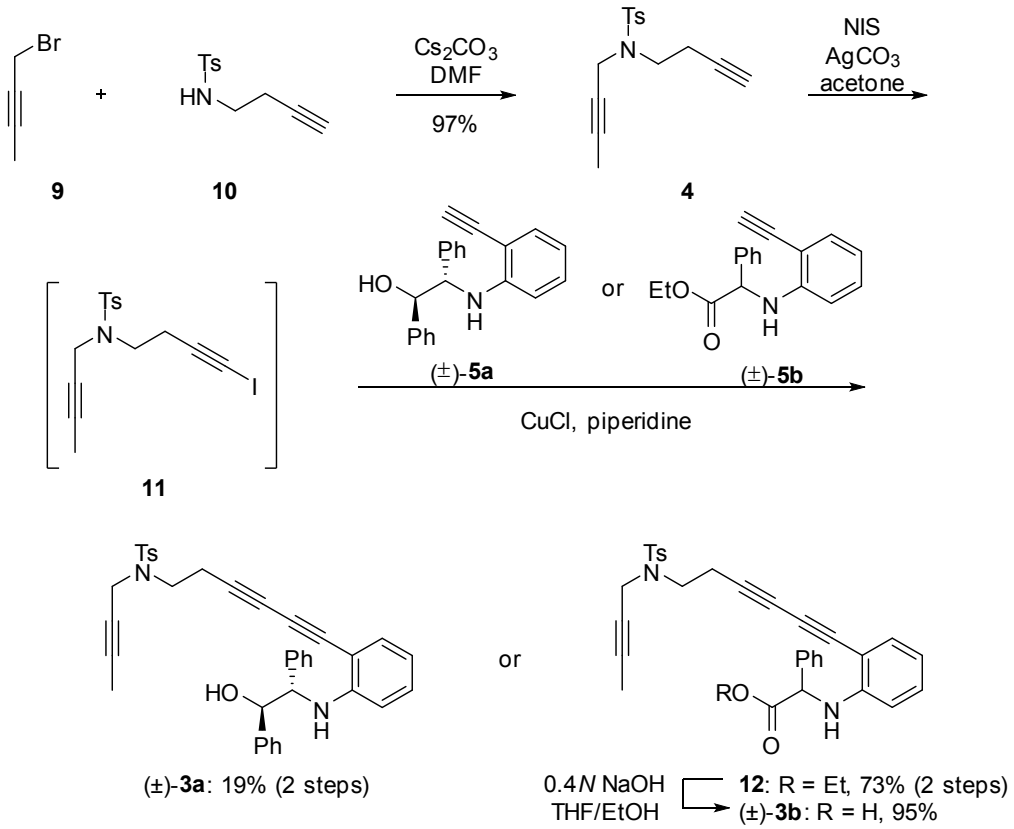


Scheme 2. Potential Regioselectivity Issues in Gold(I)-Catalyzed Cascade Reaction

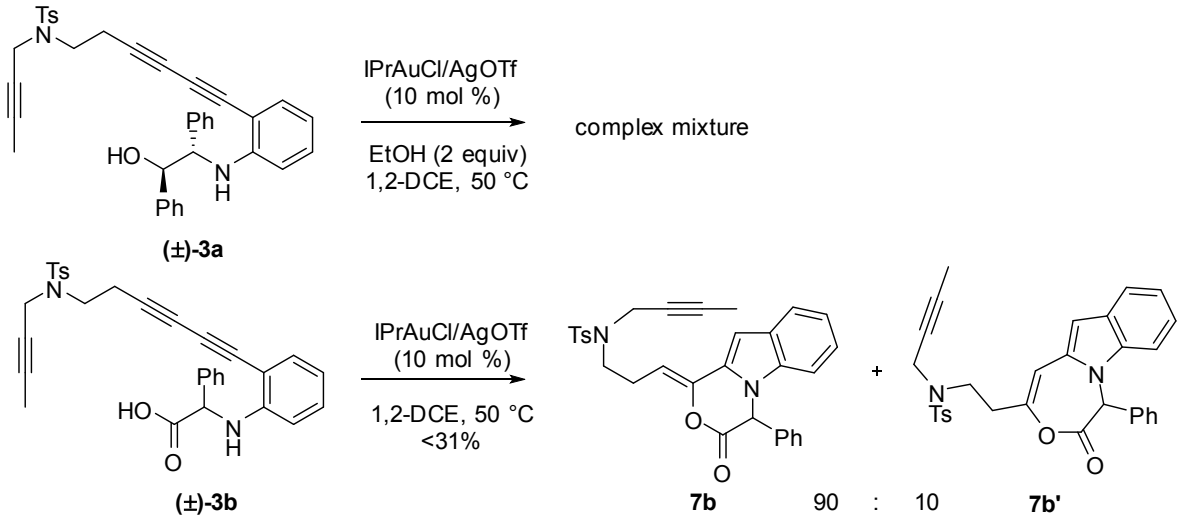
As described in Section 1, the author succeeded in gold-catalyzed fused indole formation. Based on these results, the author designed a novel strategy for the synthesis of conolidine via gold(I)-catalyzed cascade reaction of conjugated diynes (Scheme 1). The author expected that the known conolidine precursor indole **1**[2,3d] could be synthesized from conjugated diyne-substituted aniline **3** by a gold(I)-catalyzed cascade reaction followed by deprotection. The aniline **3** was retrosynthetically deconstructed into the diyne unit **4** and 2-alkynylaniline unit **5**, which would be easily connected using Sonogashira coupling. The control of the regioselectivity of the second cyclization (6-*exo*-*dig* vs 7-*endo*-*dig*) in the gold(I)-catalyzed cascade reaction is a challenging issue of this strategy. The author supposed that the desired 6-*exo*-product **7** could be selectively obtained by appropriate tuning of substrate structure **3** (X = CHPh or C=O, Scheme 2). Indeed, the reaction of a related acid derivative proceeded in a 6-*exo*-selective manner as described in section 1 (Scheme 3).

The author's synthesis commenced with the preparation of the diynes unit **4** by alkylation of the known tosylamide **10** with 1-bromobut-2-yne **9** (Scheme 3). Iodination of terminal alkyne of **4** with NIS and $AgNO_3$ and the subsequent coupling with (±)-**5a** gave the amino alcohol-type substrate (±)-**3a**. Similarly, amino acid-type diyne (±)-**3b** was obtained by coupling with (±)-**5b** followed by hydrolysis.

With the conjugated diynes **3** in hand, the author investigated the gold(I)-catalyzed cascade reaction (Scheme 4). When the conjugated diynes **3a** bearing an amino alcohol moiety was treated with IPrAuCl/AgOTf (10 mol %) and EtOH (2 equiv) in 1,2-DCE at 50 ºC for 2 h, a complex mixture of unidentified products was obtained. On the other hand, use of the acid **3b** led to the formation of the bis-cyclization product **7b** and **7b'** in good regioselectivity (**7b**/**7b'** = 90/10) and low yields (<31%). Unfortunately, further attempts of this reaction to promote further piperidine formation all failed. This is presumably due to the insufficient nucleophilicity of the enol ester moiety of **7b** bearing an electron withdrawing group.

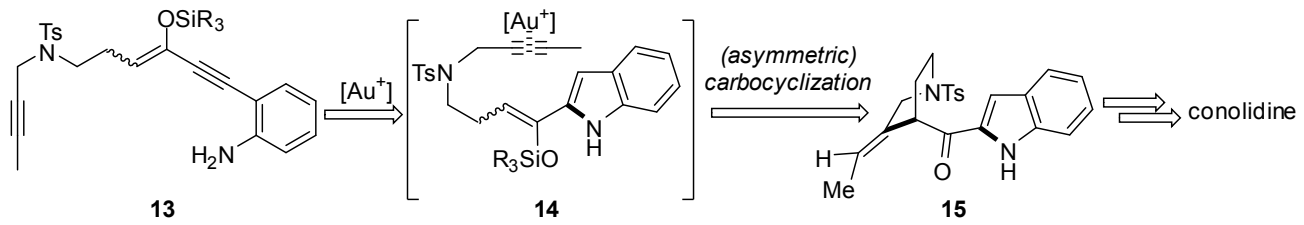


Scheme 3. Preparation of the conjugated diynes (±)-**3a** and (±)-**3b**



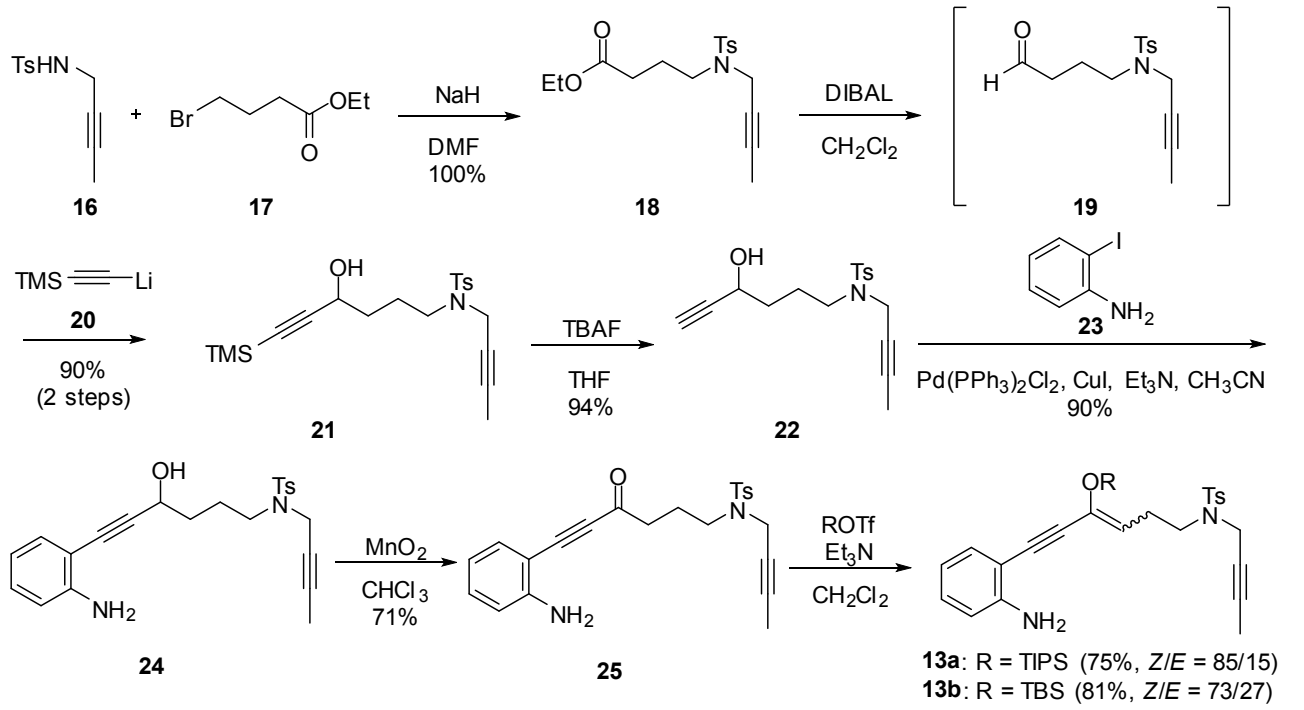
Scheme 4. Gold(I)-Catalyzed Cascade Reaction of **(±)-3a** and **(±)-3b**

To secure the nucleophilicity of the enol moiety, the author designed the second strategy using conjugated enynes **13** bearing a silyl enol ether moiety (Scheme 5). In this modified strategy, the control of the regioselectivity in the second cyclization in Scheme 2 is unnecessary because the oxygen atom is already introduced as the silyl ether.[4] The author expected that the nucleophilicity of the silyl enol ether would be increased by formation of the indole ring to promote the piperidine formation.



Scheme 5. The Author's Strategy (2): Gold(I)-Catalyzed Cascade Cyclization of Conjugated Enyene-type Silyl Enol Ether

The preparation of the conjugated enynes **13** bearing a silyl enol ether moiety was initiated by alkylation of the tosylamide **16** (Scheme 6). Reduction of the resulting ester **18** followed by introduction of alkyne **20** and removal of the TMS group with TBAF afforded the terminal alkyne **22** in excellent yields. The Sonogashira coupling of the resulting terminal alkyne **22** and 2-iodoaniline **23** provided the alkynylaniline **24** in 90% yield. Oxidation of **24** with MnO_2 gave the ketone **25** in 71% yield, which was converted into the conjugated enynes-type silyl enol ether **13** by treatment with TIPSOTf or TBSOTf in the presence of Et_3N (75% or 81%, respectivity).[5]

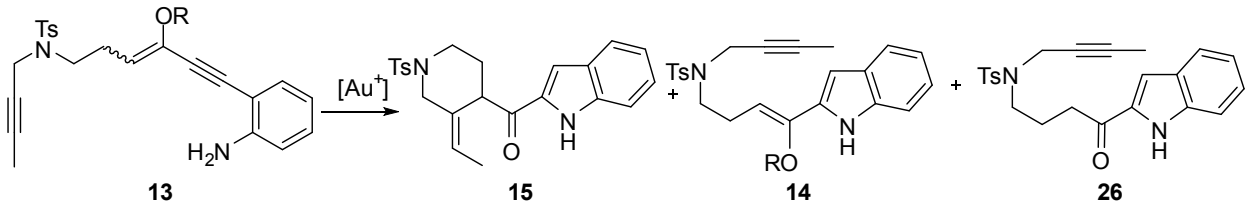


Scheme 6. Preparation of the Conjugated Enynes **13**

The author investigated the gold(I)-catalyzed cascade reaction using the conjugated enynes (Table 1). The conjugated enyne **13a** was treated with JohnPhosAu(MeCN)SbF_6 (5 mol %) in toluene-d_8 at rt to afford the desired product **15** (16%), monocyclization product **14**[6] (34%), and ketone **26** (14%). To drive the reaction to completion, the author investigated the use of additive as a proton source as well as silyl scavenger. Fortunately, addition of H_2O as proton source and silyl scavenger improved the yields of **15** to 38% (entry 2), while use of MeOH was less efficient (entry 3). IPr ligand was not suitable for this reaction (entry 4). Similarly, other attempts using NaBARF as the

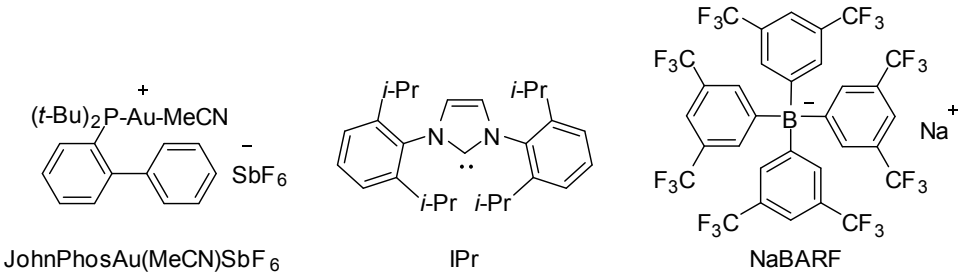
counter anion (entry 5), CD_2Cl_2 as solvent (entry 6), **13b** (R = TBS) as a substrate (entry 7), or higher reaction temperature (entry 8) did not improve the yield**.**

Table 1. Optimization of Reaction Conditions[a]



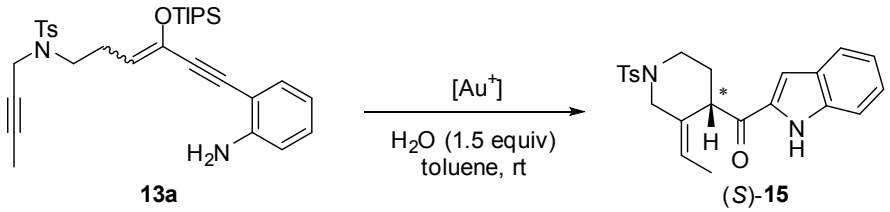
entry	catalyst (5 mol %)	R	additive (1.5 equiv)	time (h)	Conv. (%)[b]	yield(%)[b] 15	14	26
1	JohnPhosAu(MeCN)SbF_6	TIPS	-	24	100	16	34	14
2	**JohnPhosAu(MeCN)SbF_6**	**TIPS**	**H_2O**	**24**	**100**	**38(30)[c,d]**	**-**	**2**
3	JohnPhosAu(MeCN)SbF_6	TIPS	MeOH	19	100	29	-	2
4	IPrAuCl/$AgSbF_6$	TIPS	H_2O	24	92	3	45	10
5	JohnPhosAuCl/NaBARF	TIPS	H_2O	24	100	15	5	45
6[e]	JohnPhosAu(MeCN)SbF_6	TIPS	H_2O	24	100	16	-	43
7	JohnPhosAu(MeCN)SbF_6	TBS	H_2O	24	100	33	-	-
8[f]	JohnPhosAu(MeCN)SbF_6	TIPS	H_2O	1.5	100	37	-	2

[a] Reactions were carried out using **13** (0.1 mmol) in toluene-d_8 at rt. [b] NMR yields were evaluated using mesitylene as an internal standard. [c] Isolated yields in parentheses. [d] Using **13a** (0.5 mmol). [e] Using CD_2Cl_2 as solvent instead of toluene-d_8. [f] The reaction was carried out at 50 °C.



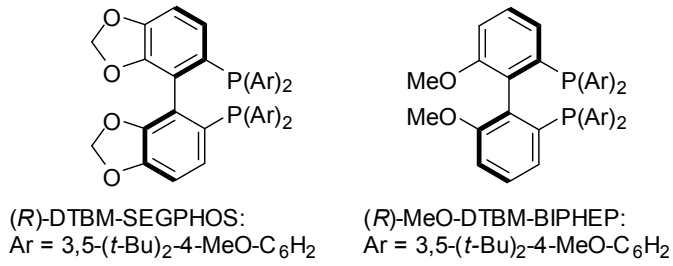
Next, the author investigated the enantioselective gold(I)-catalyzed cascade reaction of the conjugated enynes **13a** (Table 2). According to a related asymmetric carbocyclization of silyl enol ether reported by Toste *et al*,[4h] the author chose biarylphosphine-type dinuclear chiral gold complexes. Preliminary results are shown in Table 2. When the conjugated enyne **13a** was treated with (*R*)-DTBM-SEGPHOS$(AuCl)_2$/$AgSbF_6$ (5/10 mol %), the ketone **26** derived from the hydrolysis of the silyl enol ether was obtained as the major product (entry 1). The reactions using (*R*)-MeO-BIPHES gave the desired product **15**[7] in *ca.*10% yield and 76% ee (entry 2). Decreased loading of catalysts (5/10 mol %) slightly improved the yield to 13% and ee to 89% (entry 3).

Table 2. Enantioselective Gold(I)-Catalyzed Cascade Reaction of Conjugated Enynes **13a**

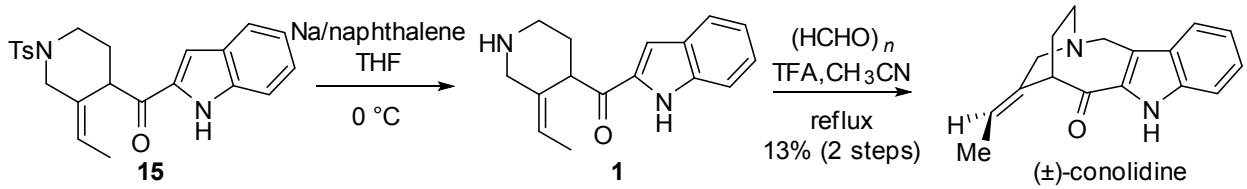


entry	catalyst (mol %)	time (h)	yield (%)[a]	ee (%)[b]
1	(*R*)-DTBM-SEGPHOS$(AuCl)_2/AgSbF_6$ (5/10)	24	N.D.[c,d]	-
2	(*R*)-MeO-BIPHES$(AuCl)_2/AgSbF_6$ (10/20)	6	*ca.*10	76
3	**(*R*)-MeO-BIPHES$(AuCl)_2/AgSbF_6$ (5/10)**	**19**	**13**	**89**

[a] Isolated yields. [b] Determined by chiral HPLC. [c] **26** was obtained as the major product. [d] N.D. = not detected.



Finally, conversion of the bis-cyclization product **(±)-15** to conolidine was investigated. Removal of the Ts group with Na/naphthalene afforded the known conolidine precursor **1** (Scheme 7). According to the procedure reported by Bohn,[2] the author obtained (±)-conolidine although in low yield. The spectroscopic data for the synthetic conolidine were identical to those reported.[1,2]



Scheme 7. Total Synthesis of (±)-Conolidine

In conclusion, the author has achieved the total synthesis of conolidine (Scheme 7). This study demonstrated that the gold(I)-catalyzed cascade reaction is effective for construction of stemmadenine-type scaffold, although further investigation is necessary to improve.

Experimental Section

General Methods. For open column chromatography, silica gel (Wakogel C-200E: Wako Pure Chemical Industries, Ltd) or NH_2 silica gel (Chromatorex NH-DM1020: Fuji Silysia Chemical Ltd.) was employed. Thin layer chromatography was performed on Merck TLC silica gel 60 F_{254} or Wako 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). ^{1}H NMR spectra were recorded using a JEOL ECA-500 spectrometer, and chemical shifts are reported in δ (ppm) relative to TMS as internal standard. ^{13}C NMR spectra were recorded using a JEOL ECA-500 spectrometer and 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). Exact mass (HRMS) spectra were recorded on a JMS-HX/HX 110A mass spectrometer. Infrared (IR) spectra were obtained on a JASCO FT/IR-4100 FT-IR spectrometer with JASCO ATR PRO410-S.

The compounds **9**, **17**, and **23** were obtained commercially and used without further purification.
Synthesis of the compounds **5a** and **5b** is described in Section 1.
The known compounds **10**[8] and **16**[9] were prepared according to the literature.

1. Preparation of Starting Materials

***N*-(But-2-yn-1-yl)-*N*-(but-3-yn-1-yl)-4-methylbenzenesulfonamide (4)**

A mixture of **10** (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 **9** (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 **4** (5.33 g, 97%) as colorless oil: IR (neat): 3288 (C≡H), 2120 (C≡C), 1343, 1156 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.57-1.58 (br m, 3H), 2.00-2.01 (br m, 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: 3.17, 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-[(*erythro*-2-hydroxy-1,2-diphenylethyl)amino]phenyl}hexa-3,5-diyn-1-yl)-4-methylbenzenesulfonamide ((±)-3a)**

A mixture of **4** (1.10 g, 4.0 mmol), $AgNO_3$ (0.20 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 material **11** was used for the next reaction without further purification.

According to the reported method, the copper-mediated coupling of **(±)-5a** and **11** was conducted as follows:[10] **11**, **(±)-5a** (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 **(±)-3a** (0.31 g, 19%) as colorless amorphous: IR (neat): 3396 (OH), 2230 (C≡C), 22143 (C≡C), 1327 (S=O), 1157 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.58-1.58 (br m, 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), 127.8, 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 (12)

According to the procedure described for the preparation of **(±)-3a**, **(±)-5b** (12.0 g, 3.0 mmol) was converted to **12** (0.80 g, 73%) by the reaction with **11** 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, 2146 (C≡C), 1735 (C=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), 7.30-7.35 (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: 3.26, 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 ((±)-3b)

THF (*ca*. 2 mL) was added to the mixture **12** (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 **(±)-3b** (0.14 g, 95%) as brown powder; mp 64–65 °C; IR (neat): ; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.50 (s, 3H), 2.32 (s, 3H), 2.60-2.61 (br m, 2H), 3.33-3.35 (br m, 2H), 4.04 (br s, 2H), 4.85 (s, 1H), 6.21 (d, *J* = 8.6 Hz, 1H), 6.51-6.53 (m, 1H), 6.97-6.98 (m, 1H), 7.17-7.18 (br m, 5H), 7.27 (d, *J* = 6.9 Hz, 1H), 7.38-7.39 (m, 2H), 7.66 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 3.3, 20.3, 21.5, 37.6, 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), 127.8 (2C), 128.6, 129.0 (2C), 129.4 (2C), 130.5, 133.5, 135.7, 143.5, 148.0, 175.4; 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 (18)

The coupling of **16** and ethyl 4-bromobutanoate (**17**) was carried out according to the reported method as follows:[11] a mixture of **16** (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 (**17**) (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 **18** (0.68 g, 100%) as pale yellow oil: IR (neat): 1730 (C=O), 1345, 1157 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.26 (t, *J* = 7.2 Hz, 3H), 1.54-1.54 (br m, 3H), 1.85-1.91 (m, 2H), 2.40-2.41 (m, 5H), 3.21 (t, *J* = 6.6 Hz, 2H), 4.04-4.05 (br m, 2H), 4.14 (q, *J* = 7.3 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: 3.21, 14.2, 21.5, 22.7, 31.1, 36.8, 45.5, 60.5, 71.6, 81.6, 127.8 (2C), 129.2 (2C), 134.0, 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 (21)**

Alkynylation was carried out according to the reported method as follows:[12] to a mixture of **18** (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 a yellow liquid **19**. This crude material **19** 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 mixtute stirred at –78 ºC for 0.5 h to afford lithium trimethylsilylacetylene (**20**) solution, to which the solution of **19** 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 **21** (2.81 g, 90%) as colorless oil: IR (neat): 3511 (OH), 1736, 2170 (C≡C), 1345, 1158 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.17 (s, 9H), 1.53-1.54 (br m, 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), 4.06-4.07 (br m, 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, 79.9, 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 (22)**

To a mixture of **21** (4.48 g, 11.4 mmol) in dry THF (23 mL) at 0 ºC under argon was added *ca*. 1M TBAF in THF (11.5 mL, 11.4 mmol) dropwise and the mixtute 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 **22** (3.42 g, 94%) as pale amber oil: IR (neat): 3516 (OH), 3284 (C≡H), 2114 (C≡C), 1327, 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: 3.16. 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 (24)**

Et_3N (1.5 mL, 12.0 mmol) was added to a stirred mixture of **22** (0.97 g, 3.02 mmol), 2-iodoaniline (**23**) (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 **24** (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: 1.52-1.53 (br m, 3H), 1.78-1.90 (m, 4H), 2.40 (s, 3H), 2.49 (br s, 1H), 3.24 (t, *J* = 6.6 Hz, 2H), 4.06-4.06 (br m, 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: 3.18, 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 (25)**

According to the reported method, oxidation of **24** was conducted as follows:[13] a mixture of **24** (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 **25** (297 mg, 71%) as orange amber oil: IR (neat): 2180 (C≡C), 1658 (C=O), 1342 (S=O), 1330 (NH), 1156 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.53-1.54 (br m, 3H), 1.96-2.02 (m, 2H), 2.41 (s, 3H), 2.82 (t, *J* = 7.2 Hz, 2H), 3.22 (t, *J* = 6.6 Hz, 2H), 4.05-4.05 (m, 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: 3.18, 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*)-*N*-{6-(2-Aminophenyl)-4-[(triisopropylsilyl)oxy]hex-3-en-5-yn-1-yl}-*N*-(but-2-yn-1-yl)-4-methylbenzenesulfonamide and (*Z*)-*N*-{6-(2-Aminophenyl)-4-[(triisopropylsilyl)oxy]hex-3-en-5-yn-1-yl}-*N*-(but-2-yn-1-yl)-4-methylbenzenesulfonamide (13a)

TIPSOTf (0.9 mL, 3.24 mmol) was added dropwise to a mixture of **25** (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 mixtute stirred for 2 h. The mixture

allowed to warm slowly from –78 °C 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 **13a** (921 mg, 75%, *Z*/*E* = 85/15, determined by ^{1}H NMR).[5] Both products were isolated PTLC (silica gel) with hexane/EtOAc (10/1).

The *E*-isomer (less polar): 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 (tt, *J* = 14.9, 5.5 Hz, 3H), 1.50-1.51 (br m, 3H), 2.40 (s, 3H), 2.53 (dd, *J* = 15.2, 7.7 Hz, 2H), 3.21 (t, *J* = 7.4 Hz, 2H), 4.10-4.10 (br m, 2H), 4.27 (br s, 2H), 5.30 (t, *J* = 8.0 Hz, 1H), 6.68 (t, *J* = 8.0 Hz, 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.

The *Z*-isomer (more polar): 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), 1.51-1.58 (m, 3H), 2.41 (s, 3H), 2.47-2.53 (m, 2H), 3.22 (t, *J* = 7.4 Hz, 2H), 4.09-4.10 (br m, 2H), 4.19 (br s, 2H), 5.09 (t, *J* = 7.2 Hz, 1H), 6.68 (dd, *J* = 11.7, 4.3 Hz, 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, 62.3, 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.

(*E*)-*N*-{6-(2-Aminophenyl)-4-[(*tert*-butyldimethylsilyl)oxy]hex-3-en-5-yn-1-yl}-*N*-(but-2-yn-1-yl)-4-methylbenzenesulfonamide 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 (13b)

TBSOTf (0.2 mL, 0.81 mmol) was added dropwise to a mixture of **25** (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 mixtute 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 **13b** (171 mg, 81%, *Z*/*E* = 73/27, determined by ^{1}H NMR).[5] Both products were isolated PTLC (silica gel) with hexane/EtOAc (10/1).

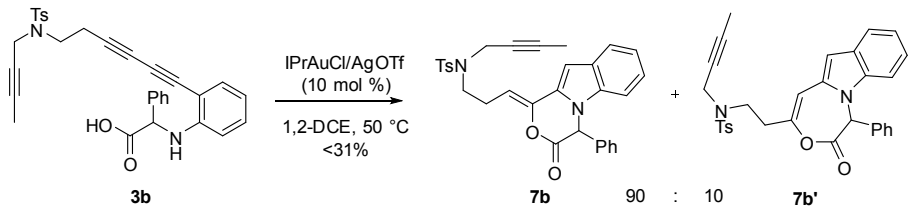
The *E*-isomer (less polar): reddish amber oil; IR (neat): 2193 (C≡C), 1616 (SiOC=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.23 (s, 6H), 0.96 (s, 9H), 1.51-1.51 (br m, 3H), 2.40 (s, 3H), 2.52 (q, *J* = 7.6 Hz, 2H), 3.22 (t, *J* = 7.4 Hz, 2H), 4.10-4.10 (br m, 2H), 4.27 (br s, 2H), 5.27 (t, *J* = 8.0 Hz, 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, 86.4, 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.

The *Z*-isomer (more polar): 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), 1.54-1.55 (br m, 3H), 2.41 (s, 3H), 2.45 (q, *J* = 7.3 Hz, 2H), 3.21 (t, *J* = 7.4 Hz, 2H), 4.09-4.09 (br m, 2H), 4.20 (br s, 2H), 5.13 (t, *J* = 7.2 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.

2. Gold(I)-Catalyzed Cascade Reactions of Conjugated Alkynes

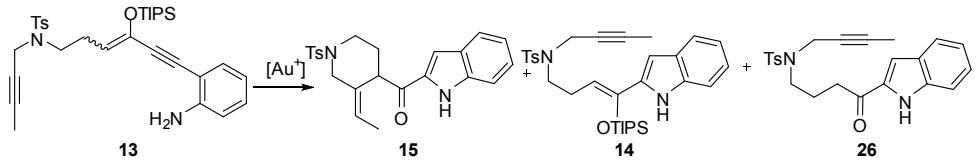
2-1. Reactions of Conjugated Diynes (Scheme 4)



(*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 (7b) and *N*-(But-2-yn-1-yl)-4-methyl-*N*-[2-(4-oxo-5-phenyl-4,5-dihydro-[1,4]oxazepino[4,5-*a*]indol-2-yl)ethyl]benzenesulfonamide (7b')

A screw-cap test tube was charged with **3b** (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 **7b**/**7b'** (16.3 mg, <31%, **7b**/**7b'** = 90/10, determined by ^{1}H NMR). **7b** was isolated PTLC (silica gel) with hexane/Et_2O (3/1): yellow oil; IR (neat): 2225 (C≡C), 1765 (C=O), 1345 (S=O), 1157 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.53-1.53 (br m, 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 (d, *J* = 8.6 Hz, 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), 123.4, 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.

2-2. Reactions of Conjugated Enyne (Table 1, Entry 2)



(*E*)-(3-Ethylidene-1-tosylpiperidin-4-yl)(1*H*-indol-2-yl)methanone ((±)-15)

A screw-cap test tube was charged with **13a** (293 mg, 0.52 mmol) 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 (±)-**15** (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), 2.04-2.18 (m, 2H), 2.44 (s, 3H), 2.86 (td, *J* = 12.2, 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 (dd, J = 6.3, 1.7 Hz, 2H), 7.70 (d, J = 7.4 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.

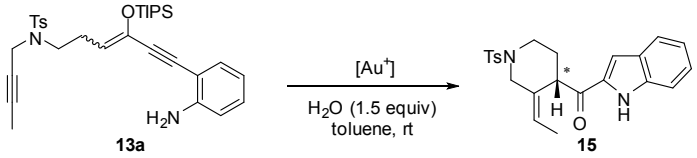
(*Z*)-*N*-{4-(1*H*-Indol-2-yl)-4-[(triisopropylsilyl)oxy]but-3-en-1-yl}-*N*-(but-2-yn-1-yl)-4-methylbenzenesulfonamide (14)[6]

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 (26)**

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: 1.52-1.52 (br m, 3H), 2.02-2.08 (m, 2H), 2.40 (s, 3H), 3.09 (t, J = 7.4 Hz, 2H), 3.31 (t, J = 6.9 Hz, 2H), 4.08-4.09 (br m, 2H), 7.14-7.16 (m, 1H), 7.24-7.29 (m, 3H), 7.31-7.35 (m, 1H), 7.43 (d, J = 8.6 Hz, 1H), 7.71-7.73 (m, 3H), 9.32 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 3.2, 21.4, 22.0, 34.9, 36.9, 45.8, 71.6, 81.6, 109.4, 112.1, 120.9, 123.1, 126.2, 127.5, 127.8 (2C), 129.2 (2C), 134.9, 135.8, 137.2, 143.2, 192.3; HRMS (FAB) calcd for $C_{23}H_{25}N_2O_3S$ (MH^+) 409.1586, found 409.1590.

2-3. Enantioselective Reactions of Conjugated Enyne (Table 2, Entry 3)



(*S*,*E*)-(3-Ethylidene-1-tosylpiperidin-4-yl)(1*H*-indol-2-yl)methanone (15)[7]

(*R*)-MeO-BIPHES(AuCl)$_2$ (8.8 mg, 5.4 μmol) and $AgSbF_6$ (3.7 mg, 0.01 mmol) was dissolved in toluene (0.1 mL) and stirred for 10 minutes at room temperature. A solution of the **13a** (56.5 mg, 0.1 mmol) in toluene was transferred to the catalyst mixture. The mixture was stirred at room temperature for 19 h. The mixture was concentrated and purified on silica gel (hexane/AcOEt = 5/1) to afford **15** as white amorphous [5.5 mg, 13% yield, 89% 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 = 12.68 min (major isomer), t_2 = 16.77 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), 2.06-2.08 (m, 1H), 2.14-2.17 (m, 1H), 2.42 (s, 3H), 2.87 (td, J = 12.3, 2.9 Hz, 1H), 3.45-3.47 (br m, 1H), 3.72-3.74 (br m, 1H), 4.10-4.12 (br m, 1H), 4.43-4.44 (br m, 1H), 5.72 (q, J = 6.9 Hz, 1H),

7.14-7.17 (m, 1H), 7.31-7.34 (m, 4H), 7.66 (d, J = 8.0 Hz, 2H), 7.70 (d, J = 8.0 Hz, 1H), 9.04 (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, 127.7 (2C), 129.6 (2C), 129.9, 133.4, 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 7)

Conolidine

According to the reported method, removal of the tosyl group was carried out as follows:[14] sodium (32.3 mg, 1.41 mmol) was added to a solution of naphthalene (225 mg, 1.76 mmol) in THF (2 mL) at room temperature and the mixture stirred for 1 h. The resulting dark green/blue solution (*ca.* 0.7 M in THF) was added dropwise to a solution of (±)-**15** (76.6 mg, 0.19 mmol) in THF (2 mL) at –78 °C until dark green/blue color persisted. Saturated aqueous $NaHCO_3$ was added and the solution allowed to warm slowly from –78 °C to room temperature. The aqueous layer was then extracted with CH_2Cl_2 and the organic layers were washed with brine, combined, dried over Na_2SO_4 and filtered. Concentration under reduced pressure, this crude material **1** was used for the next reaction without further purification.

According to the Bohn's procedure[2], the **1** was converted into (±)-conolidine as a white solid (6.9 mg, 13% in 2 steps): mp 180–190 °C; IR (neat): 3335 (NH), 1635 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.25 (t, J = 6.6 Hz, 2H), 1.42 (t, J = 15.2 Hz, 1H), 1.50 (t, J = 10.9 Hz, 3H), 1.98-2.08 (m, 1H), 2.10-2.18 (m, 1H), 3.06-3.13 (m, 1H), 3.33 (q, J = 8.4 Hz, 1H), 3.41 (ddd, J = 13.7, 8.3, 2.6 Hz, 1H), 3.86 (d, J = 16.0 Hz, 1H), 3.98 (d, J = 6.3 Hz, 1H), 4.29 (d, J = 18.3 Hz, 1H), 4.78 (t, J = 9.2 Hz, 1H), 5.45-5.50 (m, 1H), 7.11 (dq, J = 9.9, 2.5 Hz, 1H), 7.32-7.37 (m, 2H), 7.58 (t, J = 7.7 Hz, 1H), 9.12 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 12.7, 22.9, 44.2, 48.1, 53.3, 55.0, 111.8, 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 267.1493.

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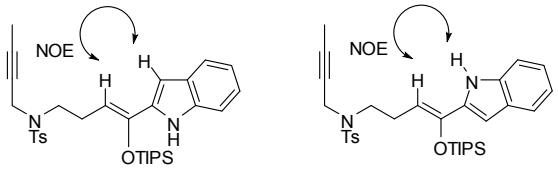
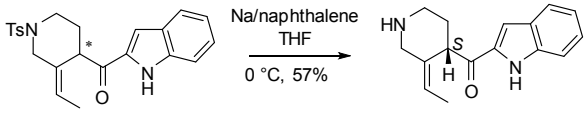
5. The geometries of **13a** and **13b** were determined according to the literature: (a) Reich, H. J.; Holtan, R. C.; Borkowsky, S. L. *J. Org. Chem*. **1987**, *52*, 312. (b) Reich, H. J.; Holtan, R. C.; Bolm, C. *J. Am. Chem. Soc.* **1990**, *112*, 5609.
6. The geometry of **14** was confirmed by an NOE experiment as shown below.



7. The absolute configuration of **15** was determined to be (*S*) by its conversion to the known amine **1**[2] as shown below.



15 (85% *ee*)

1 $[\alpha]^{28}_{D}$ = +41.0° (*c* = 0.26, MeOH)
lit. $[\alpha]^{25}_{D}$ = +45.0° (*c* = 0.24, MeOH)

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Chapter 3. Conclusions

1. The author has developed efficient methodologies for synthesis of 1,3-disubstituted naphthalenes and disubstituted chrysenes via a gold(I)-catalyzed cascade intermolecular addition-intramolecular carbocyclization reaction. It is noteworthy that the regioselectivity of the first intermolecular addition in this reaction could be completely controlled by using of terminal alkyne and internal alkyne.

2. An efficient method has been developed for the synthesis of fused indole from the conjugated diynes using a cationic gold catalyst. This reaction proceeds via 5-*endo*-*dig* indole formation and the subsequent 7-*endo*-*dig* cyclization, which is predominated over 6-*exo*-*dig* cyclization. The observed high 7-*endo*-selectivity is well rationalized by DFT calculations: oxazepino[4,5-*a*]indole ring formation proceeds through a more stable intermediate.

3. A total synthesis of conolidine has been achieved. The novel and convergent strategy used to achieve this synthesis was based on gold(I)-catalyzed cascade reactions. This study exhibited that the gold(I)-catalyzed cascade reaction is effective for construction of stemmadenine-type scaffold.

In summary, the author has achieved the development of novel gold(I)-catalyzed cascade reactions for the synthesis of fused-ring compounds. These reactions are featured by the construction of fused-ring scaffolds from linear structure such as alkynes or conjugated alkynes. The author has also demonstrated that these strategies were applicable to total synthesis of natural products such as conolidine.

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List of Publications

This study was and will be published in the following papers.

Chapter 1. Gold(I)-Catalyzed Regioselective Inter-/Intramolecular Addition Cascade of Di- and Triynes for Direct Construction of Substituted Naphthalenes
Saori Naoe, Yamato Suzuki, Kimio Hirano, Yusuke Inaba, Shinya Oishi, Nobutaka Fujii, and Hiroaki Ohno
J. Org. Chem. **2012**, *77*, 4907−4916

Chapter 2.

Section 1. Direct Construction of Fused Indoles by Gold-Catalyzed Cascade Cyclization of Conjugated Diynes
Saori Naoe, Tatsuo Saito, Masanobu Uchiyama, Shinya Oishi, Nobutaka Fujii, and Hiroaki Ohno
Org. Lett. **2015***, 17,* 1774−1777

Section 2. Total Synthesis of Conolidine by Gold-Catalyzed Cascade Cyclization of Conjugated Enyne
Saori Naoe, Shinya Oishi, Nobutaka Fujii, and Hiroaki Ohno
Manuscript in preparation.