

Synthesis of Heterocyclic Scaffolds through Transition-Metal-Catalyzed Cascade Reactions of Alkynes

Thesis Presented for
the Degree of Doctor of Kyoto University
(Pharmaceutical Sciences)

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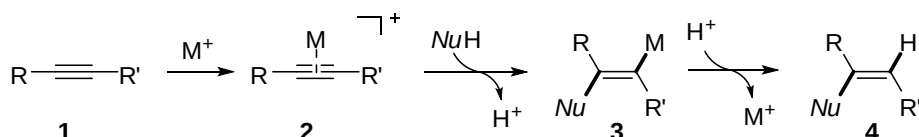
Contents

	Page
Preface	1
Chapter 1.	Synthesis of Nitrogen-Containing Heterocycles through the Cyclization of Ynamides
Section 1.	Direct Synthesis of Quinazolines through Copper-Catalyzed Reaction of Aniline-Derived Benzamidines 8
Section 2.	Gold-Catalyzed Cascade Cyclization of (Azido)ynamides: an Efficient Strategy for the Construction of Indoloquinolines 24
Section 3.	Gold-Catalyzed Cyclization of <i>N</i> -Propargyl Ynamides: a Novel Synthesis of Bicyclic Pyrroles 49
Chapter 2.	Gold-Catalyzed Cascade Cyclization of 2-Alkynylanilines via the Rearrangement of a Propargyl Group 71
Chapter 3.	Conclusions 85
Acknowledgements	86
List of Publications	87

Preface

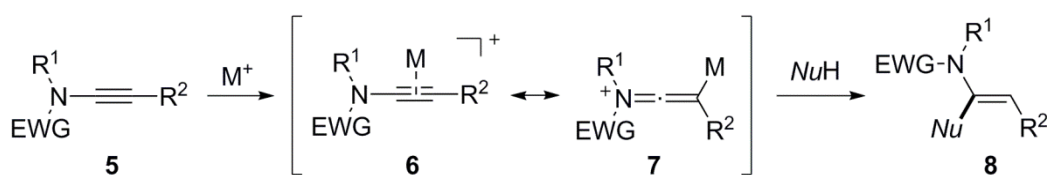
Heterocyclic scaffolds are found in various biologically active natural products and synthetic pharmaceuticals. Although numerous efficient strategies have been developed for the synthesis of a wide range of heterocyclic scaffolds, the development of new approaches is still needed to provide improved atom and step economy. With this in mind, the research described in this thesis has focus predominantly on the use of alkynes as building blocks for the construction of heterocyclic scaffolds.¹ Alkynes can be easily activated with a variety of different Brønsted and Lewis acids, including halogens and transition-metal complexes.^{1b,c} Among these acids, cationic transition-metal complexes represent particularly attractive activating agents because they can selectively activate π -bonds under mild conditions.^{1a,e} This mode of reactivity is therefore useful for the catalytic construction of complex compounds from readily available substrates.

The mechanism for transition-metal-catalyzed addition of a nucleophile to an alkyne is shown in Scheme 1. The coordination of alkyne **1** to a cationic transition-metal complex gives intermediate **2**, which makes the alkyne electrophilic and therefore promotes the addition of a nucleophile to the alkyne bond. Subsequent protodemetalation of the resulting vinyl-metal intermediate **3** then regenerates the cationic transition-metal species to give alkene **4**. Various nucleophiles can be used for this reaction, including alcohols, amines, amides, thiols, arenes, alkenes and alkynes.



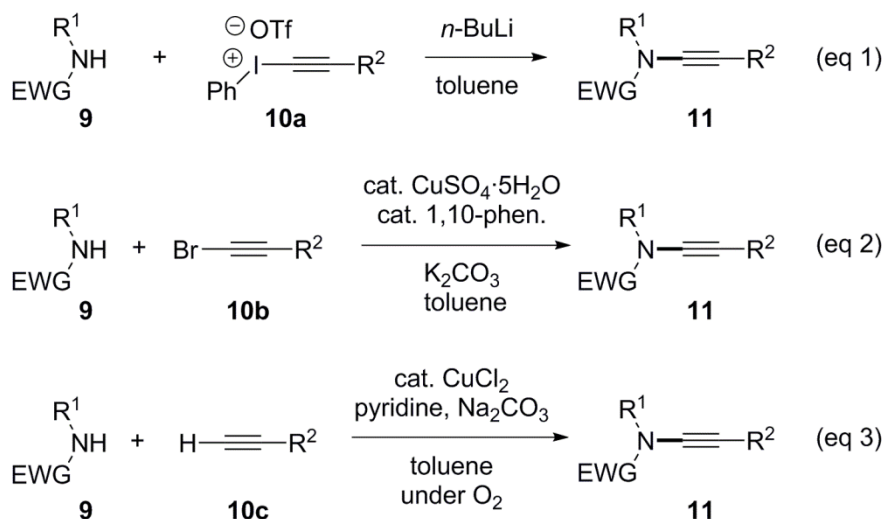
Scheme 1. Cationic Transition-Metal-Catalyzed Nucleophilic Addition to Alkynes

Ynamides are a type of alkyne, which contain a nitrogen atom directly attached to the triple bond. Ynamides are much more reactive and more strongly polarized than simple alkynes because of the electron-donating ability of their nitrogen atom.² The activation of ynamide **5** with an acid enhances the electrophilicity of the alkyne carbon atom directly attached to its nitrogen atom (i.e., α -carbon), which leads to the regioselective addition of a nucleophile to give a keteniminium intermediate **7** (Scheme 2).

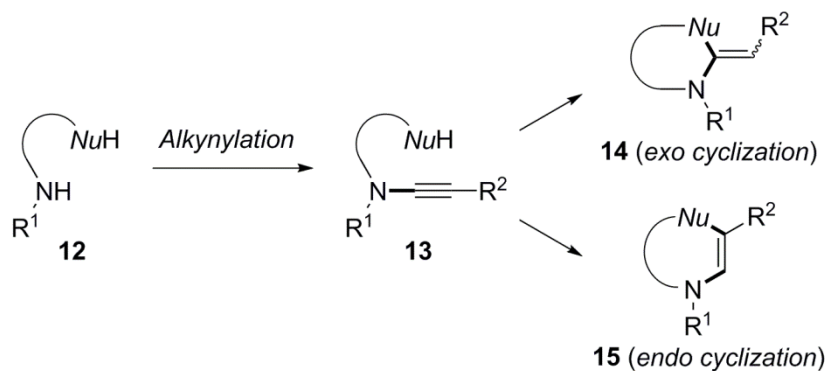


Scheme 2. General Reactivity of Ynamides with Nucleophiles under Acidic Conditions

Three notable methods are available for the synthesis of ynamides from N–H amides. As part of his pioneering work towards the synthesis of ynamides, Stang reported that the alkynyl iodonium salt **10a** was a useful reagent for the alkynylation of amide **9** to give ynamide **11** (Scheme 3, eq 1).^{3a} However, the application of this reaction has been limited by its requirement for the preparation of the unstable alkynyl iodonium salt **10a**. In 2003, Hsung developed a reliable method for the synthesis of ynamide **11** (eq 2),^{3b} where alkynyl bromide **10b** was used as an alkyne source in a copper-catalyzed amidative cross-coupling reaction with **9**. This reaction can be used to provide access to a variety of ynamides under highly concentrated conditions (*ca.* 1.0 M) and high temperatures (65–75 °C). An alternative and rather elegant method for the synthesis of ynamide **11** was reported by Stahl, which involved the oxidative amidation of terminal alkyne **10c** based on C–H and N–H coupling reactions (eq 3).^{3c} Notably, the use of five equivalents of amide **9** under an oxygen atmosphere allowed for simple alkynes to easily undergo the oxidative coupling reaction to produce ynamide **11**.



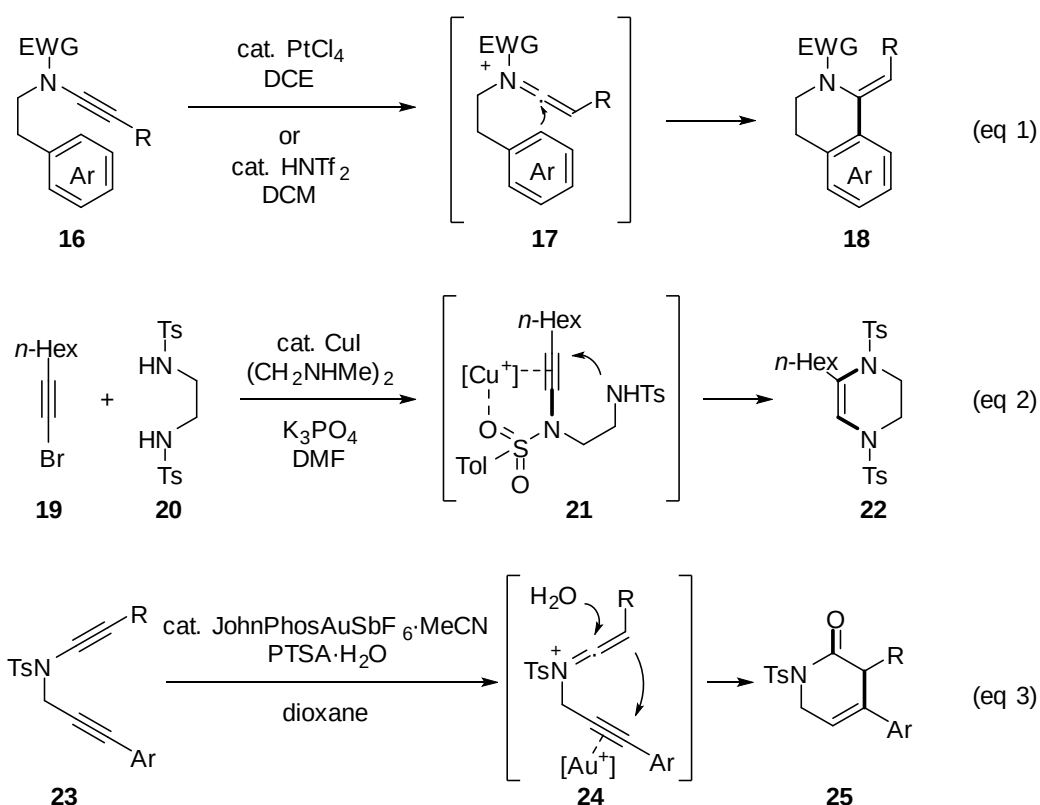
Scheme 3. Reported Methods for the Synthesis of Ynamides



Scheme 4. Easy Method for the Syntheses of Nitrogen-Containing Heterocyclic Compounds

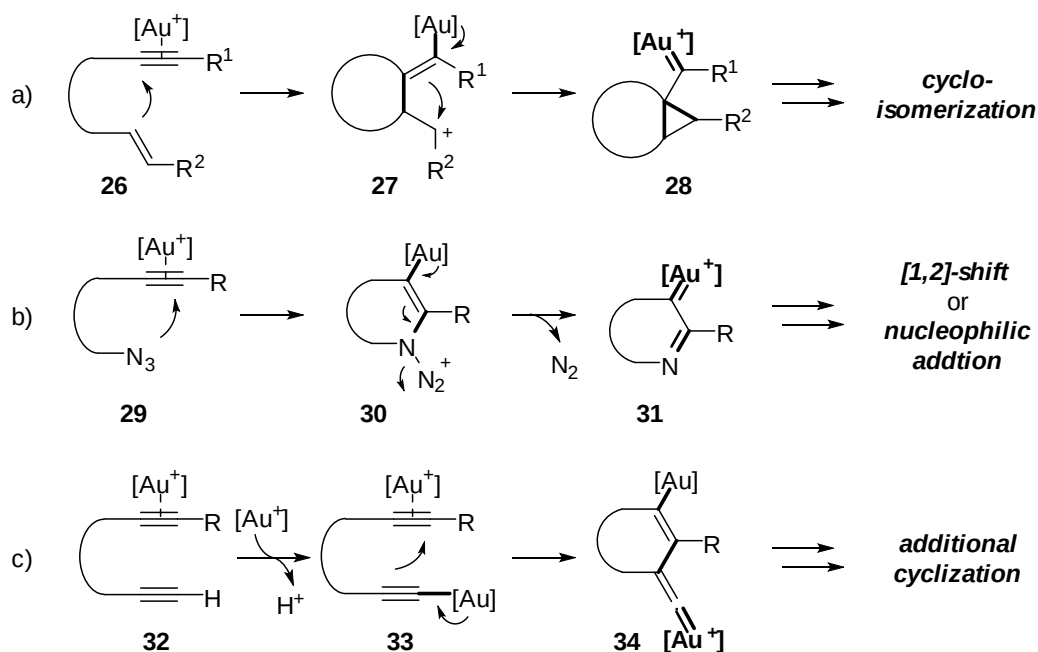
Ynamides are highly valuable building blocks for the construction of nitrogen-containing heterocycles. Ynamide molecules bearing a nucleophilic group on their nitrogen atom can be used to prepare nitrogen-containing heterocycles by addition-type cyclization reaction (Scheme 4). For examples, the *exo* and *endo* cyclization reactions of ynamide **13** would give the corresponding heterocyclic products **14** and **15**, respectively.

Various novel transformations of ynamides have been developed.^{2,4} In 2005, Hsung reported the acid-catalyzed Pictet-Spengler-type cyclization of ynamide **16** (Scheme 5, eq 1).^{5a} The activation of ynamide **16** with a catalytic amount of PtCl₄ or HNTf₂ led to the formation of keteniminium intermediate **17**, which underwent a cycloaddition from the internal arene to give heterocyclic compound **18**. In addition to ynamides bearing aryl groups, sulfonamides such as **20** can also be used as internal nucleophiles towards ynamides. In 2008, Urabe reported a one-pot alkynylation-hydroamination strategy for the synthesis of tetrahydropyrazine **22** (eq 2).^{5b} In this case, the reaction of alkynyl bromide **19** with *N,N'*-ditosylethylenediamine led to the formation of ynamide **21**, which underwent an intramolecular nucleophilic addition with the sulfonamide moiety through a 6-*endo-dig* pathway to give the tetrahydropyrazine **22**. The unusual regioselectivity of this hydroamination (**21** → **22**) most likely occurred as a consequence of the chelation of the copper complex to the sulfonylamino group. In 2013, the hydrative cyclization of *N*-propargyl ynamide was demonstrated by Sahoo (eq 3).^{5c} In this particular study, *N*-propargyl ynamide **23** was converted to dihydropyridinone **25** using a cationic Au complex and PTSA. This transformation occurred via the hydration of ynamide **24**, followed by an intramolecular cyclization towards the other alkyne moiety.



Scheme 5. Construction of Heterocyclic Scaffolds via Cyclization of Ynamides

Currently, there is a growing demand for the development of atom economical, cost and time efficient reactions that also satisfy the principles of green chemistry,⁶ and cascade reactions represent one of the most promising approaches for achieving these goals.^{6b} Reactions of this type avoid the need for the isolation of reaction intermediates and allow for the formation of multiple chemical bonds, and the construction of complex molecules in a single step. Recent progress in the field of gold-catalyzed chemistry has led to the development of new methods involving the combination of nucleophilic cyclization with other transformations.⁷ As shown above in Scheme 1, the cationic gold-catalyzed addition of a nucleophile to an alkyne would lead to a vinylgold intermediate. This electron rich species could generate a gold carbenoid species if an appropriate electrophilic centre or leaving group was present in the molecule.⁸ For example, a gold carbenoid was observed as an intermediate in the cyclization of 1,6-enyne **26** (Scheme 6a).⁹ In this reaction, the activated alkyne is attacked by an alkene, and the resulting cation, which is generated at the other carbon derived from the alkene (intermediate **27**), is trapped by the nucleophilic vinylgold species to form the gold carbenoid **28**. In a further example, azide **29** could be used to generate the imine-conjugated gold carbenoid **31** (Scheme 6b).¹⁰ In this case, the expulsion of N₂ gas from intermediate **30** would be the driving force for this transformation. Gold acetylide is another important organogold species that can also function as a precursor of gold carbenoid. For example, the intramolecular nucleophilic cyclization of gold acetylide **33** onto the other alkyne moiety present in the molecule would generate the gold vinylidene **34** (Scheme 6c).¹¹ Gold carbenoids and vinylidenes generated in this way are highly electrophilic and therefore capable of undergoing further reactions with internal or external nucleophiles. In this particular thesis, the research has focused on the potential utility of this chemistry for the constructions of complex nitrogen heterocycles.



Scheme 6. Formation of Gold Carbenoids and Gold Vinylidenes

In this thesis, several novel strategies have been developed for the synthesis of heterocyclic scaffolds using transition-metal-catalyzed alkyne cyclization reactions. Notably, multiple chemical bonds formations were achieved in a single step in all the developed reactions.

The transformations of ynamides have been described in detail in Chapter 1. Several nitrogen-containing heterocyclic compounds can be efficiently synthesized using these transformations.

The direct synthesis of quinazolines via the copper-catalyzed *N*-alkynylation of benzamidines with ethynylbenziodoxolone has been described in Section 1 of Chapter 1. An aerobic oxidation strategy using terminal alkyne has also been investigated.

An efficient strategy for the construction of indoloquinolines by the gold-catalyzed cascade reaction of (azido)ynamides has been described in Section 2 of Chapter 1.

Section 3 of Chapter 1 describes a novel strategy for the synthesis of bicyclic and tricyclic pyrroles by the gold-catalyzed reaction of *N*-propargyl ynamides.

Chapter 2 describes a cascade cyclization reaction, including a propargyl rearrangement step, where a gold-catalyzed fused indoline synthesis from *o*-alkynyl-*N*-propargylaniline results in the formation of four bonds and three rings.

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Chapter 1. Synthesis of Nitrogen-Containing Heterocycles through the Cyclization of Ynamides

Section 1. Direct Synthesis of Quinazolines through Copper-Catalyzed Reaction of Aniline-Derived Benzamidines

Summary

A novel synthesis of 2-phenyl-4-[(triisopropylsilyl)methyl]quinazolines from mono-substituted arenes has been developed. Treatment of *N*-phenylbenzamidines with 5-nitro-1-[(triisopropylsilyl)ethynyl]-1 λ^3 -benzo[d][1,2]iodaoxol-3(1H)-one and K₂CO₃ in the presence of a catalytic amount of CuBr in benzene gives 2-phenyl-4-[(triisopropylsilyl)methyl]quinazolines in moderate to good yields. The desired quinazolines can be also synthesized by the aerobic oxidation using terminal alkyne and oxygen.

Many biologically active compounds contain the quinazoline motif, including the potent anti-lung cancer agent, gefitinib,¹ and the α -adrenergic blocker, prazosin.² Most of the synthetic routes to quinazolines depend on the use of anilines bearing an *ortho*-functional group.³ This limitation prompted the author to develop a direct synthesis of these compounds from *ortho*-unfunctionalized aniline derivatives.

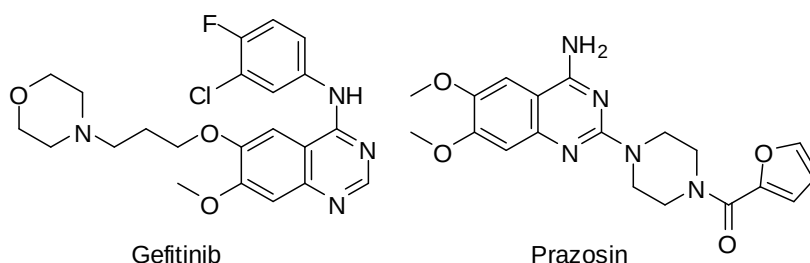
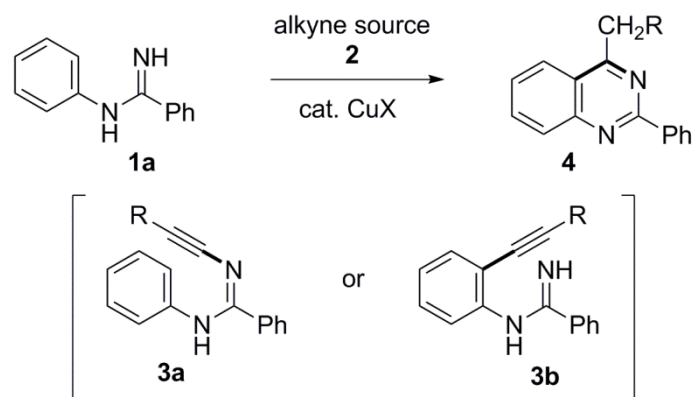


Figure 1. Drugs Containing a Quinazoline Motif.

As described in preface, ynamides can be synthesized by the coupling of N–H amides with appropriate alkyne sources. The author postulated if amidine group in *N*-phenylbenzamidine **1a** functions as an ynamide precursor, quinazoline **4** could be obtained via tautomerization–electrocyclization cascade⁴ (Scheme 1). Otherwise, aromatic C–H alkynylation^{5–10} of amidine **1a** might promote to generate the same quinazoline **4** through the nucleophilic cyclization of **3b**. The challenges of this strategy include predominant alkyne introduction over benzimidazole formation,¹¹ and regioselective alkynylation and cyclization¹² in the presence of two nitrogen atoms.



Scheme 1. Direct Synthesis of Quinazoline through Copper-Catalyzed Alkynylation and Cyclization

The author initially explored appropriate conditions for the synthesis of quinazoline **4**. When *N*-phenylbenzamidines **1a** was reacted with 2-(triisopropylsilyl)ethynyl bromide **2a** in the presence of Cu(OAc)₂ (20 mol %) and K₂CO₃ (1 equiv) in toluene, the desired quinazoline **4a** was obtained in 16% yield (Table 1, entry 1). After the screening of various series of copper (I and II) salts (entries 2–6) and solvents (entries 7–11), the highest yield of **4a** was obtained by use of CuBr in benzene (47%, entry 11).

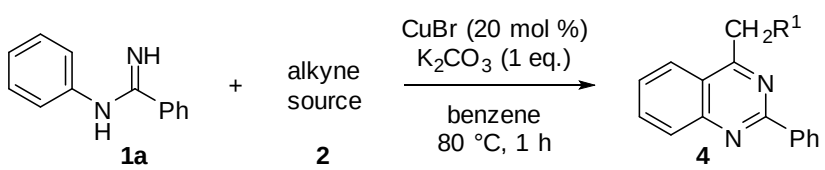
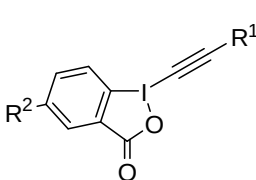
Table 1. Optimization of Reaction Conditions

entry	Cu catalyst	solvent	yield (%) ^a
1	Cu(OAc) ₂	toluene	16
2	CuBr ₂	toluene	NR ^b
3	CuOAc	toluene	5
4	CuI	toluene	19
5	CuCl	toluene	7
6	CuBr	toluene	38
7	CuBr	xylene	34
8	CuBr	DCE	24
9	CuBr	DMF	5
10	CuBr	dioxane	trace
11	CuBr	benzene	47

^a Isolated yields. ^b NR = no reaction.

Next, the author explored other alkyne sources. Although alkynyl iodonium salt **2b** led to the decomposition of amidine **1a** (Table 2, entry 1), TIPS-ethynylbenziodoxolone (TIPS-EBX) **2c**¹⁰ provided the desired quinazoline **4a** in 41% yield (entry 2). On the other hand, TMS-EBX **2d** did not produce the desired quinazoline (entry 3). The same result was obtained when Ph-EBX **2e** and *t*-Bu-EBX **2f** were used (entries 4 and 5). These results prompted the author's investigation of an appropriate substituent on the aryl ring of **2c**. Both TIPS-EBX **2g** and **2h** increased the yield of **4a** with some impurities (entries 6 and 7). TIPS-EBX **2i** showed a clear conversion to **4a** in 44–61% yield (entry 8). With the addition of MS4Å this direct synthesis of quinazoline was a reproducible reaction (entry 9).

Table 2. Investigation of Alkyne Sources

					
entry	alkyne source	R ¹	R ²	yield (%) ^a	
1	TIPS $\text{---}\equiv\text{---}\text{I}^+\text{Ph} \text{ } ^-\text{OTf}$	2b	-	-	0
2		2c	TIPS	H	41
3		2d	TMS	H	0
4		2e	Ph	H	0
5		2f	<i>t</i> -Bu	H	0
6		2g	TIPS	Me	< 61
7		2h	TIPS	F	< 61
8		2i	TIPS	NO ₂	44–61
9 ^b		2i	TIPS	NO ₂	62

^a Isolated yields. ^b MS4Å was added.

Having established the reaction conditions (Table 2, entry 9), the author examined the substrate scope of this reaction using substituted *N*-phenylbenzamidines **1b–n** (Table 3). These can be readily prepared by Lewis acid-mediated addition of anilines to benzonitrile. The reactions using amidines **1b–e**, which were derived from anilines containing a halogen atom at the 4-position, gave the corresponding 6-fluoro, chloro, bromo, and iodoquinazolines **4b–e** in moderate yields (entries 1–4). Amidines substituted with an electron-donating methyl, methoxy, or *t*-butyl group at the 4-position of the aryl ring were found to be good reaction components and provided the quinazolines **4f–h** in 60–67% yields (entries 5–7). Substitution at the *meta* position was investigated using amidine **1i** and

1j. The reaction of **1i** gave a mixture of 5-bromo- and 7-bromoquinazoline derivatives **4i**, which shows the reaction proceeds with moderate regioselectivity (48%, 1:3.7, entry 8). The use of amidine **1j** resulted in the highest yield of the desired 5-methoxy- and 7-methoxyquinazolines **4j** without regioselectivity (77%, 1:1.25, entry 9). The amidine **1k** bearing *t*-butyl group did not give any of the desired products (entry 10). Quinazolines **4l** and **4m** with a substituted arene at the 2-position were produced in 50% and 61% yield, respectively (entries 11 and 12). This reaction is applicable to the synthesis of 2-(heteroaryl)quinazolines. For example, amidine **1n** was allowed to give 2-(thiophen-2-yl)quinazoline **4n** in 46% yield (entry 13). In all cases, benzimidazole formation was not observed.

Table 3. Reactions of Various *N*-Phenylbenzamidines.

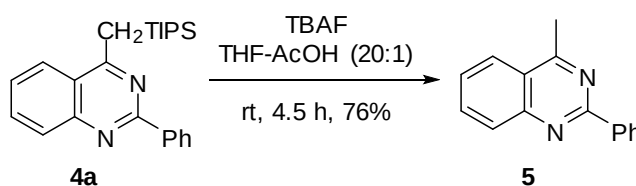
entry		substrate		yield (%) ^a
		R ¹	R ²	
1	1b	4-F	Ph	52
2	1c	4-Cl	Ph	46
3	1d	4-Br	Ph	49
4	1e	4-I	Ph	57
5	1f	4-Me	Ph	60
6	1g	4-OMe	Ph	61
7	1h	4- <i>t</i> -Bu	Ph	67
8	1i	3-Br	Ph	48 ^b
9	1j	3-OMe	Ph	77 ^c
10	1k	H	<i>t</i> -Bu	0
11	1l	H	4-(CF ₃)C ₆ H ₄	50
12	1m	H	4-(OMe)C ₆ H ₄	61
13	1n	H	thiophen-2-yl	46

^a Isolated yields. ^b 3.7:1 mixture of 7- and 5-bromoquinazolines.

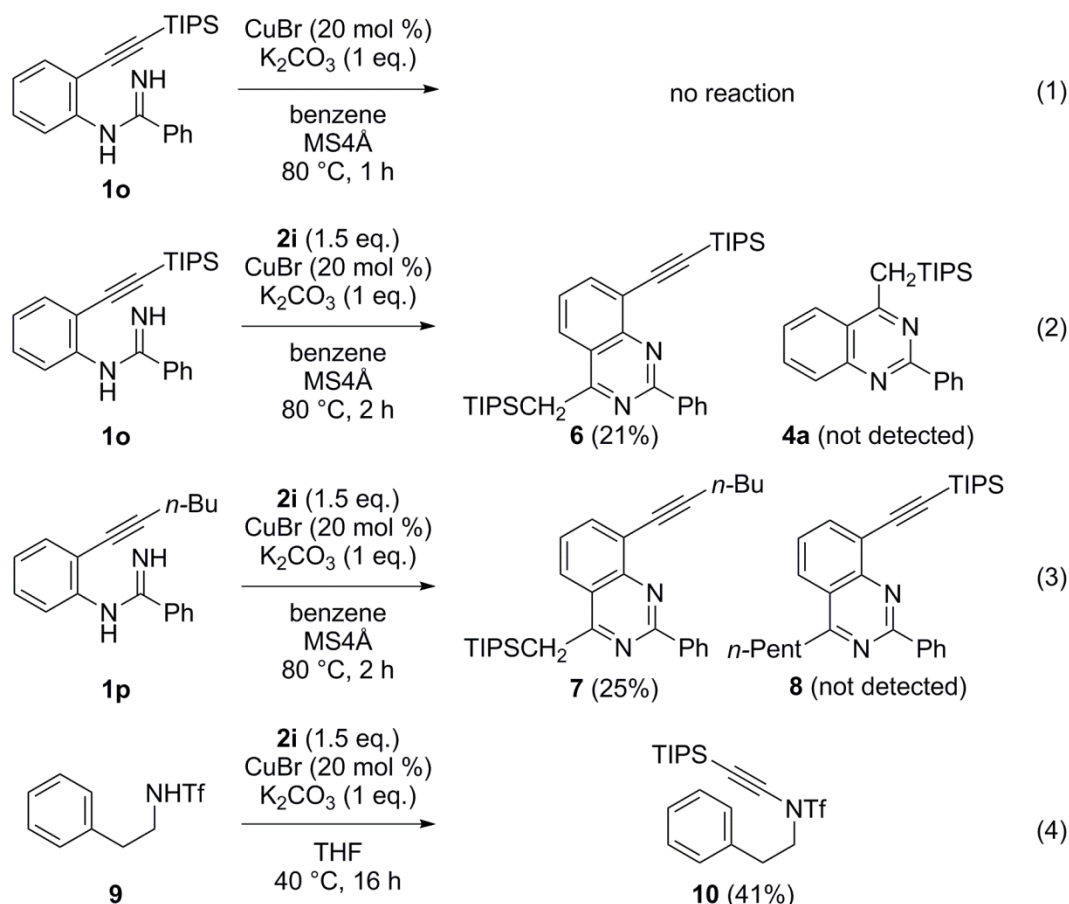
^c 1.25:1 mixture of 7- and 5-methoxyquinazolines.

The known quinazoline **5**¹³ could be obtained under desilylation conditions of silyl groups. The

reaction of the resulting quinalzoline **4a** with TBAF in THF–AcOH (20:1) at room temperature led to efficient cleavage of the TIPS group to give **5** in 76% yield (Scheme 2).



Scheme 2. Removal of TIPS Group

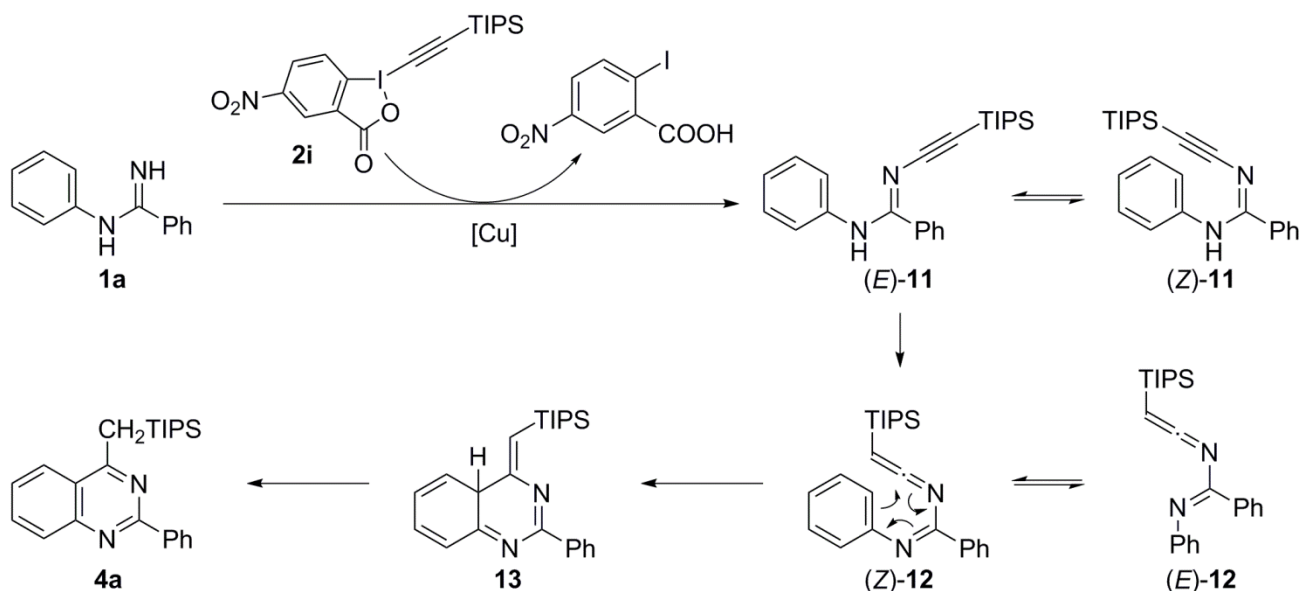


Scheme 3. Investigation for Determination of the Reaction Mechanism

To gain the insight of the reaction mechanism, the author conducted the reactions in Scheme 3. As shown in Scheme 1, there are two possible pathways to give quinalzoline **4**: N–H alkynylation and C–H alkynylation of *N*-phenylbenzamidines. The treatment with CuBr did not promote the cyclization of *o*-alkynylated benzamidine **1o** (eq 1), which is thought to be the intermediate in the C–H alkynylation pathway. On the other hand, the addition of TIPS-EBX **2i** led to cyclization of **1o** at the other *ortho*-position to give quinalzoline **6** without the formation of **4a** (eq 2). A similar result was observed in the reaction of benzamidine **1p** (eq 3). In this case, the cyclization of amidine took

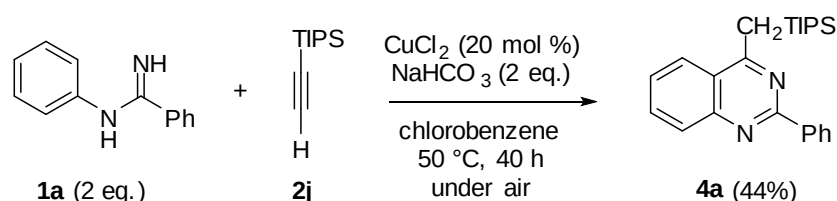
place only with TIPS acetylene and no detectable amount of **8** was formed. These experiments suggested that the reaction proceeds through the N–H alkynylation pathway, not through the C–H alkynylation pathway. The result that TIPS-EBX **2i** can be used as the alkynylation agent for trifluoromethanesulfonamide **9** (eq 4), also supports the N–H alkynylation of *N*-phenylbenzamidines being the first step of the quinazoline formation.

A plausible reaction mechanism is proposed in Scheme 4. First, amidine **1a** is transformed into ynamidine **11** by the reaction with TIPS-EBX **2i** in the presence of copper catalyst. Ynamidine **11** is then isomerized to kenenimine **12** and the *Z*-isomer of **12** affords the electrocyclic reaction. Finally, aromatization of **13** generates the quinazoline **4a**. At present, it can not be ruled out the alternative pathway that the *Z*-isomer of ynamidine **11** is converted to the quinazoline **4a** via the nucleophilic cyclization from the *ortho*-position of aniline to the ynamidine.



Scheme 4. A Plausible Reaction Mechanism

In light of Stahl's oxidative ynamide formation,¹⁴ the author finally examined the oxidative coupling reaction using terminal alkyne (Scheme 5). After considerable experimentation using various copper salts, solvents, bases, and oxidants, the desired quinazoline **4a** was obtained in a moderate yield (44%) under the aerobic conditions using CuCl₂ and NaHCO₃ in benzene.



Scheme 5. Application of Oxidative Ynamide Formation to the Synthesis of Quinazoline

In conclusion, the author developed a novel synthesis of quinazolines through copper-catalyzed alkynylation and cyclization of *N*-phenylbenzamidines. The reaction would proceed through the N–H alkynylation of *N*-phenylbenzamidine with TIPS-EBX. In combination with the oxidative coupling conditions, terminal alkyne can be used in this reaction. This reaction is synthetically useful since functionalized quinazolines can be directly constructed from *ortho*-unsubstituted amidines, readily prepared from commercially available anilines.

Experimental Section

General Methods. IR spectra were obtained on a JASCO FT/IR-4100 spectrometer. Exact mass (HRMS) spectra were recorded on JMS-HX/HX 110A mass spectrometer (FAB) or Shimadzu LC-ESI-IT-TOF-MS equipment (ESI). ^1H NMR spectra were recorded using a JEOL AL-500 spectrometer at 500 MHz frequency. Chemical shifts are reported in δ (ppm) relative to Me_4Si (in CDCl_3) as internal standard. ^{13}C NMR spectra were recorded using a JEOL AL-500 and referenced to the residual CHCl_3 signal. Melting points were measured by a hot stage melting points apparatus (uncorrected). For column chromatography, Wakosil C-300 or Merck Aluminum oxide 90 standardized was employed.

The known compounds **1b**,¹⁵ **1c**,¹⁶ **1d**,¹⁷ **1e**,¹⁸ **1f**,¹⁹ **1g**,¹⁹ **1j**,²⁰ **1k**,²¹ **1m**,¹⁹ **1n**,²² **2a**,²³ **2b**,²⁴ **2c-f**,²⁵ and **9**²⁶ were prepared according to the literatures.

1. Synthesis of Amidine.

***N*-(4-*tert*-Butylphenyl)benzamidine (1h)**

A mixture of 4-(*t*-butyl)aniline (1.85 mL, 11.6 mmol), benzonitrile (1.00 g, 9.70 mmol), and AlCl_3 (1.27 g, 9.70 mmol) in a pressure flask was reacted at 120 °C for 45 min, and then taken out of the oil bath. Ice water was added to the vigorously stirred hot mixture. After aqueous saturated NaOH was added to this mixture until the pH reached 14, it was extracted with CHCl_3 (3 times). The extract was dried over MgSO_4 and concentrated under reduced pressure. The residue was recrystallized from CHCl_3 –hexane to give pure **1h** (1.79 g, 71% from benzonitrile): colorless silky needles; mp 174–176 °C; ^1H NMR (500 MHz, CDCl_3) δ 1.33 (s, 9H), 4.85 (br s, 2H), 6.92 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.41–7.47 (m, 3H), 7.87 (d, J = 6.3 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 31.5 (3C), 34.2, 121.0 (2C), 126.3 (2C), 126.7 (2C), 128.5 (2C), 130.4, 136.0, 145.6, 147.0, 154.6; *Anal.* Calcd for $\text{C}_{17}\text{H}_{20}\text{BrN}_2$: C, 80.91; H, 7.99; N, 11.10. Found: C, 81.00; H, 7.93; N, 11.03.

***N*-(3-Bromophenyl)benzamidine (1i)**

By a procedure described for the preparation of amidine **1h**, benzonitrile (1.00 g, 9.70 mmol) was converted into **1i** (1.24 g, 47% from benzonitrile) by the reaction with 3-bromoaniline (1.27 mL, 11.6 mmol): colorless prisms; mp 123–125 °C; ^1H NMR (500 MHz, CDCl_3) δ 4.90 (br s, 2H), 6.90 (d, J = 6.9 Hz, 1H), 7.15–7.22 (m, 3H), 7.42–7.50 (m, 3H), 7.82 (d, J = 5.7 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 120.5, 123.0, 124.7, 126.0, 126.8 (2C), 128.6 (2C), 130.81, 130.83, 135.3, 151.2, 155.2; *Anal.* Calcd for $\text{C}_{13}\text{H}_{11}\text{BrN}_2$: C, 56.75; H, 4.03; N, 10.18. Found: C, 56.75; H, 4.06; N, 10.10.

***N*-Phenyl-4-(trifluoromethyl)benzamidine (1l)**

By a procedure described for the preparation of amidine **1h**, 4-(trifluoromethyl)benzonitrile (1.30 mL, 9.70 mmol) was converted into **1l** (1.24 g, 48% from 4-(trifluoromethyl)benzonitrile) by the reaction with aniline (1.06 mL, 11.6 mmol): colorless plates; mp 157–159 °C; ^1H NMR (500 MHz, CDCl_3) δ 4.89 (br s, 2H), 6.98 (d, J = 7.4 Hz, 2H), 7.09 (t, J = 7.4 Hz, 1H), 7.37 (dd, J = 7.4, 7.4 Hz, 2H), 7.70 (d, J = 8.0 Hz, 2H), 7.99 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 121.3 (2C), 122.8, 123.8 (q, J = 272.3 Hz), 125.5 (q, J = 3.6 Hz, 2C), 127.2 (2C), 129.6 (2C), 132.4 (q, J = 32.4 Hz), 139.2, 149.3, 153.3; *Anal.* Calcd for $\text{C}_{14}\text{H}_{11}\text{F}_3\text{N}_2$: C, 66.63; H, 4.20; N, 10.60. Found: C, 63.38; H, 4.17; N, 10.56.

***N*-{2-[(Triisopropylsilyl)ethynyl]phenyl}benzimidamide (1o)**

To a solution of 2-[(triisopropylsilyl)ethynyl]aniline (500 mg, 1.83 mmol) in toluene (17 mL), trimethylaluminum (2 M in toluene, 1.55 μ L, 3.11 mmol) was added dropwise at 0 °C under argon. The reaction mixture was warmed to room temperature and stirred for 3 h. A solution of benzonitrile (283 mg, 2.74 mmol) in toluene (8 mL) was added to the mixture, and the resulting mixture was warmed to 100 °C for 10 h. The solution was cooled and poured into a slurry of silica gel (6.0 g) in the solution of CHCl_3 (60 mL) and CH_3OH (30 mL). The silica gel was filtered off and washed with a solution of $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ (2:1). The combined filtrates were concentrated under reduced pressure and the residue was purified by column chromatography over alumina with hexane–EtOAc (15:1) to give **1o** (437 mg, 63%): colorless solid; mp 66 °C; IR (neat) 3451 (NH), 2231 ($\text{C}\equiv\text{C}$) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 0.96–1.05 (m, 21H), 4.75 (brs, 2H), 6.95–7.01 (m, 2H), 7.28–7.31 (m, 1H), 7.40–7.53 (m, 4H), 7.01–7.92 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 11.2 (3C), 18.6 (6C), 93.6, 104.6, 115.4, 121.9, 122.6, 126.9 (2C), 128.2 (2C), 129.6, 130.5, 133.8, 135.3, 151.8, 154.1; *Anal.* Calcd for $\text{C}_{24}\text{H}_{32}\text{N}_2\text{Si}$: C, 76.54; H, 8.56; N, 7.44. Found: C, 76.38; H, 8.52; N, 7.45.

***N*-[2-(Hex-1-yn-1-yl)phenyl]benzimidamide (1p)**

By a procedure described for the preparation of amidine **1o**, 2-(hex-1-yn-1-yl)aniline (300 mg, 1.73 mmol) was converted into **1p** (237 mg, 50%): a pale yellow solid; mp 80 °C; IR (neat) 3457 (NH), 2156 ($\text{C}\equiv\text{C}$) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 0.77 (t, J = 7.2 Hz, 3H), 1.31–1.38 (m, 2H), 1.43–1.46 (m, 2H), 2.35 (t, J = 6.6 Hz, 2H), 4.74 (brs, 2H), 6.97–7.05 (m, 2H), 7.24–7.27 (m, 1H), 7.41–7.49 (m, 4H), 7.86–7.94 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 13.5, 19.2, 21.8, 30.8, 77.9, 93.7, 115.7, 121.5, 122.6, 126.8 (2C), 128.4 (2C), 128.6, 130.4, 132.7, 135.8, 151.1, 154.5; *Anal.* Calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2$: C, 82.57; H, 7.29; N, 10.14. Found: C, 82.49; H, 7.46; N, 9.96.

2. Synthesis of ethynylbenziodoxolone (EBX).

5-Methyl -1-[(triisopropylsilyl)ethynyl]-1 λ^3 -benzo[d][1,2]iodaoxol-3(1H)-one (2g)

To the stirred suspension of 5-methyl-2-iodosylbenzoic acid (1.05 g, 3.79 mmol) in CH_3CN was added dropwise trimethylsilyl triflate (0.75 mL, 4.17 mmol) at room temperature under argon. After (trimethylsilyl)(triisopropylsilyl)acetylene (1.06 mL, 4.17 mmol) was added dropwise to the reaction mixture at room temperature, it was stirred at this temperature for 15 min. Then pyridine (0.34 mL, 4.17 mmol) was added dropwise. After 20 min, the solvent was removed under reduced pressure. The residue was extracted with CH_2Cl_2 , washed with 1 N HCl and aqueous saturated NaHCO_3 , and dried over MgSO_4 . Concentration under reduced pressure gave a yellow solid, which was recrystallized from CH_3CN to give **2g** (1.0 g, 59%) as colorless needles: mp 189–191 °C; IR (neat) 1619 (CO) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 1.09–1.22 (m, 21H), 2.52 (s, 3H), 7.59 (dd, J = 8.6, 2.0 Hz, 1H), 8.13 (d, J = 8.6 Hz, 1H), 8.24 (d, J = 2.0 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 11.2 (3C), 18.5 (6C), 20.7, 64.6, 111.8, 113.8, 125.8, 131.2, 133.0, 135.6, 142.5, 166.6; *Anal.* Calcd for $\text{C}_{19}\text{H}_{27}\text{IO}_2\text{Si}$: C, 51.58; H, 6.15. Found: C, 51.34; H, 6.00.

5-Fluoro -1-[(triisopropylsilyl)ethynyl]-1 λ^3 -benzo[d][1,2]iodaoxol-3(1H)-one (2h)

A mixture of 5-fluoro-2-iodobenzoic acid (1.00 g, 3.76 mmol) and NaIO_4 (0.84 g, 3.95 mmol) in 30% (v/v) aqueous AcOH (7 mL) was stirred under reflux for 4 h. The mixture was diluted with cold water (20 mL). The precipitate was collected by filtration, washed with ice water and acetone, and air-dried in the dark to give 5-fluoro-2-iodosylbenzoic acid (1.01 g, 94%), which was used without further purification. To the stirred suspension of 5-fluoro-2-iodosylbenzoic acid (0.50 g, 1.77 mmol) in CH_3CN was added dropwise trimethylsilyl triflate (0.34 mL, 1.95 mmol) at room temperature under argon. After (trimethylsilyl)(triisopropylsilyl)acetylene (0.50 mL, 1.95 mmol) was added dropwise to the reaction mixture at

room temperature, it was stirred at room temperature for 15 min. Then pyridine (0.16 mL, 1.95 mmol) was added dropwise. After 20 min, the solvent was removed under reduced pressure. The residue was extracted with CH₂Cl₂, washed with 1 N HCl and aqueous saturated NaHCO₃, and dried over MgSO₄. Concentration under reduced pressure gave a yellow solid, which was recrystallized from CH₃CN to give **2h** (0.59 g, 75%) as colorless needles: mp 181–183 °C; IR (neat) 1623 (CO) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.08–1.25 (m, 21H), 7.46–7.50 (m, 1H), 8.09–8.11 (m, 1H), 8.24 (dd, *J* = 9.2, 4.0 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 11.2 (3C), 18.5 (6C), 64.1, 108.0 (d, *J* = 6.0 Hz), 114.8–114.9 (m), 119.3 (d, *J* = 24.0 Hz), 122.2 (d, *J* = 25.2 Hz), 127.8, 134.2–134.3 (m), 165.1 (d, *J* = 7.2 Hz), 165.5 (d, *J* = 253.1 Hz). *Anal.* Calcd for C₁₈H₂₄FIO₂Si: C, 48.43; H, 5.42. Found: C, 48.33; H, 5.34.

5-Nitro-1-[(triisopropylsilyl)ethynyl]-1λ³-benzo[d][1,2]iodaoxol-3(1*H*)-one (**2i**)

By a procedure described for the preparation of benziiodoxolone derivative **2g**, 5-nitro-2-iodosylbenzoic acid (2.00 g, 6.47 mmol) was converted into **2i** (1.84 g, 60%): colorless silky needles; mp 201–203 °C; IR (neat) 1624 (CO) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.20–1.30 (m, 21H), 8.52 (dd, *J* = 9.2, 2.3 Hz, 1H), 8.63 (d, *J* = 9.2 Hz, 1H), 9.06 (dd, *J* = 2.3 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 11.3 (3C), 18.5 (6C), 63.0, 115.0, 123.0, 126.5, 128.2, 129.2, 134.5, 150.7, 166.7; *Anal.* Calcd for C₁₈H₂₄INO₄Si: C, 45.67; H, 5.11; N, 2.96. Found: C, 45.60; H, 4.93; N, 2.97.

3. Synthesis of Quinazoline

2-Phenyl-4-[(triisopropylsilyl)methyl]quinazoline (**4a**) (Table 2, entry 9)

A mixture of **1a** (25.0 mg, 0.13 mmol), CuBr (3.7 mg, 0.03 mmol), **2i** (90.4 mg, 0.19 mmol), K₂CO₃ (17.6 mg, 0.13 mmol), and MS4Å (300 mg) in benzene (1 mL) was stirred at 80 °C for 1 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography over silica gel with hexane–EtOAc (50:1) to give **4a** (29.8 mg, 62 %) as colorless oil: ¹H NMR (500 MHz, CDCl₃) δ 1.03 (d, *J* = 7.4 Hz, 18H), 1.15–1.26 (m, 3H), 2.99 (s, 2H), 7.42–7.56 (m, 4H), 7.78–7.84 (m, 1H), 8.00–8.05 (m, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 8.32–8.64 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 11.5 (3C), 18.6 (6C), 19.4, 122.8, 125.1, 126.3, 128.4 (2C), 128.5, (2C), 129.4, 130.2, 133.2, 138.5, 150.6, 159.5, 172.8; MS (FAB) *m/z* (%): 377 (MH⁺, 100), 333 (60); HRMS (FAB) calcd for C₂₄H₃₃N₂Si (MH⁺): 377.2413; found: 377.2422.

6-Fluoro-2-phenyl-4-[(triisopropylsilyl)methyl]quinazoline (**4b**) (Table 3, entry 1)

By a procedure described for the preparation of **4a**, **1b** (27.3 mg, 0.13 mmol) was converted into **4b** (26.0 mg, 52%) as pale yellow solid: mp 72–74 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.04 (d, *J* = 6.9 Hz, 18H), 1.17–1.25 (m, 3H), 2.91 (s, 2H), 7.46–7.53 (m, 3H), 7.57–7.61 (m, 1H), 7.71 (dd, *J* = 9.2, 2.9 Hz, 1H), 8.04 (dd, *J* = 9.2, 5.2 Hz, 1H), 8.59–8.61 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 11.5 (3C), 18.6 (6C), 19.5, 108.7 (d, *J* = 22.8 Hz), 123.1 (d, *J* = 8.4 Hz), 123.3 (d, *J* = 25.2 Hz), 128.4 (2C), 128.5 (2C), 130.3, 132.0 (d, *J* = 8.4 Hz), 138.2, 147.7, 159.2 (d, 2.4 Hz), 160.0 (d, *J* = 248.3 Hz), 172.3 (d, *J* = 4.8 Hz); MS (FAB) *m/z* (%): 395 (MH⁺, 100), 351 (80); HRMS (FAB) calcd for C₂₄H₃₂FN₂Si (MH⁺): 395.2319; found: 395.2310.

6-Chloro-2-phenyl-4-[(triisopropylsilyl)methyl]quinazoline (**4c**) (Table 3, entry 2)

By a procedure described for the preparation of **4a**, **1c** (29.4 mg, 0.13 mmol) was converted into **4c** (24.2 mg, 46%) as pale yellow solid: mp 74–76 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.04 (d, *J* = 7.4 Hz, 18H), 1.16–1.24 (m, 3H), 2.93 (s, 2H), 7.47–7.53 (m, 3H), 7.75 (dd, *J* = 9.2, 2.3 Hz, 1H), 7.96 (d, *J* = 9.2 Hz, 1H), 8.08 (d, *J* = 2.3 Hz, 1H), 8.59–8.61 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 11.5 (3C), 18.5 (6C), 19.6, 123.3, 124.2, 128.5 (4C), 130.5,

131.1, 131.7, 134.0, 138.1, 149.1, 159.8, 172.2; MS (FAB) m/z (%): 411 (MH^+ , 100), 367 (80); HRMS (FAB) calcd for $C_{24}H_{32}ClN_2Si$ (MH^+): 411.2023; found: 411.2024.

6-Bromo-2-phenyl-4-[(triisopropylsilyl)methyl]quinazoline (**4d**) (Table 3, entry 3)

By a procedure described for the preparation of **4a**, **1d** (35.1 mg, 0.13 mmol) was converted into **4d** (28.4 mg, 49%) as pale yellow solid: mp 76–78 °C; 1H NMR (500 MHz, $CDCl_3$) δ 1.04 (d, J = 7.4 Hz, 18H), 1.16–1.25 (m, 3H), 2.93 (s, 2H), 7.47–7.53 (m, 3H), 7.86–7.90 (m, 2H), 8.25 (d, J = 2.3 Hz, 1H), 8.59–8.61 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.5 (3C), 18.5 (6C), 19.7, 119.6, 123.8, 127.6, 128.5 (4C), 130.5, 131.2, 136.6, 138.1, 149.3, 159.8, 172.1; MS (FAB) m/z (%): 457 (MH^+ , ^{81}Br , 100), 455 (MH^+ , ^{79}Br , 100), 413 (80), 411 (80); HRMS (FAB) calcd for $C_{24}H_{32}BrN_2Si$ (MH^+ , ^{79}Br): 455.1513; found: 455.1516.

6-Iodo-2-phenyl-4-[(triisopropylsilyl)methyl]quinazoline (**4e**) (Table 3, entry 4)

By a procedure described for the preparation of **4a**, **1e** (40.9 mg, 0.13 mmol) was converted into **4e** (36.6 mg, 57%) as pale yellow solid: mp 97–99 °C; 1H NMR (500 MHz, $CDCl_3$) δ 1.04 (d, J = 7.4 Hz, 18H), 1.16–1.23 (m, 3H), 2.93 (s, 2H), 7.48–7.53 (m, 3H), 7.75 (d, J = 8.6 Hz, 1H), 8.03 (dd, J = 8.6, 1.7 Hz, 1H), 8.48 (d, J = 1.7 Hz, 1H), 8.60 (dd, J = 7.7, 1.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.6 (3C), 18.5 (6C), 19.8, 90.9, 124.4, 128.5 (4C), 130.5, 131.2, 134.3 (d, J = 8.4 Hz), 138.1, 141.8, 149.6, 159.9, 171.8; MS (FAB) m/z (%): 503 (MH^+ , 100), 459 (75); HRMS (FAB) calcd for $C_{24}H_{32}IN_2Si$ (MH^+): 503.1379; found: 503.1374.

6-Methyl-2-phenyl-4-[(triisopropylsilyl)methyl]quinazoline (**4f**) (Table 3, entry 5)

By a procedure described for the preparation of **4a**, **1f** (26.8 mg, 0.13 mmol) was converted into **4f** (30.0 mg, 60%) as pale yellow solid: mp 78–79 °C; 1H NMR (500 MHz, $CDCl_3$) δ 1.04 (d, J = 7.4 Hz, 18H), 1.16–1.25 (m, 3H), 2.56 (s, 3H), 2.95 (s, 2H), 7.44–7.52 (m, 3H), 7.64 (dd, J = 8.6, 1.7 Hz, 1H), 7.86–7.88 (m, 1H), 7.92 (d, J = 8.6 Hz, 1H), 8.59–8.68 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.6 (3C), 18.6 (6C), 19.3, 21.9, 122.7, 124.1, 128.35 (2C), 128.40 (2C), 129.1, 130.0, 135.3, 136.1, 138.7, 149.1, 158.9, 172.0; MS (FAB) m/z (%): 391 (MH^+ , 100), 347 (50); HRMS (FAB) calcd for $C_{25}H_{35}N_2Si$ (MH^+): 391.2569; found: 391.2575.

6-Methoxy-2-phenyl-4-[(triisopropylsilyl)methyl]quinazoline (**4g**) (Table 3, entry 6)

By a procedure described for the preparation of **4a**, **1g** (28.8 mg, 0.13 mmol) was converted into **4g** (31.6 mg, 61%) as pale yellow solid; mp 92–93 °C; 1H NMR (500 MHz, $CDCl_3$) δ 1.05 (d, J = 7.4 Hz, 18H), 1.17–1.27 (m, 3H), 2.93 (s, 2H), 3.96 (s, 3H), 7.34 (d, J = 2.9 Hz, 1H), 7.44–7.52 (m, 4H), 7.95 (d, J = 9.2 Hz, 1H), 8.28–8.60 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.6 (3C), 18.6 (6C), 19.4, 55.6, 103.1, 123.4, 125.5, 128.1 (2C), 128.4 (2C), 129.8, 130.9, 138.7, 146.5, 157.5, 157.9, 170.9; MS (FAB) m/z (%): 407 (MH^+ , 100), 363 (60); HRMS (FAB) calcd for $C_{25}H_{35}N_2OSi$ (MH^+): 407.2519; found: 407.2509.

6-tert-Butyl-2-phenyl-4-[(triisopropylsilyl)methyl]quinazoline (**4h**) (Table 3, entry 7)

By a procedure described for the preparation of **4a**, **1h** (32.1 mg, 0.13 mmol) was converted into **4h** (37 mg, 67%) as colorless oil; 1H NMR (500 MHz, $CDCl_3$) δ 1.04 (d, J = 6.9 Hz, 18H), 1.16–1.25 (m, 3H), 1.44 (s, 9H), 3.00 (s, 2H), 7.45–7.52 (m, 3H), 7.91 (dd, J = 8.9, 2.0 Hz, 1H), 7.96 (d, J = 8.9 Hz, 1H), 8.04 (d, J = 2.0 Hz, 1H), 8.59–8.62 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.6 (3C), 18.6 (6C), 19.4, 31.2 (3C), 35.2, 120.2, 122.4, 128.4 (2C), 128.9 (3C), 130.0, 132.0, 138.7, 149.0, 149.1, 159.1, 172.4; MS (FAB) m/z (%): 433 (MH^+ , 100); HRMS (FAB) calcd for $C_{28}H_{41}N_2Si$ (MH^+): 433.3039; found: 433.3031.

Mixture of 5-Bromo- and 7-Bromo-2-phenyl-4-[(triisopropylsilyl)methyl]quinazolines (4i) (Table 3, entry 8)

By a procedure described for the preparation of **4a**, **1i** (35.1 mg, 0.13 mmol) was converted into **4i** (27.7 mg, 48%, 3.7:1 inseparable mixture) as colorless oil: ^1H NMR (500 MHz, CDCl_3) δ 0.99 (d, $J = 7.4$ Hz, 14.2H), 1.03 (d, $J = 7.4$ Hz, 3.8H), 1.16-1.25 (m, 3H), 2.94 (s, 0.4H), 3.72 (s, 1.6H), 7.47-7.62 (m, 4H), 7.82 (d, $J = 7.4$ Hz, 0.8H), 7.96 (d, $J = 8.6$ Hz, 0.2H), 7.99 (d, $J = 9.2$ Hz, 0.8H), 8.21 (d, $J = 1.7$ Hz, 0.2H), 8.58-8.61 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 11.5 (0.6C), 11.6 (2.4C), 18.5 (1.3C), 18.7 (4.7C), 19.6 (0.2C), 23.1 (0.8C), 119.2 (0.8C), 121.4 (0.2C), 122.7 (0.8C), 126.5 (0.2C), 127.7 (0.2C), 128.5 (2C), 128.6 (2C), 129.8 (0.2C), 130.1 (0.8C), 130.6 (1C), 131.8 (0.2C), 132.6 (0.8C), 133.8 (0.8C), 137.5 (0.8C), 138.1 (0.2C), 151.5 (0.2C), 153.3 (0.8C), 158.4 (0.8C), 160.4 (0.2C), 172.9 (0.8C), 173.1 (0.2C); MS (FAB) m/z (%): 457 (MH^+ , ^{81}Br , 75), 455 (MH^+ , ^{79}Br , 75), 413 (100), 411 (100); HRMS (FAB) calcd for $\text{C}_{24}\text{H}_{32}\text{BrN}_2\text{Si}$ (MH^+ , ^{79}Br): 455.1513; found: 455.1509.

Mixture of 5-Methoxy- and 7-Methoxy-2-phenyl-4-[(triisopropylsilyl)methyl]quinazolines (4j) (Table 3, entry 9)

By a procedure described for the preparation of **4a**, **1j** (28.8 mg, 0.13 mmol) was converted into **4j** (40.1 mg, 77%, 1.25:1 inseparable mixture) as colorless solid: mp 66–68 °C; ^1H NMR (500 MHz, CDCl_3) δ 1.00-1.04 (m, 18H), 1.16-1.25 (m, 3H), 2.90 (s, 0.9H), 3.46 (s, 1.1H), 3.98 (s, 3H), 6.84 (d, $J = 7.4$ Hz, 0.55H), 7.14 (dd, $J = 8.9$, 2.6 Hz, 0.45H), 7.32 (d, $J = 2.6$ Hz, 0.45H), 7.45-7.52 (m, 3H), 7.59-7.60 (m, 0.55H), 7.95-7.68 (m, 0.55H), 7.99 (d, $J = 8.9$ Hz, 0.45H), 8.59-8.62 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 11.47 (1.5C), 11.52 (1.5C), 18.56 (3C), 18.64 (3C), 19.3 (0.5C), 27.7 (0.5C), 55.4 (0.5C), 55.7 (0.5C), 105.6 (0.5C), 107.0 (0.5C), 115.7 (0.5C), 118.1 (0.5C), 119.2 (0.5C), 121.8 (0.5C), 126.6 (0.5C), 128.36 (1C), 128.40 (1C), 128.44 (1C), 128.5 (1C), 130.11 (0.5C), 130.14 (0.5C), 132.9 (0.5C), 138.3 (0.5C), 138.7 (0.5C), 153.1 (0.5C), 153.2 (0.5C), 157.2 (0.5C), 159.1 (0.5C), 160.1 (0.5C), 163.4 (0.5C), 171.6 (0.5C), 172.8 (0.5C); MS (FAB) m/z (%): 407 (MH^+ , 100), 363 (60); HRMS (FAB) calcd for $\text{C}_{25}\text{H}_{35}\text{N}_2\text{OSi}$ (MH^+): 407.2519; found: 407.2513.

2-[4-(Trifluoromethyl)phenyl]-4-[(triisopropylsilyl)methyl]quinazoline (4l) (Table 3, entry 11)

By a procedure described for the preparation of **4a**, **1l** (33.7 mg, 0.13 mmol) was converted into **4l** (28.6 mg, 50%) as colorless solid: mp 64–66 °C; ^1H NMR (500 MHz, CDCl_3) δ 1.03 (d, $J = 7.4$ Hz, 18H), 1.13-1.26 (m, 3H), 3.00 (s, 2H), 7.56-7.60 (m, 1H), 7.76 (d, $J = 8.6$ Hz, 2H), 7.83-7.87 (m, 1H), 8.04 (d, $J = 8.0$ Hz, 1H), 8.15 (d, $J = 8.0$ Hz, 1H), 8.74 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 11.5 (3C), 18.5 (6C), 19.5, 123.0, 124.1 (q, $J = 272.3$ Hz), 125.2, 125.4 (q, $J = 3.6$ Hz), 126.9, 128.7 (2C), 129.5, 131.7 (q, $J = 32.4$ Hz, 2C), 133.5, 141.9, 150.5, 158.1, 173.3; MS (FAB) m/z (%): 445 (MH^+ , 80), 401 (100); HRMS (FAB) calcd for $\text{C}_{25}\text{H}_{32}\text{F}_3\text{N}_2\text{Si}$ (MH^+): 445.2287; found: 445.2285.

2-(4-Methoxyphenyl)-4-[(triisopropylsilyl)methyl]quinazoline (4m) (Table 3, entry 12)

By a procedure described for the preparation of **4a**, **1m** (28.8 mg, 0.13 mmol) was converted into **4m** (31.4 mg, 61%) as colorless solid: mp 69–71 °C; ^1H NMR (500 MHz, CDCl_3) δ 1.03 (d, $J = 7.4$ Hz, 18H), 1.15-1.26 (m, 3H), 2.96 (s, 2H), 3.89 (s, 3H), 7.01-7.04 (m, 2H), 7.47-7.51 (m, 1H), 7.77-7.80 (m, 1H), 7.98 (d, $J = 8.0$ Hz, 1H), 8.09 (d, $J = 8.6$ Hz, 1H), 8.56-8.59 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 11.5 (3C), 18.6 (6C), 19.3, 55.3, 113.8 (2C), 122.6, 125.1, 125.8, 129.2, 130.1 (2C), 131.3, 133.1, 150.7, 159.3, 161.5, 172.6; MS (FAB) m/z (%): 407 (MH^+ , 100), 363 (55); HRMS (FAB) calcd for $\text{C}_{25}\text{H}_{35}\text{N}_2\text{OSi}$ (MH^+): 407.2519; found: 407.2531.

2-(Thiophen-2-yl)-4-[(triisopropylsilyl)methyl]quinazoline (4n) (Table 3, entry 13)

By a procedure described for the preparation of **4a**, **1n** (25.8 mg, 0.13 mmol) was converted into **4n** (22.2 mg, 46%) as colorless oil: ^1H NMR (500 MHz, CDCl_3) δ 1.03 (d, J = 7.4 Hz, 18H), 1.15-1.26 (m, 3H), 2.93 (s, 2H), 7.17 (dd, J = 4.9, 3.7 Hz, 1H), 7.47-7.51 (m, 2H), 7.77-7.81 (m, 1H), 7.95 (d, J = 8.6 Hz, 1H), 8.07-8.09 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 11.5 (3C), 18.6 (6C), 19.1, 122.7, 125.2, 126.0, 128.1, 128.6, 129.0, 129.4, 133.4, 144.8, 150.5, 156.6, 173.1; MS (FAB) m/z (%): 383 (MH^+ , 100), 339 (65); HRMS (FAB) calcd for $\text{C}_{22}\text{H}_{31}\text{N}_2\text{SSi}$ (MH^+): 383.1977; found: 383.1979.

4-Methyl-2-phenylquinazoline (5) (Scheme 2)

To a stirred solution of **4a** (79 mg, 0.21 mmol) in THF (0.87 mL) and AcOH (0.044 mL) was added dropwise TBAF (1.0 mol/L in THF; 0.315 mL, 0.315 mmol) at room temperature. After stirring the mixture at this temperature for 4.5 h, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography over alumina with hexane–EtOAc (30:1) to give **5** (35 mg, 76%) as colorless solid: mp 85–87 °C; ^1H NMR (500 MHz, CDCl_3) δ 3.00 (s, 3H), 7.47-7.57 (m, 4H), 7.82-7.85 (m, 1H), 8.06 (d, J = 8.6 Hz, 2H), 8.61-8.63 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 22.0, 123.0, 124.9, 126.8, 128.5 (4C), 129.2, 130.3, 133.5, 138.3, 150.4, 160.2, 168.2; MS (FAB) m/z (%): 221 (MH^+ , 100); HRMS (FAB) calcd for $\text{C}_{15}\text{H}_{13}\text{N}$ (MH^+): 221.1087; found: 221.1084.

2-Phenyl-8-[(triisopropylsilyl)ethynyl]-4-[(triisopropylsilyl)methyl]quinazoline (6) (Scheme 3, eq 2)

By a procedure described for the preparation of **4a**, **1o** (50.0 mg, 0.18 mmol) was converted into **6** (15.6 mg, 21%) as yellow oil. In this case the reaction was conducted for 2 h at 80 °C; IR (neat) 2156 ($\text{C}\equiv\text{C}$) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 1.03-1.05 (m, 18H), 1.13-1.22 (m, 6H), 1.25 (s, 18H), 2.97 (s, 2H), 7.43-7.49 (m, 4H), 8.02 (dd, J = 7.4, 1.4 Hz, 1H), 8.08 (dd, J = 8.3, 1.4 Hz, 1H), 8.73-8.75 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 11.5 (6C), 18.6 (6C), 18.8 (6C), 19.5, 97.6, 103.9, 122.7, 123.8, 125.4 (2C), 128.2 (2C), 128.9 (2C), 130.3, 137.8, 138.4, 151.2, 159.5, 173.1; HRMS (ESI) calcd for $\text{C}_{35}\text{H}_{53}\text{N}_2\text{Si}_2$ (MH^+): 557.3747; found: 557.3745.

8-(Hex-1-yn-1-yl)-2-phenyl-4-[(triisopropylsilyl)methyl]quinazoline (7) (Scheme 3, eq 3)

By a procedure described for the preparation of **4a**, **1p** (50.0 mg, 0.18 mmol) was converted into **7** (21.0 mg, 25%) as yellow solid: In this case the reaction was conducted for 2 h at 80 °C; mp 81–83 °C; ^1H NMR (500 MHz, CDCl_3) δ 1.02-1.09 (m, 25H), 1.17-1.24 (m, 3H), 1.65-1.72 (m, 2H), 1.74-1.80 (m, 2H), 2.66 (t, J = 6.9 Hz, 2H), 2.97 (s, 2H), 7.43 (dd, J = 8.0, 8.0 Hz, 1H), 7.47-7.52 (m, 3H), 7.92 (d, J = 6.9 Hz, 1H), 8.03 (d, J = 8.0 Hz, 1H), 8.70–8.71 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 11.5 (3C), 13.8, 18.5 (2C), 18.6 (6C), 19.6, 19.7, 22.2, 31.0, 77.8, 97.5, 122.8, 124.3, 124.5, 125.6, 128.3 (2C), 128.7 (2C), 130.3, 136.8, 138.5, 150.9, 159.5, 173.3; HRMS (FAB) calcd for $\text{C}_{30}\text{H}_{39}\text{N}_2\text{Si}$ (MH^+): 455.2883; found: 455.2873.

1,1,1-Trifluoro-*N*-phenethyl-*N*-[(triisopropylsilyl)ethynyl]methanesulfonamide (10) (Scheme 3, eq 4)

By a procedure described for the preparation of **4a**, **9** (25.3 mg, 0.099 mmol) was converted into **10** (17.6 mg, 41%) as yellow oil. In this case the reaction was conducted for 16 h at 40 °C using THF as a solvent; IR (neat) 2181 ($\text{C}\equiv\text{C}$) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 1.08-1.10 (m, 21H), 3.09 (t, J = 7.7 Hz, 2H), 3.78 (t, J = 7.7 Hz, 2H), 7.21-7.22 (m, 2H), 7.25-7.28 (m, 1H), 7.31-7.36 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 11.3 (3C), 18.5 (6C), 34.4, 54.7, 71.4, 91.5, 119.7 (q, J = 325.1 Hz), 127.2, 128.8 (2C), 128.9 (2C), 136.2; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{30}\text{F}_3\text{NNaO}_2\text{SSi}$ (MNa^+): 456.1616; found: 456.1614.

4.Quinazoline Synthesis through Copper-Catalyzed Oxidative Alkynylation and Cyclization:

2-Phenyl-4-[(triisopropylsilyl)methyl]quinazoline (**4a**) (Scheme 5)

A mixture of *N*-phenylbenzamidine **1a** (64.4 mg, 0.33 mmol), CuCl₂ (4.4 mg, 0.03 mmol), triisopropylsilylacetylene (36.9 μ L, 0.16 mmol), and NaHCO₃ (27.6 mg, 0.33 mmol) in chlorobenzene was stirred at 50 °C for 40 h under air. The reaction mixture was concentrated under reduced pressure and purified by column chromatography over silica gel with hexane–EtOAc (50:1) to give **4a** (27.3 mg, 44%).

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Section 2. Gold-Catalyzed Cascade Cyclization of (Azido)ynamides: an Efficient Strategy for the Construction of Indoloquinolines

Summary

(Azido)ynamides were efficiently converted into indoloquinolines by use of cationic gold catalyst. The reaction proceeds through the formation of α -amidino gold-carbenoid and nucleophilic addition onto the gold-carbenoid. While reactions of ynamides bearing an allylsilane gave indoloquinolines bearing a terminal alkene, those of ynamides bearing a simple alkene gave indoloquinolines bearing a cyclopropane. Aryl group was also useful for the trapping functional group to give the azocine- or azepine-fused pentacyclic indoles.

During the last decade, gold has attracted considerable attention as an effective π -acid for the activation of alkynes and allenes,¹ and the gold-catalyzed reactions of alkynes and alkenes have been used extensively to synthesize a broad range of natural products and complex molecules in an efficient and chemoselective manner.² As described in preface, gold ions bearing alkenyl or alkynyl ligands are electron-donating and have the ability to form gold-carbenoid species. Azide bearing alkyne moiety is widely usable for generating the gold carbenoid because it allows the construction of heterocyclic compounds. In 2005, Toste *et al.*^{3a} reported novel construction of pyrrole scaffold by gold-catalyzed cyclization of azide-alkynes. Following on from this pioneering work, Gagosz^{3b} and Zhang^{3c} independently reported the development of a novel method for the synthesis of indoles from alkynyl azides by the nucleophilic addition of alcohols or arenes onto gold-carbenoids. In contrast to these studies, there had been no reports in the literature pertaining to the reactivity of ynamides with azides, despite the potential utility of this reaction in the synthesis of α -carboline-type fused indoles.

During the research toward the development of transition-metal-catalyzed reactions for the efficient construction of the complex heterocyclic compounds, the author became interested in the direct synthesis of the α -carbolines and indoloquinolines. These heterocyclic frameworks can be found in numerous bioactive natural products (Figure 1),⁴ as well as a wide range of synthetic derivatives exhibiting antimalarial and antitumor activities.⁵

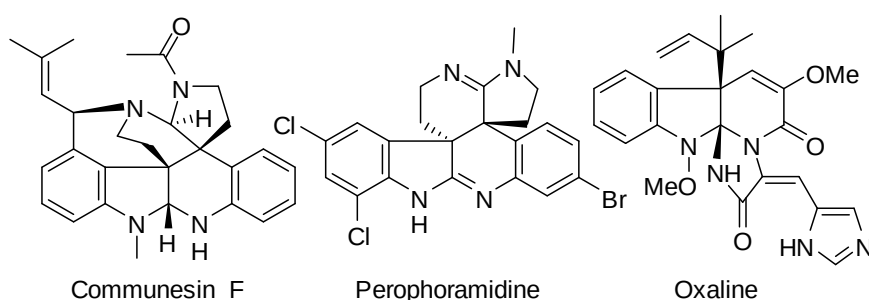
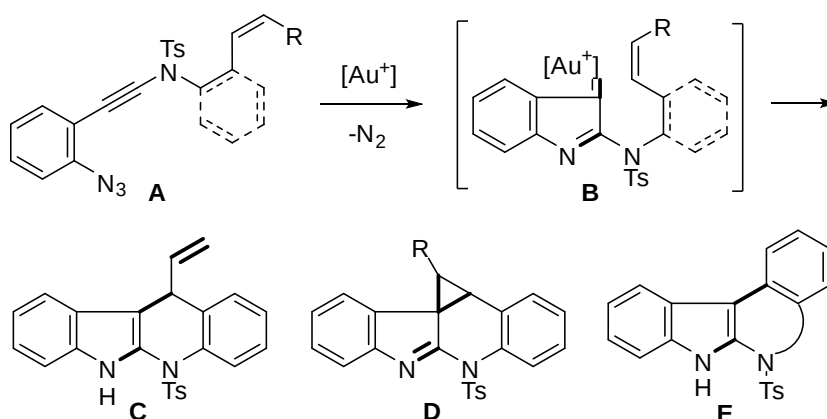


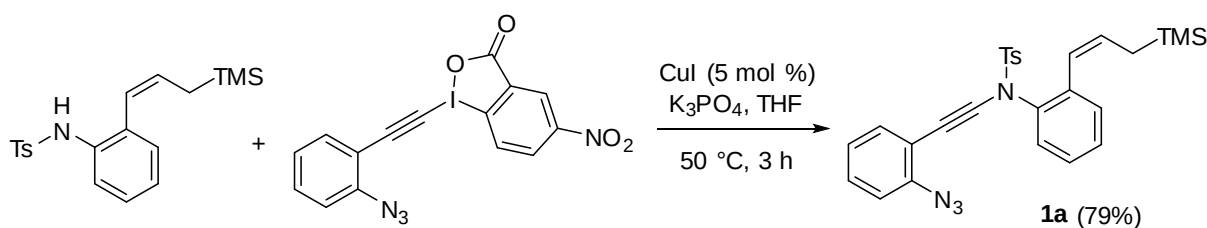
Figure 1. Natural Products Containing an α -Carboline/Indoloquinoline Framework.

It was envisaged that the gold-catalyzed reaction of (azido)ynamide **A** would lead to the formation of an α -amidino gold-carbenoid **B**, which could be used to produce various indoloquinolines **C–E** through an intramolecular trapping reaction with an alkene or arene (Scheme 1). For example, the reaction of the carbenoid **B** with an allylsilane or simple alkene moiety would give terminal alkene **C** or cyclopropane **D**, respectively. It was also envisaged that the reaction of carbenoid **B** with an arene would be effective for formation of fused indole **E**. Herein, the author describes the development of a novel method for the construction of indoloquinoline compounds by the gold-catalyzed cascade cyclization of (azido)ynamides.



Scheme 1. Concept of This Work

The (azido)ynamide **1a** was prepared by the reaction of tosylamides with ethynylbenziodoxolone (EBX).⁶ It is noteworthy that bromoalkyne, which has been widely used as an alkynylating reagent for the preparation of ynamides,⁷ was ineffective in our hands for the preparation of (azido)ynamides. Ynamides **1b–g** were also prepared in a similar manner.



Scheme 2. Preparation of (Azido)ynamide **1a**

For the initial experiments, the author investigated the optimization of the reaction conditions for the synthesis of indoloquinoline **2a** using ynamide **1a** as a model substrate (Table 1). The reaction of **1a** with 5 mol % of $\text{IPrAuCl}/\text{AgNTf}_2$ in 1,2-dichloroethane (DCE) at 50°C gave the desired product **2a**, albeit in a low yield of 11% (entry 1). The use of $\text{PPh}_3\text{AuCl}/\text{AgNTf}_2$ as the catalyst led to a significant improvement in the yield, with **2a** being isolated in 64% yield within 10 min at room temperature (entry 2). Several other phosphine ligands were also screened in the reaction (entries

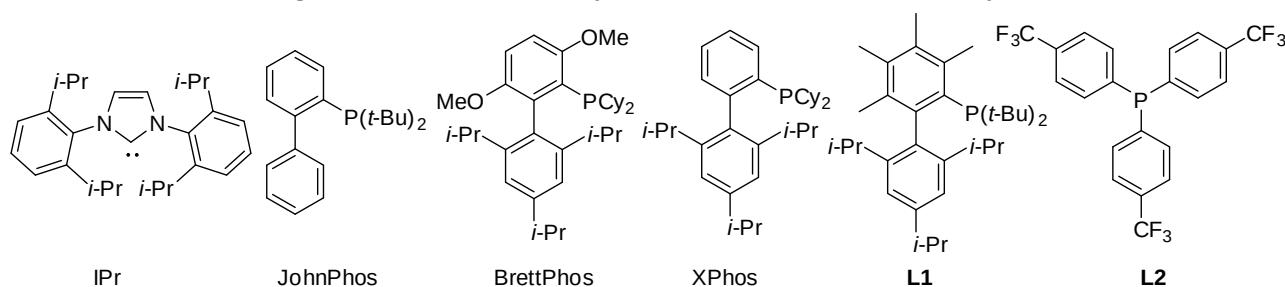
3–7) with the use of the triarylphosphine **L2** providing **2a** in 78% yield after 10 min at room temperature (entry 7). PtCl₄ was also found to catalyze the reaction, whereas PtCl₂ showed barely any activity (entries 8 and 9). Following an extensive period of screening, the author found that a combination of **L2**AuCl/AgOTf in nitromethane provided the highest level of activity with **2a** being formed in 94% yield with a decreased loading of the catalyst (1 mol %) (entries 10–12). To the best of the author's knowledge, this reaction represents the first example of the use of allylsilane as a nucleophilic trapping agent for the capture of a gold-carbenoid species.⁸

Table 1. Optimization of Reaction Conditions

entry	catalyst	solvent	conditions	yield (%) ^a
1	IPrAuCl/AgNTf ₂	DCE	50 °C, 15 h	11
2	PPh ₃ AuCl/AgNTf ₂	DCE	rt, 10 min	64
3	JohnPhosAuCl/AgNTf ₂	DCE	50 °C, 1.5 h	74
4	BrettPhosAuCl/AgNTf ₂	DCE	50 °C, 10 h	43
5	XPhosAuCl/AgNTf ₂	DCE	50 °C, 10 h	47
6	L1 AuCl/AgNTf ₂	DCE	50 °C, 4 h	37
7	L2 AuCl/AgNTf ₂	DCE	rt, 10 min	78
8	PtCl ₄	DCE	40 °C, 12 h	63
9	PtCl ₂	DCE	70 °C, 2 h	trace
10	[L2 AuCl/AgOTf] ^b	DCE	rt, 10 min	90
11	[L2 AuCl/AgOTf] ^b	CH ₃ NO ₂	rt, 10 min	94
12	[L2 AuCl/AgOTf] ^{b,c}	CH ₃ NO ₂	rt, 30 min	94

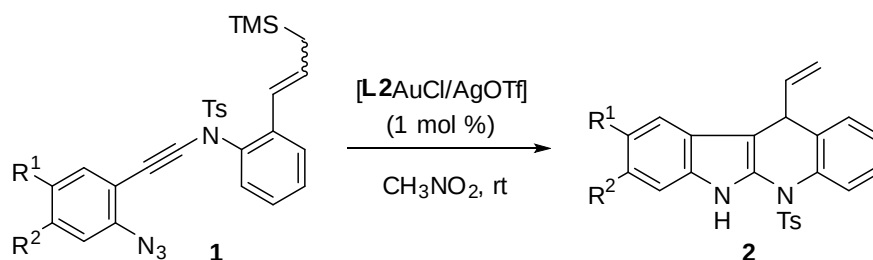
^a Isolated yields. ^b To simplify the protocol, the catalyst was prepared in advance by mixing

L2AuCl and AgOTf in DCM followed by filtration. ^c 1 mol % of the catalyst was used.



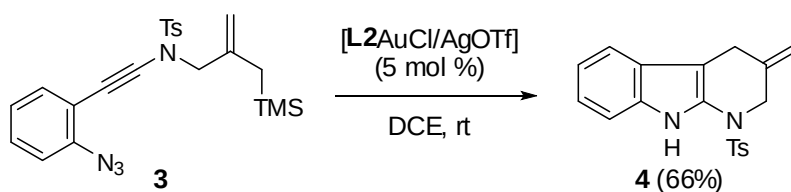
With the optimal reaction conditions in hand (Table 1, entry 12), the author proceeded to evaluate the substituent effect of the (azido)ynamide **1** (Table 2). Ynamide **1b** bearing an electron-donating methoxy group as the R¹ substituent reacted smoothly under the optimized conditions to give the desired product in 91% yield (entry 1). In contrast, ynamide **1c** bearing an electron-withdrawing trifluoromethyl group at the same position reacted much less efficiently, and gave the corresponding product in only 60% yield (entry 2). Electron-donating and -withdrawing groups (i.e., methyl, and methoxycarbonyl and chloro groups, respectively) positioned *para* (R²) to the alkyne were well tolerated (entries 3–5), although the electron-deficient ynamides **1e** and **1f** required an increase in the loading of the catalyst to 2 mol % (entries 4 and 5). The application of the optimized reaction conditions to (*E*)-allylsilane **1g** resulted in the formation of **2a** in 95% yield (entry 6), which was the same product as that obtained from the corresponding (*Z*)-isomer **1a** (Table 1). These reaction conditions were also successfully applied to the allylamine-type ynamide **3**, where they gave exomethylene derivative **4** in 66% yield (Scheme 3).⁹

Table 2. Evaluation of the Substituent Effect



entry	substrate (<i>E/Z</i>)	R ¹	R ²	product (%) ^a
1	1b (<i>Z</i>)	OMe	H	2b (91)
2	1c (<i>Z</i>)	CF ₃	H	2c (60)
3	1d (<i>Z</i>)	H	Me	2d (97)
4	1e (<i>Z</i>)	H	CO ₂ Me	2e (90) ^b
5	1f (<i>Z</i>)	H	Cl	2f (86) ^b
6	1g (<i>E</i>)	H	H	2a (95)

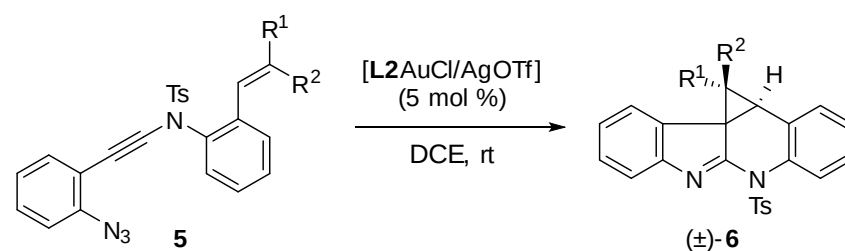
^a Isolated yields. ^b 2 mol % of the catalyst was used.



Scheme 3. Reaction of Allylamine-Type Ynamides **3**.

The author then moved on to investigate the reaction of (azido)ynamides with simple alkenes with the aim of synthesizing cyclopropane-fused indoloquinolines (Table 3). As expected, ynamides **5a–d**, which had a phenyl or *n*-butyl group as one of their alkene substituents, provided the corresponding cyclopropane compounds **6a–d** in good to excellent yields (entries 1–4).¹⁰ PPh₃AuCl/AgNTf₂ was used as the catalyst for the reaction of ynamide **5b** because the reaction did not proceed to completion with L2AuCl/AgOTf (entry 2). These reactions were found to be stereospecific and provided different products depending on the geometry of the alkene (compare entry 1 vs 3 or entry 2 vs 4). In contrast, the reaction of ynamide **5e** bearing a terminal alkene moiety afforded cyclopropane **6e** as an inseparable mixture of products, presumably because of its instability (entry 5).

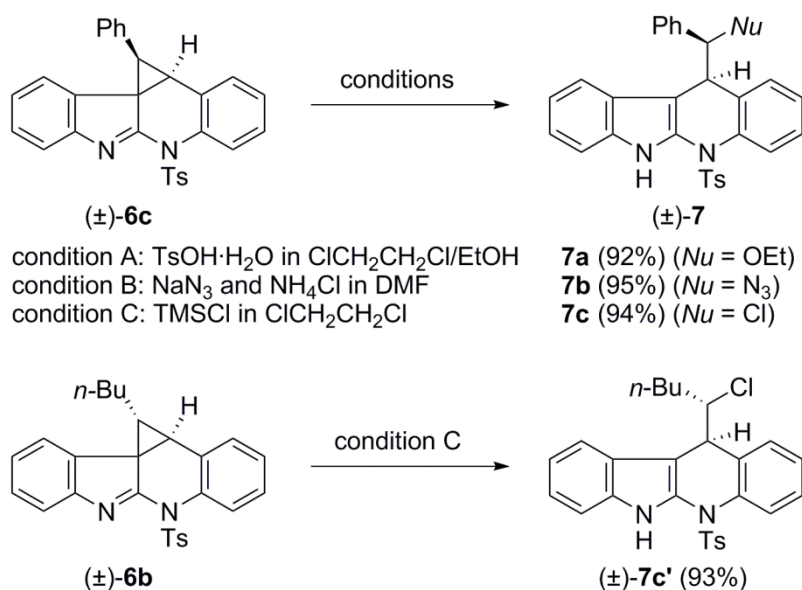
Table 3. Reaction Scope for the Synthesis of Cyclopropanes^a



entry	substrate	R ¹	R ²	product (%) ^b
1	5a	Ph	H	6a (94)
2	5b	<i>n</i> -Bu	H	6b (74) ^c
3	5c	H	Ph	6c (75)
4	5d	H	<i>n</i> -Bu	6d (93)
5	5e	H	H	6e ^d

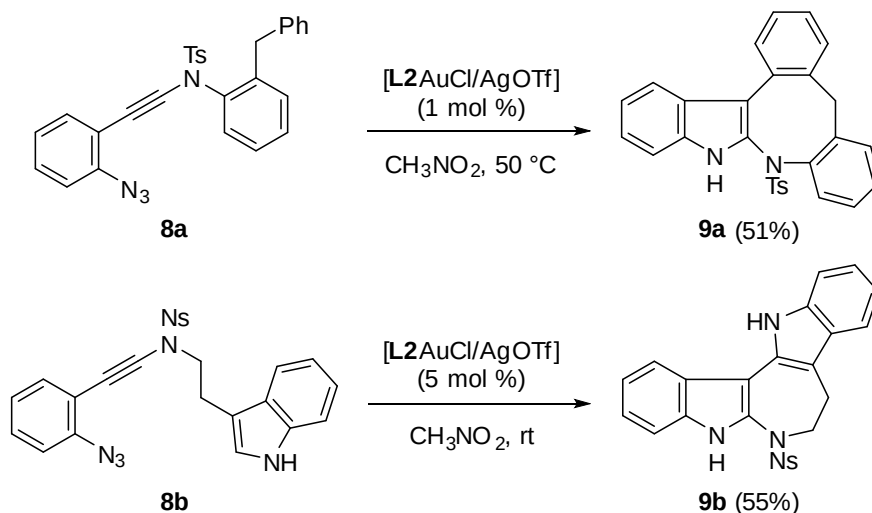
^a Reactions were conducted with 5 mol % of [L2AuCl/AgOTf] in 1,2-dichloroethane. ^b Isolated yields. ^c 5 mol % of PPh₃AuCl/AgNTf₂ was used as the catalyst. ^d Produced as an inseparable mixture.

The author also investigated the ring opening reactions of cyclopropane **6c** to evaluate the synthetic utility of these cyclopropane-fused indoloquinolines **6** (Scheme 4). The use of ethanol, NaN₃ and TMSCl as nucleophiles for the ring opening reaction of **6c** led to the efficient diastereoselective cleavage of the cyclopropane ring to give the corresponding indoloquinoline derivatives **7a–c** in excellent yields.¹⁰ Similarly, cyclopropane **6b** was also converted smoothly to indoloquinoline **7c'** in a stereospecific manner. These results indicated that the nucleophilic attack and C–C bond cleavage of cyclopropanes proceeded in the concerted pathway without forming cationic intermediate under the acidic conditions.



Scheme 4. Ring-Opening Reactions of Cyclopropanes

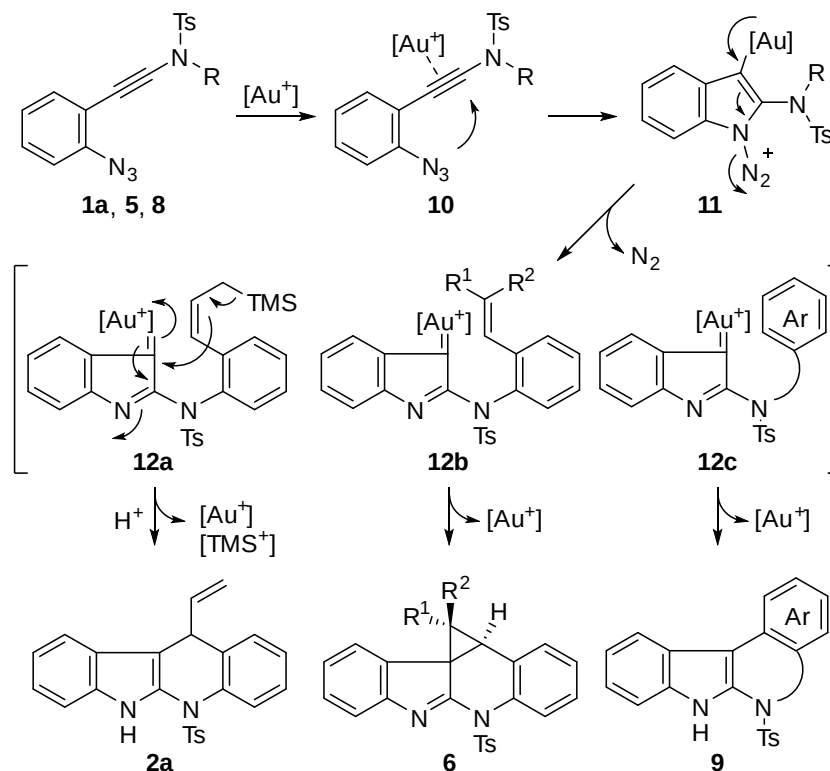
To complete this research, the author examined the reaction of (azido)niamides **8** bearing an aryl group as the trapping functional group (Scheme 5). As expected, the (azido)niamides **8** underwent a cascade cyclization reaction via the arylation of the corresponding gold carbenoids with a benzene or indole ring to give the azocine- or azepine-fused pentacyclic indoles **9a** and **9b**, respectively, in moderate yields.



Scheme 5. Construction of Medium-Sized Rings through Arylation

Plausible reaction mechanisms for the formation of **2a**, **6**, and **9** by the intramolecular reactions of (azido)niamides are shown in Scheme 6. Coordination of the gold catalyst to the alkyne as shown in **10** would induce the nucleophilic attack of the azide nitrogen to form **11**. The gold-carbenoids **12a–c** would then be formed by the release of molecular nitrogen. The carbenoid **12a** derived from **1a** bearing an allylsilane moiety would undergo an electrophilic cyclization reaction to give a

carbocation, and subsequent elimination of the TMS group followed by deauration with concomitant aromatization would give indoloquinoline **2a**. The carbenoid **12b** without a silyl group would undergo cyclopropanation to give **6**.¹¹ Compound **2a** could also be formed from the cyclopropane intermediate **6** ($R^1 = \text{H}$, $R^2 = \text{CH}_2\text{TMS}$) by the desilylative cleavage of the cyclopropane ring. In the case of ynamides bearing an aryl group, arylation of the carbenoid moiety would take place from **12c** to give **9** via a nucleophilic addition or C–H insertion pathway.¹²



Scheme 6. Plausible Mechanisms for the Reactions of (Azido)ynamides

In summary, the author has developed a novel method for the synthesis of indoloquinoline compounds via the gold-catalyzed cascade cyclization of (azido)ynamides. It has shown that a variety of different carbon-carbon double bonds can be used for this reaction, including allylsilanes, simple alkenes and arenes. This reaction provides a new approach for the synthesis of biologically interesting α -carboline and indoloquinoline-type compounds.

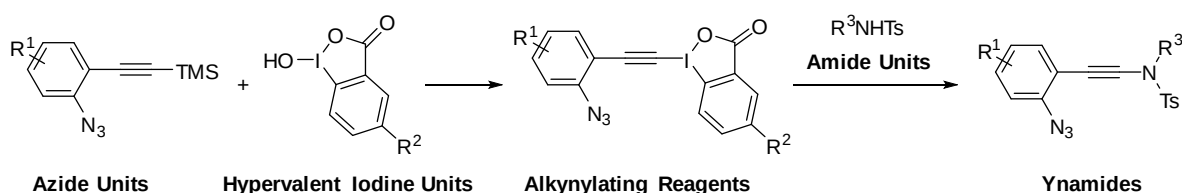
Experimental Section

General Methods. IR spectra were obtained on a JASCO FT/IR-4100 spectrometer. Exact mass (HRMS) spectra were recorded on JMS-HX/HX 110A mass spectrometer (FAB) or Shimadzu LC-ESI-IT-TOF-MS equipment (ESI). ^1H NMR spectra were recorded using a JEOL AL-500 spectrometer at 500 MHz frequency. Chemical shifts are reported in δ (ppm) relative to Me_4Si (in CDCl_3) as internal standard. ^{13}C NMR spectra were recorded using a JEOL AL-500 and referenced to the residual solvent signal. Melting points were measured by a hot stage melting points apparatus (uncorrected). For flash chromatography, silica gel (Wakosil C-300 or Wakogel C-300E: Wako Pure Chemical Industries, Ltd) or NH_2 silica gel (Chromatorex NH-DM1020: Fuji Silysia Chemical Ltd.) was employed. The crystal structures of **6c** and **7b** were collected with a Rigaku R-Axis RAPID diffractometer using graphite monochromated $\text{Mo-K}\alpha$ radiation at -180°C .

The known compounds **S6**,¹³ **S12**,¹⁴ **S13**,¹⁵ **S16**,¹⁴ **S20**,¹⁶ **S25**,¹⁷ **S28**,¹⁸ **S30**,¹⁹ **S32**,²⁰ **S34**,²¹ **S37**,²² and **S38**²³ were synthesized according to the literature.

The ^1H NMR data of **S35**,²⁴ corresponds to that reported in literature.

1. Preparation of (Azido)ynamides



1-1. Synthesis of Azide Units

4-Methoxy-2-[(trimethylsilyl)ethynyl]aniline (**S1**)

To a stirred suspension of 2-bromo-4-methoxyaniline (4.04 g, 20.0 mmol), trimethylsilylacetylene (4.15 mL, 30.0 mmol), $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ (208 mg, 0.80 mmol) and tri(*tert*-butyl)phosphine (323 mg, 1.60 mmol) in toluene (80 mL) under argon were added CuI (152 mg, 0.80 mmol) and diisopropylamine (20 mL). After stirring for 2 h at 50°C , the reaction mixture was diluted with Et_2O and filtered through a pad of Celite. The filtrate was concentrated in vacuo and the residue was chromatographed on silica gel (hexane/ EtOAc = 10/1) to afford **S1** (4.29 g, 98%): brown oil; IR (neat) 3470 (NH), 3375 (NH), 2144 ($\text{C}\equiv\text{C}$) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 0.27 (s, 9H), 3.72 (s, 3H), 3.94 (s, 2H), 6.63 (d, J = 8.6 Hz, 1H), 6.75 (dd, J = 8.6, 2.9 Hz, 1H), 6.84 (d, J = 2.9 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ : 0.1 (3C), 55.8, 99.7, 101.8, 108.4, 115.8 (2C), 117.8, 142.5, 151.7; HRMS (FAB) calcd for $\text{C}_{12}\text{H}_{18}\text{NOSi}$ (MH^+): 220.1158; found: 220.1154.

[(2-Azido-5-methoxyphenyl)ethynyl]trimethylsilane (**S2**)

To a stirred suspension of **S1** (1.10 g, 5.00 mmol) in TFA (10 mL) was added a solution of NaNO_2 (1.72 g, 25.0 mmol) in water (10 mL) at 0°C . After stirring for 1 h at 0°C , a solution of NaN_3 (3.25 g, 50.0 mmol) in water (10 mL) was added. After stirring for 1 h at 0°C , water was added and the reaction mixture was extracted with EtOAc twice. The combined organic layer was washed with brine, dried over MgSO_4 , and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/ EtOAc = 50/1) to afford **S2** (513 mg, 42%): yellow oil; IR (neat) 2125 ($\text{C}\equiv\text{C}$), 2094 (N_3) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 0.27 (s, 9H), 3.78 (s, 3H), 6.87

(dd, $J = 8.6, 2.9$ Hz, 1H), 6.94 (d, $J = 2.9$ Hz, 1H), 6.97 (d, $J = 8.6$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ : -0.2 (3C), 55.6, 100.0, 101.0, 116.1, 116.9, 117.9, 120.3, 133.8, 156.3; *Anal.* Calcd for $\text{C}_{12}\text{H}_{15}\text{N}_3\text{OSi}$: C, 58.74; H, 6.16; N, 17.13. Found: C, 58.88; H, 6.16; N, 17.07.

5-Methyl-2-[(trimethylsilyl)ethynyl]aniline (S3)

According to the procedure described for the preparation of **S1**, 2-bromo-5-methylaniline (1.86 g, 10.0 mmol) was converted into **S3** (1.89 g, 93%). Column chromatography: silica gel (hexane/EtOAc = 10/1): yellow oil; IR (neat) 3466 (NH), 3379 (NH), 2141 ($\text{C}\equiv\text{C}$) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 0.26 (s, 9H), 2.25 (s, 3H), 4.17 (s, 2H), 6.49 (d, $J = 7.4$ Hz, 1H), 6.51 (s, 1H), 7.18 (d, $J = 7.4$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ : 0.2 (3C), 21.6, 98.9, 102.0, 105.0, 114.8, 118.9, 132.0, 140.2, 148.2; HRMS (FAB) calcd for $\text{C}_{12}\text{H}_{16}\text{NSi}$ (MH $^+$): 202.1052; found: 202.1057.

[(2-Azido-4-methylphenyl)ethynyl]trimethylsilane (S4)

According to the procedure described for the preparation of **S2**, **S3** (1.85 g, 9.10 mmol) was converted into **S4** (1.37 g, 66%). Column chromatography: silica gel (hexane): pale yellow solid; mp 53 °C; IR (neat) 2157 ($\text{C}\equiv\text{C}$), 2102 (N_3) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 0.26 (s, 9H), 2.34 (s, 3H), 6.86-6.87 (m, 2H), 7.31 (d, $J = 8.6$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ : -0.1 (3C), 21.4, 100.1, 100.3, 112.5, 119.4, 125.5, 133.9, 140.3, 140.8; *Anal.* Calcd for $\text{C}_{12}\text{H}_{15}\text{N}_3\text{Si}$: C, 62.84; H, 6.59; N, 18.32. Found: C, 62.86; H, 6.56; N, 18.31.

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

According to the procedure described for the preparation of **S2**, methyl 3-amino-4-[(trimethylsilyl)ethynyl]benzoate **S6** (1.55 g, 6.26 mmol) was converted to **S5** (1.10 g, 64%) by the reaction with NaNO_2 (2.16 g, 31.3 mmol) and NaN_3 (4.07 g, 62.6 mmol). In this case, a mixed solvent of AcOH (14 mL) and CH_3CN (14 mL) was used instead of TFA. Column chromatography: silica gel (hexane/EtOAc = 50/1): colorless solid; mp 74 °C; IR (neat) 2120 ($\text{C}\equiv\text{C}$), 1725 (CO) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 0.28 (s, 9H), 3.93 (s, 3H), 7.50 (d, $J = 8.0$ Hz, 1H), 7.72 (dd, $J = 8.0, 1.7$ Hz, 1H), 7.74 (d, $J = 1.7$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ : -0.3 (3C), 52.5, 99.3, 104.5, 119.7, 119.9, 125.4, 131.1, 134.1, 141.5, 165.7; *Anal.* Calcd for $\text{C}_{13}\text{H}_{15}\text{N}_3\text{O}_2\text{Si}$: C, 57.12; H, 5.53; N, 15.37. Found: C, 57.03; H, 5.65; N, 15.41.

5-Chloro-2-[(trimethylsilyl)ethynyl]aniline (S7)

According to the procedure described for the preparation of **S1**, 2-bromo-5-chloroaniline (2.06 g, 10.0 mmol) was converted into **S7** (2.23 g, quant). Column chromatography: silica gel (hexane/EtOAc = 12/1): yellow oil; IR (neat) 3484 (NH), 3387 (NH), 2145 ($\text{C}\equiv\text{C}$) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 0.26 (s, 9H), 4.29 (br s, 2H), 6.62 (dd, $J = 8.0, 2.3$ Hz, 1H), 6.67 (d, $J = 2.3$ Hz, 1H), 7.19 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ : 0.1 (3C), 100.7 (2C), 106.3, 113.9, 117.9, 133.2, 135.5, 149.1; HRMS (FAB) calcd for $\text{C}_{11}\text{H}_{15}\text{ClNSi}$ (MH $^+$): 224.0662; found: 224.0663.

[(2-Azido-4-chlorophenyl)ethynyl]trimethylsilane (S8)

According to the procedure described for the preparation of **S5**, **S7** (900 mg, 4.02 mmol) was converted into **S8** (290 mg, 29%). Column chromatography: silica gel (hexane): red oil; IR (neat) 2159 ($\text{C}\equiv\text{C}$), 2115 (N_3) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 0.26 (s, 9H), 7.01-7.03 (m, 2H), 7.32-7.34 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ : -0.3 (3C), 98.9, 102.3, 114.1, 119.3, 124.8, 134.9, 135.3, 142.1; *Anal.* Calcd for $\text{C}_{11}\text{H}_{12}\text{ClN}_3\text{Si}$: C, 52.90; H, 4.84; N, 16.82. Found: C, 52.65; H, 4.89; N, 16.85.

1-Azido-2-iodo-4-(trifluoromethyl)benzene (S9)

According to the procedure described for the preparation of **S2**, 2-iodo-4-(trifluoromethyl)aniline (4.30 g, 15.0 mmol) was converted into **S9** (4.34 g, 92%). Column chromatography: silica gel (hexane): brown oil; IR (neat) 2109 (N₃) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 7.19 (d, *J* = 8.0 Hz, 1H), 7.63 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.02 (d, *J* = 1.7 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ: 87.4, 118.1, 122.7 (q, *J* = 272.3 Hz), 126.5 (q, *J* = 4.0 Hz), 128.1 (q, *J* = 33.6 Hz), 137.1 (q, *J* = 4.0 Hz), 145.4; *Anal.* Calcd for C₇H₃F₃IN₃: C, 26.86; H, 0.97; N, 13.42. Found: C, 26.75; H, 1.00; N, 13.66.

{[2-Azido-5-(trifluoromethyl)phenyl]ethynyl}trimethylsilane (S10)

According to the procedure described for the preparation of **S1**, **S9** (3.13 g, 10.0 mmol) was converted into **S10** (390 mg, 14%). In this case, the reaction was conducted using PdCl₂(PPh₃)₂ (702 mg, 1.00 mmol) and triethylamine (30 mL) in THF (60 mL). Column chromatography: silica gel (hexane): red oil; IR (neat) 2126 (C≡C), 2091 (N₃) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 0.28 (s, 9H), 7.14 (d, *J* = 8.6 Hz, 1H), 7.53 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.70 (d, *J* = 2.0 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ: -0.3 (3C), 98.4, 103.3, 116.0, 119.4, 123.4 (q, *J* = 272.0 Hz), 126.3 (q, *J* = 3.6 Hz), 126.9 (q, *J* = 33.2 Hz), 131.3 (q, *J* = 3.6 Hz), 144.3; *Anal.* Calcd for C₁₂H₁₂F₃N₃Si·1/7H₂O: C, 50.41; H, 4.33; N, 14.70. Found: C, 50.34; H, 4.21; N, 14.55.

1-2. Synthesis of ethynylbenziodoxolone (EBX)

1-[(2-Azidophenyl)ethynyl]-5-nitro-1λ³-benzo[d][1,2]iodaoxol-3(1H)-one (S11)

To a stirred suspension of 5-nitro-2-iodosylbenzoic acid **S12** (10.6 g, 34.2 mmol) in CH₃CN (160 mL) was added dropwise trimethylsilyl triflate (6.74 mL, 37.3 mmol) at room temperature under argon. After [(2-azidophenyl)ethynyl]trimethylsilane **S13** (6.70 g, 31.1 mmol) in CH₃CN (40 mL) was added dropwise at this temperature, the mixture was stirred for 1 h. Then pyridine (3.60 mL, 37.3 mmol) was added to the mixture. After stirring for 1 h, the precipitate was collected by filtration, and suspended in hot CH₃CN (ca. 600 mL). After cooling, the precipitate was collected by filtration, washed with CH₃CN, and dried in vacuo to give **S11** (10.8 g, 80%): colorless solid; mp 201 °C (decomposition); IR (neat) 2142 (C≡C), 1643 (CO) cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆) δ: 7.30 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.61 (ddd, *J* = 8.0, 8.0, 1.1 Hz, 1H), 7.71 (dd, *J* = 7.4, 1.1 Hz, 1H), 8.65-8.70 (m, 3H); ¹³C NMR (125 MHz, DMSO-*d*₆) δ: 56.8, 100.8, 111.6, 119.3, 123.1, 124.7, 125.0, 128.6, 129.4, 132.1, 134.0, 134.2, 142.3, 150.2, 164.2; *Anal.* Calcd for C₁₅H₇IN₄O₄: C, 41.50; H, 1.63; N, 12.91. Found: C, 41.23; H, 1.68; N, 12.77.

1-[(2-Azido-5-methoxyphenyl)ethynyl]-5-nitro-1λ³-benzo[d][1,2]iodaoxol-3(1H)-one (S14)

According to the procedure described for the preparation of **S11**, the alkyne **S2** (250 mg, 1.02 mmol) was converted into **S14** (292 mg, 62%): brown solid; mp 160 °C (decomposition); IR (neat) 2110 (C≡C), 2076 (N₃), 1649 (CO) cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆) δ: 3.81 (s, 3H), 7.22 (dd, *J* = 8.6, 2.9 Hz, 1H), 7.26 (d, *J* = 2.9 Hz, 1H), 7.41 (d, *J* = 8.6 Hz, 1H), 8.64-8.72 (m, 3H); ¹³C NMR (125 MHz, DMSO-*d*₆) δ: 55.7, 56.9, 100.6, 112.4, 118.3, 118.8, 120.6, 123.0, 124.7, 128.6, 129.5, 133.9, 134.7, 150.2, 156.1, 164.2; *Anal.* Calcd for C₁₆H₉IN₄O₅: C, 41.40; H, 1.95; N, 12.07. Found: C, 41.22; H, 1.98; N, 11.82.

Methyl 3-Azido-4-[(3-oxo-1λ³-benzo[d][1,2]iodaoxol-1(3H)-yl)ethynyl]benzoate (S15)

To a stirred suspension of 2-iodosylbenzoic acid **S16** (290 mg, 1.10 mmol) in CH₃CN (4 mL) was added trimethylsilyl triflate (217 μL, 1.20 mmol) dropwise at room temperature under argon. The alkyne **S5** (273 mg, 1.00 mmol) in CH₃CN (2 mL) was added dropwise at that temperature and the mixture was stirred for 1 h, followed by

the addition of pyridine (96.7 μ L, 1.20 mmol). After stirring for 1 h, the mixture was extracted with CH_2Cl_2 , washed with water and brine, dried over MgSO_4 , and concentrated under reduced pressure. The residue was recrystallized from CH_3CN to give **S15** (273 mg, 61%): colorless silky needles; mp 171 $^\circ\text{C}$ (decomposition); IR (neat) 2115 ($\text{C}\equiv\text{C}$), 1722 (CO), 1606 (CO) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 3.98 (s, 3H), 7.62 (d, J = 8.0 Hz, 1H), 7.77-7.84 (m, 3H), 7.90 (d, J = 1.7 Hz, 1H), 8.40-8.44 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ : 52.8, 59.4, 100.7, 116.3, 116.5, 119.4, 125.6, 126.6, 131.1, 131.7, 132.5, 133.0, 134.4, 135.1, 143.3, 165.2, 166.5; *Anal.* Calcd for $\text{C}_{17}\text{H}_{10}\text{IN}_3\text{O}_4$: C, 45.66; H, 2.25; N, 9.40. Found: C, 45.48; H, 2.12; N, 9.35.

1-[(2-Azido-5-(trifluoromethyl)phenyl)ethynyl]-1 λ^3 -benzo[d][1,2]iodaoxol-3(1H)-one (**S17**)

According to the procedure described for the preparation of **S15**, **S10** (283 mg, 1.00 mmol) was converted into **S17** (335 mg, 73%): colorless silky needles; mp 181 $^\circ\text{C}$ (decomposition); IR (neat) 2130 ($\text{C}\equiv\text{C}$), 1605 (CO) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 7.35 (d, J = 8.3 Hz, 1H), 7.72 (dd, J = 8.3, 2.0 Hz, 1H), 7.78-7.84 (m, 3H), 8.38 (dd, J = 8.3, 1.1 Hz, 1H), 8.44 (dd, J = 7.2, 2.0 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ : 58.7, 99.8, 113.1, 116.3, 119.0, 123.1 (q, J = 272.3 Hz), 126.5, 127.3 (q, J = 33.6 Hz), 128.4 (q, J = 3.6 Hz), 131.1, 131.6 (q, J = 4.0 Hz), 131.7, 132.6, 135.1, 146.3, 166.5; *Anal.* Calcd for $\text{C}_{16}\text{H}_7\text{F}_3\text{IN}_3\text{O}_2$: C, 42.04; H, 1.54; N, 9.19. Found: C, 41.83; H, 1.57; N, 9.00.

1-[(2-Azido-4-methylphenyl)ethynyl]-1 λ^3 -benzo[d][1,2]iodaoxol-3(1H)-one (**S18**)

According to the procedure described for the preparation of **S15**, **S4** (344 mg, 1.50 mmol) was converted into **S18** (275 mg, 45%): yellow silky needles; mp 169 $^\circ\text{C}$ (decomposition); IR (neat) 2121 ($\text{C}\equiv\text{C}$), 1601 (CO) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 2.44 (s, 3H), 7.00 (d, J = 8.6 Hz, 1H), 7.03 (s, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.75-7.81 (m, 2H), 8.37-8.39 (m, 1H), 8.42 (dd, J = 7.2, 2.0 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ : 21.7, 54.9, 102.4, 109.6, 116.4, 119.1, 125.9, 126.5, 131.3, 131.5, 132.4, 134.3, 134.9, 142.8, 143.1, 166.5; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{10}\text{IN}_3\text{NaO}_2$ (MNa^+): 425.9715; found: 425.9713.

1-[(2-Azido-4-chlorophenyl)ethynyl]-1 λ^3 -benzo[d][1,2]iodaoxol-3(1H)-one (**S19**)

According to the procedure described for the preparation of **S15**, **S8** (250 mg, 1.00 mmol) was converted into **S19** (263 mg, 62%): pale yellow silky needles; mp 175 $^\circ\text{C}$ (decomposition); IR (neat) 2154 ($\text{C}\equiv\text{C}$), 2112 (N_3), 1604 (CO) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 7.18 (dd, J = 8.6, 2.0 Hz, 1H), 7.23 (d, J = 2.0 Hz, 1H), 7.48 (d, J = 8.6 Hz, 1H), 7.77-7.82 (m, 2H), 8.36 (dd, J = 7.4, 1.7 Hz, 1H), 8.43 (dd, J = 7.2, 2.0 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ : 57.5, 100.7, 111.1, 116.3, 119.0, 125.4, 126.4, 131.2, 131.7, 132.5, 135.0, 135.3, 137.9, 144.2, 166.4; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_7\text{ClIKN}_3\text{O}_2$ (MK^+): 461.8909; found: 461.8904.

1-3. Synthesis of Amide Units

N-[2-(2,2-Dibromovinyl)phenyl]-4-methylbenzenesulfonamide (**S21**)

To a mixture of 2-(2,2-dibromovinyl)aniline **S20** (4.81 g, 17.3 mmol) in pyridine (3 mL) and THF (22 mL) was added *p*-toluenesulfonyl chloride (3.80 g, 19.9 mmol) at 0 $^\circ\text{C}$. After stirring for 9 h at room temperature, the reaction mixture was poured into water. The whole was extracted with CH_2Cl_2 , dried over MgSO_4 , and concentrated in vacuo. The residue was chromatographed on NH_2 silica gel (hexane/EtOAc = 3/1) and recrystallized from CHCl_3 -hexane to give pure **S21** (5.89 g, 79%): colorless plates; mp 119 $^\circ\text{C}$; IR (neat) 3266 (NH), 3241 (NH) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 2.40 (s, 3H), 6.49 (br s, 1H), 6.92 (s, 1H), 7.18 (dd, J = 7.4, 8.0 Hz, 1H), 7.24-7.33 (m, 4H), 7.45 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ :

21.6, 94.9, 124.6, 126.1, 127.2 (2C), 129.4, 129.6, 129.8 (2C), 130.1, 133.0, 133.3, 136.3, 144.1; *Anal.* Calcd for $C_{15}H_{13}Br_2NO_2S$: C, 41.79; H, 3.04; N, 3.25. Found: C, 41.78; H, 3.16; N, 3.24.

(Z)-N-[2-(2-Bromovinyl)phenyl]-4-methylbenzenesulfonamide (S22)

To a mixture of **S21** (3.02 g, 7.0 mmol) and $Pd(PPh_3)_4$ (404 mg, 0.35 mmol) in CH_2Cl_2 (70 mL) was added Bu_3SnH (5.65 mL, 21.0 mmol) at room temperature under argon. After stirring for 18 h, a solution of KF (4.07 g, 70 mmol) in H_2O (200 mL) was added. After stirring for 3 h, the reaction mixture was extracted with EtOAc twice. The combined organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/EtOAc = 6/1) to afford **S22** (2.40 g, 97%): colorless solid; mp 112 °C; IR (neat) 3267 (NH) cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ : 2.39 (s, 3H), 6.40 (br s, 1H), 6.53 (d, J = 8.0 Hz, 1H), 6.69 (d, J = 8.0 Hz, 1H), 7.17 (dd, J = 7.7, 8.0 Hz, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.29 (dd, J = 7.7, 8.0 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ : 21.6, 112.3, 123.7, 125.6, 127.2 (2C), 129.0 (2C), 129.2, 129.5, 129.7 (2C), 133.6, 136.4, 144.0; *Anal.* Calcd for $C_{15}H_{14}BrNO_2S$: C, 51.15; H, 4.01; N, 3.98. Found: C, 51.24; H, 3.94; N, 3.99.

(Z)-4-Methyl-N-{2-[3-(trimethylsilyl)prop-1-en-1-yl]phenyl}benzenesulfonamide (S23)

To a mixture of **S22** (1.06 g, 3.0 mmol) and $NiCl_2(dppp)$ (48.8 mg, 0.090 mmol) in THF (10 mL) was added dropwise a solution of $TMSCH_2MgCl$ (1.2 M) in THF (20.0 mL, 24.0 mmol) at room temperature under argon. After stirring for 24 h, pH 7 phosphate buffer was added. The reaction mixture was extracted with EtOAc twice. The combined organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/EtOAc = 13/1) to afford **S23** (0.965 g, 89%): colorless solid; mp 124 °C; IR (neat) 3272 (NH), 2950 (C=C) cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ : -0.07 (s, 9H), 1.36 (d, J = 8.6 Hz, 2H), 2.36 (s, 3H), 5.78 (d, J = 10.9 Hz, 1H), 5.86 (dt, J = 10.9 Hz, 8.6 Hz, 1H), 6.64 (br s, 1H), 6.99-7.05 (m, 2H), 7.19-7.20 (m, 3H), 7.57 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ : -1.8 (3C), 19.9, 21.5, 120.2, 121.3, 124.3, 127.2 (2C), 127.8, 128.8, 129.5 (2C), 129.9, 134.1 (2C), 136.6, 143.8; *Anal.* Calcd for $C_{19}H_{25}NO_2SSi$: C, 63.47; H, 7.01; N, 3.90. Found: C, 63.30; H, 7.04; N, 3.89.

(E)-4-Methyl-N-{2-[3-(trimethylsilyl)prop-1-en-1-yl]phenyl}benzenesulfonamide (S24)

To a mixture of *N*-(2-iodophenyl)-4-methylbenzenesulfonamide **S25** (373 mg, 1.0 mmol), allyltrimethylsilane (634 μ L, 4.0 mmol), 1,4-diazabicyclo[2.2.2]octane (336 mg, 3.0 mmol), *n*- Bu_4NCl (278 mg, 1.0 mmol) in CH_3CN (3 mL) was added bis(dibenzylideneacetone)palladium(0) (57.6 mg, 0.10 mmol) at room temperature under argon. After stirring for 32 h at 50 °C, the reaction mixture was diluted with Et_2O and filtered through a pad of Celite. The filtrate was concentrated in vacuo and the residue was chromatographed on silica gel (hexane/EtOAc = 10/1) and recrystallized from diisopropylether-hexane to afford **S24** (220 mg, 61%): colorless needles; mp 108 °C; IR (neat) 3289 (NH), 2953 (C=C) cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ : 0.00 (s, 9H), 1.58 (d, J = 8.0 Hz, 2H), 2.37 (s, 3H), 5.86-5.97 (m, 2H), 6.39 (br s, 1H), 7.09 (dd, J = 7.4, 7.4 Hz, 1H), 7.15 (ddd, J = 7.4, 7.4, 1.8 Hz, 1H), 7.20-7.22 (m, 3H), 7.37 (d, J = 7.4 Hz, 1H), 7.61 (d, J = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ : -1.9 (3C), 21.5, 24.5, 122.0, 124.0, 126.0, 127.0, 127.2 (2C), 127.4, 129.6 (2C), 132.7 (2C), 133.2, 136.7, 143.7; HRMS (FAB) calcd for $C_{19}H_{26}NO_2Si$ (MH^+): 360.1454; found: 360.1455.

(E)-N-[2-(Hex-1-en-1-yl)phenyl]-4-methylbenzenesulfonamide (S26)

According to the procedure described for the preparation of **S24**, **S25** (558 mg, 1.50 mmol) was converted into **S26** (298 mg, 60%) by the reaction with hex-1-ene (505 mg, 6.0 mmol). Column chromatography: silica gel

(hexane/EtOAc = 10/1): colorless solid; mp 96 °C; IR (neat) 3195 (NH), 2956 (C=C) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 0.92 (t, J = 7.2 Hz, 3H), 1.28-1.40 (m, 4H), 2.06-2.10 (m, 2H), 2.38 (s, 3H), 5.91 (dt, J = 15.5, 6.9 Hz, 1H), 6.05 (d, J = 15.5 Hz, 1H), 6.45 (br s, 1H), 7.11 (dd, J = 7.7, 7.7 Hz, 1H), 7.17 (ddd, J = 7.7, 7.7, 1.7 Hz, 1H), 7.21 (d, J = 8.6 Hz, 2H), 7.25-7.26 (m, 1H), 7.36 (d, J = 7.7 Hz, 1H), 7.60 (d, J = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ : 13.9, 21.5, 22.2, 31.2, 32.8, 123.7, 124.6, 126.2, 127.1, 127.2 (2C), 127.7, 129.6 (2C), 132.5, 132.8, 136.0, 136.6, 143.7; *Anal.* Calcd for $\text{C}_{19}\text{H}_{23}\text{NO}_2\text{S}$: C, 69.27; H, 7.04; N, 4.25. Found: C, 69.02; H, 7.16; N, 4.02.

(Z)-4-Methyl-N-(2-styrylphenyl)benzenesulfonamide (S27)

To a mixture of (Z)-2-styrylaniline **S28** (544 mg, 2.79 mmol) in pyridine (3 mL) and THF (8 mL) was added *p*-toluenesulfonyl chloride (443 mg, 2.32 mmol) at 0 °C. After stirring for 1 h at 50 °C, the reaction mixture was extracted with EtOAc, washed with 1 N HCl and aqueous saturated NaHCO_3 , dried over MgSO_4 , and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 8/1) to afford **S27** (622 mg, 77%): colorless solid; mp 108 °C; IR (neat) 3257 (NH) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 2.34 (s, 3H), 6.12 (d, J = 12.0 Hz, 1H), 6.55 (br s, 1H), 6.64 (d, J = 12.0 Hz, 1H), 6.93 (d, J = 7.4 Hz, 2H), 7.01-7.07 (m, 2H), 7.10-7.19 (m, 5H), 7.21-7.24 (d, J = 8.0 Hz, 1H), 7.50-7.54 (m, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ : 21.5, 121.6, 124.5, 125.1, 127.2 (2C), 127.9, 128.3 (2C), 128.4, 128.7 (2C), 129.5 (2C), 129.6, (2C), 133.6, 134.1, 135.4, 136.4, 143.7; *Anal.* Calcd for $\text{C}_{21}\text{H}_{19}\text{NO}_2\text{S}$: C, 72.18; H, 5.48; N, 4.01. Found: C, 72.34; H, 5.58; N, 4.03.

(Z)-N-[2-(Hex-1-en-1-yl)phenyl]-4-methylbenzenesulfonamide (S29)

According to the procedure described for the preparation of **S27**, (Z)-2-(hex-1-en-1-yl)aniline **S30** (913 mg, 5.20 mmol) was converted to **S29** (335 mg, 73%). Column chromatography: silica gel (hexane/EtOAc = 10/1): red oil; IR (neat) 3275 (NH) 2955 (C=C) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 0.82 (t, J = 7.2 Hz, 3H), 1.18-1.31 (m, 4H), 1.86-1.90 (m, 2H), 2.36 (s, 3H), 5.79 (dt, J = 11.0, 7.5 Hz, 1H), 5.89 (d, J = 11.0 Hz, 1H), 6.58 (s, 1H), 7.01 (dd, J = 7.7, 1.4 Hz, 1H), 7.04-7.07 (m, 1H), 7.19-7.22 (m, 3H), 7.55 (d, J = 7.7 Hz, 1H), 7.63 (d, J = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ : 13.8, 21.5, 22.2, 28.0, 31.4, 120.8, 123.3, 124.5, 127.1 (2C), 128.0, 129.1, 129.5 (2C), 129.7, 134.1, 136.5, 137.8, 143.8; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{23}\text{NNaO}_2\text{S}$ (MNa^+): 352.1347; found: 352.1344.

N-(2-Benzylphenyl)-4-methylbenzenesulfonamide (S31)

According to the procedure described for the preparation of **S27**, 2-benzylaniline **S32** (5.90 g, 27.1 mmol) was converted to **S31** (3.18 g, 35%): purified by recrystallization from CHCl_3 -hexane; colorless plates; mp 137 °C; IR (neat) 3365 (NH) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 2.39 (s, 3H), 3.64 (s, 2H), 6.29 (br s, 1H), 6.96 (d, J = 7.4 Hz, 2H), 7.07 (d, J = 7.4 Hz, 1H), 7.12 (dd, J = 7.4, 7.4 Hz, 1H), 7.18-7.27 (m, 6H), 7.37 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ : 21.5, 37.7, 124.5, 126.1, 126.7, 127.1 (2C), 127.7, 128.4 (2C), 129.0 (2C), 129.6 (2C), 130.9, 133.6, 134.7, 136.6, 138.5, 143.7; *Anal.* Calcd for $\text{C}_{20}\text{H}_{19}\text{NO}_2\text{S}$: C, 71.19; H, 5.68; N, 4.15. Found: C, 70.91; H, 5.53; N, 4.01.

4-Methyl-N-{2-[(trimethylsilyl)methyl]allyl}benzenesulfonamide (S33)

To a mixture of *N*-(2-bromoallyl)-4-methylbenzenesulfonamide **S34** (580 mg, 2.0 mmol) and $\text{NiCl}_2(\text{dppp})$ (54.2 mg, 0.10 mmol) in THF (3.3 mL) was added dropwise $\text{TMSCH}_2\text{MgCl}$ (1.5 M) in THF (6.7 mL, 10.0 mmol) at room temperature under argon. After stirring for 3 h at 80 °C, pH 7 phosphate buffer was added and the reaction mixture was extracted with EtOAc twice. The combined organic layer was 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 **S33** (355 mg, 60%): yellow oil; IR (neat) 3262 (NH), 2954 (C=C) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : -0.03 (s,

9H), 1.46 (s, 2H), 2.43 (s, 3H), 3.42 (d, $J = 6.1$ Hz, 2H), 4.54 (t, $J = 6.1$ Hz, 1H), 4.62 (s, 1H), 4.76 (s, 1H), 7.31 (d, $J = 8.0$ Hz, 2H), 7.75 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ : -1.6 (3C), 21.5, 24.0, 49.3, 109.6, 127.2 (2C), 129.6 (2C), 137.0, 142.4, 143.4; HRMS (FAB) calcd for $\text{C}_{14}\text{H}_{24}\text{NO}_2\text{Si}$ (MH^+): 298.1297; found: 298.1301.

4-Methyl-*N*-(2-vinylphenyl)benzenesulfonamide (S35)

According to the procedure described for the preparation of **S22**, **S21** (862 mg, 2.0 mmol) was converted to **S35** (419 mg, 77%). Column chromatography: silica gel (hexane/EtOAc = 5/1): pale yellow solid. The ^1H NMR data corresponds to that reported in literature.²²

1-4. Synthesis of Ynamides

(*Z*)-*N*-[(2-Azidophenyl)ethynyl]-4-methyl-*N*-{2-[3-(trimethylsilyl)prop-1-en-1-yl]phenyl}benzenesulfonamide (**1a**)

To a stirred suspension of **S23** (539 mg, 1.5 mmol), CuI (14.3 mg, 0.075 mmol), and K_3PO_4 (637 mg, 3.0 mmol) in THF (15 mL) were added **S11** (977 mg, 2.25 mmol) at room temperature. After stirring for 3 h at 50 °C, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel (toluene/hexane = 2/1) to afford **1a** (592 mg, 79%): pale yellow oil; IR (neat) 2953 (C=C), 2237 (C≡C), 2105 (N_3) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 0.00 (s, 9H), 1.71 (d, $J = 9.2$ Hz, 2H), 2.46 (s, 3H), 5.76 (dt, $J = 12.0, 9.2$ Hz, 1H), 6.44 (d, $J = 12.0$ Hz, 1H), 6.99-7.06 (m, 3H), 7.16 (dd, $J = 7.4, 7.4$ Hz, 1H), 7.23-7.34 (m, 5H), 7.42 (d, $J = 7.4$ Hz, 1H), 7.83 (d, $J = 7.4$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ : -1.6 (3C), 19.8, 21.7, 65.4, 89.0, 115.3, 118.6, 122.7, 124.5, 127.2, 128.3, 128.7 (2C), 128.9 (2C), 129.5 (2C), 130.5, 131.3, 133.4, 134.4, 136.6, 137.7, 140.8, 144.8; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{28}\text{N}_4\text{NaO}_2\text{SSi}$ (MNa^+): 523.1600; found: 523.1600.

(*Z*)-*N*-[(2-Azido-5-methoxyphenyl)ethynyl]-4-methyl-*N*-{2-[3-(trimethylsilyl)prop-1-en-1-yl]phenyl}benzenesulfonamide (**1b**)

According to the procedure described for the preparation of **1a**, **S23** (71.9 mg, 0.20 mmol) and **S14** (139 mg, 0.30 mmol) were converted into **1b** (95.0 mg, 89%). Column chromatography: silica gel (hexane/EtOAc = 10/1): brown oil; IR (neat) 2953 (C=C), 2236 (C≡C), 2118 (N_3) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 0.02 (s, 9H), 1.73 (d, $J = 9.2$ Hz, 2H), 2.48 (s, 3H), 3.74 (s, 3H), 5.79 (dt, $J = 11.5, 9.2$ Hz, 1H), 6.46 (d, $J = 11.5$ Hz, 1H), 6.81-6.84 (m, 2H), 6.97 (d, $J = 8.0$ Hz, 1H), 7.02 (d, $J = 8.0$ Hz, 1H), 7.18 (dd, $J = 8.0, 7.4$ Hz, 1H), 7.32-7.36 (m, 3H), 7.45 (d, $J = 7.4$ Hz, 1H), 7.85 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ : -1.6 (3C), 19.8, 21.7, 55.6, 65.4, 88.8, 115.8, 116.0, 117.4, 119.7, 122.6, 127.2, 128.3, 128.7 (2C), 128.9, 129.5 (2C), 130.5, 131.3, 133.5, 134.3, 136.5, 137.7, 144.9, 156.3; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{30}\text{N}_4\text{NaO}_3\text{SSi}$ (MNa^+): 553.1706; found: 553.1706.

(*Z*)-*N*-{[2-Azido-5-(trifluoromethyl)phenyl]ethynyl}-4-methyl-*N*-{2-[3-(trimethylsilyl)prop-1-en-1-yl]phenyl}benzenesulfonamide (**1c**)

According to the procedure described for the preparation of **1a**, **S23** (108 mg, 0.30 mmol) and **S17** (206 mg, 0.45 mmol) were converted into **1c** (103 mg, 61%). Column chromatography: silica gel (toluene/hexane/EtOAc = 2/1/0.02): pale yellow solid; mp 53 °C; IR (neat) 2955 (C=C), 2237 (C≡C), 2122 (N_3) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 0.03 (s, 9H), 1.74 (d, $J = 9.2$ Hz, 2H), 2.49 (s, 3H), 5.80 (dt, $J = 12.0, 9.2$ Hz, 1H), 6.42 (d, $J = 12.0$ Hz, 1H), 7.04 (d, $J = 8.0$ Hz, 1H), 7.15 (d, $J = 8.0$ Hz, 1H), 7.21 (d, $J = 8.0, 8.0$ Hz, 1H), 7.35-7.38 (m, 3H), 7.46-7.49 (m, 2H), 7.51 (s, 1H), 7.85 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ : -1.7 (3C), 19.8, 21.7, 64.6, 90.4, 116.0, 118.8, 122.4, 123.5 (q, $J = 273.5$ Hz), 125.4 (q, $J = 3.6$ Hz), 126.8 (q, $J = 33.2$ Hz), 127.3, 128.3, 128.6 (2C),

129.1, 129.6 (2C), 130.2 (q, $J = 4.0$ Hz), 130.5, 131.5, 134.3, 136.1, 137.6, 143.9, 145.1; HRMS (ESI) calcd for $C_{28}H_{27}F_3KN_4O_2SSi$ (MK^+): 607.1213; found: 607.1213.

(Z)-N-[(2-Azido-4-methylphenyl)ethynyl]-4-methyl-N-{2-[3-(trimethylsilyl)prop-1-en-1-yl]phenyl}benzenesulfonamide (1d)

According to the procedure described for the preparation of **1a**, **S23** (108 mg, 0.30 mmol) and **S18** (181 mg, 0.45 mmol) were converted into **1d** (135 mg, 87%). Column chromatography: silica gel (hexane/EtOAc = 15/1): yellow oil; IR (neat) 2952 (C=C), 2237 (C≡C), 2108 (N_3) cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ : 0.02 (s, 9H), 1.73 (d, $J = 9.2$ Hz, 2H), 2.33 (s, 3H), 2.48 (s, 3H), 5.79 (dt, $J = 12.0, 9.2$ Hz, 1H), 6.48 (d, $J = 12.0$ Hz, 1H), 6.84 (d, $J = 8.0$ Hz, 1H), 6.87 (s, 1H), 7.02 (d, $J = 8.0$ Hz, 1H), 7.16-7.19 (m, 2H), 7.32-7.35 (m, 3H), 7.44 (d, $J = 7.4$ Hz, 1H), 7.84 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ : -1.6 (3C), 19.7, 21.4, 21.7, 65.2, 88.1, 112.3, 119.1, 122.7, 125.5, 127.2, 128.3, 128.7 (2C), 128.8, 129.4 (2C), 130.4, 131.2, 133.4, 134.3, 136.7, 137.6, 139.6, 140.7, 144.8; HRMS (ESI) calcd for $C_{28}H_{30}KN_4O_2SSi$ (MK^+): 553.1496; found: 553.1494.

Methyl (Z)-3-Azido-4-[(4-methyl-N-{2-[3-(trimethylsilyl)prop-1-en-1-yl]phenyl}phenyl)sulfonamido]ethynyl}benzoate (1e)

According to the procedure described for the preparation of **1a**, **S23** (108 mg, 0.30 mmol) and **S15** (201 mg, 0.45 mmol) were converted into **1e** (148 mg, 88%). Column chromatography: silica gel (hexane/EtOAc = 7/1): yellow oil; IR (neat) 2953 (C=C), 2232 (C≡C), 2114 (N_3), 1722 (CO) cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ : 0.02 (s, 9H), 1.72 (d, $J = 9.2$ Hz, 2H), 2.48 (s, 3H), 3.92 (s, 3H), 5.78 (dt, $J = 11.5, 9.2$ Hz, 1H), 6.41 (d, $J = 11.5$ Hz, 1H), 7.02 (dd, $J = 8.0, 1.1$ Hz, 1H), 7.19 (dd, $J = 8.0, 8.0, 1.5$ Hz, 1H), 7.31 (d, $J = 8.0$ Hz, 1H), 7.34-7.37 (m, 3H), 7.45 (dd, $J = 8.0, 1.1$ Hz, 1H), 7.68 (dd, $J = 8.0, 1.1$ Hz, 1H), 7.74 (d, $J = 1.1$ Hz, 1H), 7.85 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ : -1.6 (3C), 19.8, 21.7, 52.4, 65.8, 92.0, 119.4, 119.9, 122.4, 125.4, 127.3, 128.3, 128.6 (2C), 129.1, 129.6 (2C), 130.0, 130.5, 131.5, 132.6, 134.2, 136.2, 137.6, 140.7, 145.1, 165.8; HRMS (ESI) calcd for $C_{29}H_{30}KN_4O_2SSi$ (MK^+): 597.1394; found: 597.1392.

(Z)-N-[(2-Azido-4-chlorophenyl)ethynyl]-4-methyl-N-{2-[3-(trimethylsilyl)prop-1-en-1-yl]phenyl}benzenesulfonamide (1f)

According to the procedure described for the preparation of **1a**, **S23** (108 mg, 0.30 mmol) and **S19** (191 mg, 0.45 mmol) were converted into **1f** (117 mg, 73%). Column chromatography: silica gel (hexane/EtOAc = 15/1): amber oil; IR (neat) 2953 (C=C), 2237 (C≡C), 2109 (N_3) cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ : 0.01 (s, 9H), 1.72 (d, $J = 8.6$ Hz, 2H), 2.48 (s, 3H), 5.78 (dt, $J = 12.0, 8.6$ Hz, 1H), 6.43 (d, $J = 12.0$ Hz, 1H), 6.99-7.02 (m, 2H), 7.05 (d, $J = 1.7$ Hz, 1H), 7.16-7.22 (m, 2H), 7.32-7.35 (m, 3H), 7.44 (d, $J = 7.4$ Hz, 1H), 7.82 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ : -1.6 (3C), 19.8, 21.7, 64.5, 89.8, 114.0, 118.9, 122.5, 124.9, 127.2, 128.3, 128.6 (2C), 128.9, 129.5 (2C), 130.5, 131.4, 134.1, 134.3, 134.4, 136.4, 137.6, 141.9, 145.0; HRMS (ESI) calcd for $C_{27}H_{27}ClN_4NaO_2SSi$ (MNa^+): 557.1210; found: 557.1209.

(E)-N-[(2-Azidophenyl)ethynyl]-4-methyl-N-{2-[3-(trimethylsilyl)prop-1-en-1-yl]phenyl}benzenesulfonamide (1g)

According to the procedure described for the preparation of **1a**, **S24** (71.9 mg, 0.20 mmol) and **S11** (130 mg, 0.30 mmol) were converted into **1g** (83.1 mg, 83%). Column chromatography: silica gel (hexane/EtOAc = 15/1): yellow oil; IR (neat) 2957 (C=C), 2238 (C≡C), 2106 (N_3) cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ : 0.04 (s, 9H), 1.64 (d, $J = 8.0$ Hz, 2H), 2.46 (s, 3H), 6.27 (dt, $J = 15.5, 8.0$ Hz, 1H), 6.46 (d, $J = 15.5$ Hz, 1H), 6.96 (dd, $J = 8.0, 1.1$ Hz,

1H), 7.02-7.12 (m, 3H), 7.27-7.35 (m, 5H), 7.54 (d, $J = 8.0, 1.1$ Hz, 1H), 7.84 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ : -1.8 (3C), 21.7, 24.6, 65.3, 89.1, 115.3, 118.6, 123.1, 124.5, 126.0, 126.8, 128.6, 128.7 (2C), 128.9, 129.4, 129.5 (2C), 131.2, 133.5, 134.3, 134.9, 137.8, 140.9, 144.8; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{28}\text{N}_4\text{NaO}_2\text{SSi}$ (MNa^+): 523.1600; found: 523.1602.

***N*-[(2-Azidophenyl)ethynyl]-4-methyl-*N*-{2-[(trimethylsilyl)methyl]allyl}benzenesulfonamide (3)**

To a stirred suspension of **S33** (178 mg, 0.60 mmol) and Cs_2CO_3 (391 mg, 1.2 mmol) in DMSO (6 mL) were added **S11** (391 mg, 0.90 mmol) at room temperature. After stirring for 4 h at 50 °C, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo and the residue was chromatographed on silica gel (toluene/hexane = 2/1) to afford **3** (155 mg, 59%): pale yellow solid; mp 67 °C; IR (neat) 2236 ($\text{C}\equiv\text{C}$), 2124 (N_3) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 0.05 (s, 9H), 1.56 (s, 2H), 2.45 (s, 3H), 3.91 (s, 2H), 4.78 (br s, 1H), 4.90 (br s, 1H), 7.03-7.08 (m, 2H), 7.27 (ddd, $J = 7.6, 7.6, 1.4$ Hz, 1H), 7.31 (dd, $J = 7.6, 1.4$ Hz, 1H), 7.35 (d, $J = 8.3$ Hz, 2H), 7.91 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ : -1.5 (3C), 21.6, 23.2, 58.2, 66.7, 88.2, 112.6, 115.3, 118.6, 124.5, 127.9 (2C), 128.7, 129.6 (2C), 133.1, 134.7, 140.1, 140.5, 144.6; Anal. Calcd for $\text{C}_{22}\text{H}_{26}\text{N}_4\text{O}_2\text{SSi}$: C, 60.24; H, 5.98; N, 12.77. Found: C, 60.34; H, 6.07; N, 12.77.

***(E)*-*N*-[(2-Azidophenyl)ethynyl]-4-methyl-*N*-(2-styrylphenyl)benzenesulfonamide (5a)**

According to the procedure described for the preparation of **1a**, (*E*)-4-methyl-*N*-(2-styrylphenyl)benzenesulfonamide **S37** (105 mg, 0.30 mmol) and **S11** (195 mg, 0.45 mmol) were converted into **5a** (111 mg, 75%). Column chromatography: silica gel (toluene/hexane = 2/1): colorless solid; mp 140 °C; IR (neat) 3034 ($\text{C}=\text{C}$), 2240 (N_3), 2106 (N_3) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 2.23 (s, 3H), 6.93 (d, $J = 16.0$ Hz, 1H), 7.02 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.07 (d, $J = 8.0$ Hz, 1H), 7.11 (d, $J = 16.0$ Hz, 1H), 7.20 (d, $J = 8.0$ Hz, 2H), 7.23-7.40 (m, 10H), 7.71 (d, $J = 8.0$ Hz, 1H), 7.79 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ : 21.5, 66.0, 88.4, 114.9, 118.4, 123.0, 124.5, 126.2, 126.8 (2C), 127.9, 128.2, 128.5 (4C), 129.3, 129.6 (3C), 130.1, 131.0, 133.8, 134.1, 135.8, 136.1, 136.9, 141.3, 145.2; Anal. Calcd for $\text{C}_{29}\text{H}_{22}\text{N}_4\text{O}_2\text{S}$: C, 71.00; H, 4.52; N, 11.42. Found: C, 70.72; H, 4.60; N, 11.30.

***(E)*-*N*-[(2-Azidophenyl)ethynyl]-*N*-[2-(hex-1-en-1-yl)phenyl]-4-methylbenzenesulfonamide (5b)**

According to the procedure described for the preparation of **1a**, **S26** (164 mg, 0.50 mmol) and **S11** (326 mg, 0.75 mmol) were converted into **5b** (191 mg, 81%). Column chromatography: silica gel (hexane/EtOAc = 12/1): yellow solid; mp 67 °C; IR (neat) 2239 ($\text{C}\equiv\text{C}$), 2122 (N_3), 2102 (N_3) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 0.87-0.90 (m, 3H), 1.27-1.40 (m, 4H), 2.08-2.12 (m, 2H), 2.46 (s, 3H), 6.20 (dt, $J = 15.5, 6.9$ Hz, 1H), 6.51 (d, $J = 15.5$ Hz, 1H), 7.02-7.09 (m, 3H), 7.16 (ddd, $J = 7.7, 7.7, 1.1$ Hz, 1H), 7.25-7.34 (m, 5H), 7.57 (dd, $J = 8.0, 1.1$ Hz, 1H), 7.82 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ : 13.9, 21.7, 22.3, 31.2, 32.9, 65.6, 88.8, 115.1, 118.5, 124.4, 124.5, 126.3, 127.4, 128.7 (2C), 128.9, 129.0, 129.4, 129.5 (2C), 133.5, 134.1 (2C), 135.2, 136.9, 140.9, 144.9; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{26}\text{N}_4\text{NaO}_2\text{S}$ (MNa^+): 493.1674; found: 493.1677.

***(Z)*-*N*-[(2-Azidophenyl)ethynyl]-4-methyl-*N*-(2-styrylphenyl)benzenesulfonamide (5c)**

According to the procedure described for the preparation of **1a**, **S27** (105 mg, 0.30 mmol) and **S11** (195 mg, 0.45 mmol) were converted into **5c** (125 mg, 85%). Column chromatography: silica gel (toluene/hexane = 2/1): yellow amorphous solid; IR (neat) 2237 ($\text{C}\equiv\text{C}$), 2107 (N_3) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 2.42 (s, 3H), 6.59 (d, $J = 12.0$ Hz, 1H), 6.62 (d, $J = 12.0$ Hz, 1H), 6.99 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.03-7.05 (m, 1H), 7.11-7.25 (m, 11H), 7.30 (d, $J = 8.0$ Hz, 2H), 7.87 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ : 21.7, 65.9, 88.4, 115.1, 118.5, 124.5,

125.9, 127.2, 128.1 (2C), 128.2, 128.5, 128.6 (2C), 128.9 (2C), 129.1 (2C), 129.6 (2C), 131.0, 132.2, 133.2, 134.3, 136.5, 136.8, 137.2, 140.7, 145.0; HRMS (ESI) calcd for $C_{29}H_{22}N_4NaO_2S$ (MNa^+): 513.1361; found: 513.1357.

(Z)-N-[(2-Azidophenyl)ethynyl]-N-[2-(hex-1-en-1-yl)phenyl]-4-methylbenzenesulfonamide (5d)

According to the procedure described for the preparation of **1a**, **S29** (98.8 mg, 0.30 mmol) and **S11** (195 mg, 0.45 mmol) were converted into **5d** (118 mg, 84%). Column chromatography: silica gel (hexane/EtOAc = 15/1); amber oil; IR (neat) 2237 ($C\equiv C$), 2107 (N_3) cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ : 0.84 (d, J = 7.2 Hz, 3H), 1.27-1.41 (m, 4H), 2.16-2.21 (m, 2H), 2.47 (s, 3H), 5.70 (dt, J = 11.5, 7.0 Hz, 1H), 6.47 (d, J = 11.5 Hz, 1H), 7.01-7.09 (m, 3H), 7.21 (ddd, J = 7.7, 7.4, 2.0 Hz, 1H), 7.25-7.31 (m, 2H), 7.33-7.37 (m, 4H), 7.83 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ : 13.9, 21.7, 22.4, 28.4, 31.9, 65.5, 88.7, 115.2, 118.6, 124.4, 124.5, 127.6, 128.3, 128.6 (2C), 128.9 (2C), 129.5 (2C), 130.7, 133.3, 134.4, 135.2, 136.5, 137.3, 140.8, 144.9; HRMS (ESI) calcd for $C_{27}H_{26}KN_4O_2S$ (MK^+): 509.1414; found: 509.1412.

N-[(2-Azidophenyl)ethynyl]-4-methyl-N-(2-vinylphenyl)benzenesulfonamide (5e)

According to the procedure described for the preparation of **1a**, **S35** (137 mg, 0.50 mmol) and **S11** (326 mg, 0.75 mmol) were converted into **5e** (164 mg, 79%). Column chromatography: silica gel (hexane/EtOAc = 12/1): pale yellow solid; mp 100 °C; IR (neat) 2238 ($C\equiv C$), 2134 (N_3), 2112 (N_3) cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ : 2.47 (s, 3H), 5.30 (d, J = 10.9 Hz, 1H), 5.76 (d, J = 17.8 Hz, 1H), 6.98-7.09 (m, 4H), 7.22 (ddd, J = 7.7, 7.7, 1.4 Hz, 1H), 7.28 (ddd, J = 7.7, 7.7, 1.4 Hz, 1H), 7.32-7.38 (m, 4H), 7.66 (dd, J = 7.7, 1.4 Hz, 1H), 7.81 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ : 21.7, 65.6, 88.8, 115.0, 116.5, 118.6, 124.5, 126.3, 128.5 (2C), 128.7 (2C), 129.1, 129.5, 129.6 (2C), 131.7, 133.4, 133.7, 136.0, 136.9, 140.9, 145.1; *Anal.* Calcd for $C_{23}H_{18}N_4O_2S$: C, 66.65; H, 4.38; N, 13.52. Found: C, 66.50; H, 4.40; N, 13.74.

N-[(2-Azidophenyl)ethynyl]-N-(2-benzylphenyl)-4-methylbenzenesulfonamide (8a)

According to the procedure described for the preparation of **1a**, **S31** (101 mg, 0.30 mmol) and **S11** (195 mg, 0.45 mmol) were converted into **8a** (141 mg, 98%). Column chromatography: silica gel (toluene/hexane = 2/1): brown amorphous solid; IR (neat) 2237 ($C\equiv C$), 2105 (N_3) cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ : 2.48 (s, 3H), 4.15 (br s, 2H), 6.94 (d, J = 8.0, 1.1 Hz, 1H), 7.01-7.08 (m, 2H), 7.11-7.15 (m, 2H), 7.18-7.29 (m, 8H), 7.36 (d, J = 8.0 Hz, 2H), 7.85 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ : 21.7, 37.0, 65.3, 88.9, 115.0, 118.6, 124.5, 126.1, 127.1, 128.0, 128.4 (2C), 128.7 (2C), 129.1, 129.6 (5C), 131.1, 133.5, 134.0, 137.2, 139.9, 140.9, 141.1, 145.1; HRMS (ESI) calcd for $C_{28}H_{22}N_4NaO_2S$ (MNa^+): 501.1361; found: 501.1359.

N-[2-(1H-Indol-3-yl)ethyl]-N-[(2-azidophenyl)ethynyl]-2-nitrobenzenesulfonamide (8b)

According to the procedure described for the preparation of **3**, *N*-[2-(1H-indol-3-yl)ethyl]-2-nitrobenzenesulfonamide **S38** (104 mg, 0.30 mmol) and **S11** (195 mg, 0.45 mmol) were converted into **8b** (105 mg, 70%). Column chromatography: silica gel (toluene/EtOAc = 50/1): yellow amorphous solid; IR (neat) 3419 (NH), 2237 ($C\equiv C$), 2125 (N_3) cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ : 3.31 (t, J = 7.4 Hz, 2H), 3.97 (t, J = 7.4 Hz, 2H), 7.05-7.18 (m, 5H), 7.28-7.31 (m, 3H), 7.56 (dd, J = 7.4, 7.4 Hz, 1H), 7.60-7.66 (m, 3H), 7.99 (br s, 1H), 8.13 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ : 24.5, 52.5, 68.3, 86.1, 111.2 (2C), 114.7, 118.5 (2C), 119.5, 122.0, 122.9, 124.2, 124.7, 127.1, 129.1, 130.7, 131.5, 131.9, 133.1, 134.4, 136.2, 140.6, 147.7; HRMS (ESI) calcd for $C_{24}H_{18}N_6NaO_4S$ (MNa^+): 509.1008; found: 509.1007.

2. Preparation of Catalyst

[L2AuCl/AgOTf] (S36)

To a mixture of chloro{tris[4-(trifluoromethyl)phenyl]phosphine}gold(I) (69.9 mg, 0.10 mmol) in CH₂Cl₂ (1 mL) was added AgOTf (25.7 mg, 0.10 mmol) at room temperature under argon. After stirring for 3 h, the mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo to give **S36** (80.1 mg): colorless solid; mp 145 °C (decomposition); ¹H NMR (500 MHz, CDCl₃) δ: 7.68-7.69 (m, 6H), 7.74-7.78 (m, 6H); ¹³C NMR (125 MHz, CDCl₃) δ: 123.1, (q, *J* = 273.5 Hz), 126.3 (m), 131.9 (d, *J* = 62.4 Hz), 134.4 (q, *J* = 36.0 Hz), 134.7 (d, *J* = 14.4 Hz).

3. Gold-Catalyzed Cascade Cyclization of (Azido)ynamides.

5-Tosyl-11-vinyl-6,11-dihydro-5H-indolo[2,3-*b*]quinoline (2a) (Table 1, entry 12)

The catalyst solution, [L2AuCl/AgOTf] (**S36**, 2.0 mg) in CH₃NO₂ (1.0 mL), was prepared in advance.

To a stirred mixture of **1a** (25.0 mg, 0.050 mmol) in CH₃NO₂ (0.8 mL) was added **S36** (0.4 mg, 1 mol%) in CH₃NO₂ (0.2 mL) at room temperature. After stirring for 0.5 h at room temperature, the reaction mixture was concentrated in vacuo and the residue was purified by column chromatography on silica gel (hexane/EtOAc = 12/1) to afford **2a** (18.8 mg, 94%). In a similar manner, **1g** (25.0 mg, 0.050 mmol) was converted into **2a** (19.1 mg, 95%) by the reaction for 1 h at room temperature (Table 2, entry 6): colorless amorphous solid; ¹H NMR (500 MHz, CDCl₃) δ: 2.29 (s, 3H), 4.40 (d, *J* = 8.0 Hz, 1H), 4.53 (ddd, *J* = 16.6, 9.7, 8.0 Hz, 1H), 4.61 (dd, *J* = 9.7, 1.7 Hz, 1H), 4.91 (dd, *J* = 16.6, 1.7 Hz, 1H), 7.01-7.05 (m, 4H), 7.10 (ddd, *J* = 7.7, 7.7, 1.1 Hz, 1H), 7.17-7.28 (m, 3H), 7.34 (ddd, *J* = 7.7, 7.7, 1.1 Hz, 1H), 7.41-7.45 (m, 2H), 8.03 (dd, *J* = 7.7, 1.1 Hz, 1H), 8.84 (br s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ: 21.4, 41.5, 104.6, 111.2, 113.9, 118.2, 119.9, 122.3, 125.2, 126.2, 126.9 (2C), 127.9 (2C), 129.4 (2C), 129.7, 130.0, 131.8, 133.6, 134.3, 135.1, 139.9, 144.6; HRMS (FAB) calcd for C₂₄H₂₁N₂O₂S (MH⁺): 401.1324; found: 401.1321.

9-Methoxy-5-tosyl-11-vinyl-6,11-dihydro-5H-indolo[2,3-*b*]quinoline (2b) (Table 2, entry 1)

According to the procedure described for the preparation of **2a** (Table 1, entry 12), **1b** (25.0 mg, 0.047 mmol) was converted into **2b** (18.4 mg, 91%) by the reaction for 10 min at room temperature. Column chromatography: silica gel (hexane/EtOAc = 10/1): pale yellow amorphous solid; ¹H NMR (500 MHz, CDCl₃) δ: 2.30 (s, 3H), 3.82 (s, 3H), 4.35 (d, *J* = 8.0 Hz, 1H), 4.53 (ddd, *J* = 16.6, 9.5, 8.0 Hz, 1H), 4.61 (dd, *J* = 9.5, 1.4 Hz, 1H), 4.90 (dd, *J* = 16.6, 1.4 Hz, 1H), 6.86-6.89 (m, 2H), 7.01-7.05 (m, 4H), 7.18 (d, *J* = 7.4 Hz, 1H), 7.25-7.28 (m, 1H), 7.30-7.36 (m, 2H), 8.02 (dd, *J* = 8.0, 1.1 Hz, 1H), 8.73 (br s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ: 21.4, 41.5, 55.8, 100.9, 104.4, 111.6, 111.9, 113.8, 125.7, 126.2, 126.9 (2C), 127.9 (2C), 129.4 (3C), 129.7, 130.6, 131.9, 133.5, 135.1, 139.9, 144.6, 154.2; HRMS (FAB) calcd for C₂₅H₂₃N₂O₃S (MH⁺): 431.1429; found: 431.1432.

5-Tosyl-9-(trifluoromethyl)-11-vinyl-6,11-dihydro-5H-indolo[2,3-*b*]quinoline (2c) (Table 2, entry 2)

According to the procedure described for the preparation of **2a** (Table 1, entry 12), **1c** (25.0 mg, 0.044 mmol) was converted into **2c** (12.3 mg, 60%) by the reaction for 5 h at room temperature. Column chromatography: silica gel (hexane/EtOAc = 10/1): colorless solid; mp 215 °C; ¹H NMR (500 MHz, acetone-*d*₆) δ: 2.34 (s, 3H), 4.46-4.56 (m, 2H), 4.69 (dd, *J* = 9.7, 1.7 Hz, 1H), 5.08 (dd, *J* = 16.3, 1.7 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.28 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.36 (ddd, *J* = 7.7, 7.7, 1.4 Hz, 1H), 7.43 (ddd, *J* = 7.7, 7.7, 1.4 Hz, 1H), 7.48 (dd, *J* = 8.6, 1.4 Hz, 1H), 7.76 (d, *J* = 8.6 Hz, 1H), 7.80 (s, 1H), 7.98 (dd, *J* = 7.7, 1.4 Hz, 1H), 10.93 (br s, 1H); ¹³C NMR (125 MHz, acetone-*d*₆) δ: 21.4, 42.0, 106.0 (d, *J* = 4.4 Hz), 113.2 (d, *J* = 6.0 Hz), 114.9, 116.4 (q, *J* = 4.4 Hz), 119.3 (q, *J* = 3.6 Hz), 122.2 (q, *J* = 31.6 Hz), 125.2 (d, *J* = 6.0 Hz), 126.5 (q, *J* = 270.6 Hz), 127.0, 127.8, 128.1,

128.8 (2C), 130.5 (2C), 130.8, 132.9, 133.1 (d, J = 16.0 Hz), 134.8, 136.2, 137.3 (d, J = 18.0 Hz), 140.9, 146.3; HRMS (ESI) calcd for $C_{25}H_{20}F_3N_2NaO_2S$ (MH^+): 469.1198; found: 469.1195.

8-Methyl-5-tosyl-11-vinyl-6,11-dihydro-5H-indolo[2,3-b]quinoline (2d) (Table 2, entry 3)

According to the procedure described for the preparation of **2a** (Table 1, entry 12), **1d** (25.0 mg, 0.049 mmol) was converted into **2d** (19.5 mg, 97%). Column chromatography: silica gel (hexane/EtOAc = 15/1): colorless amorphous solid; 1H NMR (500 MHz, $CDCl_3$) δ : 2.28 (s, 3H), 2.47 (s, 3H), 4.35 (d, J = 8.0 Hz, 1H), 4.52 (ddd, J = 16.0, 9.7, 8.0 Hz, 1H), 4.60 (dd, J = 9.7, 1.7 Hz, 1H), 4.89 (dd, J = 16.0, 1.7 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 6.99-7.04 (m, 4H), 7.17 (dd, J = 7.4, 1.1 Hz, 1H), 7.21 (s, 1H), 7.24-7.27 (m, 1H), 7.31-7.35 (m, 2H), 8.02 (dd, J = 8.0, 1.1 Hz, 1H), 8.71 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ : 21.4, 21.8, 41.5, 104.5, 111.2, 113.8, 117.9, 121.5, 123.0, 126.2, 126.8 (2C), 127.9 (2C), 129.3, 129.4 (2C), 129.7, 131.8, 132.2, 133.6, 134.7, 135.2, 140.0, 144.5; HRMS (ESI) calcd for $C_{25}H_{23}N_2O_2S$ (MH^+): 415.1480; found: 415.1476.

Methyl 5-Tosyl-11-vinyl-6,11-dihydro-5H-indolo[2,3-b]quinoline-8-carboxylate (2e) (Table 2, entry 4)

According to the procedure described for the preparation of **2a** (Table 1, entry 12), **1e** (25.0 mg, 0.045 mmol) was converted into **2e** (18.5 mg, 90%). In this case, after [L2AuCl/AgOTf] (**S36**) (0.36 mg, 1 mol%) in CH_3NO_2 (0.2 mL) was added and the mixture was stirred for 1 h at room temperature, the second portion of the catalyst **S36** (0.36 mg, 1 mol%) in CH_3NO_2 (0.2 mL) was added, and the resulting mixture was stirred for additional 1 h at room temperature. Column chromatography: silica gel (hexane/EtOAc = 6/1): pale yellow amorphous solid; IR (neat) 1697 (CO) cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ : 2.30 (s, 3H), 3.95 (s, 3H), 4.40 (d, J = 8.0 Hz, 1H), 4.53 (ddd, J = 16.6, 9.7, 8.0 Hz, 1H), 4.63 (dd, J = 9.7, 1.4 Hz, 1H), 4.89 (dd, J = 16.6, 1.4 Hz, 1H), 7.01-7.05 (m, 4H), 7.19 (dd, J = 7.7, 1.1 Hz, 1H), 7.28 (dd, J = 7.7, 1.1 Hz, 1H), 7.36 (dd, J = 7.7, 1.1 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.80 (dd, J = 7.7, 1.1 Hz, 1H), 8.03 (d, J = 8.0 Hz, 1H), 8.17 (d, J = 1.1 Hz, 1H), 9.09 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ : 21.4, 41.2, 52.0, 104.9, 113.3, 114.2, 117.7, 121.2, 123.9, 126.1, 127.1 (2C), 127.8 (2C), 128.7, 129.5 (2C), 129.7, 131.8, 133.0, 133.1, 133.4, 134.8, 139.5, 144.9, 167.9; HRMS (ESI) calcd for $C_{26}H_{22}KN_2O_4S$ (MK^+): 497.0937; found: 497.0938.

8-Chloro-5-tosyl-11-vinyl-6,11-dihydro-5H-indolo[2,3-b]quinoline (2f) (Table 2, entry 5)

According to the procedure described for the preparation of **2a** (Table 1, entry 12), **1f** (25.0 mg, 0.047 mmol) was converted into **2f** (17.4 mg, 86%). In this case, after [L2AuCl/AgOTf] (**S36**) (0.36 mg, 1 mol%) in CH_3NO_2 (0.2 mL) was added and the mixture was stirred for 1 h at room temperature, the second portion of **S36** (0.36 mg, 1 mol%) in CH_3NO_2 (0.2 mL) was added, and the mixture was stirred for additional 1 h at room temperature. Column chromatography: silica gel (toluene/hexane/EtOAc = 2/1/0.03): yellow oil; 1H NMR (500 MHz, $CDCl_3$) δ : 2.30 (s, 3H), 4.33 (d, J = 8.0 Hz, 1H), 4.52 (ddd, J = 16.6, 9.7, 8.0 Hz, 1H), 4.63 (dd, J = 9.7, 1.7 Hz, 1H), 4.89 (dd, J = 16.6, 1.7 Hz, 1H), 7.03 (m, 4H), 7.06 (dd, J = 8.0, 2.0 Hz, 1H), 7.17 (dd, J = 8.0, 1.1 Hz, 1H), 7.25-7.28 (m, 1H), 7.32-7.37 (m, 2H), 7.40 (d, J = 1.1 Hz, 1H), 8.02 (dd, J = 8.6, 1.1 Hz, 1H), 8.86 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ : 21.4, 41.3, 104.6, 111.2, 114.2, 119.1, 120.6, 123.7, 126.2, 127.0 (2C), 127.9 (2C), 128.1, 129.4 (2C), 129.7, 130.6, 131.7, 133.2, 134.5, 134.9, 139.6, 144.8; HRMS (ESI) calcd for $C_{24}H_{19}ClKN_2O_2S$ (MK^+): 473.0493; found: 473.0489.

3-Methylene-1-tosyl-2,3,4,9-tetrahydro-1H-pyrido[2,3-b]indole (4) (Scheme 3)

To a stirred mixture of **3** (50.0 mg, 0.114 mmol) in DCE (1 mL) was added [L2AuCl/AgOTf] (**S36**) (2.3 mg, 5 mol%) at room temperature. After stirring for 0.5 h at 50 °C, K_2CO_3 (23.5 mg, 0.170 mmol) and MeOH (1 mL)

were added to the mixture at room temperature (to completely remove the undesired side product). After stirring for 6 h at that temperature, the reaction mixture was extracted with CH₂Cl₂. The combined organic layer was washed with water and brine, dried over MgSO₄, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/EtOAc = 12/1) to afford **4** (25.5 mg, 66%): pale yellow amorphous solid; IR (neat) 3387 (NH), 2921 (C=C) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 2.34 (s, 3H), 3.23 (s, 2H), 4.24 (s, 2H), 4.76 (s, 1H), 4.83 (s, 1H), 7.09-7.13 (m, 3H), 7.19 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.35-7.37 (m, 2H), 7.43 (d, *J* = 8.6 Hz, 2H), 8.88 (br s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ: 21.5, 27.3, 52.9, 100.3, 110.9, 114.3, 117.5, 119.8, 121.9, 125.8, 127.5 (2C), 129.5 (2C), 130.9, 133.5, 134.3, 136.0, 144.1; HRMS (FAB) calcd for C₁₉H₁₉N₂O₂S (MH⁺): 339.1167; found: 339.1164.

(±)-(1*R*,1*aR*)-1-Phenyl-6-tosyl-1*a*,6-dihydro-1*H*-cyclopropa[*c*]indolo[2,3-*b*]quinoline (6a) (Table 3, entry 1)

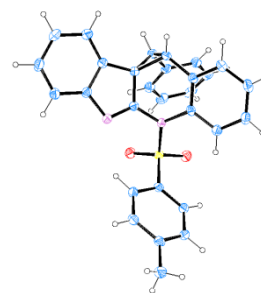
To a stirred mixture of **5a** (25.0 mg, 0.051 mmol) in DCE (1 mL) was added [L2AuCl/AgOTf] (**S39**) (2.0 mg, 5 mol%) at room temperature. After stirring for 32 h at that temperature, the reaction mixture was concentrated in vacuo and the residue was chromatographed on silica gel (hexane/EtOAc = 5/1) to afford **6a** (22.1 mg, 94%): red oil; ¹H NMR (500 MHz, CDCl₃) δ: 2.42 (s, 3H), 3.31 (d, *J* = 6.0 Hz, 1H), 3.87 (d, *J* = 6.0 Hz, 1H), 6.14 (d, *J* = 7.4 Hz, 2H), 6.87 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.08-7.09 (m, 2H), 7.16 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.23-7.33 (m, 5H), 7.38 (d, *J* = 8.6 Hz, 2H), 7.42 (d, *J* = 7.4 Hz, 1H), 7.59 (d, *J* = 8.6 Hz, 1H), 7.74 (d, *J* = 7.4 Hz, 1H), 8.29 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 21.6, 36.6, 41.3, 49.6, 120.2, 121.3, 122.0, 123.8, 125.0, 126.7, 127.4 (2C), 128.0, 128.2, 128.3 (2C), 128.5 (2C), 129.3 (2C), 129.9 (2C), 133.2, 133.3, 135.4, 137.1, 144.8, 155.2, 166.7; HRMS (FAB) calcd for C₂₉H₂₃N₂O₂S (MH⁺): 463.1480; found: 463.1483.

(±)-(1*R*,1*aS*)-1-Butyl-6-tosyl-1*a*,6-dihydro-1*H*-cyclopropa[*c*]indolo[2,3-*b*]quinoline (6b) (Table 3, entry 2)

A solution of AgNTf₂ (5.0 mg) in DCE (1 mL) was prepared in advance. To a stirred mixture of **5b** (25.0 mg, 0.053 mmol) and PPh₃AuCl (1.3 mg, 5 mol%) in DCE (0.8 mL) was added AgNTf₂ (1.0 mg, 5 mol%) in DCE (0.2 mL) at room temperature. After stirring for 1 h, the reaction mixture was concentrated in vacuo and the residue was chromatographed on silica gel (hexane/EtOAc = 7/1) to afford **6b** (17.3 mg, 74%): amber oil; ¹H NMR (500 MHz, CDCl₃) δ: 0.85 (t, *J* = 6.9 Hz, 3H), 1.16-1.31 (m, 4H), 1.70-1.76 (m, 1H), 1.81-1.88 (m, 1H), 2.04 (ddd, *J* = 7.2, 7.2, 5.7 Hz, 1H), 2.44 (s, 3H), 3.19 (d, *J* = 5.7 Hz, 1H), 7.09 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.15-7.25 (m, 4H), 7.37-7.42 (m, 3H), 7.46 (d, *J* = 7.7 Hz, 1H), 7.79 (d, *J* = 7.7 Hz, 1H), 8.29 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 13.9, 21.6, 22.2, 28.6, 30.9, 38.4, 39.9, 48.7, 120.0, 121.6 (2C), 123.9, 124.8, 127.0, 127.3, 127.8, 127.9, 128.2 (2C), 129.9 (2C), 134.2, 135.0, 137.4, 144.6, 155.6, 167.6; HRMS (ESI) calcd for C₂₇H₂₇N₂O₂S (MH⁺): 443.1793; found: 443.1793.

(±)-(1*R*,1*aS*)-1-Phenyl-6-tosyl-1*a*,6-dihydro-1*H*-cyclopropa[*c*]indolo[2,3-*b*]quinoline (6c) (Table 3, entry 3)

According to the procedure described for the preparation of **6a**, **5c** (25.0 mg, 0.051 mmol) was converted into **6c** (17.6 mg, 75%) by the reaction for 0.5 h at room temperature using DCE (1 mL) as the solvent. Column chromatography: silica gel (hexane/EtOAc = 5/1): colorless solid; mp 196 °C (decomposition); ¹H NMR (500 MHz, CDCl₃) δ: 2.41 (s, 3H), 3.94 (d, *J* = 8.9 Hz, 1H), 3.98 (d, *J* = 8.9 Hz, 1H), 6.93 (d, *J* = 7.4 Hz, 2H), 7.04-7.12 (m, 3H), 7.18 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.23-7.30 (m, 3H), 7.33 (d, *J* = 8.6 Hz, 2H), 7.44-7.47 (m, 2H), 7.83 (d, *J* = 8.0 Hz, 1H), 8.34 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 21.6, 38.8, 40.0, 47.1, 117.8, 118.7, 121.1, 122.5, 124.1 (2C), 127.5, 127.6, 127.7, 127.9 (2C), 128.4 (2C), 129.0, 129.9 (2C),



crystal structure of **6c**

130.2 (2C), 131.3, 136.6, 136.8, 138.1, 144.3, 154.4, 165.5; HRMS (FAB) calcd for C₂₉H₂₃N₂O₂S (MH⁺): 463.1480; found: 463.1483.

Crystal data of **6c**: Crystal Dimensions 0.500 X 0.500 X 0.500 mm; Crystal System orthorhombic; Lattice Type Primitive; Lattice Parameters a = 19.672(2) Å, b = 18.279(1) Å, c = 12.5149(7) Å, V = 4500.3(5) Å³; Space Group Pbca (#61); Z value 8; D_{calc} 1.365 g/cm³; F₀₀₀ 1936.00; μ(MoKa) 1.747 cm⁻¹.

(±)-(1*R*,1*aR*)-1-Butyl-6-tosyl-1*a*,6-dihydro-1*H*-cyclopropa[*c*]indolo[2,3-*b*]quinoline (**6d**) (Table 3, entry 4)

According to the procedure described for the preparation of **6a**, **5d** (25.0 mg, 0.053 mmol) was converted into **6d** (21.7 mg, 93%) by the reaction for 4 h at room temperature using DCE (1 mL) as the solvent. Column chromatography: silica gel (hexane/EtOAc = 8/1): amber oil; ¹H NMR (500 MHz, CDCl₃) δ: 0.76 (t, *J* = 7.2 Hz, 3H), 1.20-1.37 (m, 4H), 1.66-1.80 (m, 2H), 2.46 (s, 3H), 2.62 (dt, *J* = 8.6, 7.4 Hz, 1H), 3.66 (d, *J* = 8.6 Hz, 1H), 7.09-7.13 (m, 2H), 7.17 (ddd, *J* = 7.7, 7.7, 1.4 Hz, 1H), 7.22 (dd, *J* = 7.7, 7.4 Hz, 1H), 7.31 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.36-7.40 (m, 2H), 7.42 (d, *J* = 8.6 Hz, 2H), 7.76 (d, *J* = 7.4 Hz, 1H), 8.51 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 13.8, 21.7, 22.0, 22.8, 31.3, 38.5, 40.1, 46.0, 117.4, 119.6, 121.0, 123.1, 124.0, 124.3, 127.1, 127.2, 128.2 (2C), 129.4, 129.9 (2C), 137.1, 137.5, 138.1, 144.5, 154.2, 166.0; HRMS (ESI) calcd for C₂₇H₂₇N₂O₂S (MH⁺): 443.1793; found: 443.1793.

10-Tosyl-10,11-dihydro-5*H*-dibenzo[4,5:7,8]azocino[2,3-*b*]indole (**9a**) (Scheme 5)

According to the procedure described for the preparation of **2a**, **8a** (25.0 mg, 0.052 mmol) was converted into **9a** (11.9 mg, 51%) by the reaction for 2.5 h at 50 °C. Column chromatography: silica gel (hexane/EtOAc = 3/1): colorless solid; mp 218 °C (decomposition); IR (neat) 3338 (NH) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 2.27 (s, 3H), 3.66 (s, 2H), 6.74-6.78 (m, 4H), 7.15-7.25 (m, 7H), 7.28-7.34 (m, 2H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 8.57 (br s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ: 21.4, 41.0, 111.7, 116.9, 119.9, 120.6, 123.8, 125.0, 126.6, 127.1 (2C), 127.3 (2C), 127.6 (2C), 128.7, 128.8, 129.0 (2C), 130.3, 132.0, 133.5, 134.2, 134.6, 135.3, 135.9, 136.9, 143.0; HRMS (FAB) calcd for C₂₈H₂₃N₂O₂S (MH⁺): 451.1480; found: 441.1485.

6-[(2-Nitrophenyl)sulfonyl]-6,7,8,13-tetrahydro-5*H*-azepino[2,3-*b*:4,5-*b'*]diindole (**9b**) (Scheme 5)

According to the procedure described for the preparation of **6a**, **8b** (25.0 mg, 0.051 mmol) was converted into **9b** (13.0 mg, 55%) by the reaction for 0.5 h at room temperature. Column chromatography: silica gel (hexane/EtOAc = 3/1): brown solid; mp 170 °C (decomposition); IR (neat) 3416 (NH), 3394 (NH) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 3.20 (t, *J* = 5.7 Hz, 2H), 4.29 (t, *J* = 5.7 Hz, 2H), 7.10 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.18 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.25-7.35 (m, 3H), 7.38-7.41 (m, 2H), 7.43-7.49 (m, 3H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 8.50 (br s, 1H), 9.04 (br s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ: 25.6, 48.9, 101.3, 108.3, 110.6, 112.0, 117.6, 118.9, 119.8, 121.2, 122.0, 123.3, 123.4, 124.2, 128.7, 129.2, 129.7, 131.6, 132.5, 132.6, 133.8, 134.0, 135.7, 148.2; HRMS (ESI) calcd for C₂₄H₁₉N₄O₄S (MH⁺): 459.1127; found: 459.1122.

4. Ring-Opening Reactions of Cyclopropanes.

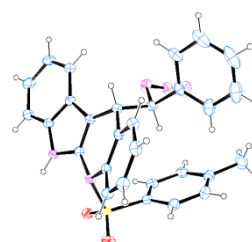
(±)-(*R*)-11-[(*R*)-Ethoxy(phenyl)methyl]-5-tosyl-6,11-dihydro-5*H*-indolo[2,3-*b*]quinolone (**7a**) (Scheme 4, Condition A)

To a mixture of **6c** (25.0 mg, 0.054 mmol) in DCE (0.5 mL) and EtOH (0.5 mL) was added TsOH·H₂O (1.0 mg, 0.005 mmol). After stirring for 0.5 h at 50 °C, water was added at room temperature. The reaction mixture was extracted with CH₂Cl₂, washed with brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified

by column chromatography on silica gel (hexane/EtOAc = 10/1) to give **7a** (25.4 mg, 92%): colorless solid; mp 110 °C; IR (neat) 3459 (NH) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 0.84 (t, J = 6.9 Hz, 3H), 2.25-2.27 (m, 4H), 2.52 (dq, J = 9.0, 6.9 Hz, 1H), 2.86 (dq, J = 9.0, 6.9 Hz, 1H), 4.09 (d, J = 9.7 Hz, 1H), 5.78 (d, J = 7.4 Hz, 1H), 6.71 (dd, J = 8.0, 7.4 Hz, 1H), 6.77 (br s, 2H), 7.11-7.25 (m, 8H), 7.39 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.0 Hz, 2H), 7.82 (d, J = 8.0 Hz, 1H), 8.02 (d, J = 8.6 Hz, 1H), 8.84 (br s, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ : 15.5, 21.5, 45.7, 63.8, 88.9, 107.7, 110.5, 119.4, 120.8, 122.0, 125.2, 125.3, 126.6, 127.2, 127.6, 127.7 (2C), 127.8 (2C), 128.2 (2C), 129.7 (3C), 131.0, 131.5, 133.3, 134.4, 136.5, 140.8, 144.8; HRMS (ESI) calcd for $\text{C}_{31}\text{H}_{28}\text{N}_2\text{NaO}_3\text{S}$ (MNa^+): 531.1718; found: 531.1715.

(±)-(R)-11-[(R)-Azido(phenyl)methyl]-5-tosyl-6,11-dihydro-5H-indolo[2,3-b]quinolone (7b**)**
(Scheme 4, Condition B)

To a mixture of **6c** (25.0 mg, 0.054 mmol) in DMF (1 mL) was added NaN_3 (17.6 mg, 0.27 mmol) and NH_4Cl (14.4 mg, 0.27 mmol). After stirring for 7 h at 60 °C, the reaction mixture was extracted with Et_2O , washed with water (three times) and brine, dried over MgSO_4 , and concentrated in vacuo to give **7b** (25.9 mg, 95%): colorless solid; mp 110 °C; IR (neat) 3398 (NH), 2101 (N_3) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 2.25 (d, J = 10.3 Hz, 1H), 2.29 (s, 3H), 4.10 (d, J = 10.3 Hz, 1H), 5.89 (dd, J = 8.0, 1.7 Hz, 1H), 6.76-6.82 (m, 3H), 7.17-7.33 (m, 8H), 7.43-7.46 (m, 3H), 7.71 (d, J = 8.0 Hz, 1H), 8.06 (dd, J = 8.0, 1.7 Hz, 1H), 8.91 (br s, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ : 21.5, 44.5, 73.9, 105.8, 111.0, 119.2, 120.2, 122.5, 125.5, 125.7, 126.4, 127.1, 127.8 (2C), 128.0 (2C), 128.4 (2C), 128.5, 130.0 (2C), 130.5, 130.8, 130.9, 133.2, 134.5, 136.4, 138.2, 145.4; HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{24}\text{N}_5\text{O}_2\text{S}$ (MH^+): 506.1651; found: 506.1649.



crystal structure of **7b**

Crystal data of **7b**: Crystal Dimensions 0.500 X 0.500 X 0.500 mm; Crystal System triclinic; Lattice Type Primitive; Cell Determination (2θ range) 8180 (6.1 - 55.0 °); Omega Scan Peak Width at Half-height 0.00; Lattice Parameters a = 9.4716(10) Å, b = 10.8769(13) Å, c = 11.9856(13) Å, α = 83.113(3) °, β = 83.385(3) °, γ = 87.083(3) °, V = 1216.8(2) Å³; Space Group P-1 (#2); Z value 2; D_{calc} 1.380 g/cm³; F_{000} 528.00; $\mu(\text{MoK}\alpha)$ 1.713 cm^{-1} .

(S)-11-[(S)-Chloro(phenyl)methyl]-5-tosyl-6,11-dihydro-5H-indolo[2,3-b]quinoline (7c**)**
(Scheme 4, Condition C)

To a mixture of **9c** (21.0 mg, 0.045 mmol) in DCE (1 mL) was added TMSCl (17.3 μL , 0.136 mmol) at room temperature under argon. After stirring for 3 h, the solvent was removed under reduced pressure to give **7c** (21.3 mg, 94%): colorless solid; mp 185 °C (decomposition); IR (neat) 3401 (NH) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 2.29 (s, 3H), 2.55 (d, J = 10.9 Hz, 1H), 4.43 (d, J = 10.9 Hz, 1H), 5.91 (d, J = 7.4 Hz, 1H), 6.73 (dd, J = 7.4, 7.4 Hz, 1H), 6.83-6.84 (m, 2H), 7.17-7.27 (m, 8H), 7.42 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 8.6 Hz, 2H), 7.78 (d, J = 7.4 Hz, 1H), 8.05 (d, J = 8.0 Hz, 1H), 8.89 (br s, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ : 21.6, 46.7, 70.0, 106.8, 110.9, 119.7, 120.0, 122.5, 125.5 (2C), 126.6, 127.2, 127.7 (2C), 127.8 (2C), 128.2 (2C), 128.3, 130.1 (2C), 130.7, 130.8, 131.1, 133.0, 134.5, 136.3, 140.3, 145.4; HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{23}\text{ClKN}_2\text{O}_2\text{S}$ (MK^+): 537.0806; found: 537.0802.

(S)-11-((S)-1-chloropentyl)-5-tosyl-6,11-dihydro-5H-indolo[2,3-b]quinoline (7c'**)**
(Scheme 4, Condition C)

According to the procedure described for the preparation of **7c**, **6b** (10.0 mg, 0.023 mmol) was converted into **7c'** (10.1 mg, 93%): colorless solid; mp 160 °C; IR (neat) 3421 (NH) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 0.67-0.74

(m, 1H), 0.84 (t, J = 7.4 Hz, 3H), 1.10-1.17 (m, 2H), 1.30-1.43 (m, 3H), 1.79-1.82 (m, 1H), 2.33 (s, 3H), 4.16 (d, J = 9.7 Hz, 1H), 7.12-7.15 (m, 3H), 7.18-7.26 (m, 3H), 7.35-7.40 (m, 4H), 7.63 (d, J = 8.0 Hz, 1H), 8.15 (d, J = 8.0 Hz, 1H), 8.88 (br s, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ : 14.1, 21.6, 22.3, 28.7, 35.4, 45.3, 70.3, 107.2, 110.9, 119.6, 119.9, 122.3, 125.8, 126.1 (2C), 127.5 (3C), 129.9 (2C), 130.5, 130.9, 132.0, 133.1, 134.4, 136.6, 145.0; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{27}\text{ClN}_2\text{NaO}_2\text{S}$ (MNa^+): 501.1379; found: 501.1378.

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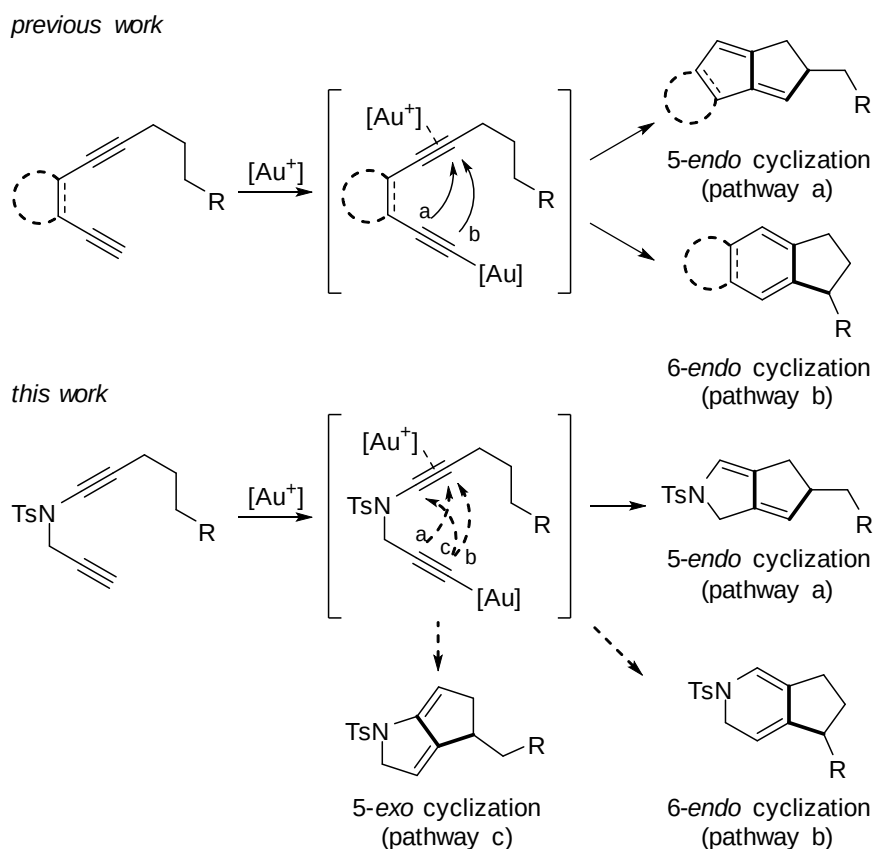
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Section 3. Gold-Catalyzed Cyclization of *N*-Propargyl Ynamides: a Novel Synthesis of Bicyclic Pyrroles

Summary

Various *N*-propargyl ynamides were converted to bicyclic and tricyclic pyrroles by use of a cationic dual-activation gold catalyst. This reaction starts with the nucleophilic addition of gold acetylide onto ynamide triple bond at the β -position of the nitrogen atom. Thus, gold vinylidene is formed, and then a second cyclization takes place. The formation of gold vinylidene is indicated by the evidence that alkylethynyl-type ynamides also undergo the *C*-*H* activation in these reactions.

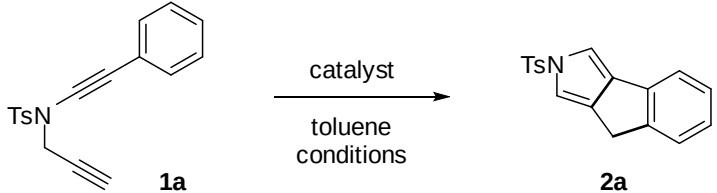
Pyrrole is well known as an important heterocyclic scaffold which is contained in a wide range of biological active compounds as well as important functional materials.¹ Although a variety of efficient methods to synthesize pyrrole derivatives have been developed,² many of the existing approaches require multistep reactions in order to construct fused-pyrroles. Hence, the method to construct fused-pyrroles from easily accessible *N*-propargyl ynamides might become one of the important synthetic routes to pyrroles.



Scheme 1. Reactivity of Gold Acetylide onto the Other Alkyne

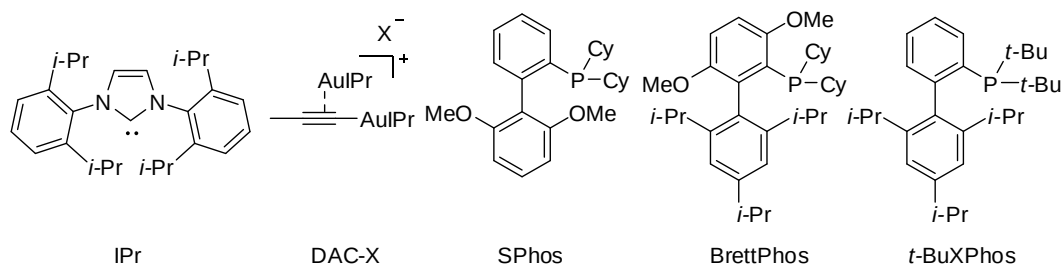
Recently, the groups of Hashmi and Zhang independently reported the novel and fascinating gold-catalyzed cascade cyclization of diynes involving a C–H activation step (Scheme 1).³ In these reactions, a cationic gold catalyst activates two alkynes, the terminal by σ -coordination and the internal by π -coordination, thus promoting the nucleophilic attack of gold acetylide onto the internal alkyne. The nucleophilic position of gold acetylide depends on the tether of two alkynes. While 5-*endo-dig* cyclization takes place with phenylene-,^{3a-c} 3,4-thiophenylene-,^{3j} or ethylene-tethered^{3k} diynes (pathway a), 6-*endo-dig* cyclization takes place with vinylene-^{3g} or 2,3-thiophenylene-tethered^{3e} diynes (pathway b). Although the computational studies^{3i,j} suggested that the electronic effect of the tether is important for the selectivity, additional experimental studies are needed to clarify the whole picture of diyne reactions. As part of the collaboration with Hashmi group, the author focused on the reactivity of *N*-propargyl ynamides. In this case, 5-*exo-dig* cyclization (pathway c) would be another possible reaction course, considering the general regioselectivity in the ynamide reactions⁴, in addition to the 5-*endo-dig* and 6-*endo-dig* pathways (a and b). Herein the author describes that the selective synthesis of bicyclic and tricyclic pyrroles based on

Table 1. Optimization of Reaction Conditions



entry	catalyst (mol %)	conditions	yield (%) ^a
1	DAC-NTf ₂ (5)	80 °C, 1 h	62
2	IPrAuNTf ₂ (5)	80 °C, 8 h	< 66 ^b
3	PPh ₃ AuNTf ₂ (5)	80 °C, 15 h	10
4	SPhosAuNTf ₂ (5)	80 °C, 7 h	35
5	BrettPhosAuNTf ₂ (5)	80 °C, 2 h	46
6	<i>t</i> -BuXphosAuNTf ₂ (5)	80 °C, 4 h	42
7	DAC-PF ₆ (5)	80 °C, 1 h	86
8	DAC-PF ₆ (2.5)	80 °C, 1 h	74
9	-	110 °C, 1 h	decomp.

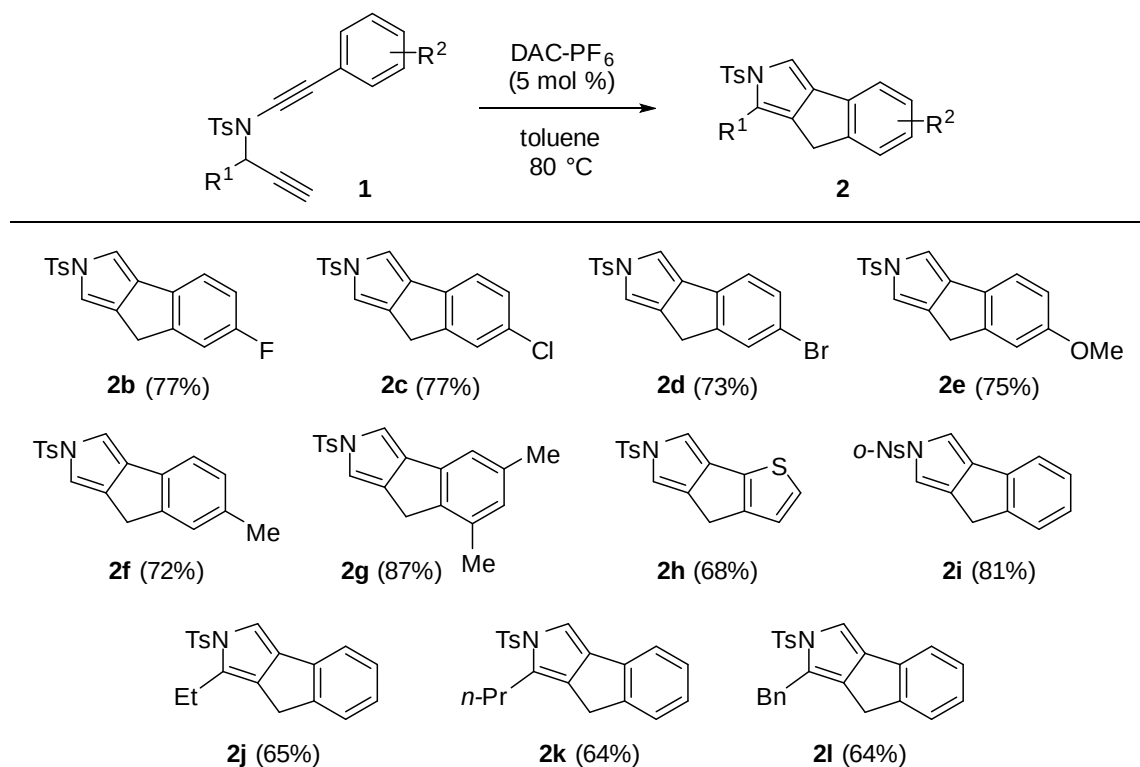
^a Isolated yields. ^b Produced as an inseparable mixture.



gold(I)-catalyzed ynamide cyclization via the pathway a.

At the outset of this work, the author examined the reaction of *N*-propargyl ynamide **1a** with 5 mol % of a gold catalyst. The use of DAC-NTf₂ (DAC = dual activation catalyst)^{3e} allowed the formation of tricyclic pyrrole **2a** in 62% yield (Table 1, entry 1). Though IPrAuNTf₂ showed a similar reactivity, the desired pyrrole **2a** was obtained as an inseparable mixture (entry 2). Several phosphine ligands were also tested for the reaction (entries 3–6). While use of PPh₃ significantly decreased the reaction rate and yield (entry 3), other phosphine ligands such as SPhos, BrettPhos, and *t*-BuXPhos gave the pyrrole **2a** in slightly better yields (35–46%, entries 4–6). Fortunately, employment of DAC-PF₆ improved the yield to 86% (entry 7). When the loading of DAC-PF₆ was decreased to 2.5 mol %, 74% yield of **2a** was produced (entry 8). Without using any catalysts, only the decomposition of starting material **1a** was observed upon heating at 110 °C (entry 9).

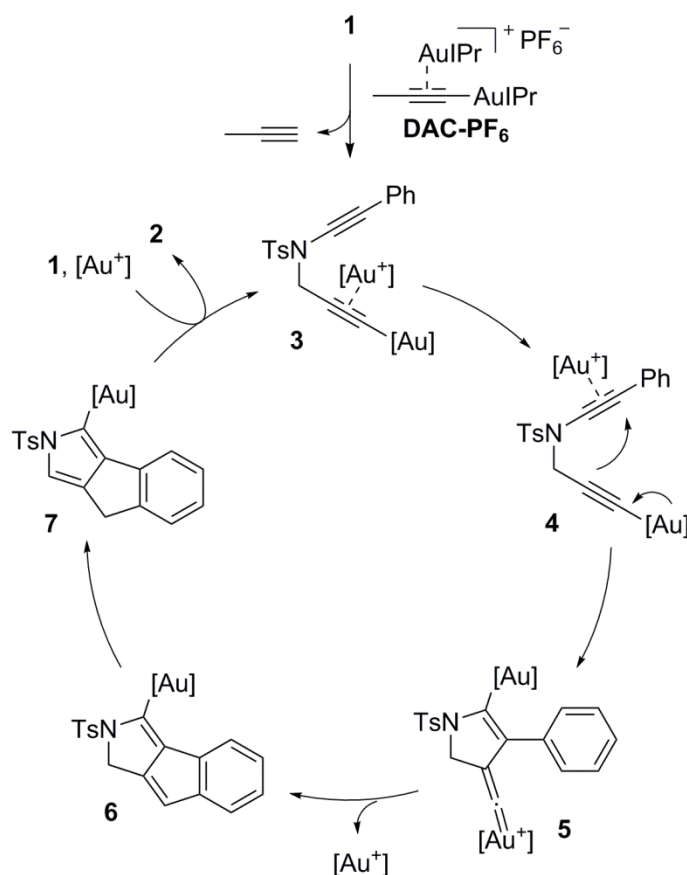
Having established efficient conditions for the synthesis of pyrrole **2a** (Table 1, entry 7), the substrate scope was evaluated (Figure 1). Both electron-withdrawing and -donating functional groups were tolerated in the *para* position of the phenyl group, including the synthetically useful halogen substituents (**2b–f**; 72–77% yields). 3,5-Dimethylphenyl-substituted *N*-propargyl ynamide **1g** showed the most efficient conversion to give pyrrole **2g** in 87% yield. A thiophene-based substrate could also be used, providing the corresponding pyrrole **2h** containing a 5,5,5-fused ring system (68%). Replacement of the tosyl (Ts) by a 2-nosyl (*o*-Ns) group was also successful (**2i**; 81%). Branched propargyl ynamides (R¹ = alkyl) provided the corresponding pyrroles **2j–l** in moderate yields (64–65%).



^a Isolated yields.

Figure 1. Gold-Catalyzed Cyclization of Aryl-Substituted *N*-Propargyl Ynamides.^a

In light of the results that the catalyst reactivity and the substrate scope of this reaction were in good accordance with the reported reactions,^{3b} a plausible reaction mechanism is proposed in Scheme 2. First, *N*-propargyl ynamide **1** is converted to dual σ/π -activated alkyne intermediate **3** by the action of DAC-PF₆.^{3b,k} The cationic gold is transferred to the ynamide alkyne (intermediate **4**), which facilitates the nucleophilic addition of the gold acetylide, leading to formation of gold vinylidene **5**. The subsequent arylation of the gold vinylidene forms vinylgold complex **6** via nucleophilic addition or C–H insertion pathway. After the aromatization of intermediate **6** (which might also occur after the protodeauration of **6**), the catalytic cycle can be terminated by a catalyst transfer from intermediate **7** to *N*-propargyl ynamide **1** to produce pyrrole **2**.⁴ It is worth mentioning that the electrophilic carbon of ynamide triple bond in this reaction is not the α - but the β -position to the nitrogen atom, contrary to the general preference in many gold-catalyzed reactions of ynamides.⁵



Scheme 2. Plausible Reaction Mechanism

To confirm the formation of gold vinylidene **5** (Scheme 2), the author then investigated C(sp³)–H activation reactions using alkyl-substituted *N*-propargyl ynamides **8** (Table 2). In the case of *N*-propargyl ynamides **8a** and **8b**, both 5-membered (**9**) and 6-membered ring compounds (**10**) were formed (52 and 51% combined yields, entries 1 and 2), the former of which was the major isomer (**9/10** = 93:7). It is notable that a tertiary C–H bond in a cycloalkyl substituent was more reactive than a secondary C–H bond; predominantly, the spirocyclic compound **9c** with a quaternary carbon

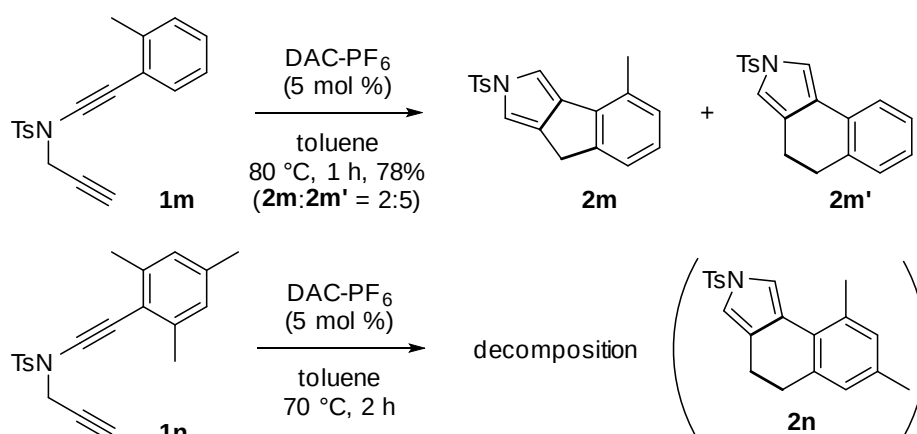
Table 2. Gold-Catalyzed Cyclization of Alkyl-Substituted *N*-Propargyl Ynamides

entry	substrate	product (ratio ^a)	yield (%) ^b
1		 9a + 10a	52 (9a:10a = 93:7)
2		 9b + 10b	51 (9b:10b = 93:7)
3		 9c	50 ^c
4		 9d	36
5		 (±)-9e	44
6		 9f	60
7		 9g	49
8		 10h	57

^a The ratio of **9:10** was determined by NMR analysis. ^b Isolated yields. ^c NMR yield. ^d Cp = cyclopentyl

atom is produced (entry 3).⁶ Selective formation of cyclopenta[*c*]pyrrole derivative **9d** from substrate **3d** bearing a benzyl group showed higher reactivity of the benzylic C(sp³)–H bond than that of the C(sp²)–H bond of the phenyl group. With *N*-propargyl ynamides **8e–g** not having an appropriate C–H bond for the 6-membered ring formation, only the cyclopentane-fused pyrroles **9e–g** were obtained (44–60%, entries 5–7) as the author expected. The pyrrole **9g** was produced from *N*-propargyl ynamide **8g** via the elimination of OTBS group (entry 7). In the case using **8h**, bearing a conjugated enynamide moiety, the pyrrole **10h** containing 6-membered ring was obtained (57%, entry 8) via the reaction with a C(sp³)–H bond at the allylic position.

At the end, the author checked the reaction of aryl *N*-propargyl ynamides bearing a methyl group at the *ortho* position of the phenyl group (Scheme 3). In this case, both aryl C–H and benzyl C–H bonds are potentially reactive. The reaction of *N*-propargyl ynamide **1m** generated a mixture of **2m** and **2m'** with a moderate regioselectivity (2:5; 78% combined yield). On the other hand, the reaction of *N*-propargyl ynamide **1n** with two *ortho* methyl groups led to decomposition without formation of detectable amount of **2n**, presumably due to the steric hindrance of the ynamide moiety.⁷



Scheme 3. Reaction of 2-Methylphenyl-Substituted *N*-Propargyl Ynamides

In conclusion, the author has developed a novel cyclization reaction of *N*-propargyl ynamides for the synthesis of multisubstituted pyrroles. Both aryl and alkyl C–H bonds can be used for the second cyclization step, and corresponding bicyclic and tricyclic pyrroles are obtained in moderate to good yields. The first cyclization step selectively proceeded via 5-*endo-dig* cyclization on the β-carbon of the ynamide, contrary to the general preference for the α-carbon in many gold-catalyzed reactions of ynamides.

Experimental Section

General Methods. IR spectra were obtained on a JASCO FT/IR-4100 spectrometer. Exact mass (HRMS) spectra were recorded on Shimadzu LC-ESI-IT-TOF-MS equipment. ^1H NMR spectra were recorded using a JEOL AL-500 spectrometer at 500 MHz frequency. Chemical shifts are reported in δ (ppm) relative to Me_4Si (in CDCl_3) as internal standard. ^{13}C NMR spectra were recorded using a JEOL AL-500 and referenced to the residual solvent signal. Melting points were measured by a hot stage melting points apparatus (uncorrected). For flash chromatography, silica gel (Wakogel C-200E or C-300E; Wako Pure Chemical Industries, Ltd) was employed.

The known compounds **S2**,⁸ **S5**,⁹ **S7**,⁹ **S10**,¹⁰ **S12**,¹¹ **S13**,¹¹ **S14**,¹¹ **S15**,¹¹ **S17**,¹² **S18**,¹³ **S19**,¹¹ **S20**,¹⁴ and **S22**¹⁵ were synthesized according to the literature.

The ^1H NMR data of **S8**,¹⁶ **S11**,¹⁷ **2a**¹⁸ corresponds to those reported in literature.

1. Preparation of *N*-Propargyl Sulfonamide

N-[3-(*tert*-Butyldimethylsilyl)prop-2-yn-1-yl]-4-methylbenzenesulfonamide (**S1**)

To a stirred solution of HMDS (10.2 mL, 48.0 mmol) in THF (20 mL) was added *n*-BuLi (2.65 M in hexane; 18.1 mL, 48.0 mmol) at -78°C under argon. After stirring for 5 min at room temperature, this solution was added dropwise to the mixture of 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (**S2**) (4.18 g, 20.0 mmol) in THF (40 mL) at -78°C . After stirring for 5 min at room temperature, TBSCl (3.31 g, 22.0 mmol) in THF (40 mL) was added dropwise to the mixture at -78°C and the mixture was gradually warmed to room temperature. After checking the disappearance of the starting material by TLC, the reaction mixture was quenched with aqueous saturated NH_4Cl and extracted with EtOAc twice. The combined organic layer was washed with brine, dried over MgSO_4 , and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10/1 to 3/1) to give **S1** (5.70 g, 88%): colorless solid; mp 58°C ; IR (neat) 3290 (NH), 3250 (NH), 2186 ($\text{C}\equiv\text{C}$), 1343 (NSO_2), 1156 (NSO_2) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : -0.03 (s, 6H), 0.82 (s, 9H), 2.43 (s, 3H), 3.89 (d, $J = 5.7$ Hz, 2H), 4.55 (t, $J = 5.7$ Hz, 1H), 7.31 (d, $J = 8.0$ Hz, 2H), 7.77 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ : -4.9 (2C), 16.3, 21.6, 25.9 (3C), 33.9, 88.1, 100.0, 127.3 (2C), 129.7 (2C), 136.7, 143.7; *Anal.* Calcd for $\text{C}_{16}\text{H}_{25}\text{NO}_2\text{SSi}$: C, 59.40; H, 7.79; N, 4.33. Found: C, 59.39; H, 7.72; N, 4.38.

2-Nitro-*N*-(prop-2-yn-1-yl)benzenesulfonamide (**S3**)

To a stirred solution of propargylamine (606 mg, 11.0 mmol) in THF (20 mL) and pyridine (20 mL) was added *o*-NsCl (2.21 g, 10.0 mmol) at 0°C . After stirring for 10 h at room temperature, water was added and the reaction mixture was extracted with EtOAc twice. The combined organic layer was washed with brine, dried over MgSO_4 , and concentrated in vacuo. The residue was recrystallized from CHCl_3 /hexane to give **S3** (1.55 g, 65%): red silky needles; mp 91°C ; IR (neat) 3320 (NH), 3297 ($\text{C}\equiv\text{CH}$), 2125 ($\text{C}\equiv\text{C}$), 1536 (NO_2), 1367 (NSO_2), 1331 (NO_2), 1159 (NSO_2) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 1.98 (t, $J = 2.6$ Hz, 1H), 4.02 (dd, $J = 6.0, 2.6$ Hz, 2H), 5.71 (t, $J = 6.0$ Hz, 1H), 7.75-7.79 (m, 2H), 7.91-7.94 (m, 1H), 8.19-8.23 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ : 33.4, 73.3, 77.3, 125.5, 131.5, 132.9, 133.8, 133.9, 147.9; *Anal.* Calcd for $\text{C}_9\text{H}_8\text{N}_2\text{O}_4\text{S}$: C, 45.00; H, 3.36; N, 11.66. Found: C, 44.80; H, 3.24; N, 11.69.

N-[1-(*tert*-Butyldimethylsilyl)pent-1-yn-3-yl]-4-methylbenzenesulfonamide (**S4**)

To a stirred solution of (*tert*-butyldimethylsilyl)acetylene (280 μL , 1.50 mmol) in THF (10 mL) was added

n-BuLi (1.5 M in hexane; 1.1 mL, 1.65 mmol) at -78°C under argon. After stirring for 5 min at room temperature, 4-methyl-*N*-propylidenebenzenesulfonamide (**S5**) (349 mg, 1.65 mmol) in THF (5 mL) was added dropwise to the mixture at -78°C . The mixture was gradually warmed to -20°C and stirred for 16 h at that temperature. The reaction mixture was quenched with aqueous saturated NH_4Cl and extracted with EtOAc twice. The combined organic layer was washed with brine, dried over MgSO_4 , and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10/1 to 3/1) to give **S4** (357 mg, 66%): colorless oil; IR (neat) 3248 (NH), 2176 ($\text{C}\equiv\text{C}$), 1328 (NSO_2), 1160 (NSO_2) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : -0.08 (s, 3H), -0.07 (s, 3H), 0.79 (s, 9H), 1.00 (t, $J = 7.4$ Hz, 3H), 1.65–1.76 (m, 2H), 2.42 (s, 3H), 4.00–4.05 (m, 1H), 4.60 (d, $J = 9.2$ Hz, 1H), 7.29 (d, $J = 8.0$ Hz, 2H), 7.77 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ : -4.9 (2C), 9.8, 16.3, 21.5, 25.8 (3C), 30.3, 47.6, 87.3, 104.0, 127.3 (2C), 129.6 (2C), 137.4, 143.3; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{29}\text{NNaO}_2\text{SSi}$ (MNa^+): 374.1586; found: 374.1588.

***N*-[1-(*tert*-Butyldimethylsilyl)hex-1-yn-3-yl]-4-methylbenzenesulfonamide (**S6**)**

According to the procedure described for the preparation of **S4**, *N*-butylidene-4-methylbenzenesulfonamide (**S7**) (805 mg, 3.57 mmol) was converted into **S6** (862 mg, 66%) by the reaction with lithium acetylide generated from (*tert*-butyldimethylsilyl)acetylene (666 μL , 3.57 mmol) and *n*-BuLi (1.5 M in hexane; 2.4 mL, 3.57 mmol): colorless solid; mp 82°C ; IR (neat) 3258 ($\text{C}\equiv\text{CH}$), 2171 ($\text{C}\equiv\text{C}$), 1314 (NSO_2), 1155 (NSO_2) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : -0.09 (s, 3H), -0.08 (s, 3H), 0.79 (s, 9H), 0.92 (t, $J = 7.4$ Hz, 3H), 1.42–1.50 (m, 2H), 1.60–1.69 (m, 2H), 2.41 (s, 3H), 4.05–4.10 (m, 1H), 4.61 (d, $J = 9.2$ Hz, 1H), 7.28 (d, $J = 8.0$ Hz, 2H), 7.77 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ : -4.9 (2C), 13.4, 16.2, 18.6, 21.5, 25.8 (3C), 39.1, 46.1, 87.1, 104.2, 127.3 (2C), 129.6 (2C), 137.5, 143.3; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{31}\text{KNO}_2\text{SSi}$ (MK^+): 404.1482; found: 404.1486.

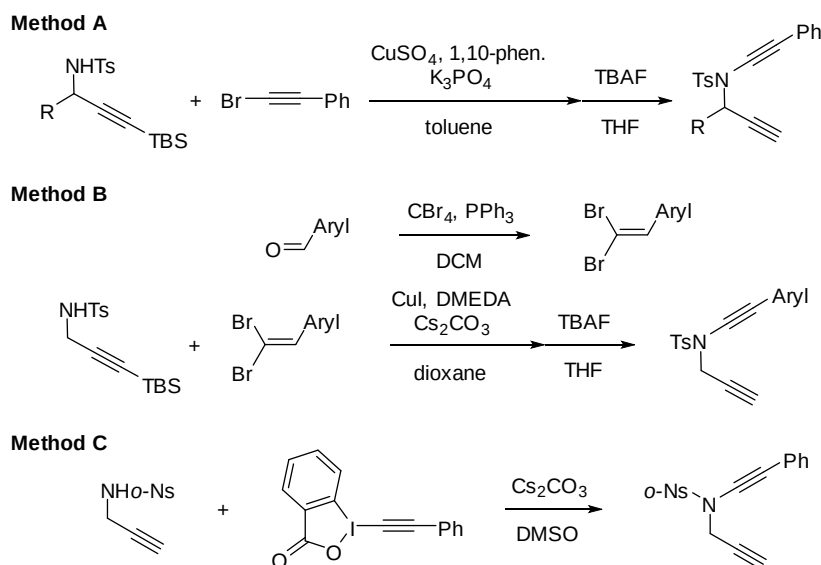
***N*-[4-(*tert*-Butyldimethylsilyl)-1-phenylbut-3-yn-2-yl]-4-methylbenzenesulfonamide (**S9**)**

4-Methyl-*N*-(2-phenylethylidene)benzenesulfonamide (**S8**) was prepared according to the literature procedure for the synthesis of **S5**:² a mixture of phenylacetaldehyde (2.24 mL, 20.0 mmol), *p*-toluenesulfonamide (3.42 g, 20.0 mmol) and sodium *p*-toluenesulfinate (3.56 g, 20.0 mmol) in formic acid (30 mL) and H_2O (30 mL) was stirred for 24 h at room temperature. The resulting white precipitate was filtered off, washed with H_2O and hexane, and then dissolved in CH_2Cl_2 . The solution was washed rapidly with aqueous saturated NaHCO_3 . The organic layer was dried rapidly over MgSO_4 and concentrated in vacuo to give crude **S8** (2.57 g, 47%). ^1H NMR (500 MHz, CDCl_3) δ : 2.45 (s, 3H), 3.79 (d, $J = 5.2$ Hz, 2H), 7.16–7.38 (m, 7H), 7.89 (d, $J = 8.0$ Hz, 2H), 8.61 (t, $J = 5.2$ Hz, 1H). The ^1H NMR spectra were in good agreement with those reported.⁹ This material was used without further purification.

According to the procedure described for the preparation of **S4**, (*tert*-butyldimethylsilyl) (729 μL , 3.90 mmol), *n*-BuLi (1.5 M in hexane; 2.6 mL, 3.9 mmol) and **S8** (820 mg, 3.00 mmol) were converted into **S9** (750 mg, 60%): pale yellow solid; mp 76°C ; IR (neat) 3266 ($\text{C}\equiv\text{CH}$), 2173 ($\text{C}\equiv\text{C}$), 1323 (NSO_2), 1161 (NSO_2) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : -0.10 (s, 6H), 0.75 (s, 9H), 2.40 (s, 3H), 2.91–2.95 (m, 1H), 3.00–3.04 (m, 1H), 4.35–4.40 (m, 1H), 4.59 (t, $J = 9.7$ Hz, 1H), 7.23–7.27 (m, 7H), 7.73 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ : -5.0 (2C), 16.2, 21.5, 25.8 (3C), 42.7, 47.1, 88.7, 103.4, 127.1, 127.3 (2C), 128.3 (2C), 129.6 (2C), 130.1 (2C), 135.4, 137.3, 143.4; Anal. Calcd for $\text{C}_{23}\text{H}_{31}\text{NO}_2\text{SSi}$: C, 66.78; H, 7.55; N, 3.39. Found: C, 66.86; H, 7.55; N, 3.25.

2. Preparation of *N*-Propargyl Ynamides

2-1. Preparation of *N*-Propargyl Arylated Ynamides



General Procedure for Method A:

4-Methyl-*N*-(phenylethynyl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide (1a**)**

To a stirred suspension of **S1** (971 mg, 3.00 mmol), CuSO₄ (47.9 mg, 0.30 mmol), 1,10-phenanthroline (108 mg, 0.60 mmol), and K₃PO₄ (1.27 g, 6.00 mmol) in toluene (6 mL) was added (bromoethynyl)benzene (**S10**) (652 mg, 3.60 mmol) at room temperature. After stirring for 16 h at 70 °C, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo and the residue was roughly purified by column chromatography (silica gel, hexane/EtOAc = 10/1) to give the silylated ynamide as an oil.

This oil was dissolved in THF (30 mL) and TBAF (1.0 M in THF; 3.6 mL, 3.6 mmol) was added to the mixture at 0 °C. After stirring for 1 h at this temperature, the reaction mixture was quenched with aqueous saturated NH₄Cl and extracted with EtOAc twice. The combined organic layer was washed with brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, toluene/hexane = 2/1) to give **1a** (740 mg, 80%): pale yellow solid; mp 65 °C; IR (neat) 3288 (C≡CH), 2231 (C≡C), 2126 (C≡C), 1355 (NSO₂), 1161 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 2.22 (t, *J* = 2.3 Hz, 1H), 2.45 (s, 3H), 4.34 (d, *J* = 2.3 Hz, 2H), 7.28-7.30 (m, 3H), 7.34-7.40 (m, 4H), 7.88 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 21.7, 41.8, 71.2, 74.7, 75.8, 81.4, 124.4, 128.0, 128.2 (4C), 129.6 (2C), 131.5 (2C), 134.0, 145.0; *Anal.* Calcd for C₁₈H₁₅NO₂S: C, 69.88; H, 4.89; N, 4.53. Found: C, 69.65; H, 4.83; N, 4.40.

General Procedure for Method B:

***N*-[(4-Fluorophenyl)ethynyl]-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (**1b**)**

To a stirred suspension of **S1** (324 mg, 1.00 mmol), CuI (38.1 mg, 0.20 mmol), *N,N'*-dimethylethylenediamine (32.3 μL, 0.30 mmol), and Cs₂CO₃ (1.30 g, 4.00 mmol) in dioxane (2 mL) was added 1-(2,2-dibromovinyl)-4-fluorobenzene (**S11**) (420 mg, 1.50 mmol) at room temperature. After stirring for 20 h at 70 °C, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo and the residue was roughly purified by column chromatography (silica gel, hexane/EtOAc = 10/1) to give the silylated ynamide as an oil.

This oil was dissolved in THF (10 mL) and TBAF (1.0 M in THF; 1.2 mL, 1.2 mmol) was added to the mixture at 0 °C. After stirring for 1 h at that temperature, the reaction mixture was quenched with aqueous saturated NH₄Cl and extracted with EtOAc twice. The combined organic layer was washed with brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 8/1) to give **1b** (229 mg, 70%): yellow oil; IR (neat) 3294 (C≡CH), 2240 (C≡C), 2127 (C≡C), 1365 (NSO₂), 1167 (NSO₂)

cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 2.23 (t, *J* = 2.6 Hz, 1H), 2.45 (s, 3H), 4.33 (d, *J* = 2.6 Hz, 2H), 6.97-7.01 (m, 2H), 7.35-7.38 (m, 4H), 7.86 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 21.6, 41.7, 70.1, 74.7, 75.7, 81.0, 115.5 (d, *J* = 21.6 Hz, 2C), 118.4 (d, *J* = 3.6 Hz), 128.1 (2C), 129.6 (2C), 133.6 (d, *J* = 8.4 Hz, 2C), 133.9, 145.1, 162.3 (d, *J* = 249.5 Hz); HRMS (ESI) calcd for C₁₈H₁₄FNNaO₂S (MNa⁺): 350.0627; found: 350.0632.

1-(2,2-Dibromovinyl)-4-fluorobenzene (S11)

S11 was prepared according to the literature procedure for the synthesis of 1-chloro-4-(2,2-dibromovinyl)benzene (**S12**).⁴ To the mixture of 4-fluorobenzaldehyde (372 mg, 3.00 mmol) and CBr₄ (995 mg, 3.00 mmol) in DCM (15 mL) was added PPh₃ (1.57 g, 6.00 mmol) portionwise at 0 °C under argon. After stirring for 2 h at that temperature, hexane (40 mL) and Et₃N (20 mL) were added to the mixture. After stirring for 15 min, the mixture was filtrated through a pad of Celite. The filtrate was concentrated in vacuo and the residue was purified by column chromatography (silica gel, hexane) to give **S11** (717 mg, 85%): colorless oil; ¹H NMR (500 MHz, CDCl₃) δ: 7.06 (dd, *J* = 8.6, 8.6 Hz, 2H), 7.44 (s, 1H), 7.52 (dd, *J* = 8.6, 8.6 Hz, 2H). The ¹H NMR spectra were in good agreement with those reported.¹⁰

N-[(4-Chlorophenyl)ethynyl]-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide (1c)

According to the procedure described for the preparation of **1b** (Method B), **S1** (324 mg, 1.00 mmol) was converted into **1c** (272 mg, 79%) by the reaction with 1-chloro-4-(2,2-dibromovinyl)benzene (**S12**) (444 mg, 1.50 mmol) for 12 h at 70 °C followed by desilylation for 1 h at 0 °C. Column chromatography: silica gel (hexane/EtOAc = 10/1): pale yellow solid; mp 71 °C; IR (neat) 3289 (C≡CH), 2237 (C≡C), 2127 (C≡C), 1366 (NSO₂), 1168 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 2.22 (t, *J* = 2.3 Hz, 1H), 2.45 (s, 3H), 4.33 (d, *J* = 2.3 Hz, 2H), 7.25-7.27 (m, 2H), 7.29-7.31 (m, 2H), 7.35 (d, *J* = 8.6 Hz, 2H), 7.88 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 21.7, 41.7, 70.4, 74.7, 75.7, 82.4, 121.0, 128.1 (2C), 128.5 (2C), 129.7 (2C), 132.7 (2C), 134.0 (2C), 145.1; *Anal.* Calcd for C₁₈H₁₄ClNO₂S: C, 62.88; H, 4.10; N, 4.07. Found: C, 62.92; H, 4.07; N, 3.93.

N-[(4-Bromophenyl)ethynyl]-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide (1d)

According to the procedure described for the preparation of **1b** (Method B), **S1** (324 mg, 1.00 mmol) was converted into **1d** (320 mg, 82%) by the reaction with 1-bromo-4-(2,2-dibromovinyl)benzene (**S13**) (511 mg, 1.50 mmol) for 18 h at 70 °C followed by desilylation for 1 h at 0 °C. Column chromatography: silica gel (hexane/EtOAc = 10/1): pale yellow solid; mp 55 °C; IR (neat) 3305 (C≡CH), 2237 (C≡C), 2127 (C≡C), 1359 (NSO₂), 1162 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 2.23 (t, *J* = 2.3 Hz, 1H), 2.45 (s, 3H), 4.33 (d, *J* = 2.3 Hz, 2H), 7.23 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.6 Hz, 2H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.86 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 21.7, 41.7, 70.4, 74.8, 75.6, 82.5, 121.4, 122.1, 128.1 (2C), 129.6 (2C), 131.4 (2C), 132.8 (2C), 133.9, 145.1; *Anal.* Calcd for C₁₈H₁₄BrNO₂S: C, 55.68; H, 3.63; N, 3.61. Found: C, 55.89; H, 3.59; N, 3.39.

N-[(4-Methoxyphenyl)ethynyl]-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide (1e)

According to the procedure described for the preparation of **1b** (Method B), **S1** (324 mg, 1.00 mmol) was converted into **1e** (212 mg, 62%) by the reaction with 1-(2,2-dibromovinyl)-4-methoxybenzene (**S14**) (438 mg, 1.50 mmol) for 48 h at 70 °C followed by desilylation for 1 h at 0 °C. Column chromatography: silica gel (hexane/EtOAc = 8/1): yellow oil; IR (neat) 3289 (C≡CH), 2236 (C≡C), 2125 (C≡C), 1361 (NSO₂), 1248 (OMe), 1160 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 2.23 (t, *J* = 2.3 Hz, 1H), 2.43 (s, 3H), 3.77 (s, 3H), 4.31 (d, *J* = 2.3 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 7.31-7.34 (m, 4H), 7.86 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ:

21.5, 41.7, 55.1, 70.8, 74.6, 75.8, 80.0, 113.8 (2C), 114.1, 128.0 (2C), 129.5 (2C), 133.4 (2C), 133.8, 144.9, 159.5; HRMS (ESI) calcd for $C_{19}H_{17}KNO_3S$ (MK^+): 378.0566; found: 378.0569.

4-Methyl-*N*-(prop-2-yn-1-yl)-*N*-(*p*-tolylethynyl)benzenesulfonamide (**1f**)

According to the procedure described for the preparation of **1b** (Method B), **S1** (324 mg, 1.00 mmol) was converted into **1f** (241 mg, 75%) by the reaction with 1-(2,2-dibromovinyl)-4-methylbenzene (**S15**) (414 mg, 1.50 mmol) for 12 h at 70 °C followed by desilylation for 1 h at 0 °C. Column chromatography: silica gel (hexane/EtOAc = 10/1): pale yellow solid; mp 52 °C; IR (neat) 3301 (C≡CH), 2239 (C≡C), 2126 (C≡C), 1355 (NSO₂), 1160 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 2.21 (t, *J* = 2.3 Hz, 1H), 2.35 (s, 3H), 2.45 (s, 3H), 4.33 (d, *J* = 2.3 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.6 Hz, 2H), 7.87 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 21.4, 21.6, 41.8, 71.2, 74.6, 75.8, 80.7, 119.3, 128.2 (2C), 129.0 (2C), 129.5 (2C), 131.6 (2C), 134.0, 138.2, 144.9; HRMS (ESI) calcd for $C_{19}H_{17}KNO_2S$ (MK^+): 362.0617; found: 362.0619.

N-[(3,5-Dimethylphenyl)ethynyl]-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (**1g**)

According to the procedure described for the preparation of **1b** (Method B), **S1** (324 mg, 1.00 mmol) was converted into **1g** (202 mg, 60%) by the reaction with 1-(2,2-dibromovinyl)-3,5-dimethylbenzene (**S16**) (435 mg, 1.50 mmol) for 30 h at 70 °C followed by desilylation for 1 h at 0 °C. Column chromatography: silica gel (hexane/EtOAc = 10/1): colorless solid; mp 109 °C; IR (neat) 3298 (C≡CH), 2239 (C≡C), 2126 (C≡C), 1359 (NSO₂), 1167 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 2.21 (t, *J* = 2.6 Hz, 1H), 2.27 (s, 6H), 2.45 (s, 3H), 4.32 (d, *J* = 2.6 Hz, 2H), 6.93 (s, 1H), 7.02 (s, 2H), 7.34 (d, *J* = 8.6 Hz, 2H), 7.87 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 21.0 (2C), 21.7, 41.8, 71.5, 74.6, 75.8, 80.7, 122.0, 128.2 (2C), 129.2 (2C), 129.6 (2C), 129.9, 134.0, 137.8 (2C), 144.9; *Anal.* Calcd for $C_{20}H_{19}NO_2S$: C, 71.19; H, 5.68; N, 4.15. Found: C, 70.90; H, 5.75; N, 4.17.

1-(2,2-Dibromovinyl)-3,5-dimethylbenzene (**S16**)

According to the procedure described for the preparation of **S11**, 3,5-dimethylbenzaldehyde (403 mg, 3.00 mmol) was converted into **S16** (791 mg, 91%) by the reaction for 0.5 h at 0 °C. Column chromatography: silica gel (hexane): colorless oil; ¹H NMR (500 MHz, CDCl₃) δ: 2.31 (s, 6H), 6.95 (s, 1H), 7.12 (s, 2H), 7.38 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ: 21.3 (2C), 89.0, 126.1 (2C), 130.2, 135.1, 137.0, 137.8 (2C); *Anal.* Calcd for $C_{10}H_9Br_2$: C, 41.56; H, 3.14. Found: C, 41.35; H, 3.39.

4-Methyl-*N*-(prop-2-yn-1-yl)-*N*-(thiophen-2-ylethynyl)benzenesulfonamide (**1h**)

According to the procedure described for the preparation of **1b** (Method B), **S1** (324 mg, 1.00 mmol) was converted into **1h** (230 mg, 73%) by the reaction with 2-(2,2-dibromovinyl)thiophene (**S17**) (402 mg, 1.50 mmol) for 20 h at 70 °C followed by desilylation for 1 h at 0 °C. Column chromatography: silica gel (hexane/EtOAc = 8/1): colorless solid; mp 68 °C; IR (neat) 3295 (C≡CH), 2225 (C≡C), 2127 (C≡C), 1361 (NSO₂), 1162 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 2.25 (t, *J* = 2.6 Hz, 1H), 2.45 (s, 3H), 4.33 (d, *J* = 2.6 Hz, 2H), 6.38 (dd, *J* = 3.0, 1.4 Hz, 1H), 6.63 (d, *J* = 3.0 Hz, 1H), 7.35 (d, *J* = 8.6 Hz, 2H), 7.39 (d, *J* = 1.4 Hz, 1H), 7.85 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 21.6, 41.8, 62.1, 74.9, 75.5, 85.6, 111.0, 117.6, 128.0 (2C), 129.7 (2C), 133.9, 136.3, 144.1, 145.2; *Anal.* Calcd for $C_{16}H_{13}NO_2S_2$: C, 60.93; H, 4.15; N, 4.44. Found: C, 60.67; H, 4.22; N, 4.46.

Procedure for Method C:

2-Nitro-*N*-(phenylethynyl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide (**1i**)

To a stirred solution of **S3** (240 mg, 1.00 mmol) and Cs₂CO₃ (650 mg, 2.00 mmol) in DMSO (10 mL) was added 1-(phenylethynyl)-1λ³-benzo[d][1,2]iodaoxol-3(1*H*)-one (**S18**) (522 mg, 1.50 mmol) at room temperature. After stirring for 3.5 h at 50 °C, water was added and the reaction mixture was extracted with EtOAc twice. The combined organic layer was washed with brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, toluene/hexane = 3/2) to give **1i** (160 mg, 47%): yellow oil; IR (neat) 3292 (C≡CH), 2239 (C≡C), 2129 (C≡C), 1542 (NO₂), 1373 (NSO₂), 1328 (NO₂), 1176 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 2.41 (t, *J* = 2.6 Hz, 1H), 4.51 (d, *J* = 2.6 Hz, 2H), 7.27-7.33 (m, 3H), 7.36-7.40 (m, 2H), 7.73-7.82 (m, 3H), 8.22-8.24 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ: 42.3, 72.5, 74.9, 76.1, 79.8, 121.9, 124.6, 128.3 (2C), 128.4, 130.5, 131.7 (2C), 131.9, 132.1, 134.9, 148.0; HRMS (ESI) calcd for C₁₇H₁₂KN₂O₄S (MK⁺): 379.0155; found: 379.0157.

4-Methyl-*N*-(pent-1-yn-3-yl)-*N*-(phenylethynyl)benzenesulfonamide (**1j**)

According to the procedure described for the preparation of **1a** (Method A), **S4** (176 mg, 0.50 mmol) was converted into **1j** (78.2 mg, 46%) by the reaction with **S10** (299 mg, 0.75 mmol) for 24 h at 70 °C followed by desilylation for 1 h at 0 °C. Column chromatography: silica gel (hexane/EtOAc = 10/1): yellow oil; IR (neat) 3283 (C≡CH), 2238 (C≡C), 2120 (C≡C), 1361 (NSO₂), 1168 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 1.05 (t, *J* = 7.2 Hz, 3H), 1.85-1.97 (m, 2H), 2.17 (d, *J* = 2.3 Hz, 1H), 2.43 (s, 3H), 4.63 (td, *J* = 7.7, 2.3 Hz, 1H), 7.27-7.30 (m, 3H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.37-7.39 (m, 2H), 7.87 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 10.4, 21.6, 28.0, 53.8, 73.0, 73.8, 79.2, 79.4, 122.8, 127.8, 128.1 (2C), 128.2 (2C), 129.5 (2C), 131.4 (2C), 134.6, 144.7; HRMS (ESI) calcd for C₂₀H₁₉NNaO₂S (MNa⁺): 360.1034; found: 360.1035.

N-(Hex-1-yn-3-yl)-4-methyl-*N*-(phenylethynyl)benzenesulfonamide (**1k**)

According to the procedure described for the preparation of **1a** (Method A), **S6** (422 mg, 1.20 mmol) was converted into **1k** (101 mg, 24%) by the reaction with **S10** (326 mg, 1.80 mmol) for 30 h at 85 °C followed by desilylation for 1 h at 0 °C. Column chromatography: silica gel (hexane/EtOAc = 10/1): yellow oil; IR (neat) 3288 (C≡CH), 2237 (C≡C), 2119 (C≡C), 1361 (NSO₂), 1168 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 0.97 (t, *J* = 7.4 Hz, 3H), 1.47-1.54 (m, 2H), 1.79-1.95 (m, 2H), 2.15 (d, *J* = 2.3 Hz, 1H), 2.44 (s, 3H), 4.73 (td, *J* = 7.7, 2.3 Hz, 1H), 7.28-7.31 (m, 3H), 7.33 (d, *J* = 8.6 Hz, 2H), 7.37-7.39 (m, 2H), 7.87 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 13.3, 18.9, 21.6, 36.4, 52.0, 73.0, 73.7, 79.3, 79.5, 122.8, 127.8, 128.1 (2C), 128.2 (2C), 129.5 (2C), 131.4 (2C), 134.6, 144.7; HRMS (ESI) calcd for C₂₁H₂₁KNO₂S (MK⁺): 390.0930; found: 390.0929.

4-Methyl-*N*-(1-phenylbut-3-yn-2-yl)-*N*-(phenylethynyl)benzenesulfonamide (**1l**)

According to the procedure described for the preparation of **1a** (Method A), **S9** (165 mg, 0.40 mmol) was converted into **1l** (79.0 mg, 49%) by the reaction with **S10** (218 mg, 1.20 mmol) and K₃PO₄ (340 mg, 1.60 mmol) for 48 h at 85 °C followed by desilylation for 1 h at 0 °C. Column chromatography: silica gel (hexane/EtOAc = 10/1): yellow oil; IR (neat) 3283 (C≡CH), 2237 (C≡C), 2120 (C≡C), 1362 (NSO₂), 1166 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 2.23 (d, *J* = 1.9 Hz, 1H), 2.42 (s, 3H), 3.13 (dd, *J* = 13.7, 7.6 Hz, 1H), 3.21 (dd, *J* = 13.7, 7.6 Hz, 1H), 4.96 (ddd, *J* = 7.6, 7.6, 1.9 Hz, 1H), 7.24-7.33 (m, 10H), 7.42-7.44 (m, 2H), 7.71 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 21.6, 40.7, 53.7, 73.8, 74.6, 79.1, 79.2, 122.7, 127.1, 128.0 (3C), 128.2 (2C), 128.5 (2C), 129.4 (4C), 131.5 (2C), 134.4, 135.7, 144.6; HRMS (ESI) calcd for C₂₅H₂₁KNO₂S (MK⁺): 438.0930; found: 438.0934.

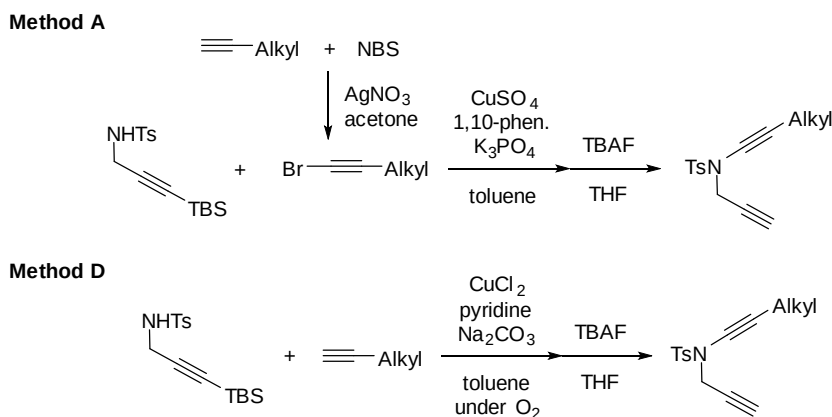
4-Methyl-*N*-(prop-2-yn-1-yl)-*N*-(*o*-tolylethynyl)benzenesulfonamide (**1m**)

According to the procedure described for the preparation of **1b** (Method B), **S1** (324 mg, 1.00 mmol) was converted into **1m** (236 mg, 73%) by the reaction with 1-(2,2-dibromovinyl)-2-methylbenzene (**S19**) (414 mg, 1.50 mmol) for 15 h at 70 °C followed by desilylation for 1 h at 0 °C. Column chromatography: silica gel (hexane/EtOAc = 15/1): colorless solid; mp 83 °C; IR (neat) 3278 (C≡CH), 2239 (C≡C), 2123 (C≡C), 1348 (NSO₂), 1162 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 2.21 (t, *J* = 2.3 Hz, 1H), 2.36 (s, 3H), 2.44 (s, 3H), 4.36 (d, *J* = 2.3 Hz, 2H), 7.10-7.13 (m, 1H), 7.16-7.20 (m, 2H), 7.33-7.35 (m, 3H), 7.88 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 20.7, 21.7, 41.9, 70.2, 74.6, 75.9, 85.2, 122.3, 125.4, 128.0, 128.2 (2C), 129.3, 129.6 (2C), 131.6, 134.1, 140.0, 145.0; HRMS (ESI) calcd for C₁₉H₁₇KNO₂S (MK⁺): 362.0617; found: 362.0617.

***N*-(Mesitylethynyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (1n)**

According to the procedure described for the preparation of **1b** (Method B), **S1** (324 mg, 1.00 mmol) was converted into **1n** (260 mg, 74%) by the reaction with 2-(2,2-dibromovinyl)-1,3,5-trimethylbenzene (**S20**) (456 mg, 1.50 mmol) for 36 h at 70 °C followed by desilylation for 1 h at 0 °C. Column chromatography: silica gel (hexane/EtOAc = 15/1): colorless solid; mp 100 °C; IR (neat) 3264 (C≡CH), 2234 (C≡C), 2124 (C≡C), 1350 (NSO₂), 1163 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 2.19 (t, *J* = 2.6 Hz, 1H), 2.26 (s, 3H), 2.32 (s, 6H), 2.43 (s, 3H), 4.37 (d, *J* = 2.6 Hz, 2H), 6.84 (s, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.87 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 20.9 (2C), 21.2, 21.6, 41.9, 69.0, 74.6, 75.9, 88.5, 119.2, 127.5 (2C), 128.1 (2C), 129.6 (2C), 134.1, 137.4, 139.9 (2C), 144.9; *Anal.* Calcd for C₂₁H₂₁NO₂S: C, 71.77; H, 6.02; N, 3.99. Found: C, 71.50; H, 6.00; N, 3.94.

2-2. Preparation of *N*-Propargyl Alkylated Ynamides



General Procedure for Method D:

***N*-(Hex-1-yn-1-yl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (8a)**

To a stirred suspension of **S1** (324 mg, 1.00 mmol), CuCl₂ (26.9 mg, 0.20 mmol), pyridine (161 μL, 2.00 mmol), and Na₂CO₃ (212 mg, 2.00 mmol) in toluene (10 mL) was added hex-1-yne (570 μL, 5.00 mmol) at room temperature under O₂. After stirring for 10 h at 70 °C, additional hex-1-yne (342 μL, 3.00 mmol) was added to the mixture. After stirring for another 12 h at 70 °C, the reaction mixture was concentrated in vacuo and the residue was roughly purified by column chromatography (silica gel, hexane/EtOAc = 10/1) to give the silylated ynamide as an oil.

This oil was dissolved in THF (10 mL), and TBAF (1.0 M in THF; 1.2 mL, 1.2 mmol) was added to the mixture at 0 °C. After stirring for 1 h at this temperature, the reaction mixture was quenched with aqueous saturated NH₄Cl and extracted with EtOAc twice. The combined organic layer was washed with brine, dried over MgSO₄, and

concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 12/1) to give **8a** (142 mg, 49%): yellow oil; IR (neat) 3285 (C≡CH), 2254 (C≡C), 2125 (C≡C), 1364 (NSO₂), 1166 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 0.89 (t, *J* = 7.2 Hz, 3H), 1.33-1.41 (m, 2H), 1.43-1.49 (m, 2H), 2.18 (t, *J* = 2.3 Hz, 1H), 2.27 (t, *J* = 6.9 Hz, 2H), 2.45 (s, 3H), 4.21 (d, *J* = 2.3 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.82 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 13.5, 18.0, 21.6 (2C), 30.7, 41.6, 71.0, 72.2, 74.2, 76.0, 128.1 (2C), 129.4 (2C), 134.0, 144.6; HRMS (ESI) calcd for C₁₆H₁₉NNaO₂S (MNa⁺): 312.1034; found: 312.1034.

4-Methyl-*N*-(oct-1-yn-1-yl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide (**8b**)

According to the procedure described for the preparation of **8a** (Method D), **S1** (324 mg, 1.00 mmol) and 1-octyne (739 + 443 μL, 5.00 + 3.00 mmol) were converted into **8b** (132 mg, 42%). Column chromatography: silica gel (hexane/EtOAc = 12/1): yellow oil; IR (neat) 3284 (C≡CH), 2253 (C≡C), 2125 (C≡C), 1365 (NSO₂), 1166 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 0.88 (t, *J* = 7.2 Hz, 3H), 1.21-1.37 (m, 6H), 1.44-1.50 (m, 2H), 2.16 (t, *J* = 2.3 Hz, 1H), 2.26 (t, *J* = 7.2 Hz, 2H), 2.45 (s, 3H), 4.22 (d, *J* = 2.3 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.82 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 14.0, 18.3, 21.6, 22.5, 28.3, 28.7, 31.2, 41.6, 71.1, 72.3, 74.2, 76.0, 128.1 (2C), 129.4 (2C), 134.0, 144.6; HRMS (ESI) calcd for C₁₈H₂₃NNaO₂S (MNa⁺): 340.1347; found: 340.1348.

N-(3-Cyclopentylprop-1-yn-1-yl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (**8c**)

To a mixture of 3-cyclopentylprop-1-yne (260 mg, 2.40 mmol) and NBS (427 mg, 2.40 mmol) in acetone (12 mL) was added AgNO₃ (40.8 mg, 0.24 mmol) at room temperature. After stirring for 4 h at that temperature, the mixture was diluted with hexane and filtrated through a pad of silica gel. The filtrate was carefully concentrated in vacuo to give the bromoalkyne, which was used without further purification.

According to the procedure described for the preparation of **1a** (Method A), **S1** (259 mg, 0.80 mmol) was converted into **8c** (155 mg, 61%) by the reaction with this bromoalkyne for 20 h at 70 °C followed by desilylation for 1 h at 0 °C. Column chromatography (silica gel, hexane/EtOAc = 15/1): colorless oil; IR (neat) 3283 (C≡CH), 2254 (C≡C), 2132 (C≡C), 1357 (NSO₂), 1164 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 1.19-1.26 (m, 2H), 1.47-1.61 (m, 4H), 1.69-1.75 (m, 2H), 1.96-2.05 (m, 1H), 2.16 (t, *J* = 2.6 Hz, 1H), 2.27 (d, *J* = 6.9 Hz, 2H), 2.45 (s, 3H), 4.22 (d, *J* = 2.3 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.82 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 21.6, 24.1, 25.3 (2C), 31.8 (2C), 39.1, 41.7, 70.6, 72.4, 74.2, 76.1, 128.2 (2C), 129.4 (2C), 134.1, 144.6; HRMS (ESI) calcd for C₁₈H₂₁NNaO₂S (MNa⁺): 338.1191; found: 338.1192.

4-Methyl-*N*-(4-phenylbut-1-yn-1-yl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide (**8d**)

According to the procedure described for the preparation of **8a** (Method D), **S1** (324 mg, 1.00 mmol) and 4-phenylbut-1-yne (708 + 425 μL, 5.00 + 3.00 mmol) were converted into **8d** (188 mg, 56%). Column chromatography: silica gel (hexane/EtOAc = 12/1): colorless oil; IR (neat) 3298 (C≡CH), 2253 (C≡C), 2122 (C≡C), 1360 (NSO₂), 1161 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 2.14 (t, *J* = 2.3 Hz, 1H), 2.43 (s, 3H), 2.57 (t, *J* = 7.4 Hz, 2H), 2.80 (t, *J* = 7.4 Hz, 2H), 4.17 (d, *J* = 2.3 Hz, 2H), 7.19-7.22 (m, 3H), 7.25-7.28 (m, 4H), 7.72 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 20.5, 21.6, 35.0, 41.6, 70.2, 73.0, 74.3, 76.0, 126.1, 128.0 (2C), 128.3 (2C), 128.4 (2C), 129.4 (2C), 134.0, 140.4, 144.6; HRMS (ESI) calcd for C₂₀H₁₉KNO₂S (MK⁺): 376.0774; found: 376.0777.

N-(Cyclopentylethynyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (**8e**)

According to the procedure described for the preparation of **8c** (Method A), **S1** (194 mg, 0.60 mmol) was converted into **8e** (67.2 mg, 37%) by the reaction with (bromoethynyl)cyclopentane which was synthesized from cyclopentylacetylene (170 mg, 1.80 mmol), NBS (320 mg, 1.80 mmol) and AgNO₃ (30.6 mg, 0.18 mmol) for 32 h at 70 °C followed by desilylation for 1 h at 0 °C. Column chromatography: silica gel (hexane/EtOAc = 12/1): yellow oil; IR (neat) 3281 (C≡CH), 2253 (C≡C), 2124 (C≡C), 1361 (NSO₂), 1166 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 1.52-1.60 (m, 4H), 1.64-1.73 (m, 2H), 1.83-1.90 (m, 2H), 2.17 (t, *J* = 2.3 Hz, 1H), 2.45 (s, 3H), 2.67-2.73 (m, 1H), 4.20 (d, *J* = 2.3 Hz, 2H), 7.33 (d, *J* = 8.6 Hz, 2H), 7.81 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 21.6, 24.7 (2C), 29.8, 33.8 (2C), 41.6, 72.1, 74.2, 75.2, 76.0, 128.1 (2C), 129.3 (2C), 133.9, 144.6; HRMS (ESI) calcd for C₁₇H₁₉NNaO₂S (MNa⁺): 324.1034; found: 324.1033.

***N*-(3,3-Dimethylbut-1-yn-1-yl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (8f)**

According to the procedure described for the preparation of **8a** (Method D), **S1** (324 mg, 1.00 mmol) and 3,3-dimethylbut-1-yne (613 + 368 μL, 5.00 + 3.00 mmol) were converted into **8f** (116 mg, 40%). Column chromatography: silica gel (hexane/EtOAc = 10/1): colorless solid; mp 83 °C; IR (neat) 3285 (C≡CH), 2248 (C≡C), 2126 (C≡C), 1359 (NSO₂), 1165 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 1.20 (s, 9H), 2.15 (t, *J* = 2.6 Hz, 1H), 2.45 (s, 3H), 4.19 (d, *J* = 2.6 Hz, 2H), 7.33 (d, *J* = 7.4 Hz, 2H), 7.82 (d, *J* = 7.4 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 21.6, 27.4, 31.0 (3C), 41.7, 71.5, 74.1, 75.9, 79.1, 128.3 (2C), 129.3 (2C), 133.9, 144.6; HRMS (ESI) calcd for C₁₆H₁₉KNO₂S (MK⁺): 328.0774; found: 328.0775.

***N*-(4-[(*tert*-Butyldimethylsilyloxy)but-1-yn-1-yl]-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (8g)**

According to the procedure described for the preparation of **8a** (Method D), **S1** (324 mg, 1.00 mmol) and 4-(*tert*-butyldimethylsilyloxy)but-1-yne (618 + 412 μL, 3.00 + 2.00 mmol) were converted into 141 mg of *N*-(4-hydroxybut-1-yn-1-yl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (**S21**) as an inseparable mixture including other unidentified compounds. In this case an increased amount of TBAF (1.0 M in THF; 2.4 mL, 2.4 mmol) was used for desilylation. The crude **S21** was dissolved in DMF (1 mL) at room temperature, followed by the addition of imidazole (69.4 mg, 1.02 mmol) and TBSCl (154 mg, 1.02 mmol). After stirring for 2 h at this temperature, water was added and the whole was extracted with Et₂O twice. The combined organic layer was washed with brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10/1) to give **8g** (143 mg, 37% from **S1**): yellow oil; IR (neat) 3289 (C≡CH), 2255 (C≡C), 2125 (C≡C), 1367 (NSO₂), 1168 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 0.05 (s, 6H), 0.88 (s, 9H), 2.17 (t, *J* = 2.3 Hz, 1H), 2.45 (s, 3H), 2.49 (t, *J* = 7.4 Hz, 2H), 3.68 (t, *J* = 7.4 Hz, 2H), 4.21 (d, *J* = 2.3 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.82 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: -5.3 (2C), 18.3, 21.7, 22.8, 25.8 (3C), 41.6, 62.0, 68.0, 73.3, 74.3, 76.0, 128.1 (2C), 129.5 (2C), 134.1, 144.7; HRMS (ESI) calcd for C₂₀H₂₉NNaO₃SSi (MNa⁺): 414.1535; found: 414.1536.

***N*-(3-Cyclohexylideneprop-1-yn-1-yl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (8h)**

According to the procedure described for the preparation of **1a** (Method A), **S1** (243 mg, 0.75 mmol) was converted into **8h** (176 mg, 72%) by the reaction with (3-bromoprop-2-yn-1-ylidene)cyclohexane (179 mg, 0.90 mmol) for 24 h at 70 °C followed by desilylation for 1 h at 0 °C. Column chromatography: silica gel (hexane/EtOAc = 12/1): colorless solid; mp 64 °C; IR (neat) 3291 (C≡CH), 2220 (C≡C), 2130 (C≡C), 1363 (NSO₂), 1164 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 1.52-1.56 (m, 6H), 2.13-2.17 (m, 2H), 2.18 (t, *J* = 2.6 Hz, 1H), 2.30-2.32 (m, 2H), 2.45 (s, 3H), 4.28 (d, *J* = 2.6 Hz, 2H), 5.26 (s, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.82 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 21.6, 26.2, 27.5, 28.2, 31.5, 35.9, 41.8, 68.8, 74.4, 76.0, 82.6, 100.5, 128.2

(2C), 129.5 (2C), 134.1, 144.7, 156.3; *Anal.* Calcd for C₁₉H₂₁NO₂S: C, 69.69; H, 6.46; N, 4.28. Found: C, 69.68; H, 6.52; N, 4.30.

3. Gold-Catalyzed Cyclization of *N*-Propargyl Ynamides

General Procedure for Gold-Catalyzed Cyclization of *N*-Propargyl Ynamides:

2-Tosyl-2,8-dihydroindeno[1,2-*c*]pyrrole (2a)

To the solution of **1a** (50.0 mg, 0.162 mmol) in toluene (1.5 mL) was added DAC-PF₆ (**S22**) (11.0 mg, 0.0081 mmol) at room temperature under argon. After stirring for 1 h at 80 °C, the reaction mixture was concentrated in vacuo and the residue was purified by column chromatography (silica gel, hexane/EtOAc = 14/1) to give **2a** (43.0 mg, 86%): colorless solid; ¹H NMR (500 MHz, CDCl₃) δ: 2.36 (s, 3H), 3.65 (s, 2H), 7.03 (m, 1H), 7.17-7.27 (m, 5H), 7.37 (d, *J* = 7.5 Hz, 1H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.76 (d, *J* = 8.1 Hz, 2H). The ¹H NMR spectra were in good agreement with those reported.¹⁷

6-Fluoro-2-tosyl-2,8-dihydroindeno[1,2-*c*]pyrrole (2b)

According to the procedure described for the preparation of **2a**, **1b** (40.0 mg, 0.122 mmol) was converted into **2b** (30.7 mg, 77%) by the reaction for 1 h at 80 °C. Column chromatography: silica gel (hexane/EtOAc = 12/1): colorless solid; mp 130 °C; IR (neat) 1368 (NSO₂), 1166 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 2.37 (s, 3H), 3.64 (s, 2H), 6.96 (ddd, *J* = 8.6, 8.6, 1.7 Hz, 1H), 7.03 (m, 1H), 7.07 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.22 (m, 1H), 7.27 (d, *J* = 8.6 Hz, 2H), 7.41 (dd, *J* = 8.6, 4.6 Hz, 1H), 7.77 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 21.6, 30.4 (d, *J* = 2.4 Hz), 109.2, 113.0 (d, *J* = 22.8 Hz), 113.5, 114.0 (d, *J* = 22.8 Hz), 122.1 (d, *J* = 9.6 Hz), 126.8 (2C), 129.9 (2C), 131.7 (d, *J* = 2.4 Hz), 133.0, 135.0, 136.2, 144.8, 149.4 (d, *J* = 8.4 Hz), 162.0 (d, *J* = 245.9 Hz); *Anal.* Calcd for C₁₈H₁₄FNO₂S: C, 66.04; H, 4.31; N, 4.28. Found: C, 65.97; H, 4.18; N, 4.26.

6-Chloro-2-tosyl-2,8-dihydroindeno[1,2-*c*]pyrrole (2c)

According to the procedure described for the preparation of **2a**, **1c** (40.0 mg, 0.116 mmol) was converted into **2c** (30.7 mg, 77%) by the reaction for 2 h at 80 °C. Column chromatography: silica gel (hexane/EtOAc = 12/1): colorless solid; mp 133 °C; IR (neat) 1367 (NSO₂), 1169 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 2.38 (s, 3H), 3.63 (s, 2H), 7.03 (d, *J* = 1.7 Hz, 1H), 7.22-7.28 (m, 4H), 7.34 (m, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 21.7, 30.2, 109.8, 113.5, 122.1, 125.8, 126.8 (2C), 127.2, 129.9 (2C), 132.1, 132.8, 134.2, 134.8, 136.1, 144.9, 148.9; *Anal.* Calcd for C₁₈H₁₄ClNO₂S: C, 62.88; H, 4.10; N, 4.07. Found: C, 62.72; H, 4.14; N, 4.04.

6-Bromo-2-tosyl-2,8-dihydroindeno[1,2-*c*]pyrrole (2d)

According to the procedure described for the preparation of **2a**, **1d** (40.0 mg, 0.103 mmol) was converted into **2d** (29.1 mg, 73%) by the reaction for 2 h at 80 °C. Column chromatography: silica gel (hexane/EtOAc = 12/1): colorless solid; mp 162 °C; IR (neat) 1365 (NSO₂), 1170 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 2.37 (s, 3H), 3.63 (s, 2H), 7.03 (d, *J* = 1.7 Hz, 1H), 7.25-7.28 (m, 3H), 7.32-7.38 (m, 2H), 7.50 (m, 1H), 7.77 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 21.6, 30.1, 109.9, 113.4, 120.1, 122.5, 126.8 (2C), 128.7, 129.9 (2C), 130.0, 132.6, 134.6, 134.8, 136.1, 144.9, 149.1; *Anal.* Calcd for C₁₈H₁₄BrNO₂S: C, 55.68; H, 3.63; N, 3.61. Found: C, 55.72; H, 3.60; N, 3.68.

6-Methoxy-2-tosyl-2,8-dihydroindeno[1,2-*c*]pyrrole (2e)

According to the procedure described for the preparation of **2a**, **1e** (40.0 mg, 0.118 mmol) was converted into **2e** (29.8 mg, 75%) by the reaction for 1 h at 80 °C. Column chromatography: silica gel (hexane/EtOAc = 10/1): pale yellow solid; mp 168 °C; IR (neat) 1361 (NSO₂), 1282 (OMe), 1164 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 2.38 (s, 3H), 3.63 (s, 2H), 3.81 (s, 3H), 6.82 (dd, *J* = 8.0, 2.3 Hz, 1H), 6.94 (m, 1H), 7.00 (m, 1H), 7.15-7.16 (m, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 21.5, 30.4, 55.4, 108.5, 111.4, 112.8, 113.4, 122.0, 126.7 (2C), 128.4, 129.8 (2C), 133.3, 135.8, 136.4, 144.6, 149.1, 158.9; HRMS (ESI) calcd for C₁₉H₁₇NNaO₃S (MNa⁺): 362.0827; found: 362.0829.

6-Methyl-2-tosyl-2,8-dihydroindeno[1,2-c]pyrrole (**2f**)

According to the procedure described for the preparation of **2a**, **1f** (40.0 mg, 0.124 mmol) was converted into **2f** (28.9 mg, 72%) by the reaction for 1 h at 80 °C. Column chromatography: silica gel (hexane/EtOAc = 14/1): colorless solid; mp 157 °C; IR (neat) 1358 (NSO₂), 1163 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 2.35 (s, 3H), 2.36 (s, 3H), 3.61 (s, 2H), 7.01 (d, *J* = 1.7 Hz, 1H), 7.07 (d, *J* = 7.4 Hz, 1H), 7.19-7.25 (m, 4H), 7.38 (d, *J* = 7.4 Hz, 1H), 7.75 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 21.5 (2C), 30.1, 109.2, 113.4, 121.1, 126.3, 126.7 (2C), 127.7, 129.8 (2C), 132.8, 133.3, 136.0, 136.3, 136.4, 144.6, 147.5; *Anal.* Calcd for C₁₉H₁₇NO₂S: C, 70.56; H, 5.30; N, 4.33. Found: C, 70.58; H, 5.31; N, 4.23.

5,7-Dimethyl-2-tosyl-2,8-dihydroindeno[1,2-c]pyrrole (**2g**)

According to the procedure described for the preparation of **2a**, **1g** (40.0 mg, 0.119 mmol) was converted into **2g** (34.8 mg, 87%) by the reaction for 2 h at 80 °C. Column chromatography: silica gel (hexane/EtOAc = 12/1): colorless solid; mp 131 °C; IR (neat) 1369 (NSO₂), 1168 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 2.25 (s, 3H), 2.33 (s, 3H), 2.35 (s, 3H), 3.48 (s, 2H), 6.84 (s, 1H), 7.02 (d, *J* = 1.1 Hz, 1H), 7.16 (s, 1H), 7.22 (d, *J* = 1.1 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 2H), 7.74 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 18.7, 21.2, 21.5, 28.7, 109.5, 113.4, 119.5, 126.7 (2C), 128.6, 129.8 (2C), 133.5, 134.3, 135.2, 136.3, 136.4, 136.8, 143.0, 144.6; *Anal.* Calcd for C₂₀H₁₉NO₂S: C, 71.19; H, 5.68; N, 4.15. Found: C, 71.44; H, 5.73; N, 4.06.

6-Tosyl-4,6-dihydrothieno[2',3':3,4]cyclopenta[1,2-c]pyrrole (**2h**)

According to the procedure described for the preparation of **2a**, **1h** (40.0 mg, 0.127 mmol) was converted into **2h** (27.2 mg, 68%) by the reaction for 3 h at 80 °C. Column chromatography: silica gel (hexane/EtOAc = 12/1): pale green solid; mp 145 °C; IR (neat) 1362 (NSO₂), 1167 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 2.38 (s, 3H), 3.48 (s, 2H), 6.97 (d, *J* = 5.2 Hz, 1H), 7.01 (m, 1H), 7.06 (m, 1H), 7.23-7.27 (m, 3H), 7.75 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 21.5, 27.8, 107.4, 113.8, 122.9, 126.7 (2C), 127.7, 129.8 (2C), 131.4, 135.1, 136.2, 137.1, 144.7, 151.4; HRMS (ESI) calcd for C₁₆H₁₃NNaO₂S₂ (MNa⁺): 338.0285; found: 338.0285.

2-[(2-Nitrophenyl)sulfonyl]-2,8-dihydroindeno[1,2-c]pyrrole (**2i**)

According to the procedure described for the preparation of **2a**, **1i** (40.0 mg, 0.118 mmol) was converted into **2i** (32.4 mg, 81%) by the reaction for 1 h at 80 °C. Column chromatography: silica gel (hexane/EtOAc = 5/1): brown solid; mp 156 °C; IR (neat) 1536 (NO₂), 1367 (NSO₂), 1348 (NO₂), 1164 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 3.74 (s, 2H), 7.14 (m, 1H), 7.25 (ddd, *J* = 7.4, 7.4, 1.4 Hz, 1H), 7.30 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.36 (d, *J* = 1.4 Hz, 1H), 7.43 (d, *J* = 7.4 Hz, 1H), 7.56 (d, *J* = 7.4 Hz, 1H), 7.61-7.66 (m, 2H), 7.70-7.76 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 30.2, 110.4, 114.3, 121.7, 124.7, 125.7, 127.0, 127.1, 129.3, 132.6, 132.7, 133.4, 134.6, 135.1, 136.3, 147.2, 147.6; *Anal.* Calcd for C₁₇H₁₂N₂O₄S: C, 59.99; H, 3.55; N, 8.23. Found: C, 59.88; H, 3.54; N, 7.97.

1-Ethyl-2-tosyl-2,8-dihydroindeno[1,2-c]pyrrole (2j)

According to the procedure described for the preparation of **2a**, **1j** (40.0 mg, 0.119 mmol) was converted into **2j** (25.8 mg, 65%) by the reaction for 1 h at 80 °C. Column chromatography: silica gel (hexane/EtOAc = 15/1): pale yellow solid; mp 135 °C; IR (neat) 1354 (NSO₂), 1167 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 1.25 (t, *J* = 7.4 Hz, 3H), 2.38 (s, 3H), 2.81 (q, *J* = 7.4 Hz, 2H), 3.67 (s, 2H), 7.19 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.25-7.29 (m, 3H), 7.37 (d, *J* = 7.4 Hz, 1H), 7.43 (s, 1H), 7.53 (d, *J* = 7.4 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 12.7, 20.6, 21.5, 31.0, 110.8, 121.3, 125.5, 126.4, 126.6 (2C), 126.9, 128.9, 129.9 (2C), 130.4, 133.3, 135.7, 136.6, 144.5, 147.2; *Anal.* Calcd for C₂₀H₁₉NO₂S: C, 71.19; H, 5.68; N, 4.15. Found: C, 71.02; H, 5.77; N, 4.12.

1-Propyl-2-tosyl-2,8-dihydroindeno[1,2-c]pyrrole (2k)

According to the procedure described for the preparation of **2a**, **1k** (40.0 mg, 0.114 mmol) was converted into **2k** (25.5 mg, 64%) by the reaction for 1 h at 80 °C. Column chromatography: silica gel (hexane/EtOAc = 17/1): colorless solid; mp 117 °C; IR (neat) 1362 (NSO₂), 1173 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 0.91 (t, *J* = 7.2 Hz, 3H), 1.65-1.72 (m, 2H), 2.38 (s, 3H), 2.74 (t, *J* = 7.7 Hz, 2H), 3.63 (s, 2H), 7.20 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.25-7.29 (m, 3H), 7.37 (d, *J* = 7.4 Hz, 1H), 7.43 (s, 1H), 7.53 (d, *J* = 7.4 Hz, 1H), 7.66 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 14.0, 21.5, 21.8, 29.0, 30.9, 111.0, 121.4, 125.5, 126.4, 126.6 (2C), 126.9, 127.8, 129.8 (2C), 131.0, 133.3, 135.8, 136.7, 144.4, 147.1; *Anal.* Calcd for C₂₁H₂₁NO₂S: C, 71.77; H, 6.02; N, 3.99. Found: C, 71.99; H, 5.99; N, 4.01.

1-Benzyl-2-tosyl-2,8-dihydroindeno[1,2-c]pyrrole (2l)

According to the procedure described for the preparation of **2a**, **1l** (40.0 mg, 0.100 mmol) was converted into **2l** (25.7 mg, 64%) by the reaction for 1 h at 80 °C. Column chromatography: silica gel (hexane/EtOAc = 15/1): colorless solid; mp 153 °C; IR (neat) 1354 (NSO₂), 1168 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 2.38 (s, 3H), 3.00 (s, 2H), 4.16 (s, 2H), 7.04-7.06 (m, 2H), 7.14 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.19-7.26 (m, 7H), 7.49 (s, 1H), 7.51 (d, *J* = 7.4 Hz, 1H), 7.59 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 21.6, 30.3, 33.1, 111.1, 121.3, 125.4, 125.7, 126.4 (2C), 126.7 (2C), 126.8, 128.3 (2C), 129.2 (2C), 129.8 (2C), 132.6, 133.3, 135.5, 136.4, 137.9, 144.5, 147.2; *Anal.* Calcd for C₂₅H₂₁NO₂S: C, 75.16; H, 5.30; N, 3.51. Found: C, 74.91; H, 5.29; N, 3.38.

5-Ethyl-2-tosyl-2,4,5,6-tetrahydrocyclopenta[c]pyrrole (9a) and

5-Methyl-2-tosyl-4,5,6,7-tetrahydro-2H-isoindole (10a)

According to the procedure described for the preparation of **2a**, **8a** (40.0 mg, 0.138 mmol) was converted into an inseparable mixture of **9a** and **10a** (20.8 mg, 52% combined isolated yield, **9a/10a** = 93:7) by the reaction for 1.5 h at 80 °C. Column chromatography: silica gel (hexane/EtOAc = 14/1): colorless amorphous solid; IR (neat) 1361 (NSO₂), 1168 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: (Major isomer **9a**) 0.91 (t, *J* = 7.2 Hz, 3H), 1.45-1.51 (m, 2H), 2.18 (dd, *J* = 15.5, 8.0 Hz, 2H), 2.39 (s, 3H), 2.46-2.55 (m, 1H), 2.69 (dd, *J* = 15.5, 8.0 Hz, 2H), 6.74 (s, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.71 (d, *J* = 8.0 Hz, 2H); (Minor isomer **10a**): 0.99 (d, *J* = 7.2 Hz, 3H), 1.21-1.24 (m, 1H), 1.62-1.77 (m, 2H), 1.99-2.04 (m, 1H), 2.39 (s, 3H), 2.42-2.45 (m, 1H), 2.59-2.63 (m, 2H), 6.79-6.80 (m, 2H), 7.25-7.27 (m, 2H), 7.70-7.72 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: (Major isomer **9a**) 12.7, 21.6, 28.6, 30.9 (2C), 48.3, 121.1 (2C), 126.7 (2C), 129.8 (2C), 135.6 (2C), 136.7, 144.7; (Minor isomer **10a**) 21.3, 21.4, 21.8, 30.3, 30.9, 31.5, 115.5, 115.6, 125.4, 126.1, 126.8 (2C), 129.8 (2C), 136.6, 144.4; HRMS (ESI) calcd for C₁₆H₂₀NO₂S (MH⁺): 290.1215; found: 290.1219.

5-Butyl-2-tosyl-2,4,5,6-tetrahydrocyclopenta[c]pyrrole (9b) and

5-Propyl-2-tosyl-4,5,6,7-tetrahydro-2H-isoindole (10b)

According to the procedure described for the preparation of **2a**, **8b** (40.0 mg, 0.126 mmol) was converted into an inseparable mixture of **9b** and **10b** (20.4 mg, 51% combined isolated yield, **9b/10b** = 93:7) by the reaction for 1.5 h at 80 °C. Column chromatography: silica gel (hexane/EtOAc = 14/1): colorless amorphous solid; IR (neat) 1361 (NSO₂), 1170 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: (Major isomer **9b**) 0.88 (t, *J* = 7.2 Hz, 3H), 1.24-1.32 (m, 4H), 1.43-1.48 (m, 2H), 2.17 (dd, *J* = 15.5, 8.3 Hz, 2H), 2.39 (s, 3H), 2.53-2.59 (m, 1H), 2.69 (dd, *J* = 15.5, 8.3 Hz, 2H), 6.74 (m, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.71 (d, *J* = 8.0 Hz, 2H); (Minor isomer **10b**): 0.87-0.92 (m, 4H), 1.24-1.36 (m, 3H), 1.54-1.58 (m, 1H), 1.78-1.81 (m, 1H), 1.99-2.05 (m, 1H), 2.14-2.26 (m, 1H), 2.39 (s, 3H), 2.42-2.44 (m, 1H), 2.61-2.64 (m, 1H), 2.66-2.71 (m, 1H), 6.79 (m, 2H), 7.25-7.27 (m, 2H), 7.70-7.73 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: (Major isomer **9b**) 14.1, 21.6, 22.8, 30.5, 31.3 (2C), 35.6, 46.5, 112.1 (2C), 126.7 (2C), 129.8 (2C), 135.6 (2C), 136.7, 144.3; (Minor isomer **10b**): 14.3, 20.0, 21.4, 28.4, 29.7, 34.3, 35.7, 38.5, 115.5, 115.6, 125.7, 126.0, 126.8 (2C), 129.8 (2C), 136.7, 144.4; HRMS (ESI) calcd for C₁₈H₂₃NNaO₂S (MNa⁺): 340.1347; found: 340.1347.

2'-Tosyl-2',6'-dihydro-4'H-spiro(cyclopentane-1,5'-cyclopenta[c]pyrrole) (9c)

According to the procedure described for the preparation of **2a**, **8c** (40.0 mg, 0.127 mmol) was converted into **9c** (25.6 mg) as an inseparable mixture including some unidentified compounds by the reaction for 2 h at 80 °C. The yield of **4c** was evaluated as 50% by NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. Column chromatography: silica gel (hexane/EtOAc = 17/1): colorless solid; mp 72 °C; IR (neat) 1358 (NSO₂), 1166 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 1.53-1.55 (m, 4H), 1.64-1.66 (m, 4H), 2.39 (s, 3H), 2.45 (s, 4H), 6.74 (s, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 21.6, 24.1 (2C), 37.5 (2C), 39.1 (2C), 58.4, 112.4 (2C), 126.6 (2C), 129.8 (2C), 135.4 (2C), 136.7, 144.3; HRMS (ESI) calcd for C₁₈H₂₂NO₂S (MH⁺): 316.1371; found: 316.1376.

5-Phenyl-2-tosyl-2,4,5,6-tetrahydrocyclopenta[c]pyrrole (9d)

According to the procedure described for the preparation of **2a**, **8d** (40.0 mg, 0.119 mmol) was converted into **9d** (14.4 mg, 36%) by the reaction for 2 h at 80 °C. Column chromatography: silica gel (hexane/EtOAc = 10/1): colorless solid; mp 126 °C; IR (neat) 1361 (NSO₂), 1170 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 2.41 (s, 3H), 2.68 (dd, *J* = 15.5, 8.6 Hz, 2H), 3.00 (dd, *J* = 15.5, 8.0 Hz, 2H), 3.76-3.82 (m, 1H), 6.83 (s, 2H), 7.19-7.23 (m, 3H), 7.27-7.30 (m, 4H), 7.74 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 21.6, 33.0 (2C), 51.2, 112.3 (2C), 126.4, 126.7 (2C), 126.9 (2C), 128.4 (2C), 129.8 (2C), 134.9 (2C), 136.5, 144.4, 144.7; *Anal.* Calcd for C₂₀H₁₉NO₂S: C, 71.19; H, 5.68; N, 4.15. Found: C, 71.16; H, 5.70; N, 4.10.

(±)-(3b*R*,6a*R*)-2-Tosyl-3b,4,5,6,6a,7-hexahydro-2H-pentaleno[1,2-*c*]pyrrole (9e)

According to the procedure described for the preparation of **2a**, **8e** (40.0 mg, 0.132 mmol) was converted into **9e** (17.5 mg, 44%) by the reaction for 3 h at 80 °C. Column chromatography: silica gel (hexane/EtOAc = 12/1): colorless solid; mp 90 °C; IR (neat) 1359 (NSO₂), 1168 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 1.31-1.37 (m, 1H), 1.49-1.58 (m, 3H), 1.75-1.82 (m, 1H), 1.84-1.92 (m, 1H), 2.27-2.31 (m, 1H), 2.39 (s, 3H), 2.77-2.83 (m, 1H), 3.06-3.13 (m, 1H), 3.27-3.31 (m, 1H), 6.68-6.69 (m, 1H), 6.74 (m, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 21.6, 26.6, 31.4, 33.9, 34.6, 42.5, 50.2, 111.7, 111.9, 126.7 (2C), 129.8 (2C), 136.0, 136.7, 141.3, 144.3; HRMS (ESI) calcd for C₁₇H₁₉NNaO₂S (MNa⁺): 324.1034; found: 324.1033.

4,4-Dimethyl-2-tosyl-2,4,5,6-tetrahydrocyclopenta[c]pyrrole (9f)

According to the procedure described for the preparation of **2a**, **8f** (40.0 mg, 0.138 mmol) was converted into **9f** (24.0 mg, 60%) by the reaction for 1 h at 80 °C. Column chromatography: silica gel (hexane/EtOAc = 12/1): colorless amorphous solid; IR (neat) 1361 (NSO₂), 1172 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 1.19 (s, 6H), 2.03 (t, *J* = 7.2 Hz, 2H), 2.40 (s, 3H), 2.56 (t, *J* = 7.2 Hz, 2H), 6.69-6.70 (m, 1H), 6.72 (m, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.71 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 21.6, 23.2, 28.5 (2C), 38.8, 47.0, 110.7, 111.9, 126.7 (2C), 129.8 (2C), 134.7, 136.7, 144.3, 145.5; HRMS (ESI) calcd for C₁₆H₁₉NNaO₂S (MNa⁺): 312.1034; found: 312.1037.

2-Tosyl-2,4-dihydrocyclopenta[c]pyrrole (**9g**)

According to the procedure described for the preparation of **2a**, **8g** (40.0 mg, 0.102 mmol) was converted into **9g** (13.0 mg, 49%) by the reaction for 1.5 h at 80 °C. Column chromatography: silica gel (hexane/EtOAc = 10/1): colorless solid; mp 140 °C; IR (neat) 1358 (NSO₂), 1168 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 2.38 (s, 3H), 3.12 (m, 2H), 6.31-6.33 (m, 1H), 6.50-6.51 (m, 1H), 6.93-6.94 (m, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 21.6, 31.4, 108.3, 112.6, 124.5, 126.7 (2C), 129.8 (2C), 133.7, 136.5, 137.6, 138.7, 144.5; HRMS (ESI) calcd for C₁₄H₁₃NNaO₂S (MNa⁺): 282.0565; found: 282.0565.

2-Tosyl-4,4a,5,6,7,8-hexahydro-2H-benzof[*f*]isoindole (**10h**)

According to the procedure described for the preparation of **2a**, **8h** (40.0 mg, 0.122 mmol) was converted into **10h** (22.8 mg, 57%) by the reaction for 6 h at 80 °C. Column chromatography: silica gel (hexane/EtOAc = 15/1): colorless solid; mp 167 °C; IR (neat) 1362 (NSO₂), 1166 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 1.15-1.43 (m, 3H), 1.75-1.81 (m, 2H), 1.86-1.90 (m, 1H), 2.05-2.11 (m, 1H), 2.22-2.38 (m, 6H), 2.81 (dd, *J* = 15.2, 7.2 Hz, 1H), 6.01 (s, 1H), 6.75-6.79 (m, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 21.6, 26.2, 27.2, 27.4, 35.2, 35.7, 36.7, 112.6, 113.3, 115.6, 123.6, 125.4, 126.7 (2C), 129.8 (2C), 136.4, 143.1, 144.4; Anal. Calcd for C₁₉H₂₁NO₂S: C, 69.69; H, 6.46; N, 4.28. Found: C, 69.46; H, 6.44; N, 4.17.

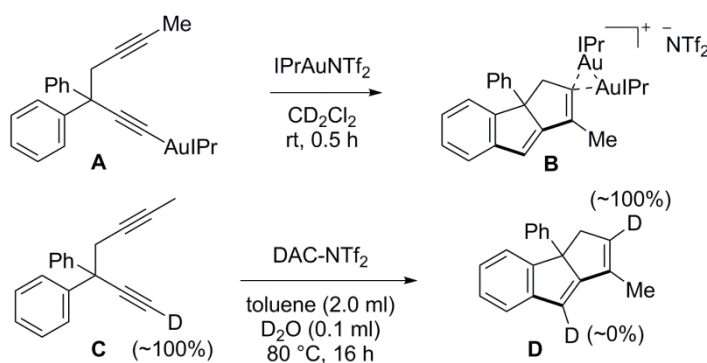
4-Methyl-2-tosyl-2,8-dihydroindeno[1,2-*c*]pyrrole (**2m**) and

2-Tosyl-4,5-dihydro-2H-benzo[*e*]isoindole (**2m'**)

According to the procedure described for the preparation of **2a**, **1m** (40.0 mg, 0.124 mmol) was converted into **2m** and **2m'** (31.1 mg, 78% combined yield, **2m/2m'** = 2:5) by the reaction for 1 h at 80 °C. Column chromatography: silica gel (hexane/EtOAc = 13/1): yellow oil; IR (neat) 1365 (NSO₂), 1168 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: (Major isomer **2m'**) 2.38 (s, 3H), 2.65-2.68 (m, 2H), 2.80-2.83 (m, 2H), 6.93 (m, 1H), 7.04-7.22 (m, 3H), 7.26-7.27 (m, 2H), 7.37 (d, *J* = 1.7 Hz, 1H), 7.43 (d, *J* = 7.4 Hz, 1H), 7.75-7.77 (m, 2H); (Minor isomer **2m**) 2.37 (s, 3H), 2.45 (s, 3H), 3.66 (s, 2H), 7.04-7.22 (m, 4H), 7.24-7.27 (m, 3H), 7.75-7.77 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: (Major isomer **2m'**) 20.5, 21.6, 29.6, 114.0, 115.9, 123.4, 125.7, 126.0, 126.7, 126.8 (3C), 128.6, 129.8, 129.9 (2C), 135.9, 136.1, 144.8; (Minor isomer **2m**) 19.9, 21.5, 30.2, 110.5, 113.4, 122.8, 126.7 (3C), 127.8, 129.9 (2C), 132.4, 133.2, 135.0, 136.0, 136.3, 144.7, 147.0; HRMS (ESI) calcd for C₁₉H₁₇KNO₂S (MK⁺): 362.0617; found: 362.0616.

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- (6) In this case, **9c** was obtained as an inseparable mixture including some unidentified compounds. The NMR

yield of **9c** was evaluated using 1,1,2,2-tetrachloroethane as an internal standard.

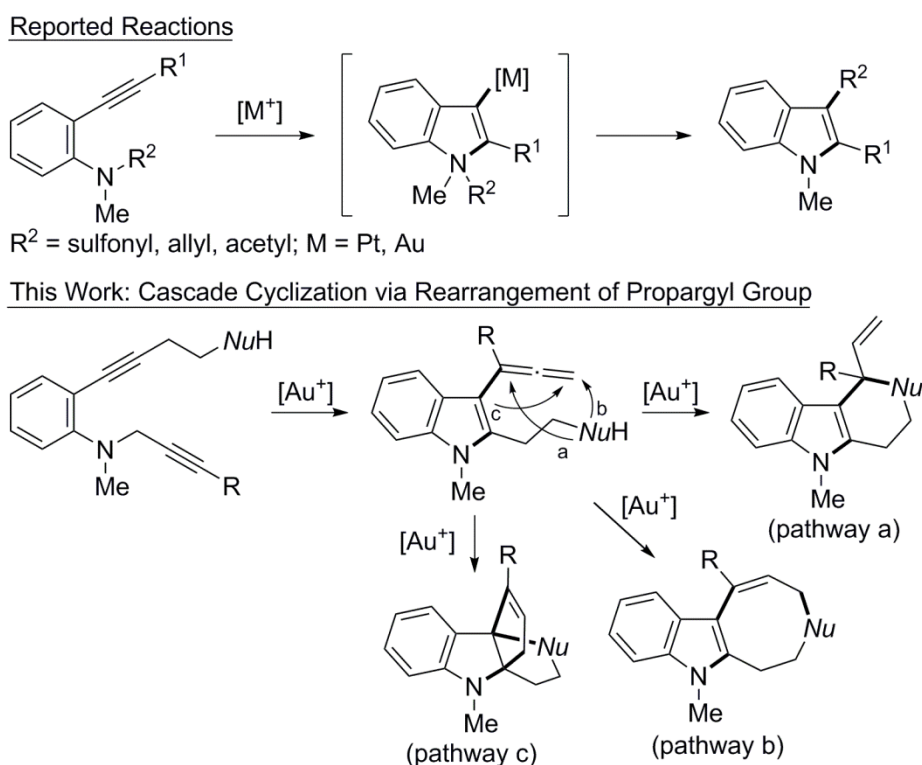
- (7) The same trend was observed with the reaction of 3,4-thiophenylene-tethered diynes. See ref 2e for more information.
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Chapter 2. Gold-Catalyzed Cascade Cyclization of 2-Alkynylanilines via the Rearrangement of a Propargyl Group

Summary

A new reaction has been developed for the gold-catalyzed cascade cyclization of *o*-alkynyl-*N*-propargylaniline. This reaction allowed for the synthesis of fused indolines from easily prepared substrates via the formation of four bonds and three rings in a single reaction. Following the cyclization of the aniline nitrogen onto the alkyne, the propargyl group migrated to the C3 position of the indole, and the resulting allene was activated by the gold catalyst to undergo a further cyclization reaction with the indole to give the fused indoline product.

The transition-metal-catalyzed cyclization of *o*-alkynylanilines is an efficient method for the construction of indoles.¹ Several groups have recently reported that certain substituents on the aniline nitrogen, including sulfonyl,² allyl,³ and acetyl⁴ groups, can migrate to the C3 position of indole through indolylmetal intermediates (Scheme 1). Although these reactions are valuable for the preparation of synthetically useful 2,3-disubstituted indole derivatives, there have been no reports in the literature applying this types of migration reactions to cascade reactions. With this in mind, the author envisaged that the use of *N*-propargyl-*o*-alkynylaniline as a substrate would lead to the formation of an indole bearing an allene moiety at the C3 position via the migration of its

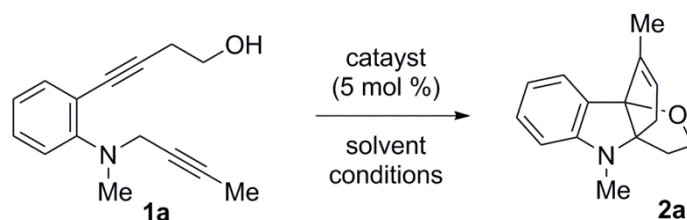


Scheme 1. Transition-Metal-Catalyzed Indole Formation and Rearrangement of *N*-Substituents

propargyl group, which could undergo further cyclization reactions.⁵ For example, the intramolecular reaction of an allene moiety of this type with an internal nucleophile (pathways a and b) or indole (pathway c) would give the corresponding fused indole or indoline, respectively. Herein, the author has described the gold-catalyzed cascade cyclization of *o*-alkynyl-*N*-propargylanilines to give fused indolines via pathway c. As far as the author aware, this work represents the first example of the migration of a propargyl substituent from the aniline nitrogen atom.

Work towards examining the feasibility of this strategy was initially focused on the cyclization of *N*-propargylaniline **1a** (Table 1). The reaction of **1a** with 5 mol % of PPh₃AuCl/AgSbF₆ in THF at 60 °C gave cyclization product **2a** in 13% yield (entry 1). Among the gold catalysts examined for this reaction, IPrAuCl/AgSbF₆ and JohnPhosAuSbF₆·MeCN showed the highest activities, with compound **2a** being isolated in 74% yield in both cases (entries 3 and 4). Several other solvents were investigated for the reaction, including toluene, DCE, CH₃NO₂, CH₃CN and dioxane, but all of these solvents led to a decrease in the yield of **2a** (entries 5–9). In contrast, the use of 2-propanol led to an improvement in the yield to 81% (entry 10). The results of an extensive period of screening revealed

Table 1. Optimization of Reaction Conditions

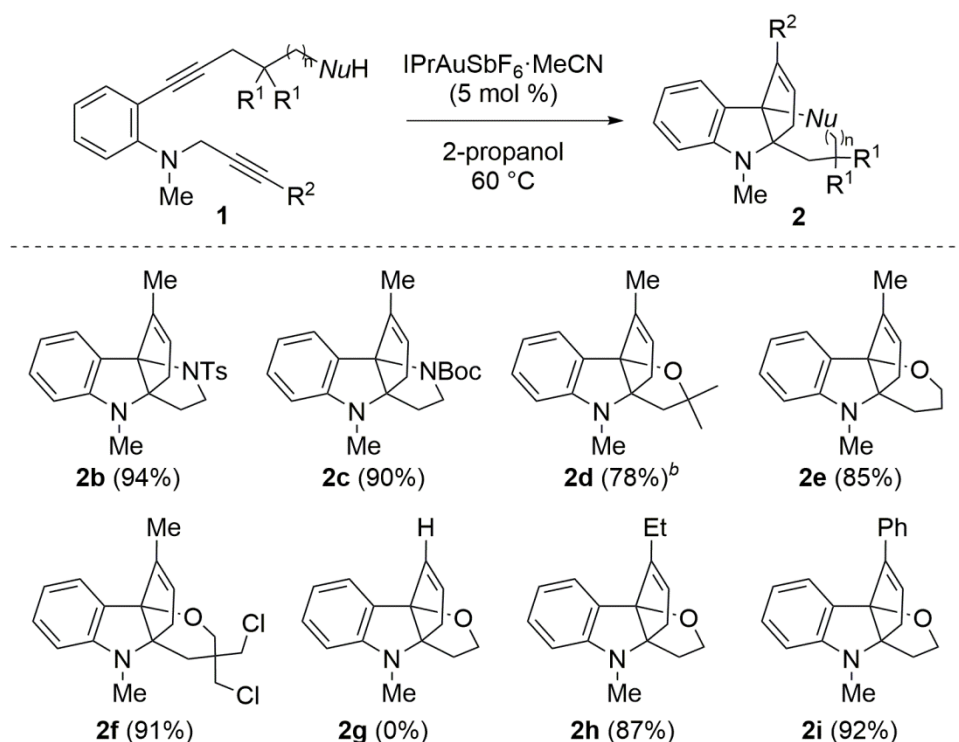


entry	catalyst	solvent	conditions	yield (%) ^a
1	PPh ₃ AuCl/AgSbF ₆	THF	60 °C, 5 h	13
2	BrettPhosAuSbF ₆ ·MeCN	THF	60 °C, 1 h	49
3	IPrAuCl/AgSbF ₆	THF	60 °C, 1 h	74
4	JohnPhosAuSbF ₆ ·MeCN	THF	60 °C, 1 h	74
5	JohnPhosAuSbF ₆ ·MeCN	toluene	60 °C, 2 h	41
6	JohnPhosAuSbF ₆ ·MeCN	DCE	60 °C, 1 h	16
7	JohnPhosAuSbF ₆ ·MeCN	CH ₃ NO ₂	60 °C, 2 h	13
8	JohnPhosAuSbF ₆ ·MeCN	CH ₃ CN	60 °C, 2 h	58
9	JohnPhosAuSbF ₆ ·MeCN	dioxane	60 °C, 4 h	58
10	JohnPhosAuSbF ₆ ·MeCN	2-propanol	60 °C, 2 h	81
11	IPrAuCl/AgSbF ₆	2-propanol	60 °C, 1 h	81
12	IPrAuSbF ₆ ·MeCN	2-propanol	60 °C, 1 h	89
13	AgSbF ₆	2-propanol	rt, 2 h	decomp. ^b

^a Isolated yields. ^b Complete consumption of starting material was observed.

that the advanced preparation of the gold catalyst led to a further improvement in the yield of the desired reaction to 89% (entry 12 vs entry 11). This increase was attributed to the negative effect of the remaining AgSbF₆ present in the reaction mixture. Actually, the treatment of **1a** with AgSbF₆ led to the decomposition of aniline **1a** (entry 13).

With the optimized conditions in hand (Table 1, entry 12), the author proceeded to investigate the scope of the reaction using a variety of different substrates. Changing the internal nucleophile from an alcohol to a tosylamide or *t*-butylcarbamate (*NuH* = NHTs or NHBoc) led to the formation of the pyrrolidine-fused indolines **2b** and **2c** in excellent yields (94 and 90%, respectively). Aniline **1d** (R¹ = Me) bearing a sterically hindered alcohol also reacted efficiently to give **2d** (78%). Furthermore, anilines **1e** and **1f** bearing a longer carbon tether (*n* = 1) were smoothly converted to the corresponding indolines with a fused tetrahydropyran ring (85% and 91%, respectively). Although aniline **1g** (R² = H) bearing a terminal alkyne decomposed under these conditions, aniline **1h** (R² = Et) and **1i** (R² = Ph) bearing an internal alkyne reacted smoothly to give indolines **2h** (87%) and **2i** (92%), respectively.



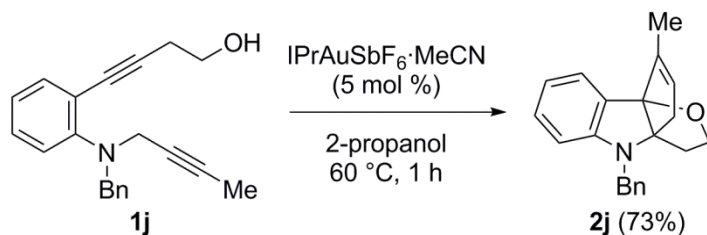
^a Isolated yields. ^b The reaction was conducted at 40 °C.

Figure 1. Gold-Catalyzed Cyclization of *o*-Alkynyl-*N*-propargyl-aniline.^a

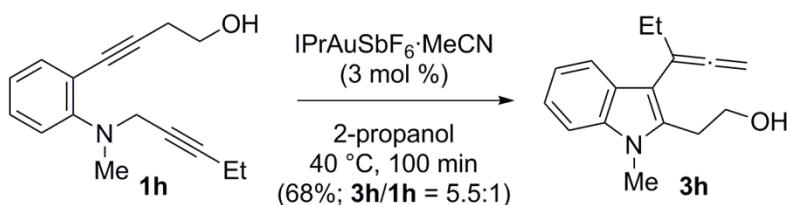
Benzyl groups have been reported to migrate in some transition-metal-catalyzed cyclization reactions.^{4b,6} To determine the migratory aptitude of different functional groups towards the C3 position of the indole, aniline **1j** bearing a propargyl and benzyl group was subjected to the optimized conditions (Scheme 2). In this case, the propargyl group exhibited a greater migratory aptitude than the benzyl group to give indoline **2j** as the major product in 73% yield. This result

revealed that benzyl-type substituents can be used as nitrogen protecting groups for the current indoline formation.

Two experiments were subsequently conducted to develop a deeper understanding of the mechanism of this reaction. In the first of these experiments, the reaction was quenched before it reached completion to give allene **3h** as a mixture containing a small amount of the starting material (Scheme 3; **3h/1h** = 5.5:1, 68% combined yield). The reaction of **1h** was also analyzed by ¹H NMR spectroscopy with 3 mol % of IPrAuSbF₆·MeCN in MeOD-*d*₃ at 40 °C, using CHCl₂CHCl₂ as an



Scheme 2. Gold-Catalyzed Cyclization of *N*-Benzylaniline **1j**



Scheme 3. Isolation of the Reaction Intermediate **3h**

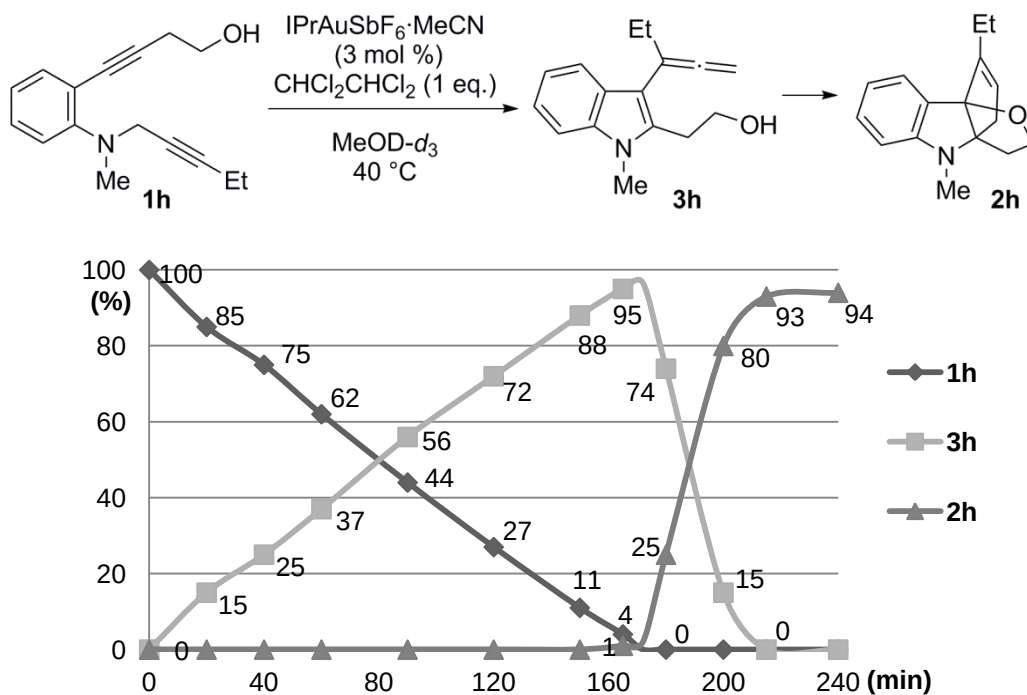
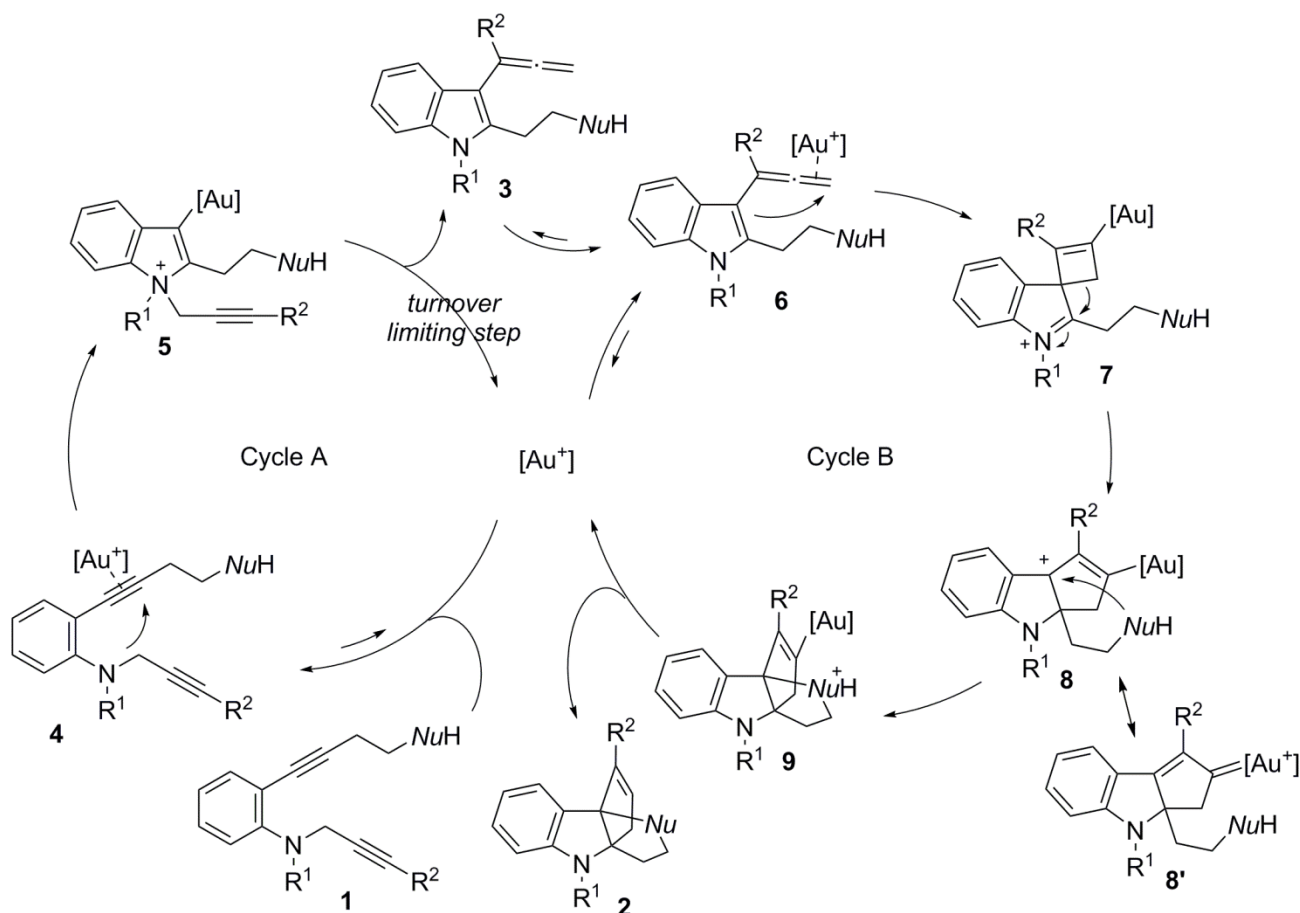


Figure 2. NMR Analysis of the Reaction of **1h**.

internal standard (Figure 2). During the first period of the reaction, the conversion of aniline **1h** to allene **3h** proceeded at a constant rate. After 165 min, only 4% of the original aniline **1h** charge remained in the reaction mixture, and **3h** was produced in 95% yield. Interestingly the formation of indoline **2h** was only observed after the complete consumption of **1h**, with a substantial amount of **2h** having been generated at 215 min. This result clearly demonstrated that the formation of indoline **2h** does not proceed without the gold catalyst. Furthermore, the gold catalyst selectively promoted the allene formation during the first part of the reaction.

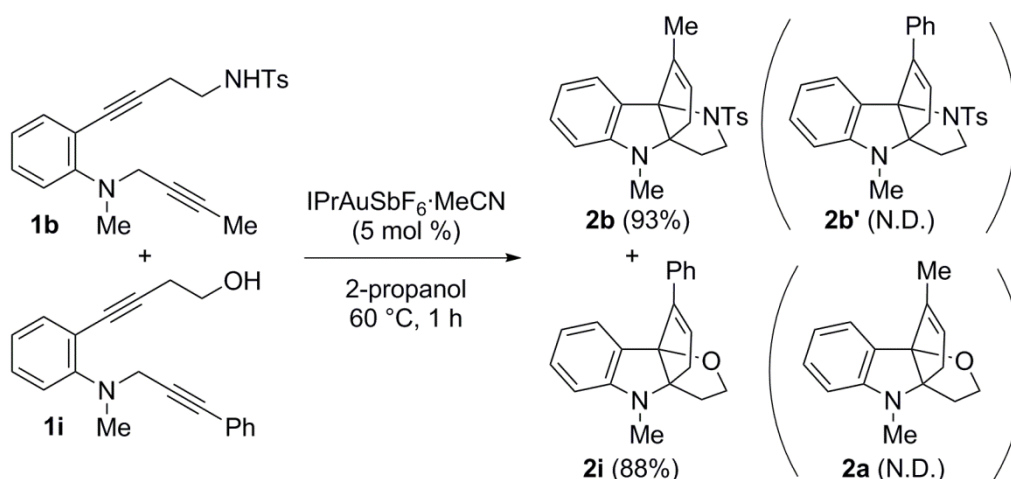
A plausible reaction mechanism was proposed based on the results of these experiments, which is shown in Scheme 4. The reaction starts with the coordination of a cationic gold catalyst to *o*-alkynylaniline **1** to give **4**, which undergoes a nucleophilic cyclization reaction from the aniline nitrogen to give indole **5**. The subsequent [3,3] migration of the propargyl group from the nitrogen atom of indolylgold intermediate **5** to the C3 position of the indole gives allene **3**, which is activated by the gold catalyst to give intermediate **6**. Cyclization of activated allene **6**, followed by the ring expansion of the resulting vinyl gold intermediate **7** gives cationic intermediate **8**, which was stabilized by the vinylgold moiety as shown in **8'**. The reaction is then terminated by the intramolecular nucleophilic addition and subsequent protodeauration of **9** to produce the fused indoline **2**.



Scheme 4. Plausible Reaction Mechanism

The result of the NMR experiment can be rationalized as follows: the cycle A is much slower than cycle B⁷ because of the slow nature of the propargyl migration step, whereas the indole formation step (i.e., **4** to **5**) would be sufficiently fast. In other words, the presence of the relatively stable intermediate **5** in the cycle A traps the gold catalyst, which therefore prevents cycle B from progressing prior to the completion of cycle A. It was hypothesized that the turnover limiting step of this reaction would be the [3,3] migration of the propargyl group (i.e., **5** to **3**), and this result was supported in part by the isolable character of a related *N,N*-dimethyl indolylgold intermediate.⁸

A crossover reaction was also conducted to provide further insights into the reaction mechanism (Scheme 5). The exposure of a mixture of anilines **1b** and **1i** to the optimized conditions gave the corresponding indolines **2b** and **2i**, respectively. Notably, the corresponding crossover products **2b'** and **2a** were not detected in the reaction mixture. This result suggested that the migration of the propargyl group occurs in an intramolecular manner.⁹



Scheme 5. Crossover Experiment

In conclusion, a novel gold-catalyzed cascade cyclization reaction has been developed for *o*-alkynyl-*N*-propargylanilines. The migration of the propargyl group led to the formation of indole bearing an allene moiety at the C3 position, which underwent an intramolecular cyclization reaction with a pendant nucleophile to give a fused indoline. This reaction provided rapid access to fused indolines in a single operation involving the formation of four bonds and three rings. NMR analysis revealed that the formation of the fused indoline only started after the complete consumption of the *o*-alkynyl-*N*-propargylaniline starting material. This work could also be used in combination with the versatile reactivity of allenes to allow for the synthesis of fused indolines and indoles in a one-pot manner.

Experimental Section

General Methods. IR spectra were obtained on a JASCO FT/IR-4100 spectrometer. Exact mass (HRMS) spectra were recorded on Shimadzu LC-ESI-IT-TOF-MS equipment (ESI). ^1H NMR spectra were recorded using a JEOL AL-500 spectrometer at 500 MHz frequency. Chemical shifts are reported in δ (ppm) relative to Me_4Si (in CDCl_3) as internal standard. ^{13}C NMR spectra were recorded using a JEOL AL-500 and referenced to the residual CHCl_3 signal. Melting points were measured by a hot stage melting points apparatus (uncorrected). For column chromatography, Wakogel C-200E or Merck Aluminum oxide 90 was employed. The crystal structure of **2b** was collected with a Rigaku R-Axis RAPID diffractometer using graphite monochromated Mo-K α radiation at -180 °C.

The known compounds **S2**,² **S5**,¹⁰ **S6**,¹¹ **S8**¹² were synthesized according to the literature.

1. Synthesis of *o*-Alkynyl-*N*-propargyl-aniline **1**

2-{4-[(*tert*-Butyldimethylsilyl)oxy]but-1-yn-1-yl}-*N*-methylaniline (**S1**)

To a stirred mixture of 2-iodo-*N*-methylaniline (**S2**) (2.33 g, 10.0 mmol), (but-3-yn-1-yloxy)(*tert*-butyl)-dimethylsilane (3.10 mL, 15.0 mmol), and $\text{PdCl}_2(\text{PPh}_3)_2$ (351 mg, 0.50 mmol) in THF (20 mL) and Et_3N (5 mL) under argon was added CuI (95.2 mg, 0.50 mmol) at room temperature. After stirring for 6 h at that temperature, additional (but-3-yn-1-yloxy)(*tert*-butyl)dimethylsilane (1.03 mL, 5.00 mmol) was added to the mixture. After stirring for 18 h at that temperature, the reaction mixture was diluted with Et_2O and filtered through a pad of Celite. The filtrate was concentrated in vacuo and the residue was chromatographed on silica gel (hexane/ EtOAc = 10/1) to afford **S1** (2.89 g, 99%): yellow oil; IR (neat) 3420 (NH) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 0.10 (s, 6H), 0.92 (s, 9H), 2.68 (t, J = 6.9 Hz, 2H), 2.88 (d, J = 4.6 Hz, 3H), 3.82 (t, J = 6.9 Hz, 2H), 4.63 (q, J = 4.6 Hz, 1H), 6.56 (d, J = 8.3 Hz, 1H), 6.60 (dd, J = 7.7, 7.4 Hz, 1H), 7.18 (ddd, J = 8.3, 7.4, 1.1 Hz, 1H), 7.24 (dd, J = 7.7, 1.1 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ : -5.3 (2C), 18.3, 24.1, 25.9 (3C), 30.3, 62.0, 78.1, 92.8, 107.9, 108.7, 116.0, 129.3, 131.8, 149.8; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{28}\text{NOSi}$ (MH^+): 290.1940; found: 290.1938.

4-{2-[But-2-yn-1-yl(methyl)amino]phenyl}but-3-yn-1-ol (**1a**)

To a stirred mixture of **S1** (869 mg, 3.00 mmol) and K_2CO_3 (622 mg, 4.50 mmol) in CH_3CN (6 mL) was added 1-bromobut-2-yne (394 μL , 4.50 mmol) at room temperature. After stirring for 5 h at 80 °C, water was added to the mixture. The mixture was extracted with EtOAc twice. The combined organic layer was washed with brine, dried over MgSO_4 , and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/ EtOAc = 30/1) to give the silylated aniline as an oil.

This oil was dissolved in THF (15 mL) and TBAF (1.0 M in THF; 5.4 mL, 5.4 mmol) was added to the mixture at 0 °C. After stirring for 2 h at that temperature, the reaction mixture was quenched with aqueous saturated NH_4Cl and extracted with DCM twice. The combined organic layer was washed with brine, dried over MgSO_4 , and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/ EtOAc = 3/1) to afford **1a** (480 mg, 70%): pale yellow oil; IR (neat) 2228 ($\text{C}\equiv\text{C}$) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 1.83 (t, J = 2.3 Hz, 3H), 2.41 (t, J = 6.3 Hz, 1H), 2.76 (t, J = 6.0 Hz, 2H), 2.90 (s, 3H), 3.84 (dt, J = 6.3, 6.0 Hz, 2H), 4.02 (q, J = 2.3 Hz, 2H), 6.92 (ddd, J = 7.7, 7.7, 1.1 Hz, 1H), 7.03 (dd, J = 7.7, 1.1 Hz, 1H), 7.24 (ddd, J = 7.7, 7.7, 1.4 Hz, 1H), 7.38 (dd, J = 7.7, 1.4 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ : 3.4, 24.3, 39.4, 45.8, 60.9, 74.8, 80.5, 80.9, 92.5, 116.6, 118.7, 121.8, 128.6, 133.9, 152.9; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{18}\text{NO}$ (MH^+): 228.1388; found: 228.1387.

***tert*-Butyl (4-{2-[But-2-yn-1-yl(methyl)amino]phenyl}but-3-yn-1-yl)(tosyl)carbamate (S3)**

To a stirred mixture of **1a** (227 mg, 1.00 mmol), *tert*-butyl tosylcarbamate (407 mg, 1.50 mmol), and PPh₃ (786 mg, 3.00 mmol) in THF (10 mL) under argon was added DEAD (2.2 M in toluene; 1.13 mL, 2.50 mmol) dropwise at room temperature. After stirring for 1 h at that temperature, the reaction mixture was concentrated in vacuo and the residue was purified by column chromatography on silica gel (hexane/EtOAc = 6/1) to afford **S3** (460 mg, 96%): yellow oil; IR (neat) 1725 (CO), 1353 (NSO₂), 1154 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 1.34 (s, 9H), 1.81 (t, *J* = 2.0 Hz, 3H), 2.42 (s, 3H), 2.91 (s, 3H), 2.96 (t, *J* = 7.4 Hz, 2H), 4.05 (q, *J* = 2.0 Hz, 2H), 4.12 (t, *J* = 7.4 Hz, 2H), 6.88 (dd, *J* = 7.6, 7.4 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 7.22 (ddd, *J* = 8.0, 7.6, 1.3 Hz, 1H), 7.28 (d, *J* = 8.6 Hz, 2H), 7.33 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.83 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 3.5, 21.3, 21.6, 27.8 (3C), 39.4, 45.4, 45.6, 74.9, 80.3, 81.1, 84.4, 91.7, 116.2, 118.4, 121.3, 127.9 (2C), 128.6, 129.2 (2C), 134.3, 137.2, 144.1, 150.7, 152.9; HRMS (ESI) calcd for C₂₇H₃₃N₂O₄S (MH⁺): 481.2161; found: 481.2159.

***N*-(4-{2-[But-2-yn-1-yl(methyl)amino]phenyl}but-3-yn-1-yl)-4-methylbenzenesulfonamide (1b)**

A mixture of **S3** (160 mg, 0.33 mmol) in DCM (1 mL) and TFA (0.5 mL) was stirred for 8 h at room temperature. The reaction mixture was quenched with aqueous saturated NaHCO₃ and extracted with DCM twice. The combined organic layer was washed with water and brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 3/1) to afford **1b** (113 mg, 90%): colorless solid; mp 87 °C; IR (neat) 3198 (NH), 2233 (C≡C), 1330 (NSO₂), 1156 (NSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 1.81 (t, *J* = 2.3 Hz, 3H), 2.40 (s, 3H), 2.62 (t, *J* = 6.3 Hz, 2H), 2.90 (s, 3H), 3.21 (td, *J* = 6.3, 6.0 Hz, 2H), 3.97 (q, *J* = 2.3 Hz, 2H), 5.25 (t, *J* = 6.0 Hz, 1H), 6.93 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.07 (d, *J* = 7.7 Hz, 1H), 7.24-7.31 (m, 4H), 7.76 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 3.5, 21.0, 21.5, 39.5, 41.8, 45.8, 74.7, 80.7, 81.8, 91.3, 116.4, 119.0, 121.9, 127.0 (2C), 128.9, 129.7 (2C), 133.5, 137.1, 143.4, 153.3; *Anal.* Calcd for C₂₂H₂₄N₂O₂S: C, 69.44; H, 6.36; N, 7.36. Found: C, 69.57; H, 6.43; N, 7.39.

***tert*-Butyl (4-{2-[But-2-yn-1-yl(methyl)amino]phenyl}but-3-yn-1-yl)carbamate (1c)**

A mixture of **S3** (160 mg, 0.33 mmol) and Mg (243 mg, 10.0 mmol) in MeOH (6.6 mL) was sonicated for 1 h at room temperature. Aqueous saturated NH₄Cl was added to the reaction mixture and the mixture was extracted with DCM twice. The combined organic layer was washed with water and brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 5/1) to afford **1c** (88.0 mg, 82%): yellow oil; IR (neat) 3358 (NH), 2230 (C≡C), 1713 (CO) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 1.46 (s, 9H), 1.82 (t, *J* = 2.3 Hz, 3H), 2.68 (t, *J* = 6.3 Hz, 2H), 2.91 (s, 3H), 3.39 (td, *J* = 6.3, 6.0 Hz, 2H), 4.03 (q, *J* = 2.3 Hz, 2H), 5.13 (t, *J* = 6.0 Hz, 1H), 6.92 (ddd, *J* = 7.7, 7.4, 1.1 Hz, 1H), 7.04 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.23 (ddd, *J* = 8.0, 7.7, 1.5 Hz, 1H), 7.37 (dd, *J* = 7.4, 1.5 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ: 3.4, 21.3, 28.3 (3C), 39.3, 39.4, 45.6, 74.8, 79.2, 80.4, 80.7, 92.9, 116.6, 118.7, 121.6, 128.6, 133.6, 153.1, 155.7; HRMS (ESI) calcd for C₂₀H₂₇N₂O₂ (MH⁺): 327.2073; found: 327.2069.

***N*-(But-2-yn-1-yl)-2-ethynyl-*N*-methylaniline (S4)**

To a stirred mixture of 2-ethynyl-*N*-methylaniline (**S5**) (2.62 g, 20.0 mmol) and K₂CO₃ (4.15 g, 30.0 mmol) in CH₃CN (40 mL) was added 1-bromobut-2-yne (2.62 mL, 30.0 mmol) at room temperature. After stirring for 5 h at 80 °C, additional K₂CO₃ (1.38 g, 10.0 mmol) and 1-bromobut-2-yne (0.87 mL, 10.0 mmol) were added to the mixture. After stirring for another 5 h at 80 °C, water was added to the mixture. The mixture was extracted with EtOAc twice. The combined organic layer was washed with brine, dried over MgSO₄, and concentrated in vacuo.

The residue was purified by column chromatography on silica gel (hexane/EtOAc = 30/1) to afford **S4** (3.62 g, 99%): yellow oil; IR (neat) 3279 (C≡CH), 2101 (C≡C) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 1.80 (t, J = 2.3 Hz, 3H), 2.93 (s, 3H), 3.43 (s, 1H), 4.07 (q, J = 2.3 Hz, 2H), 6.93 (dd, J = 8.0, 7.4 Hz, 1H), 7.06 (d, J = 8.6 Hz, 1H), 7.28 (ddd, J = 8.6, 8.0, 1.1 Hz, 1H), 7.46 (dd, J = 7.4, 1.1 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ : 3.6, 39.6, 45.6, 74.5, 80.6, 82.5, 82.7, 115.2, 118.9, 121.5, 129.5, 134.7, 153.8; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{14}\text{N}$ (MH^+): 184.1126; found: 184.1125.

5-{2-[But-2-yn-1-yl(methyl)amino]phenyl}-2-methylpent-4-yn-2-ol (**1d**)

To a stirred mixture of **S4** (91.6 mg, 0.50 mmol) in THF (2.5 mL) was added *n*-BuLi (1.55 M in hexane; 0.48 mL, 0.75 mmol) at -78°C under argon. After stirring for 1 h at this temperature, $\text{BF}_3\cdot\text{Et}_2\text{O}$ (94.2 μL , 0.75 mmol) was added to the mixture. After stirring for 5 min at this temperature, 2,2-dimethyloxirane (67.6 μL , 0.75 mmol) was added to the mixture. The mixture was gradually warmed to room temperature. After checking the disappearance of the starting material by TLC, the reaction mixture was quenched with aqueous saturated NH_4Cl and extracted with EtOAc twice. The combined organic layer was washed with brine, dried over MgSO_4 , and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 3/1) to afford **1d** (86.1 mg, 67%): yellow oil; IR (neat) 2229 (C≡C) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 1.38 (s, 6H), 1.81 (t, J = 2.3 Hz, 3H), 2.35 (s, 1H), 2.67 (s, 2H), 2.90 (s, 3H), 4.03 (q, J = 2.3 Hz, 2H), 6.92 (dd, J = 7.7, 7.4 Hz, 1H), 7.05 (d, J = 8.0 Hz, 1H), 7.24 (ddd, J = 8.0, 7.7, 1.3 Hz, 1H), 7.39 (dd, J = 7.4, 1.3 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ : 3.5, 28.7 (2C), 35.5, 39.5, 45.7, 70.1, 74.8, 80.6, 82.1, 92.1, 116.8, 118.9, 121.7, 128.6, 133.9, 153.0; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{22}\text{NO}$ (MH^+): 256.1701; found: 256.1700.

5-{2-[But-2-yn-1-yl(methyl)amino]phenyl}pent-4-yn-1-ol (**1e**)

According to the procedure described for the preparation of **1d**, **S4** (367 mg, 2.00 mmol) and oxetane (195 μL , 3.00 mmol) were converted into **1e** (302 mg, 63%): yellow oil; IR (neat) 2224 (C≡C) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 1.81 (t, J = 2.3 Hz, 3H), 1.87-1.92 (m, 2H), 1.97 (s, 1H), 2.62 (t, J = 6.9 Hz, 2H), 2.90 (s, 3H), 3.83 (t, J = 6.0 Hz, 2H), 4.04 (q, J = 2.3 Hz, 2H), 6.91 (dd, J = 7.7, 7.7 Hz, 1H), 7.03 (d, J = 7.7 Hz, 1H), 7.22 (ddd, J = 7.7, 7.7, 1.4 Hz, 1H), 7.36 (dd, J = 7.7, 1.4 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ : 3.5, 16.6, 31.3, 39.4, 45.7, 62.0, 74.9, 79.7, 80.4, 95.1, 117.0, 118.8, 121.7, 128.4, 133.8, 152.9; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{20}\text{NO}$ (MH^+): 242.1545; found: 242.1544.

5-{2-[But-2-yn-1-yl(methyl)amino]phenyl}-2,2-bis(chloromethyl)pent-4-yn-1-ol (**1f**)

According to the procedure described for the preparation of **1d**, **S4** (91.6 mg, 0.50 mmol) and 3,3-bis(chloromethyl)oxetane (116 mg, 0.75 mmol) were converted into **1f** (93.0 mg, 55%): colorless oil; IR (neat) 2224 (C≡C) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 1.82 (t, J = 2.3 Hz, 3H), 2.47 (t, J = 5.2 Hz, 1H), 2.72 (s, 2H), 2.98 (s, 3H), 3.70-3.75 (m, 4H), 3.79 (d, J = 5.2 Hz, 2H), 3.98 (q, J = 2.3 Hz, 2H), 6.94 (dd, J = 7.7, 7.4 Hz, 1H), 7.05 (d, J = 8.0 Hz, 1H), 7.25 (ddd, J = 8.0, 7.7, 1.5 Hz, 1H), 7.39 (dd, J = 7.4, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ : 3.6, 22.8, 39.6, 45.2, 46.0, 46.2 (2C), 63.2, 74.7, 80.7, 82.1, 89.8, 116.7, 119.1, 122.0, 128.9, 133.9, 153.2; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{22}\text{Cl}_2\text{NO}$ (MH^+): 338.1078; found: 338.1075.

4-{2-[Methyl(prop-2-yn-1-yl)amino]phenyl}but-3-yn-1-ol (**1g**)

According to the procedure described for the preparation of **1a**, **S1** (290 mg, 1.00 mmol) was converted into **1g** (101 mg, 47%) by the reaction with 3-bromoprop-1-yne (129 μL , 1.50 mmol): pale yellow oil; IR (neat) 3289 (C≡CH), 2231 (C≡C), 2105 (C≡C) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 2.25 (t, J = 2.3 Hz, 1H), 2.43 (s, 1H), 2.76

(t, J = 5.7 Hz, 2H), 2.91 (s, 3H), 3.83 (t, J = 6.3 Hz, 2H), 4.11 (d, J = 2.3 Hz, 2H), 6.94 (dd, J = 7.7, 7.7 Hz, 1H), 7.04 (d, 7.7 Hz, 1H), 7.25 (ddd, J = 7.7, 7.7, 1.4 Hz, 1H), 7.39 (dd, J = 7.7, 1.4 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ : 24.3, 39.4, 45.3, 61.0, 72.8, 79.5, 80.9, 92.5, 116.7, 118.9, 122.1, 128.7, 133.9, 152.5; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{16}\text{NO}$ (MH^+): 214.1232; found: 214.1227.

4-{2-[Methyl(pent-2-yn-1-yl)amino]phenyl}but-3-yn-1-ol (1h)

According to the procedure described for the preparation of **1a**, **S1** (435 mg, 1.50 mmol) was converted into **1h** (244 mg, 67%) by the reaction with 1-bromopent-2-yne (230 μL , 2.25 mmol): yellow oil; IR (neat) 2225 ($\text{C}\equiv\text{C}$) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 1.12 (t, J = 7.4 Hz, 3H), 2.17-2.22 (m, 2H), 2.60 (s, 1H), 2.75 (t, J = 6.0 Hz, 2H), 2.90 (s, 3H), 3.83 (t, J = 6.0 Hz, 2H), 4.04 (t, J = 2.3 Hz, 2H), 6.92 (ddd, J = 7.7, 7.7, 1.1 Hz, 1H), 7.03 (dd, J = 7.7, 1.1 Hz, 1H), 7.23 (ddd, J = 7.7, 7.7, 1.4 Hz, 1H), 7.38 (dd, J = 7.7, 1.4 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ : 12.4, 14.0, 24.3, 39.3, 45.9, 61.0, 74.9, 81.0, 86.6, 92.4, 116.7, 118.8, 121.8, 128.6, 133.8, 153.0; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{20}\text{NO}$ (MH^+): 242.1545; found: 242.1543.

4-{2-[Methyl(3-phenylprop-2-yn-1-yl)amino]phenyl}but-3-yn-1-ol (1i)

According to the procedure described for the preparation of **1a**, **S1** (435 mg, 1.50 mmol) was converted into **1i** (119 mg, 27%) by the reaction with (3-bromoprop-1-yn-1-yl)benzene (439 mg, 2.25 mmol): amber oil; IR (neat) 2229 ($\text{C}\equiv\text{C}$) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 2.33 (s, 1H), 2.77 (t, J = 6.0 Hz, 2H), 2.98 (s, 3H), 3.84 (t, J = 6.0 Hz, 2H), 4.31 (s, 2H), 6.95 (dd, J = 8.0, 7.4 Hz, 1H), 7.10 (d, J = 8.0 Hz, 1H), 7.24-7.29 (m, 4H), 7.38-7.41 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ : 24.3, 39.6, 46.2, 61.1, 81.2, 85.0, 85.2, 92.5, 116.8, 119.1, 122.1, 123.0, 128.1, 128.2 (2C), 128.7, 131.6 (2C), 133.9, 152.9; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{20}\text{NO}$ (MH^+): 290.1545; found: 290.1544.

N-Benzyl-2-{4-[(*tert*-butyldimethylsilyl)oxy]but-1-yn-1-yl}aniline (S7)

According to the procedure described for the preparation of **S1**, *N*-benzyl-2-iodoaniline (**S8**) (911 mg, 2.95 mmol) was converted into **S7** (1.06 g, 98%): pale yellow oil; IR (neat) 3411 (NH) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 0.07 (s, 6H), 0.89 (s, 9H), 2.67 (t, J = 6.9 Hz, 2H), 3.80 (t, J = 6.9 Hz, 2H), 4.42 (d, J = 5.4 Hz, 2H), 5.07 (t, J = 5.4 Hz, 1H), 6.51 (d, J = 8.4 Hz, 1H), 6.60 (dd, J = 7.7, 7.4 Hz, 1H), 7.09 (ddd, J = 8.4, 7.7, 1.4 Hz, 1H), 7.26-7.27 (m, 2H), 7.32-7.37 (m, 4H); ^{13}C NMR (125 MHz, CDCl_3) δ : -5.3 (2C), 18.3, 24.1, 25.9 (3C), 47.6, 62.0, 78.1, 93.0, 108.1, 109.7, 116.4, 127.0 (2C), 127.1, 128.6 (2C), 129.2, 132.0, 139.3, 148.3 HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{32}\text{NOSi}$ (MH^+): 366.2253; found: 366.2256.

4-{2-[Benzyl(but-2-yn-1-yl)amino]phenyl}but-3-yn-1-ol (1j)

According to the procedure described for the preparation of **1a**, **S7** (731 mg, 2.00 mmol) was converted into **1j** (338 mg, 56%): pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ : 1.79-1.83 (m, 4H), 2.56 (t, J = 6.0 Hz, 2H), 3.63 (td, J = 6.0, 6.0 Hz, 2H), 3.84 (q, J = 2.3 Hz, 2H), 4.54 (s, 2H), 6.92 (dd, J = 7.4, 7.4 Hz, 1H), 7.19-7.27 (m, 3H), 7.33 (dd, J = 7.4, 7.4 Hz, 2H), 7.40 (dd, J = 7.4, 1.1 Hz, 1H), 7.46 (d, J = 7.4 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ : 3.6, 24.1, 41.4, 55.5, 61.0, 74.5, 81.1, 81.2, 91.9, 116.8, 119.8, 121.6, 127.0, 128.1 (2C), 128.2 (2C), 128.6, 134.0, 138.6, 152.6; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{22}\text{NO}$ (MH^+): 304.1701; found: 304.1701.

2. Synthesis of the indoline 2

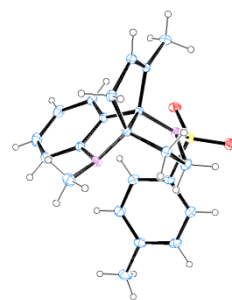
1,4-Dimethyl-3*H*,4*H*-8*b*,3*a*-(epoxyethano)cyclopenta[*b*]indole (2a)

To a stirred mixture of **1a** (30.0 mg, 0.132 mmol) in 2-propanol (1 mL) was added 5 mol % $\text{IPrAuSbF}_6\cdot\text{MeCN}$ (5.7 mg, 0.0066 mmol) at room temperature. After stirring for 1 h at 60 $^\circ\text{C}$, the reaction mixture was concentrated

in vacuo and the residue was purified by column chromatography on silica gel (hexane/EtOAc = 12/1) to afford **2a** (26.7 mg, 89%): colorless oil; ^1H NMR (500 MHz, CDCl_3) δ : 1.93 (d, J = 1.1 Hz, 3H), 1.94-1.98 (m, 1H), 2.19-2.24 (m, 1H), 2.42-2.46 (m, 1H), 2.58-2.62 (m, 1H), 2.83 (s, 3H), 3.71-3.75 (m, 1H), 3.85-3.89 (m, 1H), 5.42 (m, 1H), 6.36 (dd, J = 8.0, 1.1 Hz, 1H), 6.63 (ddd, J = 7.7, 7.4, 1.1 Hz, 1H), 7.14 (ddd, J = 8.0, 7.7, 1.1 Hz, 1H), 7.29 (dd, J = 7.4, 1.1 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ : 12.5, 29.6, 38.9, 41.3, 67.4, 83.7, 104.1, 105.6, 116.6, 124.0, 127.0, 127.1, 129.6, 139.5, 151.7; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{18}\text{NO}$ (MH^+): 228.1388; found: 228.1391.

1,4-Dimethyl-9-tosyl-3*H*,4*H*-8*b*,3*a*-(epiminoethano)cyclopenta[*b*]indole (**2b**)

According to the procedure described for the preparation of **2a**, **1b** (30.0 mg, 0.079 mmol) was converted into **2b** (28.2 mg, 94%): colorless solid; mp 183 °C; IR (neat) 1377 (NSO_2), 1154 (NSO_2) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 1.92-1.97 (m, 1H), 2.15-2.19 (m, 1H), 2.21-2.22 (m, 2H), 2.25 (s, 3H), 2.29 (s, 3H), 2.57 (s, 3H), 3.06-3.11 (m, 1H), 3.53-3.56 (m, 1H), 5.41 (d, J = 2.3 Hz, 1H), 6.30 (d, J = 8.0 Hz, 1H), 6.78 (dd, J = 7.4, 7.4 Hz, 1H), 6.97 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 7.7, 7.7 Hz, 1H), 7.79 (d, J = 7.7 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ : 15.5, 21.3, 30.4, 32.3, 36.6, 49.8, 87.5, 89.2, 107.4, 117.9, 125.7, 126.6, 127.7 (2C), 128.0, 128.8 (2C), 129.6, 135.7, 142.2, 143.2, 152.5; *Anal.* Calcd for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_2\text{S}$: C, 69.44; H, 6.36; N, 7.36. Found: C, 69.46; H, 6.39; N, 7.35.



crystal structure of **2b**

Crystal data of **2b**: Crystal Dimensions 0.300 X 0.300 X 0.300 mm; Crystal System triclinic; Lattice Type Primitive; Lattice Parameters a = 8.1473(6) Å, b = 8.8049(6) Å, c = 14.9502(13) Å, α = 97.814(4) °, β = 92.288(3) °, γ = 116.162(5) °, V = 947.63(14) Å³; Space Group P-1 (#2); Z value 2; D_{calc} 1.333 g/cm³; F_{000} 404.00; $\mu(\text{MoK}\alpha)$ 1.907 cm⁻¹.

tert-Butyl 1,4-Dimethyl-3*H*,4*H*-8*b*,3*a*-(epiminoethano)cyclopenta[*b*]indole-9-carboxylate (**2c**)

According to the procedure described for the preparation of **2a**, **1c** (30.0 mg, 0.092 mmol) was converted into **2c** (26.9 mg, 90%): colorless oil; IR (neat) 1698 (CO) cm^{-1} ; ^1H NMR (500 MHz, DMSO, 393 K) δ : 1.41 (s, 9H), 1.79-1.85 (m, 1H), 1.98-1.99 (m, 3H), 2.11-2.16 (m, 1H), 2.28-2.29 (m, 2H), 2.70 (s, 3H), 3.34-3.39 (m, 1H), 3.43-3.47 (m, 1H), 5.38-5.40 (m, 1H), 6.40 (dd, J = 8.0, 1.1 Hz, 1H), 6.56 (ddd, J = 7.7, 7.4, 1.1 Hz, 1H), 7.05 (ddd, J = 8.0, 7.7, 1.1 Hz, 1H), 7.66 (dd, J = 7.4, 1.1 Hz, 1H); ^{13}C NMR (125 MHz, DMSO, 393 K) δ : 14.8, 27.5-27.8 (3C), 28.6-28.9, 31.0, 37.0, 47.3, 78.3, 83.3, 87.0, 105.9-106.0, 115.7, 126.4-126.7 (3C), 128.1-128.2, 141.5, 151.0, 152.9; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{26}\text{N}_2\text{NaO}_2$ (MNa^+): 349.1892; found: 349.1889.

1,4,10,10-Tetramethyl-3*H*,4*H*-8*b*,3*a*-(epoxyethano)cyclopenta[*b*]indole (**2d**)

According to the procedure described for the preparation of **2a**, **1d** (30.0 mg, 0.117 mmol) was converted into **2d** (23.4 mg, 78%). In this case, the reaction was conducted for 2 h at 40 °C: colorless oil; ^1H NMR (500 MHz, CDCl_3) δ : 1.13 (s, 3H), 1.31 (s, 3H), 1.86 (d, J = 12.6 Hz, 1H), 1.96-1.97 (m, 3H), 2.33 (d, J = 12.6 Hz, 1H), 2.43-2.53 (m, 2H), 2.82 (s, 3H), 5.34 (m, 1H), 6.35 (dd, J = 8.0, 1.1 Hz, 1H), 6.62 (ddd, J = 7.7, 7.4, 1.1 Hz, 1H), 7.14 (ddd, J = 8.0, 7.7 Hz, 1H), 7.30 (dd, J = 7.4, 1.1 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ : 12.8, 29.1, 29.5, 29.9, 41.7, 49.8, 84.4, 85.3, 103.8, 105.8, 116.6, 123.7, 125.5, 129.3 (2C), 142.4, 150.9; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{22}\text{NO}$ (MH^+): 256.1701; found: 256.1702.

5,10-Dimethyl-3,4-dihydro-2*H*,5*H*-9*b*,4*a*-prop[1]enopyrano[3,2-*b*]indole (2e)

According to the procedure described for the preparation of **2a**, **1e** (30.0 mg, 0.124 mmol) was converted into **2e** (25.5 mg, 85%): colorless solid; mp 57 °C; ¹H NMR (500 MHz, CDCl₃) δ: 1.46-1.57 (m, 2H), 1.75-1.85 (m, 5H), 2.28-2.33 (m, 1H), 2.39-2.43 (m, 1H), 2.72 (s, 3H), 3.44-3.49 (m, 1H), 3.59-3.63 (m, 1H), 5.64 (m, 1H), 6.45 (dd, *J* = 8.0, 1.1 Hz, 1H), 6.71 (ddd, *J* = 7.4, 7.4, 1.1 Hz, 1H), 7.16 (ddd, *J* = 8.0, 7.4, 1.1 Hz, 1H), 7.24 (dd, *J* = 7.4, 1.1 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ: 12.2, 20.6, 26.4, 29.0, 39.5, 61.0, 73.4, 92.9, 106.8, 117.4, 123.6, 127.0, 127.5, 129.2, 140.2, 151.5; HRMS (ESI) calcd for C₁₆H₂₀NO (MH⁺): 242.1545; found: 242.1542.

3,3-Bis(chloromethyl)-5,10-dimethyl-3,4-dihydro-2*H*,5*H*-9*b*,4*a*-prop[1]enopyrano[3,2-*b*]indole (2f)

According to the procedure described for the preparation of **2a**, **1f** (30.0 mg, 0.089 mmol) was converted into **2f** (27.2 mg, 91%): colorless oil; ¹H NMR (500 MHz, CDCl₃) δ: 1.35 (d, *J* = 14.9 Hz, 1H), 1.95-1.96 (m, 3H), 2.10-2.14 (m, 1H), 2.20-2.27 (m, 2H), 2.75 (s, 3H), 3.31 (d, *J* = 12.0 Hz, 1H), 3.46 (d, *J* = 12.0 Hz, 1H), 3.57 (d, *J* = 11.5 Hz, 1H), 3.59 (d, *J* = 11.5 Hz, 1H), 3.62 (d, *J* = 10.3 Hz, 1H), 3.71 (d, *J* = 10.3 Hz, 1H), 5.59-5.60 (m, 1H), 6.52 (dd, *J* = 8.0, 1.1 Hz, 1H), 6.76 (ddd, *J* = 7.7, 7.4, 1.1 Hz, 1H), 7.23 (ddd, *J* = 8.0, 7.7, 1.1 Hz, 1H), 7.29 (dd, *J* = 7.4, 1.1 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ: 12.7, 29.3, 32.3, 38.9, 41.3, 47.1, 49.0, 64.9, 72.1, 93.2, 107.7, 118.4, 124.0, 126.6, 127.4, 129.9, 140.3, 151.2; HRMS (ESI) calcd for C₁₈H₂₂Cl₂NO (MH⁺): 338.1078; found: 338.1074.

1-Ethyl-4-methyl-3*H*,4*H*-8*b*,3*a*-(epoxyethano)cyclopenta[*b*]indole (2h)

According to the procedure described for the preparation of **2a**, **1h** (30.0 mg, 0.124 mmol) was converted into **2h** (26.1 mg, 87%): colorless oil; ¹H NMR (500 MHz, CDCl₃) δ: 1.14 (t, *J* = 7.4 Hz, 3H), 1.93-1.98 (m, 1H), 2.18-2.23 (m, 1H), 2.27-2.42 (m, 2H), 2.44-2.49 (m, 1H), 2.61-2.66 (m, 1H), 2.84 (s, 3H), 3.70-3.74 (m, 1H), 3.84-3.88 (m, 1H), 5.41-5.43 (m, 1H), 6.36 (dd, *J* = 8.0, 1.1 Hz, 1H), 6.63 (dd, *J* = 7.7, 7.4, 1.1 Hz, 1H), 7.14 (ddd, *J* = 8.0, 7.4, 1.1 Hz, 1H), 7.28 (dd, *J* = 7.4, 1.1 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ: 11.7, 19.8, 29.7, 38.7, 41.4, 67.4, 83.9, 104.4, 105.7, 116.6, 124.2, 124.6, 127.2, 129.6, 145.5, 151.7; HRMS (ESI) calcd for C₁₆H₁₉NNaO (MNa⁺): 264.1364; found: 264.1363.

4-Methyl-1-phenyl-3*H*,4*H*-8*b*,3*a*-(epoxyethano)cyclopenta[*b*]indole (2i)

According to the procedure described for the preparation of **2a**, **1i** (30.0 mg, 0.104 mmol) was converted into **2i** (27.5 mg, 92%). In this case, the reaction was conducted for 2 h at 60 °C: colorless oil; ¹H NMR (500 MHz, CDCl₃) δ: 2.02-2.07 (m, 1H), 2.31-2.36 (m, 1H), 2.68 (dd, *J* = 17.8, 2.6 Hz, 1H), 2.73 (dd, *J* = 17.8, 2.6 Hz, 1H), 2.87 (s, 3H), 3.81-3.86 (m, 1H), 4.02-4.06 (m, 1H), 6.10 (dd, *J* = 2.6, 2.6 Hz, 1H), 6.37 (d, *J* = 8.0 Hz, 1H), 6.47 (ddd, *J* = 7.4, 7.4, 1.1 Hz, 1H), 7.08-7.12 (m, 2H), 7.28-7.31 (m, 1H), 7.34-7.37 (m, 2H), 7.83-7.84 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ: 29.8, 38.8, 40.8, 67.8, 85.0, 104.4, 105.7, 116.8, 124.9, 127.2, 127.3 (2C), 127.6, 128.2 (2C), 128.9, 129.7, 134.7, 142.9, 151.8; HRMS (ESI) calcd for C₂₀H₂₀NO (MH⁺): 290.1545; found: 290.1545.

4-Benzyl-1-methyl-3*H*,4*H*-8*b*,3*a*-(epoxyethano)cyclopenta[*b*]indole (2j)

According to the procedure described for the preparation of **2a**, **1j** (30.0 mg, 0.099 mmol) was converted into **2j** (21.9 mg, 73%): amber oil; ¹H NMR (500 MHz, CDCl₃) δ: 1.94-2.00 (m, 4H), 2.20-2.25 (m, 1H), 2.46-2.50 (m, 1H), 2.61-2.65 (m, 1H), 3.81-3.85 (m, 1H), 3.88-3.92 (m, 1H), 4.44 (s, 2H), 5.42 (m, 1H), 6.20 (d, *J* = 8.0 Hz, 1H), 6.66 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.05 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.24-7.28 (m, 1H), 7.31-7.34 (m, 5H); ¹³C NMR (125 MHz, CDCl₃) δ: 12.7, 40.3, 42.4, 49.1, 67.5, 84.2, 104.3, 106.6, 117.0, 124.1, 126.7 (2C), 127.0 (2C), 127.1, 128.6 (2C), 129.5, 139.0, 139.8, 151.5; HRMS (ESI) calcd for C₂₁H₂₁KNO (MK⁺): 342.1260; found: 342.1259.

3. Synthesis of Allene **3h** (Scheme 3)

2-[1-Methyl-3-(penta-1,2-dien-3-yl)-1H-indol-2-yl]ethan-1-ol (**3h**)

According to the procedure described for the preparation of **2a**, **1h** (30.0 mg, 0.124 mmol) was converted into a mixture of **3h** and **1h** (20.4 mg, 68% combined isolated yield, **3h/1h** = 5.5:1). In this case, the reaction was conducted for 100 min at 40 °C with the use of 3 mol % of IPrAuSbF₆·MeCN (3.2 mg, 0.0037 mmol). The mixture of **3h** and **1h** was carefully separated by column chromatography (aluminum oxide; hexane/EtOAc = 12/1) to give pure **3h** (Note: **3h** was gradually decomposed during the purification by column chromatography): yellow oil; IR (neat) 1945 (C=C=C) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 1.10 (t, *J* = 6.9 Hz, 3H), 1.58 (s, 1H), 2.44-2.50 (m, 2H), 3.11 (t, *J* = 6.9 Hz, 2H), 3.72 (s, 3H), 3.83-3.87 (m, 2H), 4.84-4.85 (m, 2H), 7.09 (ddd, *J* = 7.7, 7.4, 1.1 Hz, 1H), 7.19 (ddd, *J* = 7.7, 7.4, 1.1 Hz, 1H), 7.28 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.59 (dd, *J* = 7.7, 1.1 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ: 12.7, 26.3, 28.4, 29.9, 62.1, 74.9, 100.5, 109.0, 110.2, 119.3, 119.4, 121.2, 126.6, 133.6, 137.1, 208.0; HRMS (ESI) calcd for C₁₆H₁₉NNaO (MNa⁺): 264.1364; found: 264.1368.

4. NMR Experiment (Figure 2)

To the solution of **1h** (20.0 mg, 0.083 mmol) and CHCl₂CHCl₂ (13.9 mg, 0.083 mmol) in MeOD-*d*₃ (8.5 mL) was added 3 mol % IPrAuSbF₆·MeCN (2.1 mg, 0.0025 mmol) at room temperature. The reaction was conducted at 40 °C. After stirring for 0 min, 20 min, 40 min, 60 min, 90 min, 120 min, 150 min, 165 min, 180 min, 200 min, 215 min, and 240min, ca. 0.7 ml of the solution was picked up from the reaction mixture to measure ¹H NMR. The yields were evaluated using CHCl₂CHCl₂ as an internal standard.

5. Crossover Experiment (Scheme 5)

To the solution of **1b** (26.6 mg, 0.07 mmol) and **1i** (20.2 mg, 0.07 mmol) in 2-propanol (0.7 mL) was added IPrAuSbF₆·MeCN (6.0 mg, 0.007 mmol) at room temperature. After stirring for 1 h at 60 °C, the reaction mixture was concentrated in vacuo and the residue was purified by column chromatography on silica gel (hexane/EtOAc = 12/1 → 9/1) to afford **2b** (24.8 mg, 93%) and **2i** (17.7 mg, 88%). The crossover products **2b'** and **2a** were not detected by TLC, GCMS, and ¹H NMR.

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Chapter 3. Conclusions

1. A straightforward route has been developed for the construction of quinazolines from mono-substituted arenes. Treatment of *N*-phenylbenzamidines with TIPS-EBX promoted the N-H alkynylation of the amidine nitrogen in the presence of a copper catalyst, and the resulting ynamides were transformed into quinazolines via an electrocyclic reaction. The replacement of EBX with a terminal alkyne also worked well under the oxidative conditions.
2. An efficient method has been developed for the synthesis of indoloquinolines from (azido)ynamides using a cationic gold catalyst. This reaction proceeds via the formation of an α -amidino gold-carbenoid species, and is tolerant towards a variety of different ynamides. While the reactions of ynamides bearing an allylsilane gave indoloquinolines with a terminal alkene moiety, the reaction of ynamides bearing a simple alkene gave indoloquinolines with a cyclopropane moiety. The aryl group can also be used as the trapping functionality to give azocine- or azepine-fused pentacyclic indoles.
3. Various *N*-propargyl ynamides have been converted to bicyclic and tricyclic pyrroles using a cationic dual activation gold catalyst. This reaction starts with the nucleophilic addition of a gold acetylide species to the β -position of the triple bond of an ynamide. The second cyclization is promoted by the formation of a gold vinylidene species. The formation of gold vinylidene is indicated by the evidence that alkylethynyl-type ynamides also undergo the C-H activation in these reactions.
4. A gold-catalyzed cascade cyclization has been developed for the synthesis of fused indoles from *o*-alkynyl-*N*-propargylanilines. Allenes were formed during this reaction via the migration of the propargyl group from the indole nitrogen, which subsequently induced a cyclization reaction from the indole to give the corresponding indolines. NMR experiments revealed that the indoline formation only started after the completion consumption of the *o*-alkynyl-*N*-propargylaniline starting material, which suggested that the migration of the propargyl group was involved in the turnover limiting step.

In summary, a novel strategy has been developed for the synthesis of heterocyclic scaffolds using a transition-metal-catalyzed alkyne cyclization reaction. Quinazolines, indoloquinolines, bicyclic pyrroles and fused indolines can be efficiently synthesized from ynamides or diynes using this strategy. Given that nucleophilic addition reactions onto alkynes are both fascinating and valuable as atom economical transformations, all of the multiple chemical bonds forming reactions developed in this study should represent a useful addition to the repertoire of transformations already available for green chemistry.

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List of Publications

This study was published in the following papers.

Chapter 1.

Section 1. Direct Synthesis of Quinazolines through Copper-Catalyzed Reaction of Aniline-Derived Benzamidines
Yusuke Ohta, Yusuke Tokimizu, Shinya Oishi, Nobutaka Fujii, and Hiroaki Ohno
Org. Lett. **2010**, 12, 3963–3965.

Section 2. Gold-Catalyzed Cascade Cyclization of (Azido)ynamides: An Efficient Strategy for the Construction of Indoloquinolines
Yusuke Tokimizu, Shinya Oishi, Nobutaka Fujii, and Hiroaki Ohno
Org. Lett. **2014**, 16, 3138–3141.

Section 3 Dual Gold Catalysis: A Novel Synthesis of Bicyclic and Tricyclic Pyrroles from *N*-Propargyl Ynamides
Yusuke Tokimizu, Marcel Wietek, Matthias Rudolph, Shinya Oishi, Nobutaka Fujii, A. Stephen K. Hashmi, and Hiroaki Ohno
Org. Lett. **2015**, 17, 604–607.

Chapter 2. Gold-Catalyzed Cascade Cyclization of 2-Alkynylanilines via Rearrangement of Propargyl Group
Yusuke Tokimizu, Shinya Oishi, Nobutaka Fujii, and Hiroaki Ohno
Manuscript in preparation.

The author also contributed to other related studies published in the following papers.

1. Direct Synthesis of Highly Fused Perimidines by Copper(I)-Catalyzed Hydroamination of 2-Ethynylbenzaldehydes
Tokimizu, Y.; Ohta, Y.; Chiba, H.; Oishi, S.; Fujii, N.; Ohno, H. *Tetrahedron* **2011**, 67, 5168.
2. 5,10-Dihydrobenzo[*a*]indolo[2,3-*c*]carbazole: A Highly Fluorescent Disk-shaped Electron Donor Exhibiting Dual UV-vis-NIR and Fluorescence Spectral Changes upon Electrolysis
Suzuki, T.; Tokimizu, Y.; Sakano, Y.; Katoono, R.; Fujiwara, K.; Naoe, S.; Fujii, N.; Ohno, H. *Chem. Lett.* **2013**, 42, 1001.
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