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<td>Author(s)</td>
<td>Tokimizu, Yusuke</td>
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<td>Citation</td>
<td>Kyoto University (京都大学)</td>
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<td>Issue Date</td>
<td>2015-03-23</td>
</tr>
<tr>
<td>URL</td>
<td><a href="https://doi.org/10.14989/doctor.k18928">https://doi.org/10.14989/doctor.k18928</a></td>
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Kyoto University
Synthesis of Heterocyclic Scaffolds through Transition-Metal-Catalyzed Cascade Reactions of Alkynes

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

Yusuke Tokimizu
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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.\textsuperscript{1} Alkynes can be easily activated with a variety of different Brønsted and Lewis acids, including halogens and transition-metal complexes.\textsuperscript{1b,c} Among these acids, cationic transition-metal complexes represent particularly attractive activating agents because they can selectively activate π-bonds under mild conditions.\textsuperscript{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](image)

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.\textsuperscript{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](image)
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).\(^3\) 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),\(^3\) 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).\(^3\) 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](image)

![Scheme 4. Easy Method for the Syntheses of Nitrogen-Containing Heterocyclic Compounds](image)
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. In 2005, Hsung reported the acid-catalyzed Pictet-Spengler-type cyclization of ynamide 16 (Scheme 5, eq 1). 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). In this case, the reaction of alkynyl bromide 19 with N,N’-ditosylethenediamine 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). 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, and cascade reactions represent one of the most promising approaches for achieving these goals. 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. 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. For example, a gold carbenoid was observed as an intermediate in the cyclization of 1,6-enyne 26 (Scheme 6a). 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). In this case, the expulsion of N\textsubscript{2} 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). 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.
References


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]-1H,3-benzo[d][1,2]iodoxol-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 alkynylation⁵–¹⁰ 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-phenylbenzamidine 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

<table>
<thead>
<tr>
<th>entry</th>
<th>Cu catalyst</th>
<th>solvent</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OAc)₂</td>
<td>toluene</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>CuBr₂</td>
<td>toluene</td>
<td>NR&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>CuOAc</td>
<td>toluene</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>CuI</td>
<td>toluene</td>
<td>19</td>
</tr>
<tr>
<td>5</td>
<td>CuCl</td>
<td>toluene</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>CuBr</td>
<td>toluene</td>
<td>38</td>
</tr>
<tr>
<td>7</td>
<td>CuBr</td>
<td>xylene</td>
<td>34</td>
</tr>
<tr>
<td>8</td>
<td>CuBr</td>
<td>DCE</td>
<td>24</td>
</tr>
<tr>
<td>9</td>
<td>CuBr</td>
<td>DMF</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>CuBr</td>
<td>dioxane</td>
<td>trace</td>
</tr>
<tr>
<td>11</td>
<td>CuBr</td>
<td>benzene</td>
<td>47</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yields. <sup>b</sup> 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\textsuperscript{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**

<table>
<thead>
<tr>
<th>entry</th>
<th>alkyne source</th>
<th>( R^1 )</th>
<th>( R^2 )</th>
<th>yield (%)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TIPS IPh OTf</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>2c</td>
<td>TIPS</td>
<td>H</td>
<td>41</td>
</tr>
<tr>
<td>3</td>
<td>2d</td>
<td>TMS</td>
<td>H</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>2e</td>
<td>Ph</td>
<td>H</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>2f</td>
<td>t-Bu</td>
<td>H</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>2g</td>
<td>TIPS</td>
<td>Me</td>
<td>&lt; 61</td>
</tr>
<tr>
<td>7</td>
<td>2h</td>
<td>TIPS</td>
<td>F</td>
<td>&lt; 61</td>
</tr>
<tr>
<td>8</td>
<td>2i</td>
<td>TIPS</td>
<td>NO(_2)</td>
<td>44–61</td>
</tr>
<tr>
<td>9\textsuperscript{b}</td>
<td>2i</td>
<td>TIPS</td>
<td>NO(_2)</td>
<td>62</td>
</tr>
</tbody>
</table>

\( ^a \) 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 iodoquinoxalines 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 quinoxalines 4f–h in 60–67% yields (entries 5–7). Substitution at the meta position was investigated using amidine 1i and
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.**

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>R&lt;sup&gt;1&lt;/sup&gt;</td>
<td>R&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1b</td>
<td>4-F Ph</td>
</tr>
<tr>
<td>2</td>
<td>1c</td>
<td>4-Cl Ph</td>
</tr>
<tr>
<td>3</td>
<td>1d</td>
<td>4-Br Ph</td>
</tr>
<tr>
<td>4</td>
<td>1e</td>
<td>4-I Ph</td>
</tr>
<tr>
<td>5</td>
<td>1f</td>
<td>4-Me Ph</td>
</tr>
<tr>
<td>6</td>
<td>1g</td>
<td>4-OMe Ph</td>
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<tr>
<td>7</td>
<td>1h</td>
<td>4-t-Bu Ph</td>
</tr>
<tr>
<td>8</td>
<td>1i</td>
<td>3-Br Ph</td>
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<td>9</td>
<td>1j</td>
<td>3-OMe Ph</td>
</tr>
<tr>
<td>10</td>
<td>1k</td>
<td>H t-Bu</td>
</tr>
<tr>
<td>11</td>
<td>1l</td>
<td>H 4-(CF&lt;sub&gt;3&lt;/sub&gt;)C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
</tr>
<tr>
<td>12</td>
<td>1m</td>
<td>H 4-(OMe)C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
</tr>
<tr>
<td>13</td>
<td>1n</td>
<td>thiophen-2-yl</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yields. <sup>b</sup> 3.7:1 mixture of 7- and 5-bromoquinazolines. <sup>c</sup> 1.25:1 mixture of 7- and 5-methoxyquinazolines.

The known quinazoline 5<sup>13</sup> 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**

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 quinazoline 4: N–H alkylation and C–H alkylation of N-phenylbenzamidines. The treatment with CuBr did not promote the cyclization of o-alkylated benzamidine 1o (eq 1), which is thought to be the intermediate in the C–H alkylation pathway. On the other hand, the addition of TIPS-EBX 2i led to cyclization of 1o at the other ortho-position to give quinazoline 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 \(N\text{-}H\) 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 \( \delta \) (ppm) relative to Me\(_4\)Si (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, 1c, 1d, 1e, 1f, 1g, 1j, 1k, 1m, 1n, 2a, 2b, 2c-f, and 9 were prepared according to the literatures.


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

A mixture of 4-(4-tert-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 7.5, 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\(_3\)) \( \delta \) 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\(_3\)) \( \delta \) 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 C\(_{17}\)H\(_{20}\)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\(_3\)) \( \delta \) 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\(_3\)) \( \delta \) 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 C\(_{13}\)H\(_{11}\)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 (1j)**

By a procedure described for the preparation of amidine 1h, 4-(trifluoromethyl)benzonitrile (1.30 mL, 9.70 mmol) was converted into 1j (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\(_3\)) \( \delta \) 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\(_3\)) \( \delta \) 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 C\(_{14}\)H\(_{14}\)F\(_3\)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 μL, 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 CHCl₃ (60 mL) and CH₃OH (30 mL). The silica gel was filtered off and washed with a solution of CH₂Cl₂/CH₃OH (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), 2136 (C≡C) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₇H₂₇N₃Si: 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 amide 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 (C≡C) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₉H₁₆N₂: C, 82.57; H, 7.29; N, 10.14. Found: C, 82.49; H, 7.46; N, 9.96.

2. Synthesis of ethynylbenzodioxolone (EBX)

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

To the stirred suspension of 5-methyl-2-iodosylbenzoic acid (1.05 g, 3.79 mmol) in CH₃CN was added dropwise trimethylsilyl triflate (0.75 mL, 4.17 mmol) at room temperature under argon. After (trimethylsilyl)(triisopropylsilylethynyl)acetylene (1.05 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 CH₂Cl₂, washed with 1 N HCl and aqueous saturated NaHCO₃, and dried over MgSO₄. Concentration under reduced pressure gave an yellow solid, which was recrystallized from CH₂CN to give 2g (1.0 g, 59%) as colorless needles: mp 189–191 °C; IR (neat) 1619 (CO) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₉H₂₅O₂Si: C, 51.58; H, 6.15. Found: C, 51.34; H, 6.00.

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

A mixture of 5-fluoro-2-iodobenzoic acid (1.00 g, 3.76 mmol) and NaIO₄ (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 CH₂CN 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 an yellow solid, which was recrystallized from CH₂CN 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), 119.3-119.4 (m), 119.3 (d, J = 24.0 Hz), 122.2 (d, J = 25.2 Hz), 127.8, 132.4-134.3 (m), 165.1 (d, J = 7.2 Hz), 165.5 (d, J = 253.1 Hz). Anal. Calcd for C₁₈H₂₄F₂O₂Si: C, 48.43; H, 5.42. Found: C, 48.33; H, 5.34.

5-Nitro-1-[(triisopropylsilyl)ethynyl]-1λ₂-benzo[d][1,2]iodaoxol-3(1H)-one (2i)

By a procedure described for the preparation of benzoiodoxolone 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), 7.53 (m, 3H), 7.56 (m, 4H), 7.78 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 11.5 (3C), 18.6 (6C), 19.5, 108.7 (d, J = 25.2 Hz), 127.8, 132.4, 134.5, 150.7, 166.7; Anal. Calcd for C₁₈H₂₄NO₂Si: 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), 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 C₂₄H₂₃N₂Si (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 C₂₄H₂₃FNSi (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) calc'd for C₃H₂ClNi₃Si (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, CDCl₃) δ 1.04 (d, J = 7.4 Hz, 1H), 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); ¹³C NMR (125 MHz, CDCl₃) 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⁺, 81Br, 100), 455 (MH⁺, 79Br, 100), 413 (80), 411 (80); HRMS (FAB) calc'd for C₂₃H₁₇BrN₃Si (MH⁺): 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, CDCl₃) 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), 8.05 (dd, J = 8.6, 1.7 Hz, 1H), 8.17 (d, J = 1.7 Hz, 1H), 8.60 (dd, J = 7.7, 1.4 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 11.6 (3C), 18.5 (6C), 19.8, 90.9, 124.4, 128.8 (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) calc'd for C₂₃H₁₇IN₃Si (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, CDCl₃) 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), 7.70 (d, J = 8.6 Hz, 1H), 8.59-8.68 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 11.6 (3C), 18.5 (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) calc'd for C₂₃H₁₇N₃Si (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, CDCl₃) 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), 8.29-8.60 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) 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) calc'd for C₂₃H₁₇N₂O₃Si (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, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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) calc'd for C₂₃H₁₇N₂O₃Si (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. $^1$H 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$^+$, 81Br, 75), 455 (MH$^+$, 79Br, 75), 413 (100), 411 (100); HRMS (FAB) calcld for C$_{24}$H$_{32}$BrN$_2$Si (MH$^+$): 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; $^1$H 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) calcld for C$_{25}$H$_{32}$N$_2$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; $^1$H 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) calcld for C$_{25}$H$_{32}$F$_3$N$_2$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; $^1$H 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) calcld for C$_{25}$H$_{32}$N$_2$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, CDCl3) 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); 13C NMR (125 MHz, CDCl3) 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 C22H31N2SSi (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 silica gel with hexane–EtOAc (30:1) to give 5 (35 mg, 76%) as colorless solid: mp 85–87 °C; 1H NMR (500 MHz, CDCl3) δ 2.40 (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); 13C NMR (125 MHz, CDCl3) 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 C15H13N (MH+): 221.1087; found: 221.1084.

2-Phenyl-8-[(triisopropylsilyl)ethyl]ynyl]-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 (C≡C) cm−1; 1H NMR (500 MHz, CDCl3) 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); 13C NMR (125 MHz, CDCl3) 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 C35H25N2Si2 (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, CDCl3) 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); 13C NMR (125 MHz, CDCl3) 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 C30H20N2Si (MH+): 455.2883; found: 455.2873.

1,1,1-Trifluoro-N-phenethyl-N-[(triisopropylsilyl)ethyl]ylnmethanesulfonamide (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 (C≡C) cm−1; 1H NMR (500 MHz, CDCl3) 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); 13C NMR (125 MHz, CDCl3) 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 C20H30F3NNaO2Si (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 μL, 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%).
References

(9) For a recent review, see: Dudnik, A. S.; Gevorgyan, V. Angew. Chem., Int. Ed. 2010, 49, 2096.
(21) Brasche, G.; Buchwald, S. L. Angew. Chem., Int. Ed. 2008, 47, 1932
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, and the gold-catalyzed reactions of alkynes and allenes have been used extensively to synthesize a broad range of natural products and complex molecules in an efficient and chemoselective manner. 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. reported novel construction of pyrrole scaffold by gold-catalyzed cyclization of azide-alkynes. Following on from this pioneering work, Gagosz and Zhang 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), as well as a wide range of synthetic derivatives exhibiting antimalarial and antitumor activities.

![Figure 1. Natural Products Containing an α-Carboline/Indoloquinoline Framework.](image-url)
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). It is noteworthy that bromoalkyne, which has been widely used as an alkynylating reagent for the preparation of ynamides, 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 IPrAuCl/AgNTf₂ 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 PPh₃AuCl/AgNTf₂ 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 \textbf{L2} providing \textbf{2a} in 78\% yield after 10 min at room temperature (entry 7). PtCl$_4$ was also found to catalyze the reaction, whereas PtCl$_2$ showed barely any activity (entries 8 and 9). Following an extensive period of screening, the author found that a combination of \textbf{L2}AuCl/AgOTf in nitromethane provided the highest level of activity with \textbf{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.\textsuperscript{8}

\textbf{Table 1.} Optimization of Reaction Conditions

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent</th>
<th>conditions</th>
<th>yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IPrAuCl/AgNTf$_2$</td>
<td>DCE</td>
<td>50 °C, 15 h</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>PPh$_3$AuCl/AgNTf$_2$</td>
<td>DCE</td>
<td>rt, 10 min</td>
<td>64</td>
</tr>
<tr>
<td>3</td>
<td>JohnPhosAuCl/AgNTf$_2$</td>
<td>DCE</td>
<td>50 °C, 1.5 h</td>
<td>74</td>
</tr>
<tr>
<td>4</td>
<td>BrettPhosAuCl/AgNTf$_2$</td>
<td>DCE</td>
<td>50 °C, 10 h</td>
<td>43</td>
</tr>
<tr>
<td>5</td>
<td>XPhosAuCl/AgNTf$_2$</td>
<td>DCE</td>
<td>50 °C, 10 h</td>
<td>47</td>
</tr>
<tr>
<td>6</td>
<td>\textbf{L1}AuCl/AgNTf$_2$</td>
<td>DCE</td>
<td>50 °C, 4 h</td>
<td>37</td>
</tr>
<tr>
<td>7</td>
<td>\textbf{L2}AuCl/AgNTf$_2$</td>
<td>DCE</td>
<td>rt, 10 min</td>
<td>78</td>
</tr>
<tr>
<td>8</td>
<td>PtCl$_4$</td>
<td>DCE</td>
<td>40 °C, 12 h</td>
<td>63</td>
</tr>
<tr>
<td>9</td>
<td>PtCl$_2$</td>
<td>DCE</td>
<td>70 °C, 2 h</td>
<td>trace</td>
</tr>
<tr>
<td>10</td>
<td>[\textbf{L2}AuCl/AgOTf]$^b$</td>
<td>DCE</td>
<td>rt, 10 min</td>
<td>90</td>
</tr>
<tr>
<td>11</td>
<td>[\textbf{L2}AuCl/AgOTf]$^b$</td>
<td>CH$_3$NO$_2$</td>
<td>rt, 10 min</td>
<td>94</td>
</tr>
<tr>
<td>12</td>
<td>[\textbf{L2}AuCl/AgOTf]$^{b,c}$</td>
<td>CH$_3$NO$_2$</td>
<td>rt, 30 min</td>
<td>94</td>
</tr>
</tbody>
</table>

$^a$ Isolated yields. $^b$ To simplify the protocol, the catalyst was prepared in advance by mixing \textbf{L2}AuCl 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 \( R^1 \) 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 \( \text{para} (R^2) \) 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).

### Table 2. Evaluation of the Substituent Effect

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate ((E/Z))</th>
<th>( R^1 )</th>
<th>( R^2 )</th>
<th>Product (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1b ((Z))</td>
<td>OMe</td>
<td>H</td>
<td>2b (91)</td>
</tr>
<tr>
<td>2</td>
<td>1c ((Z))</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;</td>
<td>H</td>
<td>2c (60)</td>
</tr>
<tr>
<td>3</td>
<td>1d ((Z))</td>
<td>H</td>
<td>Me</td>
<td>2d (97)</td>
</tr>
<tr>
<td>4</td>
<td>1e ((Z))</td>
<td>H</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;Me</td>
<td>2e (90)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>1f ((Z))</td>
<td>H</td>
<td>Cl</td>
<td>2f (86)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>1g ((E))</td>
<td>H</td>
<td>H</td>
<td>2a (95)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yields. <sup>b</sup> 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). 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

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>R¹</th>
<th>R²</th>
<th>product (%)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5a</td>
<td>Ph</td>
<td>H</td>
<td>6a (94)</td>
</tr>
<tr>
<td>2</td>
<td>5b</td>
<td>n-Bu</td>
<td>H</td>
<td>6b (74)²</td>
</tr>
<tr>
<td>3</td>
<td>5c</td>
<td>H</td>
<td>Ph</td>
<td>6c (75)</td>
</tr>
<tr>
<td>4</td>
<td>5d</td>
<td>H</td>
<td>n-Bu</td>
<td>6d (93)</td>
</tr>
<tr>
<td>5</td>
<td>5e</td>
<td>H</td>
<td>H</td>
<td>6e²</td>
</tr>
</tbody>
</table>

Reactions were conducted with 5 mol % of [L2AuCl/AgOTf] in 1,2-dichloroethane. Isolated yields. ² 5 mol % of PPh₃AuCl/AgNTf₂ was used as the catalyst. ² 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. 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)ynamides 8 bearing an aryl group as the trapping functional group (Scheme 5). As expected, the (azido)ynamides 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)ynamides 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.\textsuperscript{11} Compound 2a could also be formed from the cyclopropane intermediate 6 (R\textsubscript{1} = H, R\textsubscript{2} = CH\textsubscript{2}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.\textsuperscript{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-TOF-MS equipment (ESI). $^1$H NMR spectra were recorded using a JEOL AL-500 spectrometer at 500 MHz frequency. Chemical shifts are reported in $\delta$ (ppm) relative to Me$_4$Si (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 Mo-K$\alpha$ radiation at -180 °C.

The known compounds S6, S12, S13, S16, S20, S25, S28, S30, S32, S34, S37, and S38 were synthesized according to the literature. The $^1$H NMR data of S35 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), PdCl$_2$(CH$_3$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$_2$O 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 (C≡C) cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 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$_3$) $\delta$: 0.1 (3C), 55.8, 99.7, 101.8, 108.4, 115.8 (2C), 117.8, 142.5, 151.7; HRMS (FAB) calcd for C$_{12}$H$_{18}$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 NaN$_3$ (1.72 g, 25.0 mmol) in water (10 mL) at 0 °C. After stirring for 1 h at 25 °C, a solution of NaNO$_2$ (3.25 g, 50.0 mmol) in water (10 mL) was added. After stirring for 1 h at 25 °C, water was added and the reaction mixture was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc $\approx$ 50/1) to afford S2 (513 mg, 42%): yellow oil; IR (neat) 2125 (C≡C), 2094 (N$_3$) cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 0.27 (s, 9H), 3.78 (s, 3H), 6.87
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), 3387 (NH); mp 53 °C; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 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$_3$) $\delta$: 0.2 (3C), 21.4, 100.1, 100.3, 112.5, 119.4, 125.5, 133.9, 140.3, 140.8; Anal. Calcd for C$_{12}$H$_{16}$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 (C=C), 2102 (N$_2$) cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 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$_3$) $\delta$: −0.1 (3C), 21.4, 100.1, 100.3, 112.5, 119.4, 125.5, 133.9, 140.3, 140.8; Anal. Calcd for C$_{12}$H$_{15}$N$_3$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$_3$CN (14 mL) was used instead of TFA. Column chromatography: silica gel (hexane/EtOAc = 10:1): colorless solid; mp 84 °C; IR (neat) 2120 (C=C), 1725 (CO) cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 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$_3$) $\delta$: −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 C$_{13}$H$_{15}$ClN$_3$O$_2$: 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 (C=C) cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 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$_3$) $\delta$: 0.1 (3C), 100.7 (2C), 106.3, 113.9, 117.9, 133.2, 135.5, 149.1; HRMS (FAB) calcd for C$_{14}$H$_{15}$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 (C=C), 2115 (N$_2$) cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 0.26 (s, 9H), 7.01-7.03 (m, 2H) 7.32-7.34 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: −0.3 (3C), 98.9, 102.3, 114.1, 119.3, 124.8, 134.9, 135.3, 142.1; Anal. Calcd for C$_{14}$H$_{15}$ClNSi: 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 (N$_3$) cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) 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); $^{13}$C NMR (125 MHz, CDCl$_3$) 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 C$_7$H$_7$F$_3$N$_3$: C, 26.86; H, 0.97; N, 13.42. Found: C, 26.75; H, 1.00; N, 13.66.

[2-Azido-5-(trifluoromethyl)phenyl]ethyl[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 PdCl$_2$[(PPh)$_3$]$_2$ (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 (N$_3$) cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) 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); $^{13}$C NMR (125 MHz, CDCl$_3$) 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 C$_{13}$H$_2$F$_3$N$_3$Si-I/7H$_2$O: 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-1,2-benzo[d][1,2]iodaoxol-3(1H)-one (S11)

To a stirred suspension of 2-[azidophenyl]ethynyltrimethylsilane S13 (6.70 g, 31.1 mmol) in CH$_3$CN (30 mL) was added trimethylsilyl triflate (300 mL). After cooling, the precipitate was collected by filtration, and suspended in hot CH$_3$CN (ca. 600 mL). After cooling, the precipitate was collected by filtration, washed with CH$_3$CN, 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$^{-1}$; $^1$H NMR (500 MHz, DMSO-d$_6$) δ: 7.80 (dd, $J = 8.0, 7.4$ Hz, 1H), 7.47 (d, $J = 8.0$ Hz, 1H), 7.61 (dd, $J = 8.0, 8.0, 1.1$ Hz, 1H), 7.71 (dd, $J = 7.4, 1.1$ Hz, 1H); $^{13}$C 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, 143.2, 142.3, 150.2, 156.4; Anal. Calcd for C$_{10}$H$_7$N$_3$O$_4$: 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-1,2-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 (N$_3$), 1649 (CO) cm$^{-1}$; $^1$H 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); $^{13}$C 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 C$_{10}$H$_7$N$_3$O$_4$: 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-1,2-benzo[d][1,2]iodaoxol-1(3H)-yl]ethyl]benzoate (S15)

To a stirred suspension of 2-iodosybenzoic acid S16 (290 mg, 1.10 mmol) in CH$_3$CN (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 CH$_3$CN (2 mL) was added dropwise at that temperature and the mixture was stirred for 1 h, followed by
the addition of pyridine (96.7 μL, 1.20 mmol). After stirring for 1 h, the mixture was extracted with CH₂Cl₂, washed with water and brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was recrystallized from CH₂CN to give S15 (273 mg, 61%): colorless silky needles; mp 171 °C (decomposition); IR (neat) 2115 (C≡C), 1722 (CO), 1606 (CO) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₆H₁₀IN₃O₂: 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]-1λ³-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 °C (decomposition); IR (neat) 2130 (C≡C), 1605 (CO) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₆H₁₀IN₃O₂: 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]-1λ³-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 °C (decomposition); IR (neat) 2121 (C≡C), 1601 (CO) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 2.44 (s, 3H), 6.49 (br s, 1H), 6.92 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₆H₁₀IN₃NaO₂ (MNa⁺): 425.9715; found: 425.9713.

1-[(2-Azido-4-chlorophenyl)ethynyl]-1λ³-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 °C (decomposition); IR (neat) 2154 (C≡C), 2112 (N≡C), 1604 (CO) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 7.18 (dd, J = 8.6, 2.0 Hz, 1H), 7.23 (dd, 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₆H₁₀ClIKN₃O₂ (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 °C. After stirring for 9 h at room temperature, the reaction mixture was poured into water. The whole was extracted with CH₂Cl₂, dried over MgSO₄, and concentrated in vacuo. The residue was chromatographed on NH₂ silica gel (hexane/EtOAc = 3/1) and recrystallized from CHCl₃-hexane to give pure S21 (5.89 g, 79%): colorless plates; mp 119 °C; IR (neat) 3266 (NH), 3241 (NH) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) δ:
To a mixture of S21 (3.02 g, 7.0 mmol) and Pd(PPh3)4 (404 mg, 0.35 mmol) in CH2Cl2 (70 mL) was added Bu3SnH (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 H2O (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 MgSO4, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/EtOAc = 13/1) to afford S22 (2.40 g, 97%): colorless solid; mp 112 °C; IR (neat) 3267 (NH), 2950 (C=C) cm⁻¹; 1H NMR (500 MHz, CDCl3) δ: 2.39 (s, 3H), 4.00 (br s, 1H), 4.53 (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); 13C NMR (125 MHz, CDCl3) 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 C7H9ClNOS: C, 41.78; H, 3.16; N, 3.24. Found: C, 41.78; H, 3.16; N, 3.24.

To a mixture of S22 (1.06 g, 3.0 mmol) and NiCl2(dppe) (48.8 mg, 0.90 mmol) in THF (10 mL) was added dropwise a solution of TMSCH2MgCl (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 MgSO4, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/EtOAc = 10/1) to afford S23 (0.965 g, 89%): colorless solid; mp 124 °C; IR (neat) 3272 (NH) cm⁻¹; 1H NMR (500 MHz, CDCl3) δ: 0.00 (s, 9H), 1.58 (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); 13C NMR (125 MHz, CDCl3) 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, 131.4 (2C), 136.6, 143.8; Anal. Calcd for C10H13NO2SSi: C, 63.47; H, 7.01; N, 3.90. Found: C, 63.30; H, 7.04; N, 3.89.

To a mixture of N-(2-iodophenyl)-4-methylbenzenesulfonamide (S24) (373 mg, 1.0 mmol), allyltrimethylsilane (634 μL, 4.0 mmol), 1,4-diazabicyclo[2.2.2]octane (336 mg, 3.0 mmol), n-Bu4NCl (278 mg, 1.0 mmol) in CH3CN (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 Et2O 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, CDCl3) 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); 13C NMR (125 MHz, CDCl3) 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) calc'd for C15H12NO3Si (MH⁺): 360.1454; found: 360.1455.

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
(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 converted to styrylaniline S27 (544 mg, 2.79 mmol) in pyridine (3 mL) and THF (8 mL) was added. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 5/1) to afford S27 (622 mg, 77%): colorless solid; mp 108 °C; IR (neat) 3262 (NH), 2954 (C=C) \( \text{cm}^{-1} \); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \): 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\(_3\)) \( \delta \): 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 C\(_{19}\)H\(_{20}\)NO\(_2\): 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) \( \text{cm}^{-1} \); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \): 2.39 (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\(_3\)) \( \delta \): 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 C\(_{21}\)H\(_{21}\)NO\(_2\): C, 71.19; H, 5.68; N, 4.15. Found: C, 70.91; H, 5.53; N, 4.01.

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) \( \text{cm}^{-1} \); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \): 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\(_3\)) \( \delta \): 13.8, 21.5, 22.2, 28.0, 31.4, 120.8, 123.3, 124.5, 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 C\(_{20}\)H\(_{19}\)NO\(_2\): 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 NiCl\(_2\)(dppp) (54.2 mg, 0.10 mmol) in THF (3.3 mL) was added dropwise TMSCl\(_2\)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) \( \text{cm}^{-1} \); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \): 0.03 (s,
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 \(^1^H\) 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 K3PO4 (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), 1305, 1313, 1334, 1344, 136.0, 133.7, 140.8, 144.8; HRMS (ESI) calcd for C\(_{28}\)H\(_{28}\)N\(_3\)O\(_2\)Si (MH\(^+\)) 553.1606; found: 553.1606.

(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\(^{-1}\); \(^1^H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\): 0.03 (s, 9H), 1.74 (d, J = 9.2 Hz, 2H), 2.49 (s, 3H), 5.79 (dt, J = 11.5, 9.2 Hz, 1H), 6.36 (d, J = 9.2 Hz, 1H), 6.86-8.48 (m, 2H), 6.97 (d, J = 8.0 Hz, 1H), 7.09 (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); \(^1^C\) NMR (125 MHz, CDCl\(_3\)) \(\delta\): -1.6 (3C), 19.8, 21.7, 55.6, 64.6, 90.4, 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, 133.4, 134.4, 136.6, 137.7, 140.8, 144.8; HRMS (ESI) calcd for C\(_{28}\)H\(_{28}\)N\(_3\)O\(_2\)Si (MNa\(^+\)) 523.1600; found: 523.1600.

(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\(^{-1}\); \(^1^H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\): 0.03 (s, 9H), 1.74 (d, J = 9.2 Hz, 2H), 2.49 (s, 3H), 5.8 (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); \(^1^C\) NMR (125 MHz, CDCl\(_3\)) \(\delta\): -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 = 12.0 Hz, 1H), 172.2 (CO); 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, 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$_2$O$_7$Si (M$^+$): 597.1394; found: 597.1392.

(Z)-N-[(2-Azido-4-ethylphenyl)ethyl]enyl-4-methyl-N-[2-[(trimethylsilyl)prop-1-en-1-yl]phenyl]benzenesulfonamide (1e)

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 1e (148 mg, 88%). Column chromatography: silica gel (hexane/EtOAc = 1:1); yellow oil; IR (neat) 2925 (C=C), 1722 (CO); 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, 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$_2$O$_7$Si (M$^+$): 597.1394; found: 597.1392.

(Z)-N-[(2-Azido-4-chlorophenyl)ethyl]enyl-4-methyl-N-[2-[(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 = 1:1); amber oil; IR (neat) 2953 (C=C), 2237 (C=C), 2109 (N$_2$) 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$_{23}$Cl$_4$Na$_2$O$_7$Si (M$^+$): 557.1210; found: 557.1209.

(E)-N-[(2-Azidophenyl)ethyl]enyl-4-methyl-N-[2-[(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$_2$) 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 (dd, J = 8.0, 1.1 Hz, 1H), 7.19 (dd, J = 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, 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$_{23}$Cl$_4$Na$_2$O$_7$Si (M$^+$): 557.1210; found: 557.1209.
N-[(2-Azidophenyl)ethynyl]-4-methyl-N-[(trimethylsilyl)methyl][allyl]benzenesulfonamide (3)

To a stirred suspension of S33 (178 mg, 0.60 mmol) and Cs2CO3 (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 (C=C), 2124 (N3) cm⁻¹; ¹H NMR (500 MHz, CDCl3) 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); ¹³C NMR (125 MHz, CDCl3) 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 C27H28N4O2S2i (MNa⁺): 523.1600; found: 523.1602.

(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 76 °C; IR (neat) 3024 (C=C), 2240 (N3), 2106 (N3) cm⁻¹; ¹H NMR (500 MHz, CDCl3) δ: 2.23 (s, 3H), 6.93 (d, J = 16.0 Hz, 1H), 7.02 (d, 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, 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); ¹³C NMR (125 MHz, CDCl3) 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 C27H22N4O2S: C, 71.00; H, 4.52; N, 11.42. Found: C, 70.72; H, 4.60; N, 11.30.

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

According to the procedure described for the preparation of 1a, S27 (164 mg, 0.50 mmol) and S11 (326 mg, 0.75 mmol) were converted into 5c (191 mg, 81%). Column chromatography: silica gel (hexane/EtOAc = 12:1): yellow solid; mp 67 °C; IR (neat) 2239 (C=C), 2122 (N3), 2102 (N3) cm⁻¹; ¹H NMR (500 MHz, CDCl3) 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); ¹³C NMR (125 MHz, CDCl3) 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 C27H26N4O2S (MNa⁺): 493.1674; found: 493.1677.
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$_{25}$N$_{3}$O$_{3}$S (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≡C), 2107 (N$_{3}$) cm$^{-1}$; $^1$H 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$_{29}$H$_{26}$KN$_{3}$O$_{3}$S (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≡C), 2134 (N$_{3}$), 2112 (N$_{3}$) cm$^{-1}$; $^1$H 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$_{29}$H$_{27}$N$_{3}$O$_{3}$S: 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≡C), 2105 (N$_{3}$) cm$^{-1}$; $^1$H 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$_{26}$H$_{32}$N$_{3}$O$_{3}$S (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≡C), 2125 (N$_{3}$) cm$^{-1}$; $^1$H 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, 133.4, 134.4, 136.2, 140.6, 147.7; HRMS (ESI) calcd for C$_{24}$H$_{18}$N$_{5}$O$_{5}$S (MNa$^+$): 509.1008; found: 509.1007.

2. Preparation of Catalyst

40
[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 = 73.5 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 CH₂NO₂ (1.0 mL), was prepared in advance.
To a stirred mixture of 1a (25.0 mg, 0.050 mmol) in CH₂NO₂ (0.8 mL) was added S36 (0.4 mg, 1 mol%) in CH₂NO₂ (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 (dd, 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 (dd, J = 7.7, 7.7, 1.1 Hz, 1H), 7.17-7.28 (m, 3H), 7.34 (dd, 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 C₂₅H₂₁N₂O₂S (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 (dd, J = 16.6, 9.5, 8.0 Hz, 1H), 4.61 (dd, J = 9.5, 1.4 Hz, 1H), 4.90 (dd, J = 16.1, 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 C₂₅H₂₁N₂O₂S (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-d₆) 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 (dd, J = 7.7, 7.7, 1.4 Hz, 1H), 7.43 (dd, 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-d₆) 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) calcld for C_{28}H_{39}F_{13}N_{2}O_{8}S (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, CDCl3) δ: 2.28 (s, 3H), 2.47 (s, 3H), 4.35 (d, J = 8.0 Hz, 1H), 4.52 (dd, 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); ^13C NMR (125 MHz, CDCl3) δ: 21.4, 21.8, 40.5, 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) calcld for C_{28}H_{39}N_{2}O_{8}S (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_{3}NO_{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_{3}NO_{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, CDCl3) δ: 2.30 (s, 3H), 3.95 (s, 3H), 4.40 (d, J = 8.0 Hz, 1H), 4.53 (dd, 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); ^13C NMR (125 MHz, CDCl3) 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) calcld for C_{29}H_{38}KN_{2}O_{5}S (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_{3}NO_{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_{3}NO_{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, CDCl3) δ: 2.30 (s, 3H), 4.33 (d, J = 8.0 Hz, 1H), 4.52 (dd, 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); ^13C NMR (125 MHz, CDCl3) 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) calcld for C_{24}H_{16}ClKN_{2}O_{3}S (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_{2}CO_{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=H) 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.

(±)-(1R,1aR)-1-Phenyl-6-tosyl-1a,6-dihydro-1H-cyclopropac[1]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, 125.6, 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 C₉H₉N₂O₂S (MH⁺): 463.1480; found: 463.1483.

(±)-(1R,1aS)-1-Butyl-6-tosyl-1a,6-dihydro-1H-cyclopropac[1]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 Ph₃AuCl (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 C₂₇H₁₇N₂O₂S (MH⁺): 443.1793; found: 443.1793.

(±)-(1R,1aS)-1-Phenyl-6-tosyl-1a,6-dihydro-1H-cyclopropac[1]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),
(±)-(1R,1aR)-1-Butyl-6-tosyl-1a,6-dihydro-1H-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 (add, 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 C₂₇H₂₃N₅O₃S (MH⁺): 443.1793; found: 443.1793.

10-Tosyl-10,11-dihydro-5H-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), 3394 (NH); 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 C₂₈H₂₃N₅O₃S (MH⁺): 451.1480; found: 441.1485.

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

According to the procedure described for the preparation of 2a, 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); 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 C₂₅H₁₉N₄O₃S (MH⁺): 459.1127; found: 459.1122.

4. Ring-Opening Reactions of Cyclopropanes.

(±)-(R)-11-[4-(R)-Ethoxy(phenyl)methyl]-5-tosyl-6,11-dihydro-5H-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 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, CDCl₃) δ: 0.84 (t, J = 6.9 Hz, 3H), 2.25-2.27 (m, 4H), 2.52 (d, J = 9.0, 6.9 Hz, 1H), 2.86 (d, 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); ¹³C NMR (125 MHz, CDCl₃) δ: 15.5, 21.5, 45.7, 63.8, 88.9, 107.7, 110.5, 110.9, 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 C₁₁H₁₂N₂NaO₃S (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 NaN₃ (17.6 mg, 0.27 mmol) and NH₂Cl (14.4 mg, 0.27 mmol). After stirring for 7 h at 60 °C, the reaction mixture was extracted with Et₂O, washed with water (three times) and brine, dried over MgSO₄, and concentrated in vacuo to give 7b (25.9 mg, 95%): colorless solid; mp 110 °C; IR (neat) 3398 (NH), 2101 (N=) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₉H₂₃N₅O₂S (MH⁺): 506.1651; found: 506.1649.

Crystal data of 7b: Crystal Dimensions 0.500 X 0.500 X 0.500 mm; Crystal System triclinic; Lattice Type Primitive; Cell Determination (20 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; μ(MoKα) 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, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₃₉H₃₇ClKN₂O₂S (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, CDCl₃) 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 C$_{27}$H$_{27}$ClN$_2$NaO$_2$S (MNa$^+$): 501.1379; found: 501.1378.
References


(9) When CH3NO2 was used as a solvent, 4 was given in 36% yield.

(10) The unambiguous structure assignments for 6c and 7b were confirmed by X-ray analysis (see Experimental section).


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. Although a variety of efficient methods to synthesize pyrrole derivatives have been developed, 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). In these reactions, a cationic gold catalyst activates two alkynes, the terminal by $\sigma$-coordination and the internal by $\pi$-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-3,4-thiophenylene- or ethylene-tethered diynes (pathway a), 6-endo-dig cyclization takes place with vinylene- or 2,3-thiophenylene-tethered diynes (pathway b). Although the computational studies 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 reactions, 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**

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst (mol %)</th>
<th>conditions</th>
<th>yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DAC-NTf$_2$ (5)</td>
<td>80 °C, 1 h</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>IPrAuNTf$_2$ (5)</td>
<td>80 °C, 8 h</td>
<td>&lt; 66$^b$</td>
</tr>
<tr>
<td>3</td>
<td>PPh$_3$AuNTf$_2$ (5)</td>
<td>80 °C, 15 h</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>SPhosAuNTf$_2$ (5)</td>
<td>80 °C, 7 h</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>BrettPhosAuNTf$_2$ (5)</td>
<td>80 °C, 2 h</td>
<td>46</td>
</tr>
<tr>
<td>6</td>
<td>t-BuXphosAuNTf$_2$ (5)</td>
<td>80 °C, 4 h</td>
<td>42</td>
</tr>
<tr>
<td>7</td>
<td>DAC-PF$_6$ (5)</td>
<td>80 °C, 1 h</td>
<td>86</td>
</tr>
<tr>
<td>8</td>
<td>DAC-PF$_6$ (2.5)</td>
<td>80 °C, 1 h</td>
<td>74</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>110 °C, 1 h</td>
<td>decomp.</td>
</tr>
</tbody>
</table>

$a$ 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-NTf\(_2\) (DAC = dual activation catalyst)\(^{3e}\) allowed the formation of tricyclic pyrrole 2a in 62% yield (Table 1, entry 1). Though IPrAuNTf\(_2\) 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 PPh\(_3\) 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-PF\(_6\) improved the yield to 86% (entry 7). When the loading of DAC-PF\(_6\) 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 (\( R^1 = \text{alkyl} \)) provided the corresponding pyrroles 2j–l in moderate yields (64–65%).

\[
\begin{array}{cccc}
\text{TsN} & \text{R}^1 & \text{R}^2 & \text{TsN} \\
\text{F} & \text{Cl} & \text{Br} & \text{OMe} \\
\text{Me} & \text{Me} & \text{S} & \text{o-NsN} \\
\text{Et} & \text{n-Pr} & \text{Bn} & \\
\end{array}
\]

\( ^a \) 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, a plausible reaction mechanism is proposed in Scheme 2. First, N-propargyl ynamide 1 is converted to dual $\sigma/\pi$-activated alkyne intermediate 3 by the action of DAC-PF$_6$. 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. It is worth mentioning that the electrophilic carbon of ynamide triple bond in this reaction is not the $\alpha$- but the $\beta$-position to the nitrogen atom, contrary to the general preference in many gold-catalyzed reactions of ynamides.

Scheme 2. Plausible Reaction Mechanism

To confirm the formation of gold vinylidene 5 (Scheme 2), the author then investigated C(sp$^3$)–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

![Diagram of the reaction](image_url)

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

\(^a\) The ratio of 9:10 was determined by NMR analysis. \(^b\) Isolated yields. \(^c\) NMR yield. \(^d\) \(\text{Cp} = \text{cyclopentyl}\)
atom is produced (entry 3). 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−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.

![Scheme 3. Reaction of 2-Methylphenyl-Substituted N-Propargyl Ynamides](image)

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. $^1$H NMR spectra were recorded using a JEOL AL-500 spectrometer at 500 MHz frequency. Chemical shifts are reported in δ (ppm) relative to Me$_4$Si (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 (Wako Gel C-200E or C-300E: Wako Pure Chemical Industries, Ltd) was employed.

The known compounds S$_2$, S$_3$, S$_7$, S$_{10}$, S$_{11}$ S$_{12}$, S$_{13}$, S$_{14}$, S$_{15}$, S$_{17}$, S$_{18}$, S$_{19}$, S$_{20}$, S$_{22}$ were synthesized according to the literature.

The $^1$H NMR data of S$_8$, S$_{11}$, 2a 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$_4$Cl 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 (C=O) cm$^{-1}$; $^1$H 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 C$_{16}$H$_{25}$NO$_2$Si: 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 (C=CH), 2125 (C=C), 1536 (NO$_2$), 1367 (NO$_2$), 1331 (NO$_2$), 1159 (NO$_2$) cm$^{-1}$; $^1$H 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 C$_9$H$_8$N$_2$O$_3$: 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-butylidimethylsilyl)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-propyldienedibenzenesulfonamide (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 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 = 10/1 to 3/1) to give S4 (357 mg, 66%): colorless oil; IR (neat) 3248 (NH), 2176 (C≡CH), 1314 (NSO), 1155 (NSO) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₈H₂₉NNaO₂SSi (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-butyldiene-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 (C≡CH), 2171 (C≡C), 1314 (NSO), 1155 (NSO) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₈H₂₉NO₂SSi (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 S5:⁹ 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 H₂O (30 mL) was stirred for 24 h at room temperature. The resulting white precipitate was filtered off, washed with H₂O and hexane, and then dissolved in CH₂Cl₂. The solution was washed rapidly with aqueous saturated NaHCO₃. The organic layer was dried rapidly over MgSO₄ and concentrated in vacuo to give crude S8 (2.57 g, 47%). ¹H NMR (500 MHz, CDCl₃) 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 (C≡CH), 2173 (C≡C), 1323 (NSO), 1161 (NSO) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₉H₂₉NO₂SSi: 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, hexane/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’-dimethylethlenediamine (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).
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). 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 Hz, 2H), 7.31 (m, 2H), 7.35 (d, J = 8.6 Hz, 2H), 7.41 (d, J = 8.6 Hz, 2H), 7.44 (m, 2H), 7.88 (d, J = 8.6 Hz, 2H). The 1H NMR spectra were in good agreement with those reported.

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 55 °C; IR (neat) 3289 (C=CH), 2237 (C=C), 2127 (C=C), 1366 (NSO2), 1162 (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 C18H14ClNO3S: 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 C18H14BrNO3S: 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:
4-Methyl-N-(prop-2-yn-1-yl)-N-(p-tolyethynyl)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), 1555 (NSO), 1160 (NSO) 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 = 8.6 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) calcld for C₁₉H₁₇NO₂S (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), 1355 (NSO), 1167 (NSO) 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. Calcld for C₃₂H₃₆NO₂S: 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: 3.5 (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. Calcld for C₁₈H₁₃Br₂: C, 41.56; H, 3.14. Found: C, 41.35; H, 3.39.

4-Methyl-N-(prop-2-yn-1-yl)-N-(thiophen-2-yethynyl)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 (NSO), 1162 (NSO) 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. Calcld for C₁₉H₁₃NO₂S₂: 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)-1H,1,3,5-benzo[d][1,2]iodaoxol-3(1H)-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 dried 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≡H), 2237 (C≡C), 2238 (C≡N), 7.44 (m, 2H), 7.71 (m, 2H), 7.39 (s, 3H), 7.37 (m, 2H), 7.27 (m, 3H), 5.43 (t, J = 13.7, 7.6 Hz, 1H), 3.21 (dd, J = 13.7, 7.6 Hz, 2H). 1H NMR (500 MHz, CDCl3): δ: 1.05 (t, J = 7.4 Hz, 3H), 1.85-1.97 (m, 2H), 2.17 (d, J = 2.3 Hz, 1H), 2.43 (s, 3H). HRMS (ESI) calcd for C17H12N2O2S (MK⁺): 379.0155; found: 379.0157.

4-Methyl-N-(pent-1-yn-3-yl)-(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: hexane/EtOAc = 5/1; yellow oil; IR (neat) 3283 (C≡H), 2238 (C≡C), 2120 (C≡C), 1361 (NO2), 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 (dd, 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: hexane/EtOAc = 5/1; yellow oil; IR (neat) 3288 (C≡H), 2237 (C≡C), 2119 (C≡C), 1361 (NO2), 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 C21H19KO2S (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 K2PO4 (340 mg, 1.60 mmol) for 48 h at 85 °C followed by desilylation for 1 h at 0 °C. Column chromatography: hexane/EtOAc = 10/1; yellow oil; IR (neat) 3283 (C≡H), 2237 (C≡C), 2120 (C≡C), 1362 (NO2), 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 C25H21KO2S (MK⁺): 438.0934; 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: C₁₉H₁₈KNO₅S (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

**Method A**

\[
\text{Alkyl + NBS} \xrightarrow{\text{AgNO₃, acetone}} \text{CuSO₄, 1,10-phen. K₃PO₄} \xrightarrow{TBAF} \text{TsN-Alkyl} \xrightarrow{TBS} \text{Alkyl}
\]

**Method D**

\[
\text{NHTs + Alkyl} \xrightarrow{\text{CuCl₂, pyridine, Na₂CO₃}} \xrightarrow{TBAF} \text{TsN-Alkyl} \xrightarrow{TBS} \text{Alkyl}
\]

**General Procedure for Method D:**

N-(Hex-1-yne-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=H), 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 C₁₈H₁₉NNaO₂S (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=H), 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 C₁₈H₁₉NNaO₂S (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-yn (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 filtered 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=H), 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 C₁₈H₁₉NNaO₂S (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-yn (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=H), 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 C₂₉H₁₉KNO₂S (MK⁺): 376.0777; 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 (bromoethyl)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) calc'd for C₁₇H₁₉N₃NaO₃S (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-yn (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) calc'd for C₁₇H₁₉KNO₂S (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-yn (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 TBSCI (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) calc'd for C₂₀H₂₁N₂O₃Si (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
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-PF$_3$ (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 = 12/1) to give 2a (43.0 mg, 86%).

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

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

**2a** 3-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) 364 (NSO$_2$), 1169 (NSO$_2$) cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 2.37 (s, 3H), 3.64 (s, 2H), 7.39 (m, 1H), 7.77 (d, $J = 8.6$ Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 21.6, 30.1, 109.9, 113.4, 120.1, 122.5, 126.8 (2C), 128.7, 129.9 (2C), 130.0, 132.6, 133.0, 135.0, 136.2, 144.8, 149.4 (d, $J = 8.4$ Hz, 2H). The $^1$H NMR spectra were in good agreement with those reported.

**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) 368 (NSO$_2$), 1166 (NSO$_2$) cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 2.38 (s, 3H), 3.63 (s, 2H), 7.03 (d, $J = 1.7$ Hz, 1H), 7.72 (m, 4H), 7.34 (m, 1H), 7.39 (d, $J = 8.0$ Hz, 1H), 7.77 (d, $J = 8.0$ Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 21.7, 30.2, 109.8, 113.4, 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 C$_{18}$H$_{14}$ClNO$_2$: C, 66.04; H, 4.31; N, 4.28. Found: C, 65.97; H, 4.18; N, 4.26.

**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) 363 (NSO$_2$), 1170 (NSO$_2$) cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 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); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 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 C$_{18}$H$_{14}$BrNO$_2$: 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)**

Anal. Calcd for C$_{19}$H$_{23}$NO$_2$: C, 69.69; H, 6.46; N, 4.28. Found: C, 69.68; H, 6.52; N, 4.30.
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) 3613 (NO₂), 1282 (OMe), 1164 (NO₂) 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) caledd for C₁₉H₁₅N₃NaO₂S (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) 3538 (NO₂), 1163 (NO₂) 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 C₁₉H₁₇NO₅S: 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) 3639 (NO₂), 1168 (NO₂) 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 C₂₀H₁₇NO₅S: 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) 3632 (NO₂), 1167 (NO₂) 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) caledd for C₁₆H₁₃N₃NaO₂S₂ (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 (NO₂), 1348 (NO₂), 1164 (NO₂) 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 C₁₇H₁₃N₃O₂S: 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 (NSO$_2$), 1167 (NSO$_2$) cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 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); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 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 C$_{20}$H$_{16}$NO$_2$S: 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 (NSO$_2$), 1173 (NSO$_2$) cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 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); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 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 C$_{25}$H$_{24}$NO$_2$S: 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 (NSO$_2$), 1168 (NSO$_2$) cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 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); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 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 C$_{25}$H$_{24}$NO$_2$S: 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-2,4,5,6-tetrahydro-2H-isoiindole (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 (NSO$_2$), 1168 (NSO$_2$) cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: (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); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: (Major isomer 9a) 12.7, 21.6, 26.8, 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) calehd for C$_{16}$H$_{26}$NO$_2$S (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-isooindole (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 (NO2), 1170 (NO2) 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 C18H19NNaO2S (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 (NO2), 1166 (NO2) 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 C19H22NO2S (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 (NO2), 1170 (NO2) 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), 128.9 (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.

(±)-3(Rb,6aR)-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 (NO2), 1168 (NO2) 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 C17H19NNa2O2S (MNa2⁺): 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 (ΝSO₂), 1172 (ΝSO₂) 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 C₁₀H₁₉NNa₂O₂S (MNa⁺): 312.0344; found: 312.0345.

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 (ΝSO₂), 1168 (ΝSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 2.38 (s, 3H), 3.12 (m, J = 13.0 Hz, 2H), 7.71 (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 C₁₄H₁₅N₂Na₂O₂S (MNa⁺): 282.0565; found: 282.0565.

2-Tosyl-4,4a,5,6,7,8-hexahydro-2H-benzo[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 (ΝSO₂), 1166 (ΝSO₂) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 11.5-1.43 (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, 134.3, 144.4; Anal. Calcd for C₁₀H₁₉NNa₂O₂S: 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[c]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 (ΝSO₂), 1168 (ΝSO₂) 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 C₁₉H₁₉KNO₂S (MK⁺): 362.0617; found: 362.0616.
References


(4) The author investigated the reaction mechanism of a similar diyne reaction in ref 3k. In this study, the gem-diaurated compound B was isolated after treatment of gold acetylide A with one equivalent of IPrAuNTf₂. Additionally, treatment of deuterated terminal alkyne C with 5 mol% of DAC-NTf₂ gave the cyclic compound D, where the deuterium atom was transferred to the position that the gold catalyst was located after the cyclization. These results support the formation of gold complexes 3−7 in the current reaction of N-propargyl ynamide 1.


In this case, 9e 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.


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. Several groups have recently reported that certain substituents on the aniline nitrogen, including sulfonyl, allyl, and acetyl 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. 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

<table>
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<th>entry</th>
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<th>solvent</th>
<th>conditions</th>
<th>yield (%)⁴ᵃ</th>
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<tr>
<td>1</td>
<td>PPh₃AuCl/AgSbF₆</td>
<td>THF</td>
<td>60 °C, 5 h</td>
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<tr>
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<td>74</td>
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<tr>
<td>4</td>
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<td>THF</td>
<td>60 °C, 1 h</td>
<td>74</td>
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<tr>
<td>5</td>
<td>JohnPhosAuSbF₆·MeCN</td>
<td>toluene</td>
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<tr>
<td>6</td>
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<td>60 °C, 1 h</td>
<td>16</td>
</tr>
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<td>7</td>
<td>JohnPhosAuSbF₆·MeCN</td>
<td>CH₃NO₂</td>
<td>60 °C, 2 h</td>
<td>13</td>
</tr>
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<td>8</td>
<td>JohnPhosAuSbF₆·MeCN</td>
<td>CH₃CN</td>
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<td>JohnPhosAuSbF₆·MeCN</td>
<td>dioxane</td>
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<td>10</td>
<td>JohnPhosAuSbF₆·MeCN</td>
<td>2-propanol</td>
<td>60 °C, 2 h</td>
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<td>13</td>
<td>AgSbF₆</td>
<td>2-propanol</td>
<td>rt, 2 h</td>
<td>decomp.ᵇ</td>
</tr>
</tbody>
</table>

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 AgSbF$_6$ present in the reaction mixture. Actually, the treatment of 1a with AgSbF$_6$ 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 ($\text{NuH} = \text{NHTs}$ or $\text{NBoc}$) led to the formation of the pyrrolidine-fused indolines 2b and 2c in excellent yields (94 and 90%, respectively). Aniline 1d ($R^1 = \text{Me}$) 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 ($R^2 = \text{H}$) bearing a terminal alkyne decomposed under these conditions, anilines 1h ($R^2 = \text{Et}$) and 1i ($R^2 = \text{Ph}$) bearing an internal alkyne reacted smoothly to give indolines 2h (87%) and 2i (92%), respectively.

![Reaction Scheme](image)

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

$^a$ Isolated yields. $^b$ The reaction was conducted at 40 °C.
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 \(^1\)H NMR spectroscopy with 3 mol % of IPrAuSbF\(_6\)-MeCN in MeOD-\(d_3\) at 40 °C, using CHCl\(_2\)CHCl\(_2\) as an

![Scheme 2. Gold-Catalyzed Cyclization of N-Benzylaniline 1j](image)

![Scheme 3. Isolation of the Reaction Intermediate 3h](image)

![Figure 2. NMR Analysis of the Reaction of 1h.](image)
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 \(\sigma\)-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 B 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). $^1$H NMR spectra were recorded using a JEOL AL-500 spectrometer at 500 MHz frequency. Chemical shifts are reported in δ (ppm) relative to Me$_4$Si (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-Kα radiation at -180 °C.

The known compounds S2,$^5$ S5,$^{10}$ S6,$^{11}$ S8$^{12}$ were synthesized according to the literature.

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

2-[(tert-Butyl(dimethyl)silyl)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-yl-oxy)(tert-butyl)-dimethylsilane (3.10 mL, 15.0 mmol), and PdCl$_2$(PPh$_3$)$_2$ (351 mg, 0.50 mmol) in THF (20 mL) and Et$_3$N (5 mL) under argon was added Cul (95.2 mg, 0.50 mmol) at room temperature. After stirring for 6 h at that temperature, additional (but-3-yn-1-oxy)(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$_2$O 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$^{-1}$; $^1$H 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 (d, 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) calcld for C$_{17}$H$_{32}$NOSi (MH$^+$): 290.1940; found: 290.1938.

4-[(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$_2$CO$_3$ (622 mg, 4.50 mmol) in CH$_2$CN (6 mL) was added 1-bromobut-2-yn (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$_4$Cl 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 (C=C) cm$^{-1}$; $^1$H 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) calcld for C$_{16}$H$_{18}$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), 2.21 (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 C₂₇H₃₅N₂O₅S (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 C₂₀H₂₃N₂O₂ (MH⁺): 327.2073; found: 327.2069.

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

To a stirred mixture of 2-ethyl-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-ylene (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, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₃H₁₄N (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, BF₃-Et₂O (94.2 µL, 0.75 mmol) was added to the mixture. After stirring for 5 min at this temperature, 2,2-dimethoxyxirane (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 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 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, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₇H₂₅NO (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, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₆H₂₃NO (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, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₉H₂₃Cl₂NO (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%): colorless oil; IR (neat) 3289 (C≡CH), 2231 (C≡C), 2105 (C≡C) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 2.25 (t, J = 2.3 Hz, 1H), 2.43 (s, 1H), 2.76
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 (C=O) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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 (ddd, J = 7.7, 1.1 Hz, 1H), 7.23 (ddd, J = 7.7, 7.7, 1.4 Hz, 1H), 7.38 (ddd, J = 7.7, 1.4 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₄H₂₀NO (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 (C=O) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₀H₂₀NO (MH⁺): 290.1545; found: 290.1544.

N-Benzyl-2-{4-[tert-butylmethyisilyloxy]but-1-yn-1-yl]aniline (S7)

According to the procedure described for the preparation of S1, N-benzyl-2-idoaniline (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, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₁H₂₃NOSi (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, CDCl₃) 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 (ddd, 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₁H₂₂NO (MH⁺): 304.1701; found: 304.1701.

2. Synthesis of the indole 2

1,4-Dimethyl-3H,4H-8b,3a-(epoxethano)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 % IPrAuSbF₅·MeCN (5.7 mg, 0.0066 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) to afford 2a (26.7 mg, 89%); colorless oil; 1H NMR (500 MHz, CDCl3) 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); 13C NMR (125 MHz, CDCl3) 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 C15H13NO (MH+): 228.1388; found: 228.1391.

1,4-Dimethyl-9-tosyl-3H,4H-8b,3a-(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) 3777 (N=O), 1154 (NO2) cm−1; 1H NMR (500 MHz, CDCl3) 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 (d, 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); 13C NMR (125 MHz, CDCl3) 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 C22H20N2O2S: C, 69.44; H, 6.36; N, 7.36. Found: C, 69.46; H, 6.39; N, 7.35.

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; Dcalc 1.333 g/cm3; F(000) 404.00; μ(MoKa) 1.907 cm−1.

tert-Butyl 1,4-Dimethyl-3H,4H-8b,3a-(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); 13C 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 C20H20N2NaO2 (MNa+) 349.1892; found: 349.1889.

1,4,10,10-Tetramethyl-3H,4H-8b,3a-(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, CDCl3) 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 (ddd, J = 7.4, 1.1 Hz, 1H); 13C NMR (125 MHz, CDCl3) 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 C17H25NO (MH+): 256.1701; found: 256.1702.
5,10-Dimethyl-3,4-dihydro-2H,5H-9b,4a-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 (ddd, 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 C₁₈H₂₃NO (MH⁺): 242.1545; found: 242.1542.

3,3-Bis(chloromethyl)-5,10-dimethyl-3,4-dihydro-2H,5H-9b,4a-prop[1]enopyran[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 (ddd, 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, 127.4, 129.9, 140.3, 151.2; HRMS (ESI) calcd for C₁₈H₂₃Cl₂NO (MH⁺): 242.1545; found: 242.1542; HRMS (ESI) calcd for C₁₈H₂₂Cl₂NO (MH⁺): 338.1078; found: 338.1074.

1-Ethyl-4-methyl-3H,4H-8b,3a-(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 (ddd, 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, 7.4, 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 C₁₆H₁₆NNO (MNa⁺): 264.1364; found: 264.1363.

4-Methyl-1-phenyl-3H,4H-8b,3a-(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 (ddd, 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-3H,4H-8b,3a-(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 = 1:2) 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 CHCl₃CHCl₂ (13.9 mg, 0.083 mmol) in MeOD-d₃ (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 240 min, ca. 0.7 ml of the solution was picked up from the reaction mixture to measure ¹H NMR. The yields were evaluated using CHCl₃CHCl₂ 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%). Th crossover products 2b’ and 2a were not detected by TLC, GCMS, and ¹H NMR.
References


7. The coordination energy of a cationic gold catalyst to a simple allene has been reported to be slightly higher than that to a simple alkyne. This allene preference was contrary to the result observed in the current study, where cycle B only started after the completion of cycle A. A plausible explanation for this observation could be the existence of an equilibrium between intermediates 4 and 6 in the reaction, combined with the cyclobutene formation (6 to 7) being slower than that of the indole (4 to 5). For the coordination energies between a simple allene and an alkyne, see: Hashmi, A. S. K.; Lauterbach, T.; Nösel, P.; Vilhelmsen, M. H.; Rudolph, M.; Rominger, F. Chem. Eur. J. 2013, 19, 1058. For an equilibrium between MeOH and an allene coordinated gold complex, see: Paton, R. S.; Maseras, F. Org. Lett. 2009, 11, 2237. See also: Zhang, J.; Shen, W.; Li, L.; Li, M. Organometallics 2009, 28, 3129.


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 $\alpha$-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 $\beta$-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.
Acknowledgements

The author would like to take this opportunity to extend his deepest gratitude and appreciation to Professor Nobutaka Fujii (Graduate School of Pharmaceutical Science, Kyoto University) for giving him this precious and valuable opportunity to study organic chemistry as a member of the prestigious group of Fujii.

The author would like to express his wholehearted appreciation to his supervisor, Professor Hiroaki Ohno (Graduate School of Pharmaceutical Science, Kyoto University), for his tremendous support. Without Professor Ohno’s elaborate guidance, appropriate feedback and constructive discussions, this research would not have been so successful.

The author would also like to express his sincere gratitude to Dr Shinya Oishi (Graduate School of Pharmaceutical Science, Kyoto University) for his incisive comments, practical advice and positive encouragement.

The author would like to thank Professor A. Stephen K. Hashmi (Organisch-Chemisches Institut, Ruprecht-Karls-Universität Heidelberg, Germany) for providing him with an opportunity to study gold chemistry at Heidelberg University, Germany. Professor Hashmi made an invaluable contribution to the development of the novel strategy for the synthesis of bicyclic pyrroles, which was described in Chapter 1, Section 3. The author would also like to thank Dr Marcel Wieteck, Dr Matthias Rudolph and Dr Pascal Nösel from the Hashmi group, for their kind assistance and many useful discussions.

The author would like to acknowledge all on his colleagues in the Department of Bioorganic Medicinal Chemistry, Graduate School of Pharmaceutical Sciences, Kyoto University, for their kind help. The author is especially grateful to Dr Yusuke Ohta and Mr Masamitsu Taguchi for the assistance with his experiments. Furthermore, Dr Ohta made a significant contribution to the development of the strategy for the direct synthesis of quinazolines, which was described in Chapter 1, Section 1.

The author would also like to express his gratitude to the Japan Society for the Promotion of Science (JSPS) for their financial support.

Finally, the author would like to thank his parents, Yoshihiro and Keiko Tokimizu, for their constant emotional, moral and financial support during his time at Kyoto University.
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

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

Section 3 Dual Gold Catalysis: A Novel Synthesis of Bicyclic and Tricyclic Pyrroles from N-Propargyl Ynamides
Yusuke Tokimizu, Marcel Wieteck, Matthias Rudolph, Shinya Oishi, Nobutaka Fujii, A. Stephen K. Hashmi, and Hiroaki Ohno

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

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

3. The Role of Acetylides in Dual Gold Catalysis: A Mechanistic Investigation of the Selectivity Difference in the Naphthalene Synthesis from Diynes
4. Wurster's Blue-type Cation Radicals Framed in a 5,10-Dihydrobenzo[a]indolo[2,3-c]carbazole (BIC) Skeleton: Dual Electrochromism with Drastic Changes in UV-Vis-NIR and Fluorescence