Gold(I)-Catalyzed Reaction of Azido Alkynes for the Synthesis of Indole-Based Polycycles

2022

Luca Can Greiner

Gold(I)-Catalyzed Reaction of Azido Alkynes for the Synthesis of Indole-Based Polycycles

Doctoral Thesis

Presented for the Degree of Doctor of Kyoto University

Luca Can Greiner

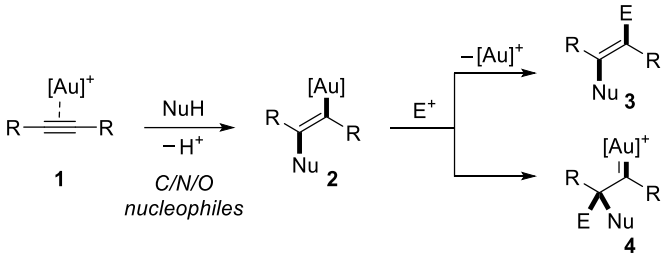
Kyoto, Japan

2022

Contents

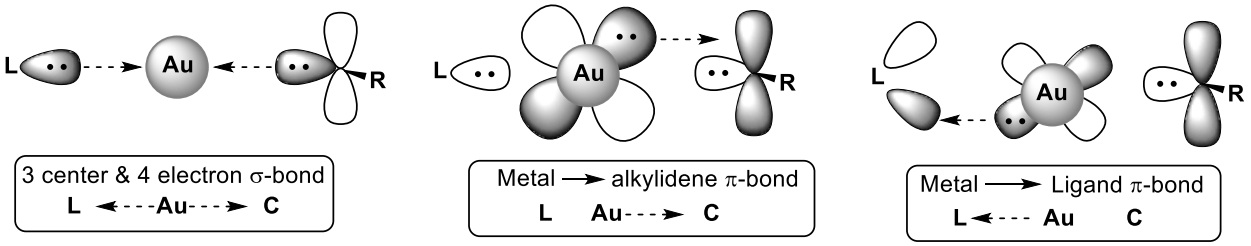
Preface

Among transition metal complexes, those based on gold possess an extraordinary selectivity toward the activation of alkynes. Once an alkyne is subjected to a cationic gold catalyst, its pronounced π-acidity results in the formation of an activated alkynyl gold complex **1** and unlocks its reactivity toward a broad scope of nucleophiles (e.g., C, N, O) (Scheme 1). Through nucleophilic *trans*-addition, the generated vinyl gold complex **2** can be further functionalized with diverse electrophiles, terminating the cascade via deauration to **3**. This reactivity can be further extended to multiple bond formations, setting the foundation of gold catalysis as a versatile and efficient tool for the construction of molecular complexity.[1,2]



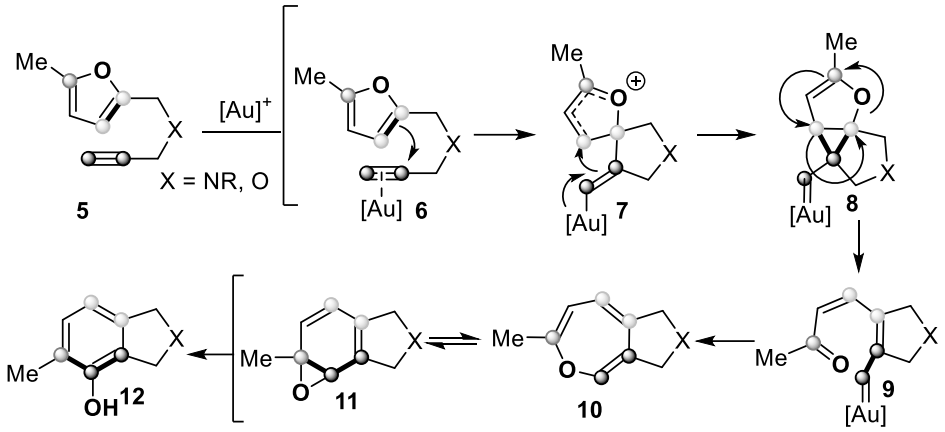
Scheme 1. Dual reactivity of vinyl gold intermediates.

Apart from the role of gold as a strong π-acid, the ability of electron back donation of the corresponding vinyl gold complexes can also facilitate a reaction with an electrophile at the β-carbon to generate gold carbene **4**.[3] The carbon–gold bond of gold carbenes can be described via σ- and π-bonding, in which the magnitude of each binding mode is strongly influenced by the structure of the carbene and ancillary ligand. The empty 6s orbital of gold is a high-affinity σ-acceptor of the electron pairs from the ligand and the carbene, forming a three-center four-electron σ-hyperbond (Scheme 2, left). Simultaneously, the ligand and carbene compete as π-acceptors for the electrons originating from the 5d-orbitals of the gold-center, enabling the generation of two π-coordination bonds via back-donation (Scheme 2, middle and right).[3]



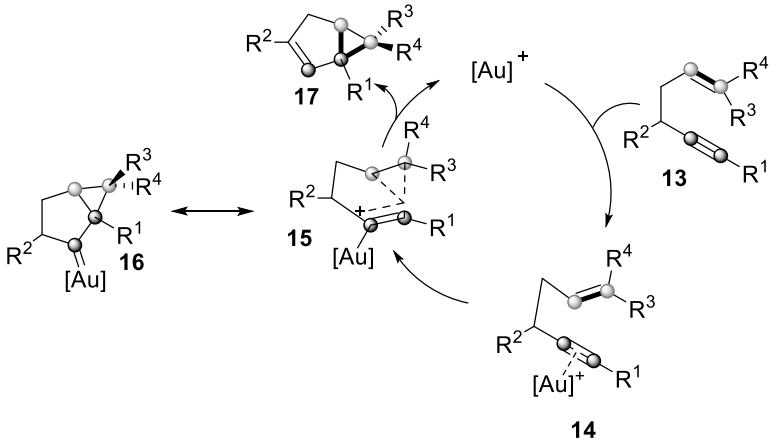
Scheme 2. Bonding interactions in L–Au(I)–CR^2 species.[3]

The formation of gold carbenes (**8**/**9**) was first suggested in the cycloisomerization of furan-ynes **5** to substituted phenols **12** in the Hashmi phenol synthesis.[4] This reaction can be regarded as a pioneering example for electron-rich enyne cycloisomerization.



Scheme 3. Hashmi's phenol synthesis.[4]

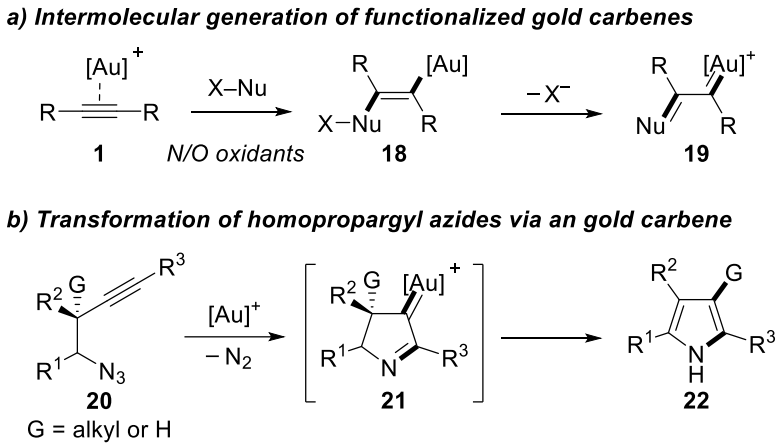
Later, closely related intermediates **16**, which originate from enynes **13** and stand in resonance with conjugated gold complex **15**, are generated from alkynyl gold complexes **14** (Scheme 4). The intermediates **16** were frequently observed in gold-catalyzed enyne cycloisomerizations for the synthesis of cyclopropanation products **17**.[5] Since then, the accumulation of a wide variety of general synthetic methods to form unfunctionalized gold-carbenes has been continuously reported.[6]



Scheme 4. Dual reactivity of vinyl gold intermediates.

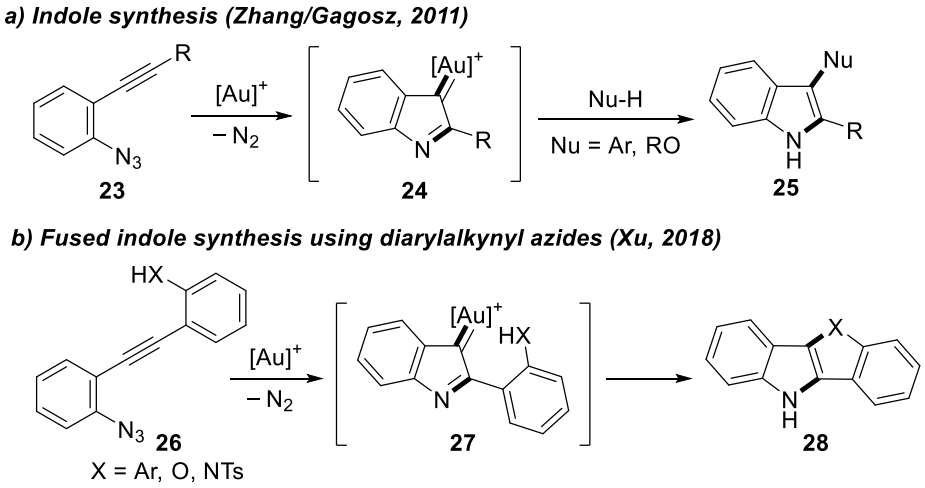
The employment of O/N oxidants with attached labile leaving groups in the reaction with gold alkynyl complexes **1** permits access to the synthetically valuable α-oxo- and α-imino gold carbenes **18** via elimination of the leaving group X in the vinyl gold intermediate **19** (Scheme 5a). The use of this carbene

formation in intramolecular reactions facilitates the efficient synthesis of *N*-heterocycles, which are important in pharmaceutical structures.[7] The pioneering work was performed by Toste *et al*., where gold-catalyzed reaction of homopropargylic azides **20** provided substituted pyrroles **22** via intramolecular generation of α-imino carbenes **21** and a 1,2-shift of a migratory group (Scheme 5b).[8a] Such reactions have become a cornerstone in the formation of various nitrogen-containing heterocycles based on gold catalysis.



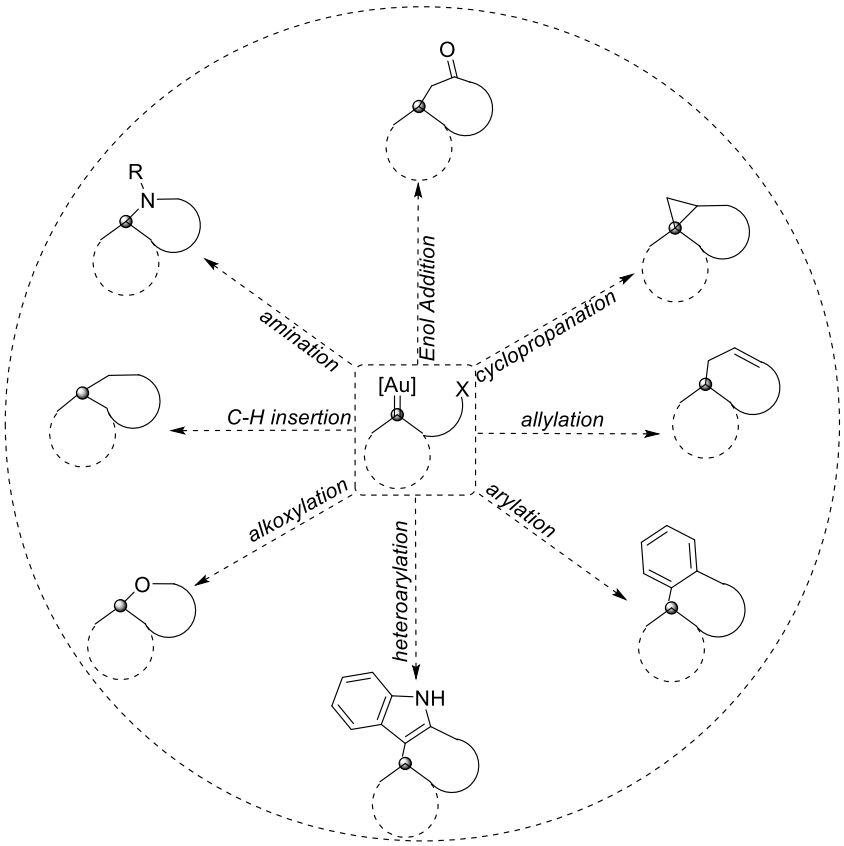
Scheme 5. Generation of gold carbenes and pyrrole synthesis reported by Toste.

Extension of this chemistry by Zhang[8b] and Gagosz[8c] employing phenylene-tethered azido-alkynes **23** as substrates led to the formation of benzene-fused α-imino gold carbenes **24** (Scheme 6a). These can be regarded as an indole synthesis via transient C3 umpolung indole equivalents, where intermolecular trapping with alcohols or arenes gives the corresponding indoles **25**. A related reaction using azido-alkyne **26** bearing a reactive functional group like a hydroxy, sulfonamido, or aryl group with a phenylene tether giving indole-fused polycycles **28** via α-imino gold carbenes **27** was reported by Xu and co-workers (Scheme 6b).[9] As a result of the previously disclosed research activities, it became obvious that substrates based on azido-alkynes have a high potential for use in gold-catalyzed generation of diverse fused-indoles in efficient cascade processes.[10]

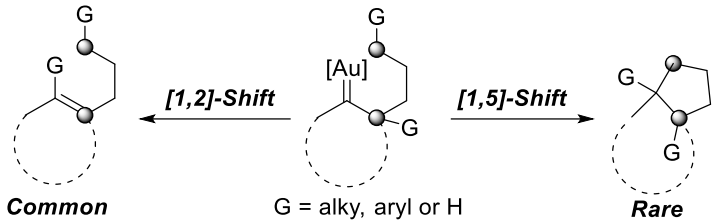


Scheme 6. Synthesis of fused indoles via α-imino gold carbenes.

The pronounced electrophilicity of gold carbenes is of major relevance for cascade cyclizations since its exploitation with diverse nucleophiles can generate plethora of valuable polycylic scaffolds with high synthetic efficiency. The most prominent transformation of such carbenes represent enol addition, cyclopropanation, allylation, arylations, heteroarylation, alkoxylation, C-H insertion, and amination (Scheme 7). Another reactivity pattern that is frequently encountered is the migration of hydride, aryl, alkyl, and alkynyl groups on to gold carbenes mainly embracing 1,2-migrations, whereas 1,5-migrations remain surprisingly rare (Scheme 8).



Scheme 7. Reaction scope of gold carbenes



Scheme 8. [1,2]-Migrations compared to [1,5]-migrations involving Au catalysis

This doctoral thesis particularly focuses on the application of reactivities like arylations and heteroarylations for the synthesis of challenging scaffolds and the discovery of unprecedented reactivities of gold carbenes to expand the gold carbene chemistry. Chapter 1 describes the exploitation of gold carbenes for the construction of biologically relevant and difficult-to-synthesis indole fused benzannulated medium sized rings. In Chapter 2, an unprecedented 1,5-hydride shift on α-imino carbenes for the divergent synthesis of indole fused N and C substituted polycycles is discussed. Chapter 3 illustrates a unique carboalkoxylation of α-imino gold carbenes generating indoline-fused polycycles.

References

[1] a) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180–3211; b) A. Fürstner, W. Davies, *Angew. Chem. Int. Ed.* **2007**, *46*, 3410–3449; c) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351–3378; d) A. Fürstner, *Chem. Soc. Rev*. **2009**, *38*, 3208–3221; e) D. Garayalde, C. Nevado, *ACS Catal*. **2012**, *2*, 1462–1479; f) R. Dorel, A. M. Echavarren, *Chem. Rev.* **2015**, *115*, 9028–9072.

[2] a) A. S. K. Hashmi, *Gold Bull.* **2004**, *37*, 51–65; b) W. A. Nugent, *Angew. Chem. Int. Ed.* **2012**, *51*, 8936–8949; c) Y. Ito, M. Sawamura, T. Hayashi, *J. Am. Chem. Soc.* **1986**, *108*, 6405–6406; d) J. Teles, S. Brode, M. Chabanas, *Angew. Chem. Int. Ed.* **1998**, *37*, 1415–1418.

[3] a) C. Nieto-Oberhuber, S. López, M. P. Muñoz, D. J. Cárdenas, E. Buñuel, C. Nevado, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2005**, *44*, 6146–6148; b) A. Fürstner, P. W. Davies, *Angew. Chem. Int. Ed.* **2007**, *46*, 3410–3449; c) A. Fürstner, L. Morency, *Angew. Chem. Int. Ed.* **2008**, *47*, 5030–5033; d) A. S. K. Hashmi, *Angew. Chem. Int. Ed*. **2008**, *47*, 6754–6756; e) D. Benitez, N. D. Shapiro, E. Tkatchouk, Y. Wang, W. A. Goddard, F. D. Toste, *Nat. Chem.* **2009**, *1*, 482-486; f) A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2010**, *49*, 5232–5241; g) Y. Wang, M. E. Muratore, A. M. Echavarren, *Chem. Eur. J.* **2015**, *21*, 7332–7339.

[4] a) A. S. K. Hashmi, T. M. Frost, J. W. Bats, *J. Am. Chem. Soc*. **2000**, *122*, 1553–1554; b) B. Martín-Matute, D. J. Cárdenas, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2001**, *40*, 4754–4757; c) B. Martín-Matute, C. Nevado, D. J. C. Cárdenas, A. M. Echavarren, *J. Am. Chem. Soc.* **2003**, *125*, 5757–5766; d) A. S. K. Hashmi, M. Rudolph, J. P. Weyrauch, M. Wölfle, W. Frey, J. W. Bats, *Angew. Chem. Int. Ed.* **2005**, *44*, 2798–2801.

[5] a) C. Nieto-Oberhuber, M. P. Muñoz, S. López, E. Jiménez-Núñez, C. Nevado, E. Herrero-Gómez, M. Raducan, A. M. Echavarren, *Chem. Eur. J.* **2006**, *12*, 1677–1693; b) C. Nieto-Oberhuber, M. P. Muñoz, E. Buñuel, C. Nevado, D. J. C Cárdenas, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2004**, *43*, 2402–2406; c) V. Mamane, T. Gress, H. Krause, A. Fürstner, *J. Am. Chem. Soc.* **2004**, *126*, 8654–8655; d) M. R. Luzung, J. P. Markham, F. D. Toste, *J. Am. Chem. Soc*. **2004**, *126*, 10858–10859; e) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev*. **2008**, *108*, 3326–3350.

[6] D. Qian, J. Zhang, *Chem. Soc. Rev.* **2015**, *44*, 677–698.

[7] a) H.-S. Yeom, E. So, S. Shin, *Chem. Eur. J*. **2011**, *17*, 1764–1767; b) C. Shu, L. Li, Y.-F. Yu, S. Jian, L.-W. Ye, *Chem. Commun.* **2014**, *50*, 2522–2525; c) L. Li, K. Ji, R. Zheng, J. Nelson, L. Zhang, *Chem. Commun*. **2014**, *50*, 4130–4133; d) Y. Wang, Z. Zheng, L. Zhang, *J. Am. Chem. Soc*. **2015**, *137*, 5316–5319; e) L. N. dos Santos Comprido, J. E. M. N. Klein, G. Knizia, J. Kästner, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2015**, *54*, 10336–10340; f) L. Batiste, P. Chen, *J. Am. Chem. Soc.* **2014**, *136*, 9296–9307; g) X. Zhao, M. Rudolph, A. M. Asiri, A. S. K. Hashmi, *Front. Chem. Sci. Eng.* **2020**, *14*, 317–349.

[8] a) D. J. Gorin, N. R. Davis, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 11260–11261; b) B. Lu, Y. Luo, L. Liu, L. Ye, Y. Wang, L. Zhang, *Angew. Chem. Int. Ed.* **2011**, *50*, 8358–8362; c) A. Wetzel, F. Gagosz, *Angew. Chem. Int. Ed.* **2011**, *50*, 7354–7358.

[9] J. Cai, B. Wu, G. Rong, C. Zhang, L. Qui, X. Xu, *Org. Lett*. **2018**, *20*, 2733–2736.

[10] a) L.-W. Ye, X.-Q. Zhu, R. L. Sahani, Y. Xu, P.-C. Qian, R.-S. Liu, *Chem. Rev.* **2021**, *121*, 9039–9112; b) F. L. Hong, L.-W. Ye, Front. *Chem. Sci. Eng*. **2020**, *14*, 317–349; c) E. Aguilar, J. Santamaria, *Org. Chem. Front.* **2019**, *6*, 1513–1540.

Chapter 1. Access to Indole-Fused Benzannulated Medium-Sized Rings through a Cascade Cyclization of Azido-Alkynes

Because benzannulated and indole-fused medium-sized rings are found in many bioactive compounds, the combination of these fragments may lead to unexplored areas of biologically relevant and uncovered chemical space. Here the author shows that α-imino gold carbene chemistry can play an important role in solving the difficulty in the formation of medium-sized rings. Namely, phenylene-tethered azido-alkynes undergo arylative cyclization through the formation of a gold carbene intermediate to afford benzannulated indole-fused medium-sized tetracycles. The reactions allow a range of different aryl substitution patterns and efficient access to these otherwise difficult-to-obtain medium-sized rings. This study also demonstrates the feasibility of the semihollow-shaped C-dtbm ligand for the construction of a nine-membered ring.

The indole group is among the top ten most occurring heterocycles in natural products and marketed drugs and is thus classified as a privileged structure in drug discovery with a wide spectrum of biological activities.[1] Especially, polycyclic indoles fused with a medium-sized ring are key structural motifs in pharmaceutically relevant compounds, such as the pharmaceutical iprindole,[2] the indole alkaloid velbanamine,[3] and the bis-indole alkaloid caulerpin (Figure 1a).[4] Given the structures of nefopam and heliannuol A, benzannulated medium-sized rings containing one or more heteroatom(s) can be considered potential drug-like structures (Figure 1b).[5] A natural product fragment-based approach, fusing both promising frameworks to the atypical molecular scaffold of indole-fused benzannulated medium-sized rings, could uncover diverse biological properties through covering biologically relevant uncharted chemical space that has not yet been explored by evolution.[6]

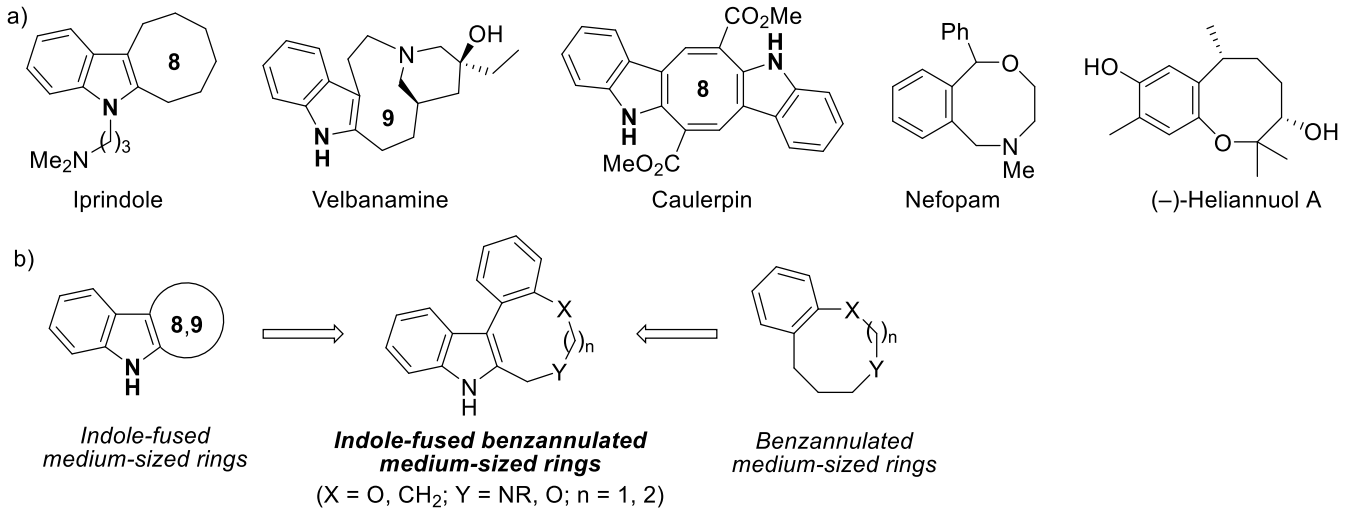
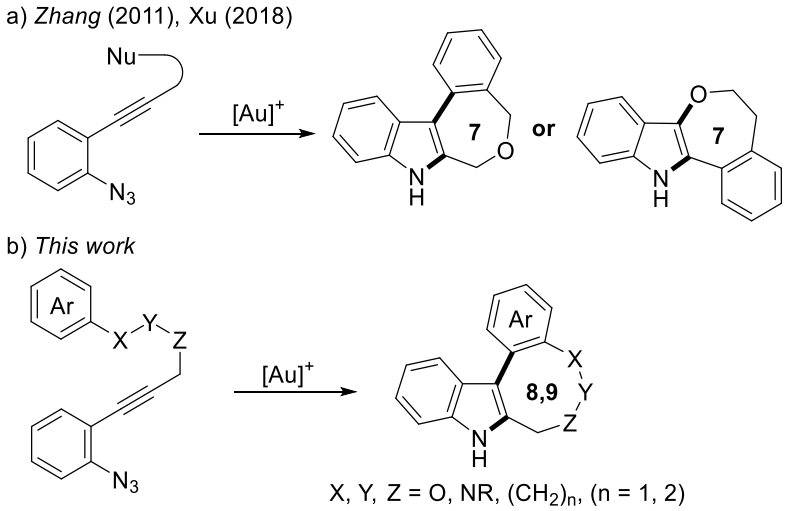


Figure 1: a) Representative structures of pharmaceuticals and natural products containing a fused indole and a medium-sized ring. b) Strategic fusion of the drug-like structures to afford indole-fused medium-sized rings.

As described in Preface, α-imino gold(I)-carbenes have manifested themselves as valuable key intermediates for the composition of pharmaceutical relevant aza-heterocycles.[7] Zhang and Xu exemplified the cyclization of α-imino gold(I)-carbenes with a tethered aryl or alcohol moiety to generate benzannulated indole-fused oxepines (Scheme 1a).[8a,c] However, an eight-membered ring formation was not reported except for the isolated example using a highly-restrained azido-ynamide precursor reported by the authors group.[9] Those circumstances and outlooks motivated the author to generate sp^3-enriched benzannulated medium-sized rings. In this Chapter, the author reports the arylative cyclization of α-imino gold(I)-carbenes to obtain indole-fused benzannulated heterocyclic medium-sized rings as potential drug-like structures, employing azido-alkynes (Scheme 1b). The applicability of the semihollow-shaped C-dtbm ligand.[10] on α-imino gold(I)-carbenes to generate an indole-fused nine-membered ring is also presented.



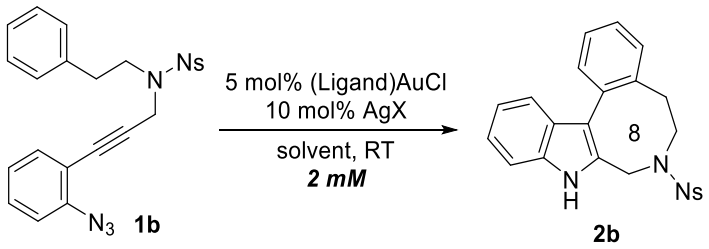
Scheme 1. Reported indole-fused medium-ring formation through gold carbenes and this work.

The author prepared azido-alkynes **1** and investigated the eight-membered ring formation using a gold(I) catalyst. The initial approach to cyclize a tosylamide **1a** to eight-membered ring **2a** using $Ph_3PAuCl/AgSbF_6$ in CH_2Cl_2 (0.5 M) solely resulted in polymerization with no traces of the desired product (Scheme 2). The substitution of the Ts group of **1a** with the stronger electron-withdrawing Ns (*o*-nitrobenzenesulfonyl) group led to the formation of the corresponding eight-membered ring (azocine) **2b** in 22% yield. The author assumed that the electron-withdrawing Ns group could positively influence the reactivity of the α-imino gold(I)-carbene in the electrophilic arylation for the azocine formation. However, the observation of significant amounts of black tar in these reactions could indicate that a polymerization process competes with the desired cyclization.

Scheme 2: Initial attempts of azocine formation.

To avoid potential intermolecular side reactions, The author optimized the reaction conditions by diluting the substrate concentration to 2 mM (Table 1). Fortunately, the author observed that the tar formation was suppressed, leading to a satisfactory 66% yield of **2b** (Table 1, entry 2). To investigate the counter anion effect[13a,b] on the reaction, the pre-catalyst Ph_3PAuCl was exposed to diverse chloride scavengers based on AgX (X = ^-OTs, $^-PF_6$, $^-NTf_2$, or $^-SbF_6$, entries 2–5). Among these counter anions, the highest catalytic activity was found for $^-SbF_6$, which generates the cationic gold(I)-complex with the lowest dissociation energy, as illustrated by Hammond, Xu, and Ujaque *et al*.[11c-e] Next, the author was interested in the ligand's influence on the eight-membered ring formation. An electron-deficient phosphine ligand such as $(p\text{-}CF_3C_6H_4)_3P$ resulted in reduced yield and catalytic activity (entry 6). While the use of Et_3P did not affect the yield significantly (entry 7) compared with Ph_3P, employment of $(t\text{Bu})_3P$ led to an optimized yield of 76% (entry 8). Application of the NHC-based IPr ligand reduced the yield to 60% with an intermediate reaction time of 45 min (entry 9). From these results, tuning of the gold carbene character through variations of the ligands *trans*-influence and π-acidity is important, as reported by Zhang[12a] and Toste.[12b] An additional investigation using the bulky BrettPhos ligand resulted in rapid polymerization without detecting the desired product (entry 10). Consecutively, the author attempted to pre-organize the cyclic transition state through the use of the semihollow-shaped C-dtbm ligand, designed by the Sawamura group.[10] Unfortunately, a sharp decrease in yield and inseparable unidentified side products were observed (entries 11 and 12). Finally, solvent screening demonstrated that non-coordinating CH_2Cl_2 is the most suitable solvent (entries 13–15). Interestingly, it was found that the presence of MS4A completely inhibited the reaction (entry 16), suggesting that MS4A may poison or neutralize the gold catalyst,[12c,13,14] or contaminating water may play a crucial role in this reaction.[14] After isolation of **2b**, the molecular structure was unambiguously confirmed by X-ray diffraction (Figure 2).

Table 1. Optimization of the reaction conditions



Entry	Ligand[a]	X	t [h]	Solvent	Yield [%][b]
1	Ph_3P	SbF_6	0.5	CH_2Cl_2[c]	22
2	Ph_3P	SbF_6	0.5	CH_2Cl_2	66
3	Ph_3P	NTf_2	24	CH_2Cl_2	65
4	Ph_3P	PF_6	24	CH_2Cl_2	55
5	Ph_3P	OTs	24	CH_2Cl_2	–[d]
6	$(p\text{-}CF_3C_6H_4)_3P$	SbF_6	1.0	CH_2Cl_2	25
7	Et_3P	SbF_6	0.5	CH_2Cl_2	63
8	**$(t\text{Bu})_3P$**	**SbF_6**	**0.5**	**CH_2Cl_2**	**76 (71)**
9	IPr	SbF_6	0.75	CH_2Cl_2	60
10	BrettPhos	SbF_6	0.75	CH_2Cl_2	–[e]
11	C-dtbm	SbF_6	0.5	CH_2Cl_2	31
12	C-dtbm	NTf_2	1.0	CH_2Cl_2	37
13	$(t\text{Bu})_3P$	SbF_6	0.5	$MeNO_2$	–[e]
14	$(t\text{Bu})_3P$	SbF_6	12	THF	NR
15	$(t\text{Bu})_3P$	SbF_6	12	MeCN	NR
16[f]	$(t\text{Bu})_3P$	SbF_6	12	CH_2Cl_2	NR

[a] The ligand structures are shown below. [b] Determined by ^{1}H-NMR analysis with TPM (triphenylmethane) as an internal standard. Yield in parenthesis is the isolated yield. [c] The reaction was conducted at 500 mM (Scheme 2). [d] An unidentified compound was formed. [e] Black tar formation was observed. [f] MS4A were added.

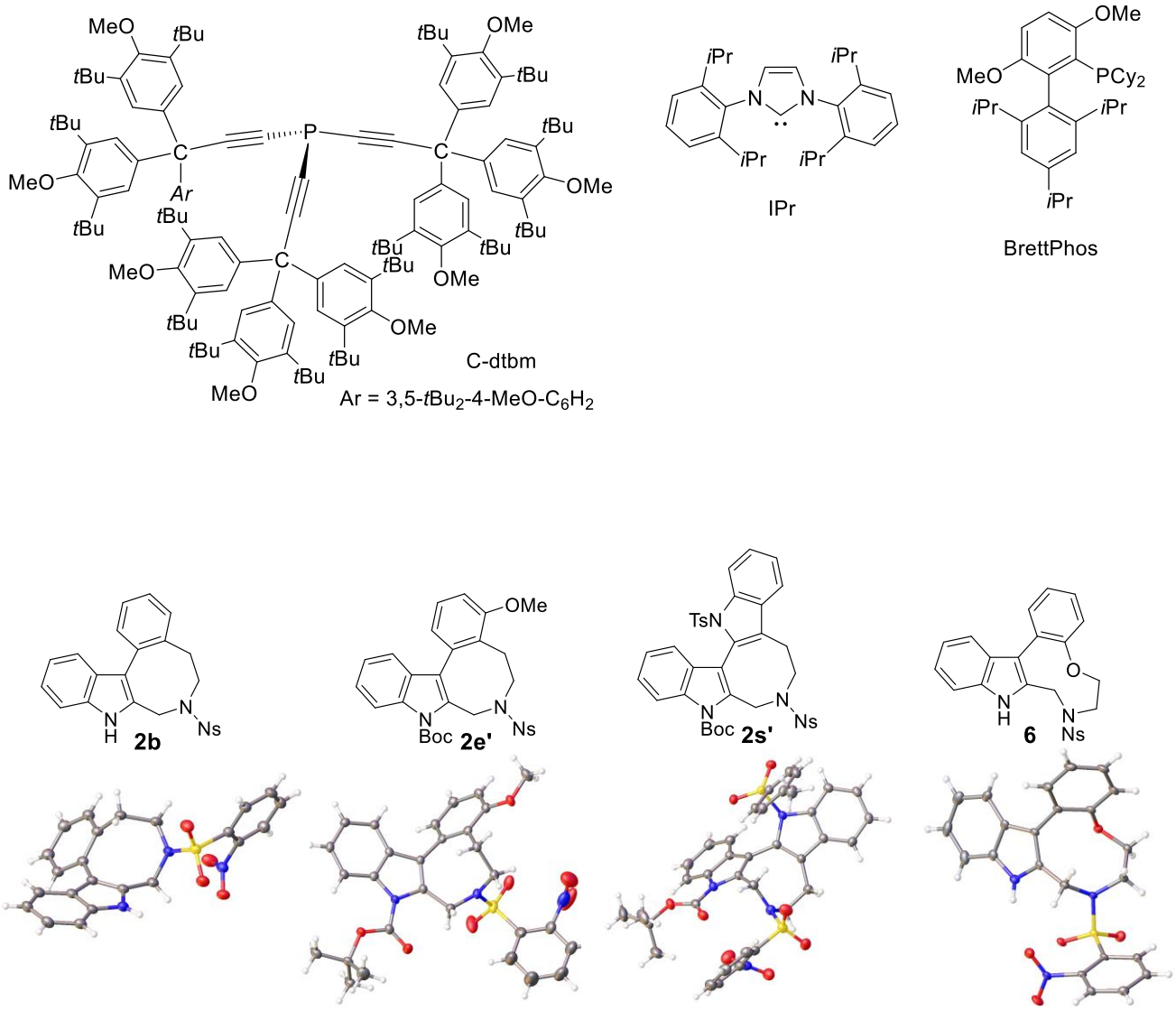
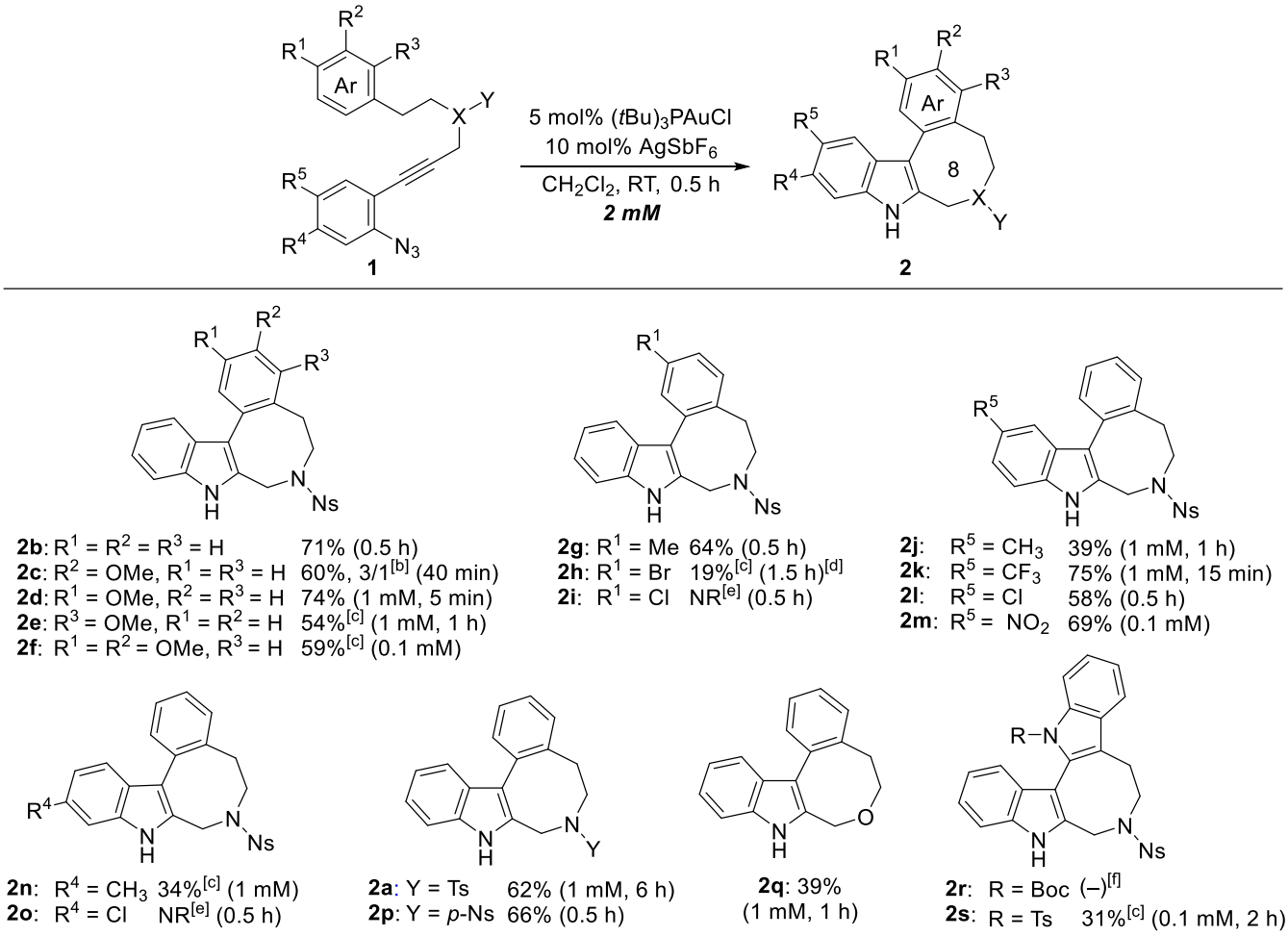


Figure 2. X-ray crystal structures of **2b**, **2e'** (Boc-**2e**), **2s'** (Boc-**2s**), and **6**.[15]

With the optimized conditions in hand, the author explored the scope of the eight-membered ring formation protocol (Table 2). First, the regioisomeric impact of various methoxyphenyl groups as the nucleophiles on the cyclization was examined. The author was interested in understanding if placing the electron-donating methoxy group in a *meta*-position relative to the alkyl tether (**1c**, R^2 = OMe) could increase the nucleophilicity of the *ortho*-position and thereby enhance the rate of the direct eight-membered ring formation. Interestingly, the opposite result to the author's expectation was observed with a significantly decreased yield of **2c** and an increased reaction time, suggesting that an alternate reaction pathway could dominate the reaction outcome. According to the Browns modification of the σ^+-values developed for aromatic electrophilic substitutions, the author estimated that the methoxy substituent of **2c** could inductively deactivate the *ipso* position at the alkyl tether, and consequently lower the nucleophilicity of an *ipso* attack on the gold carbene.[16] For clarification, the author activated the *ipso*

position with the *para*-substituted regioisomer **1d** (R^1 = OMe) and found a striking increase in reactivity (six-fold decrease in reaction time) as well as in yield (74%), suggesting that the *ipso* position plays an essential role for the azocine formation. On the contrary, a sluggish cyclization of the *ortho*-substituted methoxyphenyl precursor **1e** (R^3 = OMe) was observed to produce **2e** (54%), probably because of steric effects as well as the decreased number of reaction sites. The molecular structure of the *N*-Boc derivative obtained from **2e** was confirmed through X-ray diffraction (Figure 2). The investigation of the methoxy derivatives was finalized with the employment of the veratrole tether (R^1 = R^2 = OMe, **2f**). Surprisingly, the yield decreased significantly, and dilution to 0.1 mM was required to obtain the product in 59% yield, signaling an increased readiness of the substrate to undergo polymerization because of the high polarity difference of the reacting end groups. The order of the reactivity depending on the substituent R^1 (Me > Br > Cl) revealed that this cyclization is limited to slightly activated and neutral phenyl tethers (**2g**–**i**).

Table 2. Scope of the arylative cyclization to indole-fused heterocycles[a]



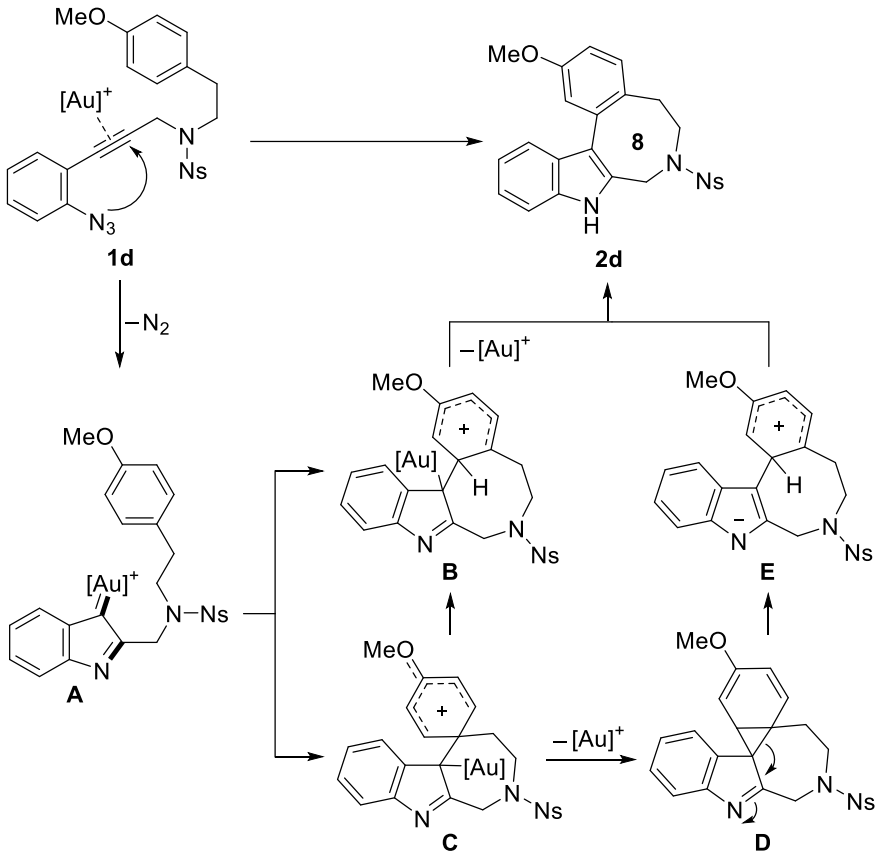
[a] Isolated yields are shown. [b] Combined isolated yield and regioisomeric ratio. [c] Characterized after *N*-Boc protection. [d] 22 mol% (tBu)$_3$PAuCl and 62 mol% $AgSbF_6$ were employed. [e] No reaction. [f] Black tar formation.

Next, the author focused on the substituent effect of the aryl azide part. When a methyl group is appended to the *meta*-position of the alkynyl group, a marginal 2% yield of **2j** was obtained at 2 mM (data not shown). Decreasing the substrate concentration to 1 mM increased the yield of **2j** to 39%. The author supposed that the methyl substituent contributes to the additional stabilization of the gold carbene and consequently decreases the required electrophilicity for the cyclization. A rationale for this result could also be found in the high nucleophilicity of the formed methyl-substituted indole that could instantaneously react with the highly electrophilic gold carbene in a diffusion-controlled manner.[17] In harmony with this notion, destabilization of the gold carbene through an electron-withdrawing CF_3 group significantly accelerated the cyclization to produce 75% of **2k**. In the case of a moderate electron-withdrawing halogen substituent with a competing positive mesomeric effect, such as chlorine, a moderate yield of **2l** (58%) was obtained. However, further increasing the electrophilicity of the gold(I)-carbene with a nitro group required even higher dilution conditions to give **2m** (69%). In close relationship to **2j**, the reaction of a methylated substrate resulted in a decreased yield of **2n** (34%). In stark contrast to **2l**, cyclization to **2o** could not be initiated through the employment of the standard conditions, presumably because the resonance contribution of the chloride-lone pair deactivates the gold carbene species. A brief investigation of the sulfonyl protecting group revealed that its electron density influenced the rate of cyclization. When the electron-withdrawing force was reduced through the application of a Ts-protecting group, the substrate concentration had to be diluted to 1 mM to suppress polymerization, hence suggesting a more sluggish cyclization with a yield of **2a** (62%). When *p*-Ns was used, no significant change in the reactivity compared with the model system was noticed (**2p**, 66%); thus, the author concluded that spatial interaction of the nitro group is not significant to enhance the cyclization reaction.

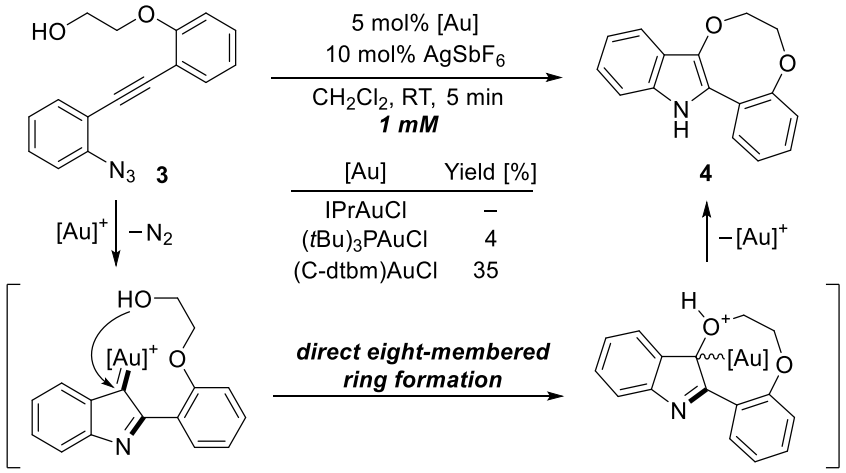
This reaction is also applicable to oxacycle formation (**2q**, 39%) by using an oxygen-tethered substrate.[7a] Finally, a nucleophilic *N*-Boc protected indole was employed as a cyclization precursor. Even when performing the reaction under 0.1 mM substrate concentrations, only a trace amount of the desired product **2r** was observed in the crude NMR while the formation of black tar dominated. In contrast, decreasing the nucleophilicity of the indole through substitution of a Boc group with a Ts group turned out to be beneficial to produce the pharmaceutically promising bisindole-fused eight-membered ring **2s** at 0.1 mM substrate concentrations in 31% yield. Its structure was confirmed by X-ray analysis of the Boc-derivative **2s'** (Figure 2).

A plausible reaction mechanism for the eight-membered ring formation is shown in Scheme 3. After the formation of α-imino gold species **A**, arylation to form **B** and deauration and rearomatization would produce the azocine **2d**. Based on the above-mentioned results on the effect of the methoxy group, the author proposes that the cyclization proceeds via a low strain and low torsional entropy demanding spirocycle pathway. Accordingly, an *ipso* attack forms the spiro compound **C**, with a subsequent 1,2-ring-expansion[18a,b] via dienone-phenol rearrangement, as described by Marx,[18c] to **B** could result in the azocine **2d**. Alternately, the spirocyclic intermediate **C** could also undergo cyclopropanation, forming norcadiene derivative **D**,[19] which could facilitate ring-opening reaction forming **E**, which can then be

converted to **2d** via rearomatization. At this stage, the involvement of a thermodynamically more challenging eight-membered ring formation to directly form **B** from **A** cannot be ruled out.



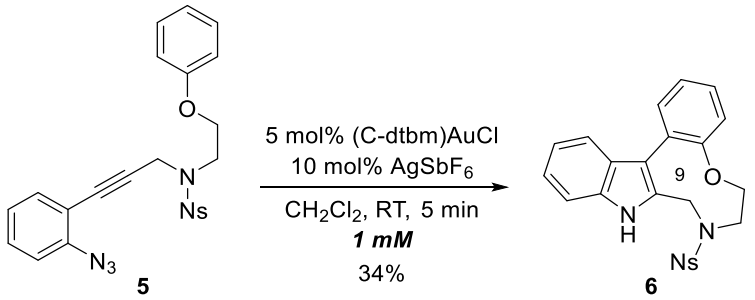
Scheme 3: Proposed mechanism of azocine formation



Scheme 4: Construction of the indole-fused dioxocine using the semihollow-shaped C-dtbm ligand.

To test the efficiency of an unambiguously direct end-to-end cyclization to the eight-membered ring (dioxocine) **4**, glycol tethered azido-alkyne **3** was exposed to the gold(I)-catalyzed cyclization conditions (Scheme 4). It was demonstrated that, compared with conventional ligands [IPr, (tBu)$_3$P], the semihollow-shaped C-dtbm[10] was significantly superior for this cyclization and allowed the isolation of **4** in 35% yield. Considering that this reaction cannot proceed through the spirocyclic pathway (intermediate **C** in Scheme 3), this result clearly shows the difficulty of direct eight-membered ring formation.

Finally, the construction of an indole-fused nine-membered ring (oxazonine) was investigated. Cyclization to nine-membered rings is generally considered to be significantly more challenging than the construction of eight-membered rings because the cyclization is afflicted with enhanced transannular strain and rotational entropy. Unfortunately, the optimized condition for the eight-membered ring formation was ineffective, and the substrate was recovered completely. The author once more attempted to utilize the C-dtbm ligand[10] and found that oxazonine **6** was isolated with 34% yield after full conversion (Scheme 5). The molecular structure was unambiguously confirmed through X-ray crystallographic analysis (Figure 2). The isolation of **4** and **6** clearly demonstrate the feasibility of the semihollow-shaped C-dtbm ligand for direct end-to-end eight-membered ring formation and arylative nine-membered ring formation.



Scheme 5: Construction of the indole-fused oxazonine using the semihollow-shaped C-dtbm ligand.

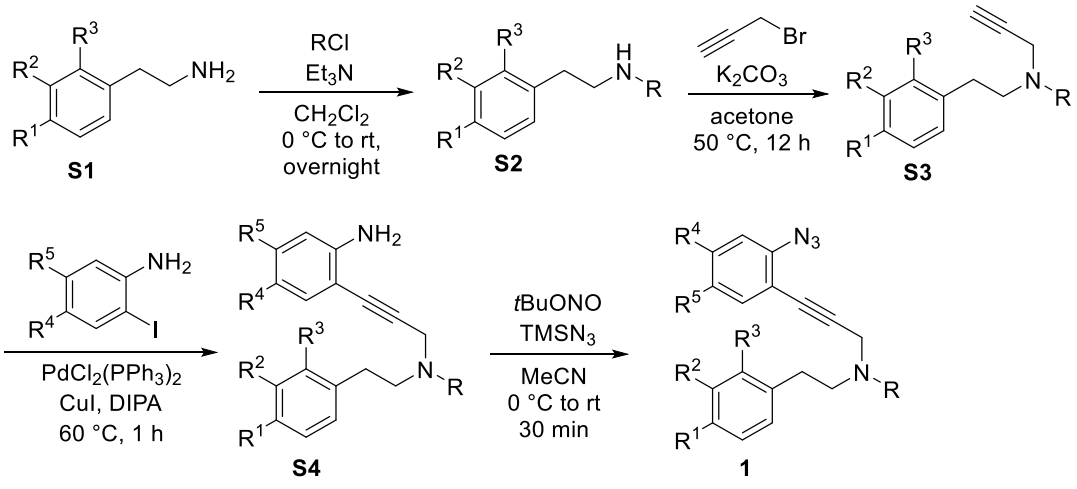
In summary, the author has shown that indole-fused benzannulated eight- and nine-membered rings can be obtained through gold-catalyzed cascade cyclizations of azido-alkynes, when arenes are used as internal nucleophiles for trapping the intermediary α-imino gold(I)-carbenes. Notably, the ease of ring closure was significantly affected by high dilution conditions, the polarization of the gold(I)-carbene, the arene moiety, and the *N*-protecting group.[20] Additionally, the author found that the semihollow-shaped C-dtbm ligand is indispensable for the alkoxylative eight-membered- and arylative nine-membered ring formation. The developed method can enter biologically relevant chemical space and created a library of a promising class of indole- and bisindole-fused medium-sized rings, potentially useful for medicinal applications.

Experimental Section

1. General Method.

Chemicals and solvents were purchased from commercial suppliers (Fujifilm Wako, Kanto Chemical Co., Inc., Merck). Dry THF was dispensed from the solvent purification system of Glass Contour MINI Nikko Hansen & Co., Ltd. NMR spectra were, if not mentioned otherwise, recorded at room temperature on JEOL AL-400 (400 MHz), JEOL ECA-500 (500 MHz) or JEOL ECZ-600 (600 MHz). Chemical shifts are given in ppm and coupling constants in Hz. ^{1}H- and ^{13}C-NMR spectra were calibrated in relation to deuterated solvents according to Fulmer *et al.* ^{13}C-NMR spectra are proton decoupled and in cases of unambiguous results interpreted with help of DEPT, HMQC, and HMBC. All spectra were integrated and processed using ALICE2 software. Exact mass (HRMS) spectra were recorded on JMS-700 mass spectrometer or Shimadzu LC-ESI-IT-TOF-MS equipment. Infrared (IR) spectra were recorded on a FT-IR spectrometer named JASCO FT/IR-4100 with a Germanium ATR-crystal. The solvent or the matrix is denoted in brackets. For the most significant bands the wave number (cm^{-1}) is given. For the flash column chromatography, silica gel (Wakogel C-200E: Wako Pure Chemical Industries, Ltd), amine silica gel (CHROMATOREX NH-DM1020: Fuji Silysia Chemical Ltd), and diol silica gel (CHROMATOREX DIOL MB100-75/200: Fuji Silysia Chemical Ltd) was used as stationary phase. As eluents, different mixtures of hexane (HE) and ethyl acetate (EA) or dichloromethane (DCM) and MeOH were used. To visualize the substances, ninhydrin, vanillin, DNP, and $KMnO_4$ were used as coloring reagents, or the TLC-plate was exposed to ultraviolet light (254 and 366 nm). If not mentioned differently, all reactions were carried out at normal laboratory conditions.

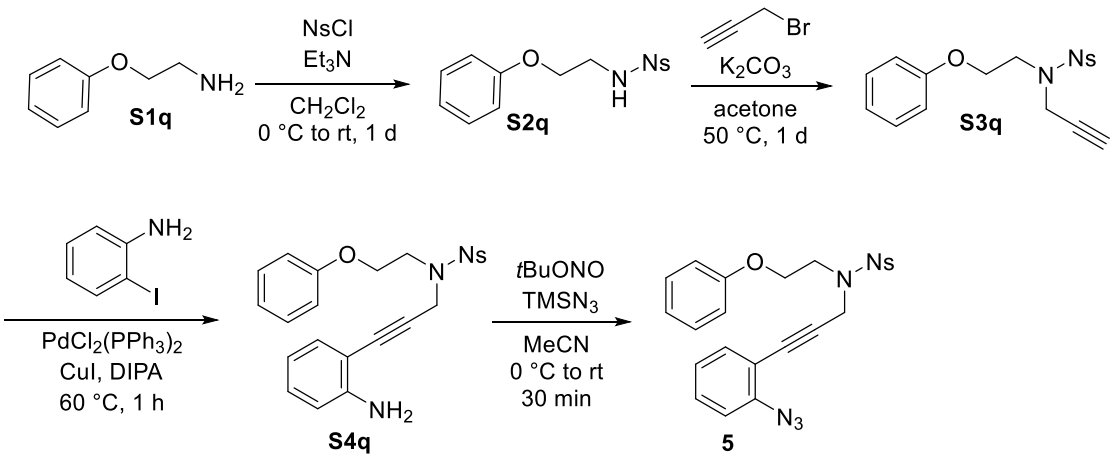
2. Preparation of the Cyclization Precursors



	R^1	R^2	R^3	R^4	R^5	R
a	H	H	H	H	H	Ts
b	H	H	H	H	H	*o*-Ns
c	H	OMe	H	H	H	*o*-Ns
d	OMe	H	H	H	H	*o*-Ns
e	H	H	OMe	H	H	*o*-Ns
f	OMe	OMe	H	H	H	*o*-Ns
g	Me	H	H	H	H	*o*-Ns
h	Br	H	H	H	H	*o*-Ns
i	Cl	H	H	H	H	*o*-Ns

	R^1	R^2	R^3	R^4	R^5	R
j	H	H	H	H	Me	*o*-Ns
k	H	H	H	H	CF_3	*o*-Ns
l	H	H	H	H	Cl	*o*-Ns
m	H	H	H	H	NO_2	*o*-Ns
n	H	H	H	Me	H	*o*-Ns
o	H	H	H	Cl	H	*o*-Ns
p	H	H	H	H	H	*p*-Ns

Scheme 6. Preparation of the cyclization precursors based on phenethylamines.



Scheme 7. Preparation of the cyclization precursors based on 2-phenoxyethan-1-amine.

General Procedures

GP1: Sulfonylation

In a round bottom flask, a solution of sulfonyl chloride (1.0 equiv) in dichloromethane (DCM) was added to a solution of phenethylamine/tryptamine **S1** (1.05–1.20 equiv) and triethylamine (1.3–4.3 equiv) in DCM via cannula, and the mixture was stirred overnight. The next day the reaction mixture was extracted with 1 M HCl, and the organic phase was washed with $NaHCO_3$, saturated NH_4Cl, and brine. The organic extract was dried with $MgSO_4$, filtered, and removed *in vacuo*. The residue was purified with silica gel column chromatography.

GP2: Propargylation

A solution of sulfonamide **S2** (1.0 equiv) was suspended with K_2CO_3 (1.5–3.0 equiv) in acetone in a two-neck-round-bottom flask, and the mixture was heated to 50 °C under argon atmosphere. After the mixture was stirred for 30 min, propargyl bromide (1.2–3.0 equiv) was added dropwise via syringe. After 12 h the reaction was quenched with H_2O and extracted with Et_2O three times. The organic extract was dried with $MgSO_4$, filtrered, and the solvent was removed *in vacuo* at 40 °C. The product was purified by silica gel column chromatography.

GP3: Preparation of Amino-ynes (S4)

CuI (5 mol%) and $Pd(PPh_3)_2Cl_2$ (5 mol %) were suspended in *i*-Pr_2NH (DIPA) under argon together with the corresponding *o*-iodoaniline (2.0 equiv). After the suspension was gradually heated to 60 °C over 30 min, alkyne **S3** (1.0 equiv) was added dropwise. The reaction mixture was stirred until all alkyne was consumed monitored by TLC with ninhydrin as a coloring agent. After letting the reaction cool to room temperature, the mixture was diluted with DCM and filtered over Celite. Solvents were removed *in vacuo.* The residue was purified by silica gel column chromatography.

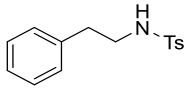
GP4: Preparation of Azido-ynes (1)

The aniline derivative **S4** (1.0 equiv) was dissolved in MeCN and cooled to 0 °C in an ice bath. To this stirred mixture were successively added *t*-BuONO (1.1–2.3 equiv) and $TMSN_3$ (1.1–2.3 equiv) dropwise. The resulting solution was stirred at room temperature for 30 min. The reaction mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography to yield the product **1**.

GP5: Gold(I)-Catalyzed Cyclization

Azido-yne **1** (1.0 equiv) was dissolved in DCM, and (*t*-Bu)$_3$PAuCl (5 mol %) together with $AgSbF_6$ (10 mol %) were added. After the mixture was stirred overnight at room temperature, the solvent was evaporated and silica gel column chromatography was performed to purify the product.

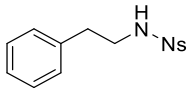
4-Methyl-*N*-phenethylbenzenesulfonamide (S2a)



S2a

According to **GP1**, **S1a** (2.09 mL, 16.5 mmol) was converted to **S2a** (1.45 g, 75%) by the reaction with NsCl (2.99 g, 15.7 mmol) and Et_3N (4.33 mL, 31.2 mmol) in DCM (120 mL) at room temperature for 12 h. Purification was performed by flash column chromatography on silica gel (hexane/EtOAc = 1/1) to afford yield as an off-white powder. The spectral data were in good agreement with those previously reported.[21]

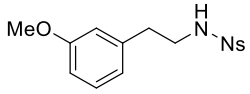
2-Nitro-*N*-phenethylbenzenesulfonamide (S2b)



S2b

According to **GP1**, **S1b** (1.26 mL, 9.90 mmol) was converted to **S2b** (2.45 g, 80%) by the reaction with NsCl (1.80 g, 9.90 mmol) and Et_3N (1.80 mL, 12.9 mmol) in DCM (18 mL) at room temperature for 12 h. Purification was performed by silica gel column (hexane/EtOAc = 10/1 to 4:1). The spectral data were in good agreement with those previously reported.[22]

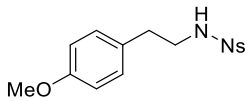
***N*-(3-Methoxyphenethyl)-2-nitrobenzenesulfonamide (S2c)**



S2c

According to **GP1**, **S1c** (1.94 mL, 13.23 mmol) was converted to **S2c** (2.30 g, 52%) by the reaction with NsCl (2.78 g, 12.6 mmol) and Et_3N (3.13 mL, 22.5 mmol) in DCM (18 mL) at room temperature for 12 h. Purification was performed by silica gel column (hexane/EtOAc = 10/1 to 3/1): off-white powder; mp 81 °C; IR (neat) 3346 (NH), 1531 (N=O), 1345 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.79 (t, J = 6.7 Hz, 2H), 3.38 (dt, J = 6.7, 6.7 Hz, 2H), 3.74 (s, 3H), 5.37-5.39 (m, 1H), 6.61 (s, 1H), 6.68 (d, J = 8.0 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 7.13 (dd, J = 8.0, 8.0 Hz, 1H), 7.70 (m, 2H), 7.79 (m, 1H), 8.06 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 35.7, 44.9, 55.0, 112.1, 114.3, 120.8, 125.3, 129.7, 130.8, 132.8, 133.5 (2C), 138.9, 147.7, 159.7; HRMS calcd for $C_{15}H_{16}N_2NaO_5S^+$ [M + Na]$^+$: 359.0672, found 359.0673.

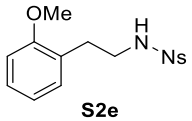
***N*-[2-(4-Methoxyphenyl)ethyl]-2-nitrobenzenesulfonamide (S2d)**



S2d

According to **GP1**, **S1d** (1.94 mL, 13.2 mmol) was converted to **S2d** in (2.70 g, 63%) as an off-white solid by the reaction with NsCl (2.78 g, 12.6 mmol) and Et_3N (3.13 mL, 22.5 mmol) in DCM (36 mL) at room temperature for 12 h. Purification was performed by flash column chromatography on silica gel (hexane/EtOAc = 4/1). The spectral data were in good agreement with those previously reported.[23]

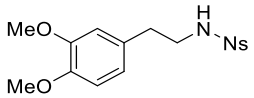
***N*-(2-Methoxyphenethyl)-2-nitrobenzenesulfonamide (S2e)**



S2e

According to **GP1**, **S1e** (0.95 mL, 6.61 mmol) was converted to **S2e** (1.30g, 58%) by the reaction with NsCl (1.39 g, 6.28 mmol) and Et_3N (1.50 mL, 11.24 mmol) in DCM (40 mL) at room temperature for 12 h. Purification was performed by flash column chromatography on silica gel (hexane/EtOAc = 4/1): off-white solid; mp 63 °C; IR (neat) 3338 (NH), 1531 (N=O), 1337 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.84 (t, J = 6.7 Hz, 2H), 3.37 (dt, J = 6.7, 6.7 Hz, 2H), 3.80 (s, 3H), 5.55 (t, J = 6.7 Hz, 1H), 6.76-6.82 (m, 2H), 6.99 (dd, J = 7.4, 1.6 Hz, 1H), 7.16 (ddd, J = 7.4, 7.4, 1.6 Hz, 1H), 7.66-7.72 (m, 2H), 7.78-7.83 (m, 1H), 8.05-8.09 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 30.5, 44.2, 55.2, 110.3, 120.7, 125.4, 125.9, 128.3, 130.6, 131.0, 132.7, 133.3, 133.8, 147.8, 157.4; HRMS calcd for $C_{15}H_{16}N_2NaO_5S^+$ $[M + Na]^+$: 359.0672, found 359.0673.

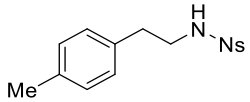
***N*-(3,4-Dimethoxyphenethyl)-2-nitrobenzenesulfonamide (S2f)**



S2f

According to **GP1**, **S1f** (1.86 mL, 11.0 mmol) was converted to **S2f** (2.60 g, 64%) by the reaction with NsCl (2.32 g, 10.5 mmol) and Et_3N (4.33 mL, 31.2 mmol) in DCM (120 mL) at room temperature for 12 h. Purification was performed by flash column chromatography on silica gel (hexane/EtOAc = 1/1): off-white powder; mp 119 °C; IR (neat) 3304 (NH), 1536 (N=O), 1363 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.78 (t, J = 6.9 Hz, 2H), 3.38 (dt, J = 6.9, 6.9 Hz, 2H), 3.80 (s, 3H), 3.84 (s, 3H), 5.39 (t, J = 5.9 Hz, 1H), 6.59 (d, J = 1.7 Hz, 1H), 6.64 (dd, J = 8.2, 1.9 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 7.68-7.74 (m, 2H), 7.81-7.85 (m, 1H), 8.05-8.09 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 35.5, 45.3, 55.9, 56.0, 111.3, 111.7, 120.8, 125.3, 130.0, 131.0, 132.9, 133.5, 134.0, 135.7, 148.0, 149.1; HRMS calcd for $C_{16}H_{18}N_2NaO_6S^+$ $[M + Na]^+$: 389.0778, found 389.0780.

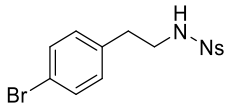
***N*-(4-Methylphenethyl)-2-nitrobenzenesulfonamide (S2g)**



S2g

According to **GP1**, **S1g** (3.12 mL, 18.8 mmol) was converted to **S2g** (1.58 g, 66%) by the reaction with NsCl (4.00 g, 18.0 mmol) and Et_3N (4.33 mL, 31.2 mmol) in DCM (70 mL) at room temperature for 12 h. Purification was performed by flash column chromatography on silica gel (hexane/EtOAc = 4/1): off-white solid; mp 95 °C; IR (neat) 3299 (NH), 1536 (N=O), 1328 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.31 (s, 3H), 2.82 (t, J = 6.9 Hz, 2H), 3.40 (dt, J = 6.9, 6.9 Hz, 2H), 5.43 (t, J = 6.9 Hz, 1H), 7.00 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 7.71-7.76 (m, 2H), 7.81-7.86 (m, 1H), 8.07-8.13 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.0, 35.5, 45.1, 125.4, 128.5 (2C), 129.4 (2C), 130.9, 132.8, 133.3, 133.8, 134.2, 136.4, 147.9; HRMS calcd for $C_{15}H_{16}N_2NaO_4S^+$ $[M + Na]^+$: 343.0723, found 343.0727.

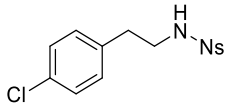
***N*-(4-Bromophenethyl)-2-nitrobenzenesulfonamide (S2h)**



S2h

According to **GP1**, **S1h** (0.77 mL, 5.00 mmol) was converted to **S2h** (1.45 g, 75%) by the reaction with NsCl (1.05 g, 4.75 mmol) and Et_3N (4.33 mL, 31.2 mmol) in DCM (120 mL) at room temperature for 12 h. Purification was performed by flash column chromatography on silica gel (hexane/EtOAc = 1/1): off-white powder; mp 130 °C; IR (neat) 3371 (NH), 1536 (N=O), 1333 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.80 (t, J = 8.0 Hz, 2H), 3.40 (dt, J = 8.0, 8.0 Hz, 2H), 5.31-5.33 (m, 1H), 6.97 (d, J = 8.0 Hz, 2H), 7.31-7.33 (m, 2H), 7.69-7.75 (m, 2H), 7.83 (dd, J = 7.4, 1.7 Hz, 1H), 8.03 (dd, J = 7.4, 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 35.6, 45.0, 120.8, 125.4, 130.4 (2C), 130.7, 131.7 (2C), 132.9, 133.5, 133.8, 136.4, 147.8; HRMS calcd for $C_{14}H_{13}BrKN_2O_4S^+$ $[M + K]^+$: 406.9672, found 406.9672.

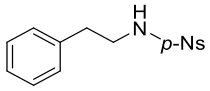
***N*-(4-Chlorophenethyl)-2-nitrobenzenesulfonamide (S2i)**



S2i

According to **GP1**, **S1i** (0.89 mL, 5.00 mmol) was converted to **S2i** (1.31 g, 60%) by the reaction with NsCl (1.05 g, 4.75 mmol) and Et_3N (4.33 mL, 31.2 mmol) in DCM (120 mL) at room temperature for 12 h. Purification was performed by flash column chromatography on silica gel (hexane/EtOAc = 1/1): off-white powder; mp 112 °C; IR (neat) 3376 (N-H), 1536 (N=O), 1333 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.81 (t, J = 6.9 Hz, 2H), 3.39 (dt, J = 6.9, 6.9 Hz, 2H), 5.34-5.36 (m, 1H), 7.03 (d, J = 8.0 Hz, 2H), 7.15-7.17 (m, 2H), 7.75-7.69 (m, 2H), 7.83 (dd, J = 7.4, 1.7 Hz, 1H), 8.03 (dd, J = 6.9, 2.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 35.3. 44.8, 125.4, 128.8 (2C), 130.1 (2C), 130.8, 132.7, 132.9, 133.5, 133.8, 135.9, 147.8; HRMS calcd for $C_{14}H_{13}ClN_2NaO_4S^+$ $[M + Na]^+$: 363.0177, found 363.0175.

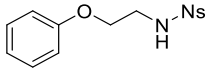
4-Nitro-*N*-phenethylbenzenesulfonamide (S2p)



S2p

According to **GP1**, **S1p** (2.09 mL, 16.5 mmol) was converted to **S2p** (1.45 g, 73%) as an off-white powder by the reaction with NsCl (2.99 g, 15.7 mmol) and Et_3N (4.33 mL, 31.2 mmol) in DCM (120 mL) at room temperature for 12 h. Purification was performed by flash column chromatography on silica gel (hexane/EtOAc = 1/1). The spectral data were in good agreement with those previously reported.[24]

2-Nitro-*N*-(2-phenoxyethyl)benzenesulfonamide (S2q)



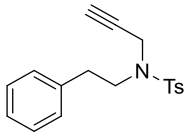
S2q

According to **GP1**, **S1q** (0.95 mL, 7.29 mmol) was converted to **S2q** (2.26 g, 95%) by the reaction with NsCl (1.53 g, 6.93 mmol) and Et_3N (4.33 mL, 31.2 mmol) in DCM (120 mL) at room temperature for 12 h. Purification was performed by flash column chromatography on silica gel (hexane/EtOAc = 1/1): off-white powder; mp 134 °C; IR (neat) 3329 (NH), 1537 (N-O), 1338 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.54 (t, J = 5.2 Hz, 2H), 4.02 (t, J = 5.2 Hz, 2H), 5.94 (br s, 1H), 6.74 (d, J = 8.0 Hz, 2H), 6.94 (t, J = 7.4 Hz, 1H), 7.22 (dd, J = 8.0, 7.4 Hz, 2H), 7.68-

7.71 (m, 2H), 7.83 (dd, *J* = 7.7, 1.4 Hz, 1H), 8.15 (dd, *J* = 7.7, 1.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 43.3, 65.7, 114.3 (2C), 121.4, 125.6, 129.5 (2C), 130.8, 132.9, 133.5, 134.0, 147.9, 157.8; HRMS calcd for $C_{14}H_{14}N_2NaO_5S^+$ $[M + Na]^+$: 345.0516, found 345.0516.

Preparation of Propargylsulfonamides (S3)

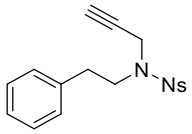
4-Methyl-*N*-phenethyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (S3a)



S3a

According to **GP2**, **S2a** (4.54 g, 16.5 mmol) was converted to **S3a** (4.04 g, 78%) by the reaction with propargyl bromide (2.50 mL, 33.0 mmol) and K_2CO_3 (2.28 g, 33.0 mmol) in acetone (50 mL) at 50 °C for 12 h: yellow oil; IR (neat) 3278 (≡C-H), 2119 (C≡C), 1346 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.06 (t, *J* = 2.3 Hz, 1H), 2.41 (s, 3H), 2.91 (t, *J* = 7.5 Hz, 2H), 3.42 (t, *J* = 7.5 Hz, 2H), 4.10 (d, *J* = 2.3 Hz, 2H), 7.20-7.31 (m, 7H), 7.69-7.71 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.6, 34.8, 37.0, 48.1, 73.9, 76.8, 126.7, 127.8 (2C), 128.7 (2C), 128.9 (2C), 129.6 (2C), 135.9, 138.3, 143.6; HRMS calcd for $C_{18}H_{19}KNO_2S^+$ $[M + K]^+$: 336.1029, found 336.1028.

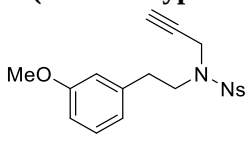
2-Nitro-*N*-phenethyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (S3b)



S3b

According to **GP2**, **S2b** (4.20 g, 13.7 mmol) was converted to **S3b** (4.40 g, 94%) by the reaction with propargyl bromide (1.56 mL, 20.6 mmol) and K_2CO_3 (2.84 g, 20.6 mmol) in acetone (50 mL) at 50 °C for 12 h: brown solid; mp 46 °C; IR (neat) 3289 (≡C-H), 2253 (C≡C), 1537 (N=O), 1361 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.22 (t, *J* = 2.6 Hz, 1H), 2.93 (t, *J* = 7.7 Hz, 2H), 3.65 (t, *J* = 7.7 Hz, 2H), 4.19 (d, *J* = 2.6 Hz, 2H), 7.19-7.27 (m, 3H), 7.62-7.77 (m, 5H), 7.99 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 34.5, 36.9, 48.3, 74.0, 76.9, 124.3, 126.7, 128.6 (2C), 128.8 (2C), 130.8, 131.7, 132.8, 133.6, 137.8, 148.2; HRMS calcd for $C_{17}H_{16}N_2NaO_4S^+$ $[M + Na]^+$: 367.0723, found 367.0722.

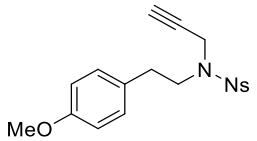
N-(3-Methoxyphenethyl)-2-nitrobenzenesulfonamide (S3c)



S3c

According to **GP2**, **S2c** (2.00 g, 5.95 mmol) was converted to **S3c** (2.10 g, 94%) by the reaction with propargyl bromide (0.54 mL, 7.14 mmol) and K_2CO_3 (1.64 g, 11.9 mmol) in acetone (50 mL) at 50 °C for 12 h: colorless oil; IR (neat) 3283 (≡C-H), 2254 (C≡C), 1541 (N=O), 1355 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.24 (t, *J* = 2.4 Hz, 1H), 2.89 (t, *J* = 7.7 Hz, 2H), 3.64 (t, *J* = 7.7 Hz, 2H), 3.77 (s, 3H), 4.18 (d, *J* = 2.4 Hz, 2H), 6.73 (dt, *J* = 4.9, 1.6 Hz, 2H), 6.80 (d, *J* = 7.4 Hz, 1H), 7.17 (ddd, *J* = 7.4, 4.9, 2.8 Hz, 1H), 7.69-7.59 (m, 3H), 7.96 (dd, *J* = 7.8, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 34.7, 37.2, 48.6, 55.4, 74.3, 77.2, 112.4, 114.8, 121.4, 124.5, 129.9, 130.9, 132.1, 132.8, 134.1, 139.6, 148.4, 160.9; HRMS calcd for $C_{18}H_{18}N_2NaO_5S^+$ $[M + Na]^+$: 397.0829, found 397.0825.

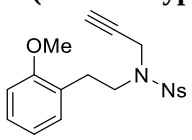
***N*-(4-Methoxyphenethyl)-2-nitro-*N*-(prop-2-yn-1-yl)benzenesulfonamide (S3d)**



S3d

According to **GP2**, **S2d** (2.00 g, 5.95 mmol) was converted to **S3d** (2.15 g, 96%) by the reaction with propargyl bromide (0.54 mL, 7.14 mmol) and K_2CO_3 (1.64 g, 11.9 mmol) in acetone (50 mL) at 50 °C for 12 h: colorless oil; IR (neat) 3303 (≡C-H), 2254 (C≡C), 1544 (N=O), 1359 (S=O); ^{1}H-NMR ($CDCl_3$) δ: 2.22 (t, J = 2.5 Hz, 1H), 2.86 (t, J = 7.7 Hz, 2H), 3.61 (t, J = 7.7 Hz, 2H), 3.77 (s, 3H), 4.19 (d, J = 2.3 Hz, 2H), 6.79 (dt, J = 9.3, 2.6 Hz, 2H), 7.10 (dt, J = 9.3, 2.6 Hz, 2H), 7.61-7.70 (m, 3H), 7.97 (dd, J = 7.8, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 33.5, 36.9, 48.5, 55.2, 73.9, 76.9, 113.9 (2C), 124.2, 129.7 (3C), 130.7, 131.6, 132.8, 133.6, 148.1, 158.3; HRMS calcd for $C_{18}H_{18}N_2NaO_5S^+$ $[M + Na]^+$: 397.0829, found 397.0829.

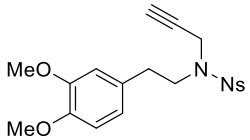
***N*-(2-Methoxyphenethyl)-2-nitro-*N*-(prop-2-yn-1-yl)benzenesulfonamide (S3e)**



S3e

According to **GP2**, **S2e** (1.20 g, 3.57 mmol) was converted to **S3e** (1.10 g, 82%) by the reaction with propargyl bromide (0.34 mL, 4.28 mmol) and K_2CO_3 (0.74 g, 5.35 mmol) in acetone (50 mL) at 50 °C for 12 h: yellow oil. IR (neat) 3304 (≡C-H), 2255 (C≡C), 1543 (N=O), 1359 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.22 (t, J = 2.4 Hz, 1H), 2.89 (t, J = 7.5 Hz, 2H), 3.64 (t, J = 7.5 Hz, 2H), 3.78 (s, 3H), 4.23 (d, J = 2.5 Hz, 2H), 6.77 (d, J = 8.2 Hz, 1H), 6.81 (ddd, J = 7.4, 7.4, 0.9 Hz, 1H), 7.09 (dd, J = 7.4, 1.7 Hz, 1H), 7.14-7.17 (m, 1H), 7.57-7.66 (m, 3H), 7.95 (dd, J = 7.7, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 29.3, 36.6, 46.4, 55.0, 73.47, 73.51, 110.0, 120.5, 124.2, 126.0, 128.1, 130.6, 130.7, 131.6, 133.0, 133.4, 148.1, 157.5; HRMS calcd for $C_{18}H_{18}N_2NaO_5S^+$ $[M + Na]^+$: 397.0829, found 397.0829.

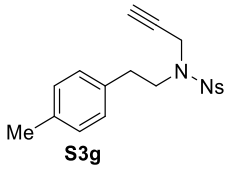
***N*-(3,4-Dimethoxyphenethyl)-2-nitro-*N*-(prop-2-yn-1-yl)benzenesulfonamide (S3f)**



S3f

According to **GP2**, **S2f** (4.30 g, 23.7 mmol) was converted to **S3f** (4.60 g, 94%) by the reaction with propargyl bromide (2.69 mL, 35.6 mmol) and K_2CO_3 (4.92 g, 35.6 mmol) in acetone (50 mL) at 50 °C for 12 h: yellow oil; IR (neat) 3285 (≡C-H), 2254 (C≡C), 1541 (N=O), 1355 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.22 (t, J = 2.5 Hz, 1H), 2.87 (t, J = 7.5 Hz, 2H), 3.64 (t, J = 7.5 Hz, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 4.18 (d, J = 2.5 Hz, 2H), 6.72-6.76 (m, 3H), 7.60-7.70 (m, 3H), 7.96-7.98 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 34.1, 37.0, 48.4, 55.8 (2C), 73.9, 77.0, 111.2, 111.9, 120.8, 124.1, 130.3, 130.7, 131.6 (2C), 132.8, 133.5, 147.7, 148.9; HRMS calcd for $C_{19}H_{20}N_2NaO_6S^+$ $[M + Na]^+$: 427.0934, found 427.0937.

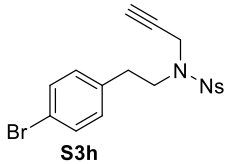
***N*-(4-Methylphenethyl)-2-nitro-*N*-(prop-2-yn-1-yl)benzenesulfonamide (S3g)**



S3g

According to **GP2**, **S2g** (1.60 g, 4.99 mmol) was converted to **S3g** (1.54 g, 86%) by the reaction with propargyl bromide (0.57 mL, 7.49 mmol) and K_2CO_3 (1.17 g, 8.49 mmol) in acetone (50 mL) at 50 °C for 12 h: yellow oil; IR (neat) 3292 (≡C-H), 2254 (C≡C), 1542 (N=O), 1357 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.22 (t, J = 2.5 Hz, 1H), 2.30 (s, 3H), 2.88 (t, J = 7.7 Hz, 2H), 3.62 (t, 7.7 Hz, 2H), 4.20 (d, J = 2.4 Hz, 2H), 7.05-7.09 (m, 4H), 7.61-7.69 (m, 3H), 7.97-7.99 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.0, 34.0, 36.9, 48.4, 73.9, 76.9, 124.2, 128.7 (2C), 129.3 (2C), 130.8, 131.6, 132.9, 133.5, 134.6, 136.2, 148.2; HRMS calcd for $C_{18}H_{18}N_2NaO_4S^+$ $[M + Na]^+$: 381.0879, found 381.0879.

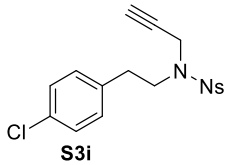
***N*-(4-Bromophenethyl)-2-nitro-*N*-(prop-2-yn-1-yl)benzenesulfonamide (S3h)**



S3h

According to **GP2**, **S2h** (2.00 g, 6.28 mmol) was converted to **S3h** (4.40 g, 94%) by the reaction with propargyl bromide (1.00 mL, 13.2 mmol) and K_2CO_3 (1.74 g, 12.6 mmol) in acetone (50 mL) at 50 °C for 12 h: orange oil; IR (neat) 3304 (≡C-H), 2254 (C≡C), 1543 (N=O), 1359 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.27 (t, J = 2.4 Hz, 1H), 2.86 (t, J = 7.4 Hz, 2H), 3.63 (t, J = 7.4 Hz, 2H), 4.19 (d, J = 2.4 Hz, 2H), 7.04 (d, J = 8.0, 1.4 Hz, 2H), 7.29-7.31 (m, 2H), 7.58-7.71 (m, 3H), 7.91 (dd, J = 8.0, 1.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 34.0, 37.2, 48.5, 74.7, 77.2, 120.9, 124.6, 131.0 (3C), 131.9 (2C), 132.3, 132.7, 134.3, 137.2, 148.3; HRMS calcd for $C_{17}H_{15}BrN_2NaO_4S^+$ $[M + Na]^+$: 444.9828, found 444.9826.

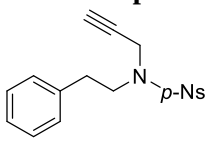
***N*-(4-Chlorophenethyl)-2-nitro-*N*-(prop-2-yn-1-yl)benzenesulfonamide (S3i)**



S3i

According to **GP2**, **S2i** (1.72 g, 5.05 mmol) was converted to **S3i** (1.05 g, 56%) by the reaction with propargyl bromide (0.77 mL, 10.1 mmol) and K_2CO_3 (1.40 g, 10.1 mmol) in acetone (50 mL) at 50 °C for 12 h: yellow oil; IR (neat) 3294 (≡C-H), 2253 (C≡C), 1543 (N=O), 1359 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.25 (t, J = 2.4 Hz, 1H), 2.88 (t, J = 7.5 Hz, 2H), 3.63 (t, J = 7.5 Hz, 2H), 4.19 (d, J = 2.4 Hz, 2H), 7.11 (dt, J = 8.8, 2.2 Hz, 2H), 7.18 (dt, J = 8.8, 2.2 Hz, 2H), 7.60-7.71 (m, 3H), 7.94 (dd, J = 7.9, 1.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 33.8, 37.1, 48.3, 74.4, 76.9, 124.3, 128.8 (2C), 130.1 (2C), 130.8, 131.9, 132.5, 132.6, 133.9, 136.3, 148.1; HRMS calcd for $C_{17}H_{15}ClKN_2O_4S^+$ $[M + K]^+$: 417.0076, found 417.0073.

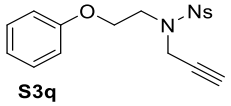
4-Nitro-*N*-phenethyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (S3p)



S3p

According to **GP2**, **S2p** (3.74 g, 12.2 mmol) was converted to **S3p** (3.50 g, 83%) by the reaction with propargyl bromide (1.84 mL, 24.4 mmol) and K_2CO_3 (3.38 g, 24.4 mmol) in acetone (100 mL) at 50 °C for 12 h: orange solid; mp 88 °C; IR (neat) 3282 (≡C-H), 2257 (C≡C), 1528 (N=O), 1348 (S=O); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.07 (t, J = 2.5 Hz, 1H), 2.94 (t, J = 7.6 Hz, 2H), 3.48 (t, J = 7.6 Hz, 2H), 4.14 (d, J = 2.5 Hz, 2H), 7.20-7.33 (m, 5H), 7.99 (dt, J = 9.2, 2.2 Hz, 2H), 8.31 (dt, J = 9.2, 2.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 34.6, 36.8, 48.1, 74.4, 75.8, 124.1 (2C), 126.9, 128.2, 128.7 (2C), 128.8 (2C), 128.9 (2C), 137.6, 144.6; HRMS calcd for $C_{17}H_{16}N_2KO_4S^+$ [M + K]$^+$: 383.0462, found 383.0466.

2-Nitro-*N*-(2-phenoxyethyl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide (S3q)

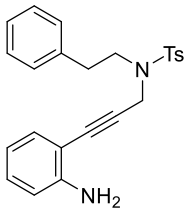


S3q

According to **GP2**, **S2q** (2.25 g, 7.00 mmol) was converted to **S3q** (1.66g, 66%) by the reaction with propargyl bromide (0.79 mL, 10.5 mmol) and K_2CO_3 (1.64 g, 11.9 mmol) in acetone (50 mL) at 50 °C for 12 h. Purification was performed by flash column chromatography on silica gel (hexane/EtOAc = 1/1): white solid; mp 109 °C; IR (neat) 3266 (≡C-H), 2254 (C≡C), 1541 (N=O), 1355 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.21 (t, J = 2.2 Hz, 1H), 3.86 (t, J = 5.3 Hz, 2H), 4.18 (t, J = 5.3 Hz, 2H), 4.39 (d, J = 2.2 Hz, 2H), 6.80 (dd, J = 8.7, 0.9 Hz, 2H), 6.96 (t, J = 7.4 Hz, 1H), 7.25-7.27 (m, 2H), 7.64-7.72 (m, 3H), 8.09 (dd, J = 7.6, 1.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 38.5, 46.3, 66.8, 74.1, 77.2, 114.5 (2C), 121.4, 124.4, 129.7 (2C), 131.1, 131.9, 133.0, 133.9, 148.3, 158.2; HRMS calcd for $C_{17}H_{16}N_2NaO_5S^+$ [M + Na]$^+$: 383.0672, found 383.0672.

Preparation of Amino-ynes (S4)

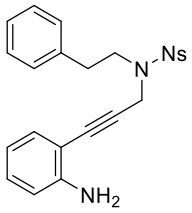
***N*-[3-(2-Aminophenyl)prop-2-yn-1-yl]-4-methyl-*N*-phenethylbenzenesulfonamide (S4a)**



S4a

According to **GP3**, **S3a** (810 mg, 2.58 mmol) was converted to **S4a** (521 mg, 50%) by the reaction with *o*-iodoaniline (1.13 g, 5.17 mmol) in the presence of $PdCl_2(PPh_3)_2$ (90.7 mg, 0.129 mmol) and CuI (24.6 mg, 0.129 mmol) in DIPA (20 mL) and acetone (3 mL) at 60 °C for 0.5 + 1 h. Purification was performed by silica gel column chromatography (hexane/EtOAc = 3/1): bright yellow oil; IR (neat) 3498 (N-H), 3396 (N-H), 2253 (C≡C), 1542 (N=O), 1357 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.30 (s, 3H), 2.93 (t, J = 7.8 Hz, 2H), 3.50 (t, J = 7.8 Hz, 2H), 3.96 (s, 2H), 4.33 (s, 2H), 6.56-6.61 (m, 2H), 6.90 (dd, J = 7.7, 1.5 Hz, 1H), 7.04-7.07 (m, 1H), 7.24 (m, 7H), 7.71 (d, J = 8.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.3, 34.7, 37.7, 47.9, 82.4, 86.9, 106.4, 114.1, 117.3, 126.5, 127.5 (2C), 128.5 (2C), 128.7 (2C), 129.5 (2C), 129.7, 132.0, 135.6, 138.1, 143.5, 147.9; HRMS calcd for $C_{24}H_{24}N_2NaO_2S^+$ [M + Na]$^+$: 427.1451, found 427.1454.

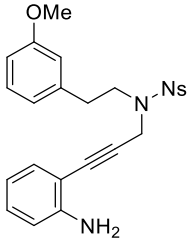
***N*-[3-(2-Aminophenyl)prop-2-yn-1-yl]-4-nitro-*N*-phenethylbenzenesulfonamide (S4b)**



S4b

According to **GP3**, **S3b** (4.40 g, 12.8 mmol) was converted to **S4b** (2.60 g, 47%) by the reaction with *o*-iodoaniline (5.60 g, 25.6 mmol) in the presence of $PdCl_2(PPh_3)_2$ (448 mg, 0.639 mmol) and CuI (122 mg, 0.639 mmol) in DIPA (50 mL) and acetone (6 mL) at 60 °C for 0.5 + 1 h. Purification was performed by silica column chromatography (hexane/EtOAc = 10/1 to 1/1): bright yellow oil; IR (neat) 3376 (≡C-H), 2223 (C≡C), 1541 (N=O), 1353 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.98 (t, J = 7.7 Hz, 2H), 3.70 (t, J = 7.7 Hz, 2H), 4.10 (br s, 2H), 4.43 (s, 2H), 6.65-6.61 (m, 2H), 7.07-7.10 (m, 2H), 7.20-7.29 (m, 5H), 7.58-7.64 (m, 3H), 8.03 (dd, J = 7.9, 1.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 34.8, 38.0, 48.6, 82.6, 87.4, 93.3 106.4, 114.3, 117.6, 124.2, 126.7, 128.6 (2C), 128.8 (2C), 130.1, 130.8, 131.7, 132.2, 132.7, 133.6, 137.8, 148.2; HRMS calcd for $C_{23}H_{21}N_3NaO_4S^+$ $[M + Na]^+$: 458.1145, found 458.1143.

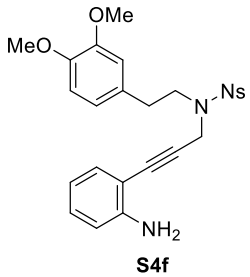
***N*-[3-(2-Aminophenyl)prop-2-yn-1-yl]-*N*-(3-methoxyphenethyl)-4-nitrobenzenesulfonamide (S4c)**



S4c

According to **GP3**, **S3c** (2.00 g, 5.34 mmol) was converted to **S4c** (589 mg, 22%) by the reaction with *o*-iodoaniline (3.51 g, 16.0 mmol) in the presence of $PdCl_2(PPh_3)_2$ (187 mg, 0.267 mmol) and CuI (50.1 mg, 0.267 mol) in DIPA (20 mL) and acetone (3 mL) at 60 °C for 0.5 + 1 h. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1 to 1/1): bright yellow oil; IR (neat) 3461 (N-H), 3388 (N-H), 2253 (C≡C), 1543 (N=O), 1358 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.95 (t, J = 7.7 Hz, 2H), 3.70 (t, J = 7.7 Hz, 2H), 3.76 (s, 3H), 4.10 (s, 2H), 4.43 (s, 2H), 6.58-6.66 (m, 2H), 6.71-6.77 (m, 2H), 6.80 (d, J = 7.4 Hz, 1H), 7.09-7.11 (m, 2H), 7.18 (dd, J = 7.4, 7.4 Hz, 1H), 7.56-7.64 (m, 3H), 799-8.03 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 34.8, 38.0, 48.5, 55.1, 82.6, 87.4, 106.3, 112.2, 114.3, 114.3, 117.6, 121.1, 124.1, 129.6, 130.1, 130.7, 131.7, 132.2, 132.6, 133.6, 139.4, 148.1, 148.3, 130.1; HRMS calcd for $C_{24}H_{23}N_3NaO_5S^+$ $[M + Na]^+$: 488.1251, found 488.1250.

***N*-[3-(2-Aminophenyl)prop-2-yn-1-yl]-*N*-(3,4-dimethoxyphenethyl)-2-nitrobenzenesulfonamide (S4f)**

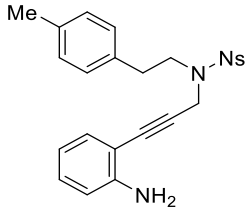


S4f

According to **GP3**, **S3f** (4.40 g, 12.8 mmol) was converted to **S4f** (525 mg, 32%) by the reaction with *o*-iodoaniline (1.48 g, 8.55 mmol) in the presence of $PdCl_2(PPh_3)_2$ (0.15 g, 0.21 mmol) and CuI (0.04 g, 0.21 mmol)

in DIPA (20 mL) and acetone (3 mL) at 60 °C for 0.5 + 1 h. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1 to 2/1): bright yellow oil; IR (neat) 3472 (N-H), 3378 (N-H), 2252 (C≡C), 1542 (N=O), 1355 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.92 (t, J = 7.5 Hz, 2H), 3.69 (t, J = 7.5 Hz, 2H), 3.81 (s, 3H), 3.83 (s, 3H), 4.12 (s, 2H), 4.42 (s, 2H), 6.56-6.64 (m, 2H), 6.72-6.75 (m, 3H), 7.06-7.11 (m, 2H), 7.56-7.62 (m, 3H), 7.98 (dd, J = 8.1, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 34.3, 38.0, 48.8, 55.8, 55.8, 82.6, 87.4, 106.3, 111.2, 111.9, 114.3, 117.6, 120.8, 124.1, 130.1, 130.3, 130.7, 131.6, 132.1, 132.6, 133.5, 147.7, 148.0, 148.2, 148.9; HRMS calcd for $C_{25}H_{25}N_3NaO_6S^+$ [M + Na]$^+$: 518.1356, found 518.1358.

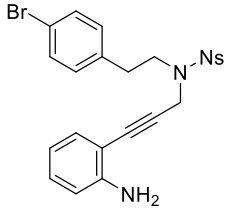
***N*-[3-(2-Aminophenyl)prop-2-yn-1-yl]-*N*-(4-methylphenethyl)-2-nitrobenzenesulfonamide (S4g)**



S4g

According to **GP3**, **S3g** (4.40 g, 12.8 mmol) was converted to **S4g** (512 mg, 36%) by the reaction with *o*-iodoaniline (1.40 g, 6.41 mmol) in the presence of $PdCl_2(PPh_3)_2$ (113 mg, 0.160 mmol) and CuI (30.5 mg, 0.160 mmol) in DIPA (20 mL) and acetone (3 mL) at 60 °C for 0.5 + 1 h. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1 to 3/1): bright yellow oil; IR (neat) 3482 (N-H), 3379 (N-H), 2253 (C≡C), 1543 (N=O), 1358 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.29 (s, 3H), 2.93 (t, J = 7.7 Hz, 2H), 3.67 (t, J = 7.7 Hz, 2H), 4.08 (s, 2H), 4.43 (s, 2H), 6.61-6.64 (m, 2H), 7.05-7.10 (m, 6H), 7.56-7.59 (m, 3H), 7.99 (d, J = 7.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.0. 37.9, 34.2, 48.6, 82.5, 87.4, 106.3, 114.2, 117.5, 124.1, 128.6 (2C), 129.2 (2C), 130.0, 130.6, 131.6, 132.1, 132.6, 133.5, 134.6, 136.1, 148.0, 148.2; HRMS calcd for $C_{24}H_{23}N_3NaO_4S^+$ [M + Na]$^+$: 472.1301, found 472.1301.

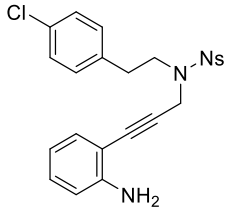
***N*-[3-(2-Aminophenyl)prop-2-yn-1-yl]-*N*-(4-bromophenethyl)-4-nitrobenzenesulfonamide (S4h)**



S4h

According to **GP3**, **S3h** (1.48 g, 3.50 mmol) was converted to **S4h** (464 mg, 28%) by the reaction with *o*-iodoaniline (2.30 g, 10.5 mmol) in the presence of $PdCl_2(PPh_3)_2$ (122 mg, 0.174 mmol) and CuI (33.0 mg, 0.174 mmol) in DIPA (20 mL) and acetone (3 mL) at 60 °C for 0.5 + 1 h. Purification was performed by silica gel column chromatography (hexane/EtOAc = 3/1): bright yellow oil; IR (neat) 3479 (N-H), 3382 (N-H), 2253 (C≡C), 1543 (N=O), 1358 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.92 (t, J = 7.4 Hz, 2H), 3.68 (t, J = 7.4 Hz, 2H), 4.11 (s, 2H), 4.43 (s, 2H), 6.59-6.66 (m, 2H), 7.03-7.14 (m, 4H), 7.33 (dt, J = 8.9, 2.2 Hz, 2H), 7.55-7.67 (m, 3H), 7.97 (dd, J = 8.0, 1.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 33.8, 37.8, 48.2, 82.6, 87.2, 106.1, 114.2, 117.5, 120.4, 124.1, 130.1, 130.5 (2C), 130.6, 131.5 (2C), 131.7, 132.1, 132.3, 133.6, 136.7, 147.8, 148.3; $C_{23}H_{20}BrKN_3O_4S^+$ [M + K]$^+$: 551.9989, found 551.9967.

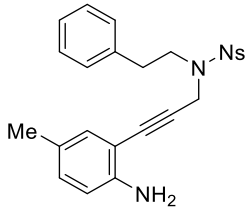
***N*-[3-(2-Aminophenyl)prop-2-yn-1-yl]-*N*-(4-chlorophenethyl)-2-nitrobenzenesulfonamide (S4i)**



S4i

According to **GP3**, **S3i** (1.05 g, 3.02 mmol) was converted to **S4i** (466 mg, 33%) by the reaction with *o*-iodoaniline (1.31 g, 6.04 mmol) in the presence of $PdCl_2(PPh_3)_2$ (106 mg, 0.151 mmol) and CuI (28.7mg, 0.151 mmol) in DIPA (20 mL) and acetone (3 mL) at 60 °C for 0.5 + 1 h. Purification was performed by silica gel column chromatography (hexane/EtOAc = 5/1): bright yellow oil; IR (neat) 3479 (N-H), 3382 (N-H), 2296 (C≡C), 1541 (N=O), 1360 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.94 (t, J = 7.5 Hz, 2H), 3.68 (t, J = 7.5 Hz, 2H), 4.10 (s, 2H), 4.43 (s, 2H), 6.60-6.65 (m, 2H), 7.05-7.22 (m, 6H), 7.59-7.64 (m, 3H), 7.99 (dd, J = 8.1, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 34.0, 38.0, 48.4, 82.7, 87.3, 106.4, 114.3, 117.6, 124.2, 128.7 (2C), 130.2, 130.2 (2C), 130.8, 131.7, 132.2, 132.5, 132.6, 133.6, 136.3, 148.0, 148.3; HRMS calcd for $C_{23}H_{20}ClN_3NaO_4S^+$ $[M + Na]^+$: 492.0755, found 492.0741.

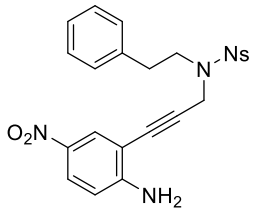
***N*-[3-(2-Amino-5-methylphenyl)prop-2-yn-1-yl]-2-nitro-*N*-phenethylbenzenesulfonamide (S4j)**



S4j

According to **GP3**, **S3j** (1.50 g, 4.36 mmol) was converted to **S4j** (873 mg, 46%) by the reaction with 2-iodo-4-methylaniline (2.03 g, 8.72 mmol) in the presence of $PdCl_2(PPh_3)_2$ (152.9 mg, 0.217 mmol) and CuI (41.5 mg, 0.217 mmol) in DIPA (20 mL) and acetone (3 mL) at 60 °C for 0.5 + 1 h. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1 to 2/1): bright yellow oil; IR (neat) 3425 (N-H), 3383 (N-H), 2297 (C≡C), 1541 (N=O), 1359 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.15 (s, 3H), 2.96 (t, J = 7.7 Hz, 2H), 3.69 (t, J = 7.7 Hz, 2H), 3.97 (br s, 2H), 4.41 (s, 2H), 6.53 (d, J = 8.1 Hz, 1H), 6.87-6.90 (m, 2H), 7.17-7.26 (m, 5H), 7.52-7.59 (m, 3H), 7.93-8.00 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.0, 34.6, 37.8, 48.4, 82.8, 86.9, 106.2, 114.4, 124.0, 126.57, 126.61, 128.5, 128.7 (2C), 130.5 (2C), 130.9, 131.7, 132.1, 132.4, 133.6, 137.7, 145.9, 147.9; HRMS calcd for $C_{24}H_{23}N_3NaO_4S^+$ $[M + Na]^+$: 472.1301, found 472.1306.

***N*-[3-(2-Amino-5-nitrophenyl)prop-2-yn-1-yl]-2-nitro-*N*-phenethylbenzenesulfonamide (S4m)**

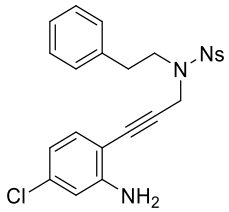


S4m

According to **GP3**, **S3m** (1.30 g, 3.79 mmol) was converted to **S4m** (1.36 g, 75%) by the reaction with 2-iodo-4-nitroaniline (2.00 g, 7.58 mmol) in the presence of $PdCl_2(PPh_3)_2$ (133 mg, 0.190 mmol) and CuI (36.1 mg, 0.190 mmol) in DIPA (20 mL) and acetone (3 mL) at 60 °C for 0.5 + 1 h. Purification was performed by silica gel column chromatography (hexane/EtOAc = 5/1 to 1/1): bright yellow oil; IR (neat) 3480 (N-H), 3379 (N-H), 2255 (C≡C),

1543 (N=O), 1543 (N=O), 1507 (N=O), 1319 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.97 (t, J = 7.6 Hz, 2H), 3.69 (t, J = 7.6 Hz, 2H), 4.40 (s, 2H), 4.99 (s, 2H), 6.62 (d, J = 8.9 Hz, 1H), 7.18-7.23 (m, 3H), 7.24-7.30 (m, 2H), 7.62-7.70 (m, 3H), 7.95-8.02 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 34.7, 37.7, 48.9, 79.9, 89.5, 105.4, 112.9, 124.3, 126.3, 126.8, 128.7 (2C), 128.7 (2C), 128.8, 130.9, 131.9, 132.3, 134.0, 137.6, 138.0, 148.0, 153.5; HRMS calcd for $C_{23}H_{20}N_4KO_6S^+$ $[M + K]^+$: 519.0735, found 519.0733.

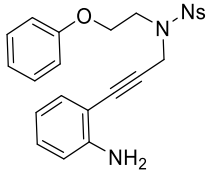
***N*-[3-(2-Amino-4-chlorophenyl)prop-2-yn-1-yl]-2-nitro-*N*-phenethylbenzenesulfonamide (S4o)**



S4o

According to **GP3**, **S3o** (1.70 g, 5.43 mmol) was converted to **S4o** (815 mg, 34%) by the reaction with 4-chloro-2-iodoaniline (2.75 g, 10.9 mmol) in the presence of $PdCl_2(PPh_3)_2$ (190 mg, 0.271 mmol) and CuI (51.7 mg, 0.271 mmol) in DIPA (25 mL) and acetone (3 mL) at 60 °C for 0.5 + 1 h. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1 to 1/1): colorless oil; IR (neat) 3498 (N-H), 3396 (N-H), 2253 (C≡C), 1542 (N=O), 1357 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.96 (t, J = 7.7 Hz, 2H), 3.72 (t, J = 7.7 Hz, 2H), 4.00 (s, 2H), 4.42 (s, 2H), 6.40 (dd, J = 8.4, 2.3 Hz, 1H), 6.57 (d, J = 2.3 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 7.15-7.127 (m, 5H), 7.48-7.56 (m, 3H), 7.95-8.01 (m, 1H); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 34.6, 38.0, 48.4, 83.7, 84.3, 110.3, 113.1, 114.7, 124.1, 126.7, 128.7 (2C), 128.9 (2C), 130.4, 131.9, 132.5, 133.7, 134.3, 136.7, 137.9, 148.2, 148.5; HRMS calcd for $C_{23}H_{20}ClN_3KO_4S^+$ $[M + K]^+$: 508.0495, found 508.0481.

***N*-[3-(2-Aminophenyl)prop-2-yn-1-yl]-2-nitro-*N*-(2-phenoxyethyl)benzenesulfonamide (S4q)**

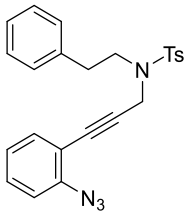


S4q

According to **GP3**, **S3q** (1.60 g, 4.44 mmol) was converted to **S4q** (1.25 g, 63%) by the reaction with *o*-iodoaniline (2.92 g, 13.3 mmol) in the presence of $PdCl_2(PPh_3)_2$ (156 mg, 0.222 mmol and CuI (42.3 mg, 0.222 mmol) in DIPA (30 mL) and acetone (4 mL) at 60 °C for 0.5 + 1 h. Purification was performed by silica gel column chromatography (hexane/EtOAc = 5/1 to 2/1): bright yellow oil; IR (neat) 3487 (N-H), 3387 (N-H), 2253 (C≡C), 1543 (N=O), 1356 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.89 (t, J = 5.2 Hz, 2H), 4.10 (s, 2H), 4.21 (t, J = 5.2 Hz, 2H), 4.62 (s, 2H), 6.57-6.61 (m, 2H), 6.83 (d, J = 6.9 Hz, 2H), 6.93-6.97 (m, 2H), 7.02 (dd, J = 7.5, 1.3 Hz, 2H), 7.06-7.10 (m, 1H), 7.23-7.27 (m, 2H), 7.57-7.62 (m, 2H), 8.09-8.11 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 39.3, 46.3, 66.8, 82.6, 87.6, 106.2, 114.2, 114.3 (2C), 117.4, 121.2, 124.1, 129.5 (2C), 130.0, 130.8, 131.7, 132.1, 132.6, 133.7, 148.0, 148.3, 157.9; HRMS calcd for $C_{23}H_{21}N_3NaO_5S^+$ $[M + Na]^+$: 474.1094, found 474.1095.

Preparation of Azido-ynes (1)

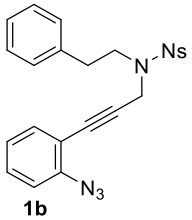
***N*-[3-(2-Azidophenyl)prop-2-yn-1-yl]-4-methyl-*N*-phenethylbenzenesulfonamide (1a)**



1a

According to **GP4**, **S1a** (395 mg, 0.98 mmol) was converted to **1a** (290 mg, 91%) by the reaction with *t*-BuONO (0.198 mL, 1.46 mmol) and $TMSN_3$ (0.222 mL, 1.46 mmol) in MeCN (20 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 2/1): bright yellow oil; IR (neat): 2238 (C≡C), 2128 (N-N), 1540 (N=O), 1346 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.29 (s, 3H), 2.95-2.98 (m, 2H), 3.50-3.54 (m, 2H), 4.38 (s, 2H), 7.01 (d, J = 4.2 Hz, 2H), 7.04 (dd, J = 8.3 Hz, 1H), 7.16-7.34 (m, 8H), 7.74 (d, J = 8.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.4, 34.8, 37.7, 48.1, 81.4, 87.7, 114.1, 118.4, 124.4, 126.5, 127.7 (2C), 128.6 (2C), 128.8 (2C), 129.4 (2C), 129.7, 133.4, 135.7, 138.2, 141.0, 143.4; HRMS calcd for $C_{24}H_{22}KN_4O_2S^+$ $[M + K]^+$: 469.1095, found 469.1095.

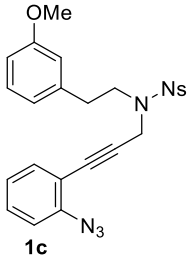
***N*-[3-(2-Azidophenyl)prop-2-yn-1-yl]-2-nitro-*N*-phenethylbenzenesulfonamide (1b)**



1b

According to **GP4**, **S4b** (2.40 g, 5.51 mmol) was converted to **1b** (2.10 g, 82%) by the reaction with *t*-BuONO (1.32 mL, 11.0 mmol) and $TMSN_3$ (1.46 mL, 11.0 mmol) in MeCN (120 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 2/1): yellow oil; IR (neat) 2254 (C≡C), 2128 (N-N), 1543 (N=O), 1363 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.01 (t, J = 7.8 Hz, 2H), 3.74 (t, J = 7.8 Hz, 2H), 4.47 (s, 2H), 7.01-7.09 (m, 2H), 7.20-7.31 (m, 6H), 7.34 (dd, J = 7.9, 7.9 Hz, 1H), 7.62 (m, 3H), 8.06 (d, J = 6.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 34.5, 37.8, 48.4, 81.5, 87.8, 113.9, 118.4, 124.0, 124.5, 126.6, 128.5 (3C), 128.7 (2C), 129.9, 130.6, 131.6, 132.6, 133.5, 137.8, 141.1, 148.2; HRMS calcd for $C_{23}H_{19}N_5NaO_4S^+$ $[M + Na]^+$: 484.1050, found 484.1050.

***N*-[3-(2-Azidophenyl)prop-2-yn-1-yl]-*N*-(3-methoxyphenethyl)-2-nitrobenzenesulfonamide (1c)**

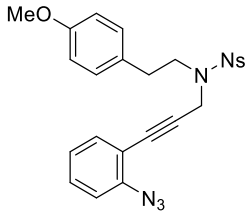


1c

According to **GP4**, **S4c** (500 mg, 1.00 mmol) was converted to **1c** (0.50 g, 84%) by the reaction with *t*BuONO (0.238 mL, 2.00 mmol) and $TMSN_3$ (0.265 mL, 2.00 mmol) in MeCN (50 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 2/1): bright yellow oil; IR (neat) 2242 (C≡C), 2128 (N-N), 1540 (N=O), 1354 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.98 (t, J = 7.8 Hz, 2H), 3.73 (t, J = 7.8 Hz, 2H), 3.78 (s, 3H), 4.47 (s, 2H), 6.75 (dd, J = 8.2, 2.3 Hz, 1H), 6.80 (s, 1H), 6.85 (d, J = 7.8 Hz, 1H), 7.06-7.09 (m, 2H), 7.19 (t, J = 7.8 Hz, 1H), 7.23-7.26 (m, 1H), 7.33-7.36 (m, 1H), 7.58-7.63 (m, 3H), 8.04-8.06 (m,

1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 34.7, 37.8, 48.4, 55.2, 81.6, 88.0, 112.1, 114.0, 114.5, 118.5, 121.2, 124.1, 124.6, 129.6, 130.0, 130.8, 131.6, 132.8, 133.4, 133.6, 139.5, 141.3, 148.3, 159.7; HRMS calcd for $C_{24}H_{21}N_5NaO_4S^+$ $[M + Na]^+$: 514.1156, found 514.1170.

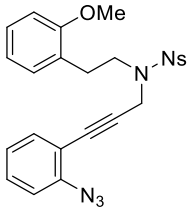
***N*-[3-(2-Azidophenyl)prop-2-yn-1-yl]-*N*-(4-methoxyphenethyl)-2-nitrobenzenesulfonamide (1d)**



1d

According to **GP3**, **S3d** (4.40 g, 12.8 mmol) was converted to **S4d** (containing some impurities) by the reaction with *o*-iodoaniline (1.87 g, 8.55 mmol) in the presence of $PdCl_2(PPh_3)_2$ (0.15 g, 0.21 mmol) and CuI (0.04 g, 0.21 mmol) in DIPA (20 mL) and acetone (3 mL) at 60 °C for 0.5 + 1 h. Column chromatography was performed using silica gel (hexane/EtOAc = 2/1). According to **GP4**, this crude **S4d** was converted to **1d** (0.35 g, 17%, 2 steps) by the reaction with *t*-BuONO (0.224 mL, 1.88 mmol) and $TMSN_3$ (0.249 mL, 1.88 mmol) in MeCN (10 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 5/1): bright yellow oil. IR (neat) 2242 (C≡C), 2128 (N-N), 1541 (N=O), 1353 (S=O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.93 (t, J = 7.7 Hz, 2H), 3.70 (t, J = 7.7 Hz, 2H), 3.77 (s, 3H), 4.45 (s, 2H), 6.80 (d, J = 8.6 Hz, 2H), 7.02-7.10 (m, 2H), 7.15 (d, J = 8.6 Hz, 2H), 7.23 (dd, J = 7.7, 1.4 Hz, 1H), 7.33 (ddd, J = 7.7, 7.7, 1.5 Hz, 1H), 7.64-7.56 (m, 3H), 8.02-8.04 (dd, J = 6.6, 2.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 34.7, 37.8, 48.4, 55.2, 81.6, 88.0, 112.1, 114.0, 114.5, 118.5, 121.2, 124.1, 124.6, 129.6, 130.0, 130.8, 131.6, 132.8, 133.4, 133.6, 139.5, 141.3, 148.3, 159.7; HRMS calcd for $C_{24}H_{21}N_5NaO_4S^+$ $[M + Na]^+$: 514.1156, found 514.1170.

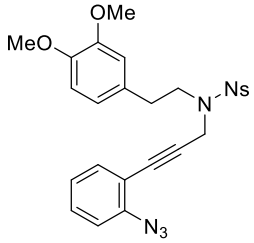
***N*-[3-(2-Azidophenyl)prop-2-yn-1-yl]-*N*-(2-methoxyphenethyl)-2-nitrobenzenesulfonamide (1e)**



1e

According to **GP3**, **S3e** (1.00 g, 2.67 mmol) was converted to **S4e** (containing some impurities) by the reaction with *o*-iodoaniline (1.75 g, 8.01 mmol) in the presence of $PdCl_2(PPh_3)_2$ (58.7 mg, 0.133 mmol) and CuI (25.4 mg, 0.133 mmol) in DIPA (20 mL) and acetone (3 mL) at 60 °C for 0.5 + 1 h. Column chromatography was performed using silica gel (hexane/EtOAc = 2/1). According to **GP4**, this crude **S4e** was converted to **1e** (225 mg, 21%, 2 steps) by the reaction with *t*-BuONO (0.280 mL, 2.36 mmol) and $TMSN_3$ (0.313 mL, 2.36 mmol) in MeCN (10 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 5/1): bright yellow oil; IR (neat) 2254 (C≡C), 2129 (N-N), 1543 (N=O), 1360 (S=O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.98 (t, J = 7.5 Hz, 2H), 3.74 (t, J = 7.5 Hz, 2H), 3.79 (s, 3H), 4.51 (s, 2H), 6.80 (d, J = 8.2 Hz, 1H), 6.85 (dd, J = 7.9, 6.9 Hz, 1H), 7.05-7.10 (m, 2H), 7.12-7.22 (m, 2H), 7.24 (dd, J = 7.7, 1.5 Hz, 1H), 7.35 (ddd, J = 8.5, 7.1, 1.1 Hz, 1H), 7.59 (m, 3H), 8.04-8.06 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 29.6, 37.8, 47.0, 55.3, 81.3, 88.6, 110.3, 114.4, 118.7, 120.7, 124.3, 124.7, 126.3, 128.2, 130.0, 130.8, 131.0, 131.6, 133.3, 133.4, 133.8, 141.3, 148.5, 157.7; HRMS calcd for $C_{24}H_{21}KN_5O_4S^+$ $[M + K]^+$: 530.0895, found 530.0898.

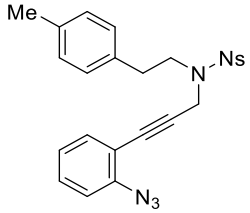
***N*-[3-(2-Azidophenyl)prop-2-yn-1-yl]-*N*-(3,4-dimethoxyphenethyl)-2-nitrobenzenesulfonamide (1f)**



1f

According to **GP4**, **S4f** (577 mg, 1.16 mmol) was converted to **1f** (580 mg, 93%) by the reaction with *t*-BuONO (0.277 mL, 2.32 mmol) followed by $TMSN_3$ (0.309 mL, 2.33 mmol) in MeCN (20 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 2/1): bright yellow oil; IR (neat) 3046 (C-H), 2954 (C-H), 2254 (C≡C), 2129 (N-N), 1542 (N=O), 1354 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.92 (t, J = 7.6 Hz, 2H), 3.71 (t, J = 7.6 Hz, 2H), 3.80 (s, 3H), 3.82 (s, 3H), 4.43 (s, 2H), 6.73-6.74 (m, 3H), 7.01-7.06 (m, 2H), 7.20 (d, J = 7.7 Hz, 1H), 7.31 (dd, J = 7.7, 7.7 Hz, 1H), 7.54-7.62 (m, 3H), 8.00 (d, J = 7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 34.2, 38.0, 48.6, 55.7, 55.8, 81.5, 88.0, 111.2, 111.9, 113.9, 118.5, 120.7, 123.0, 124.0, 124.6, 130.3, 130.6, 131.5, 132.7, 133.4, 141.2, 147.6, 148.2, 148.8; HRMS calcd for $C_{24}H_{23}KN_5O_4S^+$ [M + Na]$^+$: 544.1258, found 544.1261.

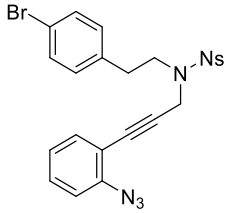
***N*-[3-(2-Azidophenyl)prop-2-yn-1-yl]-*N*-(4-methylphenethyl)-2-nitrobenzenesulfonamide (1g)**



1g

According to **GP4**, **S4g** (85.0 mg, 0.189 mmol) was converted to **1g** (76.0 mg, 85%) by the reaction with *t*-BuONO (26.9 μL, 0.226 mmol) followed by $TMSN_3$ (30.0 μL, 0.226 mmol) in MeCN (5 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 2/1): bright yellow oil; IR (neat): 2253 (C≡C), 2129 (N-N), 1543 (N=O), 1357 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.30 (s, 3H), 2.95 (t, J = 7.8 Hz, 2H), 3.71 (t, J = 7.8 Hz, 2H), 4.46 (s, 2H), 7.02-7.13 (m, 6H), 7.22-7.24 (m, 1H), 7.31-7.35 (m, 1H), 7.55-7.65 (m, 3H), 8.02-8.04 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.9, 34.1, 37.8, 48.5, 81.5, 87.9, 114.0, 118.4, 124.0, 124.5, 128.6 (2C), 129.2 (2C), 129.9, 130.7, 131.5, 132.7, 133.3, 133.5, 134.7, 136.1, 141.2, 148.2; HRMS calcd for $C_{24}H_{21}N_5NaO_4S^+$ [M + Na]$^+$: 498.1206, found 498.1207.

***N*-[3-(2-Azidophenyl)prop-2-yn-1-yl]-*N*-(4-bromophenethyl)-2-nitrobenzenesulfonamide (1h)**

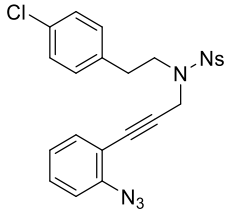


1h

According to **GP4**, **S4h** (460 mg, 0.894 mmol) was converted to **1h** (464 mg, 96%) by the reaction with *t*-BuONO (0.234 mL, 1.79 mmol) and $TMSN_3$ (0.268 mL, 1.79 mmol) in MeCN (20 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 5/1): bright yellow oil; IR

(neat): 2253 (C≡C), 2129 (N-N), 1545 (N=O), 1362 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.95 (t, J = 7.6 Hz, 2H), 3.73 (t, J = 7.6 Hz, 2H), 4.46 (s, 2H), 7.07 (m, 4H), 7.23-7.26 (m, 1H), 7.32-7.36 (m, 3H), 7.57-7.67 (m, 3H), 8.00-8.02 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 34.1, 38.1, 48.4, 81.8, 88.0, 114.1, 118.7 (2C), 120.7, 124.3, 124.8, 130.2, 130.7 (2C), 130.9, 131.8 (2C), 132.9, 133.6, 133.7, 137.0, 141.4, 148.3; HRMS calcd for $C_{23}H_{18}BrKN_5O_4S^+$ $[M + K]^+$: 577.9894, found 577.9918.

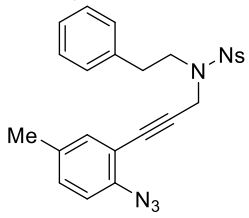
***N*-[3-(2-Azidophenyl)prop-2-yn-1-yl]-*N*-(4-chlorophenethyl)-4-nitrobenzenesulfonamide (1i)**



1i

According to **GP4**, **S4i** (200 mg, 0.426 mmol) was converted to **1i** (180 mg, 93%) by the reaction with *t*-BuONO (0.101 mL, 0.852 mmol) and $TMSN_3$ (0.113 mL, 0.852 mmol) in MeCN (20 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 2/1): bright yellow oil; IR (neat): 2253 (C≡C), 2129 (N-N), 1543 (N=O), 1359 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.97 (t, J = 7.6 Hz, 2H), 3.73 (t, J = 7.6 Hz, 2H), 4.46 (s, 2H), 7.03-7.10 (m, 2H), 7.14-7.26 (m, 4H), 7.32-7.36 (m, 1H), 7.57-7.66 (m, 4H), 8.00-8.03 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 33.9, 38.0, 48.3, 81.7, 87.8, 114.0, 118.5, 124.1, 124.6, 128.7 (2C), 130.0, 130.2 (2C), 130.8, 131.6, 132.5, 132.7, 133.5, 133.6, 136.4, 141.3, 148.2; HRMS calcd for $C_{23}H_{18}ClKN_5O_4S^+$ $[M + K]^+$: 534.0400, found 531.0405.

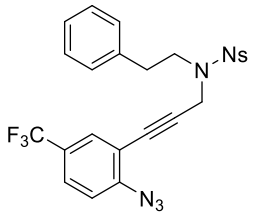
***N*-[3-(2-Azido-5-methylphenyl)prop-2-yn-1-yl]-2-nitro-*N*-phenethylbenzenesulfonamide (1j)**



1j

According to **GP4**, **S4j** (440 mg, 0.98 mmol) was converted to **1j** (441 mg, 95%) by the reaction with *t*-BuONO (0.142 mL, 1.20 mmol) followed by $TMSN_3$ (0.159 mL, 1.20 mmol) in MeCN (20 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 5/1): bright yellow oil; IR (neat): 2252 (C≡C), 2121 (N-N), 1542 (N=O), 1357 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.25 (s, 3H), 2.99 (t, J = 7.8 Hz, 2H), 3.74 (t, J = 7.8 Hz, 2H), 4.45 (s, 2H), 6.95 (d, J = 8.2 Hz, 1H), 7.03 (s, 1H), 7.12 (d, J = 8.2 Hz, 1H), 7.17-7.22 (m, 5H), 7.56-7.64 (m, 3H), 8.01-8.04 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.4, 34.5, 37.8, 48.4, 81.8, 87.4, 113.6, 118.2, 124.0, 126.6, 128.5 (2C), 128.7 (2C), 130.6, 130.8, 131.5, 132.6, 133.4, 133.8, 134.4, 137.8, 138.4, 148.2; HRMS calcd for $C_{24}H_{21}KN_5O_4S^+$ $[M + K]^+$: 514.0946, found 514.0944.

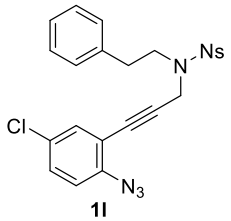
***N*-{3-[2-Azido-5-(trifluoromethyl)phenyl]prop-2-yn-1-yl}-2-nitro-*N*-phenethylbenzenesulfonamide (1k)**



1k

According to **GP3**, **S3k** (1.00 g, 2.90 mmol) was converted to **S4k** (containing some impurities) by the reaction with 2-iodo-4-trifluoromethylaniline (1.67 g, 5.81 mmol) in the presence of $PdCl_2(PPh_3)_2$ (102 mg, 0.145 mmol) and CuI (27.7 mg, 0.145 mmol) in DIPA (20 mL) and acetone (3 mL) at 60 °C for 0.5 + 1 h. Column chromatography was performed using silica gel (hexane/EtOAc = 4/1). According to **GP4**, this crude **S4k** was converted to **1k** (380 mg, 25%, 2 steps) by the reaction with *t*-BuONO (0.189 mL, 1.59 mmol) and $TMSN_3$ (0.211 mL, 1.59 mmol) in MeCN (10 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 3/1): bright yellow oil; IR (neat): 2255 (C≡C), 2120 (N-N), 1546 (N=O), 1361 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.99 (t, J = 7.7 Hz, 2H), 3.74 (t, J = 7.7 Hz, 2H), 4.46 (s, 2H), 7.22 (m, 6H), 7.40 (s, 1H), 7.54 (d, J = 8.5 Hz, 1H), 7.62 (m, 3H), 8.02-8.04 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 34.6, 37.8, 48.6, 80.0, 89.7, 114.5, 121.9, 123.3 (q, J = 272.1 Hz), 124.1, 126.6 (q, J = 7.3 Hz), 127.0, 127.3 (q, J = 4.3 Hz), 128.6 (2C), 128.7 (2C), 130.7 (q, J = 7.3 Hz), 130.8, 131.6, 132.7, 133.6, 137.7, 144.7, 148.2; HRMS calcd for $C_{24}H_{18}F_3KN_5O_4S^+$ [M + K]$^+$: 568.0663, found 568.0663.

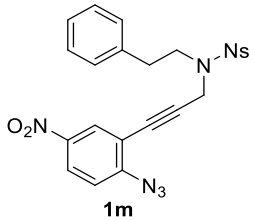
***N*-[3-(2-Azido-5-chlorophenyl)prop-2-yn-1-yl]-2-nitro-*N*-phenethylbenzenesulfonamide (1l)**



1l

According to **GP3**, **S3l** (1.00 g, 2.90 mmol) was converted to **S4l** (containing some impurities) by the reaction with 4-chloro-2-iodoaniline (1.47 g, 5.81 mmol) in the presence of $PdCl_2(PPh_3)_2$ (102 mg, 0.145 mmol) and CuI (27.7 mg, 0.145 mmol) in DIPA (20 mL) and acetone (3 mL) at 60 °C for 0.5 + 1 h. Column chromatography was performed using silica gel (hexane/EtOAc = 5/1). According to **GP4**, this crude **S4l** was converted to **1l** (380 mg, 26%, 2 steps) by the reaction with *t*-BuONO (0.152 mL, 1.28 mmol) and $TMSN_3$ (0.170 mL, 1.28 mmol) in MeCN (10 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 3/1): bright yellow oil; IR (neat): 2253 (C≡C), 2113 (N-N), 1545 (N=O), 1362 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.99 (t, J = 7.8 Hz, 2H), 3.73 (t, J = 7.8 Hz, 2H), 4.45 (s, 2H), 6.98 (d, J = 8.7 Hz, 1H), 7.15 (d, J = 2.7 Hz, 1H), 7.21-7.30 (m, 6H), 7.60-7.66 (m, 3H), 8.04 (dd, J = 7.8, 1.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 34.6, 37.8, 48.6, 80.2, 89.3, 115.4, 119.7, 124.2, 126.7, 128.7 (2C), 128.8 (2C), 129.7, 130.0, 130.8, 131.6, 132.8, 133.1, 133.5, 137.8, 139.9, 148.2; HRMS calcd for $C_{23}H_{18}ClN_5NaO_4S^+$ [M + Na]$^+$: 518.0660, found 518.0669.

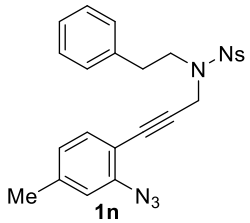
***N*-[3-(2-Azido-5-nitrophenyl)prop-2-yn-1-yl]-2-nitro-*N*-phenethylbenzenesulfonamide (1m)**



1m

According to **GP4**, **S4m** (1.00 g, 2.22 mmol) was converted to **1m** (900 mg, 85%) by the reaction with *t*-BuONO (0.529 mL, 4.45 mmol) and $TMSN_3$ (0.591 mL, 4.45 mmol) in MeCN (50 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 1/1): bright yellow oil; IR (neat): 2245 (C≡C), 2125 (N-N), 1542 (N=O), 1520 (N=O), 1343 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.98 (t, J = 7.8 Hz, 2H), 3.72 (t, J = 7.8 Hz, 2H), 4.45 (s, 2H), 7.17-7.30 (m, 6H), 7.64-7.70 (m, 3H), 7.98 (s, 1H), 8.03 (d, J = 8.0 Hz, 1H), 8.16 (dd, J = 8.9, 2.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 34.6, 37.7, 48.7, 79.2, 90.7, 114.9, 118.9, 124.3, 125.0, 126.8, 128.7 (2C), 128.8 (2C), 129.0, 130.9, 131.7, 132.7, 133.8, 137.7, 143.9, 147.6, 148.2; HRMS calcd for $C_{23}H_{18}KN_6O_6S^+$ $[M + K]^+$: 545.0640, found 545.0640.

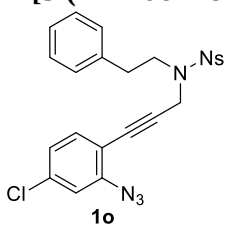
***N*-[3-(2-Azido-4-methylphenyl)prop-2-yn-1-yl]-2-nitro-*N*-phenethylbenzenesulfonamide (1n)**



1n

According to **GP3**, **S3n** (1.50 g, 4.36 mmol) was converted to **S4n** (containing some impurities) by the reaction with 2-iodo-5-methylaniline (2.03 g, 8.71 mmol) in the presence of $PdCl_2(PPh_3)_2$ (153 mg, 0.217 mmol) and CuI (41.5 mg, 0.217 mmol) in DIPA (20 mL) and acetone (3 mL) at 60 °C for 0.5 + 1 h. Column chromatography was performed using silica gel (hexane/EtOAc = 10/1 to 5/1). According to **GP4**, this crude **S4n** was converted to **1n** (763 mg, 36%, 2 steps) by the reaction with *t*-BuONO (0.460 mL, 3.87 mmol) and $TMSN_3$ (0.514 mL, 3.87 mmol) in MeCN (10 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 3/1): bright yellow oil; IR (neat): 2251 (C≡C), 2109 (N-N), 1542 (N=O), 1520 (N=O), 1357 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.33 (s, 3H), 2.99 (t, J = 7.8 Hz, 2H), 3.73 (t, J = 7.8 Hz, 2H), 4.45 (s, 2H), 6.84-6.87 (m, 2H), 7.10 (d, J = 7.8 Hz, 1H), 7.19-7.28 (m, 5H), 7.55-7.61 (m, 3H), 8.03 (dd, J = 7.7, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.5, 34.7, 38.0, 48.5, 81.8, 87.1, 111.0, 119.1, 124.1, 125.7, 126.7, 128.6 (2C), 128.8 (2C), 130.7, 131.6, 132.7, 133.3, 133.5, 137.9, 140.8, 141.0, 148.3; HRMS calcd for $C_{24}H_{21}KN_5O_4S^+$ $[M + K]^+$: 545.0640, found 545.0640.

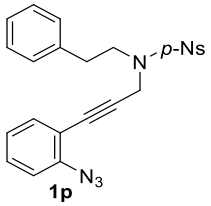
***N*-[3-(2-Azido-4-chlorophenyl)prop-2-yn-1-yl]-2-nitro-*N*-phenethylbenzenesulfonamide (1o)**



1o

According to **GP4**, **S4o** (818 mg, 1.74 mmol) was converted to **1o** (810 mg, 94%) by the reaction with *t*-BuONO (0.249 mL, 2.09 mmol) and $TMSN_3$ (0.277 mL, 2.09 mmol) in MeCN (50 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 2/1): colorless oil; IR (neat): 2221 (C≡C), 2112 (N-N), 1540 (N=O), 1352 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.98 (t, J = 7.7 Hz, 2H), 3.73 (t, J = 7.7 Hz, 2H), 4.45 (s, 2H), 6.84 (dd, J = 8.6, 2.3 Hz, 1H), 6.99 (d, J = 2.3 Hz, 2H), 7.16-7.28 (m, 5H), 7.55-7.63 (m, 3H), 8.00 (dd, J = 7.2, 1.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 34.6, 37.8, 48.5, 82.0, 87.6, 117.4, 118.3, 119.7, 124.2, 126.7, 128.6 (2C), 128.8 (2C), 130.6, 131.7, 132.6, 133.6, 134.4, 137.1, 137.8, 141.5, 148.2; HRMS calcd for $C_{23}H_{18}ClKN_5O_4S^+$ $[M + K]^+$: 534.0400, found 534.0395.

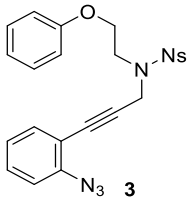
***N*-[3-(2-Azidophenyl)prop-2-yn-1-yl]-4-nitro-*N*-phenethylbenzenesulfonamide (1p)**



1p

According to **GP3**, **S3p** (1.66 g, 4.82 mmol) was converted to **S4p** (containing some impurities) by the reaction with *o*-iodoaniline (1.58 g, 7.23 mmol) in the presence of $PdCl_2(PPh_3)_2$ (167mg, 241 μmol) and CuI (45.9 mg, 241 μmol) in DIPA (20 mL) and acetone (3 mL) at 60 °C for 0.5 + 1 h. Column chromatography was performed using silica gel (hexane/EtOAc = 4/1). According to **GP4**, this crude **S4p** was converted to **1p** (605 mg, 29%, 2 steps) by the reaction with *t*-BuONO (1.15 mL, 9.64 mmol) and $TMSN_3$ (1.28 mL, 9.64 mmol) in MeCN (10 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 5/1): bright yellow oil; IR (neat): 2221 (C≡C), 2112 (N-N), 1540 (N=O), 1352 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.99 (t, J = 7.7 Hz, 2H), 3.57 (t, J = 7.7 Hz, 2H), 4.40 (s, 2H), 7.04-7.97 (m, 3H), 7.21-7.32 (m, 6H), 8.01 (dd, J = 6.9, 1.8 Hz, 2H), 8.17 (dd, J = 6.9, 1.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 34.5, 37.7, 48.1, 81.9, 86.7, 113.3, 118.4, 123.8 (2C), 124.5, 126.7, 128.6 (2C), 128.7 (2C), 128.8 (2C), 130.1, 133.0, 137.6, 140.9, 144.4, 149.7; HRMS calcd for $C_{23}H_{18}ClKN_5O_4S^+$ $[M + K]^+$: 534.0400, found 534.0396.

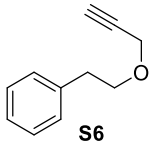
***N*-[3-(2-Azidophenyl)prop-2-yn-1-yl]-4-nitro-*N*-(2-phenoxyethyl)benzenesulfonamide (1s)**



3

According to **GP4**, **S4q** (1.60 g, 3.54 mmol) was converted to **3** (1.55 g, 92%) by the reaction with *t*-BuONO (0.53 mL, 3.90 mmol) and $TMSN_3$ (0.54 mL, 3.90 mmol) in MeCN (50 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 2/1): bright yellow oil; IR (neat): 2254 (C≡C), 2129 (N-N), 1544 (N=O), 1360 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.93 (t, J = 5.3 Hz, 2H), 4.24 (t, J = 5.3 Hz, 2H), 4.65 (s, 2H), 6.83 (dd, J = 8.7, 1.0 Hz, 2H), 6.94 (dd, J = 7.2, 3.6 Hz, 1H), 7.01-7.06 (m, 2H), 7.18 (dd, J = 7.7, 1.5 Hz, 1H), 7.23-7.27 (m, 2H), 7.30-7.33 (m, 1H), 7.60-7.65 (m, 3H), 8.13-8.15 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 39.3, 46.4, 66.7, 81.5, 88.2, 113.9, 114.3 (2C), 118.4, 121.1, 124.1, 124.5, 129.4 (2C), 129.9, 131.0, 131.7, 132.8, 133.5, 133.5, 141.1, 148.2, 158.0; HRMS calcd for $C_{23}H_{19}KN_5O_5S^+$ $[M + K]^+$: 516.0738, found 516.0748.

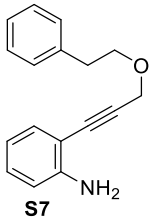
[2-(Prop-2-yn-1-yloxy)ethyl]benzene (S6)



S6

To a solution of 2-phenylethan-1-ol (2.00 g, 16.4 mmol) in anhydrous THF (50 mL) was added NaH (471 mg, 19.7 mmol) in one portion at 0 °C. The resulting mixture was stirred for 30 min. Propargyl bromide (1.23 mL, 16.4 mmol) was then added dropwise. The reaction was monitored by TLC. Upon completion, the reaction was quenched with water and extracted with ethyl ether. The combined organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc = 10/1) to afford the desired alkyne **S6** (1.37 g, 52%). The spectral data were in good agreement with those previously reported.[25]

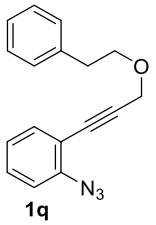
2-(3-Phenethoxyprop-1-yn-1-yl)aniline (S7)



S7

According to **GP3**, **S6** (810 mg, 2.58 mmol) was converted to **S7** (867 mg, 40%) by the reaction with *o*-iodoaniline (1.13 g, 5.17 mmol) in the presence of $PdCl_2(PPh_3)_2$ (90.7 mg, 0.129 mmol) and CuI (24.6 mg, 0.129 mmol) in DIPA (20 mL) and acetone (3 mL) at 60 °C for 0.5 + 1 h. Purification was performed by silica gel column chromatography (hexane/EtOAc = 20/1 to 10/1): colorless oil; IR (neat) 3474 (N-H), 3371 (N-H), 2220 (C≡C); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.95 (t, J = 7.1 Hz, 2H), 3.82 (t, J = 7.1 Hz, 2H), 4.16 (s, 2H), 4.44 (s, 2H), 6.66-6.69 (m, 2H), 7.12 (dd, J = 7.9, 4.0 Hz, 1H), 7.20-7.22 (m, 1H), 7.22-7.28 (m, 3H), 7.29-7.31 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 36.1, 58.8, 70.6, 82.6, 90.3, 107.0, 114.2, 117.6, 126.1, 128.2 (2C), 128.7 (2C), 129.6, 132.2, 138.4, 147. 1.4; HRMS calcd for $C_{17}H_{17}NNaO^+$ $[M + Na]^+$: 274.1202, found 274.1202

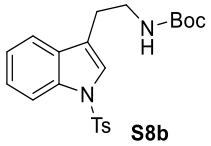
1-Azido-2-(3-phenethoxyprop-1-yn-1-yl)benzene (1r)



1q

According to **GP4**, **S4r** (667 mg, 2.65 mmol) was converted to **1r** (690 mg, 94%) by the reaction with *t*-BuONO (0.631 mL, 5.31 mmol) and $TMSN_3$ (0.704 mL, 5.31 mmol) in MeCN (20 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 20/1): bright yellow oil; IR (neat): 2224 (C≡C), 2129 (N-N); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.97 (t, J = 7.2 Hz, 2H), 3.85 (t, J = 7.2 Hz, 2H), 4.43 (s, 2H), 7.03-7.07 (m, 2H), 7.19-7.20 (m, 1H), 7.24-7.31 (m, 5H), 7.42 (dd, J = 7.7, 1.4 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 36.1, 58.9, 70.9, 81.9, 91.2, 114.7, 118.6, 124.6, 126.3, 128.4 (2C), 128.9 (2C), 129.7, 133.9, 138.7,141.2; HRMS calcd for $C_{17}H_{15}NaNO$ $[M + Na]^+$: 300.1107, found 300.1106.

***tert*-Butyl [2-(1-Tosyl-1*H*-indol-3-yl)ethyl]carbamate (S8b)**

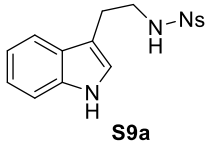


S8b

To a yellow suspension of tryptamine **S8a** (2.00 g, 12.5 mmol) in 1,4-dioxane (10 mL) was added Et_3N (3.60 mL, 25.8 mmol). A solution of $(Boc)_2O$ (3.00 g, 13.8 mmol) in 1,4-dioxane (10 mL) then was cannulated into the reaction mixture. This mixture was stirred for 1 h and the resulting yellow solution was concentrated to dryness under reduced pressure. The crude residue was purified by flash chromatography on silica gel (hexane/ether = 1/2) to give the desired *N*-Boc derivative as an amorphous white solid (1.62 g, quantitative yield). The spectral data were in good agreement with those previously reported.[26] To a stirred solution of the Boc derivative (2.40 g, 9.22 mmol) in CH_2Cl_2 (30 mL) were sequentially added Bu_4NHSO_4 (176 mg mg, 0.1 mmol) and NaOH (830 mg g, 20.74 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 5 min before addition of TsCl (3.44 g, 10.1 mmol) dissolved in CH_2Cl_2 (5 mL). The reaction mixture was allowed to be stirred at room temperature for 5 h. Water was added, and the mixture was extracted with EtOAc (10 mL × 3). The combined organic phases were washed with

brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexane = 1/5) to give **S8b** as a yellow oil. The spectral data were in good agreement with those previously reported.[27]

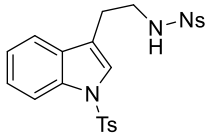
***N*-[2-(1*H*-indol-3-yl)ethyl]-2-nitrobenzenesulfonamide (S9a)**



S9a

According to **GP1**, **S8a** (5.00 g, 31.2 mmol) was converted to **S9a** (9.78 g, 90%) by the reaction with NsCl (6.57 g, 29.7 mmol) and Et_3N (8.70 mL, 62.4 mmol) in DCM (100 mL) at 0 °C for 1 h and room temperature for 12 h. Purification was performed by flash column chromatography on silica gel (hexane/Et_2O = 1/1) to afford **S9a** as a brown powder. The spectral data were in good agreement with those previously reported.[28]

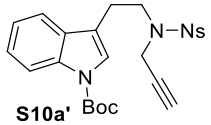
2-Nitro-*N*-[2-(1-tosyl-1*H*-indol-3-yl)ethyl]benzenesulfonamide (S9b)



S9b

To a solution of **S8b** (2.10 g, 5.07 mmol) in 1,4-dioxane (22 mL) was added a 4 M HCl dioxane solution (18 mL) at 0 °C, and the mixture was stirred for 30 min and allowed to warm to room temperature. After 2 h, the solution was concentrated in vacuo and the resulting suspension was dissolved in DCM (20 mL) and cooled to 0 °C. After addition of Et_3N (1.41 mL, 10.1 mmol), a solution of NsCl (1.07 g, 4.81 mmol) in DCM (5 mL) was added dropwise to the solution and allowed to warm to room temperature. The reaction was stirred for 12 h and concentrated in vacuo. The purification was performed by silica gel column chromatography (hexane/EtOAc = 4/1) to give **S9b** (1.70 g, 67%) as an off-white solid; mp 103 °C; IR (neat): 3356 (N-H), 1540 (N=O), 1363 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.32 (s, 3H), 2.91 (t, J = 6.4 Hz, 2H), 3.48 (td, J = 6.4, 5.9 Hz, 2H), 5.40 (t, J = 5.9 Hz, 1H), 7.16-7.22 (m, 3H), 7.26-7.31 (m, 2H), 7.36 (d, J = 6.4 Hz, 1H), 7.58 (ddd, J = 7.7, 7.7, 1.3 Hz, 1H), 7.66 (ddd, J = 7.7, 7.7, 1.3 Hz, 1H), 7.73 (dd, J = 6.7, 1.8 Hz, 2H), 7.77 (dd, J = 7.7, 1.3 Hz, 1H), 7.90 (d, J = 8.3 Hz, 1H), 7.94 (dd, J = 7.7, 1.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 21.5, 25.6, 43.0, 113.7, 118.1, 119.0, 123.1, 123.9, 124.8, 125.4, 126.7, 129.9 (2C), 130.0, 130.4, 132.2, 132.7, 133.5 (2C), 134.9, 135.1, 145.1, 147.6; $C_{23}H_{21}KN_3O_6S_2^+$ $[M + K]^+$: 522.0764, found 522.0767.

***tert*-Butyl 3-(2-{[2-Nitro-*N*-(prop-2-yn-1-yl)phenyl]sulfonamido}ethyl)-1*H*-indole-1-carboxylate (S10a')**

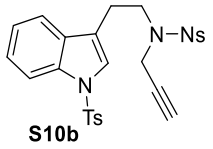


S10a'

According to **GP2**, **S9a** (3.00 g, 8.69 mmol) was suspended with K_2CO_3 (1.80 g, 13.0 mmol) in acetone (50 mL). Propargyl bromide (0.79 mL, 10.4 mmol) was added dropwise to the mixture at 50 °C and stirred for 3 h. After completion monitored by TLC the reaction was quenched with water and extracted with EtOAc. After concentration *in vacuo* the residue was dissolved in THF (20 mL) with 4-(*N*,*N*-dimethylamino)pyridine (53.7 mg, 0.44 mmol), Boc_2O (4.54 g, 20.8 mmol) was added in one portion to the mixture at ambient temperature. After the mixture was stirred for 1 h, 20 mL water was added and extracted with EtOAc three times. Subsequently washed with brine and dried with Na_2SO_4. The product was purified with silica gel column chromatography (hexane/EtOAc = 2/1) to give **S10a'** (3.44 g, 82%) as a yellow oil; IR (neat) 3476 (≡C-H), 2253(C≡C), 1546 (N=O), 1370 (S=O);

^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.66 (s, 9H), 2.28 (t, J = 2.3 Hz, 1H), 3.01 (t, J = 7.2 Hz, 2H), 3.74 (t, J = 7.2 Hz, 2H), 4.32 (d, J = 2.3 Hz, 2H), 7.23 (dd, J = 7.7, 7.7 Hz, 1H), 7.27-7.32 (m, 1H), 7.35-7.43 (m, 2H), 7.50 (d, J = 7.7 Hz, 1H), 7.54-7.59 (m, 2H), 7.84 (d, J = 8.1 Hz, 1H), 8.05 (d J = 8.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 23.6, 27.4, 28.2 (3C), 36.6, 46.4, 74.1, 77.1, 115.4, 116.2, 118.7, 122.6, 123.3, 124.1, 124.4, 129.8, 130.6, 131.5, 132.7, 133.5, 146.7, 147.6, 149.5; HRMS calcd for $C_{24}H_{25}N_3NaO_6S^+$ [M + Na]$^+$: 506.1356, found 506.1354.

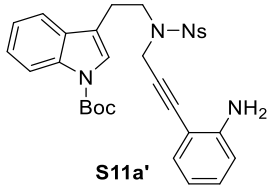
2-Nitro-*N*-(prop-2-yn-1-yl)-*N*-[2-(1-tosyl-1*H*-indol-3-yl)ethyl]benzenesulfonamide (S10b)



S10b

According to **GP2**, **S9b** (1.70 g, 3.40 mmol) was converted to **S10b** (1.40 g, 76%) by the reaction with propargyl bromide (0.31 mL, 4.08 mmol) and K_2CO_3 (704 mg, 5.10 mmol) in acetone (25 mL) at 50 °C for 2 h: colorless oil; IR (neat) 3290 (≡C-H), 2253 (C≡C), 1547 (N-O), 1372 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.25 (t, J = 2.3 Hz, 1H), 2.31 (s, 3H), 3.00 (t, J = 7.2 Hz, 2H), 3.71 (t, J = 7.2 Hz, 2H), 4.21 (d, J = 2.3 Hz, 2H), 7.19-7.24 (m, 3H), 7.30 (dd, J = 7.7, 3.9 Hz, 1H), 7.39 (s, 1H), 7.46-7.52 (m, 2H), 7.55-7.66 (m, 2H), 7.73 (d, J = 8.0 Hz, 2H), 7.86 (dd, J = 8.0, 1.0 Hz, 1H), 7.92 (d, J = 8.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.5, 23.7, 36.7, 46.3, 74.1, 76.8, 113.7, 118.3, 119.1, 123.2, 123.7, 124.3, 124.7, 126.7 (2C), 129.8 (2C), 130.3, 130.3, 131.6, 132.4, 133.7, 135.0, 135.0, 144.9, 147.8; HRMS calcd for $C_{26}H_{23}N_3NaO_6S_2^+$ [M + Na]$^+$: 560.0920, found 560.0916.

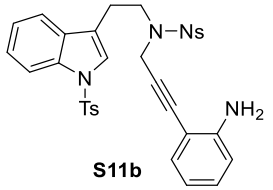
***tert*-Butyl 3-[2-({*N*-[3-(2-Aminophenyl)prop-2-yn-1-yl]-2-nitrophenyl}sulfonamido)ethyl]-1*H*-indole-1-carboxylate (S11a')**



S11a'

According to **GP3**, *o*-iodoaniline (217 mg, 0.99 mmol) was suspended together with $PdCl_2(PPh_3)_2$ (7.69 mg, 0.025 mmol) and CuI (4.75 mg, 0.025 mmol) in DIPA (10 mL) at 60 °C for 30 min under argon atmosphere. Subsequently a solution of **S10a'** (240 mg, 0.49 mmol) in DIPA (2mL) was added dropwise. After 1 h, the reaction was quenched with water and extracted with EtOAc. After concentration in *vacuo*, the product was purified by silica gel column chromatography (hexane/EtOAc = 2/1 to 1/1) to give **S11a'** (128.3 mg, 45%) as a yellow oil; IR (neat) 3383 (N-H), 2254 (C≡C), 1730 (C=O), 1541 (N=O), 1370 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.64 (s, 9H), 3.06 (t, J = 7.2 Hz, 2H), 3.78 (t, J = 7.2 Hz, 2H), 4.13 (s, 2H), 4.56 (s, 2H), 6.60-6.67 (m, 2H), 7.09-7.15 (m, 2H), 7.17-7.21 (m, 1H), 7.27-7.32 (m, 1H), 7.39-7.42 (m, 2H), 7.49-7.56 (m, 3H), 7.89 (d, J = 7.4 Hz, 1H), 8.06-8.07 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 23.9, 28.1 (3C), 37.7, 46.6, 82.7, 83.6, 87.5, 106.4, 114.7, 115.3, 116.3, 117.6, 118.6, 122.6, 123.7, 124.0, 124.4, 129.9, 130.1, 130.6, 131.5, 132.3, 132.6, 133.4, 138.9, 147.7, 148.3, 149.5; HRMS calcd for $C_{30}H_{30}N_4NaO_6S^+$ [M + Na]$^+$: 597.1778, found 597.1770.

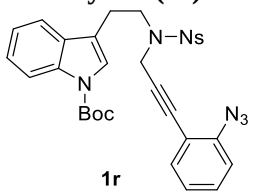
***N*-[3-(2-Aminophenyl)prop-2-yn-1-yl]-2-nitro-*N*-[2-(1-tosyl-1*H*-indol-3-yl)ethyl]benzenesulfonamide (S11b)**



S11b

According to **GP3**, *o*-iodoaniline (1.26 g, 5.75 mmol) was suspended together with $PdCl_2(PPh_3)_2$ (86.3 mg, 0.11 mmol) and CuI (23.4 mg, 0.11 mmol) in DIPA (20 mL) at 60 °C for 30 min under argon atmosphere. Subsequently a solution of **S10b** (1.20 g, 2.23 mmol) in DIPA (5 mL) was added dropwise. After 1 h, the reaction was quenched with water and extracted with EtOAc. After concentration in *vacuo*, the product was purified by silica gel column chromatography (hexane/EtOAc = 2/1 to 1/1) to give **S11b** (751 mg, 53%) as a yellow oil; IR (neat) 3378 (N-H), 2253 (C≡C), 1543 (N=O), 1370 (S=O); ^{1}H-NMR ($CDCl_3$) δ: 2.31 (s, 3H), 3.05 (t, J = 7.2 Hz, 2H), 3.76 (t, J = 7.2 Hz, 2H), 4.12 (s, 2H), 4.46 (s, 2H), 6.60-6.67 (m, 2H), 7.06-7.14 (m, 2H), 7.15-7.23 (m, 3H), 7.29 (dd, J = 7.7, 3.9 Hz, 1H), 7.40 (s, 1H), 7.46-7.50 (m, 2H), 7.59 (d, J = 4.6 Hz, 2H), 7.72 (d, J = 8.0 Hz, 2H), 7.92 (dd J = 7.7, 2.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.5, 24.0, 37.9, 36.6, 46.6, 82.7, 87.5, 103.2, 106.3, 113.7, 114.3, 117.6, 118.5, 119.2, 123.9, 124.3, 124.8, 126.8 (2C), 129.9 (2C), 130.2, 130.3, 130.5, 131.6, 132.3, 132.5, 133.7, 135.0, 135.1, 144.9, 148.4; HRMS calcd for $C_{32}H_{28}N_4NaO_6S^+$ [M + Na]$^+$: 651.1342, found 651.1342.

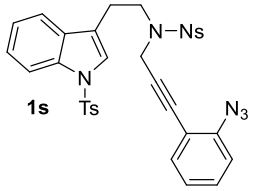
***tert*-Butyl 3-[2-({*N*-[3-(2-Azidophenyl)prop-2-yn-1-yl]-2-nitrophenyl}sulfonamido)ethyl]-1*H*-indole-1-carboxylate (1r)**



1r

According to **GP4**, **S11a** (200 mg, 0.35 mmol) was converted to **1r** (160 mg, 76%) by the reaction with *t*-BuONO (83.3 μL, 0.70 mmol) and $TMSN_3$ (92.9 μL, 0.70 mmol) in MeCN (20 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 2/1): bright yellow oil; IR (neat) 2254 (C≡C), 2128 (N-N), 1542 (N=O), 1362 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$): IR (neat) 2129 (N-N), 1729 (C=O), 1543 (N-O), 1369 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$): 1.88 (s, 9H), 3.32 (t, J = 7.4 Hz, 2H), 4.06 (t, J = 7.4 Hz, 2H), 4.83 (s, 2H), 7.29 (ddd, J = 7.6, 7.6, 1.1 Hz, 1H), 7.32 (d, J = 8.2 Hz, 1H), 7.39-7.42 (m, 1H), 7.49-7.58 (m, 3H), 7.65-7.69 (m, 2H), 7.76-7.80 (m, 3H), 8.16 (d, J = 7.8 Hz, 1H), 8.25-8.36 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 23.8, 28.2 (3C), 37.7, 46.7, 81.7, 83.6, 88.1, 114.1, 115.3, 116.4, 118.5, 118.7, 122.6, 123.7, 124.1, 124.4, 124.6, 129.9, 130.0, 130.7, 131.5, 132.9, 133.3, 133.7, 135.4, 141.4, 148.0, 149.7; HRMS calcd for $C_{30}H_{28}N_6NaO_6S^+$ [M + Na]$^+$: 623.1683, found 623.1671.

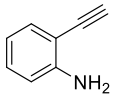
***N*-[3-(2-Azidophenyl)prop-2-yn-1-yl]-2-nitro-*N*-[2-(1-tosyl-1*H*-indol-3-yl)ethyl]benzenesulfonamide (1s)**



1s

According to **GP4**, **S11b** (705 mg, 1.12 mmol) was converted to **1s** (720 mg, 98%) by the reaction with *t*-BuONO (0.266 mL, 2.24 mmol) and $TMSN_3$ (0.295 mL, 2.24 mmol) in MeCN (15 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 2/1): bright yellow oil; IR (neat) 2254 (C≡C), 2128 (N-N), 1542 (N=O), 1362 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$): 2.33 (s, 3H), 3.08 (t, J = 7.2 Hz, 2H), 3.80 (t, J = 7.2 Hz, 2H), 4.49 (s, 2H), 7.05-7.07 (m, 1H), 7.08 (d, J = 7.4 Hz, 1H), 7.15-7.21 (m, 3H), 7.28 (dd, J = 7.2, 7.2 Hz, 1H), 7.23 (dd, J = 7.7, 1.4 Hz, 1H), 7.32-7.35 (m, 1H), 7.42 (s, 1H), 7.48-7.52 (m, 2H), 7.57-7.60 (m, 2H), 7.73 (d, J = 8.0 Hz, 2H), 7.90-7.97 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.8, 23.9, 38.0, 46.7, 81.7, 88.0, 113.7, 113.9, 118.5, 118.6, 119.3, 123.2, 123.8, 124.3, 124.6, 124.8, 126.8 (2C), 129.9 (2C), 130.1, 130.4, 130.6, 131.5, 132.7, 133.5, 133.7, 135.1, 135.2, 141.4, 144.9, 148.1; HRMS calcd for $C_{32}H_{26}N_6NaO_6S_2^+$ [M + Na]$^+$: 677.1247, found 677.1243.

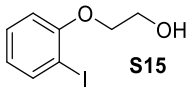
2-Ethynylaniline (S14)



S14

According to **GP3**, **S13** (2.00 g, 9.13 mmol) was converted to **S14** (470 mg, 44%) by the reaction with TMS-Acetylene (1.35 g, 13.7 mmol) in the presence of $PdCl_2(PPh_3)_2$ (320 mg, 0.46 mmol) and CuI (87.0 mg, 0.456 mmol) in DIPA (20 mL) at 60 °C for 3 h. The crude was concentrated and diluted with methanol (10 mL). To this solution, KF (1.06 g, 18.26 mmol) was added and the suspension was stirred at room temperature overnight. Purification was performed by silica gel column chromatography (hexane/EtOAc = 5/95) as to give **S14** ethynylaniline derivative. The spectral data were in good agreement with those previously reporteded.[29]

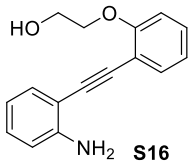
2-(2-Iodophenoxy)ethan-1-ol (S15)



S15

To **S13** (5.00 g, 22.7 mmol**)** dissolved in DMF (20 mL) were added Cs_2CO_3 (11.1 g, 34.09 mol) and stirred at room temperature for 30 min. Subsequently, bromoethylalcohol (1.93 mL, 27.5 mmol) was added dropwise and the reaction was heated to 90 ºC, overnight. The reaction was cooled to room temperature and water was added. Extraction was performed ethyl acetate (20 mL x 2). The organic layers were combined and washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo. Purification was performed by silica gel column chromatography (hexane/EtOAc = 5/1) as to give **S15** (2.80 g, 47%). The spectral data were in good agreement with those reported.[30]

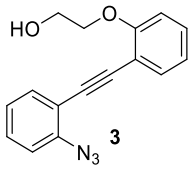
2-{2-[(2-Aminophenyl)ethynyl]phenoxy}ethan-1-ol (S16)



S16

According to **GP3**, **S15** (1.35 g, 5.12 mmol) was converted to **S16** (300 mg, 46%) by the reaction with **S14** (300 mg, 2.56 mmol) in the presence of $PdCl_2(PPh_3)_2$ (89.9 mg, 0.128 mmol) and CuI (24.3 mg, 0.128 mmol) in DIPA (25 mL) for 1 h. Purification was performed by silica gel column chromatography (hexane/EtOAc = 5/1 to 2/1) as to give pure **S16**. IR (neat) 3474, 3370 (N-H) 2220 (C≡C), 2128 (N-N); ^{1}H NMR (600 MHz, $CDCl_3$): 2.96 (s, 1H), 3.98 (m, 2H), 4.16 (t, *J* = 4.4 Hz, 2H), 4.52 (br s, 2H), 6.75 (m, 2H), 6.91 (d, *J* = 8.1 Hz, 1H), 6.98 (dd, *J* = 7.6, 3.8 Hz, 1H), 7.14 (dd, *J* = 7.8, 3.8 Hz, 1H), 7.28-7.31 (m, 1H), 7.35 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.48 (dd, *J* = 7.6, 1.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 61.3, 70.3, 90.9, 91.6, 108.8, 111.9, 113.2, 114.7, 118.4, 121.1, 129.6 (2C), 131.0, 132.1, 148.0, 158.9.; HRMS calcd for $C_{16}H_{15}N_1NaO_2^+$ $[M + Na]^+$: 276.0995, found 276.0993

2-{2-[(2-Azidophenyl)ethynyl]phenoxy}ethan-1-ol (3)



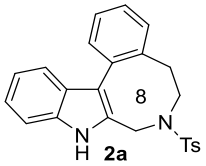
3

According to **GP4**, **S16** (300 mg, 1.18 mmol) was converted to **3** (170 mg, 52%) by the reaction with *t*-BuONO (0.128 mL, 2.36 mmol) and $TMSN_3$ (0.313 mL, 2.36 mmol) in MeCN (20 mL) at 0 °C then allowed to warm to

room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 2/1): bright yellow oil;. IR (neat) 2252 (C≡C), 2126 (N-N), ; ^{1}H NMR (600 MHz, $CDCl_3$): 2.95 (s, 1H), 4.01 (s, 2H), 4.18 (t, *J* = 4.5 Hz, 2H), 6.91 (d, *J* = 8.3 Hz, 1H), 6.98 (dd, *J* = 7.9, 7.1 Hz, 1H), 7.11-7.16 (m, 2H), 7.28-7.37 (m, 2H), 7.51 (d, *J* = 7.7 Hz, 2H);^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 61.3, 70.2, 89.4, 91.3, 112.5, 112.9, 115.5, 118.5, 121.2, 124.7, 129.5, 130.1, 133.1, 133.4, 140.8, 159.1.; HRMS calcd for $C_{16}H_{13}N_3NaO_2^+$ [M + Na]$^+$: 302.0900, found 302.0894

3. Gold-Catalyzed Cyclization

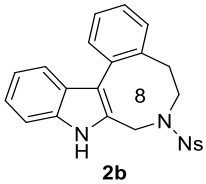
7-Tosyl-6,7,8,9-tetrahydro-5*H*-benzo[5,6]azocino[3,4-*b*]indole (2a)



2a

According to **GP5**, azido-yne **1a** (150 mg, 348 µmol) was converted to **2a** (86.8 mg, 62%) by the reaction with (*t*Bu)$_3$PAuCl (7.57 mg, 17.4 µmol) and $AgSbF_6$ (11.2 mg, 34.8 µmol) in DCM (180 mL) at room temperature for 6 h. Purification was performed by silica gel column chromatography (hexane/Et_2O = 10/1 to 3/1): off-white solid; mp 205-207 °C; IR (neat): 3402 (N-H), 1336 (S=O); ^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 2.37 (s, 3H), 2.54 (dd, *J* = 14.3, 10.3 Hz, 1H), 2.89-3.05 (m, 2H), 3.55 (d, *J* = 16.0 Hz, 1H), 4.08 (dd, *J* = 14.3, 6.3 Hz, 1H), 4.86 (dd, *J* = 16.0 Hz, 1H), 7.14-7.18 (m, 1H), 7.23-7.35 (m, 7H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.59 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 2H), 8.63 (br s, 1H); ^{13}C-NMR, 125 MHz, $CDCl_3$) *δ*: 21.5, 35.1, 44.1, 49.3, 111.4, 115.4, 119.5, 120.3, 122.8, 126.5, 126.8, 126.9, 127.3, 129.8, 130.2 (2C), 130.6, 131.4, 133.7, 135.7, 136.7, 139.5, 143.4 (2C); HR-MS $C_{24}H_{22}KN_2O_2S^+$ [M + K$^+$] calcd for 441.1034, found 441.1035.

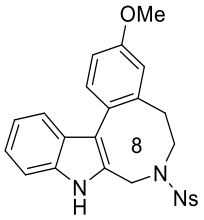
7-[(2-Nitrophenyl)sulfonyl]-6,7,8,9-tetrahydro-5*H*-benzo[5,6]azocino[3,4-*b*]indole (2b)



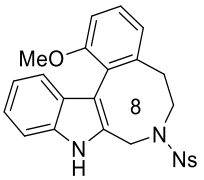
2b

According to **GP5**, azido-yne **1b** (44.0 mg, 95.3 µmol) was converted to **2b** (29.5 mg, 71%) by the reaction with (*t*Bu)$_3$PAuCl (2.07 mg, 4.77 µmol) and $AgSbF_6$ (3.28 mg, 9.53 µmol) in DCM (48 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1 to 2/1): off-white powder; mp 201-203 °C; IR (neat): 3391 (NH), 1543 (N=O), 1344 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 2.69 (dd, *J* = 14.3, 10.3 Hz, 1H), 3.06 (dd, *J* = 14.3, 10.3 Hz, 1H), 3.11 (dd, *J* = 14.3, 10.3 Hz, 1H), 3.70 (d, *J* = 16.0 Hz, 1H), 4.08 (dd, *J* = 14.3, 10.3 Hz, 1H), 4.91 (d, *J* = 16.0 Hz, 1H), 7.16, (dd, *J* = 7.5, 7.5 Hz, 1H), 7.24-7.38 (m, 4H), 7.45 (d, *J* = 8.6 Hz, 1H), 7.53-7.75 (m, 5H), 8.00 (d, *J* = 7.5 Hz, 1H), 8.63 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 35.5, 44.3, 49.5, 111.5, 115.7, 119.5, 120.2, 122.9, 125.0, 126.7, 127.4, 130.1, 130.5, 130.6 (2C), 131.0, 132.0, 133.4, 133.6 (2C), 135.7, 139.3, 147.8; HRMS calcd for $C_{23}H_{19}KN_3O_4^+$ [M + K]$^+$: 472.0728, found 472.0733.

3-Methoxy-7-[(4-nitrophenyl)sulfonyl]-6,7,8,9-tetrahydro-5*H*-benzo[5,6]azocino[3,4-*b*]indole (2c) and Its 1-Methoxy-Isomer (2c')



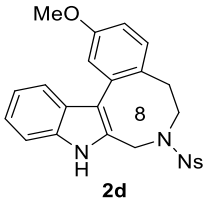
2c



2c`

According to **GP5**, azido-yne **1c** (50.0 mg, 102 μmol) was converted to an inseparable mixture of regioisomers **2c** and **2c'** (3:1, 28.5 mg, 60%) by the reaction with (tBu)$_3$PAuCl (3.50 mg, 5.09 μmol) and $AgSbF_6$ (3.50 mg, 10.2 μmol) in DCM (508 mL) at room temperature overnight. Purification was performed by silica gel column chromatography (hexane/Et_2O = 10/1 to 2/1): yellow oil; IR (neat) 3410 (N-H), 3390 (N-H), 1540 (N=O), 1340 (S=O); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.50 (dd, J = 15.0, 10.5 Hz, 0.25H), 2.65 (dd, J = 14.4, 9.9 Hz, 0.75H), 2.96-3.02 (m, 1.25H), 3.10 (dd, J = 11.0, 7.1 Hz, 0.75H), 3.66 (d, J = 14.7 Hz, 0.25H), 3.74 (d, J = 15.8 Hz, 0.75H), 3.79 (s, 0.75H), 3.85 (s, 2.25H), 4.02-4.13 (m, 1H), 4.84-4.95 (m, 1H), 6.83 (d, J = 2.3 Hz, 0.75H), 6.88 (d, J = 7.7 Hz, 0.25H), 6.90-6.93 (m, 1H), 7.10 (dd, J = 7.7, 7.7 Hz, 0.25H), 7.13 (dd, J = 7.7, 7.7 Hz, 0.75H), 7.21-7.25 (m, 1H), 7.32 (dd, J = 7.7, 7.7 Hz, 0.25H), 7.39-7.43 (m, 1H), 7.51 (d, J = 8.3 Hz, 0.75H), 7.58-7.70 (m, 4H), 7.97 (d, J = 7.6 Hz, 0.75H), 8.0 (J = 7.8 Hz, 0.25H), 8.63 (br s, 0.75H), 8.72 (br s, 0.25H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 35.4, 35.7, 43.8, 44.2, 49.2, 49.4, 55.2, 55.4, 108.8, 111.6 (2C), 112.5, 112.6, 115.4, 115.7, 119.6, 119.8, 120.2, 121.7, 122.5, 122.6 (2C), 122.9, 124.4 (2C), 126.2, 127.0 (2C), 128.8, 130.6, 130.7, 130.9, 131.3, 131.5, 132.0 (2C), 133.4, 133.5, 133.7, 133.8, 135.8, 140.8, 142.1, 147.9 (2C), 158.0, 158.0, 159.0; HRMS calcd for $C_{24}H_{21}KN_3O_5S^+$ [M + K]$^+$: 502.0833, found 502.0832.

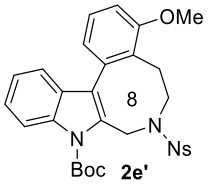
2-Methoxy-7-[(2-nitrophenyl)sulfonyl]-6,7,8,9-tetrahydro-5*H*-benzo[5,6]azocino[3,4-*b*]indole (2d)



2d

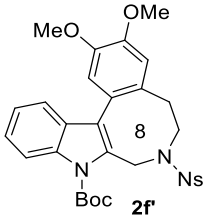
According to **GP5**, azido-yne **1d** (50.0 mg, 101 μmol) was converted to **2d** (35.0 mg, 74%) by the reaction with (tBu)$_3$PAuCl (2.21 mg, 5.09 μmol) and $AgSbF_6$ (3.50 mg, 10.2 μmol) in DCM (100 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/Et_2O = 3/1): an off-white solid; mp 128-130 °C; IR (neat) 3418 (N-H), 1607 (C=C), 1536 (N=O), 1322 (S=O); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.62 (dd, J = 14.8, 9.9 Hz, 1H), 3.00 (dd, J = 14.8, 6.7 Hz, 1H), 3.09 (dd, J = 13.9, 9.9 Hz, 1H), 3.82 (d, J = 16.0 Hz, 1H), 3.84 (s, 3H), 4.03 (dd, J = 13.9, 6.7 Hz, 1H), 4.90 (d, J = 16.0 Hz, 1H), 6.88 (dd, J = 8.6, 2.9 Hz, 1H), 7.12 (d, J = 2.9 Hz, 1H), 7.16 (ddd, J = 7.5, 7.5, 1.2 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.25-7.29 (m, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.61-7.73 (m, 4H), 7.98 (dd, J = 7.5, 1.7 Hz, 1H), 8.63 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 34.6, 44.3, 49.9, 55.4, 111.5, 113.7, 114.5, 115.7, 119.4, 120.3, 122.9, 124.2, 126.6, 130.6, 131.1, 131.6, 131.8, 133.5, 133.6 (2C), 134.8, 135.7, 147.6, 158.1; HRMS calcd for $C_{24}H_{21}N_3NaO_5S^+$ [M + Na]$^+$: 486.1094, found 486.1096.

***tert*-Butyl 4-Methoxy-7-[(4-nitrophenyl)sulfonyl]-5,6,7,8-tetrahydro-9*H*-benzo[5,6]azocino[3,4-*b*]indole-9-carboxylate (2e')**



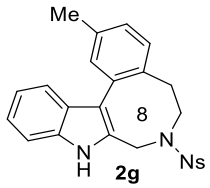
According to **GP5**, azido-yne **1e** (50.0 mg, 102 µmol) was converted to the corresponding cyclization product by the reaction with (tBu)$_3$PAuCl (2.21 mg, 5.09 µmol) and $AgSbF_6$ (3.50 mg, 10.2 µmol) in DCM (102 mL) at room temperature for 1 h. After the crude product was dissolved in DCM, Boc_2O (44.0 mg, 203 µmol) and DMAP (1.24 mg, 10.2 µmol) were added, and the reaction mixture was stirred for 5 min. After concentration *in vacuo*, silica gel column chromatography (hexane/Et_2O = 2/1) was performed to give **2e'** (31.0 mg, 54%, 2 steps) as an off-white solid mp 83-85 °C; IR (neat) 3418 (N-H), 1607 (C=C), 1536 (N-O), 1322 (S=O), 1252 (C-O); ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.70 (s, 9H), 2.72 (ddd, J = 13.8, 13.8, 4.6 Hz, 1H), 3.34 (ddd, J = 13.8, 4.6, 1.7 Hz, 1H), 3.52 (ddd, J = 13.8, 4.6 1.7 Hz, 1H), 3.87 (m, 4H), 4.77 (d, J = 18.9 Hz, 1H), 5.38 (d, J = 18.9 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 7.00 (dd, J = 8.0 Hz, 1H), 7.18 (dd, J = 7.7, 3.9 Hz, 1H), 7.22 (dd, J = 7.7, 3.9 Hz, 1H), 7.29 (dd, J = 7.7, 3.9 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.50-7.57 (m, 2H), 7.60 (ddd, J = 8.0, 8.0, 1.1 Hz, 1H), 7.74 (dd, J = 8.0, 1.1 Hz, 1H), 8.08 (d, J = 8.6 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 25.7, 28.3 (3C), 31.6, 49.0, 51.0, 55.6, 84.8, 109.1, 115.3, 119.1, 122.7, 122.8, 124.0, 124.4, 125.2, 127.0, 129.8, 130.6, 131.7, 132.4, 132.9, 133.6, 134.3, 135.9, 147.6, 150.8, 157.0; HR-MS calcd for $C_{29}H_{29}N_3NaO_7S^+$ [M + Na^+] 586.1618, found 586.1616.

tert-Butyl 2,3-Dimethoxy-7-[(4-nitrophenyl)sulfonyl]-5,6,7,8-tetrahydro-9*H*-benzo[5,6]azocino[3,4-*b*]indole-9-carboxylate (2f')



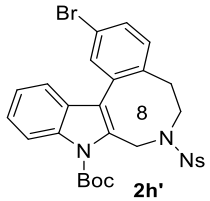
According to **GP5**, azido-yne **1f** (40.0 mg, 76.7 µmol) was converted to the corresponding cyclization product by the reaction with (tBu)$_3$PAuCl (1.67 mg, 3.83 µmol) and $AgSbF_6$ (2.64 mg, 7.64 µmol) in DCM (766 mL) at room temperature for 30 min. After the crude product was dissolved in DCM, Boc_2O (33.5 mg, 153 µmol) and DMAP (1.00 mg, 7.67 µmol) were added, and the reaction mixture was stirred for 5 min. After concentration in vacuo, silica gel column chromatography (hexane/Et_2O = 1/1) was performed to give **2f** (26.8 mg, 59%, 2 steps) as a yellow oil; IR (neat) 1730 (C=O), 1615 (C=C), 1542 (N-O), 1350 (S=O); ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.72 (s, 9H), 2.74 (dd, J = 13.7, 3.7 Hz, 1H), 2.95-3.02 (m, 1H), 3.63-3.68 (m, 1H), 3.79 (s, 3H), 3.83-3.95 (m, 4H), 4.81 (d, J = 19.5 Hz, 1H), 5.49 (d, J = 19.5 Hz, 1H), 6.70 (s, 1H), 6.76 (s, 1H), 7.18 (dd, J = 7.8, 4.0 Hz, 1H), 7.29 (dd, J = 7.8, 4.0 Hz, 1H), 7.41 (d, J = 8.3 Hz, 1H), 7.49 (td, J = 7.9, 4.0 Hz, 2H), 7.58 (ddd, J = 7.7, 7.7, 1.8 Hz, 1H), 7.66 (dd, J = 8.5, 1.3 Hz, 1H), 8.10 (d, J = 8.5 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 28.3 (3C), 32.9, 48.8, 52.5, 55.8, 55.9, 84.8, 111.8, 113.0, 115.5, 118.6, 119.5, 122.9, 123.7, 124.4, 125.1, 128.9, 129.9, 130.8, 131.4, 132.2, 132.9, 133.5, 135.9, 147.0, 147.6, 148.2, 150.8; HR-MS calcd for $C_{30}H_{31}N_3KO_8S^+$ [M+K^+] 632.1463, 632.1467 found

2-Methyl-7-((2-nitrophenyl)sulfonyl)-6,7,8,9-tetrahydro-5*H*-benzo[5,6]azocino[3,4-b]indole (2g)



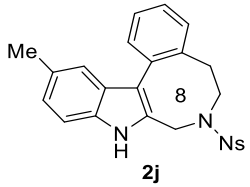
According to **GP5**, azido-yne **1g** (77.0 mg, 162 µmol) was converted to the corresponding cyclization product by the reaction with (tBu)$_3$PAuCl (3.52 mg, 8.10 µmol) and $AgSbF_6$ (5.60 mg, 16.2 µmol) in DCM (81 mL) at room temperature for 30 min.. After concentration in vacuo, silica gel column chromatography (hexane/Et_2O = 3/2) was performed to give **2g** (46.4 mg, 64%) as an off-white solid; mp 232-234 °C; IR (neat): 1729 (C=O), 1607 (C=C), 1542 (N-O); ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.71 (s, 9H), 2.33 (s, 3H), 2.79 (ddd, J = 13.6, 4.8, 1.5 Hz, 1H), 3.00 (ddd, J = 13.6, 13.6, 4.8 Hz, 1H), 3.64 (ddd, J = 13.6, 4.8, 1.5 Hz, 1H), 3.85 (ddd, J = 13.6, 13.6, 4.8 Hz, 1H), 4.78 (d, J = 19.3 Hz, 1H), 5.42 (d, J = 19.3 Hz, 1H), 7.05-7.06 (m, 1H), 7.13-7.20 (m, 3H), 7.29 (dd, J = 7.6, 7.6 Hz, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.49-7.52 (m, 2H), 7.59 (ddd, J = 7.6, 7.6, 1.4 Hz, 1H), 7.67 (dd, J = 8.3, 1.0 Hz, 1H), 8.10 (d, J = 8.3 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 21.3 (3C), 28.3, 32.8, 48.9, 52.8, 84.8, 115.4, 119.0, 119.8, 122.8, 123.9, 124.4, 128.5, 129.1, 129.9, 130.7, 130.9, 131.6, 132.3, 132.7 (2C), 133.5, 133.7, 135.7, 136.0, 147.7, 150.8; HR-MS calcd for $C_{29}H_{29}N_3NaO_6S^+$ [M + Na^+] 570.1669, found 570.1674.

tert-Butyl 2-Bromo-7-[(2-nitrophenyl)sulfonyl]-5,6,7,8-tetrahydro-9*H*-benzo[5,6]azocino[3,4-*b*]indole-9-carboxylate (2h')



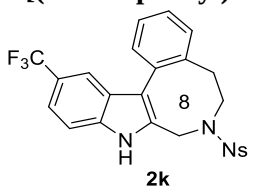
Azido-yne **1h** (76.5 mg, 141 µmol) were dissolved in DCM (77.2 mL), and (tBu)$_3$PAuCl (3.08 mg, 7.80 µmol) and $AgSbF_6$ (4.90 mg, 14.6 µmol) were added and stirred for 30 min at room temperature. Additional (tBu)$_3$PAuCl (9.20 mg, 23.4 µmol) and $AgSbF_6$ (24.5 mg, 73.0 µmol) were added to the mixture, and the reaction was stirred for further 1 h. The solvent was evaporated and the crude product was dissolved in DCM, Boc_2O (61.5 mg, 282 µmol) and DMAP (1.72 mg, 14.1 µmol) were added, and silica gel column chromatography (hexane/EtOAc = 5/1) was performed to give **2h** (16.0 mg, 22%) as a brown solid: mp 165-167 °C; IR (neat): 1730 (C=O), 1544 (N-O), 1371 (S=O); ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.73 (s, 9H), 2.79 (dd, J = 13.4, 4.9 Hz, 1H), 3.01 (ddd, J = 13.4, 5.0, 2.5 Hz, 1H), 3.62 (dd, J = 13.4, 4.9 Hz, 1H), 3.92 (ddd, J = 13.4, 5.0, 2.5 Hz, 1H), 4.75 (d, J = 18.8 Hz, 1H), 5.63 (d, J = 18.8 Hz, 1H), 7.11 (d, J = 8.1 Hz, 1H), 7.21 (dd, J = 7.8, 7.8 Hz, 1H), 7.27-7.33 (m, 2H), 7.35 (m, 2H), 7.48-7.54 (m, 2H), 7.59 (d, J = 7.8 Hz, 1H), 7.65 (ddd, J = 7.8, 7.8, 1.2 Hz, 1H), 8.10 (d, J = 9.0 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): 28.3 (3C), 32.6, 49.2, 52.6, 85.1, 115.5, 117.1, 119.3, 120.3, 123.1, 123.9, 130.4, 130.5, 130.7, 131.7 (2C), 132.8 (2C), 133.1, 133.2, 135.2 (2C), 135.6, 135.9, 147.6, 150.8; HR-MS calcd for $C_{28}H_{26}BrKN_3O_6S^+$ [M + K^+] 650.0357, found 650.0380.

12-Methyl-7-[(2-nitrophenyl)sulfonyl]-6,7,8,9-tetrahydro-5*H*-benzo[5,6]azocino[3,4-*b*]indole (2j)



According to **GP5**, azido-yne **1j** (261 mg, 791 µmol) was converted to **2j** (139 mg, 39%) by the reaction with (*t*Bu)$_3$PAuCl (11.9 mg, 27.4 µmol) and $AgSbF_6$ (27.2 mg, 79.1 µmol) in DCM (791 mL) at room temperature for 1 h. Purification was performed by silica gel column chromatography (hexane/EtOAc = 5/1): yellow oil; IR (neat): 3393 (N-H), 1541 (N-O), 1348 (S=O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.44 (s, 3H), 2.66 (dd, *J* = 12.6, 12.6 Hz, 1H), 3.04 (dd, *J* = 14.4, 7.1 Hz, 1H), 3.11 (dd, *J* = 12.6, 12.3 Hz, 1H), 3.72 (d, *J* = 15.2 Hz, 1H), 4.07 (dd, *J* = 14.4, 7.1 Hz, 1H), 4.87 (d, *J* = 15.2 Hz, 1H), 7.08 (d, *J* = 7.4 Hz, 1H), 7.24-7.40 (m, 4H), 7.41 (s, 1H), 7.59-7.70 (m, 4H), 7.99 (d, *J* = 8.0 Hz, 1H), 8.58 (br s, 1H) ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 21.1, 35.1, 44.0, 49.2, 110.8, 114.9, 118.7, 123.8, 124.1, 126.3, 126.7, 127.0, 129.2, 129.8, 130.2 (2C), 130.7, 131.5, 133.0, 133.2, 133.4, 133.6, 139.0, 147.4; HR-MS calcd for $C_{24}H_{21}KN_3O_4S^+$ [M + K^+] 486.0884, found 486.0886.

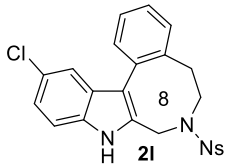
7-[(2-Nitrophenyl)sulfonyl]-12-(trifluoromethyl)-6,7,8,9tetrahydro-5*H*-benzo[5,6]azocino[3,4-*b*]indole (2k)



2k

According to **GP5**, azido-yne **1k** (89.0 mg, 236 µmol) was converted to **2k** (89.0 mg, 75%) by the reaction with (*t*Bu)$_3$PAuCl (5.13 mg, 39.5 µmol) and $AgSbF_6$ (8.11 mg, 79.1 µmol) in DCM (118 mL) at room temperature for 15 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 3/1): yellow foam; IR (neat): 3392 (N-H), 1541 (N-O), 1328 (S=O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.64 (dd, *J* = 14.3, 10.3 Hz, 1H), 3.06 (dd, *J* = 14.3, 10.3 Hz, 1H), 3.16 (dd, *J* = 14.3, 10.3 Hz, 1H), 3.79 (d, *J* = 17.2 Hz, 1H), 4.07 (dd, *J* = 14.3, 6.9 Hz, 1H), 4.92 (d, *J* = 17.2 Hz, 1H), 7.30-7.40 (m, 3H), 7.46-7.50 (m, 2H), 7.55 (dd, *J* = 7.6. 1.4 Hz, 1H), 7.63-7.71 (m, 3H), 7.89 (s, 1H), 8.00 (dd, *J* = 7.6, 2.0 Hz, 1H), 8.93 (br s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 35.4, 44.0, 49.5, 111.8, 116.4, 117.3, 119.5, 122.6 (q, *J* = 34.2 Hz), 124.2, 126.0, 126.9, 127.9, 129.9, 130.6 (m), 130.6, 131.9, 132.6, 132.7, 133.1, 133.7, 134.2, 137.0, 139.3, 147.7; HR-MS calcd for $C_{24}H_{18}F_3KN_3O_4S^+$ [M + K^+] 540.0602, found 540.0602.

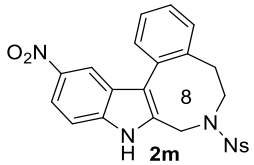
12-Chloro-7-[(2-nitrophenyl)sulfonyl]-6,7,8,9-tetrahydro-5*H*-benzo[5,6]azocino[3,4-*b*]indole (2l)



2l

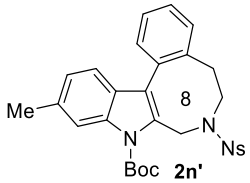
According to **GP5**, azido-yne **1l** (163 mg, 329 µmol) was converted to **2l** (89.0 mg, 58%) by the reaction with (*t*Bu)$_3$PAuCl (7.14 mg, 164 µmol) and $AgSbF_6$ (11.3 mg, 329 µmol) in DCM (164 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1 to 3/1): yellow oil; IR (neat): 3438 (N-H), 1541 (N-O), 1341 (S=O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.63 (dd, *J* = 14.6, 10.3 Hz, 1H), 3.03 (dd, *J* = 14.6, 6.6 Hz, 1H), 3.11 (dd, *J* = 13.7, 10.3 Hz, 1H), 3.75 (d, *J* = 16.0 Hz, 1H), 4.05 (dd, *J* = 13.7, 6.6 Hz, 1H), 4.87 (d, *J* = 16.0 Hz, 1H), 7.17 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.27-7.36 (m, 4H), 7.52 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.56 (d, *J* = 1.7 Hz, 1H), 7.61-7.70 (m, 3H), 7.97 (dd, *J* = 7.4, 1.7 Hz, 1H), 8.73 (br s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 35.4, 44.2, 49.6, 112.6, 115.3, 118.9, 123.1, 124.2, 126.0, 126.9, 127.7, 127.8, 129.9, 130.0, 130.6, 131.9, 132.4, 132.9, 133.2, 133.7, 134.0, 139.2, 147.8; HR-MS calcd for $C_{23}H_{18}ClN_3NaO_4S^+$ [M + Na^+] 490.0599, found 490.0600.

12-Nitro-7-[(2-nitrophenyl)sulfonyl]-6,7,8,9-tetrahydro-5*H*-benzo[5,6]azocino[3,4-*b*]indole (2m)



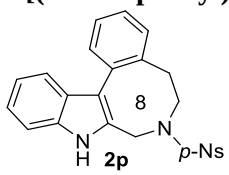
According to **GP5**, azido-yne **1m** (22 mg, 43.4 µmol) was converted to **2m** (14.6 mg, 69%) by the reaction with (tBu)$_3$PAuCl (944 µg, 2.17 µmol) and $AgSbF_6$ (1.49 mg, 4.34 µmol) in DCM (434 mL). Purification was performed by silica gel column chromatography (Et_2O only): yellow oil; IR (neat): 3382 (N-H), 1543 (N-O), 1330 (S=O); ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 2.63 (dd, J = 14.5, 10.4 Hz, 1H), 3.08-3.15 (m, 3H), 3.77 (d, J = 16.2 Hz, 1H), 4.09 (dd, J = 13.9, 7.0 Hz, 1H), 4.94 (d, J = 16.2 Hz, 1H), 7.32-7.44 (m, 1H), 7.48-7.50 (m, 2H), 7.57-7.59 (m, 1H), 7.65-7.76 (m, 3H), 8.04 (dd, J = 7.5, 1.7 Hz, 1H), 8.18 (dd, J = 9.0 Hz, 1.2 Hz, 1H), 8.58 (d, J = 1.2 Hz, 1H), 9.00 (br s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 35.6, 44.0, 49.5, 111.7, 117.1, 118.0, 118.6, 124.4, 126.2, 127.3, 128.4, 130.1, 130.7, 130.8, 131.9, 132.0, 133.1, 133.9, 134.2, 138.6, 139.4, 142.4, 147.7; HR-MS calcd for $C_{23}H_{18}N_4NaO_6S^+$ [M + Na^+] 501.0839, found 501.0846.

tert-Butyl 11-Methyl-7-[(2-nitrophenyl)sulfonyl]-5,6,7,8-tetrahydro-9*H*-benzo[5,6]azocino[3,4-*b*]indole-9-carboxylate (2n')



According to **GP5**, azido-yne **1n** (261 mg, 549 µmol) was converted to **2n** (83.0 mg, 34%) by the reaction with (tBu)$_3$PAuCl (11.9 mg, 27.4 µmol) and $AgSbF_6$ (18.9 mg, 54.9 µmol) in DCM (1098 mL) at room temperature for 45 min. After the crude product was dissolved in DCM, Boc_2O (240 mg, 1.10 mmol) and DMAP (6.70 mg, 54.9 µmol) were added, and the reaction mixture was stirred for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1 to 1/1) to give **2n'**: yellow oil; IR (neat): 1728 (C=O), 1542 (N-O), 1352 (S=O); ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.70 (s, 9H), 2.47 (s, 3H), 2.88 (ddd, J = 13.5, 4.9, 1.6 Hz, 1H), 3.05 (td, J = 13.5, 4.9 Hz, 1H), 3.60 (ddd, J = 13.5, 4.9, 1.6 Hz, 1H), 3.86 (td, J = 13.5, 4.9, Hz, 1H), 4.73 (d, J = 19.2 Hz, 1H), 5.35 (d, J = 19.2 Hz, 1H), 7.01 (d, J = 8.7 Hz, 1H), 7.26 (m, 1H), 7.27-7.29 (m, 2H), 7.36-7.37 (m, 1H), 7.49-7.55 (m, 2H), 7.50-7.54 (m, 1H), 7.59 (ddd, J = 7.7, 7.7, 1.4 Hz, 1H), 7.69 (dd, J = 8.0, 1.2 Hz, 1H), 7.95 (br s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 22.1, 28.3 (3C), 33.2, 49.0, 52.8, 84.7, 115.8, 118.9, 119.3, 124.0, 124.3, 126.6, 127.66, 127.69, 129.2, 130.2, 130.7, 131.3, 131.7, 133.0, 133.1, 133.3, 134.4, 136.3, 136.6, 147.8, 150.8; HR-MS calcd for $C_{29}H_{29}N_3NaO_6S^+$ [M + Na^+] 570.1669, found 570.1669.

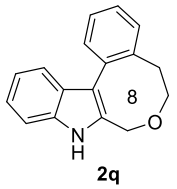
7-[(4-Nitrophenyl)sulfonyl]-6,7,8,9-tetrahydro-5*H*-benzo[5,6]azocino[3,4-b]indole (2p)



According to **GP5**, azido-yne **1p** (200 mg, 433 µmol) was converted to **2p** (124 mg, 66%) by the reaction with (tBu)$_3$PAuCl (9.42 mg, 21.4 µmol) and $AgSbF_6$ (14.9 mg, 43.3 µmol) in DCM (217 mL) at room temperature for 1 h. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1 to 3/1): yellow oil; IR (neat): 3386 (N-H), 1529 (N-O), 1338 (S=O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.65 (dd, J = 12.3, 6.1 Hz, 1H), 2.97 (dd, J =14.7, 6.5 Hz, 1H), 3.15 (dd, J = 12.3, 6.1 Hz, 1H), 3.98 (d, J = 16.7 Hz, 1H), 4.05 (dd, J = 13.5, 6.1 Hz, 1H), 4.83 (d, J = 16.7 Hz, 1H), 7.17 (dd, J = 7.4, 7.4 Hz, 1H), 7.23-7.34 (m, 4H), 7.46 (d, J = 8.0 Hz, 1H), 7.51 (d, J =

7.4 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.8 Hz, 2H), 8.24 (d, *J* = 8.8 Hz, 2H), 8.54 (br s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) *δ*: 34.8, 44.6, 50.0, 111.3, 119.6, 120.5, 123.1, 124.40, 124.41, 124.42, 126.8, 126.9, 127.4 (2C), 127.9, 130.1, 130.4, 130.4, 133.6, 135.7, 138.6, 145.7, 149.8; HR-MS calcd for $C_{23}H_{19}N_3NaO_4S^+$ [M + Na^+] 456.0988, found 456.0988.

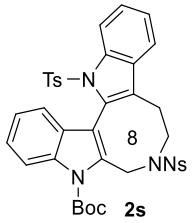
5,6,8,9-Tetrahydrobenzo[5,6]oxocino[3,4-*b*]indole (2q)



2q

According to **GP5**, azido-yne **1q** (40 mg, 0.144 mmol) was converted to **2q** (14.0 mg, 39%) by the reaction with (*t*Bu)$_3$PAuCl (3.57 mg, 7.21 μmol) and $AgSbF_6$ (4.96 mg, 14.4 μmol) in DCM (144 mL) at room temperature for 1 h. Purification was performed by silica gel column chromatography (hexane/Et_2O = 10/1 to 2/1): yellow oil; IR (neat): 3422 (N-H), 1336 (S=O); ^{1}H-NMR (600 MHz, $CDCl_3$) *δ*: 2.84-2.85 (m, 2H), 3.68-3.70 (m, 1H), 4.21-4.26 (m, 1H), 4.35 (d, *J* = 14.7 Hz, 1H), 4.85 (d, *J* = 14.7 Hz, 1H), 7.16 (dd, *J* = 7.2, 3.6 Hz, 1H), 7.24 (dd, *J* = 7.2, 3.6 Hz, 1H), 7.32-7.33 (m, 2H), 7.36-7.42 (m, 2H), 7.68 (dd, *J* = 16.2, 7.9 Hz, 2H), 8.16 (br s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) *δ*: 36.6, 65.8, 72.3, 111.0, 119.7, 120.3, 122.5, 126.3, 127.1, 127.4, 129.5, 129.7, 130.2, 133.4, 133.8, 135.6, 139.5; HR-MS calcd for $C_{17}H_{15}NNaOS^+$ [M + Na^+] 272.1046, found 272.1041..

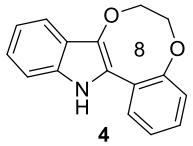
***tert*-Butyl 7-[(2-Nitrophenyl)sulfonyl]-10-tosyl-7,8,9,10-tetrahydroazocino[3,4-*b*:6,5-*b*']diindole-5(6*H*)-carboxylate (2s)**



2s

According to **GP5**, azido-yne **1u** (100 mg, 153 μmol) was converted to the corresponding cyclization product by the reaction with (*t*Bu)$_3$PAuCl (3.32 mg, 7.64 μmol) and $AgSbF_6$ (5.25 mg, 15.3 μmol) in DCM (1.53 L) at room temperature for 2 h. After the crude product was dissolved in DCM, Boc_2O (133.4 mg, 712 μmol) and DMAP (4.00 mg, 30.6 μmol) were added, and the reaction mixture was stirred for 5 min. After concentration in vacuo, silica gel column chromatography (hexane/Et_2O = 3/2) was performed to give **2u** (30.0 mg, 31%, 2 steps) as an off-white solid mp 102-105 °C; IR (neat): 1732 (C=O), 1542 (N-O), 1370 (S=O); ^{1}H-NMR (600 MHz, $CDCl_3$) *δ*: 1.75 (s, 9H), 2.28 (s, 3H), 2.47 (dd, *J* = 16.7, 8.4 Hz, 1H), 3.00 (dd, *J* = 13.5, 9.2 Hz, 1H), 3.13 (dd, *J* = 16.7, 8.4 Hz, 1H), 3.44 (d, *J* = 16.0 Hz, 1H), 3.70-3.79 (m, 1H), 5.59 (d, *J* = 16.0 Hz, 1H), 7.07 (d, *J* = 8.5 Hz, 2H), 7.29-7.48 (m, 7H), 7.60-7.62 (m, 1H), 7.67-7.72 (m, 2H), 7.77 (d, *J* = 7.70 Hz, 1H), 8.03 (d, *J* = 8.3 Hz, 1H), 8.18-8.20 (m, 1H), 8.38 (d, *J* = 8.3 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) *δ*: 21.5 (3C), 26.0, 28.3, 43.1, 45.6, 84.9, 115.2, 116.5, 116.6, 122.1, 123.1, 124.0, 124.2, 124.3, 125.4, 125.6 (2C), 126.6, 129.1 (2C), 129.2, 129.5, 131.0, 131.5, 131.6, 133.2, 133.4 (2C), 134.4, 135.0, 136.0, 138.2, 145.0, 148.0, 150.6; HR-MS $C_{37}H_{34}N_4O_8S_2^+$ [M + K^+] 765.1450, found 765.1450.

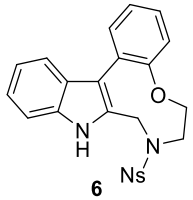
6,7-Dihydro-13*H*-benzo[7,8][1,4]dioxocino[6,5-*b*]indole (4)



4

According to **GP5**, azido-yne **3** (50 mg, 179 µmol) was converted to **4** (15.7 mg, 35%) by the reaction with (C-dtbm)AuCl (21.0 mg, 8.95 µmol) and $AgSbF_6$ (5.98 mg, 17.9 µmol) in DCM (179 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/Et_2O = 1/2): yellow oil; IR (neat): 3375 (N-H); ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 4.32-4.34 (m, 4H), 7.10 (dd, J = 7.5, 7.5 Hz, 1H), 7.17-7.21 (m, 2H), 7.23-7.30 (m, 2H), 7.33 (dd, J = 7.6, 7.6 Hz, 1H), 7.40 (s, 1H), 7.47 (d, J = 7.7 Hz, 1H), 7.63 (d, J = 7.9 Hz, 1H); ^{13}C-NMR ($CDCl_3$ 125 MHz, $CDCl_3$) δ: 66.9, 71.9, 110.8, 115.8, 118.1, 119.5, 121.8, 123.3, 123.7, 125.3, 127.0, 128.1, 129.2, 134.6, 138.3, 153.9; HR-MS: $C_{16}H_{13}NO_2^+$ [M + Na^+] 274.0838, found 274.0831.

8-[(2-Nitrophenyl)sulfonyl]-7,8,9,10-tetrahydro-6*H*-benzo[8,9][1,4]oxazonino[6,7-*b*]indole (6)



6

According to **GP5**, azido-yne **5** (53 mg, 111 µmol) was converted to **6** (16.9 mg, 34%) by the reaction with (C-dtmb)AuCl (25.0 mg, 11 µmol) and $AgSbF_6$ (7.56 mg, 22 µmol) in DCM (1.11 L) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/Et_2O = 1/2): yellow solid; mp 252-254 ℃; IR (neat): 3266 (N-H), 1542 (N-O), 1355 (S=O); ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 3.69 (t, J = 4.8 Hz, 2H), 4.36 (t, J = 4.8 Hz, 2H), 4.47 (s, 2H), 7.12 (dd, J = 7.2, 7.2 Hz, 1H), 7.17-7.22 (m, 3H), 7.33-7.37 (m, 1H), 7.40 (d, J = 8.7 Hz, 1H), 7.52-7.61 (m, 3H), 7.65-7.72 (m, 2H), 7.92 (d, J = 8.3 Hz, 1H), 8.78 (s, 1H); ^{13}C-NMR ($CDCl_3$ 125 MHz, $CDCl_3$) δ: 46.4, 51.2, 68.7, 111.4, 112.8, 118.3, 119.3, 120.2, 122.8, 123.4, 124.3, 126.9, 127.1, 128.5, 130.1, 130.6, 131.8, 131.9, 132.9, 133.7, 135.8, 148.3, 155.6; HR-MS: $C_{23}H_{19}KN_3O_5S^+$ [M + K^+] 488.0677, found 488.0679.

References

[1] a) M. E. Welsch, S. A. Snyder, B. R. Stockwell, *Curr. Opin. Chem. Biol.* **2010**, *14*, 347–361; b) F. R. de Sá Alves, E. J. Barreiro, C. A. M. Fraga, *Mini-Rev. Med. Chem.* **2009**, *9*, 782–793; c) D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.* **2003**, *103*, 893−930; d) J. F. Austin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 1172–1173; e) M. Bandini, A. Eichholzer, *Angew. Chem. Int. Ed.* **2009**, *48*, 9608–9644; f) V. Sharma, P. Kumar, D. Pathak, J. *Heterocyclic Chem.* **2010**, *47*, 491–502.

[2] a) A. Okabe, S. Harada, T. Takeda, A. Nishida, Eur. *J. Org. Chem.* **2019**, 3916–3920; b) L. M. Rice, E. Hertz, M. E. Freed, *J. Med. Chem.* **1964**, *7*, 313–319; c) B. L. Baxter, M. I. Gluckman, *Nature* **1969**, *223*, 750–752.

[3] a) M. I. Calaza, C. Cativiela, *Eur. J. Org. Chem.* **2008**, 3427–3448; b) J. Cossy, O. Mirguet, D. G. Pardo, *Synlett* **2001**, 1575–1577.

[4] a) C. R. M. Souza, W. P. Bezerra, J. T. Souto, *Mar. Drugs* **2020**, *18*, 1– 17; b) M. F. Raub, J. H. Cardellina, J. G. Schwede, *Phytochemistry* **1987**, *26*, 619–620; c) C. G. L. Veale, M. T. Davies-Coleman, *The Alkaloids: Chemistry and Biology*, **2014**, *73*, 1–64.

[5] a) Hussain, S. K. Yousuf, D. Mukherjee, *RSC Adv.* **2014**, *4*, 43241– 43257; b) F. A. Macias, R. M. Varela, A. Torres, J. M. G. Molino, F. R. Fronczek, *Tetrahedron Lett.* **1993**, *34*, 1999–2002; c) B. Hoefgen, M. Decker, P. Mohr, A. M. Schramm, S. A. F. Rostom, H. El-Subbagh, P. M. Schweikert, D. R. Rudolf, M. U. Kassack, J. Lehmann, *J. Med. Chem.* **2006**, *49*, 760–769; d) K. R. Romines, K. D. Watenpaugh, P. K. Tomich, W. J. Howe, J. K. Morris, K. D. Lovasz, A. M. Mulichak, B. C. Finzelj, J. C. Lynn, M.-M.Horng, F. J. Schwende, M. J. Ruwart, G. L. Zipp, K.-T. Chong, L. A. Dolak, L. N. Toth, G. M. Howard, B. D. Rush, Karen F. Wilkinson, P. L. Possert, R. J. Dalga, R. R. Hinshaw. *J. Med. Chem.* **1995**, *38*, 1884–1891.

[6] a) W. R. J. D. Galloway, A. Isidro-Llobet, D. R. Spring, *Nat. Commun.* **2010**, *1*, 80; b) L. Li, Z.-L. Li, F. L. Wang, Z. Guo, Y. F. Cheng, N. Wang, X. W. Dong, C. Fang, J. Liu, C. Hou, B. Tan, X.-Y. Liu, *Nat. Commun*. **2016**, *7*, 13852; c) A. Noren-Muller, I. Reis-Correa Jr., H. Prinz, C. Rosenbaum, K. Saxena, H. J. Schwalbe, D. Vestweber, G. Cagna, S. Schunk, O. Schwarz, H. Schiewe, H. Waldmann, *Proc. Natl. Acad. Sci.* **2006**, *103*, 10606–10611; d) M. Kaisera, S. Wetzel, K. Kumar, H. Waldmann, *Cell. Mol. Life Sci.* **2008**, *65*, 1186–1201; e) S. Wetzel, R. S. Bon, K. Kumar, H. Waldmann, *Angew. Chem. Int. Ed*. **2011**, *50*, 10800–10826; f) H. Ohno, S. Inuki, *Org. Biomol. Chem.* **2021**, *16*, 3551–3568; g) G. Karageorgis, D. J. Foley, L. Laraia, H. Waldmann, *Nat. Chem.* **2020**, *12*, 227–235; h) G. S. Cremosnik, J. Liu, H. Waldmann, *Nat. Prod. Rep.* **2020**, *37*, 1497–1510.

[7] R. L. Reyes, T. Iwai, M. Sawamura, *Chem. Rev*. **2021**, *121*, 8926-8947; b) J. R. Donald, W. P. Unsworth, *Chem. Eur. J.* **2017**, *23*, 8780–8799; c) A. K. Clarke, W. P. Unsworth, *Chem. Sci.* **2020**, *11*, 2876–2881; d) C. Galli, L. Mandolini, *Eur. J. Org. Chem.* **2000**, 3117–3125; e) C.

Galli, L. Mandolini, *Acc. Chem. Res.* **1981**, *14*, 95–102; f) T. Huber, R. E. Wildermuth, T. Magauer, *Chem. Eur. J.* **2018**, *24*, 12107–12120.

[8] a) L.-W. Ye, X.-Q. Zhu, R. L. Sahani, Y. Xu, P.-C. Qian, R.-S. Liu, *Chem. Rev.* **2021**, *121*, 9039–9112; b) X. Zhao, Rudolph, A. M. Asiri, A. S. K. Hashmi, *Front. Chem. Sci. Eng*. **2020**, *14*, 317–349; c) F. L. Hong, L.-W. Ye, Front. *Chem. Sci. Eng.* **2020**, *14*, 317– 349; d) E. Aguilar, J. Santamaria, *Org. Chem. Front*. **2019**, *6*, 1513–1540; e) X. Tian, L. Song, A. S. K. Hashmi, *Chem. Eur. J*. **2020**, *26*, 3197–3204.

[9] For recent works on α-imino gold(I) carbene chemistry reported by the author's group, see: a) Y. Tokimizu, S. Oishi, N. Fujii, H. Ohno, *Org. Lett*. **2014**, *16*, 3138–3141; b) Y. Kawada, S. Ohmura, M. Kobayashi, W. Nojo, M. Kondo, Y. Matsuda, J. Matsuoka, S. Inuki, S. Oishi, C. Wang, T. Saito, M. Uchiyama, T. Suzuki, H. Ohno, *Chem. Sci.* **2018**, *9*, 8416–8425; c) J. Matsuoka, Y, Matsuda, Y. Kawada, S. Oishi, H. Ohno, *Angew. Chem. Int. Ed.* **2017**, *56*, 7444−7448; d) J. Matsuoka, S. Inuki, Y. Matsuda, Y. Miyamoto, M. Otani, M. Oka, S. Oishi, H. Ohno, *Chem. Eur. J.* **2020**, *26*, 11150–11157.

[10] a) T. Iwai, H. Okochi, H. Ito, M. Sawamura, *Angew. Chem. Int. Ed*. **2013**, *52*, 4239–4242; b) T. Iwai, M. Ueno, H. Okochi, M. Sawamura, *Adv. Synth. Catal.* **2018**, *360*, 670–675; c) A. Ochida, H. Ito, M. Sawamura, *J. Am. Chem. Soc.* **2006**, *128*, 16486–16487.

[11] a) J. Schießl, J. Schulmeister, A. Doppiu, E. Wörner, M. Rudolph, R. Karch, A. S. K. Hashmi, *Adv. Synth. Catal.* **2018**, *360*, 2493–2502; b) J. Schießl, J. Schulmeister, A. Doppiu, E. Wörner, M. Rudolph, R. Karch, A. S. K. Hashmi, *Adv. Synth. Catal.* **2018**, *360*, 3949–3959; c) Z. Lu, J. Han, O. E. Okoromoba, N. Shimizu, H. Amii, C. F. Tormena, G. B. Hammond, B. Xu, *Org. Lett.* **2017**, *19*, 5848−5851; d) Z. Lu, G. Hammond, B. Xu, *Acc. Chem. Res.* **2019**, *52*, 1275−1288; e) G. Kovács, G. Ujaque, A. Lledós, *J. Am. Chem. Soc.* **2008**, *130*, 853–864; f) M. Jia, M. Bandini, *ACS Catal.* **2015**, *5*, 1638–1652.

[12] a) B. Lu, Y. Luo, L. Liu, L. Ye, Y. Wang, L. Zhang, *Angew. Chem. Int. Ed*. **2011**, *50*, 8358–8362; b) D. Benitez, N. D. Shapiro, E. Tkatchouk, Y. Wang, W. A. Goddard Ill, F. D. Toste, *Nat. Chem.* **2009**, *21*, 482–486; c) Y. Wang, M. E. Muratoe, A. M. Echavarren, *Chem. Eur. J.* **2015**, *21*, 7332–7339; d) L. N. dos Santos Comprido, J. E. M. N. Klein, G. Knizia, J. Kästner, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2015**, *54*, 10336–10340.

[13] M. Kumar, G. B. Hammond, B. Xu, *Org. Lett.* **2014**, *16*, 3452–3455.

[14] Y. Tang, B. Yu, *RSC Adv.* **2012**, *2*, 12686–12689.

[15] CCDC 2084607 (**2b**), 2084609 (**2e'**), 2084610 (**2s'**) and 2084608 (**6**), contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[16] H. C. Brown, Y. Okamoto, *J. Am. Chem. Soc*. **1957**, *79*, 1913–1917.

[17] a) T. B. Phan, M. Breugst, H. Mayr, *Angew. Chem. Int. Ed*. **2006**, *45*, 3869–3874; b) H. Mayr, A. R. Ofial, *J. Phys. Org. Chem.* **2008**, *21*, 584–595; c) S. Lakhdar, M. Westermaier, F. Terrier, R. Goumont, T. Boubaker, A. Ofial, H. Mayer, *J. Org. Chem.* **2006**, *71*, 9088–9095.

[18] a) A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2010**, *49*, 5232–5241; b) T. Lauterbach, A. M. Asiri, A. S. K. Hashmi, *Adv. Organomet. Chem.* **2014**, *62*, 261–297; c) J. N. Marx, Y.- S. P. Hahnt, *J. Org. Chem.* **1988,** *53*, 2866–2868.

[19] Gold-catalyzed retro-Buchner (decarbenation, retrocyclopropanation) of D could regenerate A: a) C. R. Solorio-Alvarado, A. M. Echavarren, *J. Am. Chem. Soc.* **2010**, *132*, 11881–11883; b) C. R. Solorio-Alvarado, Y. Wang, A. M. Echavarren, *J. Am. Chem. Soc.* **2011**, *133*, 11952–11955; c) M. Mato, C. G. Morales, A. M. Echavarren, *ChemCatChem* **2019**, *11*, 53–72.

[20] It should be noted that the reaction of *N*-alkyl derivative 1t resulted in polymerization without producing the desired product **2t**.

[21] M. K. Ghorai, A. Kumar, D. P. Tiwari, *J. Org. Chem*. **2010**, *75*, 137–151.

[22] J. Messeguer, I. Masip, M. Montolio, J. A. D. Rio, E. Soriano, A. Messeguer, *Tetrahedron*, **2010**, *66*, 2444–2454.

[23] C. Guisado, J. E. Waterhouse, W. S. Price, M. R. Jorgensen A. D. Miller, *Org. Biomol. Chem*. **2005**, *3*, 1049–1057.

[24] M. L. Duda, F. E. Michael, *J. Am. Chem. Soc*. **2013**, *135*, 18347−18349.

[25] Z. Xu, Z. Wang, A. Ying, L. Zhang, *J. Am. Chem. Soc*. **2016**, *138*, 5515–5518.

[26] K. S. Feldman, P. Ngernmeesri, *Org. Lett*. **2010**, *12*, 4502–4505.

[27] J. Xu, R. Tong, *Green Chem*. **2017**, *19*, 2952–2956.

[28] J. E. Nidhiry, K. R. Prasad, *Synlett* **2014**, 25, 2585–2590.

[29] F. L. Coelho, E. S. Gil, P. F. B. Gonzales, L. F. Campo, P. H. Schneider, *Chem. Eur. J*. **2019**, *25*, 8157–8162.

[30] B. N. Bailey, R. Docampo, I. Ujváry, S. Szajnman, J. B. Rodriguez, *J. Med. Chem*. **2002**, *45*, 3984–3999.

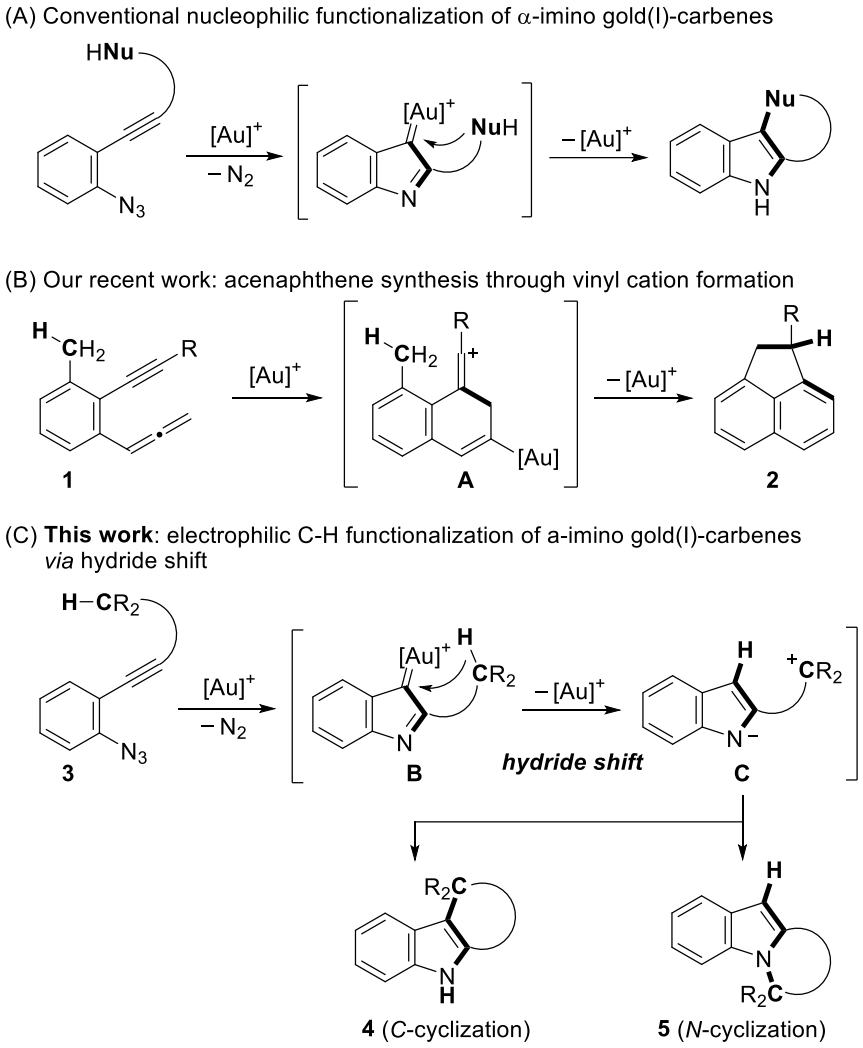
Chapter 2. Benzylic C(sp^3)-H Functionalizations: Synthesis of Indole[*a*]- and [*b*]-Fused Polycycles

Phenylazides substituted by an (alkylphenyl)ethynyl group facilitate benzylic sp^3(C-H) functionalization in the presence of a JohnPhosAu catalyst, resulting in indole-fused tetra- and pentacycles via divergent N- or C-cyclization. The chemoselectivity is influenced depending on the counter-anion, the electron density of the α-imino gold(I) carbene, and the alkyl groups stabilizing the benzylic carbocation originating from a 1,5-hydride shift. An isotopic labeling experiment demonstrates the involvement of an indolylgold(I) species resulting from a tautomerization that is much faster than the deauration. The formation of a benzylic C(sp^3)-H functionalization leading to an indole-fused seven-membered ring is also demonstrated.

Studies of C(sp^3)-H functionalizations have experienced a phenomenal growth in the field of organic synthesis. A key advantage of these transformations is found in their high atom economy originating from the omission of pre-functionalization steps to form new C–C or C–X (X = N, O, or halogen) bonds. Their integration in cascade processes is of high synthetic value for the construction of complex molecules, which allows access to untapped chemical space.[1-8] Although the development of cascade reactions involving hydrogen atom transfer[9-12] or carbene/nitrene insertion[13,14] is making great strides, functionalizations via hydride abstraction in an internal redox process are developing at a comparatively sluggish rate.[15-21]

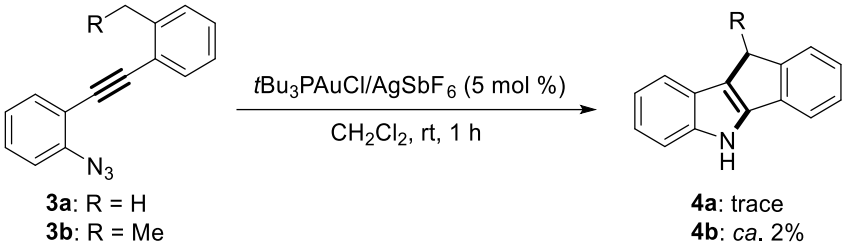
The emerging growth of gold catalysis has played an important role in cascade reactions involving a C(sp^3)-H functionalization step.[22] Although the involvement of C-H functionalization via a 1,5-hydride shift-based internal redox process has been observed for gold complexes with keteniminium,[23] furyl,[24] allenyl,[25,26] alkynyl,[27-30] vinyl cation,[31] unfunctionalized carbene,[32] and oxo carbene species,[33] these processes are unprecedented among α-imino gold carbenes (Scheme 1A).[34-36] The occurrence of 1,5-migrations onto gold carbene centers remains disproportionately rare compared with the occurrence of 1,2-migrations.[37]

In the ongoing endeavors in reaction development using gold catalysis in the author's group,[38-43] the author's group previously reported the synthesis of acenaphthenes **2**, which can be rationalized by a 1,5-hydride shift on a vinyl cationic gold complex **A** generated from allenynes **1** (Scheme 1B).[44,45] From this vantage point, the author envisioned that a 1,5-hydride shift leading to electrophilic α-imino gold carbene functionalization should also be conceivable in gold-catalyzed electrophilic C-H functionalization, leading to fused indoles such as **4** (Scheme 1C), which often exhibit biologically intriguing properties.[21] In this Chapter, the author shows that alkynylated arylazides are suitable substrates for gold-catalyzed cascade cyclizations to form indeno[*b*]-type fused indoles **4** via a 1,5-hydride shift on α-imino gold carbenes and *C*-cyclization. The selective formation of indeno[*a*]-type fused indoles **5** through *N*-cyclization is also presented.



Scheme 1. Related research and this work.

At the outset, the reaction of **3a** (R = H) with *t*Bu$_3$PAuCl/AgSbF$_6$ was investigated. The author expected that a methyl group adjacent to the phenyl-alkyne would induce sufficient benzylic activation for a 1,5-hydride shift (Scheme 2). Unfortunately, the crude ^{1}H NMR spectrum displayed the characteristics of a polymer, whereas only a trace amount of the desired product **4a** was suspected. To enhance the hydride donor reactivity, the author attempted to stabilize the corresponding benzylic cation with an additional methyl group. Indeed, when the ethylbenzene-type substrate **3b** was exposed to the gold catalyst, the desired product **4b** was obtained, although in approximately 2% yield.



3a: R = H
3b: R = Me

4a: trace
4b: *ca*. 2%

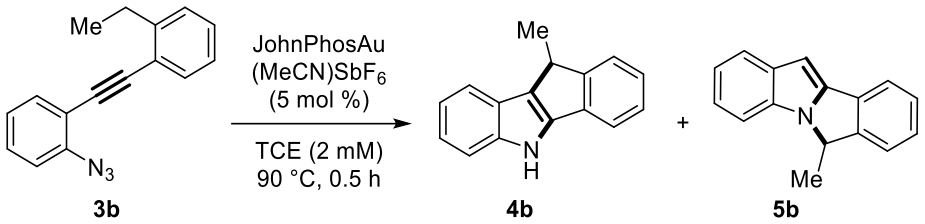
Scheme 2. Initial investigations.

Encouraged by these results, the author next optimized the reaction conditions for the synthesis of tetracyclic indoles using **4b** and several ligands including XPhos, JohnPhos, DavePhos, IPr, BrettPhos (see Table 1 footnote). The author found that the reaction of **3b** using JohnPhosAu(MeCN)SbF_6 (5 mol %) in 2 mM TCE at 90 °C for 0.5 h gave the *C*-cyclization product **4b** and an additional *N*-cyclization product in 63% combined isolated yield and a product ratio of **4b**:**5b** = 85:15 (Table 1, entry 1). In the examples (entries 2-8, 10-11 and 13-14) the author explains the low yields with the observation of significant amounts of black tar formation. Subjecting cyclization precursor to *t*Bu_3AuCl/$AgSbF_6$ using a substrate concentration of 500 mM in DCM at room temperature gave the desired product **4b** in a poor yield of 2% with a selectivity of **4b:5b** = >99:1 (entry 2). Dilution of the substrate concentration to 2 mM in the presence of (*t*Bu)$_3$PAuCl gave **4b** in 4% yield (entry 3). Use of the IPr ligand from the NHC family decreased the yield to <1%, increasing black tar formation (entry 4). A distinct improvement of the yield to 20% was observed when JohnPhosAu(MeCN)SbF_6 catalyst was employed (entry 5). Increasing the temperature to 70 °C in DCE caused no improvement (entry 6); however, elevation to 90 °C with a reaction time of 0.5 h in TCE substantially increased the yield to 63% (entry 1). Examination of prolonged reaction times—first 3 h then 72 h— showed that the increase in yield flattened as the reaction time increased (data not shown), which indicates the instability of the product **4b** under the reaction conditions. The effect of concentration for this catalytic system was once more confirmed when the reaction with the optimized catalyst was performed under a 20 mM substrate concentration, giving only 11% of the desired product (entry 7).

Next, the author screened several ligands. The less bulky CyPhos(MeCN) system turned out to be detrimental to the reaction, giving the desired product in 15% yield (entry 8). Employing the amine-functionalized ligand DavePhos inhibited the reaction completely (entry 9), whereas increasing the bulk with XPhos and *t*-BuBrettPhos did not improve the yield (entries 10 and 11). When employing the bulky and less-coordinating NaBARF system (entry 12), a combined yield of 50% of **4b** and **5b** was obtained, and the relative amount of the *N*-cyclization product **5b** significantly increased (**4b**:**5b** = 67:33), suggesting a selectivity-enhancing counter-anion effect. A brief investigation of the counter-anions using JohnPhos as the ligand showed that NTf_2^-, with a higher gold affinity and H-bonding index, significantly decreased the yield and enhanced the intermolecular polymerization process (entry 13).[46] The use of the solvent chlorobenzene, known to be tolerant to α-imino gold carbene,[47] gave 31% yield and minor amounts of black tar (entry 14). Switching the solvent to the high-boiling $PhCF_3$ gave the desired product

in 36% yield (entry 15).[48] A final examination of oxygenated solvent classes (entries 16–18) demonstrated that non-coordinating halogenated solvents with a high boiling point provide the most suitable reaction environment for this gold-catalyzed cascade process.

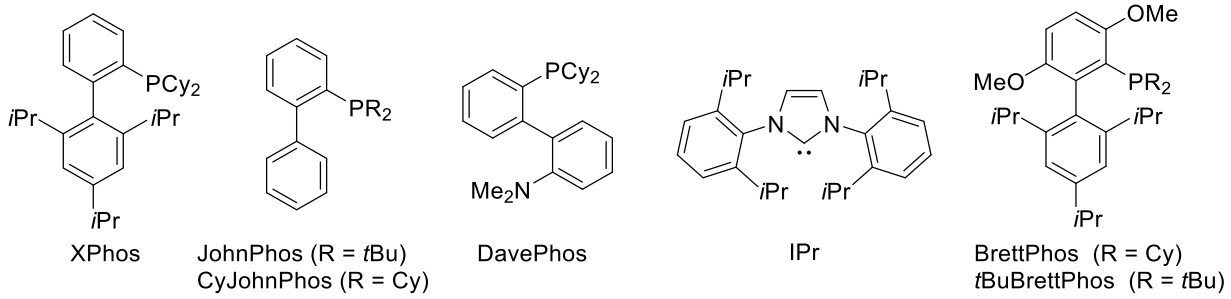
Table 1. Optimization of the Reaction Conditions.[a]



3b **4b** **5b**

Entry	Variation from entry 1	Yield (%)[b]	Ratio (**4b**:**5b**)[c]
1	none (optimized condition)	66 (63)	85:15
2	*t*Bu$_3$PAuCl/AgSbF$_6$, DCM, rt, 500 mM	(2)	>99 : 1
3	*t*Bu$_3$PAuCl/AgSbF$_6$, DCM, rt	(4)	>99 : 1
4	IPrAuCl/AgSbF$_6$, DCM, rt	<1	>99 : 1
5	DCM, rt	20	>99 : 1
6	DCE, 70 °C	19	>99 : 1
7	20 mM	11	>99 : 1
8	CyPhos(MeCN)SbF$_6$	15	>99 : 1
9	DavePhosAuCl/AgSbF$_6$	NR	—
10	XPhosAuCl/AgSbF$_6$	8	>99 : 1
11	*t*-BuBrettPhos/AgSbF$_6$	<1	>99 : 1
12	JohnPhosAuCl/NaBARF	50	67 : 33
13	JohnPhosAuCl/AgNTf$_2$	<1	>99 : 1
14	PhCl	31	>99 : 1
15	PhCF$_3$	36	>99 : 1
16	MeNO$_2$	4	>99 : 1
17	CPME	8	>99 : 1
18	diglyme	0	—

[a] Ligands and counteranion are shown below. [b] Determined by ^{1}H NMR analysis. Yields in parenthesis are the isolated yields. [c] Ratio was determined by ^{1}H NMR analysis. TCE = tetrachloroethane, DCM = dichloromethane, DCE = dichloroethane, CPME = cyclopentyl methyl ether, BARF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

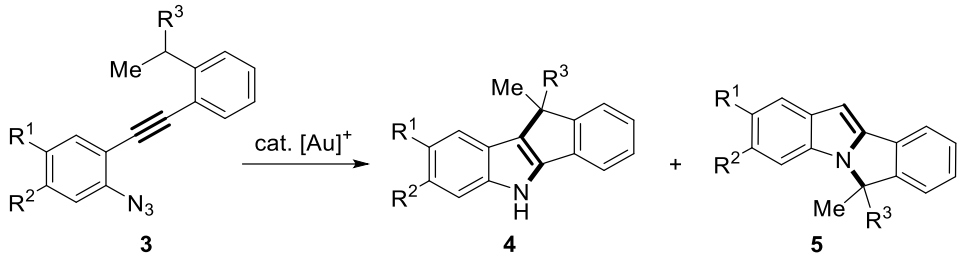


The author moved on to explore the reaction scope (Table 2). The application of the electron-donating methoxy group **3c** resulted in a pronounced decrease of the yield (**4c**, 20%), with concomitant amounts of insoluble black tar originating from intermolecular processes (entry 2). The introduction of an electron-withdrawing chlorine group for R^1 led to the emergence of the dominant *N*-cyclization (**4d**:**5d** = 45:55) in a combined yield of 55% (entry 3). The structure of **4d** was unambiguously confirmed by X-ray analysis (Figure 1). Similarly, the introduction of the CF_3 group **3e** gave 53% of an isomeric mixture with a product ratio of **4e**:**5e** = 43:57 (entry 4). While optimizing the reaction conditions, the author suspected that NaBARF induced the formation of the *N*-cyclization product (Table 1, entry 12). Indeed, this anticipation was verified by an altered product ratio (**4e**:**5e** = 30:70) with good yield (81%, entry 5). An analogous result with an increased *N*-cyclization selectivity was observed when the electron-withdrawing NO_2 derivative was used (**4f**:**5f** = 42:58, entry 6) in 70% yield. The introduction of an NO_2 group for R^2 (**3g**) had a comparable effect on the yield (65%) and selectivity (**4g**:**5g** = 34:66, entry 7) as the use of **3f** did. In the presence of NaBARF, this ratio shifted to 1:>99; however, this shift in selectivity occurred at the expense of the yield (15%) and the reaction rate (entry 8).

Next, improvement of the *N*-cyclization was attempted. Exposure of the derivative **3h** to an isopropylbenzene moiety as the hydride donor (entry 9) has proven to be significantly advantageous for the *N*-cyclization, giving a ratio of **4h**:**5h** = 18:82 in 65% combined yield. Excellent chemoselectivity (**4h**:**5h** = 1:>99) and 57% yield was eventually accomplished when JohnPhosAuCl/NaBARF was employed, highlighting the impact of the counter-anion effect (entry 10). Exposure of the chlorine derivative **3i** to JohnPhosAuCl/NaBARF gave **5i** in 80% yield with striking 1:>99 selectivity (entry 11). The trifluoromethyl derivative **3j** was likewise chemoselectively converted to the *N*-cyclization product **5j** with 76% combined yield (entry 12). When the electron-withdrawing NO_2 group was inserted for R^2, the selectivity for the C–N bond remained outstanding (**4k**:**5k** = 1:>99, entry 13), with a prolonged reaction time of 3 h. Also, the solid-state structure of **5k** confirmed the molecular connectivity (Figure 1). A prolonged reaction time was also observed for **3g** in the presence of NaBARF, suggesting that a decreased electron density of the substrate might reduce the interaction with the JohnPhosAuBARF complex, and/or the nucleophilicity required for the second cyclization to decrease the reaction rate. As a consequence, low

yield of 15% and significant amounts of black tar were present. In light of these results, the author concluded that the combined effects of electron-withdrawing groups on the aryl moiety, weakly coordinating counter-anions, and inductive stabilization of the carbocation contributed incrementally to a selective *N*-cyclization. In essence, these multi-causal factors affect the reactivity of the end groups.

Table 2. Substrate scope.[a]



3 **4** **5**

Entry	Subst.	R^1	R^2	R^3	catalyst (mol%)	Yield[b]	Ratio (**4:5**) [c]
1	**3b**	H	H	H	JohnPhosAu(MeCN)SbF_6 (5)	63	85 : 15
2	**3c**	OMe	H	H	JohnPhosAu(MeCN)SbF_6 (5)	20	>99 : 1
3	**3d**	Cl	H	H	JohnPhosAu(MeCN)SbF_6 (5)	55	45 : 55
4	**3e**	CF_3	H	H	JohnPhosAu(MeCN)SbF_6 (5)	53	43 : 57
5[d]	**3e**	CF_3	H	H	JohnPhosAuCl/**NaBARF** (10)	81	30 : 70
6	**3f**	NO_2	H	H	JohnPhosAu(MeCN)SbF_6 (5)	70	42 : 58
7	**3g**	H	NO_2	H	JohnPhosAu(MeCN)SbF_6 (5)	65	34 : 66
8[d]	**3g**	H	NO_2	H	JohnPhosAuCl/**NaBARF** (10)	15	1 : >99
9	**3h**	H	H	Me	JohnPhosAu(MeCN)SbF_6 (5)	65	18 : 82
10[d]	**3h**	H	H	Me	JohnPhosAuCl/**NaBARF** (10)	57	1 : >99
11[d]	**3i**	Cl	H	Me	JohnPhosAuCl/**NaBARF** (10)	80	1 : >99
12[d]	**3j**	CF_3	H	Me	JohnPhosAuCl/**NaBARF** (10)	76	1 : >99
13[e]	**3k**	H	NO_2	Me	JohnPhosAuCl/**NaBARF** (10)	66	1 : >99

[a] Unless otherwise stated, the reaction was conducted under the standard conditions: JohnPhosAu(MeCN)SbF_6 (5 mol %) and TCE (2 mM) at 90 °C for 0.5 h. [b] Combined isolated yield. [c] Ratio determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d] The reaction time was 4 h. [e] The reaction time was 3 h. BARF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

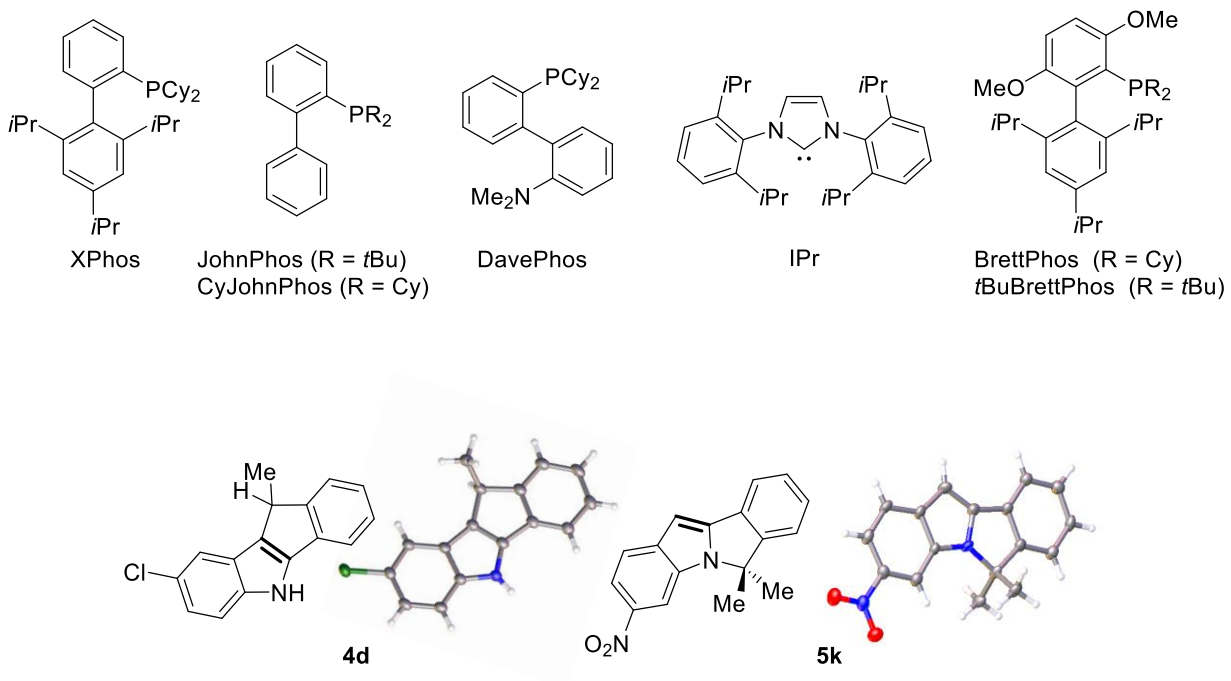
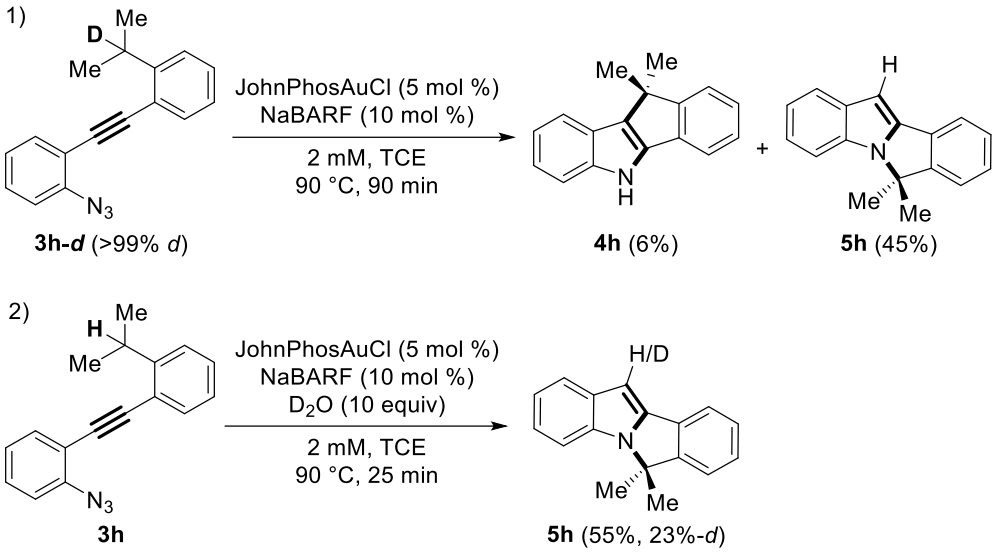


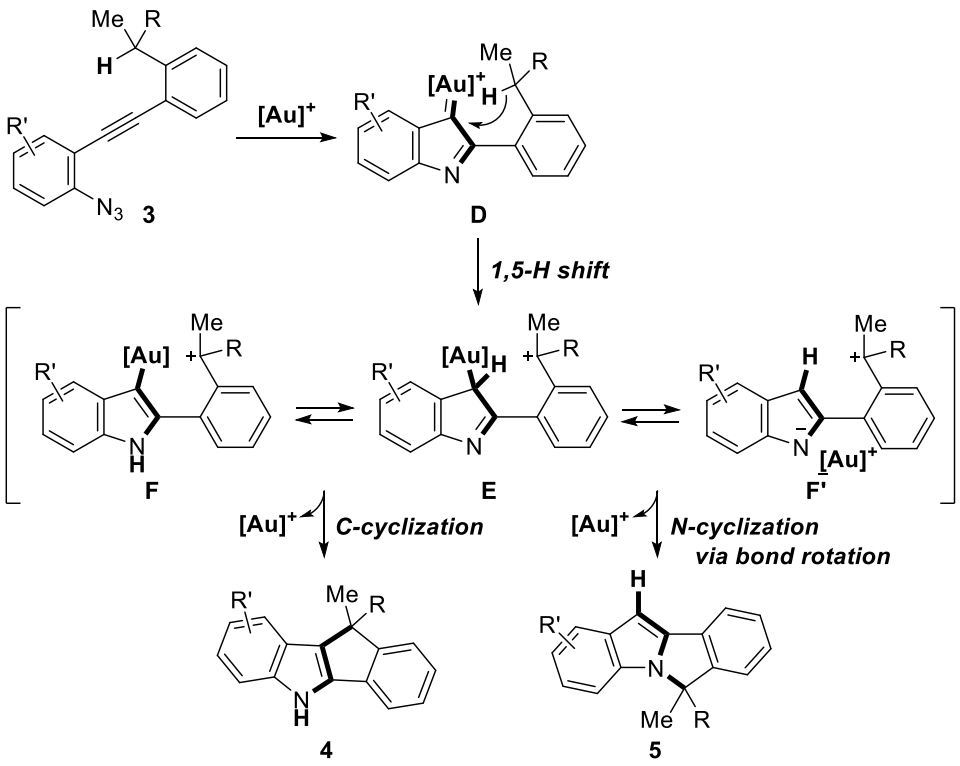
Figure 1. Solid-state structures of indeno[*b*]- and indeno[*a*]-fused indoles.

To gain insight into the benzylic C(sp^3)-H functionalization, an isotopic labeling experiment was carried out (Scheme 3). The gold(I)-catalyzed cascade cyclization of isotope-labeled **3h-*d*** (>99%-*d*) resulted in the complete loss of the deuterium labeling, affording **4h** (6%) and **5h** (45%) after a prolonged reaction time (90 min; Scheme 3, eq 1). This observation implies that a D/H exchange is involved in one of the elementary steps in the cascade sequence. Conducting the reaction of the non-labeled substrate **3h** in the presence of D_2O as a deuteron source gave the substrate **5h-*d*** in 55% yield with 23% deuterium incorporation (Scheme 3, eq 2), indicating that the H/D atom at the indole 3 position can be exchanged to D/H in the presence of D_2O, HDO, or H_2O in the reaction mixture.



Scheme 3. Isotopic labeling experiment.

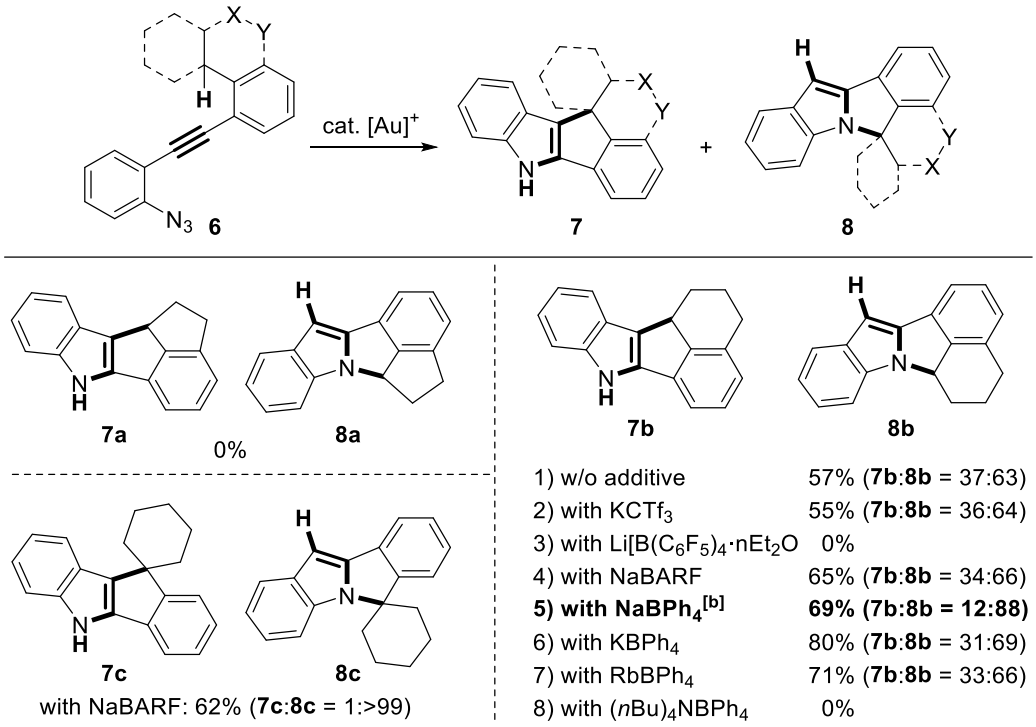
Based on these results, a proposed mechanism is outlined below (Scheme 4). When azido alkyne **3** is subjected to the gold catalyst, the α-imino gold carbene **D** is generated in an initial gold-catalyzed acetylenic Schmidt reaction. The following 1,5-hydride shift from the benzylic position on the gold carbene generates the corresponding carbocation **E**, which is in a state of equilibrium between the aromatized intermediates **F** and **F'**. Deaurative carbon-carbon bond formation via **F** affords the *C*-cyclization product **4**, whereas a bond rotation of **F** and consecutive C-N bond formation gives the *N*-cyclization product **5**.



Scheme 4. Proposed mechanism based on the 1,5-hydride shift.

Considering the result of the isotope experiments in which the deuterium labeling at the benzylic position was completely lost, the author assumed that the interconversion between **E** and **F** would be significantly faster than the cyclization. If the C-N bond formation without forming **F** is sufficiently fast, the *N*-cyclization product **5** would carry a deuterium atom at the 3-position. The deuterated substrate **3h-*d*** produced a small amount of the *C*-cyclization product **4h** (6%), in striking contrast to the reaction of **3h**, which afforded exclusively the *N*-cyclization product **5h** (entry 11, Table 1). These results might suggest that the *N*-cyclization occurs preferentially through the aromatized intermediate **F**, the formation of which requires C-H/D bond cleavage. The higher *C*-cyclization selectivity of the ethylated substrate **3b** (R = H) over the isopropyl precursor **3h** (R = Me) can be explained by the relatively high reactivity of the carbocations **E** and **F**/**F'** derived from **3b**. This high reactivity facilitates the *C*-cyclization before the bond rotation. Similarly, the substituent effect on the aromatic ring, whereby the electron-withdrawing R' group increased the ratio of the *N*-cyclization product, can be understood by the decreased nucleophilicity of the indole moiety of the carbocations **E** and **F**/**F'**, providing sufficient opportunity for bond rotation. The counter-anion effect can be explained through the decreased coordination ability of BARF as compared with SbF_6, resulting in a favored intramolecular ionic interaction with the indole aza-anion, thus increasing the selectivity for *N*-cyclization.[49] At this stage, an alternate mechanism involving *C*-cyclization via insertion cannot be ruled out.[50-53]

The benzylic methylene C-H bond of the carbocyclic substrate **6** was next investigated (Scheme 5). When using the indane derivative **6a**, polymerization was the sole reaction observed, and the desired products **7a** and **8a** were not detected. Considering the highly strained ring system of the tricyclic indene rings fused with a five-membered ring in **7a** and **8a**, the author subsequently examined the reaction of the tetralin derivative **6b**. The desired formation of the indole-fused pentacycles **7b** and **8b** was successfully achieved via edge-fusion with a yield of 57% (**7b**:**8b** = 37:63). A brief survey of the reaction conditions has revealed that the use of $NaBPh_4$ significantly improved the selectivity towards *N*-cyclization (**7b**:**8b** = 12:88), whereas the addition of $KCTf_3$, $LiB(C_6F_5)_4$, NaBARF, $KBPh_4$, $RbBPh_4$, and $(nBu)_4NBPh_4$ was less effective.[54] The decomposition of tetraphenylborate could play an important role in this process,[55] but also a counter-cation effect is conceivable that would influence the ionic character of the indole scaffold.[56] The spiro-fused pentacycle **8c** was obtained exclusively in 62% yield by the reaction of **6c** employing NaBARF.

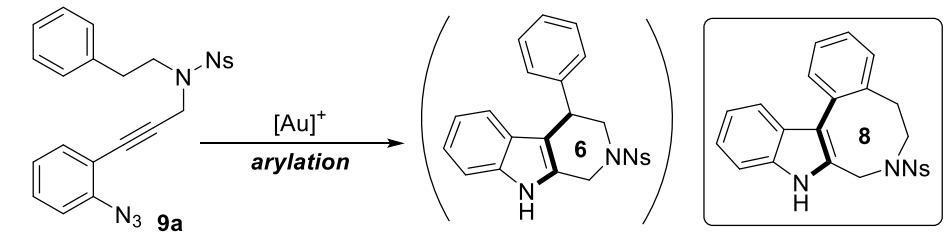


Scheme 5. Synthesis of fused-ring derivatives.

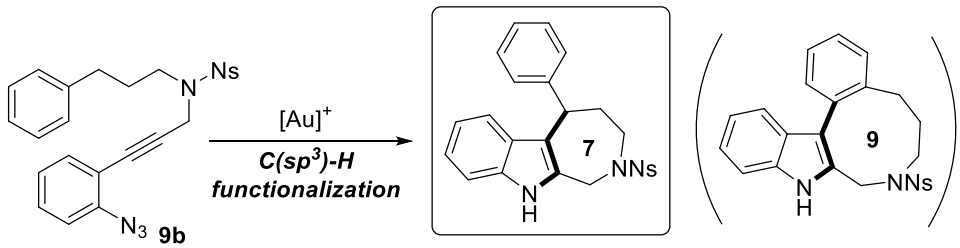
Reaction conditions: [a] Unless otherwise stated, the reaction was conducted under the standard conditions: JohnPhosAu(MeCN)SbF_6 (5 mol %) and TCE (2 mM) at 90 °C for 0.5 h. [b] $NaBPh_4$ (50 mol%) was employed. Tf = triflyl (CF_3SO_2).

Finally, the author intended to exploit the ring size of the products forming during the benzylic functionalization. When **9a** (six-membered ring precursor) was exposed to the gold(I)-catalyzed cyclization conditions, only the eight-membered ring arylation product **11a'** was obtained in 41–72% yield

(Scheme 6). This arylation was favored over the six-membered-ring-forming benzylic C-H functionalization, presumably because of the seven-membered *ipso* cyclization pathway.[43] In contrast, the reaction of the methylene homolog **9b** with JohnPhosAu(MeCN)SbF_6 resulted in the seven-membered ring via distal benzylic functionalization to generate the indole-fused product **11b** in 48% yield, without producing the nine-membered ring arylation product **11b'**. Notably, no π-conjugation for a 1,7-H shift is present in the saturated propyl tether. These observations suggest that the direct arylation towards a high-strain product such as the nine-membered ring is less favored compared to the *C*-cyclization via the benzylic C(sp^3)-H pathway.



cat. [Au]+	11a	11a'
$tBu_3PAuCl/AgSbF_6$[a]	0%	**72%**
JohnPhosAu(MeCN)SbF_6[b]	0%	41%

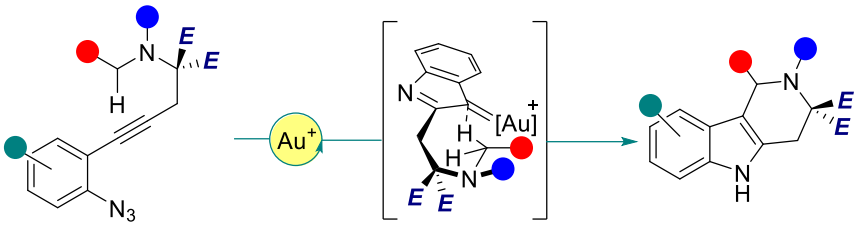


cat. [Au]+	11b	11b'
JohnPhosAu(MeCN)SbF_6[b]	**48%**	0%
$tBu_3PAuCl/AgSbF_6$[c]	12%	0%

Scheme 6. Selectivity study between arylation and C(sp^3)-H functionalization.

Reaction conditions: [a] tBu_3PAuCl (5 mol %), $AgSbF_6$ (10 mol %), dichloromethane (2 mM), rt, 30 min. [b] JohnPhosAu(MeCN)SbF_6 (5 mol %), TCE (2 mM), 90 °C, 15 min. [c] tBu_3PAuCl (5 mol %), $AgSbF_6$ (10 mol %), dichloromethane (0.2 mM), rt, 3 h.

It should be noted that in the final stage just prior to submission of the authors' paper, the related 1,6-hydride shift at the positions adjacent to nitrogen atom was published as a preprint, which was recently published (Scheme 7). [57]



Scheme 7. Gold(I)-catalyzed α-C-H bond functionalization of tertiary amines.[57]

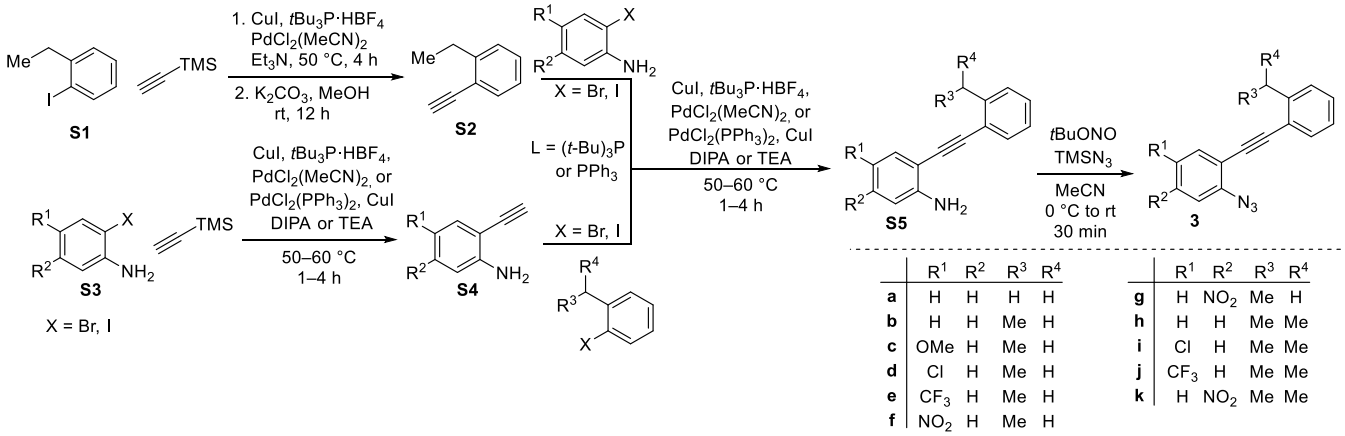
In summary, the author has demonstrated that indole-fused tetra- and pentacycles can be obtained through a gold-catalyzed C(sp^3)-H functionalization originating from azido alkynes. The reaction requires non-coordinating TCE and the cationic JohnPhosAu(MeCN)SbF_6 under dilute conditions. The investigation of the ethyl and isopropyl substrates demonstrated that two isomers can be formed via *C*-cyclization or *N*-cyclization. The selectivity can be controlled by tuning the electron density of the azido-substituted aryl moiety and the stability of the benzylic carbocation, in combination with adjusting the counter-anion effect.

Experimental Section

1. General Methods

Chemicals and solvents were purchased from commercial suppliers (Fujifilm Wako, Kanto Chemical Co., Inc., Merck). Dry THF was dispensed from the solvent purification system of Glass Contour MINI Nikko Hansen & Co., Ltd. NMR spectra were recorded at room temperature on JEOL AL-400 (400 MHz), JEOL ECA-500 (500 MHz), or JEOL ECZ600R (600 MHz) spectrometer if not mentioned otherwise. Chemical shifts are given in ppm and coupling constants in Hz. ^{1}H- and ^{13}C-NMR spectra were calibrated in relation to deuterated solvents according to Fulmer *et al.* ^{13}C-NMR spectra are proton decoupled and in cases of unambiguous results interpreted with help of DEPT, HMQC, and HMBC. All spectra were integrated and processed using ALICE2 software. Exact mass (HRMS) spectra were recorded on JMS-700 mass spectrometer or Shimadzu LC-ESI-IT-TOF-MS equipment. Infrared (IR) spectra were recorded on a FT-IR spectrometer named JASCO FT/IR-4100 with a Germanium ATR-crystal. The solvent or the matrix is denoted in brackets. For the most significant bands the wave number (cm^{-1}) is given. For the flash column chromatography, silica gel (Wakogel C-200E: Wako Pure Chemical Industries, Ltd) was used as stationary phase. As eluents, different mixtures of hexane and ethyl acetate was used. To visualize the substances, ninhydrin, vanillin, 2,4-dinitrophenylhydrazine, and $KMnO_4$ were used as coloring reagents, or the TLC-plate was exposed to ultraviolet light (254 and 366 nm). If not mentioned differently, all reactions were carried out under normal laboratory conditions.

Synthetic Scheme for the Preparation of the Cyclization Precursors



	R^1	R^2	R^3	R^4
a	H	H	H	H
b	H	H	Me	H
c	OMe	H	Me	H
d	Cl	H	Me	H
e	CF_3	H	Me	H
f	NO_2	H	Me	H

	R^1	R^2	R^3	R^4
g	H	NO_2	Me	H
h	H	H	Me	Me
i	Cl	H	Me	Me
j	CF_3	H	Me	Me
k	H	NO_2	Me	Me

General Procedures

GP1: Sonogashira Reaction for Ethyl-Substituted Alkynylanilines

CuI (5 mol %) and $Pd(PPh_3)_2Cl_2$ (5 mol %) or $PdCl_2(MeCN)_2$ (5 mol %) with tBu$_3$P·HBF$_4$ (10 mol %) were suspended in iPr$_2$NH (DIPA) under argon together with the corresponding aryl halide (1.0 equiv). After the suspension was gradually heated to 60 °C over 30 min, TMS-acetylene or **S2** (2.0 equiv) were added dropwise via syringe. After 3-12 h (full conversion monitored by TLC), the reaction was diluted with DCM and filtered through Celite®. The filtrate was washed with H_2O, aqueous NH_4Cl, and brine. After drying with $MgSO_4$ and filtration, the solvent was removed *in vacuo* at 40 °C, the product was purified with silica gel column chromatography to give **S2**, **S4** or **S5**.

GP2: Sonogashira Reaction for Isopropyl-Substituted Alkynylanilines and Related Compounds

CuI (5 mol %) and $Pd(PPh_3)_2Cl_2$ (5 mol %) or $PdCl_2(MeCN)_2$ (5 mol %) with tBu$_3$P·HBF$_4$ (10 mol %) were suspended in iPr$_2$NH (DIPA) under argon together with an aryl halide (2.0 equiv). After the suspension was

gradually heated to 60 °C over 30 min, the alkyne **S4** (1.0 equiv) was added dropwise via syringe. After 3-12 h (full conversion monitored by TLC) the reaction was diluted with DCM and filtered through Celite®. The filtrate was washed with H_2O, aqueous NH_4Cl, and brine. After drying with $MgSO_4$ and filtration, the solvent was removed *in vacuo* at 40 °C, the product was purified with silica gel column chromatography to give **S5**.

GP3: Azidation

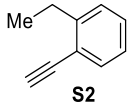
The aniline derivative **S5** (1.0 equiv) was dissolved in MeCN and the mixture was cooled to 0 °C in an ice bath. To this stirred mixture were successively added *t*BuONO (1.5 equiv) and $TMSN_3$ (1.5 equiv) dropwise. The resulting solution was stirred at room temperature for 30 min and concentrated *in vacuo*. The residue was purified with column chromatography to give the desired product **3**.

GP4: Gold(I)-Catalyzed Cyclization

Azido-yne **3** (1.0 equiv) was dissolved in TCE (*ca*. 2 mM) and heated to 90 °C under rigorous stirring. To this stirred mixture, a catalytic amount of JohnPhosAu(MeCN)SbF_6 was added and stirred until full conversion (monitored by TLC). After concentration *in vacuo* the purification was performed by silica gel column chromatography.

2. Preparation of the Cyclization Precursors

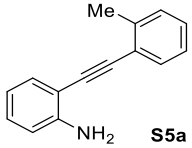
1-Ethyl-2-ethynylbenzene (S2)



S2

According to **GP1**, 1-ethyl-2-iodobenzene (**S1**) (10.0 g, 43.1 mmol) was converted to **S2** (4.90 g, 87%) by the reaction with TMS-acetylene (8.46 g, 86.2 mmol) in the presence of $PdCl_2(PPh_3)_2$ (1.52 g, 2.16 mmol) and CuI (410 mg, 2.16 mmol) in DIPA (300 mL) at 60 °C for 3 h. The crude was diluted with DCM, filtered through Celite® and the filtrate was washed with H_2O (three times), aqueous NH_4Cl (three times), and brine (three times). Purification was performed by silica gel column chromatography (hexane) to give the coupling product as a yellow oil, which was subsequently dissolved in MeOH (300 mL). Next, K_2CO_3 (11.9 g, 86.2 mmol) was added portionwise and the reaction mixture was stirred for 3 h. Purification was performed by silica gel column chromatography (hexane) to give **S2** as a bright colorless oil. The spectral data were in good agreement with those previously reported.[58]

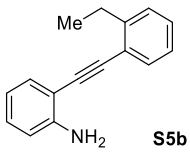
2-(*o*-Tolylethynyl)aniline (S5a)



S5a

According to **GP1**, 2-iodotoluene (1.35 g, 6.20 mmol) was converted to **S5a** (308 mg, 48%) by the reaction with 2-ethynylaniline (**S4a**) (363 mg, 3.10 mmol) in the presence of $PdCl_2(PPh_3)_2$ (109 mg, 0.155 mmol) and CuI (29.5 mg, 0.155 mmol) in DIPA (50 mL) at 60 °C for 3 h. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1) to give **S5a** as a yellow oil. The spectral data were in good agreement with those previously reported.[59]

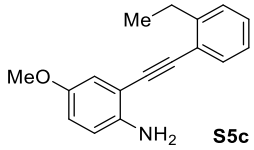
2-[(2-Ethylphenyl)ethynyl]aniline (S5b)



S5b

According to **GP1**, 1-ethyl-2-iodobenzene (**S1**) (1.00 g, 4.31 mmol) was converted to **S5b** (343 mg, 50%) by the reaction with 2-ethynylaniline (**S4a**) (363 mg, 3.10 mmol) in the presence of $PdCl_2(PPh_3)_2$ (109 mg, 0.155 mmol) and CuI (29.5 mg, 0.155 mmol) in DIPA (50 mL) at 60 °C for 3 h. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1) to give **S5b** as a brown oil; IR (neat): 3472 (N-H), 3357 (N-H), 2206 (C≡C),^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.28 (t, J = 7.6 Hz, 3H), 2.87 (q, J = 7.6 Hz, 2H), 4.22 (br s, 2H), 6.65-6.71 (m, 2H), 7.08-7.11 (m, 1H), 7.12-7.16 (m, 1H), 7.20-7.25 (m, 2H), 7.36 (d, J = 7.7 Hz, 1H), 7.48 (d, J = 7.7 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$**)** δ: 14.7, 27.8, 89.3, 93.3, 107.9, 114.2, 117.7, 122.2, 125.6, 127.9, 128.4, 129.5, 132.0 (2C), 145.5, 147.5; HRMS calcd for $C_{16}H_{16}N^+$ $[M + H]^+$: 222.1277, found 222.1275.

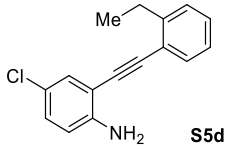
2-[(2-Ethylphenyl)ethynyl]-4-methoxyaniline (S5c)



S5c

According to **GP1**, 2-bromo-4-methoxyaniline (1.00 g, 4.27 mmol) was converted to **S5c** (429 mg, 40%) by the reaction with 1-ethyl-2-ethynylbenzene (**S2**) (1.11 g, 8.54 mmol) in the presence of $PdCl_2(MeCN)_2$ (55.4 mg, 214 μmol), tBu$_3$P·HBF$_4$ (124 mg, 428 μmol) and CuI (40.8 mg, 214 μmol) in DIPA (30 mL) at 60 °C for 12 h. Purification was performed by silica gel column chromatography (hexane/EtOAc = 5/1) to give **S5c** as a brown oil; IR (neat): 3483 (N-H), 3381 (N-H), 2209 (C≡C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.30 (t, J = 7.7 Hz, 3H), 2.89 (q, J = 7.7 Hz, 2H), 3.75 (s, 3H), 4.01 (s, 2H), 6.68 (d, J = 8.8 Hz, 1H), 6.78 (dd, J = 8.8, 2.9 Hz, 1H), 6.92 (d, J = 2.9 Hz, 1H), 7.18 (dd, J = 7.4 Hz, 1H), 7.24-7.29 (m, 2H), 7.51 (d, J = 7.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.8, 27.9, 55.8, 89.4, 93.3, 109.0, 115.91, 115.93, 117.1, 122.2, 125.7, 128.0, 128.6, 132.1, 141.8, 145.7, 151.9; HRMS calcd for $C_{17}H_{18}NO$ $[M + H]^+$: 252.1383, found 252.1383.

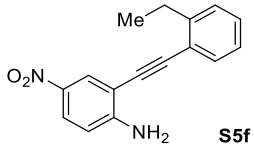
4-Chloro-2-[(2-ethylphenyl)ethynyl]aniline (S5d)



S5d

According to **GP1**, 2-bromo-4-chloroaniline (0.80 g, 3.84 mmol) was converted to **S5d** (521 mg, 53%) by the reaction with 1-ethyl-2-ethynylbenzene (**S2**) (1.00 g, 7.68 mmol) in the presence of $PdCl_2(MeCN)_2$ (49.8 mg, 192 μmol), tBu$_3$P·HBF$_4$ (111 mg, 324 μmol) and CuI (36.6 mg, 192 μmol) in DIPA (50 mL) at 60 °C for 12 h. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1) to give **S5d** as an orange oil; IR (neat): 3483 (N-H), 3381 (N-H), 2198 (C≡C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.28 (t, J = 7.6 Hz, 3H), 2.86 (q, J = 7.6 Hz, 2H), 4.25 (br s, 2H), 6.61 (d, J = 8.6 Hz, 1H), 7.06 (dd, J = 8.6, 2.6 Hz, 1H), 7.17 (ddd, J = 7.3, 7.3, 2.3 Hz, 1H), 7.23-7.29 (m, 2H), 7.32 (d, J = 2.3 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.8, 27.7, 88.0, 94.3, 106.7, 115.4, 121.8, 122.2, 125.8, 128.0, 128.8, 129.5, 131.2, 132.1, 145.8, 146.2; HRMS calcd for $C_{16}H_{14}ClNNa$ $[M + Na]^+$: 278.0707, found 278.0730.

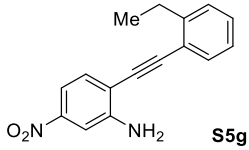
2-[(2-Ethylphenyl)ethynyl]-4-nitroaniline (S5f)



S5f

According to **GP1**, 2-bromo-4-nitroaniline (835 mg, 3.84 mmol) was converted to **S5f** (614 mg, 60%) by the reaction with 1-ethyl-2-ethynylbenzene (**S2**) (1.00 g, 7.68 mmol) in the presence of $PdCl_2(MeCN)_2$ (49.6 mg, 192 μmol), tBu$_3$P·HBF$_4$ (111 mg, 384 μmol) and CuI (36.5 mg, 192 μmol) in DIPA (40 mL) at 60 °C for 6 h. Purification was performed by silica gel column chromatography (hexane/EtOAc = 5/1) to give **S5f** as a yellow oil; IR (neat): 3482 (N-H), 3360 (N-H), 2205 (C≡C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.31 (t, J = 7.5 Hz, 3H), 2.89 (q, J = 7.5 Hz, 2H), 5.02 (br s, 2H), 6.72 (d, J = 9.3 Hz, 1H), 7.19-7.38 (m, 3H), 7.52 (d, J = 7.0 Hz, 1H), 8.05 (dd, J = 9.3, 2.9 Hz, 1H), 8.29 (d, J = 2.9 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.8, 27.8, 86.5, 95.3, 107.9, 113.2, 121.3, 125.84, 125.86, 128.1, 128.6, 129.3, 132.3, 138.6, 146.0, 152.7; HRMS calcd for $C_{16}H_{15}N_2O_2^+$ [M + H]$^+$: 267.1128, found 267.1124.

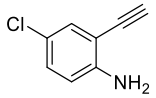
2-[(2-Ethylphenyl)ethynyl]-5-nitroaniline (S5g)



S5g

According to **GP1**, 2-bromo-5-nitroaniline (835 mg, 3.84 mmol) was converted to **S5g** (634 mg, 63%) by the reaction with 1-ethyl-2-ethynylbenzene (**S2**) (1.00 g, 7.68 mmol) in the presence of $PdCl_2(MeCN)_2$ (49.7 mg, 192 μmol), tBu$_3$P·HBF$_4$ (111 mg, 384 μmol) and CuI (36.8 mg, 193 μmol) in DIPA (40 mL) at 60 °C for 12 h. Purification was performed by silica gel column chromatography (hexane/EtOAc = 5/1) to give **S5g** as a brown oil; IR (neat): 3493 (N-H), 3393 (N-H), 2204 (C≡C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.29 (t, J = 7.6 Hz, 3H), 2.87 (q, J = 7.6 Hz, 2H), 4.64 (br s, 2H), 7.17-7.33 (m, 3H), 7.41 (d, J = 8.4 Hz, 1H), 7.48-7.54 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.6, 27.8, 87.6, 97.6, 108.2, 112.2, 114.2, 121.2, 125.7, 128.0, 129.3, 132.2, 133.3, 145.9, 147.97, 148.02; HRMS calcd for $C_{16}H_{14}N_2NaO_2^+$ [M + Na]$^+$: 289.0947, found 289.0946.

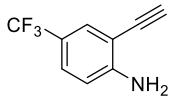
4-Chloro-2-ethynylaniline (S4i)



S4i

According to **GP1**, 4-chloro-2-iodoaniline (**S3i**) (2.0 g, 7.89 mmol) was converted to **S4i** (825 mg, 69%) by the reaction with TMS-acetylene (1.54 g, 15.8 mmol) in the presence of $PdCl_2(PPh_3)_2$ (277 mg, 395 μmol) and CuI (75.1 mg, 395 μmol) in DIPA (100 mL) at 60 °C for 3 h. The crude was diluted with DCM, filtered through Celite® and the filtrate was washed with H_2O, aqueous NH_4Cl, and brine. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1) to give the coupling product as a yellow oil, which was subsequently dissolved in 100 mL of MeOH. K_2CO_3 (2.18 g, 15.8 mmol) was added portionwise and the reaction mixture was stirred for 3 h. After purification with silica gel column chromatography (hexane/EtOAc = 10/1), the desired product was obtained as a bright yellow oil. The spectral data were in good agreement with those previously reported.[60]

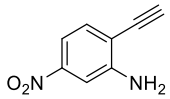
2-Ethynyl-4-(trifluoromethyl)aniline (S4j)



S4j

According to **GP1**, 2-iodo-4-(trifluoromethyl)aniline (**S3j**) (2.0 g, 6.97 mmol) was converted to **S4j** (928 mg, 72%) by the reaction with TMS-acetylene (1.36 g, 13.9 mmol) in the presence of $PdCl_2(PPh_3)_2$ (245 mg, 349 μmol) and CuI (66.5 mg, 349 μmol) in DIPA (50 mL) at 60 °C for 3 h. The crude was diluted with DCM, filtered through Celite® and the filtrate was washed with H_2O, aqueous NH_4Cl, and brine. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1) to give the coupling product as a yellow oil, which was subsequently dissolved in MeOH (50 mL). K_2CO_3 (1.9 g, 13.9 mmol) was added portionwise and the reaction mixture was stirred for 3 h. After purification with silica gel column chromatography (hexane/EtOAc = 10/1), the desired product was obtained as a colorless oil. The spectral data were in good agreement with those previously reported.[60]

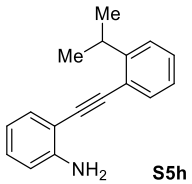
2-Ethynyl-5-nitroaniline (S4k)



S4k

According to **GP1**, 2-iodo-5-nitroaniline (**S3k**) (2.00 g, 7.55 mmol) was converted to **S4k** (967 mg, 79%) by the reaction with TMS-acetylene (1.39 g, 15.1 mmol) in the presence of $PdCl_2(PPh_3)_2$ (1.52 g, 378 μmol) and CuI (71.9 mg, 378 μmol) in DIPA (100 mL) at 60 °C for 3 h. The crude was diluted with DCM, filtered through Celite® and the filtrate was washed with H_2O, aqueous NH_4Cl, and brine. Purification was performed by silica gel column chromatography (hexane/EtOAc = 5/1) to give the coupling product as a yellow solid, which was subsequently dissolved in MeOH (100 mL). K_2CO_3 (2.09 g, 15.1 mmol) was added portionwise, and the reaction mixture was stirred for 3 h. After purification with silica gel column chromatography (hexane/EtOAc = 5/1), the desired product was obtained as a bright yellow solid. The spectral data were in good agreement with those previously reported.[61]

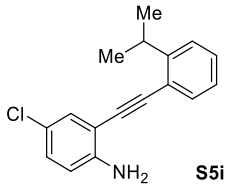
2-[(2-Isopropylphenyl)ethynyl]aniline (S5h)



S5h

According to **GP2**, 2-bromocumene (1.70 g, 8.52 mmol) was converted to **S5h** in (401 mg, 40%) by the reaction with 2-ethynylaniline (**S4a**) (500 mg, 4.26 mmol) in the presence of $PdCl_2(MeCN)_2$ (55.3 mg, 213 μmol), tBu$_3$P·HBF$_4$ (121 mg, 416 μmol) and CuI (40.6 mg, 213 μmol) in DIPA (40 mL) at 60 °C for 5 h. Purification was performed by silica gel column chromatography (hexane) to give **S5h** as a yellow oil; IR (neat): 3471 (N-H), 3384 (N-H), 2205 (C≡C); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.30 (d, J = 6.9 Hz, 6H), 3.54 (sept, J = 6.9 Hz, 1H), 4.25 (br s, 2H), 6.69-6.72 (m, 2H), 7.10-7.18 (m, 2H), 7.29-7.30 (m, 2H), 7.37 (d, J = 7.6 Hz, 1H), 7.50 (d, J = 7.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 23.0 (2C), 31.7, 89.5, 93.3, 108.2, 114.3, 117.9, 122.0, 124.9, 125.5, 128.6, 129.6, 132.0, 132.2, 147.6, 149.9; HRMS calcd for $C_{17}H_{18}N^+$ [M + H]$^+$: 236.1434, found 236.1433.

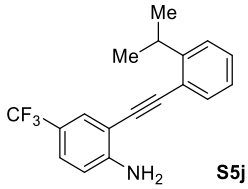
4-Chloro-2-[(2-isopropylphenyl)ethynyl]aniline (S5i)



S5i

According to **GP2**, 2-bromocumene (1.70 g, 8.52 mmol) was converted to **S5i** (502 mg, 44%) by the reaction with 4-chloro-2-ethynylaniline (**S4i**) (643 mg, 4.26 mmol) and in the presence of $PdCl_2(MeCN)_2$ (55.5 mg, 214 μmol), *t*$Bu_3P{\cdot}HBF_4$ (120 mg, 414 μmol) and CuI (40.5 mg, 213 μmol) in DIPA (40 mL) at 60 °C for 5 h. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1) to give **S5i** as an orange oil; IR (neat): 3484 (N-H), 3380 (N-H), 2199 (C≡C); ^{1}H NMR (600 MHz, $CDCl_3$) *δ*: 1.26-1.28 (m, 6H), 3.46-3.53 (m, 1H), 4.23 (br s, 2H), 6.54 (d, *J* = 9.0 Hz, 1H), 6.99-7.02 (m, 1H), 7.07-7.15 (m, 1H), 7.25-7.31 (m, 3H), 7.44-7.47 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) *δ*: 22.9 (2C), 31.6, 88.2, 94.3, 109.4, 115.3, 121.3, 121.9, 124.8, 125.5, 128.8, 129.3, 130.9, 132.2, 146.2, 149.9; HRMS calcd for $C_{17}H_{17}ClN$ $[M + H]^+$: 270.1044, found 270.1041.

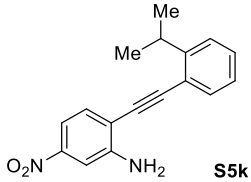
2-[(2-Isopropylphenyl)ethynyl]-4-(trifluoromethyl)aniline (S5j)



S5j

According to **GP2**, 2-bromocumene (1.70 g, 8.52 mmol) was converted to **S5j** in (711 mg, 55%) as an yellow oil by the reaction with 2-ethynyl-4-(trifluoromethyl)aniline (**S4j**) (789 mg, 4.26 mmol) in the presence of $PdCl_2(MeCN)_2$ (55.3 mg, 213 μmol), *t*$Bu_3P{\cdot}HBF_4$ (122 mg, 421 μmol) and CuI (40.5 mg, 213 μmol) in DIPA (40 mL) at 60 °C for 4 h. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1) to give **S5j** as a yellow oil as a yellow oil; IR (neat): 3488 (N-H), 3388 (N-H), 2100 (C≡C); ^{1}H NMR (600 MHz, $CDCl_3$) *δ*: 1.32 (d, *J* = 6.9 Hz, 6H), 3.52 (sept, *J* = 6.9 Hz, 1H), 4.59 (br s, 2H), 6.76 (d, *J* = 8.5 Hz, 1H), 7.18-7.21 (m, 1H), 7.32-7.37 (m, 3H), 7.51 (d, *J* = 7.7 Hz, 1H), 7.62 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) *δ*: 23.0 (2C), 31.8, 88.0, 94.4, 107.8, 113.6, 119.7 (q, *J* = 32.9 Hz), 121.4, 124.4 (q, *J* = 270.5 Hz), 125.0, 125.7, 126.4 (q, *J* = 3.6 Hz), 129.1, 129.6, 129.3 (q, *J* = 3.9 Hz), 150.08, 150.15; HRMS calcd for $C_{18}H_{17}F_3N^+$ $[M + H]^+$: 304.1308, found 304.1310.

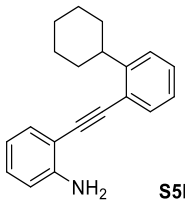
2-[(2-Isopropylphenyl)ethynyl]-5-nitroaniline (S5k)



S5k

According to **GP2**, 2-bromocumene (1.70 g, 8.52 mmol) was converted to **S5k** in (597 mg, 50%) as an off-white solid by the reaction with 5-nitro-2-ethynylaniline (**S4k**) (954 mg, 4.26 mmol) in the presence of $PdCl_2(MeCN)_2$ (55.4 mg, 214 μmol), *t*$Bu_3P{\cdot}HBF_4$ (121 mg, 416 μmol) and CuI (40.6 mg, 213 μmol) in DIPA (40 mL) at 60 °C for 5 h. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1) to give **S5k** as a brown oil; IR (neat): 3492 (N-H), 3392 (N-H), 2203 (C≡C); ^{1}H NMR (600 MHz, $CDCl_3$) *δ*: 1.31-1.33 (m, 6H), 3.50 (sept, *J* = 6.2 Hz, 1H), 4.61 (br m, 2H), 7.19-7.21 (m, 1H), 7.32-7.37 (m, 2H), 7.44-7.47 (m, 1H), 7.51-7.58 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) *δ*: 23.1 (2C), 31.8, 87.8, 97.8, 108.4, 112.5, 114.4, 120.9, 125.1, 125.8, 129.5, 132.46, 132.48, 148.0, 148.1, 150.3; HRMS calcd for $C_{17}H_{17}N_2O_2^+$ $[M + H]^+$: 267.1128, found 267.1124.

2-[(2-Cyclohexylphenyl)ethynyl]aniline (S5l)

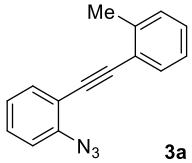


S5l

According to **GP1**, 1-bromo-2-cyclohexylbenzene (2.39 g, 10.0 mmol) was converted to **S5l** in (620 mg, 45%) as yellow oil by the reaction with 2-ethynylaniline (**S4a**) (585 mg, 5.00 mmol) in the presence of $PdCl_2(MeCN)_2$ (64.7 mg, 249 μmol), *t*$Bu_3P{\cdot}HBF_4$ (145 mg, 500 μmol) and CuI (47.5 mg, 250 μmol) in DIPA (40 mL) at 60 °C for 4 h. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1) to give **S5l** as a brown oil; IR (neat): 3487 (N-H), 3392 (N-H), 2205 (C≡C); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.25-1.29 (m, 1H), 1.43-1.50 (m, 4H), 1.76-1.79 (m, 1H), 1.85-1.90 (m, 2H), 1.97-1.98 (m, 2H), 3.12-3.18 (m, 1H), 4.29 (s, 2H), 6.71-6.76 (m, 2H), 7.13-7.20 (m, 2H), 7.25-7.32 (m, 2H), 7.37 (dd, J = 7.9, 1.4 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 26.2, 27.0 (2C), 33.5 (2C), 42.3, 89.5, 93.6, 108.5, 114.3, 118.0, 122.2, 125.48, 125.55, 128.5, 129.6, 132.1, 132.2, 147.6, 149.0; HRMS calcd for $C_{20}H_{22}N^+$ $[M + H]^+$: 276.1747, found 276.1742.

<u>Preparation of Azido-ynes</u>

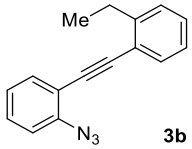
1-Azido-2-(*o*-tolylethynyl)benzene (3a)



3a

According to **GP3**, **S5a** (343 mg, 1.55 mmol) was converted to **3a** (336 mg, 93%) by the reaction with *t*BuONO (307 μL, 2.33 mmol) and $TMSN_3$ (323 μL, 2.33 mmol) in MeCN (10 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 20/1): bright yellow oil; IR (neat): 2251 (C≡C), 2126 (N≡N); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.54 (s, 3H), 7.10-7.19 (m, 3H), 7.22-7.25 (m, 2H), 7.31-7.34 (m, 1H), 7.49-7.54 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 20.7, 88.8, 94.3, 115.7, 118.7, 122.7, 124.6, 125.6, 128.6, 129.4, 129.5, 131.9, 133.5, 140.4, 140.8; HRMS calcd for $C_{15}H_{12}N_3^+$ $[M + H]^+$: 234.1026, found 234.1008.

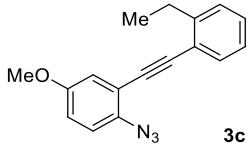
1-Azido-2-[(2-ethylphenyl)ethynyl]benzene (3b)



3b

According to **GP3**, **S5b** (343 mg, 1.55 mmol) was converted to **3b** (356 mg, 93%) by the reaction with *t*BuONO (308 μL, 2.33 mmol) and $TMSN_3$ (308 μL, 2.33 mmol) in MeCN (10 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 20/1) to give **3b** as a bright yellow oil; IR (neat):2218 (C≡C), 2110 (N≡N); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.31 (t, J = 7.5 Hz, 3H), 2.93 (q, J = 7.5 Hz, 2H), 7.10-7.16 (m, 2H), 7.18 (dd, J = 7.6 Hz, 1H), 7.23-7.30 (m, 2H), 7.32-7.35 (m, 1H), 7.50 (d, J = 7.7 Hz, 1H), 7.53 (d, J = 7.7 Hz 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.9, 27.8, 88.3, 94.0, 115.7, 118.7, 122.0, 124.59, 125.62, 128.0, 128.8, 129.3, 132.1, 133.4, 140.8, 146.4; HRMS calcd for $C_{16}H_{14}N_3$ $[M + H]^+$: 248.1182, found 248.1196.

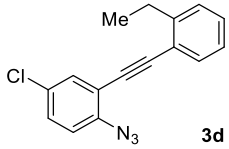
1-Azido-2-[(2-ethylphenyl)ethynyl]-4-methoxybenzene (3c)



3c

According to **GP3, S5c** (429 mg, 1.71 mmol) was converted to **3c** (422 mg, 89%) by the reaction with *t*BuONO (339 μL, 2.57 mmol) and $TMSN_3$ (356 μL, 2.57 mmol) in MeCN (10 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 15/1) to give **3c** as a bright yellow oil; IR (neat): 2252 (C≡C), 2121 (N≡N); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.31 (t, J = 7.6 Hz, 3H), 2.92 (q, J = 7.6 Hz, 2H), 3.78 (s, 3H), 6.88 (dd, J = 8.6, 3.1 Hz, 1H), 7.00-7.03 (m, 2H), 7.17 (dd, J = 7.2, 7.2 Hz, 1H), 7.22-7.23 (m, 2H), 7.53 (d, J = 7.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.9, 27.7, 55.5, 88.3, 93.8, 116.0, 116.4, 117.5, 119.8, 121.8, 125.6, 128.0, 128.8, 132.1, 133.5, 146.4, 156.3; HRMS calcd for $C_{17}H_{16}N_3^+$ $[M + H]^+$: 278.1288, found 278.1276.

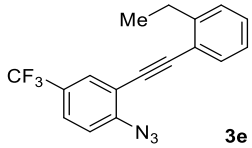
1-Azido-4-chloro-2-[(2-ethylphenyl)ethynyl]benzene (3d)



3d

According to **GP3**, **S5d** (517 mg, 2.04 mmol) was converted to **3d** (422 mg, 90%) by the reaction with *t*BuONO (404 μL, 3.06 mmol) and $TMSN_3$ (424 μL, 3.06 mmol) in MeCN (10 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 15/1) to give **3d** as a brown oil; IR (neat): 2219 (C≡C), 2125 (N≡N); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30 (t, J = 7.5 Hz, 3H), 2.91 (q, J = 7.5 Hz, 2H), 7.08-7.13 (m, 2H), 7.18 (ddd, J = 7.4, 7.4, 1.5 Hz, 1H), 7.24-7.31 (m, 2H), 7.41 (d, J = 8.7 Hz, 1H), 7.51 (dd, J = 7.5, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9, 27.8, 87.4, 95.0, 114.4, 119.1, 121.7, 125.0, 125.7, 128.0, 129.0, 132.2, 134.2, 134.9, 142.0, 146.5; HRMS calcd for $C_{16}H_{12}ClKN_3^+$ $[M + K]^+$: 320.0351, found 320.0358.

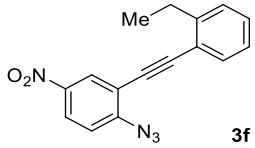
1-Azido-2-[(2-ethylphenyl)ethynyl]-4-(trifluoromethyl)benzene (3e)



3e

According to **GP2**, 2-bromo-4-trifluoromethylaniline (921 mg, 3.84 mmol) was converted to **S5e** (containing some impurities) by the reaction with 1-ethyl-2-ethynylbenzene (**S2**) (1.00 g, 7.62 mmol) in the presence of $PdCl_2(MeCN)_2$ (11.0 mg, 192 μmol), tBu$_3$P·HBF$_4$ (24.7 mg, 85.0 μmol), CuI (8.10 mg, 192 μmol) in Et_3N (15 mL) at 50 °C for 4 h. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1) to give **S5e**, which was used without further purification. According to **GP3**, the crude **S5e** was converted to **3e** (500 mg, 41%) by the reaction with *t*-BuONO (761 μL, 5.76 mmol) and $TMSN_3$ (797 μL, 5.76 mmol) in MeCN (10 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane) to give **3e** as a brown oil; IR (neat): 2213 (C≡C), 2110 (N≡N); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.31 (t, J = 7.6 Hz, 3H), 2.91 (q, J = 7.6 Hz, 2H), 7.13 (d, J = 8.4 Hz, 1H), 7.16 (ddd, J = 7.4, 7.4, 1.3 Hz, 1H), 7.23 (d, J = 7.4 Hz, 1H), 7.28 (ddd, J = 7.4, 7.4, 1.3 Hz, 1H), 7.49 (dd, J = 8.4, 1.7 Hz, 1H), 7.52 (dd, J = 7.4, 1.3 Hz, 1H), 7.72 (d, J = 1.7 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.9, 27.8, 87.0, 95.6, 116.3, 118.9, 123.5 (J = 272.1 Hz), 121.4, 125.7, 125.8 (J = 3.8 Hz), 126.9 (J = 33.2 Hz), 128.0, 129.2, 130.3 (J = 3.8 Hz), 132.3, 144.2, 146.6; HRMS calcd for $C_{17}H_{13}F_3N_3^+$ $[M + H]^+$: 316.1056, found 316.1036.

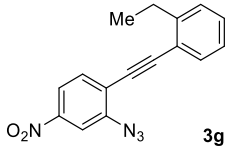
1-Azido-2-[(2-ethylphenyl)ethynyl]-4-nitrobenzene (3f)



3f

According to **GP3**, **S5f** (614 mg, 2.30 mmol) was converted to **3f** (612 mg, 91%) by the reaction with *t*BuONO (451 μL, 3.45 mmol) and $TMSN_3$ (478 μL, 3.45 mmol) in MeCN (10 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1) to give **3f** as a yellow oil; IR (neat): 2209 (C≡C), 2126 (N≡N); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.31 (t, J = 7.6 Hz, 3H), 2.91 (q, J = 7.6 Hz, 2H), 7.19-7.22 (m, 2H), 7.25-7.27 (m, 1H), 7.32 (ddd, J = 7.5, 7.5, 1.4 Hz, 1H), 7.53 (dd, J = 7.7, 1.2 Hz, 1H), 8.16 (dd, J = 8.9, 2.6 Hz, 1H), 8.33 (d, J = 2.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 15.1, 27.7, 86.3, 96.6, 116.7, 119.1, 121.0, 124.3, 126.8, 128.2, 128.6, 129.7, 132.4, 144.1, 146.8, 147.1; HRMS calcd for $C_{16}H_{12}N_4NaO_2^+$ [M + Na]$^+$: 315.0852, found 315.0864.

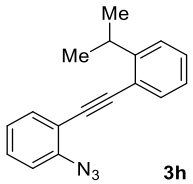
2-Azido-1-[(2-ethylphenyl)ethynyl]-4-nitrobenzene (3g)



3g

According to **GP3**, **S5g** (634 mg, 2.42 mmol) was converted to **3g** (667 mg, 95%) by the reaction with *t*BuONO (479 μL, 3.63 mmol) and $TMSN_3$ (502 μL, 3.63 mmol) in MeCN (10 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1) to give **3g** as a brown oil; IR (neat): 2212 (C≡C), 2119 (N≡N); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.31 (t, J = 7.6 Hz, 3H), 2.90 (q, J = 7.6 Hz, 2H), 7.20 (ddd, J = 7.5, 7.5, 1.4 Hz, 1H), 7.23-7.28 (m, 1H), 7.32 (ddd, J = 7.5, 7.5, 1.4 Hz, 1H), 7.52 (dd, J = 7.5, 1.4 Hz, 1H), 7.58 (d, J = 8.3 Hz, 1H), 7.91 (d, J = 2.2 Hz, 1H), 7.91-7.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9, 27.7, 87.0, 99.4, 113.8, 119.3, 120.7, 122.1, 125.8, 128.1, 129.7, 132.4, 133.6, 142.2, 146.6, 147.3; HRMS calcd for $C_{16}H_{13}N_4O_2^+$ [M + H]$^+$: 293.1033, found 293.1047.

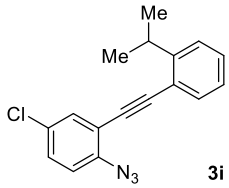
1-Azido-2-[(2-isopropylphenyl)ethynyl]benzene (3h)



3h

According to **GP3**, **S5h** (401 mg, 1.70 mmol) was converted to **3h** (426 mg, 96%) by the reaction with *t*BuONO (337 μL, 2.55 mmol) and $TMSN_3$ (353 μL, 2.55 mmol) in MeCN (10 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane) to give **3h** as a yellow oil; IR (neat): 2251 (C≡C), 2126 (N≡N); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.32 (d, J = 6.9 Hz, 6H), 3.60 (sept, J = 6.9 Hz, 1H), 7.11-7.21 (m, 3H), 7.27-7.38 (m, 3H), 7.51 (dd, J = 7.7, 1.5 Hz, 1H), 7.54 (d, J = 7.7 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 23.1 (2C), 31.6, 88.5, 94.1, 115.8, 118.7, 121.6, 124.6, 125.0, 125.5, 128.9, 129.3, 132.3, 133.4, 140.9, 150.7; HRMS calcd for $C_{17}H_{15}N_3Na^+$ [M + Na]$^+$: 284.1158, found 284.1140.

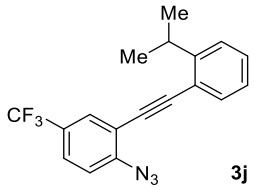
1-Azido-4-chloro-2-[(2-isopropylphenyl)ethynyl]benzene (3i)



3i

According to **GP3**, **S5i** (502 mg, 1.87 mmol) was converted to **3i** (498 mg, 90%) by the reaction with *t*BuONO (371 μL, 2.81 mmol) and $TMSN_3$ (389 μL, 2.81 mmol) in MeCN (10 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 20/1) to give **3i** as a yellow oil; IR (neat): 2210 (C≡C), 2126 (N≡N); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.32 (d, J = 7.4 Hz, 6H), 3.53-3.60 (m, 1H), 7.07 (d, J = 8.6 Hz, 1H), 7.18 (dd, J = 7.1 Hz, 1H), 7.28-7.36 (m, 4H), 7.47 (d, J = 2.3 Hz, 1H), 7.53 (d, J = 7.5 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 23.2 (2C), 31.8, 87.2, 95.4, 117.3, 120.0, 121.1, 124.9, 125.6, 129.31, 129.33, 129.7, 132.4, 132.8, 139.4, 150.8; HRMS calcd for $C_{17}H_{15}ClN_3^+$ $[M + H]^+$: 296.0949, found 296.0944.

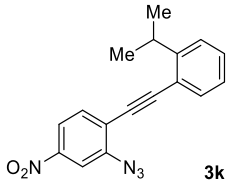
1-Azido-2-[(2-isopropylphenyl)ethynyl]-4-(trifluoromethyl)benzene (3j)



3j

According to **GP3**, **S5j** (711 mg, 2.34 mmol) was converted to **3j** (689 mg, 91%) by the reaction with *t*BuONO (464 μL, 3.51 mmol) and $TMSN_3$ (486 μL, 3.51 mmol) in MeCN (10 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 20/1) to give **3j** as a yellow oil; IR (neat): 2212 (C≡C), 2104 (N≡N); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.34 (d, J = 7.1 Hz, 6H), 3.60 (sept, J = 7.1 Hz, 1H), 7.17-7.28 (m, 2H), 7.31-7.37 (m, 2H), 7.56 (dd, J = 8.0 Hz, 2H), 7.76 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 23.2 (2C), 31.7, 87.2, 95.7, 116.4, 119.1, 121.1, 123.5 (q, J = 272 Hz), 125.1, 125.7, 126.0 (q, J = 3.7 Hz), 127.0 (q, J = 33.5 Hz), 129.5, 130.4 (q, J = 3.7 Hz), 132.5, 144.3, 150.9; HRMS calcd for $C_{18}H_{15}N_3F_3^+$ $[M +H]^+$: 330.1213, found 330.1216.

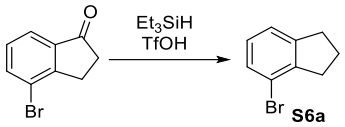
2-Azido-1-[(2-isopropylphenyl)ethynyl]-4-nitrobenzene (3k)



3k

According to **GP3**, **S5k** (597 mg, 2.13 mmol) was converted to **3k** (568 mg, 87%) by the reaction with *t*BuONO (414 μL, 3.20 mmol) and $TMSN_3$ (443 μL, 3.20 mmol) in MeCN (10 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 20/1) to give **3k** as a yellow oil; IR (neat): 2212 (C≡C), 2117 (N≡N); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.33 (d, J = 6.9 Hz, 6H), 3.57 (sept, J = 6.9 Hz, 1H), 7.21 (ddd, J = 7.4, 1.3 Hz, 1H), 7.32-7.41 (m, 2H), 7.55 (dd, J = 7.7, 1.3 Hz, 1H), 7.63 (d, J = 8.5 Hz, 1H), 7.97 (dd, J = 8.5, 2.2 Hz, 1H), 8.00 (d, J = 2.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 23.2 (2C), 31.7, 87.2, 99.6, 113.9, 119.5, 120.6, 122.3, 125.2, 125.7, 130.0, 132.6, 133.8, 142.2, 147.4, 151.1; HRMS calcd for $C_{17}H_{15}N_4O_2^+$ $[M + H]^+$: 307.1190, found 336.1174.

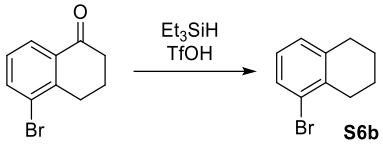
4-Bromo-2,3-dihydro-1*H*-indene (S6a)



S6a

TfOH (1.68 mL, 19.0 mmol) was added dropwise to a solution of 4-bromo-2,3-dihydro-1*H*-inden-1-one (2.0 g, 9.48 mmol) and Et_3SiH (3.03 mL, 19.0 mmol) in DCM (50 mL) while stirring at 0 °C. The mixture was allowed to warm to room temperature and stirred for 4 h. After addition of water and washing with aqueous $NaHCO_3$, the organic layer was separated and dried with Na_2SO_4. After concentration *in vacuo*, the purification was performed by silica gel column chromatography with hexane to give **S6a** (1.61 g, 86%). The spectral data were in good agreement with those previously reported.[62]

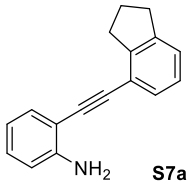
5-Bromo-1,2,3,4-tetrahydronaphthalene (S6b)



S6b

TfOH (1.57 mL, 17.8 mmol) was added dropwise to a solution of 5-bromo-3,4-dihydronaphthalen-1(*2H*)-one (2.0 g, 8.89 mmol) and Et_3SiH (2.84 mL, 17.8 mmol) in DCM (50 mL) while stirring at 0 °C. The mixture was allowed to warm to room temperature and stirred for 4 h. After addition of water and washing with aqueous $NaHCO_3$, the organic layer was separated and dried with Na_2SO_4. After concentration *in vacuo*, the purification was performed by silica gel column chromatography with hexane to give **S6b** (1.60 g, 85%). The spectral data were in good agreement with those previously reported.[63]

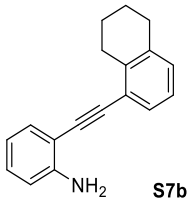
2-[(2,3-Dihydro-1*H*-inden-4-yl)ethynyl]aniline (S7a)



S7a

According to **GP2**, bromoindane **S6a** (1.97 g, 10.0 mmol) was converted to **S7a** in (537 mg, 46%) by the reaction with 2-ethynylaniline (**S4a**) (585 mg, 5.00 mmol) in the presence of $PdCl_2(MeCN)_2$ (64.9 mg, 250 µmol), (tBu$_3$)P·HBF$_4$ (145 mg, 500 µmol) and CuI (47.6 mg, 250 µmol) in DIPA (40 mL) at 60 °C for 4 h to give **S7a** as a brown oil; IR (neat): 3465 (N-H), 3387 (N-H), 2189 (C≡C); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.09 (tt, J = 7.5, 7.5 Hz, 2H), 2.95 (t, J = 7.5 Hz, 2H), 3.05 (t, J = 7.5 Hz, 2H), 4.26 (br s, 2H), 6.70-6.72 (m, 2H), 7.12 (dd, J = 7.5, 7.5 Hz, 2H), 7.18 (d, J = 7.5 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H), 7.36 (d, J = 7.5 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 24.5, 32.8, 33.2, 88.5, 93.6, 108.2, 114.3, 117.9, 119.5, 124.4, 126.2, 128.8, 129.6, 132.0, 144.2, 146.2, 147.6; HRMS calcd for $C_{17}H_{16}N^+$ [M + H]$^+$: 234.1277, found 234.1293.

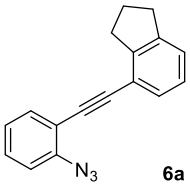
2-[(5,6,7,8-Tetrahydronaphthalen-1-yl)ethynyl]aniline (S7b)



S7b

According to **GP2**, bromotetraline **S6b** (2.11 g, 10.0 mmol) was converted to **S7b** in (606 mg, 49%) by the reaction with 2-ethynylaniline (**S4a**) (588 mg, 5.02 mmol) and in the presence of $PdCl_2(MeCN)_2$ (65.0 mg, 250 μmol), tBu$_3$P·HBF$_4$ (145 mg, 500 μmol) and CuI (47.7 mg, 250 μmol) in DIPA (40 mL) at 60 °C for 4 h to give **S7b** as a brown oil; IR (neat): 3466 (N-H), 3385 (N-H), 2185 (C≡C); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.88-2.00 (m, 4H), 2.89 (t, J = 6.4 Hz, 2H), 3.08 (t, J = 6.4 Hz, 2H), 4.38 (br s, 2H), 6.82-6.86 (m, 2H), 7.16-7.27 (m, 3H), 7.48-7.51 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 22.8, 23.1, 28.3, 29.7, 90.3, 93.6, 108.4, 114.3, 117.9, 123.0, 125.1, 129.26, 129.31, 129.5, 132.0, 137.5, 138.5, 147.5; $C_{18}H_{18}N^+$ [M + H]$^+$: 248.1434, found 248.1429.

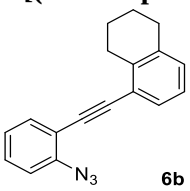
4-[(2-Azidophenyl)ethynyl]-2,3-dihydro-1*H*-indene (6a)



6a

According to **GP3**, **S7a** (537 mg, 2.30 mmol) was converted to **6a** (560 mg, 94%) by the reaction with tBuONO (456 μL, 3.45 mmol) and $TMSN_3$ (478 μL, 3.45 mmol) in MeCN (10 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane) to give **6a** as a yellow oil; IR (neat): 2250 (C≡C), 2122 (N≡N); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.11 (tt, J = 7.5, 7.5 Hz, 2H), 2.96 (t, J = 7.5 Hz, 2H), 3.10 (t, J = 7.5 Hz, 2H), 7.08-7.15 (m, 3H), 7.21 (d, J = 7.5 Hz, 1H), 7.30-7.36 (m, 2H), 7.50 (dd, J = 7.5, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.6, 32.7, 33.2, 87.5, 94.2, 115.8, 118.8, 119.0, 124.6, 124.7, 126.1, 129.0, 129.3, 133.5, 140.7, 144.2, 146.9; HRMS calcd for $C_{17}H_{13}N_3Na^+$ [M + Na]$^+$: 282.1002, found 282.1009.

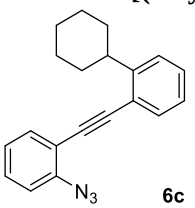
5-[(2-Azidophenyl)ethynyl]-1,2,3,4-tetrahydronaphthalene (6b)



6b

According to **GP3**, **S6b** (606 mg, 2.49 mmol) was converted to **6b** (611 mg, 91%) by the reaction with tBuONO (494 μL, 3.74 mmol) and $TMSN_3$ (518 μL, 3.74 mmol) in MeCN (10 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane) to give **6b** as a brown oil; IR (neat): 2250 (C≡C), 2126 (N≡N); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.74-1.88 (m, 4H), 2.76 (t, J = 6.3 Hz, 2H), 2.98 (t, J = 6.3 Hz, 2H), 7.03-7.12 (m, 4H), 7.30 (dd, J = 8.0 Hz, 1H), 7.36 (dd, J = 7.2, 2.0 Hz, 1H), 7.49 (dd, J = 7.7, 1.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 22.8, 23.0, 28.1, 29.7, 89.2, 94.3, 115.8, 118.7, 122.5, 124.6, 125.0, 129.2, 129.4, 129.6, 133.4, 137.4, 139.2, 140.7; HRMS calcd for $C_{18}H_{16}N_3^+$ [M + H]$^+$: 274.1344, found 274.1346.

1-Azido-2-[(2-cyclohexylphenyl)ethynyl]benzene (6c)

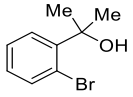


6c

According to **GP3**, **S5l** (620 mg, 2.25 mmol) was converted to **6c** (630 mg, 93%) by the reaction with tBuONO (446 μL, 3.38 mmol) and $TMSN_3$ (467 μL, 3.38 mmol) in MeCN (10 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane) to give **6c** as a brown oil; IR (neat): 2213

(C≡C), 2125 (N≡N); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.18-1.34 (m, 1H), 1.38-1.58 (m, 4H), 1.76-2.04 (m, 5H), 3.22-3.33 (m, 1H), 7.09-7.20 (m, 3H), 7.26-7.35 (m, 3H), 7.48-7.55 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 26.3, 27.1 (2C), 33.5 (2C), 42.0, 88.5, 94.2, 115.8, 118.7, 121.8, 124.6, 125.47, 125.51, 128.8, 129.3, 132.2, 133.3, 140.9, 149.8; HRMS calcd for $C_{20}H_{19}N_3Na^+$ $[M + Na]^+$: 324.1471, found 324.1472.

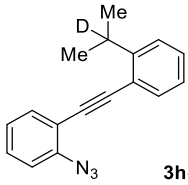
2-(2-Bromophenyl)propan-2-ol (S9)



S9

To a dry THF solution of 2-bromoacetophenone **S8** (2.0 g, 10.0 mmol) in a flame-dried three-neck flask was slowly added MeMgCl (1M solution in THF; 12.1 mL, 12.1 mmol) over a course of 5 min at 0 °C under stirring. The reaction mixture was stirred for 3 h at 0 °C and subsequently poured into a saturated aqueous NH_4Cl solution and extracted with EtOAc (3 x 50 mL). The combined organic layer was dried over Na_2SO_4 and, after concentration *in vacuo*, the residue was purified by silica column chromatography (hexane/EtOAc = 5/1) to give **S9** (1.92 g, 90%) as a colorless oil. The spectral data were in good agreement with those previously reported.[64]

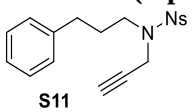
1-Azido-2-{[2-(propan-2-yl-2-*d*)phenyl]ethynyl}benzene (3h-*d*)



3h-*d*

TfOH (110 μL, 1.28 mmol) was added dropwise to a solution of **S9** (181 mg, 853 μmol) and Et_3SiD (137 μL, 853 μmol) in DCM (10 mL) under stirring at 0 °C, and the mixture was allowed to warm to room temperature and stirred for 3 h. After addition of water and washing with aqueous $NaHCO_3$, the organic layer was separated and dried with Na_2SO_4. After concentration *in vacuo*, the purification was performed by silica gel column chromatography with hexane to give 1-bromo-2-(propan-2-yl-2-*d*)benzene (>99% *d*). According to **GP2**, 2-ethynylaniline (**S4a**) (100 mg, 0.85 mmol) was coupled with the crude 1-bromo-2-(propan-2-yl-2-*d*)benzene (200 mg, 1.0 mmol) in the presence of $PdCl_2(MeCN)_2$ (11.0 mg, 42.5 μmol), *t*$Bu_3P{\cdot}HBF_4$ (24.7 mg, 85.0 μmol), CuI (8.09 mg, 42.5 μmol) in Et_3N (15 mL) at 50 °C for 4 h. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1) to give the corresponding coupling product. Subsequently this aniline derivative was exposed to *t*BuONO (169 μL, 1.28 mmol) and $TMSN_3$ (177 μL, 1.28 mmol) in MeCN (10 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane) to give the desired product **3h-*d*** as an yellow oil (55 mg, 25%; >99% *d*); IR (neat): 2251 (C≡C), 2126 (N≡N); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.31 (s, 6H), 7.11-7.18 (m, 3H), 7.30-7.35 (m, 3H), 7.51 (dd, J = 7.5, 1.5 Hz, 1H), 7.54 (d, J = 7.5 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 23.1 (2C), 31.3 (t, J = 19.7 Hz), 88.5, 94.1, 115.8, 118.8, 121.6, 124.6, 125.0, 125.6, 129.0, 129.4, 132.3, 133.4, 140.9, 150.6; HRMS calcd for $C_{17}H_{15}DN_3^+$ $[M + H]^+$: 263.1407, found 263.1404.

4-Nitro-*N*-(3-phenylpropyl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide (S11)

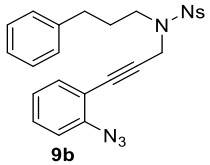


S11

To a stirred mixute of 2-nitrobenzensulfonyl chloride (2.99 g ,13.5 mmol) and triethylamine (4.13 mL, 29.6 mmol) in dichloromethane (50 mL) was added **S10** (2.00 g, 14.8 mmol) dropwise at room temperature. After stirring

for 4 h, the reaction mixture was extracted with 1 M HCl, and the organic phase was washed with aqueous $NaHCO_3$, saturated aqueous NH_4Cl and brine. The organic extract was dried with $MgSO_4$. Without further purification, the residue was suspended together with K_2CO_3 (4.09 g, 29.6 mmol) in acetone (50 mL) and heated to 50 °C under argon atmosphere. After the mixture was stirred for 30 min, propargyl bromide (2.24 mL, 29.6 mmol) was added dropwise via syringe. After 3 h, the reaction was quenched with H_2O and extracted with Et_2O three times. The organic extract was dried with $MgSO_4$, filtrered, and the solvent was removed *in vacuo* at 40 °C. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1) to give **S11** (4.14 g, 78%) as a colorless oil; IR (neat): 3289 (C≡C-H), 2253 (C≡C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.90-1.96 (m, 2H), 2.17 (t, J = 2.6 Hz, 1H), 2.63 (t, J = 7.7 Hz, 2H), 3.46 (t, J = 7.5 Hz, 2H), 4.21 (d, J = 2.3 Hz, 2H), 7.15-7.21 (m, 3H), 7.26-7.29 (m, 2H), 7.61-7.73 (m, 3H), 7.98 (dd, J = 7.5, 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.9, 32.6, 36.3, 46.9, 73.8, 76.7, 124.2, 126.1, 128.3 (2C), 128.4 (2C), 130.8, 131.6, 132.7, 133.6, 140.9, 148.2; HRMS calcd for $C_{18}H_{19}N_2O_4S^+$ $[M + H]^+$: 359.1060, found 359.1061.

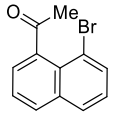
_N_-[3-(2-Azidophenyl)prop-2-yn-1-yl]-4-nitro-_N_-(3-phenylpropyl)benzenesulfonamide (9b)



9b

CuI (111 mg, 0.58 mmol) and $Pd(PPh_3)_2Cl_2$ (407 mg, 0.58 mmol) were suspended in iPr$_2$NH (150 mL) under argon together with *o*-iodoaniline (5.04 g, 23.0 mmol). After the suspension was gradually heated to 60 °C over 30 min, alkyne **S11** (4.14 g, 11.5 mmol) was added dropwise. After letting the reaction cool to room temperature, the mixture was diluted with DCM and filtered over celite. After the mixture was concentrated *in vacuo*, the residue was purified by silica gel column chromatography (hexane/EtOAc = 10/1), which was used without further purifiation. The aniline derivative containing impurities was dissolved in MeCN (150 mL) and the mixture was cooled to 0 °C in an ice bath. To the stirred mixture were successively added tBuONO (2.74 mL, 23.0 mmol) and $TMSN_3$ (3.02 mL, 23.0 mmol) dropwise. The resulting solution was stirred at room temperature for 30 min. The reaction mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10/1) to give the product **9b** (2.19 g, 40%) as a colorless oil; IR (neat): 2254 (C≡C), 2128 (N≡N); NMR (500 MHz, $CDCl_3$) δ: 1.97-2.04 (m, 2H), 2.67 (t, J = 7.7 Hz, 2H), 3.55 (t, J = 7.7 Hz, 2H), 4.48 (s, 2H), 7.02-7.08 (m, 2H), 7.16-7.19 (m, 4H), 7.24-7.27 (m, 2H), 7.33 (ddd, J = 7.8, 7.8, 1.6 Hz, 1H), 7.59-7.66 (m, 3H), 8.04-8.96 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 29.1, 32.7, 37.3, 46.7, 81.4, 87.6, 114.1, 118.5, 124.1, 124.6, 126.0, 128.3 (2C), 128.4 (2C), 129.9, 130.9, 131.5, 132.8, 133.4, 133.6, 141.0, 141.2, 148.4; HRMS calcd for $C_{24}H_{22}N_5O_4S^+$ $[M + H]^+$: 476.1387, found 476.1389.

1-(8-Bromonaphthalen-1-yl)ethan-1-one (S13)

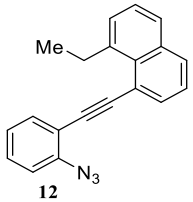


S13

N-Bromosuccinimide (4.3 g, 24 mmol), $Pd(OAc)_2$ (0.5 g, 2.0 mmol), and $K_2S_2O_8$ (6.5 g, 24 mmol) were placed in a 500 mL Schlenk flask equipped with a magnetic stir bar. The flask was evacuated and refilled with argon three times. Dichloromethane (200 mL), 1-acetonaphtone (3.2 mL, 20 mmol), and TfOH (1.0 mL, 10 mmol) were added to the mixture. The reaction mixture was stirred for 12 h and subsequently filtered through a pad of silica gel. The solid were washed with EtOAc (200 mL) and the filtrate and washings were combined and concentrated *in vacuo*,

and purified by column chromatography (hexane/EtOAc 10/1) affording the product as a white solid (4.3 g, 86%). The spectral data were in good agreement with those previously reported.[65]

1-[(2-Azidophenyl)ethynyl]-8-ethylnaphthalene (12)

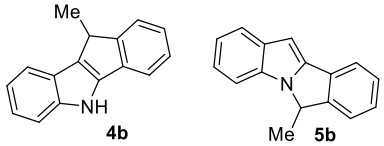


12

TfOH (0.4 mL, 4.8 mmol) was added dropwise to a solution of **S13** (0.8 g, 3.2 mmol) and Et_3SiH (0.5 mL, 3.2 mmol) in DCM (50 mL) under stirring at 0 °C, and the mixture was allowed to warm to room temperature and stirred for 3 h. The TLC showed almost no conversion of the starting material, thus additional TfOH (0.4 mL, 4.8 mmol) and Et_3SiH (0.5 mL, 3.2 mmol) were added at rt and the solution was refluxed for 2 h resulting in full conversion in the TLC analysis. After addition of water and washing with aqueous $NaHCO_3$, the organic layer was separated and dried with Na_2SO_4. After concentration *in vacuo*, purification was performed by silica gel column chromatography with hexane to gave crude **S14** with a significant amount of inseperable impurities. According to **GP2**, 2-ethynylaniline (**S4a**) (0.2 g, 2.0 mmol) was coupled with the crude **S14** in the presence of $PdCl_2(MeCN)_2$ (26 mg, 0.1 mmol), tBu$_3$P·HBF$_4$ (58 mg, 0.2 mmol), CuI (20 mg, 0.1 mmol) in Et_3N (30 mL) at 50 °C for 4 h. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1) to give the corresponding coupling product **S15**. Subsequently this crude aniline fraction was exposed to *t*BuONO (0.3 mL, 2.1 mmol) and $TMSN_3$ (0.3 mL, 2.1 mmol) in MeCN (20 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc 10/1) to give the desired product **12** as a yellow oil (10 mg, ca. 1%); IR (neat): 2250 (C≡C), 2127 (N≡N); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.36 (t, J = 7.3 Hz, 3H), 3.68 (q, J = 7.3 Hz, 2H), 7.08-7.12 (m, 2H), 7.28-7.33 (m, 2H), 7.33-7.34 (m, 2H), 7.48 (dd, J = 7.7, 1.6 Hz, 1H), 7.65 (dd, J = 7.7, 1.6 Hz, 1H), 7.78 (dd, J = 8.2, 1.3 Hz, 1H), 7.80 (dd, J = 7.2, 1.3 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 17.2, 28.7, 87.3, 99.2, 117.6, 118.4, 120.0, 124.5, 126.2, 127.7, 128.5, 129.3, 129.9, 130.9, 131.1, 132.5, 134.9, 135.1, 139.6, 141.9; HRMS calcd for $C_{20}H_{16}N_3^+$ $[M + H]^+$: 298.1339, found 298.1327.

3. Gold-Catalyzed Cyclization

10-Methyl-5,10-dihydroindeno[1,2-*b*]indole (4b) and 6-Methyl-6*H*-isoindolo[2,1-*a*]indole (5b)



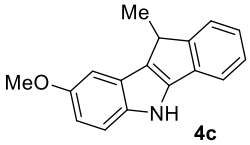
4b **5b**

According to **GP4**, azido-yne **3b** (100.0 mg, 404 μmol) was converted to **4b** (55.8 mg, 63%; **4b** : **5b** = 85 : 15) by the reaction with Johnphos(MeCN)SbF_6 (15.6 mg, 20.2 μmol) in TCE (200 mL) at 90 °C for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1).

Compound **4b**: yellow oil; IR (neat): 3395 (NH); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.59 (d, J = 7.4 Hz, 3H), 3.92 (q, J = 7.4 Hz, 1H), 7.15-7.20 (m, 2H), 7.23 (ddd, J = 7.5, 7.5, 1.1 Hz, 1H), 7.31 (dd, J = 7.1, 7.1 Hz, 1H), 7.42-7.44 (m, 2H), 7.50 (dd, J = 7.5, 1.1 Hz, 1H), 7.65-7.67 (m, 1H), 8.25 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 17.5, 37.4, 112.1, 117.3, 118.7, 120.2, 121.7, 124.2, 124.4, 125.0, 126.6, 127.5, 134.2, 140.6, 141.8, 153.9; HRMS calcd for $C_{16}H_{14}N^+$ $[M + H]^+$: 220.1121, found 220.1131.

Compoud **5b**: colorless oil; IR (neat): no specific signals; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.78 (d, J = 6.9 Hz, 3H), 5.35 (q, J = 6.9 Hz, 1H), 6.61 (s, 1H), 7.11 (dd, J = 7.6, 7.6 Hz, 1H), 7.19 (dd, J = 7.6, 7.6 Hz, 1H), 7.32 (dd, J = 7.6, 7.6 Hz, 1H), 7.39-7.44 (m, 3H), 7.67-7.71 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 20.1, 55.4, 91.2, 109.5, 119.5, 120.8, 121.4, 121.7, 122.7, 127.1, 128.2, 132.1, 133.1, 133.4, 142.8, 147.7; HRMS calcd for $C_{16}H_{14}N^+$ [M + H]$^+$: 220.1121, found 220.1149.

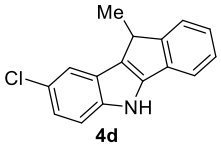
8-Methoxy-10-methyl-5,10-dihydroindeno[1,2-*b*]indole (4c)



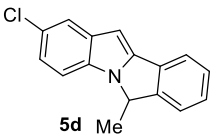
4c

According to **GP4**, azido-yne **3c** (50.0 mg, 180 μmol) was converted to **4c** (9.00 mg, 20%) by the reaction with Johnphos(MeCN)SbF_6 (6.95 mg, 9.0 μmol) in TCE (90 mL) at 90 °C for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1) to give **4c** as a yellow oil; IR (neat): 3404 (NH); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.58 (d, J = 7.4 Hz, 3H), 3.86-3.93 (m, 4H), 6.84 (dd, J = 8.8, 2.5 Hz, 1H), 7.11 (d, J = 2.4 Hz, 1H), 7.23 (ddd, J = 7.4, 7.4, 1.1 Hz, 1H), 7.28-7.34 (m, 2H), 7.42 (d, J = 7.4 Hz, 1H), 7.50 (d, J = 7.4 Hz, 1H), 8.15 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 17.5, 37.3, 55.9, 100.9, 111.3, 112.7, 117.3, 124.2, 124.8, 125.0, 126.7, 127.3, 134.2, 135.8, 142.7, 153.8, 154.4; HRMS calcd for $C_{17}H_{16}NO$ [M + H]$^+$: 250.1226, found 250.1229.

8-Chloro-10-methyl-5,10-dihydroindeno[1,2-*b*]indole (4d) and 2-Chloro-6-methyl-6*H*-isoindolo[2,1-*a*]indole (5d)



4d



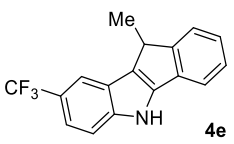
5d

According to **GP4**, azido-yne **3d** (100 mg, 356 μmol) was converted to an isomeric mixture of **4d** and **5d** (49.7 mg, 55%; **4d** : **5d** = 45 : 55) by the reaction with Johnphos(MeCN)SbF_6 (13.7 mg, 17.8 μmol) in TCE (180 mL) at 90 °C for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1).

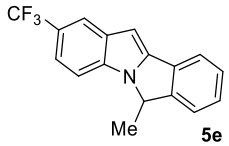
Compound **4d**: colorless solid; mp 168 °C; IR (neat): 3423 (NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.57 (d, J = 7.4 Hz, 3H), 3.90 (q, 1H), 7.13 (dd, J = 8.6, 2.0 Hz, 1H), 7.24 (m, 1H), 7.31-7.36 (m, 2H), 7.44 (d, J = 7.2 Hz, 1H), 7.51 (d, J = 7.0 Hz, 1H), 7.61 (d, J = 2.0 Hz, 1H), 8.30 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 17.5, 37.3, 112.9, 117.6, 118.2, 121.7, 124.3, 125.3, 125.6, 125.9, 126.8, 126.9, 133.7, 139.9, 143.3, 153.8; HRMS calcd for $C_{16}H_{13}ClN^+$ [M + H]$^+$: 254.0731, found 254.0728.

Compoud **5d**: colorless oil; IR (neat): no specific signals; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.74 (d, J = 6.7 Hz, 3H), 5.30 (q, J = 6.7 Hz, 1H), 6.53 (s, 1H), 7.13 (dd, J = 8.6, 2.0 Hz, 1H), 7.28-7.43 (m, 4H), 7.62 (d, J = 2.0 Hz, 1H), 7.65-7.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.0, 55.6, 90.8, 110.2, 120.95, 120.98, 121.6, 122.7, 125.1, 127.5, 128.3, 131.67, 131.74, 134.1, 144.1, 147.6; HRMS calcd for $C_{16}H_{13}ClN^+$ [M + H]$^+$: 254.0731, found 254.0732.

10-Methyl-8-(trifluoromethyl)-5,10-dihydroindeno[1,2-*b*]indole (4e) and 6-Methyl-2-(trifluoromethyl)-6*H*-isoindolo[2,1-*a*]indole (5e)



4e



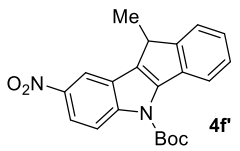
5e

According to **GP4**, azido-yne **3e** (100.0 mg, 317 μmol) was converted to an isomeric mixture of **4e** and **5e** (48.3 mg, 53%; **4e** : **5e** = 43 : 57) by the reaction with Johnphos(MeCN)SbF_6 (12.2 mg, 15.9 μmol) in TCE (160 mL) at 90 °C for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1):

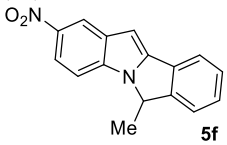
Compound **4e**: colorless solid; mp 152 °C; IR (neat): 3468 (N-H); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.60 (d, J = 7.5 Hz, 3H), 3.95 (q, J = 7.5 Hz, 1H), 7.28 (dd, J = 7.4, 7.4 Hz, 1H), 7.34 (dd, J = 7.4, 7.4 Hz, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.45-7.50 (m, 2H), 7.53 (d, J = 7.4 Hz, 1H), 7.93 (s, 1H), 8.49 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 17.5, 37.4, 112.2, 116.2 (q, J = 4.2 Hz), 117.7, 118.3 (q, J = 3.5 Hz), 122.6 (q, J = 31.7 Hz), 123.7, 124.4, 125.3 (q, J = 270.1 Hz), 125.8, 126.8, 127.8, 133.5, 141.9, 143.6, 153.8; HRMS calcd for $C_{17}H_{13}F_3N^+$ [M + H^+]: 288.0995, found 288.0992.

Compound **5e**: colorless oil; IR (neat): no specific signals; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.78 (d, J = 6.7 Hz, 3H), 5.38 (q, J = 6.7 Hz, 1H), 6.68 (s, 1H), 7.37 (ddd, J = 7.5, 7.5, 0.9 Hz, 1H), 7.40-7.45 (m, 3H), 7.47 (d, J = 8.5 Hz, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.95 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 20.1, 56.6, 92.1, 109.5, 118.1 (q, J = 3.5 Hz), 119.2 (J = 4.2 Hz), 121.2, 121.8, 125.4 (q, J = 270 Hz), 127.8, 128.4, 131.4, 132.4, 134.5, 144.6, 147.5; HRMS calcd for $C_{17}H_{13}F_3N^+$ [M + H^+]: 288.0995, found 288.1010.

tert-Butyl 10-Methyl-8-nitroindeno[1,2-_b_]indole-5(10_H_)-carboxylate (4f') and 6-Methyl-2-nitro-6_H_-isoindolo[2,1-_a_]indole (5f)



4f'



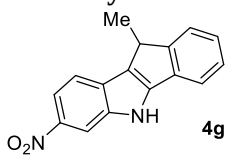
5f

According to **GP4**, azido-yne **3f** (100.0 mg, 342 μmol) was converted to an isomeric mixture of **4f** and **5f** (63.2 mg, 70%; **4f** : **5f** = 42 : 58) by the reaction with Johnphos(MeCN)SbF_6 (13.2 mg, 17.1 μmol) in TCE (170 mL) at 90 °C for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1) to give **4f** containing impurities, which was exposed to DMAP (4.18 mg, 34.2 μmol) and Boc_2O (373 mg, 1.70 mmol) in DCM (20 mL) to give the *N*-Boc derivative **4f'** (25.6 mg, 70%) via purification with silica gel column chromatography (hexane/EtOAc = 15/1).

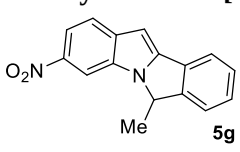
Compound **4f'**: yellow solid; mp 188 °C; IR (neat): 1738 (C=O); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.61 (d, J = 7.5 Hz, 3H), 1.81 (s, 9H), 3.92 (q, J = 7.5 Hz, 1H), 7.33 (ddd, J = 7.4, 7.4, 1.1 Hz, 1H), 7.39 (dd, J = 7.4, 7.4 Hz, 1H), 7.54 (d, J = 7.4 Hz, 1H), 8.17 (dd, J = 9.2, 2.2 Hz, 1H), 8.22 (d, J = 9.2 Hz, 1H), 8.37 (d, J = 7.4 Hz, 1H), 8.49 (d, J = 2.2 Hz, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 17.2, 28.3 (3C), 36.7, 86.0, 114.5, 116.5, 118.6, 123.2, 123.9, 125.7, 126.6, 127.1, 132.5, 133.7, 143.0, 143.8, 145.4, 149.7, 153.5; HR-MS calcd for $C_{21}H_{20}KN_2O_4^+$ [M + K^+] 403.1055, found 403.1062.

Compound **5f**: yellow solid; mp 190 °C; IR (neat): ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.79 (d, J = 6.9 Hz, 3H), 5.38 (q, J = 6.9 Hz, 1H), 6.74 (s, 1H), 7.39-7.46 (m, 4H), 7.73 (d, J = 7.6 Hz, 1H), 8.09 (dd, J = 8.6, 2.1 Hz, 1H), 8.60 (d, J = 2.1 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 20.1, 56.6, 93.5, 108.9, 117.2, 118.6, 121.4, 122.9, 128.4, 128.6, 130.7, 132.3, 136.1, 141.4, 146.0, 147.2; HRMS calcd for $C_{16}H_{12}KN_2O_2^+$ [M + K^+] 303.0530, found 303.0533.

10-Methyl-7-nitro-5,10-dihydroindeno[1,2-_b_]indole (4g) and 6-Methyl-3-nitro-6_H_-isoindolo[2,1-_a_]indole (5g)



4g



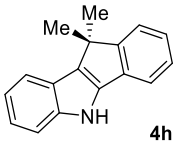
5g

According to **GP4**, azido-yne **3g** (100 mg, 342 μmol) was converted to an isomeric mixture of **4g** and **5g** (58.8 mg, 65%; **4g** : **5g** = 34 : 66) by the reaction with Johnphos(MeCN)SbF_6 (13.2 mg, 17.1 μmol) in TCE (170 mL) at 90 °C for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1).

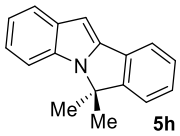
Compound **4g**: yellow solid; mp 180 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.61 (d, J = 7.4 Hz, 3H), 3.98 (q, J = 7.4 Hz, 1H), 7.32-7.41 (m, 2H), 7.54-7.58 (m, 2H), 7.65 (d, J = 8.8 Hz, 1H), 8.09 (dd, J = 8.8, 2.0 Hz, 1H), 8.42 (d, J = 2.0 Hz, 1H), 8.82 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 17.4, 37.3, 109.0, 116.4, 118.0, 118.7, 124.7, 127.0, 127.2, 127.6, 128.9, 132.7, 139.0, 142.2, 147.9, 154.6; $C_{16}H_{13}N_2O_2^+$ [M + H$^+$] 265.0972, found 265.0972.

Compound **5g**: yellow solid; mp 169 °C; IR (neat): no specific signals; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.83 (d, J = 6.8 Hz, 3H), 5.41 (q, J = 6.8 Hz, 1H), 6.70 (s, 1H), 7.39-7.51 (m, 3H), 7.66 (d, J = 8.8 Hz, 1H), 7.76 (d, J = 7.1 Hz, 1H), 8.01 (dd, J = 8.8, 2.1 Hz, 1H), 8.36 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 20.3, 57.2, 92.4, 106.2, 115.2, 121.0, 121.6, 123.0, 128.6, 128.7, 130.7, 131.6, 138.1, 142.2, 148.0, 148.7; HRMS calcd for $C_{16}H_{13}N_2O_2^+$ [M + H$^+$] 265.0972, found 265.0964.

10,10-Dimethyl-5,10-dihydroindeno[1,2-*b*]indole (4h) and 6,6-dimethyl-6*H*-isoindolo[2,1-*a*]indole (5h)



4h



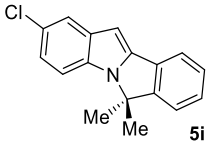
5h

According to **GP4**, azido-yne **3h** (80.0 mg, 306 μmol) was converted to an isomeric mixture of **4h** and **5h** (46.4 mg, 65%; **4h** : **5h** = 18 : 82) by the reaction with Johnphos(MeCN)SbF_6 (11.8 mg, 15.3 μmol) in TCE (150 mL) at 90 °C for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 20/1).

Compound **4h**: colorless oil; IR (neat): 3417 (N-H); (600 MHz, $CDCl_3$) δ: 1.61 (s, 6H), 7.15-7.20 (m, 2H), 7.23 (dd, J = 7.5, 7.5 Hz, 1H), 7.29 (dd, J = 7.0, 7.0 Hz, 1H), 7.41 (d, J = 7.5 Hz, 1H), 7.43-7.45 (m, 2H), 7.65 (d, J = 8.0 Hz, 1H), 8.24 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): 25.9 (2C), 43.3, 112.2, 117.5, 118.5, 120.1, 121.6, 122.5, 123.6, 125.3, 126.6, 131.8, 133.1, 140.0, 140.7, 158.7; HRMS calcd for $C_{17}H_{16}N^+$ [M + H$^+$] 234.1277, found 234.1275.

Compound **5h**: bright yellow oil; IR (neat): no specific signals; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.80 (s, 6H), 6.61 (s, 1H), 7.11 (dd, J = 7.5, 7.5 Hz, 1H), 7.20 (dd, J = 7.5, 7.5 Hz, 1H), 7.32 (dd, J = 7.6 Hz, 1H), 7.37-7.40 (m, 2H), 7.49 (d, J = 8.1 Hz, 1H), 7.69 (d, J = 7.7 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): 26.8 (2C), 64.0, 91.0, 109.7, 119.2, 120.8, 121.2, 121.4, 121.7, 127.2, 128.0, 130.7, 132.5, 133.4, 141.6, 152.4; HRMS calcd for $C_{17}H_{16}N^+$ [M + H$^+$] 234.1277, found 234.1273.

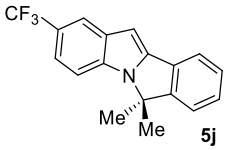
2-Chloro-6,6-dimethyl-6*H*-isoindolo[2,1-*a*]indole (5i)



5i

Azido-yne **3i** (100.0 mg, 338 μmol) was converted to **5i** (74.8 mg, 80%) by the reaction with JohnphosAuCl (8.97 mg, 16.9 μmol) and NaBARF (30.0 mg, 33.8 μmol) in TCE (170 mL) at 90 °C for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1) to give **5i** as a colorless oil; IR (neat): no specific signals; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.75 (s, 6H), 6.53 (s, 1H), 7.12 (dd, J = 8.6, 2.0 Hz, 1H), 7.29-7.39 (m, 4H), 7.63 (d, J = 2.0 Hz, 1H), 7.65-7.67 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 26.9 (2C), 64.2, 90.8, 110.4, 120.96, 121.03, 121.4, 121.5, 125.0, 127.7, 128.2, 130.6, 130.8, 134.4, 142.9, 152.4; HRMS calcd for $C_{17}H_{15}ClN^+$ [M + H$^+$] 234.1277, found 234.1273.

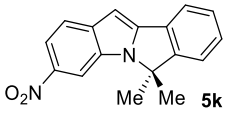
6,6-Dimethyl-2-(trifluoromethyl)-6*H*-isoindolo[2,1-*a*]indole (5j)



5j

Azido-yne **3j** (75.0 mg, 228 μmol) was converted to **5j** (52.2 mg, 76%) by the reaction with JohnphosAuCl (6.05 mg, 11.4 μmol) and NaBARF (20.2 mg, 22.8 μmol) in TCE (170 mL) at 90 °C for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1) to give **5j** as a yellow oil; IR (neat): no specific signals; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.82 (s, 6H), 6.69 (s, 1H), 7.36-7.43 (m, 4H), 7.54 (d, J = 9.0 Hz, 1H), 7.73 (d, J = 7.6 Hz, 1H), 7.97 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 27.0 (2C), 64.4, 92.1, 109.6, 117.9 (q, J = 3.5 Hz), 119.2 (q, J = 4.0 Hz), 121.2, 121.58 (q, J = 31.5 Hz), 121.60, 125.4 (q, J = 271.3 Hz), 128.0, 128.3, 130.3, 132.7, 133.7, 143.3, 152.2; HRMS calcd for $C_{18}H_{15}F_3N^+$ [M + H$^+$] 302.1151, found 302.1151.

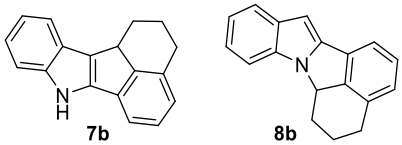
6,6-Dimethyl-2-nitro-6*H*-isoindolo[2,1-*a*]indole (5k)



5k

Azido-yne **3k** (70.0 mg, 229 μmol) was converted to **5k** (42.1 mg, 66%) by the reaction with JohnphosAuCl (6.08 mg, 11.5 μmol) and NaBARF (20.4 mg, 23.0 μmol) in TCE (170 mL) at 90 °C for 4 h. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1) to give **5k** as a yellow solid; mp 148 °C; IR (neat): 2978 (C-H), 1619 (C=C); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.82 (s, 6H), 6.68 (s, 1H), 7.46 (m, 3H), 7.65 (d, J = 8.5 Hz, 1H), 7.73 (d, J = 7.7 Hz, 1H), 8.00 (dd, J = 8.9, 1.9 Hz, 1H), 8.38 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 27.1 (2C), 65.1, 92.3, 106.3, 115.1, 121.0, 121.66, 121.70, 128.5, 128.8, 129.6, 130.7, 138.4, 142.2, 147.5, 152.8; HRMS calcd for $C_{17}H_{15}N_2O_2$ [M + H$^+$] 279.1128, found 279.1137.

2,3,7,11c-Tetrahydro-1*H*-acenaphtho[1,2-*b*]indole (7b) and 4,5,6,6a-tetrahydrobenzo[*cd*]indolo[1,2-*a*]indole (8b)



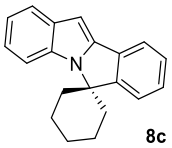
7b **8b**

Azido-yne **6b** (80 mg, 293 μmol) was converted to an isomeric mixture of **7b** and **8b** (41.0 mg, 69%; **7b** : **8b** = 12 : 88) by the reaction with Johnphos(MeCN)SbF_6 (7.78 mg, 14.7 μmol) and $NaBPh_4$ (100 mg, 293 μmol) in TCE (150 mL) at 90 °C for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1).

Compound **7b**: pale yellow oil; IR (neat): 3390 (N-H); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.18-1.23 (m, 1H), 2.16-2.21 (m, 2H), 2.65-2.68 (m, 1H), 2.72-2.77 (m, 1H), 3.06 (dt, J = 11.4, 6.0 Hz, 1H), 3.62 (dd, J = 12.4, 4.8 Hz, 1H), 6.98-7.00 (m, 1H), 7.15-7.18 (m, 2H), 7.23-7.25 (m, 2H), 7.40-7.42 (m, 1H), 7.65-7.67 (m, 1H), 8.27 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 23.3, 25.4, 25.8, 40.5, 112.1, 114.5, 118.9, 120.2, 121.5, 124.5, 124.8, 126.9, 127.0, 132.8, 135.2, 140.4, 143.0, 150.1; HRMS calcd for $C_{18}H_{15}NNa^+$ [M + Na$^+$] 246.1277, found 246.1276.

Compound **8b**: colorless oil; IR (neat): no specific signals; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.50-1.62 (m, 1H), 2.06-2.28 (m, 2H), 2.73-2.81 (m, 1H), 2.88-2.94 (m, 1H), 3.03 (dd, J = 17.5, 8.3 Hz, 1H), 4.93 (dd, J = 11.7, 4.9 Hz, 1H), 6.61 (s, 1H), 7.05-7.13 (m, 2H), 7.18 (dd, J = 7.6, 7.6 Hz, 1H), 7.32 (dd, J = 7.6, 7.6 Hz, 1H), 7.43 (dd, J = 8.2, 1.0 Hz, 1H), 7.48 (d, J = 7.5 Hz, 1H), 7.65 (ddd, J = 7.9, 1.0, 1.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 20.9, 25.2, 27.6, 58.5, 92.0, 109.6, 117.9, 119.5, 121.5, 121.7, 126.2, 128.7, 131.1, 133.0, 134.5, 134.6, 143.9, 144.2; HR-MS calcd for $C_{18}H_{15}NNa^+$ [M + Na$^+$] 246.1277, found 246.1276.

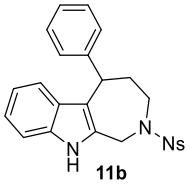
Spiro[cyclohexane-1,6'-isoindolo[2,1-*a*]indole] (8c)



8c

Azido-yne **6c** (50.0 mg, 166 μmol) was converted to **8c** (28.2 mg, 62%) by the reaction with JohnphosAuCl (4.41 mg, 8.30 μmol) and NaBARF (14.7 mg, 16.6 μmol) in TCE (80 mL) at 90 °C for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 15/1) to give **8c** as a colorless oil; IR (neat): no specific signals; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.60-1.67 (m, 1H), 1.78-1.80 (m, 2H), 1.98-2.12 (m, 5H), 2.54-2.59 (m, 2H), 6.64 (s, 1H), 7.14 (dd, J = 7.5, 7.5 Hz, 1H), 7.22 (dd, J = 7.5, 7.5 Hz, 1H), 7.31 (dd, J = 7.5, 7.5 Hz, 1H), 7.44 (dd, J = 7.5, 7.5 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.83 (d, J = 7.5 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 22.7 (2C), 25.1, 35.3 (2C), 66.6, 90.5, 110.2, 119.2, 120.9, 121.1, 121.7, 124.2, 126.5, 127.9, 131.6, 132.2, 133.6, 141.6, 151.3; HRMS calcd for $C_{20}H_{20}N^+$ [M + H^+] 274.1590, found 274.1589.

2-[(4-Nitrophenyl)sulfonyl]-5-phenyl-1,2,3,4,5,5a,10,10a-octahydroazepino[3,4-*b*]indole (11b)



11b

Azido-yne **9b** (100 mg, 0.21 mmol) was converted to **11b** (45.2 mg, 48%) by the reaction with JohnPhosAu(MeCN)SbF_6 (8.10 mg, 15.0 μmol) in TCE (105 mL) at 90 °C for 15 min. Purification was performed by silica gel column chromatography (hexane/Et_2O = 10/1 to 3/1) to give **11b** as a colorless solid; 254 °C; IR (neat): 3393 (N-H); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.40-2.55 (m, 2H), 3.39-3.44 (m, 1H), 3.70-3.73 (m, 1H), 4.57-4.59 (m, 1H), 4.75 (d, J = 16.6 Hz, 1H), 4.90 (d, J = 16.6 Hz, 1H), 6.92-6.99 (m, 1H), 7.04-7.21 (m, 7H), 7.33 (d, J = 8.3 Hz, 1H), 7.53-7.65 (m, 3H), 7.89 (d, J = 8.0 Hz, 1H), 8.12 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 34.7, 40.3, 45.1, 46.2, 111.0, 114.8, 118.9, 119.7, 122.2, 124.1, 126.3, 127.9, 128.32 (2C), 128.46 (2C), 130.9, 131.6, 132.5, 133.0, 133.4, 135.0, 142.8, 147.9; HRMS calcd for $C_{24}H_{22}N_3O_4S^+$ [M + H^+] 448.1326, found 448.1309.

References

[1] D. G. Brown, J. Boström, *J. Med. Chem.* **2016**, *59*, 4443−4458.

[2] J. Boström, D. G. Brown, R. J. Young, G. M. Keserü, *Nat. Rev. Drug Discovery* **2018**, *17*, 709−727.

[3] T. Rogge, N. Kaplaneris, N. Chatani, J. Kim, S. Chang, B. Punji, L. L. Schafer, D. G. Musaev, J. Wencel-Delord, C. A. Roberts, R. Sarpong, Z. E. Wilson, A. A. Brimble, M. J. Johansson, L. Ackermann, *Nat. Rev. Methods Primers* **2021**, *1*, 43.

[4] J. F. Hartwig, M. A. Larsen, *ACS Cent. Sci.* **2016**, *2*, 281−292.

[5] H. W. L. Davies, D. Morton, *J. Org. Chem*. **2016**, *81*, 343−350.

[6] H. M. L. Davies, J. Du Bois, J.-Q. Yu, *Chem. Soc. Rev*. **2011**, *40*, 1855–1856.

[7] C. J. Lewis, P. S. Coelho, F. H. Arnold, *Chem. Soc. Rev.* **2011**, *40*, 2003–2021.

[8] D. C. Blackmore, L. Castro, I. Churcher, D. C. Reese, A. W. Thomas, D. M. Wilson, A. Wood, *Nat. Chem.* **2018**, *10*, 383−394.

[9] S. Sarkar, K. P. S. Cheung, V. Gevorgyan, *Chem. Sci*. **2020**, *11*, 12974–12993.

[10] M. L. Stateman, K. M. Nakafuku, D. A. Nagib, *Synthesis* **2018**, *50*, 1569–1586.

[11] T. Matsuoka, S. Inuki, T. Miyagawa, S. Oishi, H. Ohno, *J. Org. Chem.* **2020**, *85*, 8271−8278.

[12] T. Miyagawa, S. Inuki, S. Oishi, H. Ohno, *Org. Lett.* **2019**, *21*, 5485–5490.

[13] H. W. L. Davies, J. R. Manning, *Nat. Chem.* **2008**, *451*, 417−424.

[14] J. C. K. Chu, T. Rovis, *Angew. Chem. Int. Ed*. **2018**, *57*, 62–101.

[15] N. Chatani, M. Tobisu, *Angew. Chem. Int. Ed.* **2006**, *45*, 1683−1684.

[16] Y. F. Zhang, A. N. Fritzpatrick, M. Das, I. P. Bedre, G. H. Yayla, S. M. Lall, P. Z. Musacchio, *Chem. Catal.* **2022**, *2*, 292−308.

[17] J. S. Pastine, K. M. McQuaid, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 12180−12181.

[18] K. Mori, K. Kurihara, S. Yabe, M. Yamanaka, T. Akiyama, *J. Am. Chem. Soc.* **2014**, *136*, 3744−3747.

[19] S. Basak, L. Winfrey, B. A. Kustiana, R. L. Melen, L. C. Morril, A. P. Pullis, *ACS Catal.* **2020**, *10*, 4835−4840.

[20] S. Basak, L. Winfrey, B. A. Kustiana, R. L. Melen, L. C. Morril, *Chem. Soc. Rev*. **2021**, *50*, 3720–3737.

[21] M. G. Ciulla, S. Zimmermann, K. Kumar, *Org. Biomol. Chem*. **2019**, *17*, 413−431.

[22] J. Xie, C. Pan, A. Abdukader, C. Zhu, *Chem. Soc. Rev*. **2014**, *43*, 5245–5256.

[23] H. Adcock, V. E. Chatzopoulou, P. W. Davies, *Angew. Chem. Int. Ed.* **2015**, *54*, 15525–15529.

[24] G. Zhou, J. Zhang, *Chem. Commun.* **2010**, *46*, 6593–6595.

[25] B. Bolte, F. Gagosz, *J. Am. Chem. Soc.* **2011**, *133*, 7696–7699.

[26] A. Boreux, G. H. Lonca, O. Riant, F. Gagosz, *Org. Lett.* **2016**, *18*, 5162−5165.

[27] B. Bolte, Y. Obadachian, F. Gagosz, *J. Am. Chem. Soc.* **2010**, *132*, 7294–7296.

[28] I. D. Jurberg, Y. I. Obadachian, F. Gagosz, *J. Am. Chem. Soc.* **2010**, *132*, 3543–3552.

[29] X. Wu, S.-S, Shen, Y. Hu, L.-Z. Gong, *Org. Lett.* **2014**, *16*, 3820−3823.

[30] P. D. Nahide, J. O. Jiménez-Halla, K. Wrobel, C. R. Solorio-Alvarado, R. O. Alvarado, B. Yahuaca-Juárez, *Org. Biomol. Chem*. **2018**, *16*, 7330−7335.

[31] T. Yamada, K. Park, T. Tachikawa, A. Fujii, M. Rudolph, A. S. K. Hashmi, H. Sajiki, *Org. Lett.* **2020**, *22*, 1883−1888.
[32] S. Bhunia, R.-S. Liu, *J. Am. Chem. Soc.* **2008**, *130*, 16488–16489.
[33] D. Chen, G. Song, A. Jia, X. Li, *J. Org. Chem.* **2011**, *76*, 8488−8494.
[34] Z. Zheng, X. Ma, X. Cheng, K. Zhao, K. Gutman, T. Li, L. Zhang, *Chem. Rev.* **2021**, *121*, 8979–9038.
[35] D. Campeau, D. F. Rayo, A. Mansour, K. Muratov, F. Gagosz, *Chem. Rev.* **2021**, *121*, 8756–8867.
[36] C. C. Chintawar, A. K. Yadav, A. Kumar, S. P. Sancheti, N. T. Patil, *Chem. Rev.* **2021**, *121*, 8478–8558.
[37] T. Wang, A. S. K. Hashmi, *Chem. Rev.* **2021**, *121*, 8948–8978.
[38] L. C. Greiner, J. Matsuoka, S. Inuki, H. Ohno, *Chem. Rec.* **2021**, *21*, 3897–3910.
[39] Y. Tokimizu, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* **2014**, *16*, 3138–3141.
[40] Y. Kawada, S. Ohmura, M. Kobayashi, W. Nojo, M. Kondo, Y. Matsuda, J. Matsuoka, S. Inuki, S. Oishi, C. Wang, T. Saito, M. Uchiyama, T. Suzuki, H. Ohno, *Chem. Sci.* **2018**, *9*, 8416–8425.
[41] J. Matsuoka, Y. Matsuda, Y. Kawada, S. Oishi, H. Ohno, *Angew. Chem. Int. Ed.* **2017**, *56*, 7444–7448.
[42] J. Matsuoka, S. Inuki, Y. Matsuda, Y. Miyamoto, M. Otani, M. Oka, S. Oishi, H. Ohno, *Chem. Eur. J.* **2020**, *26*, 11150–11157.
[43] L. C. Greiner, S. Inuki, N. Arichi, S. Oishi, R. Suzuki, T. Iwai, M. Sawamura, A. S. K. Hashmi, H. Ohno, *Chem. Eur. J.* **2021**, *27*, 12992–12997.
[44] T. Ikeuchi, S. Inuki, S. Oishi, H. Ohno, *Angew. Chem. Int. Ed*. **2019**, *58*, 7792–779.
[45] H. Komatsu, T. Ikeuchi, H. Tsuno, N. Arichi, K. Yasui, S. Oishi, S. Inuki, A. Fukazawa, H. Ohno, *Angew. Chem. Int. Ed.* **2021**, *60*, 27019–27025.
[46] Z. Lu, T. Li, S. R. Mudschige, B. Xu, G. B. Hammond, *Chem. Rev.* **2021**, *121*, 8452−8477.
[47] B. Lu, Y. Luo, L. Liu, L. Ye, Y. Wang, L. Zhang, *Angew. Chem. Int. Ed.* **2011**, *50*, 8358–8362.
[48] A. Ogawa, D. P. Curran, *J. Org. Chem.* **1997**, *62*, 450−451.
[49] I. Krossing, I. Raabe, *Angew. Chem. Int. Ed.* **2004**, *43*, 2006–2009.
[50] C. S. Solorio-Alvarado, Y. Wang, A. M. Echavarren, *J. Am. Chem. Soc.* **2011**, *133*, 11952−11955.
[51] Y. Wang, M. Zarca, L.-Z. Gong, L. Zhang, *J. Am. Chem. Soc.* **2016**, *138*, 7516–7519.
[52] Y. Horino, T. Yamamoto, K. Ueda, S. Kuroda, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 2809–2811.
[53] M. Wieteck, Y. Tokimizu, M. Rudolph, F. Rominger, H. Ohno, *Chem. Eur. J.* **2014**, *20*, 16331–16336.
[54] A. Ogawa, D. P. Curran, *J. Org. Chem.* **1997**, *62*, 450−451.
[55] S. G. Weber, D. Zahner, F. Rominger, B. F. Straub, *Chem. Commun.* **2012**, *48*, 11325–11327.
[56] J. Han, Z. Lu, G. B. Hammond, B. Xu, *iScience* **2020**, *23*, 101593.
[57] D. F. León Rayo, A. Mansour, W. Wu, B. N. Bhawal, F. Gagosz, *Angew. Chem. Int. Ed*. **2023**, *62*, e202212893.

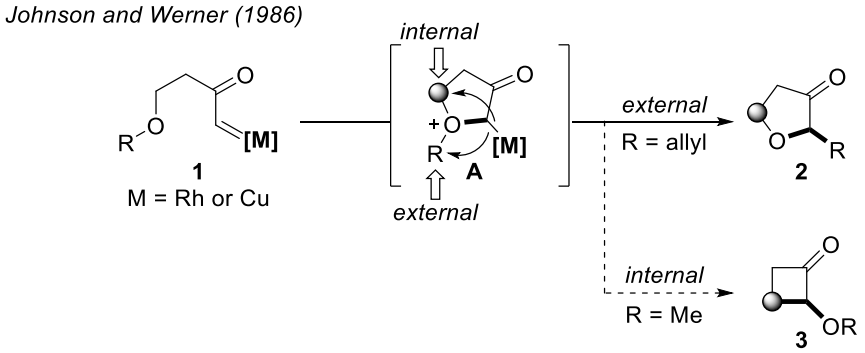
[58] U. F. Röhrig, S. R. Majjigapu, A. Grosdidier, S. Bron, V. Stroobant, L. Pilotte, D. Colau, P. Vogel, B. J. Van den Eynde, V. Zoete, O. Michielin, *J. Med. Chem.* **2012**, *55*, 5270–5290.
[59] G. L. Points, C. M. Beaudry, *Org. Lett.* **2021**, *23*, 6882–6885.
[60] X. Zhao, X. Song, H. Jin, Z. Zeng, Q. Wang, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Adv. Synth. Catal.* **2018**, *360*, 2720–2726.
[61] R. N. Nair, P. J. Lee, A. L. Rheingold, D. B. Grotjahn, *Chem. Eur. J.* **2010**, *16*, 7992–7995.
[62] G. B. M. Kostermans, P. Van Dansik, W. H. De Wolf, F. Bickelhaupt, *J. Org. Chem.* **1988**, *53*, 4531–4534.
[63] C.-Y. Lo, M. P. Kumar, H.-S, Chang, S.-F. Lush, R.-S. Liu, *J. Org. Chem.* **2005**, *70*, 10482–10487.
[64] L. Mahendar, J. Krishna, A. G. K. Reddy, B. V. Ramulu, G. A. Satyanarayana, *Org. Lett.* **2012**, *14*, 628–631.
[65] Q. H. Tran, M. Brookhart, O. Daugulis, *J. Am. Chem. Soc.* **2020**, *142*, 7198–7206.

Chapter 3. Acetylenic Schmidt Reaction/Carboalkoxylation/Aminal Formation Cascade: Rapid Synthesis of Polycyclic Indolines

The author has demonstrated a new reaction entity of α-imino gold carbenes which undergoes carboalkoxylation through addition of a methyl ether via oxonium ylide formation. An efficient gold-catalyzed synthesis of indoline-propellanes was achieved in a one-pot sequence using ethylene glycol as a trapping reagent. This method enters untapped chemical space of three-dimensional indole based polycyclic compounds.

A special advantage in the gold-catalyzed functionalization of alkynes is the ability to assemble many elementary reaction steps to a highly efficient cascade sequence. This allows the rapid built-up of molecular complexity through generation of cyclic frameworks with high sp^3-content, increasing number of stereocenters and heteroatoms in a single operation.[1-3] In this context, rearrangement reactions involving gold carbene complexes with a tethered nucleophilic functional group represent useful transformations.

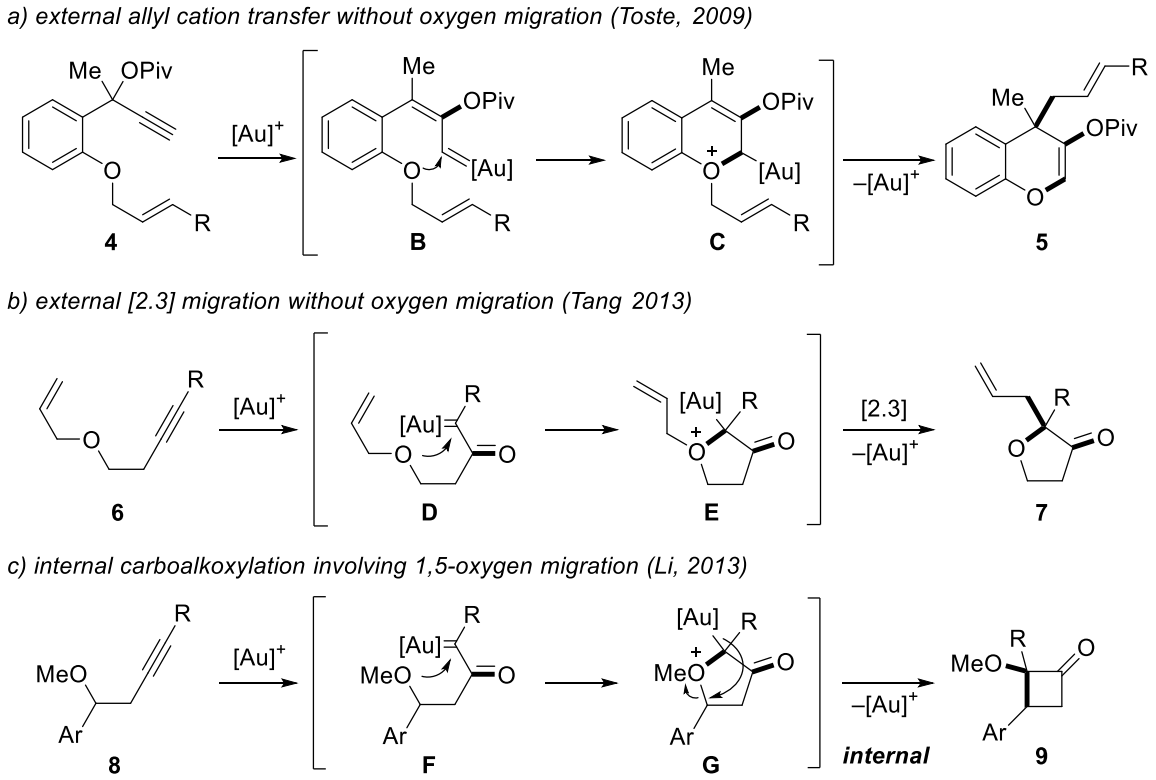
Pioneering studies on transition metal carbene chemistry have been reported by Johnson *et al.* and Werner *et al.* independently. They demonstrated the utility of copper and rhodium carbenes to facilitate nucleophilic addition of an allylic ether oxygen to generate oxonium ylide **A** (R = allyl), which undergoes subsequent sigmatropic [2,3]-rearrangement to furanones **2** via external rearrangement (Scheme 1). When using methyl ethers (R = Me), the internal rearrangement proceeded to afford cyclobutanones **3** via a ring contractive C–C bond formation and oxygen migration (carboalkoxylation). To date, only limited examples of such internal migration have been reported.[12-16]



Scheme 1. External and internal oxonium ylide rearrangements.

Analogue trapping reactions in gold carbene chemistry, especially involving carbon or oxygen migrations, are also exotic processes. Toste *et al.* showcased that benzopyrans **5** can be obtained from allyloxy-substituted phenyl propargyl esters **4** via gold carbene **B** (Scheme 2a). This carbene facilitates

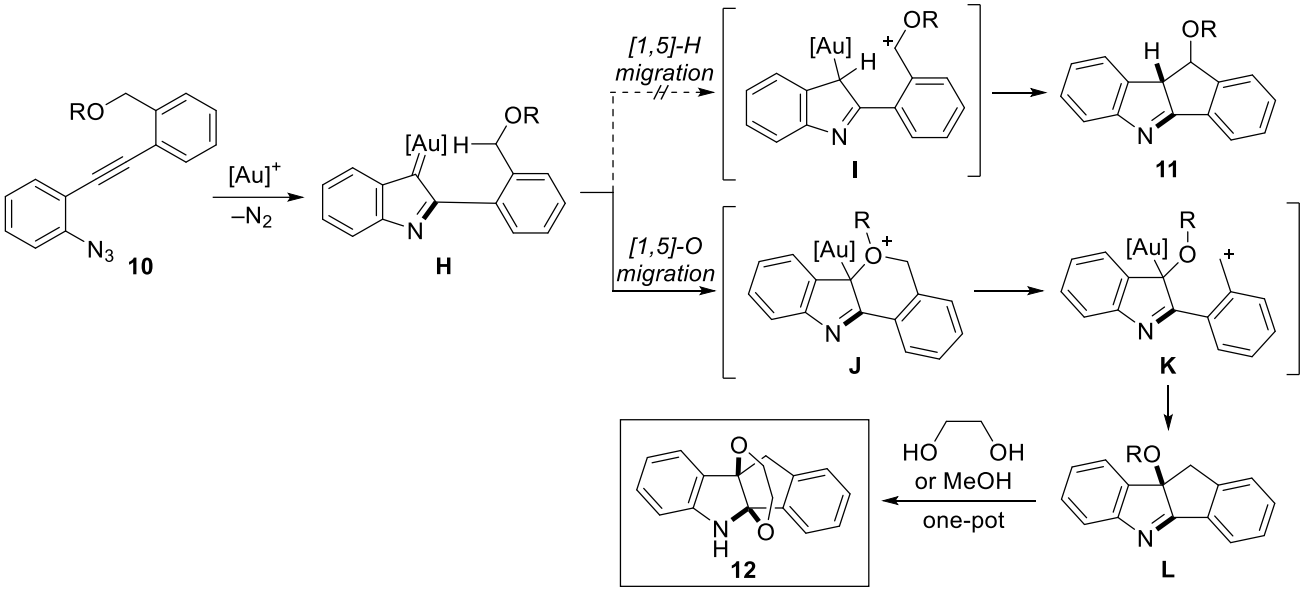
intramolecular trapping with the allylic ether oxygen as nucleophile to form oxonium ylide **C**, which undergoes intramolecular allyl cation transfer.[17] A related reaction was investigated by Tang and co-workers (Scheme 2b),[18] in which an α-oxo gold carbene **D** was generated from homopropargyl allyl ethers **6** with an oxidant such as 3,5-dichloropyridine *N*-oxides. After formation of an oxonium ylide **E**, an external [2,3]-rearrangement afforded dihydrofuranones **7**. It is noteworthy to state that no internal migration with oxygen migrating step was promoted in these reactions. On the other hand, 1,5-oxygen migration of gold carbenes via the internal process has been reported by Li and coworkers (Scheme 2c). The α-oxo gold carbene **F**, generated from homopropargylic ethers **8** and 8-ethyl quinoline *N*-oxide, gave the corresponding substituted cyclobutanones **9** via rearrangement of oxonium ylide **G** bearing a methyl ether moiety.[19]



Scheme 2. Background on reactions of ethers in the presence of gold carbenes.

In Chapter 2, the author reported that hydride migration on α-imino gold carbene is practical for the generation of polycyclic indoles.[20,21] To further facilitate the hydride transfer step on the gold carbenes, the author attempted to introduce an alkoxy group at the benzylic position by stabilizing the benzylic cation species **I** (Scheme 3). This supposition is concerning the profound research conducted by the groups of Gagosz[22,23] and Davies,[24] where the introduction of the oxygen functional group facilitates hydride transfer to electrophilic alkynyl gold complexes. On the other hand, the second reactivity pattern of α-imino gold carbene complexes **H** can be taken in consideration for the carbene **H** with an alkoxy functional

group: a nucleophilic attack of the ether oxygen could form the oxonium ylide **J**,[12-16] which can promote the oxygen migration to produce the tetracyclic product **L** through C–C bond formation from benzyl cation species **K**. This expectation is based on a broad investigation by Toste *et al.*, demonstrating that carboalkoxylation of alkynyl gold complexes are a vial pathway.[25] In this Chapter, the author describes a gold-catalyzed reaction of azido alkynes **10** to produce propellane-type indolines **12** via trapping of the imine intermediate **L** with glycol or methanol, respectively. Entrapment of the intermediate **L** with the preinstalled glycol ether (R = CH_2CH_2OH) is also presented.

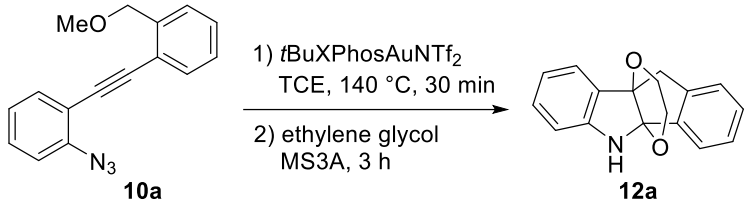


Scheme 3. Access to propellane-type indolines via alkoxy migration

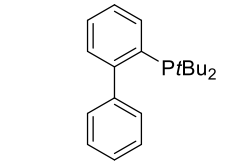
The author used a benzyl methyl ether **10a** for optimization of the reaction conditions. It turned out that subjecting the substrate **10a** to *t*BuXPhosAuNTf$_2$ in non-coordinating TCE for 30 min gave full conversion; however, chromatographic purification led to decomposition of the product. Based on observation of the crude ^{1}H-NMR the author was expecting that this unstable product would be the aforementioned imine **L**, the author then considered trapping the unstable intermediate with bis-nucleophile to form the aminal. Thus, after full consumption of the starting material **10a**, ethylene glycol and MS3Å were added to the reaction mixture, leading to formation of propellane-type product **12a** in 58% yield after 3 h (Table 1, entry 1). Variation from the optimized conditions disclosed that JohnPhos, *t*Bu$_3$P, IPr, and XPhos were less effective and decreased yields of **12a** were observed (5–30%, entries 2–5). On the contrary, bulky ligand *t*BuXPhos had a significant impact on the reaction outcome giving the desired product in fair yields of 45% (entry 6). A brief investigation of the counter anion effect and reaction temperature revealed that use of AgNTf$_2$ at 90 °C improved the yield to 51% (entry 8), and the reaction at 140 °C was most effective (58%, entry 1). The reaction without using MS3A decreased the yield to 6%

(entry 9), suggesting that MS3A would promote aminal formation step, presumably by trapping the generating methanol.

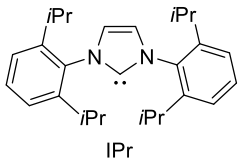
Table 1. Optimization of the reaction conditions



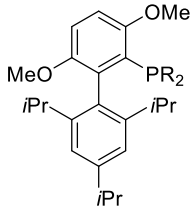
Entry	Variation from entry 1[a]	Yield (%)[b]
1	none (optimized conditions)	58[c]
2	JohnPhosAuCl/$AgSbF_6$	30
3	*t*Bu_3PAuCl/$AgSbF_6$, DCM	22
4	IPrAuCl/$AgSbF_6$, DCM, rt	5
5	XPhosAuCl/$AgSbF_6$	20
6	*t*BuXPhosAuCl/$AgSbF_6$, DCM, rt	45
7	*t*BuXPhosAuCl/$AgNTf_2$ DCM, rt	47
8	90 °C	51
9	without MS3A	6



JohnPhos



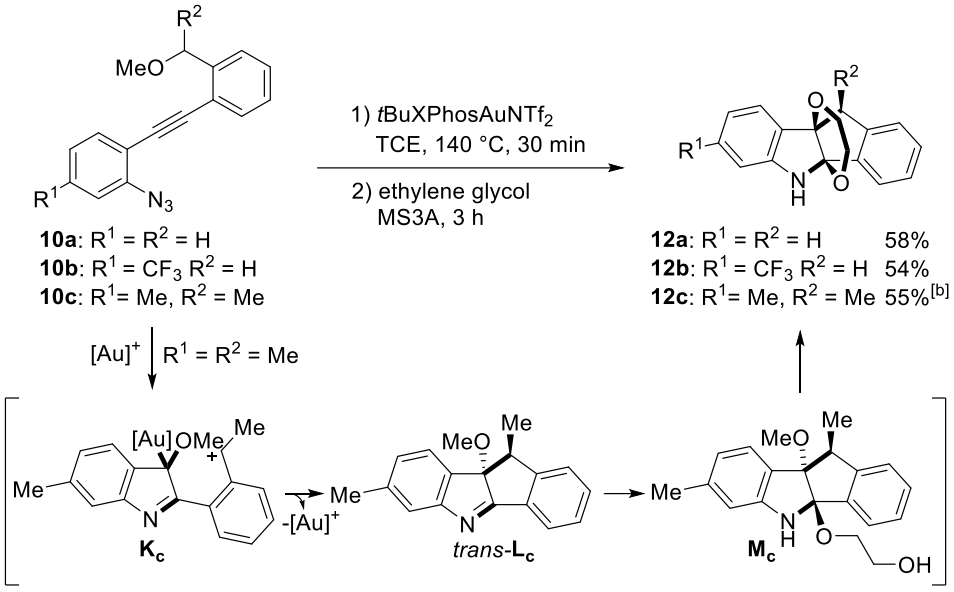
IPr



XPhos (R = Cy)
*t*BuXPhos (R = *t*Bu)

[a] Ligand structures on the right. [b] Determined by ^{1}H NMR analysis. [c] Isolated yield.

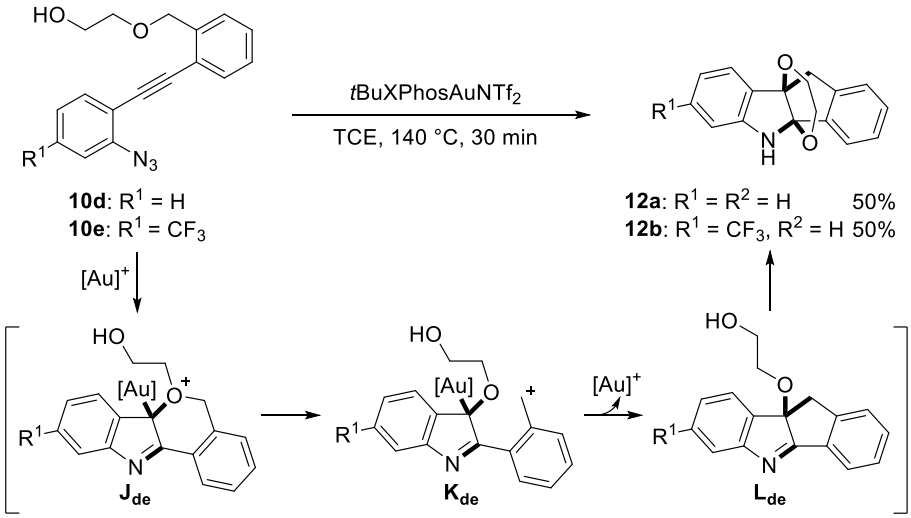
With the optimized conditions in hand, the author briefly investigated the reaction scope of one-pot process (Scheme 4). When an electron withdrawing CF_3 group was appended meta to the azido group (R^1 = CF_3), the desired product **12b** was formed with 54% yield. Interestingly, simultaneous attachment of an electron donating methyl groups as R^1 and R^2 substituent gave sterically congested **12c** with a relative *cis* configuration between the attached glycol and benzylic methyl group. This stereochemical outcome can be rationalized by stereoselective deaurative C–C bond formation step from carbocation $\mathbf{K_c}$ to fused indole $\mathbf{L_c}$, avoiding the sterically congested *cis* configuration. At this stage an intermediate deaurative rearomatization of the indole with subsequent heteroarylation of the carbocation to *trans*-$\mathbf{L_c}$ is also conceivable. The resulting *trans*-$\mathbf{L_c}$ would be trapped with glycol from the opposite side of the methoxy group to produce $\mathbf{M_c}$ stereoselectively, which will be then converted to the fused indoline **12c**.



Scheme 4. Reaction scope of gold(I)-catalyzed carboalkoxylative cyclization.[a]

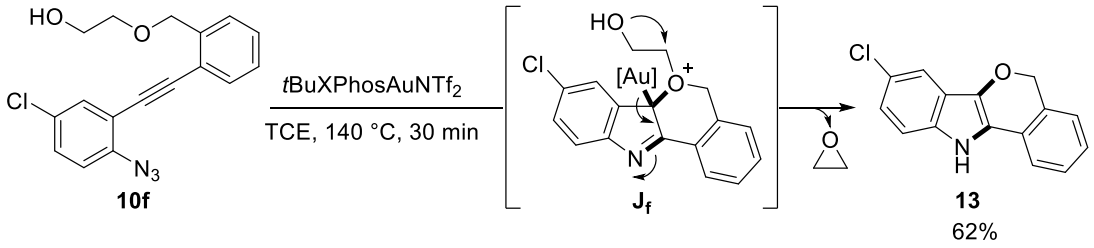
[a] Isolated yields are shown. [b] Isolated as *N*-methyl derivative **12c'**.

Next, the author designed a cascade process that does not require addition of ethylene glycol, by introducing ethylene glycol as the ether moiety. The gold-catalyzed reaction of the glycol-tethered substrates **10d** and **10e** gave **12a** and **12b**, respectively, both in 50% yield. This cascade reaction would proceed through formation of oxonium ylide $\mathbf{J_{de}}$, followed by deaurative C–C bond formation via intermediate $\mathbf{K_{de}}$, alternately this connectivity could also be generated through the rearomatized indole analogue. In the final stage aminal formation could occur through $\mathbf{K_{de}}$ and $\mathbf{L_{de}}$. At the present stage, both possibilities for the aminal formation cannot be ruled out.



Scheme 8. Gold(I)-catalyzed carboalkoxylation via intramolecular cascade sequence.

Surprisingly, the attachment of a chlorine group para to the azide position **10f** gave indole fused benzopyrane **13** in 62% yield, without forming the desired propellane product **12**. A rationale for this result can be found in the deaurative indole formation from $\mathbf{J_f}$ being facilitated by the electron-withdrawing chlorine group at the para position of the imine nitrogen, which may promote epoxidation of the glycol moiety via deprotonation by anionic indole species.



Scheme 10. Transformation to the dihydro benzopyrane fused indole.

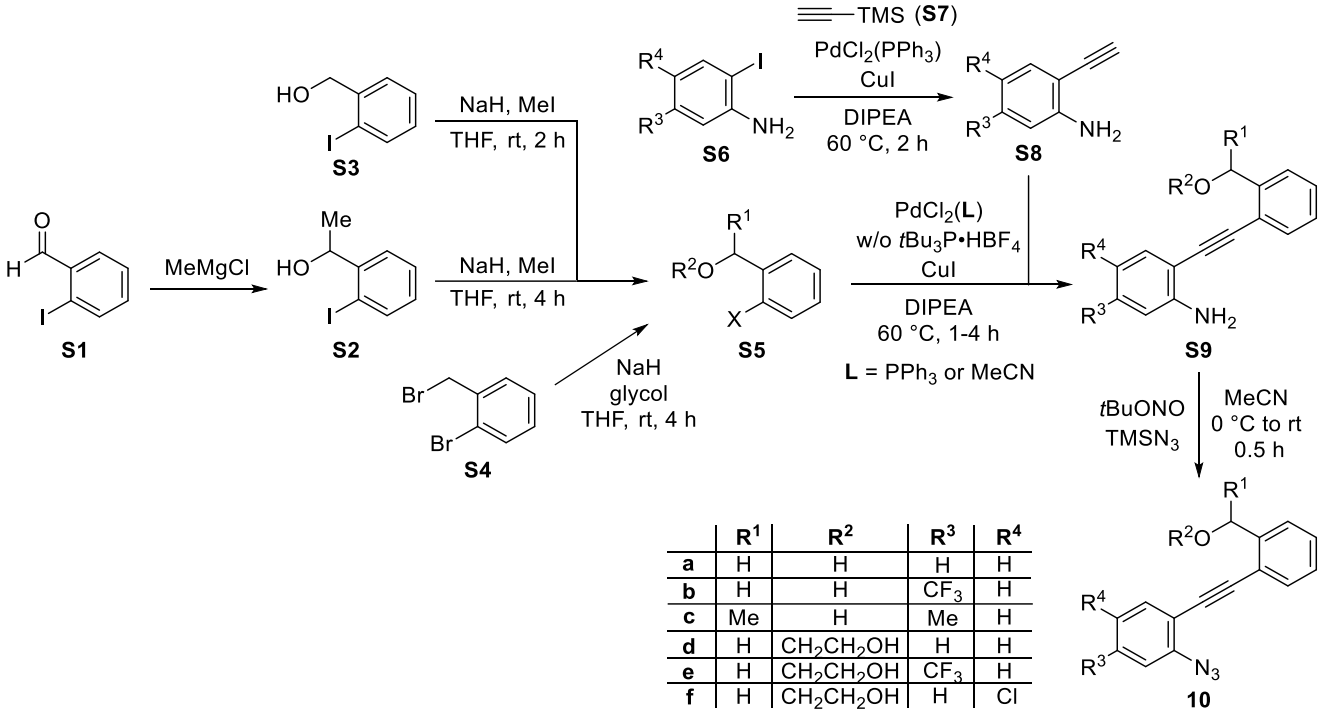
In summary, the author demonstrated a new reaction entity of α-imino gold carbene which experiences stepwise carboalkoxylation through addition of methyl ether and formation of oxonium ylide. These can be further functionalized in a one-pot or intramolecular cascade sequence giving propellane-type indolines, being considered as a biologically relevant scaffold useful for medicinal applications. The existence of oxonium ylides was strongly supported by formation of indole fused benzopyrane when using chlorine-substituted substrate. Although oxonium ylide formation via α-imino rhodium carbenes have been observed just recently, an intramolecular carboalkoxylation involving a 1,5-alkoxy migration to produce cyclic products is unprecedented.

Experimental Section

1. General Methods

Chemicals and solvents were purchased from commercial suppliers (Fujifilm Wako, Kanto Chemical Co., Inc., Merck). Dry THF was dispensed from the solvent purification system of Glass Contour MINI Nikko Hansen & Co., Ltd. NMR spectra were recorded at room temperature on JEOL AL-400 (400 MHz), JEOL ECA-500 (500 MHz), or JEOL ECZ600R (600 MHz) spectrometer if not mentioned otherwise. Chemical shifts are given in ppm and coupling constants in Hz. ^{1}H- and ^{13}C-NMR spectra were calibrated in relation to deuterated solvents according to Fulmer *et al.* ^{13}C-NMR spectra are proton decoupled and in cases of unambiguous results interpreted with help of DEPT, HMQC, and HMBC. All spectra were integrated and processed using ALICE2 software. Exact mass (HRMS) spectra were recorded on JMS-700 mass spectrometer or Shimadzu LC-ESI-IT-TOF-MS equipment. Infrared spectroscopy (IR) Infrared spectra were recorded on a FT-IR spectrometer named JASCO FT/IR-4100 with a Germanium ATR-crystal. The solvent or the matrix is denoted in brackets. For the most significant bands the wave number (cm^{-1}) is given. For the flash column chromatography, silica gel (Wakogel C-200E: Wako Pure Chemical Industries, Ltd) was used as stationary phase. As eluents, different mixtures of hexane and ethyl acetate was used. To visualize the substances, ninhydrin, vanillin, 2,4-dinitrophenylhydrazine, and $KMnO_4$ were used as coloring reagents, or the TLC-plate was exposed to ultraviolet light (254 and 366 nm). If not mentioned differently, all reactions were carried out under normal laboratory conditions. The known compounds **S2**,[26] **S5a**,[27] **S5c,**[27] **S5d**,[28] **S8a**,[29] **S8b**,[30] and **S8f**[31] were synthesized according to the reported procedures.

Synthetic Scheme for the Preparation of the Cyclization Precursors



	R1	R2	R3	R4
a	H	H	H	H
b	H	H	CF_3	H
c	Me	H	Me	H
d	H	CH_2CH_2OH	H	H
e	H	CH_2CH_2OH	CF_3	H
f	H	CH_2CH_2OH	H	Cl

General Procesures

GP1: Williamson Ether Synthesis of Alkyl Benzyl Ethers (S5)

To a suspension of NaH (1.5 equiv) of in anhydrous THF was added the corresponding benzylalcohol **S2** or **S3** (1.0 equiv) as an anhydrous THF solution dropwise at rt. The resulting mixture was stirred for 30 min. MeI (2.0 equiv.) was then added dropwise to the mixture. Upon completion of the reaction (monitored by TLC), the reaction was quenched with water and extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc = 10/1) to afford the desired benzylether **S5**. The reaction of glycol with benzyl bromide **S4** was also conducted in a same manner.

GP2: Sonogashira Reaction for Alkynylanilines

CuI (5 mol %) and $Pd(PPh_3)_2Cl_2$ (5 mol %) were suspended in iPr$_2$NH (DIPA) under argon together with the corresponding aryl iodide (1.0 equiv). After the suspension was gradually heated to 60 °C over 30 min, the alkyne (2.0 equiv) was added dropwise via syringe. After 2 h (full conversion monitored by TLC), the reaction was diluted with DCM and filtered through Celite®. The filtrate was washed with H_2O, aqueous NH_4Cl, and brine. After drying with $MgSO_4$ and filtration, the solvent was removed *in vacuo* at 40 °C, the product was purified with silica gel column chromatography to give the coupling product.

GP3: Sonogashira Reaction for Alkynylanilines (S9)

CuI (5 mol %) and Pd $PdCl_2(MeCN)_2$ (5 mol %) with tBu$_3$P·HBF$_4$ (10 mol %) were suspended in iPr$_2$NH (DIPA) under argon together with aryl bromide **S5** (2.0 equiv). After the suspension was gradually heated to 60 °C over 30 min, the alkyne **S8** (1.0 equiv) was added dropwise via syringe. After 1-4 h (full conversion monitored by TLC) the reaction was diluted with DCM and filtered through Celite®. The filtrate was washed with H_2O, aqueous NH_4Cl, and brine. After drying with $MgSO_4$ and filtration, the solvent was removed *in vacuo* at 40 °C, the product was purified with silica gel column chromatography to give **S9**.

GP4: Azidation for the Synthesis of 10

The aniline derivative **S9** (1.0 equiv.) was dissolved in MeCN and the mixture was cooled to 0 °C in an ice bath. To this stirred mixture were successively added tBuONO (1.5 equiv) and $TMSN_3$ (1.5 equiv) dropwise. The resulting solution was stirred at room temperature for 30 min and concentrated *in vacuo*. The residue was purified with column chromatography to give the desired product **10**.

GP5: Gold(I)-Catalyzed Cyclization via Cascade/One-Pot Sequence

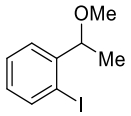
Azido-yne **10** (1.0 equiv) was dissolved in TCE (*ca*. 2 mM) and heated to 140 °C under rigorous stirring. To this stirred mixture, a catalytic amount of tBuXPhosAuNTf$_2$(MeCN)SbF$_6$ was added and stirred until full conversion (monitored by TLC). To the stirred reaction mixture were successively added 3A MS and glycol (10 equiv.), the resulting suspension was further stirred for 4 h while maintaining the temperature at 140 °C. After filtration and subsequent concentration *in vacuo* the purification was performed by silica gel column chromatography giving the desired product **12**.

GP6: Gold(I)-Catalyzed Cyclization via Cascade Reaction

Azido-yne **10** (1.0 equiv) was dissolved in TCE (*ca*. 2 mM) and heated to 140 °C under rigorous stirring. To this stirred mixture, a catalytic amount of tBuXPhosAuNTf$_2$(MeCN)SbF$_6$ was added and stirred until full conversion (monitored by TLC). After concentration *in vacuo* the purification was performed by silica gel column chromatography giving the desired product **12**.

2. Preparation of the Cyclization Precursors

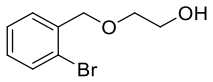
1-Iodo-2-(1-methoxyethyl)benzene (S5c)



S5c

According to **GP1**, to a solution of **S2** (1.99 g, 8.02 mmol) in anhydrous THF (50 mL) was added NaH (481 mg, 12.0 mmol) in one portion at 0 °C. The resulting mixture was stirred for 30 min. MeI (1.00 mL, 16.0 mmol) was then added dropwise. The reaction was monitored by TLC. Upon completion, the reaction was quenched with water and extracted with ethyl ether. The combined organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc = 10/1) to afford the desired alkyne **S5c** (1.53 g, 73%). The spectral data were in good agreement with those previously reported.[27]

2-[(2-Bromobenzyl)oxy]ethan-1-ol (S5d)

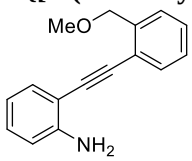


S5d

According to **GP1**, to a solution of ethyleneglycol (0.691 mL, 11.0 mmol) in anhydrous THF (50 mL) was added NaH (204 mg, 5.0 mmol) in one portion at rt. The resulting mixture was stirred for 30 min. 2-Bromobenzyl bromide (1.25 g, 5.0 mmol) was then added dropwise. Upon completion (monitored by TLC), the reaction was quenched with water and extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc = 10/3) to afford the desired ether **S5d** (0.759 g, 66%). The spectral data were in good agreement with those previously reported.[28]

Preparation of Amino-ynes

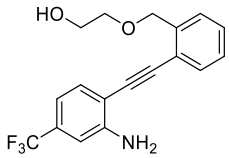
2-{[2-(Methoxymethyl)phenyl]ethynyl}aniline (S9a)



S9a

According to **GP2**, **S8a** (470 mg, 4.02 mmol) was converted to **S9a** (429 mg, 45%) by the reaction with **S5a** (2.00 g, 8.04 mmol) in the presence of $PdCl_2(PPh_3)_2$ (141 mg, 0.201 mmol) and CuI (38.3 mg, 0.201 mmol) in DIPA (25 mL) for 1 h. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1 to 2/1) to give **S9a**; IR (neat) 3464, 3350 (N-H), 2222 (C≡C); ^{1}H NMR (600 MHz, $CDCl_3$): 3.04 (s, 3H), 4.47 (br s, 2H), 4.68 (s, 2H), 6.69-6.71 (m, 2H), 7.14 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.28-7.34 (m, 2H), 7.36 (d, *J* = 7.4 Hz, 1H), 7.42 (d, *J* = 7.4 Hz, 1H), 7.52 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 58.2, 73.1, 90.6, 92.3, 107.8, 114.2, 117.6, 122.7, 127.7, 128.1, 128.4, 129.8, 131.2, 132.0, 139.1, 148.5; HRMS calcd for $C_{16}H_{16}NO^+$ $[M + H]^+$: 238.1222, found 238.1226.

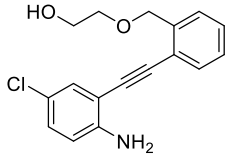
2-({2-[(2-Amino-4-(trifluoromethyl)phenyl]ethynyl}benzyl)oxy)ethan-1-ol (S9e)



S9e

According to **GP3**, **S8b** (1.00 g, 5.40 mmol) was converted to **S9e** in (723 mg, 40%) by the reaction with aryl bromide **S5d** (2.49 g, 10.8 mmol) and in the presence of $PdCl_2(MeCN)_2$ (70.0 mg, 0.27 mmol), *t*$Bu_3P{\cdot}HBF_4$ (156 mg, 0.540 mmol) and CuI (47.7 mg, 250 μmol) in DIPA (40 mL) at 60 °C for 4 h; brown oil; IR (neat): 3427 (N-H), 3355 (N-H), 2111 (C≡C); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.59 (dd, J = 4.8, 4.8 Hz, 2H), 3.74 (dd, J = 4.8, 4.8 Hz, 2H), 4.77 (s, 2H), 4.92 (br s, 2H), 6.74 (dd, J = 8.3, 8.3 Hz, 1H), 7.33-7.41 (m, 4H), 7.57-7.58 (m, 1H), 7.89 (s, 1H); ^{13}C NMR (600 MHz, $CDCl_3$) δ: 61.9, 71.0, 72.2, 89.5, 93.4, 107.2, 113.8, 119.6 (q, J = 33.3 Hz), 122.5, 124.4 (q, J = 270 Hz), 126.7 (q, J = 3.8 Hz), 128.2, 128.6, 129.2 (2C), 132.4, 138.9, 150.1; $C_{18}H_{17}F_3NO_2^+$ $[M + H]^+$: 336.1206, found 336.1225.

2-({2-[(2-Amino-5-chlorophenyl)ethynyl]benzyl}oxy)ethan-1-ol (S9f)

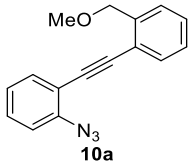


S9f

According to **GP3**, **S8f** (1.00 g, 6.60 mmol) was converted to **S9f** in (0.700 g, 35%) by the reaction with aryl bromide **S5d** (3.05 g, 13.2 mmol) in the presence of $PdCl_2(MeCN)_2$ (85.6 mg, 0.330 mmol), *t*$Bu_3P{\cdot}HBF_4$ (191 mg, 0.660 mmol) and CuI (62.8 mg, 0.330 mmol) in DIPA (40 mL) at 60 °C for 4 h: brown oil; IR (neat): 3477 (N-H), 3321 (N-H), 2249 (C≡C); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.44 (br s, 1H), 3.55-3.62 (m, 2H), 3.17-3.72 (m, 2H), 4.57 (br s, 2H), 4.75 (s, 2H), 6.63 (d, J = 8.3 Hz, 1H), 7.08 (dd, J = 8.3, 2.4 Hz, 1H), 7.31-7.35 (m, 3H), 7.39 (d, J = 7.6 Hz, 1H), 7.55 (d, J = 7.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 61.8, 71.1, 72.0, 89.6, 93.4, 109.0, 115.6, 122.1, 122.5, 128.1, 128.4, 129.1, 129.8, 131.0, 132.5, 138.9, 146.9; $C_{17}H_{17}ClNO_2^+$ $[M + H]^+$: 302.0942, found 302.0938.

Preparation of Azido-ynes 10

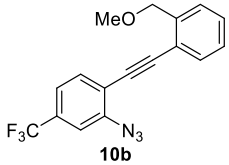
1-Azido-4-chloro-2-{[2-(methoxymethyl)phenyl]ethynyl}benzene (10a)



10a

According to **GP4**, **S9a** (400 mg, 1.69 mmol) was converted to **10a** (412 mg, 95%) by the reaction with *t*BuONO (0.302 mL, 2.54 mmol) and $TMSN_3$ (0.334 mL, 2.54 mmol) in MeCN (10 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1) to give **10a** as a yellow oil; IR (neat): 2248 (C≡C), 2091 (N≡N); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.49 (s, 3H), 4.76 (s, 2H), 7.11-7.15 (m, 2H), 7.27 (dd, J = 7.5, 7.5 Hz, 1H), 7.33-7.37 (m, 2H), 7.49-7.51 (m, 2H), 7.55 (d, J = 7.5 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 58.5, 72.6, 89.4, 92.8, 115.4, 118.6, 121.4, 124.6, 127.3, 127.4, 128.8, 129.6, 131.9, 133.4, 140.1, 140.9; $C_{16}H_{13}N_3NaO^+$ $[M + Na]^+$: 286.0951, found 286.0949.

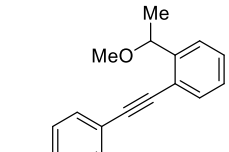
2-Azido-1-{[2-(methoxymethyl)phenyl]ethynyl}-4-(trifluoromethyl)benzene (10b)



10b

S8b (555 mg, 3.00 mmol) was converted to **10b** (200 mg, 20%) by the reaction with **S5a** (1.49 g, 6.00 mmol) in the presence of $PdCl_2(PPh_3)_2$ (105 mg, 0.150 mmol) and CuI (28.6 mg, 0.150 mmol) in DIPEA (25 mL) for 1 h, followed by azidation with *t*BuONO (0.535 mL, 4.50 mmol) and $TMSN_3$ (0.591 mL, 4.50 mmol) in MeCN (10 mL) at room temperature for 30 min. Purification for the first step was performed by silica gel column chromatography (hexane/EtOAc = 10/1 to 2/1) to give crude **S9b**. Due to impurities, the crude aniline **S9b** was directly used to the next azidation step according to **GP4**. Purification for the second step was performed by silica gel column chromatography (hexane/EtOAc = 10/1) to give **10b** as a brown oil; IR (neat): 2213 (C≡C), 2024 (N≡N); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.49 (s, 3H), 4.75 (s, 2H), 7.24 (d, J = 8.4 Hz, 1H), 7.30 (dd, J = 7.9, 7.9 Hz, 1H), 7.39 (dd, J = 7.9, 7.9 Hz, 1H), 7.51 (d, J = 7.9 Hz, 1H), 7.56-7.59 (m, 2H), 7.74-7.76 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 58.5, 72.5, 87.9, 94.3, 116.0, 119.0, 120.8, 123.5 (q, J = 271 Hz), 126.2 (q, J = 3.8 Hz), 127.3, 127.6, 129.2, 130.4 (q, J = 3.8 Hz), 131.2, 132.0, 140.3, 144.3; HRMS calcd for $C_{17}H_{12}F_3N_3NaO^+$ $[M + Na]^+$: 354.0825, found 354.0828.

2-Azido-1-{[2-(1-methoxyethyl)phenyl]ethynyl}-4-methylbenzene (10c)

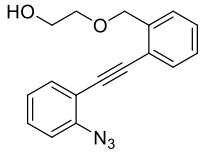


10c

S8c (500 mg, 3.81 mmol) was converted to **10c** (333 mg, 30%) by the reaction with **S5c** (1.89 g, 7.62 mmol) in the presence of $PdCl_2(PPh_3)_2$ (134 mg, 0.191 mmol) and CuI (36.4 mg, 0.191 mmol) in DIPEA (25 mL) for 1 h, followed by azidation with *t*BuONO (0.680 mL, 5.72 mmol) and $TMSN_3$ (0.752 mL, 5.72 mmol) in MeCN (10 mL) at room temperature for 30 min. Purification for the first step was performed by silica gel column chromatography (hexane/EtOAc = 15/1 to 5/1) to give crude **S9c**. Due to impurities, the aniline **S9c** was directly used to the next azidation step according to **GP4**. Purification for the second step was performed by silica gel column chromatography (hexane/EtOAc = 15/1) to give **10c** as a brown oil; IR (neat): 2251 (C≡C), 2112 (N≡N); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.50 (d, J = 6.2 Hz, 3H), 2.39 (s, 3H), 3.30 (s, 3H), 5.01 (q, J = 6.2 Hz, 1H), 6.93-6.96 (m, 2H), 7.24-7.26 (m, 1H), 7.36-7.39 (m, 2H), 7.50 (d, J = 7.6 Hz, 1H), 7.53 (d, J = 8.3 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 21.5, 23.0, 55.7, 89.8, 92.1, 112.5, 119.2, 121.4, 124.8, 125.7 (2C), 126.9, 129.0, 131.9, 133.0, 133.1, 140.3, 145.6; HRMS calcd for $C_{18}H_{17}N_3NaO^+$ $[M + Na]^+$: 314.1264, found 314.1255.

Preparation of Azido-ynes (10)

2-({2-[(2-Azidophenyl)ethynyl]benzyl}oxy)ethan-1-ol (10d)

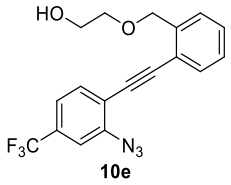


10d

S8a (500 mg, 4.26 mmol) was converted to **10d** (437 mg, 35%) by the reaction with **S5d** (1.96 g, 8.52 mmol)

in the presence of $PdCl_2(MeCN)_2$ (55.63 mg, 0.213 mmol), *t*$Bu_3P{\cdot}HBF_4$ (123 mg, 0.426 mmol) and CuI (40.6 mg, 0.213 mmol) in DIPEA (40 mL) at 60 °C for 4 h, followed by azidation with *t*BuONO (0.760 mL, 6.39 mmol) and $TMSN_3$ (0.840 mL, 6.39 mmol) in MeCN (10 mL) at room temperature for 30 min. Purification for the first step was performed by silica gel column chromatography (hexane/EtOAc = 5/1 to 2/1) to give crude **S9d**. Due to impurities, the crude aniline **S9d** was directly used to the next azidation step according to **GP4**. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1 to 5/1) to give **10d** as a yellow oil; IR (neat): 2214 (C≡C), 2091 (N≡N); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.48-3.53 (m, 2H), 3.61-3.66 (m, 2H), 4.73 (s, 2H), 6.70-7.02 (m, 2H), 7.11-7.25 (m, 3H), 7.36-7.44 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 62.4, 71.5, 72.4, 89.9, 93.3, 115.8, 119.1, 121.6, 125.1, 127.5, 127.8, 129.2, 130.0, 132.3, 133.9, 140.9, 141.4; HRMS calcd for $C_{17}H_{15}N_3NaO_2^+$ $[M + Na]^+$: 316.1056, found 316.1065.

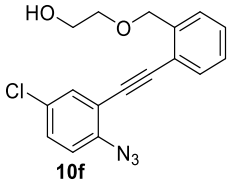
2-[(2-{[2-Azido-4-(trifluoromethyl)phenyl]ethynyl}benzyl)oxy]ethan-1-ol (10e)



10e

According to **GP4**, **S9e** (500 mg, 1.49 mmol) was converted to **10e** (485 mg, 90%) by the reaction with *t*BuONO (0.266 mL, 2.24 mmol) and $TMSN_3$ (0.294 mL, 2.24 mmol) in MeCN (10 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1 to 5/1) to give **10e** as a yellow oil; IR (neat): 2247 (C≡C), 2106 (N≡N); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.66-3.75 (m, 2H), 3.78-3.84 (m, 2H), 4.85 (s, 2H), 7.26-7.27 (m, 2H), 7.32 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.41 (dd, *J* = 6.7, 6.7 Hz, 1H), 7.52 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.59 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.76-7.78 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 61.9, 71.3, 71.7, 88.0, 94.4, 106.4, 115.8, 119.0, 121.1, 123.4 (q, *J* = 271 Hz), 126.3 (q, *J* = 3.9 Hz), 127.7, 128.0, 129.3, 130.5 (q, *J* = 3.9 Hz), 132.4, 140.0, 144.4; HRMS calcd for $C_{18}H_{14}F_3N_3O_2Na^+$ $[M + Na]^+$: 384.0930, found 384.0926.

2-({2-[(2-Azido-5-chlorophenyl)ethynyl]benzyl}oxy)ethan-1-ol (10f)

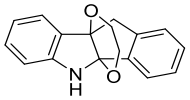


10f

According to **GP4**, **S9f** (500 mg, 1.66 mmol) was converted to **10f** (495 mg, 91%) by the reaction with *t*BuONO (0.296 μL, 2.49 mmol) and $TMSN_3$ (0.327 mL, 2.49 mmol) in MeCN (10 mL) at room temperature for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1) to give **10f** as a yellow oil; IR (neat): 2249 (C≡C), 2110 (N≡N); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.79 (t, *J* = 4.9 Hz, 2H), 4.29 (t, *J* = 4.9 Hz, 2H), 4.85 (s, 2H), 7.09 (d, *J* = 8.6 Hz, 1H), 7.29-7.33 (m, 2H), 7.53 (ddd, *J* = 7.6, 7.6, 1.3 Hz, 1H), 7.48 (d, *J* = 2.4 Hz, 1H), 7.53-7.56 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 63.6, 68.4, 71.0, 93.9, 116.8, 119.9, 121.0, 127.5, 127.6, 129.2, 129.6, 129.8, 132.1, 132.9, 139.6, 139.9, 171.1; HRMS calcd for $C_{17}H_{15}ClN_3O_2^+$ $[M + H]^+$: 328.0847, found 328.0833.

3. Gold-Catalyzed Cyclization

(4b*R*/*S*,9b*R*/*S*)-5*H*,10*H*-4b,9b-(epoxyethanooxy)indeno[1,2-*b*]indole (12a)



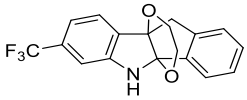
12a

One-pot procedure: according to **GP5**, azido-yne **10a** (50 mg, 0.211 mmol) was converted to **12a** (32.4 mg, 58%) by the reaction with *t*BuXPhosAuNTf$_2$ (19.0 mg, 0.0211 mmol) in TCE (20 mL) at 140 °C for 0.5 h. To the stirred reaction mixture were successively added 3A MS (500 mg) and ethylene glycol (0.12 mL, 2.11 mmol), and the resulting suspension was further stirred for 4 h while maintaining the temperature at 140 °C. After filtration and subsequent concentration *in vacuo*, purification was performed by silica gel column chromatography (hexane/EtOAc = 5/1) giving the desired product **12a** as a colorless oil.

Intramolecular procedure: according to **GP6**, **10d** (50 mg, 0.170 mmol) was converted to **12a** (22 mg, 50%) by the reaction with *t*BuXPhosAuNTf$_2$ (15.3 mg, 0.0211 mmol) in TCE (20 mL) at 140 °C for 0.5 h. After concentration *in vacuo*, purification was performed by silica gel column chromatography (hexane/EtOAc = 5/1) to give the desired product **12a** as a colorless oil.

Compound **12a**: IR (neat): 3340 (N-H); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.25 (d, J = 16.5 Hz, 1H), 3.45 (d, J = 16.5 Hz, 1H), 3.60-3.63 (m, 1H), 3.65-3.73 (m, 2H), 3.85-3.88 (m, 1H), 4.59 (br s, 1H), 6.66 (d, J = 7.6 Hz, 1H), 6.85 (dd, J = 7.6, 7.6 Hz, 1H), 7.15 (ddd, J = 7.6, 7.6, 1.3 Hz, 1H), 7.23-7.46 (m, 1H), 7.31-7.32 (m, 2H), 7.36 (d, J = 6.9 Hz, 1H), 7.43-7.47 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 42.8, 60.1, 60,5, 86.5, 98.7, 110.5, 119.9, 121.8, 122.6, 123.9, 127.5, 129.3, 129.7, 140.5, 141.7, 148.9, 151.6; HR-MS calcd for $C_{17}H_{16}NO_2^+$ [M + H]$^+$: 266.1176, found 266.1175.

(4b*R*/*S*,9b*R*/*S*)-7-(Trifluoromethyl)-5*H*,10*H*-4b,9b-(epoxyethanooxy)indeno[1,2-*b*]indole (12b)



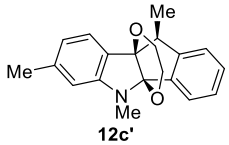
12b

One-pot procedure: According to **GP5**, azido-yne **10b** (50 mg, 0.151 mmol) was converted to **12b** (25 mg, 54%) by the reaction with *t*BuXPhosAuNTf$_2$ (13.5 mg, 0.015 mmol) in TCE (20 mL) at 140 °C for 0.5 h. To the stirred reaction mixture were successively added 3A MS (500 mg) and ethylene glycol (0.12 mL, 2.11 mmol), and the resulting suspension was further stirred for 4 h while maintaining the temperature at 140 °C. After filtration and subsequent concentration *in vacuo*, purification was performed by silica gel column chromatography (hexane/EtOAc = 5/1) to give the desired product **12b** as a colorless oil.

Intramolecular procedure: According to **GP6, 10e** (50 mg, 0.138 mmol) was converted to **12b** (23 mg, 50%) by the reaction with *t*BuXPhosAuNTf$_2$ (12.4 mg, 0.0138 mmol) in TCE (20 mL) at 140 °C for 0.5 h. After concentration *in vacuo*, purification was performed by silica gel column chromatography (hexane/EtOAc = 5/1) giving the desired product **12b** as a colorless oil.

Compound **12b**: ^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.22 (d, J = 16.4 Hz, 1H), 3.45 (d, J = 16.4 Hz, 1H), 3.62-3.63 (m, 1H), 3.66-3.72 (m, 2H), 3.81-3.83 (m, 1H), 4.86 (br s, 1H), 6.68 (d, J = 8.2 Hz, 1H), 7.25-7.27 (m, 1H), 7.30-7.34 (m, 2H), 7.41 (d, J = 8.5 Hz, 1H), 7.45-7.48 (m, 1H), 7.59-7.61 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 42.2, 60.1, 60,6, 86.1, 98.9, 109.6, 121.3 (q, J = 3.7 Hz), 121.7, 122.7, 124.8 (q, J = 271.5 Hz), 125.5, 127.5 (q, J = 3.7 Hz), 127.7, 129.5, 129.6, 139.6, 141.7, 151.6; HR-MS calcd for $C_{18}H_{15}F_3NO_2^+$ [M + H]$^+$: 334.1049, found 334.1043.

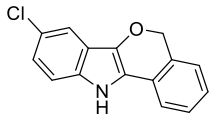
(4b*R*/*S*,9b*R*/*S*,10*S*/*S*)-5,7,10-Trimethyl-5*H*,10*H*-4b,9b-(epoxyethanooxy)indeno[1,2-*b*]indole (12c')



12c'

According to **GP5**, azido-yne **10c** (50.0 mg, 0.172 mmol) was converted to **12c'** (28.0 mg, 55%) by the reaction with *t*BuXPhosAuNTf$_2$ (15.5 mg, 0.0172 mmol) in TCE (20 mL) at room 140 °C for 0.5 h and subsequent treatment with MS3A (500 mg) and ethylene glycol (0.12 mL, 2.11 mmol) at 140 °C for 4 h, followed by methylation. Purification for the first step was performed by silica gel column chromatography (hexane/EtOAc = 5/1) giving the desired product **12c** as a colorless oil. Due to the impurities, the crude **12c** was subjected to *N*-methylation. The crude **12c** was dissolved in anhydrous THF in the presence of NaH (7.20 mg, 0.180 mmol) and stirred for 30 min. Purification was performed by silica gel column chromatography (hexane/EtOAc = 10/1) to give **12c'** as a colorless oil; IR (neat): no specific signals; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.38 (d, J = 6.9 Hz, 3H), 2.35 (s, 3H), 2.81 (s, 3H), 3.12 (q, J = 6.9 Hz, 1H), 3.40-3.45 (m, 1H), 3.49-3.51 (m, 2H), 3.67-3.71 (m, 1H), 6.84 (s, 1H), 6.65 (d, J = 6.9 Hz, 1H), 7.20 (d, J = 8.3 Hz, 1H), 7.24-7.26 (m, 1H), 7.31-7.39 (m, 2H), 7.51 (d, J = 7.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 9.76, 31.6, 47.6, 60.6, 61.4, 91.3, 102.1, 108.2, 118.8, 122.5, 123.4, 123.5, 123.9, 125.2, 126.8, 129.1, 137.4, 139.6, 148.6, 151.3; HR-MS calcd for $C_{20}H_{22}NO_2^+$ $[M + H]^+$: 308.1645, found 308.1650.

8-Chloro-5,11-dihydroisochromeno[4,3-*b*]indole (13)



13

According to **GP6**, azido-yne **10f** (50.0 mg, 0.152 mmol) was converted to **13** (24.0 mg, 62%) by the reaction with *t*BuXPhosAuNTf$_2$ (13.7 mg, 0.0152 mmol) in TCE (20 mL) at 140 °C for 0.5 h. Purification was performed by silica gel column chromatography (hexane/Et_2O = 10/1 to 2/1) to give **13** as a yellow oil. The spectral data were in good agreement with those previously reported.[32]

References

[1] L.-J. Qi, C.-Y. Shi, P. F. Chen, L. Li, G. Fang, P.-C. Fang, C. Deng, J.-M. Zhou, L.-W. Ye, *ACS Catal.* **2021**, *11*, 3679–3686.

[2] H. V. Adcock, P. W. Davies, *Synthesis* **2012**, *44*, 3401−3420.

[3] N. T. Patil, R. D. Kavthe, Y. Yamamoto, *Adv. Heterocycl. Chem.* **2010**, *101*, 75−95.

[4] J. F. Hartwig, M. A. Larsen, *ACS Cent. Sci.* **2016**, *2*, 281−292.

[5] H. W. L. Davies, D. Morton, *J. Org. Chem*. **2016**, *81*, 343−350.

[6] P. Dubé, F. D. Toste, *J. Am. Chem. Soc.* **2006**, *128*, 12062–12063.

[7] C. Kim, H. J. Bae, J. H. Lee, W. Jeong, H. Kim, V. Sampath, Y. H. Rhee, *J. Am. Chem. Soc.* **2009**, *131*, 14660–14661.

[8] H. Bae, B. Baskar, S. An, J. Cheong, D. Thangadurai, I.-C. Hwang, Y. Rhee, *Angew. Chem. Int. Ed.* **2008**, *47*, 2263–2266.

[9] H. Kim, Y. H. Rhee, *J. Am. Chem. Soc.* **2012**, *134*, 4011–4014.

[10] W. Zi, F. D. Toste, *J. Am. Chem. Soc.* **2013**, *135*, 12600–12603.

[10] W. Zi, H. Wu, F. D. Toste, *J. Am. Chem. Soc.* **2015**, *137*, 3225–3228.

[11] H. Wu, W. Zi, G. Li, H. Lu, F. D. Toste, *Angew. Chem. Int. Ed*. **2015**, *54*, 8529–8532.

[12] P. F. Marmsäter, F. G. West, *J. Am. Chem. Soc.* **2001**, *123*, 5144–5145

[13] J. S. Clark, C. A. Baxter, A. G. Dossetter, S. Poigny, J. L. Castro, W. G. Whittingham, *J. Org. Chem*. **2008**, *73*, 1040–1055.

[14] T. Chen, Z. Yan, S. Duan, Z.-F. Xu, C.-Y. Li, *Org. Chem. Front*. **2021**, *8*, 6371–6376.

[15] M. C. Pirrung, J. A. Werner, *J. Am. Chem. Soc.* **1986**, *108*, 6060–6062.

[16] E. J. Roskamp, C. R. Johnson, *J. Am. Chem. Soc.* **1986**, *108*, 6062–6063.

[17] M. Uemura, I. D. G. Watson, M. Katsukawa, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 3464−3465.

[18] J. Fu, H. Shang, Z. Wang, L. Chang, W. Shao, Z. Yang, Y. Tang, *Angew. Chem. Int. Ed.* **2013**, *52*, 4198–4202.

[19] M. Xu, T.-T. Ren, K.-B. Wang, C.-Y. Li, *Adv. Synth. Catal.* **2013**, *355*, 2488–2494.

[20] L. C. Greiner, N. Arichi, S. Inuki, H. Ohno, *Angew. Chem. Int. Ed.* **2023**, *62*, 3, e202213653.

[21] D. F. L. Rayo, A. Mansour, W. Wu, B. N. Bhawal, F. Gagosz, *Angew. Chem. Int. Ed.* **2023**, *62*, e202212893.

[22] D. Jurberg, Y. Odabachian, F. Gagosz, *J. Am. Chem. Soc.* **2010**, *132*, 3543–3552.

[23] A. Boreux, G. H. Lonca, O. Riant, F. Gagosz, *Org. Lett.* **2016**, *18*, 5162–5165.

[24] D. H. V. Adcock, E. Chatzopoulou, P. W. Davies, *Angew. Chem. Int. Ed.* **2015**, *54*,15525–15529.

[25] P. Dubé, F. D. Toste, *J. Am. Chem. Soc.* **2006**, *128*, 12062–12063.

[26] Y. C. Fan, O. Kwon, *Org. Lett.* **2012**, *14*, 3264–3267.

[27] H. Kinoshita, H. Fukumoto, T. Tohjima, K. Miura, *Tetrahedron Lett*. **2016**, *57*, 3571–3574.

[28] A. Archambeau, F. Miege, C. Meyer, J. Cossy, *Angew. Chem. Int. Ed.* **2015**, *124*, 11708–11712.

[29] L. C. Greiner, S. Inuki, N. Arichi, S. Oishi, R. Suzuki, T. Iwai, M. Sawamura, A. S. K. Hashmi, H. Ohno, *Chem. Eur. J.* **2021**, *27*, 12992–12997.

[30] N. Sakai, K. Tamura, K. Shimamura, R. Ikeda, T. Konakahara, *Org. Lett.* **2012**, *14*, 836–839.

[31] X. Zhao, X. Song, H. Jin, Z. Zeng, Q. Wang, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Adv. Synth. Catal.* **2018**, *360*, 2720–2726.
[32] J. Cai, B. Wu, G. Rong, C. Zhang, L. Qui, X. Xu, *Org. Lett*. **2018**, *20*, 2733–2736.

Acknowledgements

First and foremost, the author would like to express his highest gratitude to Professor Hiroaki Ohno (Graduate School of Pharmaceutical Sciences, Kyoto University), for the kind guidance and patience in teaching even in the most challenging times. Constant encouragement and fruitful intercultural discussions strongly contributed to the author's personal and professional development throughout this study.

The author wants to express his sincere appreciation for the constructive professional and joyful dialogues with Professor Shinsuke Inuki (Graduate School of Pharmaceutical Sciences, Kyoto University) for giving necessary scientifically conceptual ideas and technical advice strongly beneficial in synthesis. Heartfelt gratitude is expressed by the author to Professor Shinya Oishi (Kyoto Pharmaceutical University) for the scientific advice during the beginning of the doctoral course. The author is profoundly grateful for the useful advices in the discussions with Professor Norihito Arichi (Graduate School of Pharmaceutical Sciences, Kyoto University) about international research and the introduction of other fields in organic chemistry.

The author wants to express high recognition for Professor A. Stephen Hashmi (Heidelberg University) for introducing the author to the research group of Professor Hiroaki Ohno. Additional gratefulness is expressed by the author for all the fruitful discussions concerning gold catalysis from the times in Heidelberg up to now.

The supports and advice from Professor Kiyosei Takasu (Graduate School of Pharmaceutical Sciences, Kyoto University) and Professor Hirohisa Ohmiya (Graduate School of Pharmaceutical Sciences, Kyoto University) are greatly appreciated.

The author would like to demonstrate his thankfulness to Professor Masaya Sawamura (Hokkaido University) and Professor Tomohiro Iwai (Tokyo University), for offering the necessary ligand for the synthesis of medium sized rings.

The author wants to show sincere gratefulness to his family who constantly supported him during the doctoral course.

The author wants to deeply dedicate his contributions to his father Wolfgang Greiner who passed away during the course.

List of Publications

This study was published in the following papers.

Chapter 1.

Access to Indole-Fused Benzannulated Medium-Sized Rings through Gold(I)-Catalyzed Cascade Cyclization of Azido-Alkynes
Luca Can Greiner, Shinsuke Inuki, Norihito Arichi, Shinya Oishi, Rikito Suzuki, Tomohiro Iwai, Masaya Sawamura, A. Stephen K. Hashmi, Hiroaki Ohno
Chem. Eur. J. **2021**, *27*, 12992–12997.

Azido-Alkynes in Gold(I)-Catalyzed Indole Syntheses
Luca Can Greiner, Junpei Matsuoka, Shinsuke Inuki, Hiroaki Ohno
Chem. Rec. **2021**, *21*, 3897–3910.

Chapter 2.

Gold(I)-Catalyzed Benzylic C(sp^3)-H Functionalizations: Divergent Synthesis of Indole[*a*]- and [*b*]-Fused Polycycles
Luca Can Greiner, Norihito Arichi, Shinsuke Inuki, Hiroaki Ohno
Angew. Chem. Int. Ed., **2023**, *62*, e202213653.

Chapter 3.

Azido Alkynes to Functionalized Indolines via Gold(I)-Catalyzed Alkoxy Migration
Luca Can Greiner, Norihito Arichi, Shinsuke Inuki, Hiroaki Ohno
Manuscript in preparation.