Azido-alkynes in Gold(I)-Catalyzed Indole Syntheses

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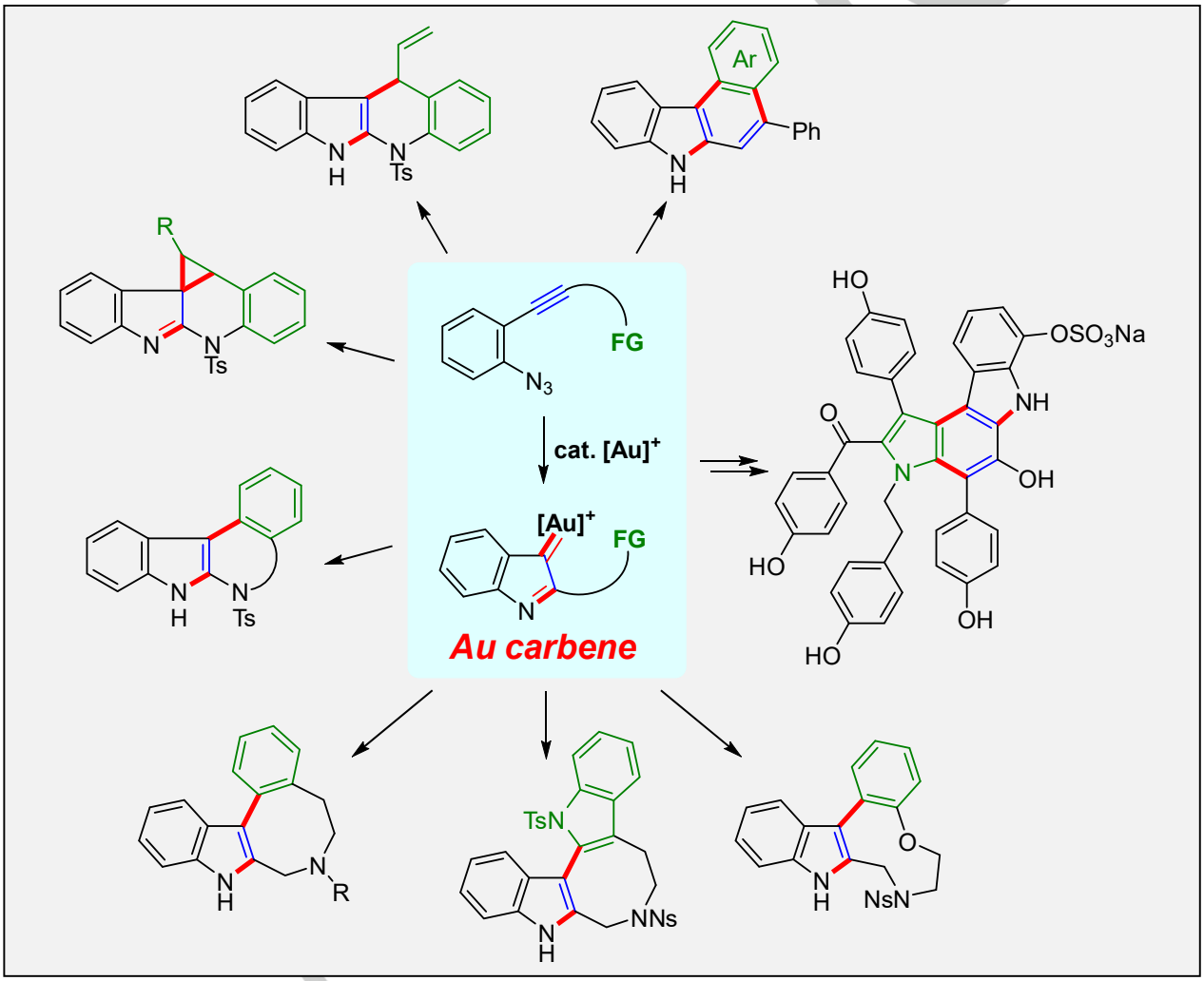

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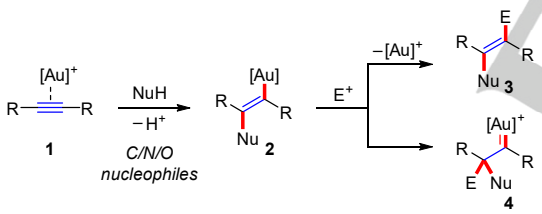
Abstract: The exploitation of nitrogen-functionalized reactive intermediates plays an important role in the synthesis of biologically relevant scaffolds in the field of pharmaceutical sciences. Those based on gold carbenes carry a strong potential for the design of highly efficient cascade processes toward the synthesis of compounds containing a fused indole core structure. This personal account gives a detailed explanation of our contribution to this sector, and embraces the reaction development of efficient gold-catalyzed cascade processes based on diversely functionalized azido-alkynes. Challenging cyclizations and their subsequent application in the synthesis of pharmaceutically relevant scaffolds and natural products conducted in an intra- or intermolecular fashion are key features of our research.

1. Introduction

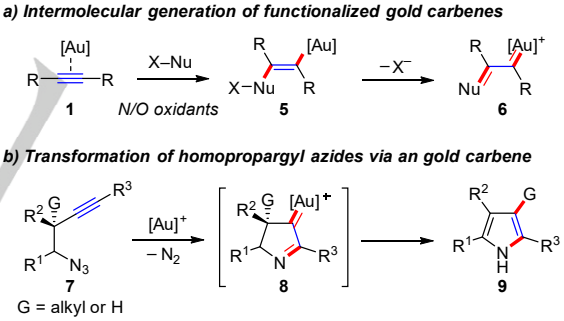
Among transition metal-complexes, those based on gold possess an extraordinary selectivity toward the activation of alkynes. Once an alkyne is subjected to a cationic gold catalyst, its pronounced π-acidity results in the formation of an activated alkynyl gold complex **1** and unlocks its reactivity 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 produce **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. 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.[3e]

The formation of gold carbenes was first suggested in the cycloisomerization of furan-ynes to substituted phenols in the Hashmi phenol synthesis.[4] Later, these intermediates were frequently reported in gold-catalyzed enyne cycloisomerizations,[5] and the accumulation of a wide variety of general synthetic methods to form unfunctionalized gold-carbenes have been continuously reported.[6] 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 **6** via elimination of the leaving group X in the vinyl gold intermediate **5** (Scheme 2a). 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 **7** provided substituted pyrroles **9** via intramolecular generation of α-imino carbenes **8** and a 1,2-shift of a migratory group (Scheme 2b).[8a] Such reactions have become a cornerstone in the formation of various nitrogen-containing heterocycles based on gold catalysis.



Scheme 2. 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 **10** as substrates led to the formation of benzene-fused α-imino gold carbenes **11** (Scheme 3a). These can be regarded as transient C3 umpolung indole equivalents, where intermolecular trapping with alcohols or arenes gives the corresponding indoles **12**. Ye and co-workers demonstrated that the formal OH and NH insertions could also participate in intramolecular capture of α-amidino gold carbenes **14** by generating heterocyclic fused indoles **15** from azido-ynamides **13** (Scheme 3b).[9a,b] A related reaction using azido-alkyne **16** bearing a reactive functional group with a phenylene tether was reported by Xu and co-workers (Scheme 3c).[10] The Ye group also disclosed that pyrrole-fused indoles **21** can be

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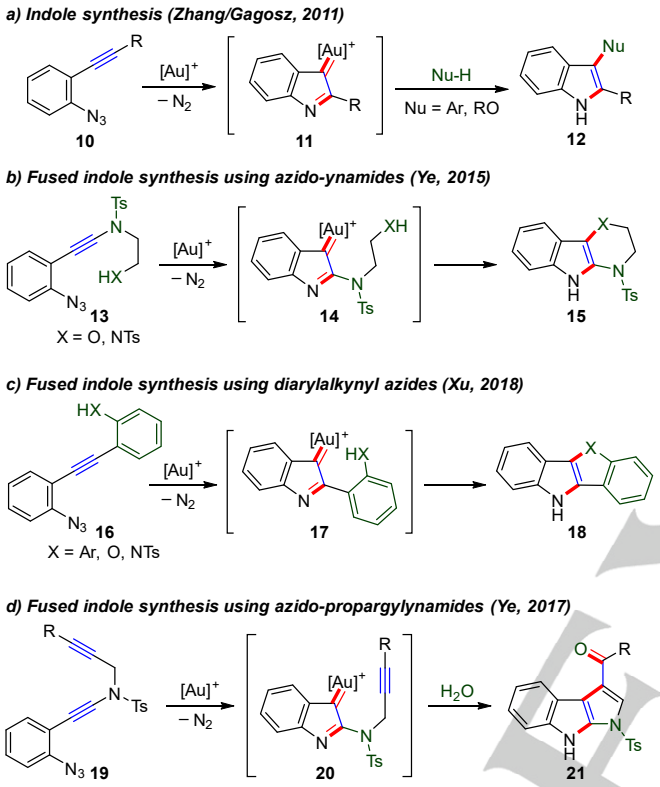
synthesized via α-amidino gold carbenes **20** when azido-ynamides **19** with an *N*-propargyl group are subjected to gold catalysis (Scheme 3d).[9c] As a result of the previously conducted research activities, it became obvious that substrates based on azido-alkynes have a high potential for use in gold-catalyzed generation of diverse fused-indoles in efficient cascade processes.[11]

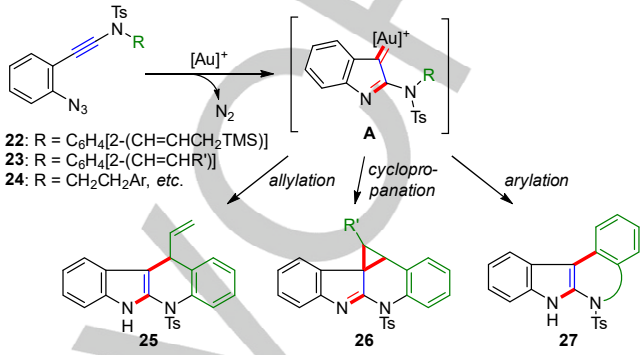


Scheme 3. Synthesis of fused indoles via α-imino gold carbenes.

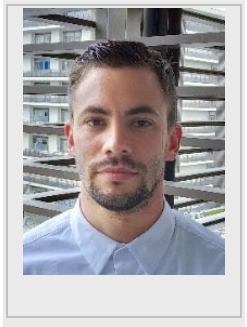
This personal account highlights our recent contributions to intra- and intermolecular reaction design and the total synthesis of natural products containing indole-fused polycycles via exploitation of *N*-functionalized gold carbenes that originate from diversely functionalized azido-alkynes. In this context, special attention is paid to the efficiency of the cascade processes, their application in total synthesis, and effective transformations for the construction of medium-sized heterocycles.

2. Cyclizations of Azido-ynamides to Indoloquinolines

Driven by ambitions to develop gold-catalyzed reactions for the construction of biologically relevant libraries, our group designed an efficient route to indoloquinolines based on bis-cyclization of azido-ynamide substrates (Scheme 4).[12a] Thus, we expected that in the presence of gold cations, these ynamides **22**–**24** would undergo gold carbene formation to produce α-amidino-type intermediate **A** with concomitant nitrogen expulsion. Intramolecular trapping with tethered alkenes and arenes allowed the establishment of a diverse library of indoloquinolines through cyclizative allylation (**25**), cyclopropanation, (**26**) and arylation (**27**).



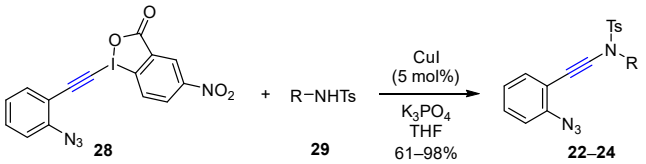
Scheme 4. Synthesis of fused indoles via α-imino gold carbenes.



Luca Can Greiner received his Bachelor of Science from Aalen University in 2016 under the supervision of Professor Dirk Flottmann in a collaborative project with the Bayer AG. After entering the master's program at Heidelberg University, he obtained his master's degree in 2019 under the guidance of Professor A. Stephen K. Hashmi during a collaborative international research project with the research group of Professor Hiroaki Ohno at Kyoto University. Currently, he is pursuing his PhD at Kyoto University under the direction of Professor Ohno and is interested in the reaction development of gold-catalyzed reactions for indole synthesis through gold carbene chemistry.

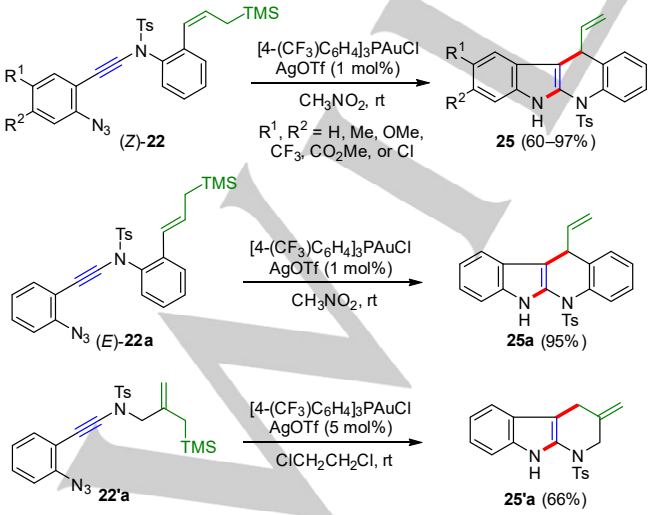
Junpei Matsuoka received his bachelor's degree from the Faculty of Pharmacy, Meijo University in 2016, and his Ph.D. degree in Pharmaceutical Sciences from Kyoto University in 2020 under the supervision of Professor Hiroaki Ohno (2018–2020 as a JSPS Research Fellow). He joined the research group of Associate Professor Yasutomo Yamamoto at Doshisha Women's College of Liberal Arts as a Research Associate in 2020. His research interests include the development of transition-metal-catalyzed reactions, as well as the total synthesis of natural products.

The azido-ynamides **22**–**24** were easily prepared by use of a Waser-type alkynylating agent **28**[12b] and the sulfonamide **29** (Scheme 5). It should be noted that the highly active reagent **28** was previously developed by our group through modification of Waser's alkynylating reagent.



Scheme 5. Preparation of the azido-ynamide.

After optimization of the reaction conditions using several phosphine ligands, it was found that allylsilane (*Z*)-**22a** ($R^1 = R^2 = H$) was most efficiently transformed to indoloquinoline **25a** with [4-$(CF_3)C_6H_4]_3$PAuCl and AgOTf in CH_3NO_2 (94%, Scheme 6). This result can be rationalized as the ynamide-derived α-imino gold carbene with a relatively electron-rich character requires the electron-deficient phosphine ligand for the nucleophilic addition step. It should be underlined that this was the first reaction where allylsilane was used as a nucleophilic allylation agent for the capture of α-imino gold-carbenes. The ynamide with an electron-donating methoxy group as the R^1 substituent reacts smoothly to give the desired product in 91% yield. In stark contrast, when the same position was substituted with an electron-withdrawing trifluoromethyl group, the yield decreased significantly to 60%. Investigation of the R^2 group, *para* positioned to the alkyne, demonstrated that electron-donating and -withdrawing groups, such as methyl, methoxycarbonyl, and chloro were well tolerated. When the optimized conditions were applied to the allylsilane (*E*)-**22a**, the same product **25a** as in the transformation of allylsilane (*Z*)-**22a** was obtained with 95% yield. Under similar reaction conditions, allylamine-type ynamide **22'a** transformed readily to the exo-methylene derivative **25'a** in 66% yield.

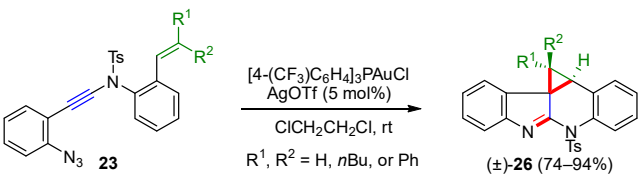


Scheme 6. Allylation of the azido-ynamide

Shinsuke Inuki received his PhD in Pharmaceutical Sciences from Kyoto University in 2011 under the supervision of Professors Hiroaki Ohno and Nobutaka Fujii (2008–2011; JSPS Research Fellow). After working as a researcher at Fujifilm corporation (2011–2014), he joined the research group of Professor Yukari Fujimoto (Keio University) as a Research Associate (2014–2017). In 2017, he moved to Kyoto University as an Assistant Professor in the Ohno research group. Then he was promoted as an Associate Professor in 2020. His research interests include the synthesis of natural products and the elaboration of their derivatives for elucidation of biological mechanisms and the discovery of drug leads.

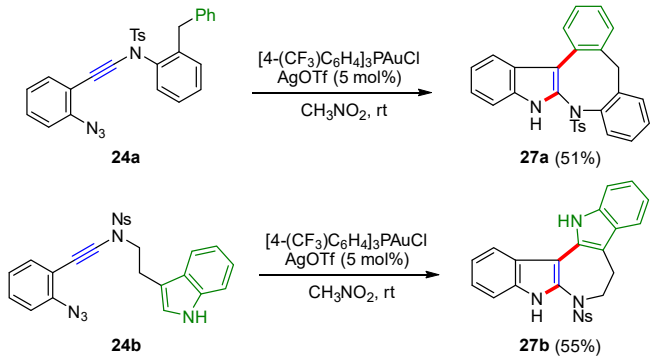
Hiroaki Ohno graduated from the Faculty of Pharmaceutical Sciences, Kyoto University in 1996. After his doctoral work at the same university (1996–1999; JSPS Research Fellow in 1999) under the direction of Professor Toshiro Ibuka, he joined the research group of Professor Tetsuaki Tanaka at Osaka University as a Research Associate in 1999. After receiving his PhD degree from Kyoto University in 2002, he accepted a position as Associate Professor of Kyoto University (Professor Nobutaka Fujii's research group) in 2005. In 2014, he was appointed as a full professor to the Graduate School of Pharmaceutical Sciences, Kyoto University. His research interests include the development of cascade reactions, synthesis of biologically active natural products, and their application to drug discovery.

The gold-catalyzed transformation of simple alkenes **23** that contained an *n*-butyl or phenyl group as an alkene substituent resulted in the formation of cyclopropane indoloquinolines (±)-**26** from good to excellent yields (Scheme 7). It is noteworthy that the reaction of the terminal alkene ($R^1 = R^2 = H$) resulted in a mixture of inseparable products.



Scheme 7. Cyclopropanation of azido-ynamides.

The arylation of the azido-ynamides **24a** or **24b** generated dibenzannulated indole-fused azocine **27a** or bisindole-fused azepine **27b** in moderate yields (Scheme 8). Thus, this reaction provides a diversity-oriented approach for the synthesis of biologically interesting indoloquinoline and fused indole derivatives.



Scheme 8. Arylation of azido-ynamides.

3. Direct Synthesis of Aryl-annulated [*c*]carbazoles Using Azido-diynes and Arenes

3.1. Reaction Development

Carbazoles are nitrogen-containing heterocycles that exhibit a high degree of importance in applied pharmaceutical- and material sciences. The charge-transport properties, together with their thermal stability, make benzo[*c*]carbazoles an attractive scaffold for utilization in organic electronics (Figure 1).[13] Furthermore, heteroaryl-annulated [*c*]carbazoles are abundant scaffolds in biologically relevant compounds, such as the marine indole alkaloid family of dictyodendrins (pyrrolo[2,3-*c*]carbazoles).

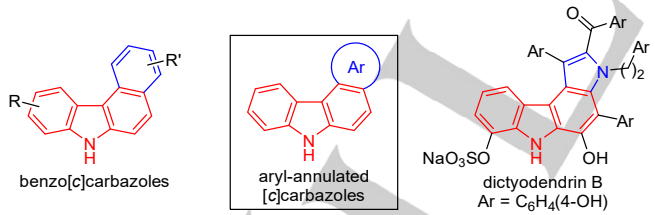
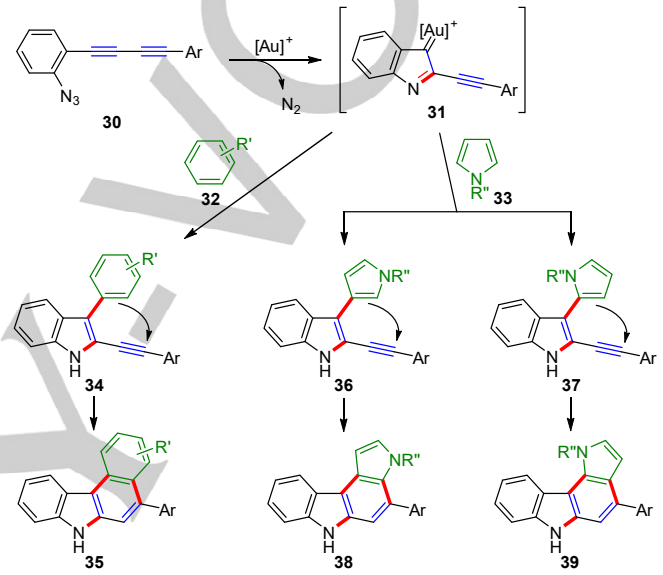


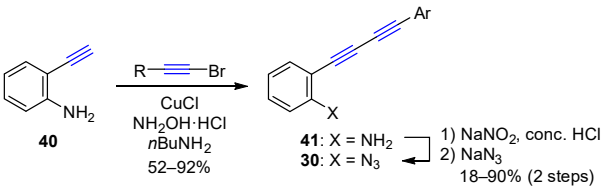
Figure 1. Aryl-annulated [*c*]carbazoles.

In this seminal work, which would later find its application in dictyodendrins total synthesis (Section 3.2), we employed azido-diyne **30** as a cyclization precursor to furnish access to diverse aryl- and heteroaryl-annulated [*c*]carbazoles via exploitation of α-imino gold carbenes (Scheme 9).[14] This reaction would form the gold carbene **31** bearing a pendant alkynyl group, which would undergo intermolecular Friedel Crafts-type arylation with various substituted arene derivatives **32** to generate intermediate **34**. Finally, an intramolecular hydroarylation would terminate the cascade sequence and yield the benzo[*c*]carbazole **35**. When applying pyrrole-type heteroarenes as the coupling partners, we anticipated that the control of the regioselectivity would manifest as the major difficulty in this strategy. Thus, while the initial nucleophilic attack at the C3-position of pyrrole **33** would result in the pyrrolo[2,3-*c*]carbazole **38**, the attack at the C2 position would generate pyrrolo[3,2-*c*]carbazole **39**. Additionally, the regioselectivity of the second arylation must also be taken into consideration in the cases of arenes **32** and heteroarenes **33**.



Scheme 9. Our concept: the reaction of azido-diynes with arenes.

The azido-diyne **30** was easily accessible via a Cadiot-Chodkiewicz coupling of 2-ethynylaniline **40** and bromoalkynes, with subsequent azidation of the aniline derivative **41** through a Sandmeyer reaction (Scheme 10).

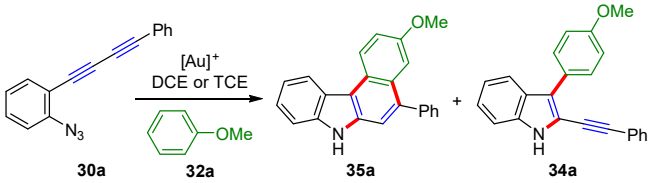


Scheme 10. Preparation of azido-diynes.

In the search for suitable reaction conditions, we observed that JohnPhosAu(MeCN)SbF_6 facilitated the annulation reaction of **30a** with anisole **32a** in DCE at 80 °C to afford the fused carbazole **35a** and 3-anisylindole intermediate **34a** in 44% and 26% yields, respectively (Table 1). To accomplish the subsequent intramolecular hydroarylation step of the cascade sequence, we elevated the reaction temperature to 140 °C after consumption of

30a, and obtained the desired **35a** in 75% yield after 16 h (condition A). When anisole was used as the solvent and reactant simultaneously in the presence of BrettPhosAu(MeCN)SbF_6 (condition B), **35a** was obtained after 19.5 h at 140 °C with the highest yield of 86%.

Table 1. Optimization for benzo[*d*]carbazole synthesis.



cond.	[Au]+ (5 mol%)	32a	temp. (time)	35a	34a
–	JohnPhosAu(MeCN)SbF_6	10 equiv.	80 °C (26 h)	44%	26%
A	JohnPhosAu(MeCN)SbF_6	10 equiv.	80 °C (1 h), 140 °C (16 h)	75%	0%
B	BrettPhosAu(MeCN)SbF_6	solvent	140 °C (19.5 h)	86%	0%

With the established optimized conditions in hand, we next investigated the scope of this reaction. Under condition B utilizing arenes **32** as the solvent, the nucleophiles 1,2- and 1,3-dimethoxybenzenes were efficiently converted in the gold-catalyzed annulation cascade to their corresponding benzo[*c*]carbazoles **35b** (quant) and **35c** (95%) in excellent yields (Figure 2). Condition A (using 10 equiv. of **32**) resulted in the formation of **35b** (70%) and **35c** (40%) in lower yields. When using benzodioxole, pentacyclic benzo[*c*]carbazole **35d** was generated in 76% yield. Employment of the less reactive *o*-xylene gave dimethyl substituted benzo[*c*]carbazole derivative **35e** in moderate yield (42%) and required a higher loading of gold catalyst (20 mol%). Unfortunately, the reactivities of benzene and toluene were not sufficient for the benzo[*c*]carbazole formation. The product formation of **35** proceeded regioselectively, where the first arylation occurred at the *para*-position of the electron-donating substituent, while the consecutive intramolecular hydroarylation occurred at the sterically less hindered carbon of the attached aryl moiety. The reaction of various *para*-substituted phenyl derivatives shows that the reaction tolerated electron-donating and -withdrawing groups (Me, Cl, NO_2, and OMe) to give the corresponding benzo[*c*]carbazole derivatives **35f–i** (43–74%).

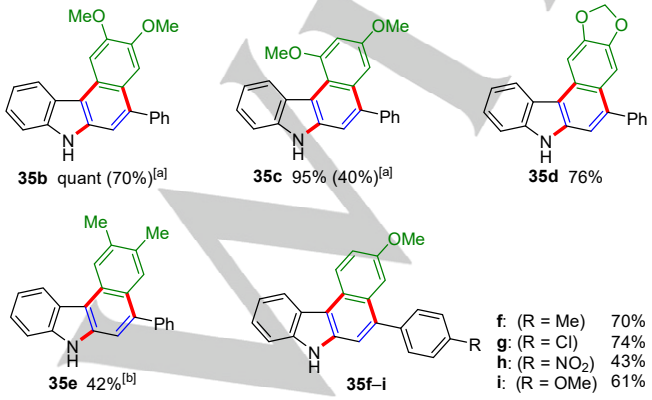
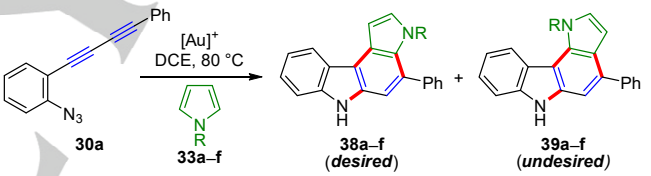


Figure 2. Reaction scope. The reactions were carried out under condition B (Table 1) unless otherwise stated. [a] Yields in parenthesis are those under the condition A (Table 1). [b] Catalyst loading was increased to 20 mol%.

Next, the construction of pyrrolocarbazoles via the reaction of azido-diyne **30a** and pyrroles **33a–f** was investigated (Table 2). The reaction with unsubstituted pyrrole **33a** using BrettPhosAu(MeCN)SbF_6 (5 mol%) in DCE at 80 °C (condition C) formed an isomeric mixture of annulation products **38a** and **39a** in *ca.* 62% yield with concomitant formation unidentified side products, while **39a** represented the major isomer (**38a**:**39a** = 25:75) (entry 1). This result can be rationalized by considering the more nucleophilic nature of the C2-position compared with that of the C3-position of the unsubstituted pyrrole.[15] We next examined the impact of different substituents at the pyrrole nitrogen (entries 2–6) and found that the regioselectivity was strongly influenced through the *N*-substituent, where *N*-Boc pyrrole demonstrated the highest regioselectivity toward the formation of the corresponding pyrrolo[2,3-*c*]carbazole **38f** (**38f**:**39f** = 92:8) in 60% yield of the isomeric mixture (entry 6). Changing the solvent to TCE and increasing the temperature to 110 °C (condition D) decreased the reaction time and increased the regioselectivity forming **38f** (**38f**:**39f** = 95:5) in 58% combined isolated yield.

Table 2. Optimization for pyrrolo[2,3-*c*]carbazole synthesis.[a]

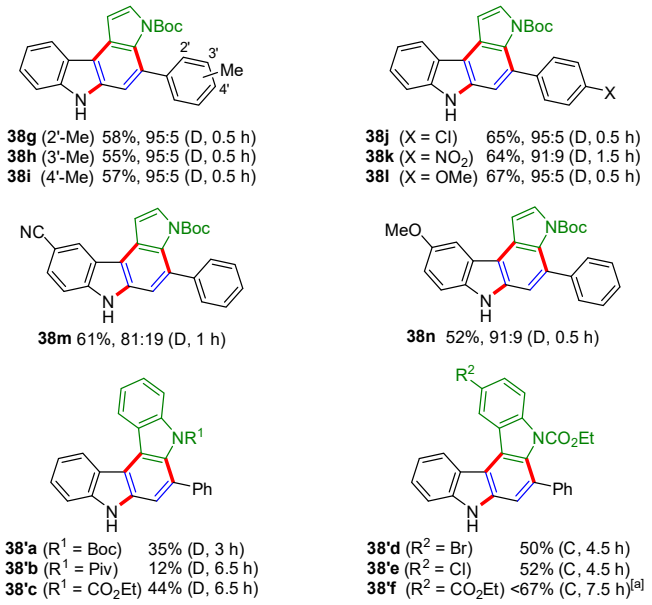


Entry (Cond.)	Pyrrole	R	Time (h)	Yield (%)[b]	Ratio (**38** : **39**)
1 (C)	**33a**	H	8	<62	25 : 75
2 (C)	**33b**	Bn	10	62	18 : 82
3 (C)	**33c**	Ts	0.5	34	58 : 42
4 (C)	**33d**	CO_2Me	1.5	62	81 : 19
5 (C)	**33e**	Piv	1.5	60	82 : 18
6 (C)	**33f**	Boc	1.5	60	92 : 8
7 (D)[c]	**33f**	Boc	0.5	58	95 : 5

[a] Reaction conditions: **33** (5 equiv.), BrettPhosAu(MeCN)SbF_6 (5 mol%), DCE, 80 °C (condition C). [b] Combined isolated yields. [c] The reaction was carried out in TCE at 110 °C (condition D).

With these optimized conditions using *N*-Boc pyrrole **33f** in hand, we started to investigate the scope of the gold-catalyzed pyrrolo[2,3-*c*]carbazole formation (Figure 3). Diynes with electron-withdrawing or -donating substituents attached on the terminal aryl group readily underwent pyrrolo[2,3-*c*]carbazole formation to produce **38g–l** in good regioselectivities (mostly 95:5) under condition D. Conversely, diynes with a nitro group on the terminal phenyl group (**30k**), and a methoxy or cyano group at the *para*-position to the azido group (**30m**, **30n**) showed decreased selectivities (**38**:**39** = 81:19–91:9). Application of the indole derivatives as the intercepting nucleophiles revealed that relatively electron-deficient indole derivatives were more suitable

for the formation of indolo[2,3-*c*]carbazoles **38'** (**d**–**f**, 50–67% yield under conditions C), compared with simple *N*-protected indoles (**a**–**c**, 12–44% yield under condition D).



38g (2'-Me) 58%, 95:5 (D, 0.5 h)
38h (3'-Me) 55%, 95:5 (D, 0.5 h)
38i (4'-Me) 57%, 95:5 (D, 0.5 h)

38j (X = Cl) 65%, 95:5 (D, 0.5 h)
38k (X = NO_2) 64%, 91:9 (D, 1.5 h)
38l (X = OMe) 67%, 95:5 (D, 0.5 h)

38m 61%, 81:19 (D, 1 h)

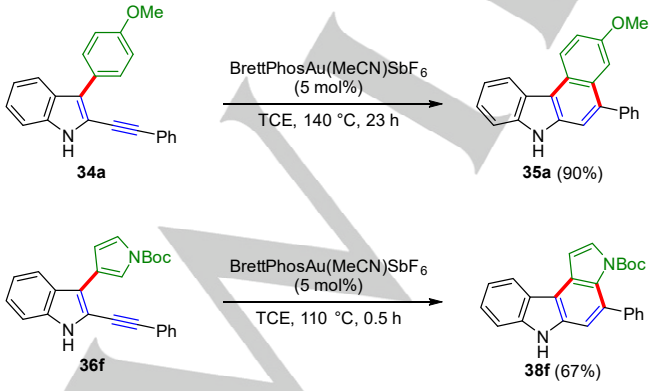
38n 52%, 91:9 (D, 0.5 h)

38'a (R^1 = Boc) 35% (D, 3 h)
38'b (R^1 = Piv) 12% (D, 6.5 h)
38'c (R^1 = CO_2Et) 44% (D, 6.5 h)

38'd (R^2 = Br) 50% (C, 4.5 h)
38'e (R^2 = Cl) 52% (C, 4.5 h)
38'f (R^2 = CO_2Et) <67% (C, 7.5 h)[a]

Figure 3. Reaction scope. Reaction conditions: **33** or indole derivative (5 equiv.), BrettPhosAu(MeCN)SbF_6 (5 mol%). The reaction conditions employed (condition C or D, Table 2) and reaction time are shown in parentheses. [a] Contained small amounts of impurities.

To get a deeper understanding of the reaction mechanism, additional reactions were conducted. The exposure of intermediate **34a** to the optimized reaction conditions showed conversion to benzo[*c*]carbazole **35a** in 90% yield (Scheme 11). Additionally, the exposure of pyrrolylindole **36f** under the optimized conditions generated pyrrolocarbazole **38f** (67%). These results suggested that a stepwise nucleophilic attack of the arene on the gold carbene with subsequent intramolecular hydroarylation would be the major reaction pathway as we expected.

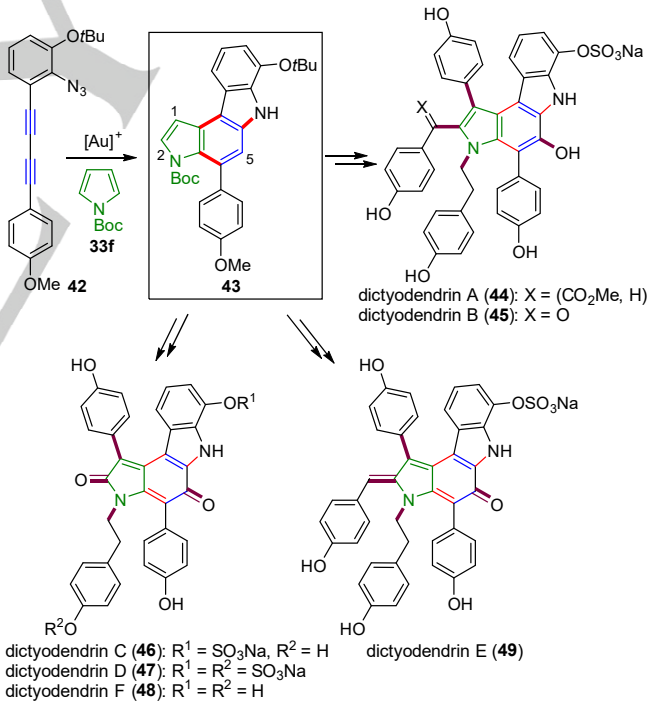


34a
35a (90%)
36f
38f (67%)

Scheme 11. Hydroarylation of the monocyclization intermediates.

3.2. Total Synthesis of Dictyodendrins

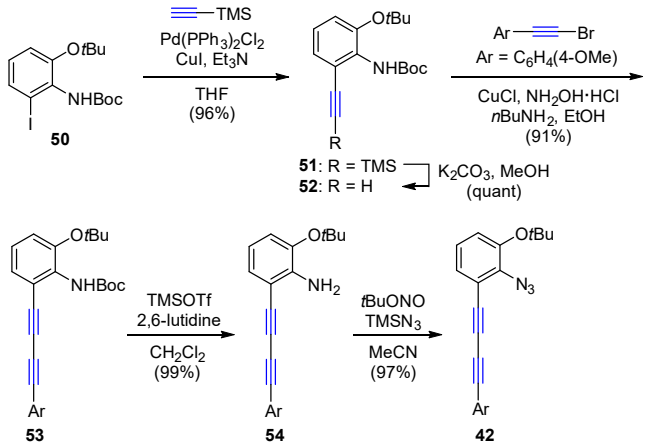
Dictyodendrins A–F were initially isolated from the Japanese marine sponge *Dictyodendrilla verongiformis* and the Australian marine sponge *Ianthella sp*.[16] These compounds belong to a family of marine indole alkaloids and have potential as agents against cancer and Alzheimer's disease. From a structural viewpoint, dictyodendrins consist of a highly substituted pyrrolo[2,3-*c*]carbazole core, which fascinated many groups of synthetic chemists. In 2005, the Fürstner group reported the first total synthesis of dictyodendrins B, C, E, and F through a well-designed stepwise construction of the fused ring systems.[17] Afterward, more total syntheses of dictyodendrins were reported by Ishibashi (dictyodendrin B),[18] Tokuyama (A–E),[19] Jia (B, C, and E),[20] Gaunt (B),[21] Yamaguchi/Itami/Davies (A and F),[22] Ready (F, H, and I)[23] and He (F, G, H and I).[24] We envisioned that our newly-developed gold-catalyzed regioselective pyrrolo[2,3-*c*]carbazole synthesis (Section 3.1) could be applied for the construction of the core structure **43** of the dictyodendrins by using azido-diyne **42** as the cyclization precursor and Boc-substituted pyrrole **33f** (Scheme 12). Successive introduction of diverse substituents would offer access to a diversity-oriented synthesis of dictyodendrins A–F (**44**–**49**) and their derivatives.[25]



Scheme 12. Our strategy for the diversity-oriented synthesis of dictyodendrins.

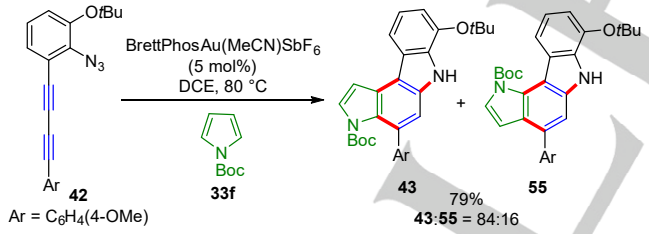
To synthesize the cyclization precursor **42** bearing an oxygen functional group, *tert*-butoxy-substituted iodoaniline derivative **50** was transformed to **51** via a Sonogashira coupling with trimethylsilylacetylene (Scheme 13). The subsequent desilylation of **51** and Cadiot-Chodkiewicz coupling with a bromoalkyne gave

the corresponding conjugated diyne **53**. Utilization of TMSOTf and 2,6-lutidine for selective removal of the Boc group followed by diazotization with *t*BuONO and azidation with $TMSN_3$ produced the desired azido-diyne **42** in 97%.



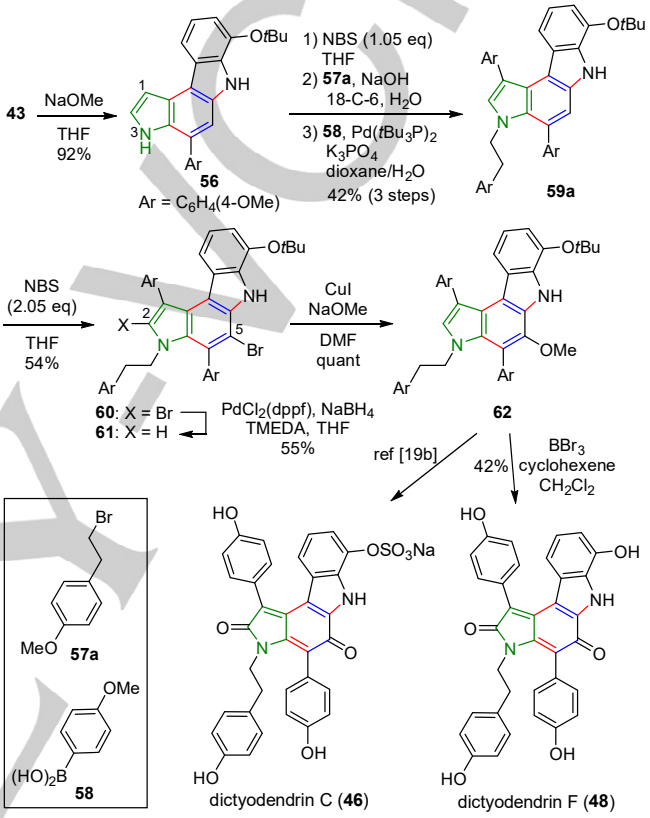
Scheme 13. Preparation of diyne **42** bearing an oxygen functional group.

As we expected, the employment of **42** and Boc derivative **33f** in the gold-catalyzed pyrrolo[2,3-*c*]carbazole synthesis in the presence of BrettPhosAu(MeCN)SbF_6 at 80 °C resulted in the regioselective formation of **43** with a yield of 79% (Scheme 14). It should be noted that the introduction of the oxygen functional group at the *ortho*-position of the azido group slightly decreased the regioselectivity of the annulation reaction [**43**:**55** = 84:16 after optimization; compare with the reaction of **30a** (95:5, Table 2)].

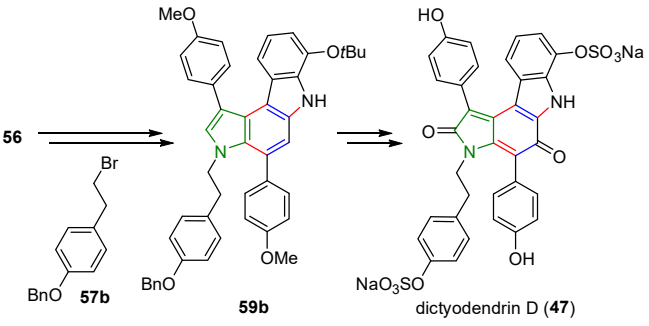


Scheme 14. Pyrrolo[2,3-*c*]carbazole synthesis using **42**.

Then we proceeded to the diversity-oriented total synthesis of dictyodendrins. Our first targets were dictyodendrins C (**46**) and F (**48**), which contained a 2,5-dioxo moiety on the core structure. The Boc group of **43** was removed with NaOMe in THF, forming **56** in 92% yield (Scheme 15). Following a one-pot C1 bromination/N3-alkylation sequence with *N*-bromosuccinimide and bromide **57a**, a Suzuki-Miyaura coupling with boronic acid **58** generated **59a** in 42% yield (3 steps). Although we encountered various problems in the introduction of the second oxygen functional group at the C5 position, the dibromination–debromination protocol worked well for the C5 oxidation. Thus, treatment of **59a** with NBS (2.05 equiv.) gave the dibromide **60** in 54% yield, and subsequent C2-selective mono-debromination using $NaBH_4$ and $PdCl_2$(dppf) allowed us to obtain the mono-bromide **61** in 55% yield. Ullmann coupling of **61** utilizing NaOMe and CuI resulted in the methyl ether **62** in quantitative yield, which has been reported by Tokuyama for the synthesis of dictyodendrin C (**46**).[19b] The total synthesis of dictyodendrin F (**48**) was finalized via deprotection of **62** with BBr_3.



Scheme 15. Total synthesis of dictyodendrins C and F.

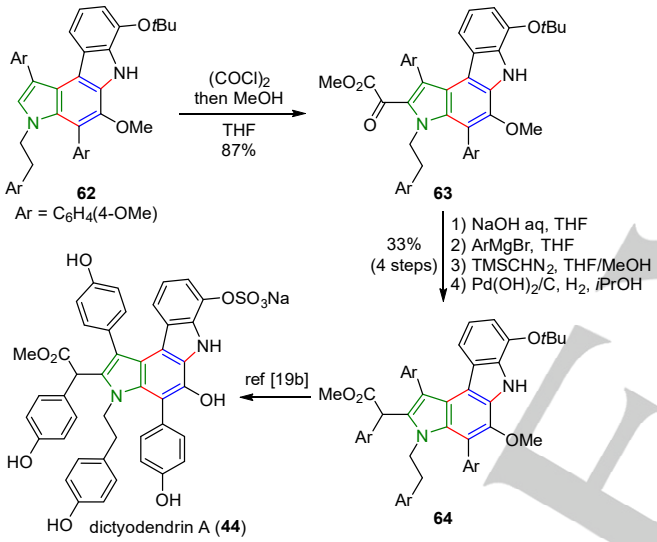


Scheme 16. Total synthesis of dictyodendrin D.

In analogy, a formal total synthesis of dictyodendrin D (**47**) was accomplished (Scheme 16). Because of the appended sulfate at the *N*-alkyl group in dictyodendrin D, the *N*-alkylation

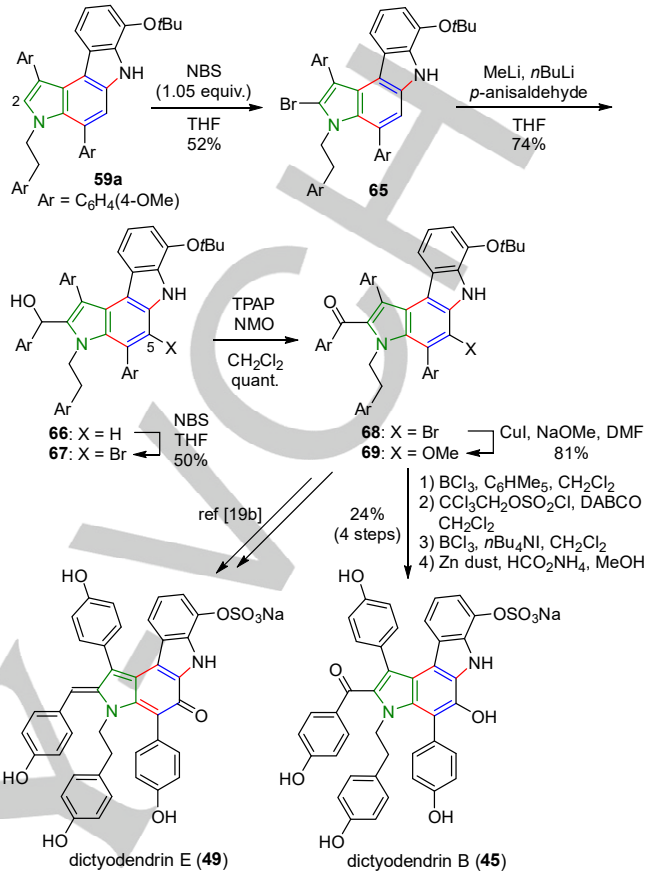
step was modified following the Tokuyama protocol.[19b] Accordingly, intermediate **59b** was synthesized via C1-bromination by using benzyl-protected bromide **57b**.

Our next target molecule was dictyodendrin A (**44**), which necessitated a (4-hydroxyphenyl)acetate moiety at the C2 position. Preliminary trials via a C-H insertion and Friedel-Crafts reaction under diverse reaction conditions led to the decomposition of the starting material **62** (Scheme 17). In comparison, acylation of **62** with oxalyl chloride followed by methanolysis formed keto-ester **63** in 87% yield. Hydrolysis of the methyl ester in **63**, followed by a Grignard reaction of the resulting carboxylic acid, esterification with $TMSCHN_2$, and final hydrogenation, gave ester **64** in 33% yield (4 steps). The total synthesis of dictyodendrin A (**44**) was finally accomplished by removal of methyl- and *tert*-butyl groups as reported by Tokuyama.[19b]



Scheme 17. Total synthesis of dictyodendrin A.

Because dictyodendrins B and E contain acyl and benzylidene groups, respectively, the C2 acylation strategy designed by the Fürstner group[17] was employed (Scheme 18). Regioselective bromination of **59a** at C2 with NBS (1.05 equiv.) resulted in mono-bromide **65** in 52% yield, which was converted to **66** in 74% yield via lithiation and subsequent nucleophilic addition to anisaldehyde. The second bromination with NBS at the C5 position, Ley-Griffith oxidation of the resulting alcohol **67**, and Ullmann coupling of **68** with NaOMe resulted in methoxy derivative **69**. The total synthesis of dictyodendrin B (**45**) was finalized through cleavage of the *tert*-butyl group via BCl_3 at –78 °C, a subsequent introduction of the trichloroethylsulfate ester, demethylation, and salt formation as reported.[19b] The Tokuyama protocol starting from **69** would also lead to dictyodendrin E (**49**).[19b]



Scheme 18. Total synthesis of dictyodendrins B and E.

Thus, our newly-developed pyrrolo[2,3-*c*]carbazole synthesis has proven to be extremely useful for a highly diversity-oriented total synthesis of dictyodendrins. Some of the dictyodendrin derivatives synthesized during this study showed inhibitory activity against CDK2/CycA2 and GSK3β (data not shown),[25b] which demonstrated the promise of our diversity-oriented synthesis in medicinal applications of dictyodendrin derivatives and related pyrrolocarbazoles.

4. Synthesis of Indole-Fused Benzannulated Medium-Sized Rings using Azido-alkynes

Because compounds of the class of benzannulated- and indole-fused medium-sized rings are found in numerous biologically relevant compounds, a natural product fragment-based approach fusing both promising frameworks to the new class of medium-sized rings could uncover various biological properties through exploring uncharted biologically relevant chemical space (Figure 4).[26] However, relatively high magnitudes of transannular strain in combination with detrimental entropic factors restrict direct access to the rigidified cyclic transition state, making medium-sized rings (eight to eleven-membered) the most difficult ones to synthesize.[27] These facts impede a straightforward and efficient

establishment of a compound collection consisting of various benzannulated indole-fused medium-sized rings.

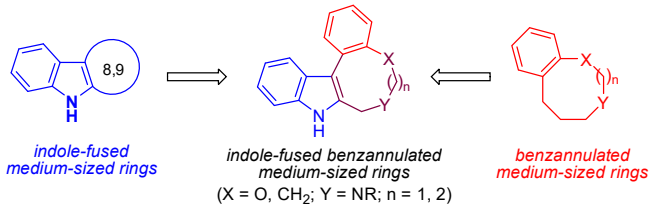
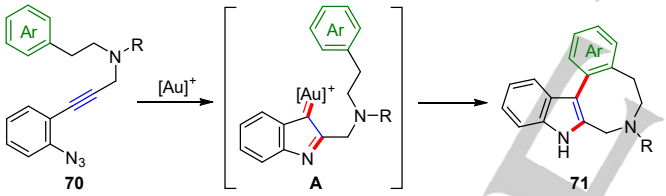
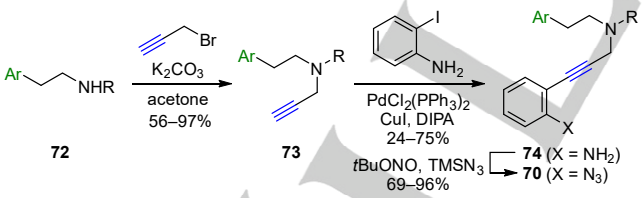


Figure 4. Strategic fusion of the drug-like structures to afford indole-fused medium-sized rings.

We anticipated that the utilization of reactive intermediates could play a decisive role in overcoming this challenge. Zhang[8b] and Xu[10] exemplified the cyclization of α-imino gold(I)-carbenes with a tethered aryl or alcohol moiety to generate benzannulated indole-fused oxepines. However, an eight-membered ring remained unreported except for an outlying example utilizing a highly-restrained azido-ynamide precursor disclosed by us (Scheme 8).[12a] These backgrounds inspired us to construct sp^3-enriched benzannulated medium-sized-fused indoles **71** through α-imino gold(I)-carbene **A** generated from azido-alkynes **70** (Scheme 19).[28]

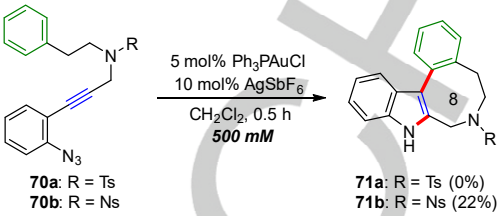


Scheme 19. Indole formation through gold carbenes in this work.



Scheme 20. Preparation of azido-alkynes **70**.

The requisite azido-alkynes **70** were easily prepared from amines in a straightforward manner. Typically, protected (2-aryl)ethylamines **72** were converted to **70** via propargylation, Sonogashira-coupling, and azidation (Scheme 20). Next, we proceeded to investigate the gold-catalyzed eight-membered ring formation (Scheme 21). Although the desired azocine formation was ineffective when using Ts-protected substrate **70a** even at 500 mM substrate concentrations, a more electron-withdrawing Ns (2-nitrobenzenesulfonyl) precursor **70b** produced the indole-fused azocine derivative **71b** in 22% yield (Scheme 21). We assumed that the electron-withdrawing force had a crucial effect on the reactivity of the gold carbene.



Scheme 21. Initial investigation for the eight-membered ring formation.

The optimization of the reaction conditions revealed that the reaction with $(t\text{Bu})_3$PAuCl with $AgSbF_6$ in DCM for 0.5 h under high dilution conditions (2 mM) is most favorable for the eight-member ring formation, which gave **71b** in 71% yield (Figure 5). The investigation of the reaction scope indicated that the substituent on the arylative benzene ring influences the reaction efficacy. Especially, the regioisomeric impact of diverse methoxyphenyl groups as internal nucleophiles on the eight-membered ring formation led to an interesting observation: a methoxy group as the R^1 substituent significantly accelerated the eight-membered ring formation (**71d**, 74%, 5 min), whereas a methoxy group as the R^2 substituent decreased the reactivity to produce **71c** (60%, 40 min), which was opposite of our initial expectation. A trend of the reactivity depending on the substituent R^1 (Me > Br > Cl) indicated that the cyclization is limited to slightly activated and neutral phenyl tethers (**71g–i**).

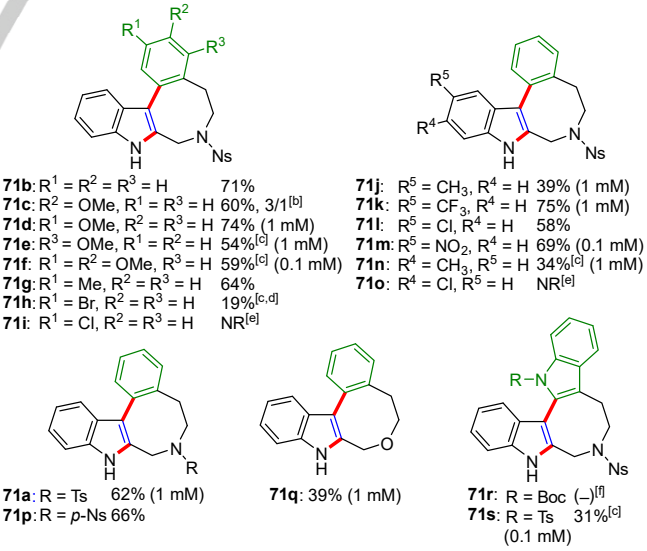
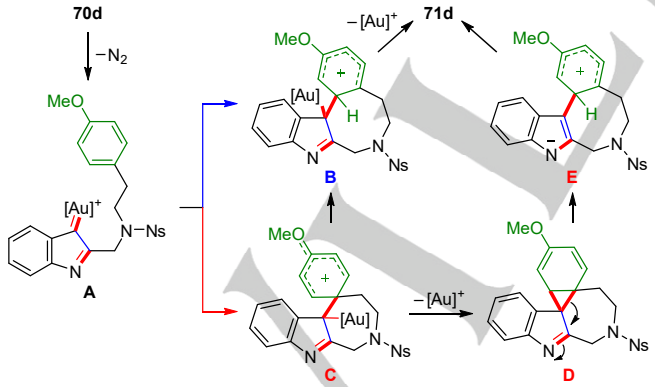


Figure 5. Scope of the eight-membered ring formation.[a] Unless otherwise noted, the reaction was conducted using $(t\text{Bu})_3$PAuCl with $AgSbF_6$ in DCM (2 mM) for 0.5 h. [a] Isolated yields are shown. [b] Combined isolated yield and regioisomeric ratio. [c] Characterized after *N*-Boc protection. [d] 22 mol%

*t*Bu$_3$PAuCl and 62 mol% AgSbF$_6$ were employed. [e] No reaction. [f] Black tar formation.

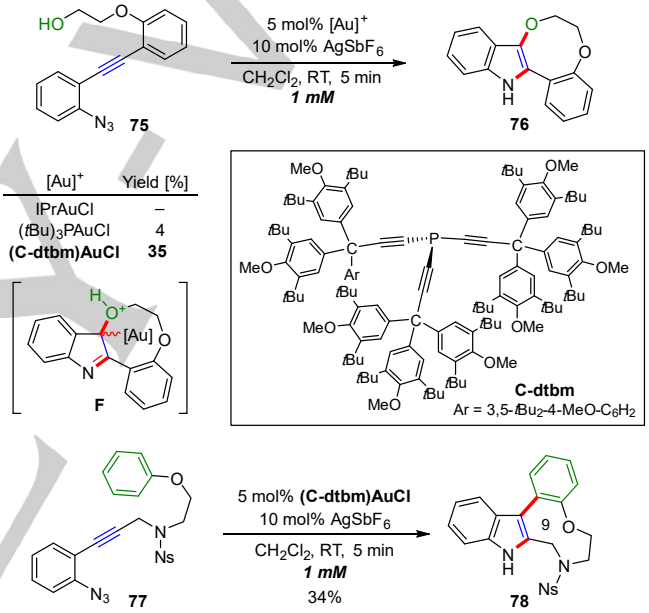
Attachment of a methyl substituent on the azidophenyl group as the R^4 or R^5 substituent has a negative impact on the reactivity (**71j** and **71n**), presumably because of the stabilization effect of a methyl group on the gold carbene and the high nucleophilicity of the formed methyl-substituted indole.[29] In contrast, the introduction of an electron-withdrawing (CF_3, Cl, NO_2) group as the R^4 or R^5 substituent showed a remarkable acceleration of the cyclization in most cases, affording **71k**–**m** in 58–75% yields. Contrary to **70l**, no conversion of **70o** was observed when the standard conditions were employed, probably because the resonance contribution of the chloride-lone pair could inhibit the reaction. Examination of the sulfonyl protecting group showed that its electron density had a significant impact on the cyclization rate (**71b**, and **71p**), although the spatial interaction of the nitro group in the cyclization is negligible. This transformation also turned out to be feasible for oxacycle **71q** and bisindole-fused eight-membered ring **71s**.

A reaction mechanism that can explain the eight-membered ring formation is proposed in Scheme 22. After α-imino gold carbene **A** generation, cyclizative arylation to **B** and subsequent deauration/rearomatization would form the eight-membered ring **71d**. When taking the influence of the methoxy group into account, the cyclization should preferably proceed through a low-strain and less torsional entropy requiring spirocycle route: *ipso* attack[30] should generate spiro compound **C**, with a following 1,2-ring-expansion[31a,b] via dienone-phenol rearrangement[31c] to **B** should lead to the azocine **71d**. Another possibility is that the spirocyclic intermediate **C** could undergo cyclopropanation, giving norcadiene derivative **D**,[32] which would undergo ring-opening reaction to form **E**, which can then be transformed to **71d** through rearomatization.



Scheme 22. Proposed mechanism of the eight-membered ring formation.

Our final challenge was the direct end-to-end cyclization toward the eight-membered ring (dioxocine) using a hydroxy group and arylative nine-membered ring formation (Scheme 23). The first trials, where glycol-tethered azido-alkyne **75** was subjected to the conventional gold(I)-catalyzed cyclization conditions (IPr, *t*Bu$_3$P), were unsuccessful. In sharp contrast, when the substrate was exposed to the semi-hollow shaped (C-dtbm) ligand,[33] its superiority in cyclization efficiency was easily recognizable and allowed the isolation of **76** in 35% yield. Because the formation of a spirocyclic pathway (through a type of intermediate **C** in Scheme 22) is impossible, this example clearly demonstrated the difficulty of the direct eight-membered ring formation through intermediate **F**. The employment of C-dtbm ligand also led us to obtain **78** (34% yield) through a nine-membered ring formation, which is significantly more demanding compared with the cyclization to eight-membered rings. These results unambiguously illustrate the utility of the semihollow-shaped C-dtbm ligand for direct end-to-end eight-membered ring formation and arylative nine-membered ring formation.



Scheme 23. Direct eight-membered ring formation and arylative nine-membered ring formation.

5. Conclusions

We have developed gold-catalyzed cascade cyclization reactions of azido-alkynes. Through the formation of highly reactive α-imino gold(I) carbenes, intramolecular allylation, cyclopropanation, and arylation produce a variety of fused indole derivatives, including indoloquinolines, benzo[*c*]carbazoles, pyrrolo[2,3-*c*]carbazoles, and benzannulated medium-ring fused indoles. For the success of these reactions, controlling the reactivity of the functional groups toward gold carbenes by tuning the substituent pattern and reaction conditions are crucial. In most cases, electron-rich functional groups such as allylsilanes, anisole, and heteroarenes are good reaction partners for the α-imino gold(I) carbenes, whereas protection with electron-withdrawing groups is sometimes useful for control of the regioselectivities and

nucleophilic character of the resulting products. The developed method provides a nonbiomimetic synthetic strategy[26f] for a promising class of indole- and bisindole-fused derivatives and natural products, which are potentially useful for medicinal applications.

Acknowledgements

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Keywords: gold(I)-carbenes • gold-catalysis • heterocycles • natural product synthesis • medium-sized rings

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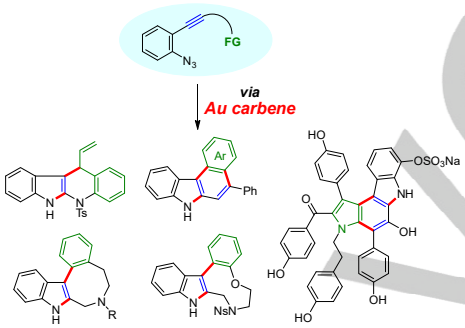
Layout 1:

PERSONAL ACCOUNT

Gold-catalyzed cascade cyclizations of azido-alkynes provide facile access to a variety of fused indole derivatives, including indoloquinolines, benzo[*c*]carbazoles, pyrrolo[2,3-*c*]carbazoles, and benzannulated medium-ring fused indoles. These reactions proceed through the formation of highly reactive α-imino gold(I) carbenes, which efficiently undergo intramolecular allylation, cyclopropanation, and arylation.



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