Published in final edited form as:

Angew Chem Int Ed Engl. 2013 July 22; 52(30): 7795–7799. doi:10.1002/anie.201301057.

Gold-Catalyzed Cyclizations of *cis*-Endiynes: Insights into the Nature of Gold-Aryne Interaction

Youliang Wang,

Department of Chemistry and Biochemistry University of California Santa Barbara, California (USA) Fax: (+1) 805-893-4120, Homepage: <http://www.chem.ucsb.edu/~zhang/index.html>

Akop Yepremyan,

Department of Chemistry and Biochemistry University of California Santa Barbara, California (USA) Fax: (+1) 805-893-4120, Homepage: <http://www.chem.ucsb.edu/~zhang/index.html>

Dr. Subir Ghorai,

Catalysis Research and Development, Sigma-Aldrich Chemical Corp. Milwaukee, Wisconsin (USA)

Dr. Robert Todd,

Catalysis Research and Development, Sigma-Aldrich Chemical Corp. Milwaukee, Wisconsin (USA)

Donald H. Aue, and

Department of Chemistry and Biochemistry University of California Santa Barbara, California (USA) Fax: (+1) 805-893-4120, aue@chem.ucsb.edu, Homepage: <http://www.chem.ucsb.edu/~zhang/index.html>

Liming Zhang

Department of Chemistry and Biochemistry University of California Santa Barbara, California (USA) Fax: (+1) 805-893-4120 zhang@chem.ucsb.edu Homepage: <http://www.chem.ucsb.edu/~zhang/index.html>

Keywords

gold; C-H insertion; aryne; indane; catalysis

Ortho-Benzyne^[1]/aryne^[2] are reactive and versatile intermediates in organic synthesis.^[3] Their diverse chemistry has been further enriched via the formation of metal aryne complexes.^[3b, 4] They are mostly generated via elimination of two adjacent groups/atoms on an arene ring. The elimination strategy, however, can be synthetically limiting due to difficulties in access to suitably substituted arenes, demanding reaction conditions and/or

Correspondence to: Donald H. Aue; Liming Zhang.

[**]LZ thank NSF (CAREER CHE-0969157) and NIGMS (R01 GM084254) for generous financial support. DHA acknowledges support from the Center for Scientific Computing at the CNSI and MRL (NSF MRSEC DMR- 1121053 and NSF CNS-0960316) and the National Center for Supercomputing Applications (NSF TG-CHE100123) utilizing the NCSA Gordon and Blacklight systems. Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

operational hazard. A notable exception is a *de novo* aryne formation via intramolecular hexadehydro-Diels-Alder reactions.^[5]

Considering that the coordination of alkynes to gold complexes often serves as the point of entry into versatile gold catalysis,^[6] it is notable that aryne has seldom served as the substrate for gold catalysis. Although aryne is highly electrophilic due to its low lying LUMO, the HOMO of benzyne was computed to have an energy level similar to that of 2-butyne.^[7] Hence, it is not unreasonable to anticipate the interaction between electrophilic gold complexes and aryne would be plausible. In fact, the study by Zhang^[8] has invoked a benzyne gold complex albeit the interaction between in-situ generated benzyne and Ph₃PAuCl is not clearly defined, leaving doubt to its existence. In contrast, another study^[9] used in situ generated benzyne to trap a gold intermediate en route to anthracene derivatives, where no interaction between gold and benzyne is proposed. We envisioned that gold aryne interaction, if understood, can serve to spur further advance in gold catalysis. Herein, we disclose a study inferring that the interaction between a cationic gold complex and an aryne (i.e., a gold aryne complex) is a transition state and leads to regioisomeric *ortho*-aurophenyl cation intermediates, which could either be trapped by weak nucleophiles or undergo intramolecular C-H insertions via α -carbene gold carbene mesoisomers.

In our attempt to generate gold aryne complexes, we reasoned conceptually that aryne could be formed upon the addition of a deprotonated terminal alkyne to the other C-C triple bond in a *cis*-enediynes substrate with the assistance of a metal catalyst (Scheme 1A). Notable in this design is that the strained C-C triple bond in aryne is originally the terminal alkyne in the substrate and, in contrast to the typical elimination approach, formally not the bond formed. To implement it, we envisioned that an additional metal could facilitate the pivotal cyclization,^[10] as shown in Scheme 1B, thereby potentially leading to the generation of a metal aryne complex. Moreover, we reasoned that a cationic Au(I) complex could serve as the metal catalyst for both M¹ and M² in Scheme 1B. It is well established that gold complexes can activate carbon-carbon triple bonds efficiently and, at the meantime, alkynylgold can be readily formed in situ upon reacting with terminal alkynes.^[11]

We^[11] have recently reported the generation of gold vinylidenes (i.e. **A**) from benzene-1,2-dialkyne via a highly regioselective, goldpromoted 5-*endo-dig* cyclization (Scheme 2a).^[12] DFT calculations on that energy surface revealed that this intermediate was formed by a bifurcation mechanism in competition with α -aurophenyl cation **B_{ben}** from 6-*endo-dig* cyclization^[13] (see the SI of that work); moreover, **B_{ben}** rearranges to its more stable structural isomer **C_{ben}** following a low-barrier gold migration. The calculation also predicted the formation of a gold carbene intermediate **E_{ben}** from **C_{ben}** upon a carbene C(sp³)-H insertion in the following step, thereby indicating the contribution of a mesomeric α -carbene gold carbene (i.e., **C'_{ben}**). While the naphthalene-type products were not detected as bulky BrettPhos^[14] was used in place of PH₃ as the real ligand in our experiments, we were nevertheless intrigued by the 6-*endo-dig* reaction path.

The isomerization from **B_{ben}** to **C_{ben}** was calculated to go through a transition state along the reaction coordinate that is an arynecoordinated gold complex (i.e., **D_{ben}**). The phenyl cationic structures **B_{ben}** and **C_{ben}** can be viewed as resulting from gold atom slippage to the

ends of the coordinating triple bond in **D_{ben}**. As a result, **B_{ben}**/**C_{ben}** appear to be the appropriate structures from the interaction between cationic gold(I) and aryne; moreover, they should be more electrophilic than typical arynes due to their aryl cation nature, which would be consistent with known silver catalysis[15] where insitu generated benzyne in the presence of Ag⁺ reacts with significantly enhanced electrophilicity.

With no success with benzene-1,2-dialkyne substrates in achieving the desired 6-*endo-dig* cyclization, we switched to the *cis*endiynes **1a**, and the reaction discovery and optimizations are shown in Table 1. Much to our delight, the C-H insertion product **2a** was indeed formed when the substrate was treated with BrettPhosAuNTf₂ (5 mol %) and 2,6-lutidine *N*-oxide (**5a**, 0.5 equiv) in 1,2-dichloroethane (DCE) (entry 1). The formation of **2a** can be readily rationalized by invoking a mechanism shown in Scheme 2b, which is further supported by further DFT calculations (see SI). The additive **5a**, in line with our previous study, acted as a mild base to facilitate the formation of the alkynylgold entry species in Scheme 2. This mechanism can also explain the formation of the phenol **4a**, which is attributed to the addition of adventitious H₂O selectively to the *ortho*-aurophenyl cation **C**. The side product **3a**, though in trace amount, is likely formed following a mechanism similar to that reported by Liu using PtCl₂ as the catalyst.^[16]

Other base additives and gold complexes were then examined to improve the intended chemistry. In the absence of a base, only 24% of **2a** was obtained (entry 2). Other bases such as 2,6-dibromopyridine *N*-oxide (**5b**, entry 3) and TsNa (conjugate acid *p*K_a = 1.99^[17], entry 4) could not improve the reaction, either. With more basic lutidine (entry 5), the reaction was slower but resulted in an identical yield to that of entry 1. With regard to the gold catalyst, ^tBuBrettPhosAuNTf₂ (entry 6), a bulkier catalyst than BrettPhosAuNTf₂, and JackiePhosAuNTf₂ (entry 7), a more Lewis acidic catalyst, were less efficient. However, Mor-DalPhos^[18] turned out to be the most efficient ligand, affording **2a** in 83% yield (entry 8). The use of less coordinating BAr^F₄⁻,^[19] however, did not lead to further improvement (entry 9). While in all the cases discussed above **3a** was formed in trace amounts, much to our surprise the Gagosz catalyst, Ph₃PAuNTf₂,^[20] promoted the formation of **3a** at the expense of **2a** (entry 10). It appears that the smaller steric size of the ligand Ph₃P is the cause for the switch of selectivity.^[21]

With the optimized conditions in hand, we then studied the scope of the reaction featuring C-H insertions, and the results are shown in Table 2, entries 1-8. In these reactions, 4Å molecular sieve was added to minimize the formation of phenol derivatives. Various types of aliphatic C-H bonds, including a primary C-H (entry 1), a tertiary C-H (entry 2), a benzylic C-H (entry 3) and a C-H α to a silyoxy group (entry 4) were readily inserted, leading to indane derivatives in mostly excellent yields. Changing the cyclohexane ring in the endiynes substrates discussed so far revealed that a smaller cyclopentene ring hindered

the reaction as the corresponding substrate mostly remained unchanged; however, a bigger cycloheptene ring was inconsequential, and the indane **2f** was isolated in 79% yield (entry 5). Moreover, the ring could be completely removed (entry 6) or replaced with *n*-butyl at either end of the C-C double bond (entries 7 and 8) without significantly impacting the reaction yield. Notably, in several cases the further optimized conditions deviated from the optimized ones shown in Table 1, entry 8 by the catalyst (e.g., BrettPhosAuNTf₂ in entries 2, 4 and 6) and/or the base (e.g., **5b** in entry 6).

Besides the C-H insertions by the carbene-type reactivity from the mesoisomer **C'**_{cy} (Scheme 2), the phenyl cation character from the mesoisomer of **C**_{cy} could also be harvested. For example, a tethered phenyl group could be the reacting nucleophile partner, and the reaction led to the formation of 9,10-dihydrophenanthrene (i.e., **2j**, entry 9) in a good 80% yield. When a phenanthrene was the tethered nucleophile, the reaction resulted in a direct transformation of an endiynes into pentacyclic benzo[*e*]acephenanthrylene in a serviceable yield (entry 10). We were pleased to find out that a tethered HO group worked well as the nucleophile, and the tetrahydrooxepin **2l** was formed in 90% yield (entry 11). This highly efficient formation of a 7-membered *O*-heterocycle and the lack of competing C-H insertion are particularly noteworthy, suggesting that **C**_{cy}/**C'**_{cy} prefers to react as a phenyl cation (i.e., in the form of **C**_{cy}). This observation is consistent with cationic gold complexes as strong soft Lewis acids^[6] but weak π -back donors.^[22] Similarly, a tethered sulfonamide was able to trap the cationic intermediate to deliver the seven-membered *N*-heterocycle **2m** in a moderate yield (entry 12). Again, no competing intramolecular C-H insertion was detected.

During the scope study of C-H insertion reactions, we found that a 4-chlorobutyl group at the alkyne terminus did not undergo C-H insertion into the side chain. While this result again suggests that the carbene reactivity derived from **C'**_{cy} might be limited, the chloride substrate was used to examine intermolecular trapping of **C**_{cy}. With wet DCE as solvent, the phenol **2n** was indeed formed in a very good yield (entry 13); similarly, ethanol and *p*-toluic acid, also used in excess, were suitable trapping nucleophiles as well, and the phenyl ether **2o** and the phenyl ester **2p** were isolated in 79% and 68% yields, respectively (entries 14 and 15). Importantly, these intermolecular trapping reactions were highly regioselective as the isomer anticipated in each case from trapping of the phenyl cation of type **B**_{cy} (see Scheme 2) was not detected.

(1)

Attempts to switch the regioselectivity were unsuccessful. For example, subjecting the endiynes **1q** to the typical reaction conditions in DCE led to the formation of the phenol **5** in 75% yield in 42 h (Eq. 1). Neither the regioisomeric phenol **5'** nor the C-H insertion product

2q by an α -carbene gold carbene regioisomeric with **C'** was not detected, which is consistent with the DFT calculations (Figure 1A), where **B_{cy-Me}** has a very low barrier to rearrangement to **C_{cy-Me}** and is 6.5 kcal mol⁻¹ less stable. It is expected that **B_{cy-Me}** would not be trappable, due to its predicted very short lifetime in solution. The reason for the enhanced stability for **C_{cy-Me}** could be attributed to the contribution of its mesomeric bent allene form, **C''_{cy-Me}** (Figure 1B),^[23] consistent with the DFT optimized structure, in which the bond length of C2-C3 is 1.33 Å, significantly shorter than 1.40 Å in naphthalene. In contrast, the corresponding bond length for **B_{cy-Me}** is 1.45 Å.

(2)

It is well known that arynes can undergo [4+2] cycloaddition with furan;^[3] however, our attempts to perform the reaction with the endiynes substrates in the presence of gold catalysts led to no desired product. On the other hand, the reaction of **1n** with *trans-p*-methoxycinnamaldehyde did lead to the formation of the [4+2] adduct **6**. The formation of the [2+2+2] adduct **7** as the major product suggests that **6** is most likely generated via a step-wise process involving an *ortho*-aurophenyl cation of type **C_{cy}**.

(3)

(4)

(5)

Deuterium labeling studies were performed to gain further experimental support for the reaction mechanism. First, the alkyne terminus of **1c** was labeled by a deuterium. With 10 equivalents of H₂O added, the reaction resulted in nearly complete loss of the isotope (Eq. 3). On the other hand, with a similar amount of D₂O as the additive, the non-labeled **1c** proceeded to give **2c** with significant amount of deuterium at the C4 but little at the C9 (Eq. 4). These two experiments confirm that the alkyne terminal hydrogen is removed as a proton during the reaction and the C4 hydrogen is installed via protonation. The origin of the C9 hydrogen was revealed experimentally by deuterium-labeling the side chain in a related substrate (Eq. 5). All the isotope-labeling results are consistent with the mechanism shown in Scheme 2b.

The remaining question with this chemistry is how the lack of the fused benzene ring in the substrates led to a complete switch of the initial cyclization from 5-*endo-dig*^[11] to 6-*endo-dig* (Scheme 2). It can be explained by considering the difference in gained aromatic stabilization: when ring A is a benzene ring, the additional resonance energy gained upon the 6-*endo-dig* cyclization is 28 kcal mol⁻¹ (64 kcal mol⁻¹ for naphthalene and 36 kcal mol⁻¹ for benzene); however, when ring A is not a benzene or nonexistent, the aromaticity gained by the newly formed benzene ring would be 8 kcal mol⁻¹ larger at 36 kcal mol⁻¹. Our DFT calculations in methylene chloride solution at 298 K confirm this idea. We find that the free energies for the formation of **A** and **B** (Scheme 2) favor **B** by 12.0 kcal mol⁻¹ when the fused ring is cyclohexene and by 15.6 kcal mol⁻¹ when there is no fused ring, which are much larger than 2.2 kcal mol⁻¹ difference with the fused ring as a benzene, where the 5-*endo-dig* product is favored.^[11] It is not unreasonable to imagine in the bifurcation mechanism that making the 6-*endo-dig* product much more stable relative to the 5-*endo-dig* product could skew the energy surface in a fashion that the 6-*endo-dig* path is favored.

In summary, we have disclosed a dual gold-catalyzed cyclization^[24] of *cis*-endiynes, which offers a *de novo* approach to various substituted indanes, heterocycle-fused benzenes and phenol derivatives. This represents a dramatic switch of the initial cyclization from the previously observed 5-*endo-dig*^[11] to 6-*endo-dig* in the bifurcation mechanism. Besides its synthetic utility, this chemistry offers for the first time insights on the interaction between cationic gold(I) and aryne. This interaction can be viewed as leading to a gold-aryne transition state that results in formation of two regioisomeric ortho-auroaryl cation intermediates, which can be considered as the results of the extreme slippage of the metal along the highly strained C-C triple bond. The more stable of these aryl cation forms reacts very regiospecifically with a range of nucleophiles in a manner similar to arynes, though the cation is more electrophilic. While cycloaddition reactions observed with arynes could not

be realized, new reactivities with these polarized forms such as facile intramolecular insertions into C(sp³)-H bonds via mesomeric α -carbene gold carbenes are realized.

Experimental Section

General procedure for the dual gold catalyzed cyclization of *cis*-endynes

2,6-dibromopyridine *N*-oxide or lutidine *N*-oxide (0.15 mmol), BrettPhosAuNTf₂ (15.3 mg, 0.015 mmol) or Mor-DalPhosAuNTf₂ (14.4 mg, 0.015 mmol), and 4 Å Molecular Sieves (75 mg) were added in this order to a solution of *cis*-enediyne **1** (0.30 mmol) in DCE (6.0 mL) at room temperature. The reaction mixture was stirred at 60 °C and the progress of the reaction was monitored by TLC. Upon completion, the mixture was concentrated and the residue was purified by chromatography on silica gel (eluent: hexanes/ethyl acetate) to afford the desired product **2**.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Wentrup C. *Aust J Chem.* 2010; 63:979–986.
2. Wenk HH, Winkler M, Sander W. *Angew Chem, Int Ed.* 2003; 42:502–528.
3. For selected reviews on arynes, see: Kessar SV. *Comprehensive organic synthesis : selectivity, strategy, and efficiency in modern organic chemistry* (1). 4Trost BM, Fleming I. Pergamon Press Oxford, England; New York 1991; :483–515.; Pellissier H, Santelli M. *Tetrahedron.* 2003; 59:701–730.; Sanz R. *Org Prep Proc Int.* 2008; 40:215–291.; Kitamura T. *Aust J Chem.* 2010; 63:987–1001.; Gampe CM, Carreira EM. *Angew Chem, Int Ed.* 2012; 51:3766–3778.; Tadross PM, Stoltz BM. *Chem Rev.* 2012; 112:3550–3577. [PubMed: 22443517]
4. For examples of metal aryne chemistry, see: Gowling EW, Kettle SFA, Sharples GM. *Chem Commun.* 1968:21–22.; Buchwald SL, Nielsen RB. *Chem Rev.* 1988; 88:1047–1058.; Broene R, Buchwald S. *Science.* 1993; 261:1696–1701. [PubMed: 8378769]; Tidwell JH, Buchwald SL. *J Am Chem Soc.* 1994; 116:11797–11810.; Houseknecht KL, Stockman KE, Sabat M, Finn MG, Grimes RN. *J Am Chem Soc.* 1995; 117:1163–1164.; Jones WM, Klosin J. *Adv Organomet Chem.* 1998; 42:147–221.
5. (a) Hoyer TR, Baire B, Niu D, Willoughby PH, Woods BP. *Nature.* 2012; 490:208–212. [PubMed: 23060191] (b) Bradley AZ, Johnson RP. *J Am Chem Soc.* 1997; 119:9917–9918. (c) Miyawaki K, Suzuki R, Kawano T, Ueda I. *Tetrahedron Lett.* 1997; 38:3943–3946. (d) Karmakar R, Mamidipalli P, Yun SY, Lee D. *Org Lett.* 2013; 15:1938–1941. [PubMed: 23540274]
6. For selected reviews, see: Hashmi ASK. *Chem Rev.* 2007; 107:3180–3211. [PubMed: 17580975]; Gorin DJ, Sherry BD, Toste FD. *Chem Rev.* 2008; 108:3351–3378. [PubMed: 18652511]; Zhang L, Sun J, Kozmin SA. *Adv Synth Catal.* 2006; 348:2271–2296.; Jiménez-Núñez, Es; Echavarren, AM. *Chem Rev.* 2008; 108:3326–3350. [PubMed: 18636778]; Li Z, Brouwer C, He C. *Chem Rev.* 2008; 108:3239–3265. [PubMed: 18613729]; Patil NT, Yamamoto Y. *Chem Rev.* 2008; 108:3395–3442. [PubMed: 18611054]; Abu Sohel SM, Liu R-S. *Chem Soc Rev.* 2009; 38:2269–2281. [PubMed: 19623349]; Hopkinson MN, Gee AD, Gouverneur V. *Isr J Chem.* 2010; 50:675–690.; Fürstner A, Davies PW. *Angew Chem, Int Ed.* 2007; 46:3410–3449.; Sengupta S, Shi X. *Chemcatchem.* 2010; 2:609–619.; Lopez F, Mascarenas JL. *Beilstein J Org Chem.* 2011; 7:1075–1094. [PubMed: 21915211]; Corma A, Leyva-Perez A, Sabater MJ. *Chem Rev.* 2011; 111:1657–1712. [PubMed: 21391565]; Biannic B, Aponick A. *Eur J Org Chem.* 2011; 2011:6605–6617.
7. Rondan NG, Domelsmith LN, Houk KN, Bowne AT, Levin RH. *Tetrahedron Lett.* 1979; 20:3237–3240.
8. Xie C, Zhang Y, Yang Y. *Chem Commun.* 2008:4810–4812.

9. Asao N, Sato K. *Org Lett.* 2006; 8:5361–5363. [PubMed: 17078718]
10. For examples of this type of bond formation, see: Odabachian Y, Le Goff XF, Gagosz F. *Chem Eur J.* 2009; 15:8966–8970. [PubMed: 19650093] ; Sun S, Kroll J, Luo Y, Zhang L. *Synlett.* 2012; 2012:54–56. [PubMed: 22904604]
11. Ye L, Wang Y, Aue DH, Zhang L. *J Am Chem Soc.* 2012; 134:31–34. [PubMed: 22176593]
12. (a) Hashmi ASK, Wietek M, Braun I, Nösel P, Jongbloed L, Rudolph M, Rominger F. *Adv Synth Catal.* 2012; 354:555–562. (b) Hashmi ASK, Braun I, Rudolph M, Rominger F. *Organometallics.* 2012; 31:644–661. (c) Hashmi ASK, Wietek M, Braun I, Rudolph M, Rominger F. *Angew Chem, Int Ed.* 2012; 51:10633–10637. (d) Hashmi ASK, Braun I, Nösel P, Schädlich J, Wietek M, Rudolph M, Rominger F. *Angew Chem, Int Ed.* 2012; 51:4456–4460.
13. For a study involving 6-endo-dig cyclization, see: Naoe S, Suzuki Y, Hirano K, Inaba Y, Oishi S, Fujii N, Ohno H. *J Org Chem* 2012. 77:4907–4916.; for a closely related work, which was published after our work was submitted, see: Hansmann MM, Rudolph M, Rominger F, Hashmi ASK. *Angew Chem, Int Ed.* 2013:2593–2598.
14. (a) Fors BP, Watson DA, Biscoe MR, Buchwald SL. *J Am Chem Soc.* 2008; 130:13552–13554. [PubMed: 18798626] (b) Ye L, He W, Zhang L. *Angew Chem, Int Ed.* 2011; 50:3236–3239.
15. (a) Friedman L. *J Am Chem Soc.* 1967; 89:3071–3073. (b) Vedejs E, Shepherd RA. *Tetrahedron Lett.* 1970; 11:1863–1864. (c) Paquette LA. *J Chem Soc Chem Commun.* 1971:1076–1077.
16. Taduri BP, Ran YF, Huang CW, Liu RS. *Org Lett.* 2006; 8:883–886. [PubMed: 16494465]
17. Burkhard RK, Sellers DE, DeCou F, Lambert JL. *J Org Chem.* 1959; 24:767–769.
18. (a) Hesp KD, Stradiotto M. *J Am Chem Soc.* 2010; 132:18026–18029. [PubMed: 21133383] (b) Lundgren RJ, Peters BD, Alsabeh PG, Stradiotto M. *Angew Chem, Int Ed.* 2010; 49:4071–4074. (c) Luo Y, Ji K, Li Y, Zhang L. *J Am Chem Soc.* 2012; 134:17412–17415. [PubMed: 23039251]
19. Nishida H, Takada N, Yoshimura M, Sonoda T, Kobayashi H. *Bull Chem Soc Jpn.* 1984; 57:2600–2604.
20. Mézailles N, Ricard L, Gagosz F. *Org Lett.* 2005; 7:4133–4136. [PubMed: 16146370]
21. Detailed studies of this switch of regioselectivity will be disclosed soon.
22. Seidel G, Mynott R, Fürstner A. *Angew Chem, Int Ed.* 2009; 48:2510–2513.
23. For bent allenes, see: Hänninen MM, Peuronen A, Tuononen HM. *Chem Eur J.* 2009; 15:7287–7291. [PubMed: 19551788] ; Reetz MT, Sommer K. *Eur J Org Chem.* 2003:3485–3496.. A related structure was mentioned in Hashmi's work in ref. 13b.
24. Gomez-Suarez A, Nolan SP. *Angew Chem, Int Ed.* 2012; 51:8156–8159.

Figure 1.

A) The rearrangement of **B**_{cy-Me} to **C**_{cy-Me}, energy diagram with electronic energies and free energies in methylene chloride in parentheses, and structures optimized at the M06/6-31+G(d,p)/SDD(Au) level. B) The resonance structures of **C**_{cy-Me}.

Scheme 1.

New approach to the aryne moiety and metal aryne

Scheme 2.

a) With ring A = benzene and R = Me, previous DFT calculations predict a bifurcation to form two possible intermediates A_{ben} and B_{ben} ; the structures in the computed mechanism are indicated by a subscript ben. b) With ring A = cyclohexene and R = Et, the computed mechanism for the formation of **2a**; the structures in the computed mechanism are indicated by a subscript cy.

Table 1Initial reaction discovery and optimization.^[a]

en.	catalyst	base	temp/time	2a/3a/4a ^[b]
1	BrettPhosAuNTf ₂	5a	rt/17 h	61%/trace/9%
2	BrettPhosAuNTf ₂	-	rt/24 h	24%/trace/4%
3	BrettPhosAuNTf ₂	5b	rt/24 h	28%/trace/4%
4	BrettPhosAuNTf ₂	TsNa	rt/24 h	30%/trace/5%
5	BrettPhosAuNTf ₂	lutidine	60 °C /24 h	61%/trace/4%
6	^t BuBrettPhosAuNTf ₂	5a	60 °C/24 h	45%/trace/10%
7	JackiePhosAuNTf ₂	5b ^[c]	rt/20 h	50%/ trace/trace
8	Mor-DalPhosAuNTf ₂	5a	60 °C/11 h	83% ^[d] /trace/trace
9	Mor-DalPhosAuCl/NaBAR ^F ₄	5a	60 °C/20 h	76%/ trace/trace
10	Ph ₃ PAuNTf ₂	5a	60 °C/3.5 h	8%/54%/trace

^[a] Reaction run in flame-dried vial using dry DCE as solvent. [1a] = 0.05 M.^[b] Estimated by ¹H NMR using diethyl phthalate as the internal reference.^[c] 1.1 Equiv.^[d] Isolated yield.

Table 2

Reaction Scope of aryne gold Chemistry^[a]

 2b (60%, 5a, 30 h)	 2c (87%, 5a, 11 h)	 2d (95%, 5a, 14 h)
 2e (84%, 5a, 4 h)	 2f (79%, 5a, 16 h)	 2g (67%, 5b, rt, 23 h)
 2h (67%, 5a, 36 h)	 2i (71%, 5a, 7 h)	 2j (80%, 5b, 16 h)
 2k (43%, [a] 5a, 80°C, 24 h)	 2l (90%, 5a, rt, 9 h)	 2m (52%, 5a, 24 h)
 2n (89%, 5a, 6 h)	 2o (79%, 5a, rt, 10 h)	 2p (68%, 5a, 24 h)

[a] [1] = 0.05 M. Reactions were run in flame-dried vials in the presence of 4 Å MS except entry 13. Isolated yield were reported.

[b] MorDalPhosAuNTf₂ was used.

[c] BrettPhosAuNTf₂ was used.

[d] Wet