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Practical and modular construction of benzo[*c*]phenanthridine compounds

Cheng Zhang[1†*], Qian Chen[3†], Lei Wang[3], Qiaoying Sun[1], Yangyang Yang[1], Matthias Rudolph[1], Frank Rominger[1] & A. Stephen K. Hashmi[1,2*]

[1]*Organisch-Chemisches Institut, Heidelberg University, Heidelberg 69120, Germany;*
[2]*Chemistry Department, Faculty of Science, King Abdulaziz University (KAU), Jeddah 21589, Saudi Arabia;*
[3]*Cellular Immunotherapy Lab, the Medical Faculty of Heidelberg University, Heidelberg University Hospital, Heidelberg 69120, Germany*

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Here, we describe a general and modular strategy for the rapid assembly of benzo[*c*]phenanthridine (BCP) derivatives using homogeneous gold catalysis. Notably, in contrast to traditional methods based on the specially preformed substrates that have an inherent preference for the formation of this class of compounds with limited flexibility, this protocol is achieved *via* a selectively intramolecular cascade of a diazo-tethered alkyne and subsequently an intermolecular cyclization with a nitrile to facilitate the successive C–N and C–C bonds formation. This methodology uses readily available nitriles as the nitrogen source to deliver the products in good yield with excellent functional group compatibility. A preliminary anti-tumor activity study of these generated products exhibits high anticancer potency against five tumor cell lines, including HeLa, Mel624, SW-480, 8505C, LAN-1. Besides, we report a catalyst-controlled intermolecular cycloaddition/intramolecular insertion of the substrate with a fulvene to provide fused polycarbocycles containing a seven-membered ring.

selectivity, homogeneous gold catalysis, domino cyclization, benzo[*c*]phenanthridine (BCP), anticancer activity

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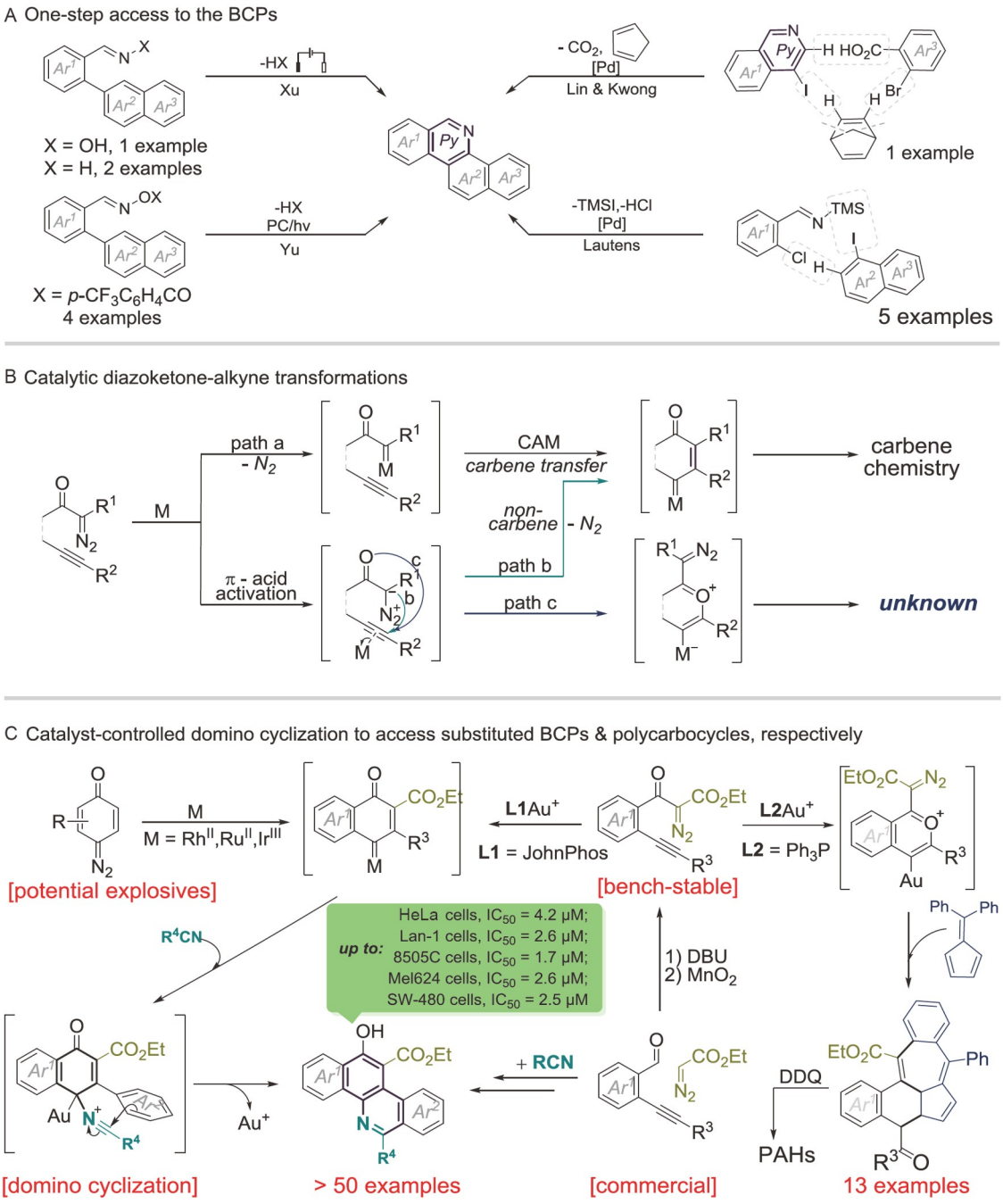
1 Introduction

The streamlined and efficient synthesis of complex molecules has been a long-standing challenge in organic synthesis. In this context, the search for improved techniques as flexible access to a diverse array of potential target structures is of ongoing interest with an impact on natural product synthesis, pharmaceutical chemistry and material science. An important synthetic motif is the benzo[*c*]phenanthridine scaffold, which as a core unit is commonly found in a number of biologically active molecules which possess antimicrobial, antifungal, antiinflammatory, antiproliferative and optoelectronic properties [1–3]. In addition, some derivatives are used as antiprotozoal, antibacterial and anticancer agents [4–7]. So far, over 80 alkaloids containing this structure have been discovered and were isolated from Fumariaceae, Papaverace and Rutaceae plants [8]. Recent approaches for the synthesis of the benzo[*c*]phenanthridine skeleton include the domino direct arylation/*N*-arylation [9], π-extensions of aryl halides [10], and intramolecular homolytic aromatic substitutions (HAS) [11–13]. However, these synthetic strategies generally rely on specially preformed substrates, which often contain a naphthyl group that is imbedded into the final core by the reaction with a complex nitrogen-source (Scheme 1A). Still, the exploration of a practical, modular, and efficient synthetic protocol to access structurally diverse and/or novel fused BCPs remains highly

†These authors contributed equally to this work.
*Corresponding authors (email: cheng.zhang@uni-heidelberg.de;hashmi@hashmi.de)



Scheme 1 One-step access to substituted BCPs and catalytic metal carbene formation (color online).

sought after.

Cascade reactions have inspired the imagination of organic chemists because it provides an efficient and universal strategy to assemble complex molecules [14–18]. Instead of time-consuming and costly procedures, including the purification of intermediates and protection/deprotection steps of functional groups, this strategy relies on a consecutive series of chemical reactions proceeding in a concurrent fashion [19,20]. Among these, the transition metal-catalyzed diazo-yne transformation has emerged as a powerful tool for the synthesis of polycyclic molecules [21,22]. Much of the early work in this context was based on a diazo-derived carbene/alkyne metathesis process (CAM), which after transfer of the initial carbene species onto the pendant alkyne, gives rise to a host of transformations, including cyclopropanations, (asymmetric) C−H insertions, oxidative rearrangements and a myriad of cascade reactions (path a, Scheme 1B) [23–27]. Exceptional results were observed with

the combination of a variety of pendant nucleophiles, especially those containing heteroatomic substituents capable of assembling heterocyclic frameworks during the cascade event [28–34]. Still, one drawback of this approach is the inherent features of a substrate with limited opportunity to modify the patterns of reactivity and selectivity. In recent years, this situation has changed with the development of homogeneous catalysts with different electronic and steric properties, which can overcome some of the inherent preferences for functionalization in a specific group [35–37]. In the catalytic diazo-yne cascade process, Rh^{I}-, Rh^{II}-, Cu^{II}-, Pd^{0}-, and Ag^{I}-complexes often directly decompose the diazo group to deliver the corresponding carbene species [21–34], whereas the use of gold catalysts in the combination of appropriate ligands can provide the opportunity to prioritize the activation of alkynes toward intra- or intermolecular nucleophiles (path b, Scheme 1B) [38–40]. In this direction, Toste *et al*. [41], Doyle *et al*. [42] and Xu *et al*. [38] elegantly showed examples of unparalleled selectivity and reactivity patterns in gold-catalyzed diazo-yne cascade reactions, respectively, where the gold catalyst primarily acted as a highly carbophilic π-Lewis acid to activate the alkyne rather than to decompose the diazo group.

Within the frame of our program devoted to the development of gold-catalyzed alkyne cascade cyclizations [43,44], Xu's and our group [40] recently developed an efficient method for the rapid assembly of a wide set of *o*-alkynyl diazoacetylbenzene reagents derived from the DBU-catalyzed condensation of *o*-ethynylbenzaldehyde derivatives with a commercial diazoacetate. This approach circumvents previously reported material-consuming and dangerous procedures, including the use of diazomethane [45] or diazo transfer reagents [46]. In comparison with diazo quinones (or so-called quinone diazides) as the on-ring carbene (ORC) precursors [47–49], these reagents, as potential ORC precursors generated *in-situ via* a gold-promoted 6-*endo-dig* diazo-yne carbocyclization (Scheme 1C), can provide an ideal platform for the construction of cyclic molecules with high structural complexity. Inspired by these findings, we became interested in further exploring the reactivity of this ORC with unsaturated bonds and envisioned that the method might be applied to access biologically relevant heterocyclic frameworks. Herein, we report our discovery and development of gold-catalyzed cascade reactions of alkyne-tethered diazoketones and nitriles as modular access to BCPs with excellent functional group compatibility. These structures contain a core skeleton that frequently occurs in a plethora of alkaloids, which show high anticancer activity against a variety of human tumor cell lines [50]. Moreover, a catalyst-controlled carbonyl-yne heterocyclization trapped by the diphenylfulvene to access fused polycycles in high yields is described.

2 Experimental

2.1 General procedure for benzo[*c*]phenanthridines2–52

The substrate **1** (0.2 mmol), dry 1,2-dichloroethane (DCE, 0.5 mL), nitrile (0.4 mmol, dry before use), and activated 4 Å molecular (30 mg) were successively mixed in a 5 mL glass bottle containing a magnetic stirring bar. Then, the gold catalyst (JohnphosAuSbF$_6$, 7.3 mg, 0.01 mmol) in dry DCE (0.5 mL) using a syringe was added over 2 min at room temperature. After the addition, the reaction mixture was stirred at 60 °C for 12.0 h. Then, the solvent was removed under reduced pressure and the crude product was purified by column chromatography on a silica gel (solvents: ethyl acetate/petroleum ether = 1/10) to afford the pure benzo[*c*] phenanthridine derivatives.

2.2 General procedure for polycarbocycles 56–68

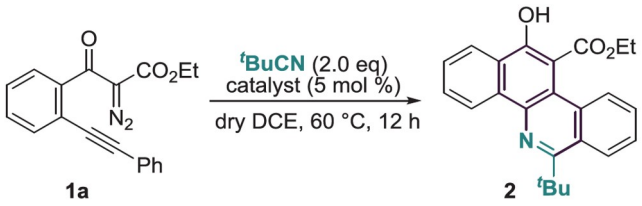
A solution of PPh$_3$AuNTf$_2$ (7.40 mg, 0.01 mmol) in DCE (0.5 mL), was added a solution of **1** (0.2 mmol) and the diphenylfulvene (92.12 mg, 0.4 mmol) in DCE (0.5 mL) at25 °C, then the reaction mixture was stirred for 12.0 h under these conditions. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on a silica gel (solvents: ethyl acetate/petroleum ether = 1/10) to afford the pure polycarbocycles.

3 Results and discussion

3.1 Reaction optimization

We began with trimethylacetonitrile (2 equivalents) to test the feasibility of an intramolecular diazo-yne (**1a**) cyclization/intermolecular cascade reaction (Table 1). In the first experiments, the uncatalyzed reaction between the two components did not occur, and a catalytic amount ofPh$_3$ PAuSbF$_6$ proved to be ineffective (entries 1 and 2). Encouragingly, when the more sterically hindered *t*Bu$_3$PAuSbF$_6$ was employed, a substantial amount of decomposition of **1a** was observed, together with a small amount of the desired cascade product **2** (entry 3). The IPr ligand gave a more efficient reaction, with the product observed in 56% yield (entry 4). Gratifyingly, the reaction with 5 mol% of JohnPhosAuSbF$_6$ in dry DCE at 60 °C, proceeded smoothly to give the desired product **2** in 74% yield (entry 5). Further changes in counterions, including NTf_2^-, OTf^-, BF_4^-, $BArF_4^-$, and Cl^- were investigated (entries 6 and 9−12). Notably, varying the counterion of gold catalyst from SbF_6^- to NTf_2^- or $BArF_4^-$ showed little effect (entries 6 and 11). However, the corresponding chloride salt, JohnPhosAuCl, showed very low reactivity, and most of **1a** were recovered (entry 12). The use of toluene as solvent showed minimal

Table 1 Optimization of the reaction conditions[a] (color online)



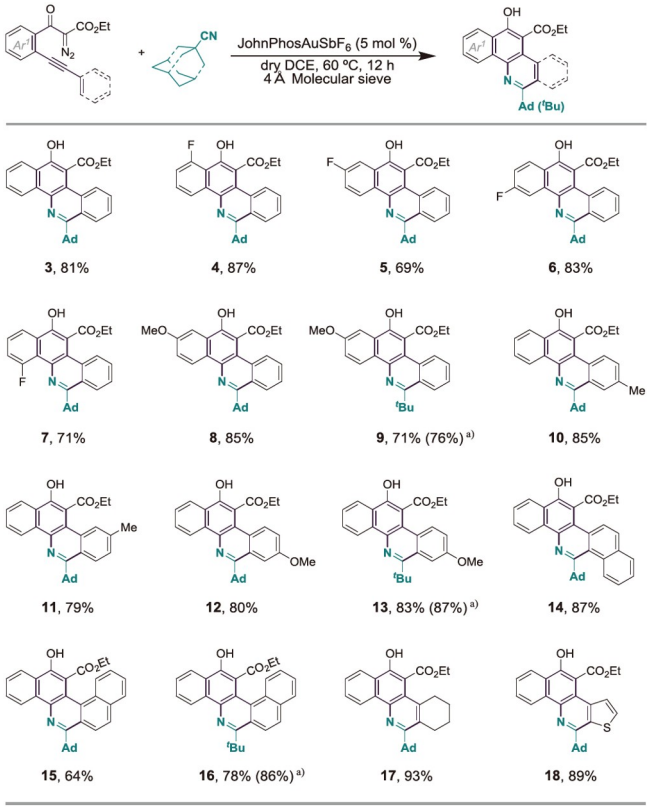
entry	catalyst	conv. (%) [b]	**2** (%) [b]
1	None	Nr	-
2	$Ph_3PAuSbF_6$	< 10	-
3	$^tBu_3PAuSbF_6$	79	31
4	$IPrAuSbF_6$	85	56
5	$JohnPhosAuSbF_6$	100	74
6	$JohnPhosAuNTf_2$	100	69
7 [c]	$JohnPhosAuSbF_6$	< 10	-
8 [d]	$JohnPhosAuSbF_6$	100	83 (80) [e]
9	JohnPhosAuOTf	100	59
10	$JohnPhosAuBF_4$	100	47
11	$JohnPhosAuBArF_4$	100	72
12[f]	JohnPhosAuCl	< 10	-

a) Reaction conditions: in the glove box, a solution of catalyst (5 mol%) in dry DCE (0.5 mL), was added to the solution of **1a** (63.6 mg, 0.2 mmol), trimethylacetonitrile (45.0 μL, 0.4 mmol) and dry DCE (0.5 mL) in a 5 mL screw cap vial. Then the reaction mixture was stirred for 12.0 h outside the glove box at 60 °C. b) Yields were determined by proton nuclear magnetic resonance (NMR) with 1,3,5-trimethoxybenzene as the internal standard. c) Toluene was used in the reaction instead of DCE. d) 4 Å molecular sieve (200 mg) was added to the reaction. e) The result in the parentheses is isolated yield. f) Most of **1a** (>90%) was recovered.

evidence of productive cycloaddition (entry 7). Further careful optimization of the reaction parameters led to a combination of 4 Å molecular sieves, giving **2** in 80 % isolated yield with full conversion (entry 8). Notably, no O–H insertion products were observed in this reaction.

3.2 Substrate scope

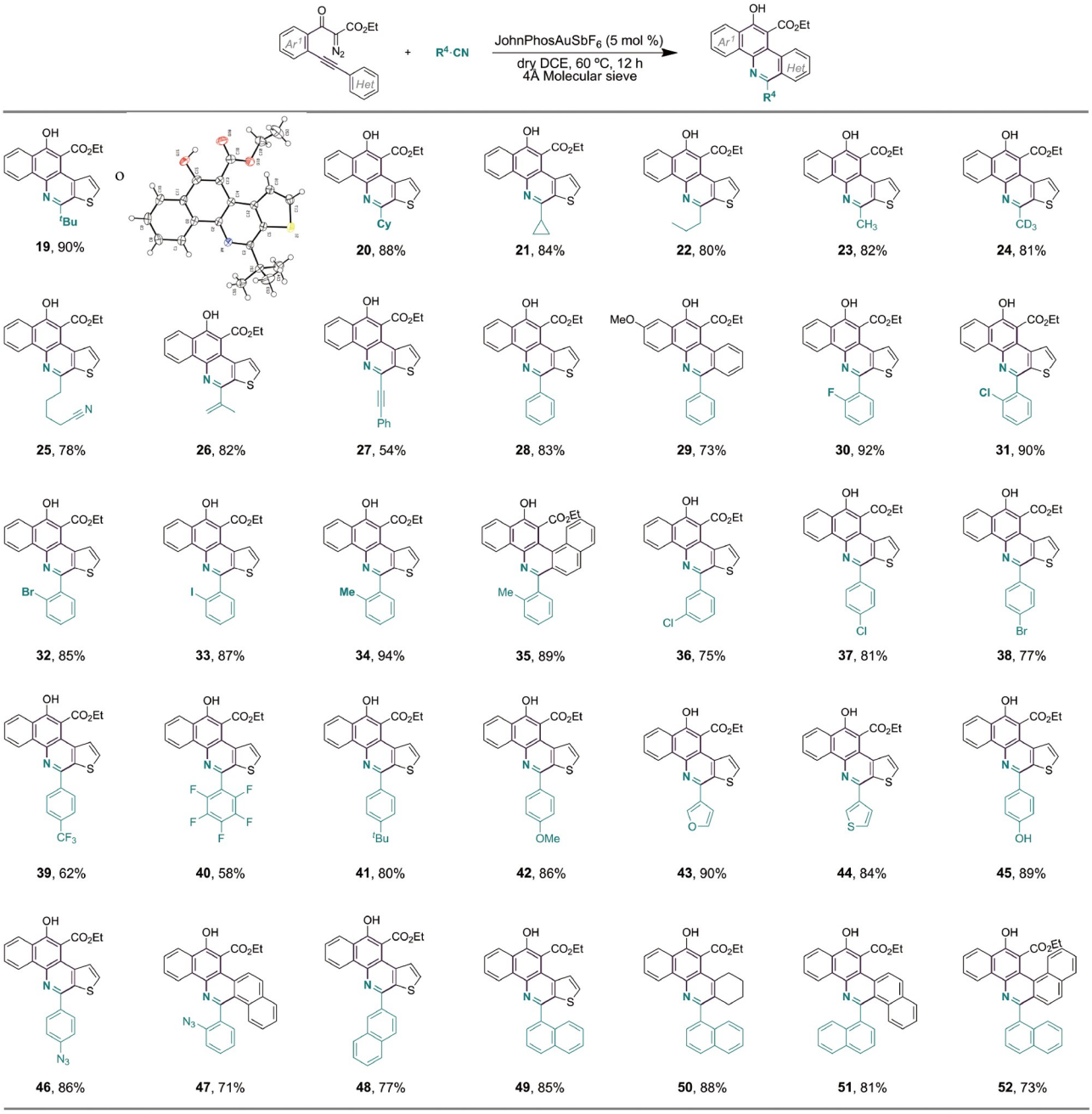
After identification of the optimal conditions, we first investigated the generality and utility of this gold-catalyzed domino cyclization of diazo-tethered alkynes **1** in combination with 1-adamantylnitrile using $JohnPhosAuSbF_6$ as the catalyst. As shown in Scheme 2, a series of fluorine substituents (**3**–**7**) and a methoxy group (**8** and **9**) on the linking aryl unit (Ar^1) were well tolerated, delivering the corresponding products in moderate to high yields (69%–87%). Methyl- (**10** and **11**) and methoxy- (**12** and **13**) substituted aryl alkynes were also applicable to this transformation without a noticeable yield deterioration. Additionally, we found that sterically hindered naphthalene rings (**14**–**16**) at the alkynyl terminus reacted smoothly, indicating that the steric properties of the alkynes have no obvious effects on the reaction's efficiency. Alkenyl (**17**) and thienyl (**18**) alkynes gave a higher yield than other aryl substituents, presumably because of the increased nucleophilicity of these electron-rich aryl groups. In particular, the reaction showed excellent regioselectivity, including that *m*-tolyl, cyclohexenyl, and 3-thienyl-substituted substrates all promoted the reaction smoothly and provided the corresponding products in high to excellent yield. In particular, the reaction showed excellent regioselectivity, including that *m*-tolyl, cyclohexenyl, and 3-thienyl-substituted substrates all promoted the reaction smoothly and provided the corresponding products in high to excellent yield (**11**, **17** and **18**). This cascade



Scheme 2 Scope of diazo compounds **1**. Reaction condition: a solution of $JohnPhosAuSbF_6$ (7.32 mg,0.01 mmol) in dry DCE (0.5 mL) was added to a solution of **1** (0.2 mmol), the nitrile (0.4 mmol) and 4 Å molecular sieve (200 mg) in dry DCE (0.5 mL) in the glove box, then the reaction mixture was stirred for 12.0 h at 60 °C outside the glove box. Isolated yields are listed. Note: all reagents should be dried before use. a) At 2.0 mmol scale (color online).

strategy was also scalable and provided comparable yields on a 2.0 mmol scale cyclization (**9**, **13** and **16**).

Scope of nitriles. Next, we continued to explore this protocol with respect to nitriles under the optimal reaction conditions (Scheme 3). Tertiary (**19**), secondary (**20**), strained-cyclic (**21**), primary (**22**, **23**) and deuterated (**24**) nitriles successfully underwent the domino cyclization with diazo-yne substrate **1n** to afford the desired products in good yields. The structure of product **19** was unambiguously confirmed by single crystal X-ray analysis. The introduction of cyano (**25**), alkenyl (**26**) and alkynyl (**27**) groups to the nitrile were compatible with the applied conditions. Going further, a variety of aryl nitriles bearing electron-withdrawing, electron-neutral and electron-donating substituents underwent this reaction, providing the corresponding adducts **28**–**42** in moderate to excellent yield. Substrates with *ortho*- (**30**–**35**), *meta*- (**36**), and *para*- (**37**–**42**) substituents on the aryl moiety effectively reacted with nitriles to produce the desired products in synthetically useful to high yields. The reaction also proceeded smoothly with heteroaromatic



Scheme 3 Scope of nitriles. Reaction condition: a solution of JohnPhosAuSbF$_6$ (7.32 mg,0.01 mmol) in dry DCE (0.5 mL) was added to the solution of **1** (0.2 mmol), the nitrile (0.4 mmol) and 4 Å molecular sieve (200 mg) in dry DCE (0.5 mL) in the glove box, then the reaction mixture was stirred for 12.0 h at 60 °C. Isolated yields are listed. Note: all reagents should be dried before use (color online).

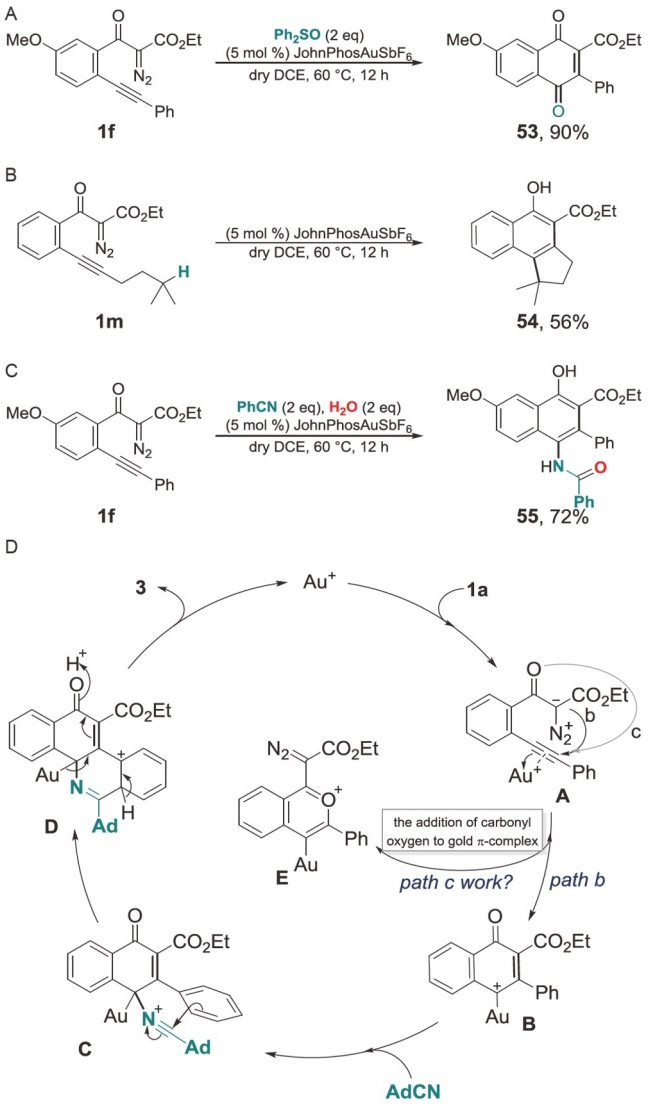
nitriles, providing the corresponding products **43** and **44** in excellent yields. Notably, substrates bearing common sensitive functional groups such as azide and unprotected phenols underwent the reaction and gave the corresponding products **45**–**47** in good to high yield. This is noteworthy as these units are known to react in traditional carbene transformations. Heteroaromatic, alkenyl and naphthyl substrates were successfully cyclized with a α-cyanonaphthalene to afford the naphththyl-substituted BCPs (**49**–**52**) in good yields, which enriched the library of biaryl compounds.

3.3 Mechanistic discussion

We conducted a series of control experiments to gain some insight into the mechanism. To verify the existence of the ORC intermediate, the oxidation reaction with the substrate 1f in the presence of diphenylsulfoxide, instead of the nitrile, was conducted under standard conditions, and the corresponding oxidation product **53** was isolated in 90% yield (Scheme 4A). As further evidence of the intermediacy of the carbene intermediate, a gold-catalyzed 6-*endo-dig* diazo-yne carbocyclization was terminated by a tertiary C−H bond insertion to form the polycyclic product **54** in 56% yield (Scheme 4B). In addition, a non-concerted, step-wise mechanism of the intermolecular cyclization process was well supported by the interception reaction with an external acceptor. The identifiable three-component product **55** was isolated in 72% yield when the reaction was carried out in the presence of water (Scheme 4C). Based on the above studies and literature reports [38–43], a possible mechanism is proposed for this cascade reaction in Scheme 4D. Initially, Au(I) acts as a highly carbophilic π-Lewis acid, selectively activating the alkynyl group to form the gold π-complex **A**. Subsequently, an intramolecular 6-*endo-dig* nucleophilic addition of the diazo-carbon atom onto the gold-activated alkyne and then irreversible extrusion of N_2 can generate the ORC species **B**. It should be noted that other possible reaction pathway(s) to access this intermediate, such as the carbene transfer process, could not be completely ruled out so far. This ORC intermediate is trapped by the nitrile to furnish a nitrile ylide-type intermediate **C** [51,52], followed by a domino cyclization with the pendant aryl group (**D**)/aromatization, furnishing the corresponding polycyclic product **3** under liberation of the gold catalyst.

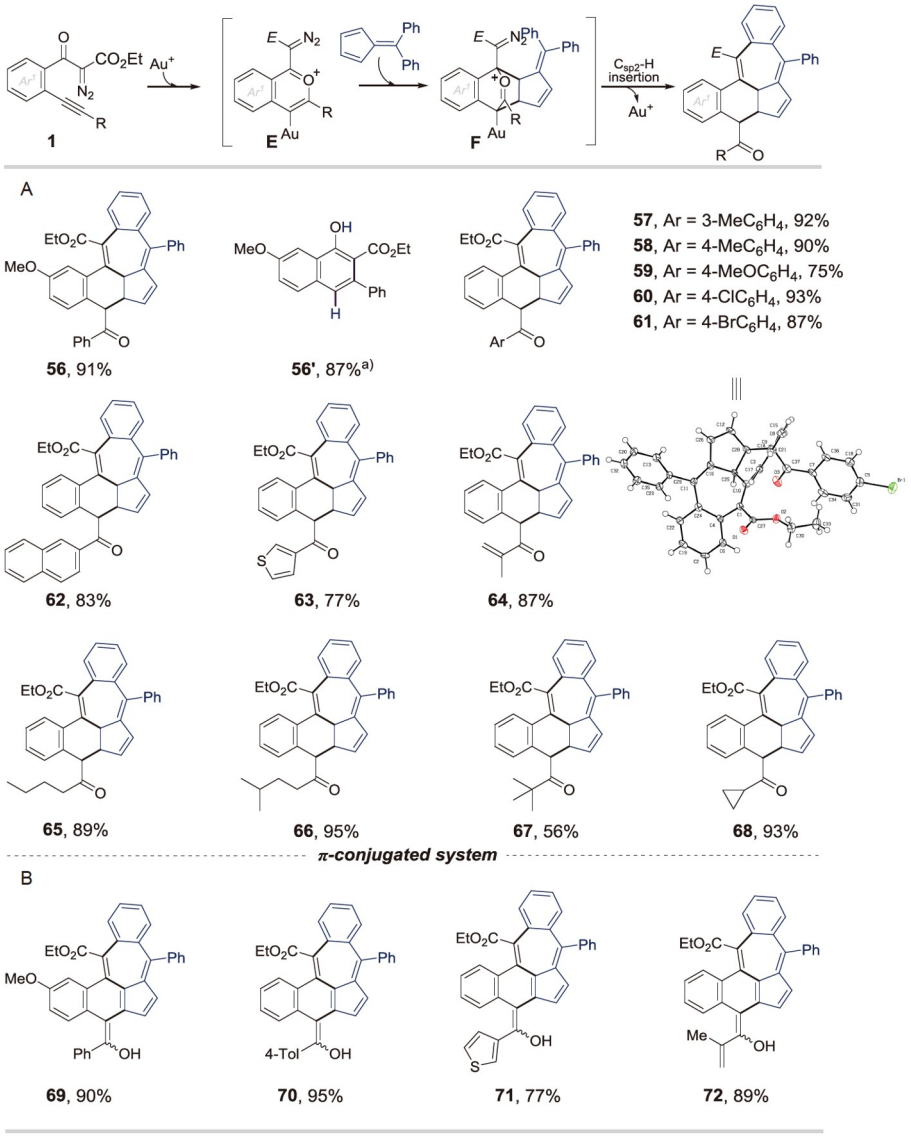
3.4 Ligand-controlled chemoselectivity

Encouraged by the fascinating domino cyclizations, we questioned whether equidistant carbonyl oxygen might act as an intramolecular nucleophile to add across the gold-activated alkyne **A**, which can provide a transient oxidopyrylium ylide with a pendant diazo group **E** (path c, Scheme 4D) [53,54]. After a series of optimization experiments, we were



Scheme 4 Proposed mechanism (color online).

pleased to trap this intermediate with diphenylfulvene to provide fused polycarbocycles (Scheme 5A), and ultimately identified the optimal reaction conditions as follows: the product **56** was afforded in 91% yield with signal diastereomer under the catalysis of PPh_3AuNTf_2 (5 mol%) at 25 °C. By contrast, it was found that an unexpected product **56'**, a hydrogen abstraction process, was isolated in 87% yield, together with the desired product **56** in only 6% yield, when JohnPhos was used as a ligand instead of PPh_3. Electron-neutral (**57**, **58**), electron-rich (**56**, **59**), and electron-poor (**60**, **61**) substrates were successfully adducted with the fulvene to afford the desired polycarbocycles in good yield with high diastereoselectivity. The structure of compound **61** was unambiguously confirmed by single crystal X-ray analysis. Naphthyl (**62**) and heteroaryl (**63**) groups were also applicable to this protocol without a noticeable yield deterioration. It is noteworthy that the cascade cyclization of substrates

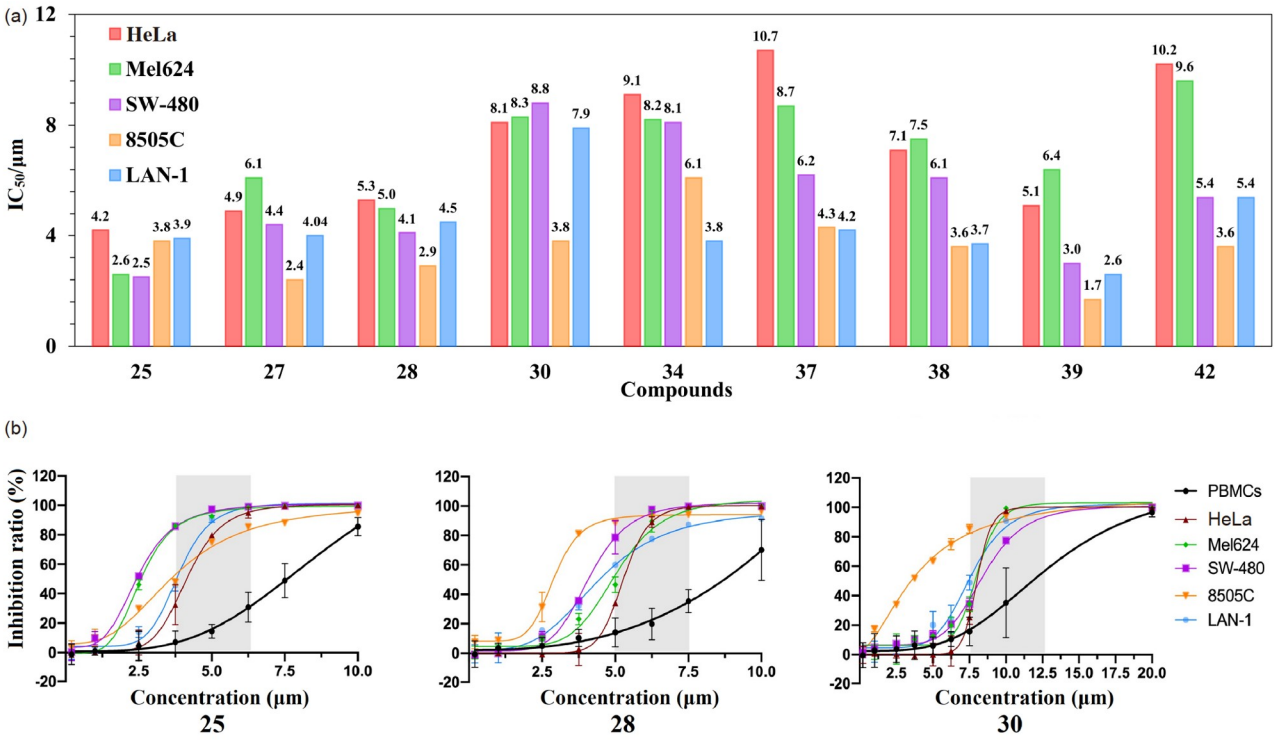


Scheme 5 Reaction condition A: a solution of PPh_3AuNTf_2 (7.40 mg,0.01 mmol) in DCE (0.5 mL), was added a solution of **1** (0.2 mmol) and the diphenylfulvene (92.12 mg, 0.4 mmol) in DCE (0.5 mL) at 25 °C, then the reaction mixture was stirred for 12.0 h under these conditions. Reaction condition B: the generated formal adducts (0.10 mmol), DDQ (25.0 mg, 0.11 mmol), and DCM (3.0 mL) were added in sequence at 25 °C, and the reaction mixture was stirred for 12.0 h under these conditions. a) JohnPhosAuSbF$_6$ was used as the catalyst instead of PPh_3AuNTf_2 (color online).

with an alkenyl (**64**), alkyl (**65**, **66**) substituents and even a strained ring (**67**) can also deliver the corresponding products in excellent yield. Furthermore, we embarked on their transformation into π-conjugated system, a class of polycycle-aromatic hydrocarbons (PAHs) containing a seven-membered ring (Scheme 5B). The oxidation occurred smoothly in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) under mild and neutral conditions and assembling representative CPHs **68**–**71** in high to excellent yields.

3.5 Bioactivity study

The effect of representative BCPs on cell viability was evaluated *via* CellTiter-Glo luminescent cell viability assay in HeLa (cervix carcinoma), Mel624 (Melanoma), SW-480 (colon adenocarcinoma), 8505C (thyroid carcinoma), and LAN-1 (neuroblastoma) human cancer cell lines (see Table S1 in Supporting Information online for details). Among these products, the compound **39** exhibits the highest anticancer potency against the five tumor cell lines (HeLa cells, IC_{50} = 5.1 μM; Mel624 cells, IC_{50} = 6.4 μM; SW-480 cells, IC_{50} = 3.0 μM; 8505C cells, IC_{50} = 1.7 μM; Lan-1 cells, IC_{50} = 2.6 μM, Scheme 6a). Furthermore, these compounds were tested against peripheral blood mononuclear cells (PBMCs) in cytotoxicity to evaluate their selectivity (see Table S2, S3 for details). Strikingly, these results indicated that compounds **25**, **28** and **30** showed better biosafety, as they killed



Scheme 6 (a) IC_{50} value of obtained compounds against human cancer cell lines. (b) Anti-tumor activity study of obtained products on the inhibition of human cancer cell lines Hela, Mel624, SW-480, 8505C, LAN-1 and PBMCs from 3 healthy donors. Gray boxes indicate the discrepancy between cancer cells and PBMCs (color online).

tumor cells with little harm to peripheral blood mononuclear cells (Scheme 6b).

4 Conclusions

In conclusion, we have developed a gold-catalyzed domino reaction with high chemoselectivity, accomplished with easily available diazoacetate-derived substrates **1** and low cost, simple starting nitriles, leading to a variety of BCPs. The enabling feature of this reaction is the use of nitrile as a nitrogen source through a programmed insertion/cation-transfer strategy. This methodology complements the common C_{sp2}-H insertion strategies for the formation of BCP skeleton in terms of reaction efficiency and structural diversity. These generated products exhibited significant and broad anticancer potency, and further bioactivity study with different human cancer cell lines is ongoing in our group. Besides, an oxidopyrylium ylide, generated *via* a gold-catalyst-controlled intramolecular carbonyl-yne cyclization, was trapped by the diphenylfulvene through an intermolecular [4+2] cycloaddition and subsequent C-H insertion to provide fused carbocycles containing a seven-membered ring.

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Conflict of interest The authors declare no conflict of interest.

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