Pt(II) and Au(III)-mediated intermolecular divergent annulations of benzofurazans and ynamides highlighted the N- to O-selectivity of tunable metal carbene intermediates. \( \text{PtCl}_2 \) with a bulky phosphite ligand resulted in the specific synthesis of six-membered quinoxaline N-oxides and successfully suppressed the in-situ deoxygenation of N-oxides. On the other hand, an unique gold(III) catalyst (2,6-di-MeO-PyrAuCl\(_3\)) led to the five-membered ring products, benzimidazoles. A broad scope of functional groups was well compatible, delivering better yields and selectivities in contrast to conventional gold(I) catalysts. The different behavior of presumed platinum(II) and gold(III) carbenes with respect to chemoselectivity was intensively examined by experiments and DFT calculations. A detailed mechanistic study, based on DFT calculations, revealed that the highly electrophilic carbocation-like gold(III) carbene triggers an oxophilic cyclization, followed by a cascade ring contraction and acyl migration. On the contrary, the Pt carbene species is less cationic, favoring the formation of the six-membered ring via N-attack.
Gold-catalyzed intermolecular formal cycloadditions have attracted enormous attention as robust, flexible tool for the construction of heterocyclic frameworks. Here, gold carbenes usually serve as the key electrophilic intermediates. Recently, the intermolecular access to α-imino gold(I) carbenes via direct nitrene transfer to alkynes has significantly expanded the synthetic possibilities of gold catalysis. However, the study of gold(III) carbene analogues that behave and react distinctly to gold(I) carbenes has been realized seldom. Very recently, in the reaction of ynamides with 7-methylanthranil, the cyclization pathway of gold carbene intermediate depends on ligands but also the oxidation state of gold. While gold(I) carbenes were facilely trapped by the oxygen atom of aldehyde, leading to the epoxidation product, presumed gold(III) carbenes favored to react with the aryl moiety of anthranil, delivering the indole framework after 1,4-acyl migration.

Gold- and platinum catalysts only occasionally have been systematically compared in chemo-divergent reactions of the same substrates, especially in the field of carbene intermediates. Ye's group speculated on the involvement of α-imino platinum carbenes in the reaction of isoxazoles with ynamides. Different from the carbophilic gold(I) carbene, furnishing a [3 + 2] annulation, the platinum(II) carbene turned out to be more oxophilic, giving rise to a [5 + 2] cyclization pattern. The significance with relevance to the synthetic flexibility and catalytic efficiency, the switching of chemo-selectivity by fine-tunable metal catalysts remains highly desirable.

In this work, Pt(II) and Au(III) catalysts are examined in order to overcome above problems. A bulky phosphite ligand affords a raw protocol to the synthesis of quinoxaline N-oxides. However, the inevitable gold(I)-catalyzed in situ deoxygenation of quinoxaline N-oxide by reacting with residual ynamide delivered a mountain of quinoxaline by-product, decreasing the feasibility of this strategy in practice. Moreover, in comparison with the distinct nucleophilicity of carbon and oxygen atom in previous work, the nucleophilicity of nitrogen and oxygen atom is much closer. Thus, the promotion of tunable N- and O-selective annulations of nitroso with metal carbenes still remains a challenge.

Fig. 1 Tunable gold and platinum carbene annulations. a Selectivity of gold(I) and gold(III) carbene. b Selectivity of platinum(II) and gold(I) carbene. c This work: Selectivity of platinum(II) and gold(III) carbene.
cooperating with PtCl₂ improve the catalytic activity of platinum but also successfully suppress the annoying in situ deoxygenation, giving outstanding yields of N-oxides. Intriguingly, taking advantage of a pyridine-based gold(III) catalyst (2,6-di-MeO-PyrAuCl₃) result in valuable 2-aminobenzimidazole derivatives. Rather than the Pt carbene, being always intercepted by the nitrogen atom, the Au(III) carbene is trapped by the terminal oxygen atom of the nitrosyl group and then undergoes further C–C bond cleavage and rearrangement. DFT calculations examine the different free energy activation barriers for the formation of six- and seven-membered ring transition states and elucidate the different free energy activation barriers for the formation of various regioselective products.

Results and discussion

Reaction optimization. Initially, the reaction of 2 equiv. benzofurazan 1a and ynamide 2a with 5 mol% Me₄tBuXPhosAuCl/AgNTf₂ in 1,2-DCE at 70 °C (Table 1, entry 1) provided a mixture of the products 3a (20%), 5a (45%) and a trace amount of 4a. The product 5a is confirmed from the in situ deoxygenation of 4a with residual ynamides48. Other gold(I) catalysts still afforded a mixture, whether we altered ligands, counter anions or temperature (entry 2–4). Simple AuCl₃ increased the yield of 3a as well as 4a (entry 4). Gold(III) with bidentate ligands just led to a trace amount of 3a (entry 5–6). A pyridine-coordinated gold(III) complex could provide higher selectivity for 3a (entry 7–8). With the take-up of 4 equiv. 1 and Pyr-2, the gold(III) complex 6 (Pyr-2AuCl₃) could give rise in 70% yield of 3a (entry 9). A similar result was obtained with Pyr-3AuCl₃ (entry 10). In contrast to gold(III) catalyst, platinum catalysis only gave quinoxaline derivatives without the benzoimidazol-3-oxide. Simple PtCl₂ had less catalytic reactivity (entry 11). The addition of ligands led to higher total yields (entry 12–14). PtCl₂ in combination with bulky phosphite ligands L₂ reacted selectively (entry 15). Ligand L₃ with large cone angle afforded the quinoxaline N-oxide 4a even in 90% yield and with specific selectivity (entry 16). This suggested that the bulky umbrella-shaped phosphite ligand might protect the platinum carbene from the intermolecular oxidation with 4a. Pt(0) catalyst could not promote this reaction (entry 17).

Substrate scope for the synthesis of benzimidazole by Au(III) catalysis. Under the optimized reaction conditions, the scope of reaction was evaluated. A range of ynamides was investigated under the gold(III) catalysis (Fig. 3). Benzyl-, methyl- and phenyl-substituted ynamides reacted smoothly. In general, ynamides bearing electron-withdrawing aryl groups gave better yields. Different functional groups, including halogen (3b, 3f), trifluoromethyl (3e) and ester (3d) groups, were tolerated. The scope of benzofurazans was also checked. Apart from methoxy group, benzofurazans bearing other electron-donating substituents, such as an amide (3n) and a methyl group (3p) were also suitable, delivering moderate to good yields. Besides of β-substitution, the α-substituted benzofurazan also performed well (3o). The solid state molecular structure of 3i was confirmed by single-crystal X-ray diffraction. Benzofurazan with electron-withdrawing group could not afford the benzoimidazole (3r), which may owe to the low nucleophilicity of oxygen atom on nitroso induced by negative inductive effect. Alkyl-substituted ynamides easily decomposed to α,β-unsaturated amides due to α-H elimination of carbene intermediate.

Substrate scope for the synthesis of quinoxaline N-oxides by Pt(II) catalysis. Then, the treatment of ynamides with diverse benzofurazans was conducted under platinum catalysis (Fig. 4). An array of substituted derivatives was explored to check the reaction with ynamides. Due to the positive conjugative effect of an electron-rich substituent on the nucleophilicity of adjacent nitrogen atom, the ynamide prefers to react with the proximal nitrogen to the β-methoxy (4a, b) or amide (4f) group, inducing good regioselectivity. The solid state molecular structure of 4b could be obtained by an X-ray single-crystal structure analysis and is shown in Fig. 4. Because of the steric effect, the reaction of α-substituted benzofurazans also showed excellent regioselectivity (4e, 4g). The non-substituted benzofurazan also worked well. Variations on the aryl moiety of the ynamide was investigated. A wide range of functional groups, including halogen (4j, 4n, 4o), thiophene (4l) and methoxy substituents (4k), were all tolerated, offering quinoxaline N-oxides in good to excellent yields. Ms, Bs and the easily removable nosyl protected ynamides also reacted smoothly (4p–r).

Further modifications of quinoxaline N-oxide. A gram-scale synthesis of 4i was completed in 80% yield by 5 mol% PtCl₂/L₃, which prove the synthetic feasibility of the Pt(II) catalytic system. By taking the advantage of N-oxides as directing groups, the further decoration could be accomplished via a direct C–H functionalization (Fig. 5). The quinoxaline N-oxide 4i was suitable for iridium-/rhodium-catalyzed selective C8-amination and iodination40,41.
Table 1 Optimization of reaction conditions.

| Entry | Catalyst | Solvent | Yield (%)b |
|-------|----------|---------|------------|
| 1     | 5 mol% Me₃BuXPhosAuCl/AgNTf₂ | 1, 2-DCE | 20%<5%45% |
| 2     | 5 mol% Me₃BuXPhosAuCl/AgSbF₆ | 1, 2-DCE | 10%13%30% |
| 3     | 5 mol% L₁AuCl³/AgSbF₆ | 1, 2-DCE | 8%<5%40% |
| 4c    | 5 mol% tBuXPhosAuCl³/AgSbF₆ | 1, 2-DCE | 12%36%18% |
| 4     | 10 mol% AuCl³ | 1, 2-DCE | 38%36%13% |
| 5     | 10 mol% PicAuCl³ | 1, 2-DCE | <5%67%10% |
| 6     | 10 mol% AuppyCl³ | 1, 2-DCE | <5%<5%0% |
| 7d    | 10 mol% PyrAuCl³ | 1, 2-DCE | 43%32%<5% |
| 8d    | 10 mol% Pyr-1AuCl³ | 1, 2-DCE | 35%30%<5% |
| 9d, f | 10 mol% Pyr-2AuCl³ | 1, 2-DCE | 70%19%<5% |
| 10d   | 10 mol% Pyr-3AuCl³ | 1, 2-DCE | 67%20%<5% |
| 11    | 10 mol% PtCl² | 1, 2-DCE | 0%8%0% |
| 12    | 10 mol% PtCl² (1 atm. CO) | Toluene | 0%37%<5% |
| 13e   | 10 mol% PtCl²/Ph(C₆F₅)₂ | Toluene | 0%21%0% |
| 14e   | 10 mol% PtCl²/L₁ | Toluene | 0%62%<5% |
| 15f   | 10 mol% PtCl²/L₂ | Toluene | 0%84%0% |
| 16f   | 10 mol% PtCl²/L₃ | Toluene | 0%90%0% |
| 17f   | 10 mol% Pt(PPh₃)₃ | Toluene | 0%0%0% |

Ad = adamantyl, 1, 2-DCE = 1, 2-dichloroethane, NTf₂ = bis(trifluoromethanesulfonyl)imide.

bIsolated yield.

cAt 25 °C.

d1a (0.4 mmol, 4 equiv.) and 2a (0.1 mmol) in 2 ml solvent at 70 °C.

The best condition.
Mechanism studies. For gold(III)-catalyzed the formation of benzimidazole, an intermolecular control experiment did not show intermolecular cross-over (Fig. 6a), which suggests an intramolecular acyl migration process. Notably, in contrast with the both isomers of N-oxide were observed, only 1-acyl substituted benzimidazole was produced. It may indicate same kind of acyl migration precursor was produced whether the proximal or distal nitrogen to the methoxy group of 1a attack the C–C triple bond initially. The acyl migration always prefers to the proximal N atom due to the higher nucleophilicity. The 18O-labeling experiment showed that the O atom of acyl group owes to the substrate rather than ambient H218O (Fig. 6b). Moreover, the quinoxaline N-oxide 4a could not be convert to benzimidazole under the standard condition (Fig. 6c).

A plausible reaction mechanism is depicted in Fig. 7. The α-imino gold or platinum carbene species C/C′ is generated via initial nucleophilic attack of benzo[f]uran 1a to the metal-ligated

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**Fig. 3 Scope with respect to the Au(III)-catalyzed tandem annulations.** Reaction conditions: 1 (0.4 mmol), 2 (0.1 mmol), 10 mol% Au(III) catalyst 6 in 4 ml 1,2-dichloroethane at 70 °C for 12 h. Isolated yields were listed.
ynamide (A), followed by N–O bond cleavage. While the Pt(II) carbene prefers N-attack, leading to the six-membered ring D, the gold(III) carbene favors O-attack, furnishing the seven-membered ring intermediate E, which then releases intermediate F after ligand exchange. Following the electrocyclization and the second N–O bond cleavage, a ring contraction reaction gives the five-membered ring intermediate I. After intramolecular 1,2-acyl migration, the product 3a is afforded eventually.

Computational calculations. In order to gain further insights into the reaction mechanism and to clarify the different annihilation pathways of gold(III) and platinum(II) carbene intermediates, density functional theory (DFT) calculations were carried out (DFT calculations were performed by Gaussian program under the level of M06/6-311++G**/SDD-SMD(CH2Cl2)// B3LYP(D3BJ)/6-31G*/SDD. The CM5 atomic partial charges were calculated by Multiwfn program under the M06/6-311+....
**G/SDD-SMD(CH2Cl2)** level. See Supplementary Information for computational details. Since the mechanism for the generation of Au/Pt carbene is similar to those of previous analogous reports35,41, here we do not discuss it but give the corresponding energetic details in Supplementary Information (Figs. S2, S3).

Starting from metal-carbene species (C/C’), both annulation pathways are compared for Au(III) and Pt(II) system respectively, and the corresponding calculated free energy profiles are shown below. For the Pt(II) system (Fig. 8), the formation of six-membered ring occurs facilely via TS1, crossing a free energy activation barrier of 6.0 kcal/mol. The resulting complex D is lower than C by 22.7 kcal/mol, in which the product 4a is already formed and can be easily released by ligand exchange. However, producing a seven-membered ring by O-attack is unfavorable. Although the activation barrier of 12.0 kcal/mol (TS1’ relative to C) is accessible, the resulting complex D’ is quite unstable, which is higher than C by 10.4 kcal/mol. This is also supported by the weak C–O bond (the resulted C–O bond length is 1.587 Å, which is obviously longer than normal C–O bonds, see Fig. S4 in Supplementary Information). Thus, the annulation en route to the seven-membered ring is reversible and is highly inclining towards C, whereas the six-membered ring annulation pathway is both kinetically and thermodynamically feasible. The calculated results well consist with the experimental observation that the Pt(II) catalyst shows specific selectivity for product 4a.

On the contrary, the seven-membered ring cyclization process is preferable in the case of gold(III) carbene (Fig. 9). The nucleophilic attack of nitrosyl oxygen to the carbene carbon crosses a free energy activation barrier of 15.0 kcal/mol via TS2, leading to the seven-membered ring complex E with energy decreased by 11.4 kcal/mol. Alternatively, the attack of nitrosyl nitrogen atom to the carbene has to overcome a free energy activation barrier of 22.4 kcal/mol (TS2’ relative to C’). Despite kinetic disfavor, we could not thoroughly exclude this route. Once...
Overall, the annulation via O-attack to form E is still kinetically more favorable as the major pathway. After ligand exchange to G, which is prone to N–O bond cleavage with an activation energy of only 2.2 kcal/mol (TS4 relative to G). Next, a ring contraction takes place, resulting in the five-membered ring intermediate I with energy reduced by 33.6 kcal/mol (from H to I). In agreement with experimental result, the 1,2-acyl migration prefers the nitrogen proximal to methoxy group under thermodynamic control. Overall, the final benzimidazole product 3a is thermodynamically more stable than the six-membered ring by-product 4a by 43.6 kcal/mol. The calculation on the other gold(III) catalyst, PicAuCl2, was also carried out in contrary to above Au system, which further disclosed the annulation selectivity relied on the electronic character of gold carbene (see Fig. S6).

The optimized geometries and atomic partial charges for Au(III) and Pt(II) carbene intermediates are shown in Fig. 9. The Au(III) carbene is cationic species because of alkyn coordination instead of coordination to a Cl− ion. In addition, the pyridine is a weaker electron-donating ligand than the phosphite L3. Therefore, the Au(III) center is much more electron deficient than the Pt(II) core, which is supported by the calculated partial atomic charges (+0.497 vs. +0.198). As a result, the π-back donation from Au(III) center to the carbene carbon is weaker than that from platinum to the carbene carbon, leading to the carbocation-like gold carbene C'. This is well supported by comparing the metal-carbene bond lengths and atomic charges of carbene atoms. The Au–C bond length of C' is 2.056 Å, which is apparently longer than those of most prior Au carbene species,26 while the Pt–C bond length of C is 2.000 Å, which is obviously shorter than the Au–C bond, indicating stronger π-back donation. The calculated partial atomic charges of the carbene carbon also show that the Au(III) carbene is obviously more cationic than Pt(II) carbene (+0.037 vs. +0.018). On the basis of the above results, the discrepancy between the current Au(III) and Pt(II) systems should be mainly attributed to the different electronic characteristics of the metal-carbene species. The Au(III) carbene favors the O-attack through a seven-membered ring owing to the carbocation-like trait (because the oxygen atom is more electron rich than the nitrogen atom, −0.176 vs. −0.017). By taking advantage of electron-rich aryl group to reduce the cationic character of gold carbene, only product 4a was observed (see Supplementary Information). It supported that the high electrophilicity is crucial to the formation of seven-membered ring intermediate. In contrast, the Pt(II) carbene features carbene-like character and the less cationic carbene carbon is not effective to accept electrons from the strong electronegative O-atom (supported by the unfavorable O-attack and the weak resulted C–O bond, 1.587 Å, vide supra), but prefers the N-attack to form the more stable six-membered ring. We further explored the size effect of formed ring on the selectivity of annulation in theory. The calculations indicated that with extending the ring size, the electronic effect is not predominant. The formation of smaller ring is favorable (Figs. S7, S8). Although this was out of the scope of the reactions, it suggested the annulation selectivity may not only depend on electronic effect.

In conclusion, the difference between gold and platinum catalysts was studied in detail. The platinum catalyst shows higher chemo-selectivity for the synthesis of quinoxaline N-oxides than...
gold(I) catalysts. In contrast to Pt(II) catalysis, the gold(III) complex 6 enables the selective synthesis of benzimidazoles via tandem annulation/ ring contraction/ acyl migration. DFT calculations support the experimentally observed selectivity for gold(III) and Pt(II) systems well. Analysis of geometric and electronic structures of key metal-carbene intermediates reveals that the electronic effect is the main reason for the annulation selectivity. The Au(III) carbene shows carboxation-like character, favoring O-attack, while the Pt(II) carbene prefers forming a six-membered ring via N-attack, which rationalizes the divergent annulation routes. These insight in transition metal catalysis can help to on purpose switch to certain reaction channels of metal-carbene intermediates in future methodology development.

**Methods**

**Representative procedure for Au(III)-catalyzed tandem annulation.** A round bottom flask equipped with a magnetic stirrer bar was added 10 mol% 2,6-dimethoxypyrrAuCl₃ (4.4 mg), 1a (0.4 mmol), 2a (0.1 mmol) and 1,2-DCE (4 ml). The reaction was heated at 70 °C for 12 h. After cooling to room temperature, the solvent was reduced in vacuo, and the residue was purified by column chromatography (SiO₂, hexanes/EtOAc = 10/1) to provide the title compound 3a as a colorless solid.

**Representative procedure for Pt(II)-catalyzed formal [4 + 2] annulation.** A round bottom flask equipped with a magnetic stirrer bar was added 10 mol% PtCl₂ (2.6 mg), 10 mol% L₃ (9.2 mg), 1a (0.2 mmol), 2a (0.1 mmol) and toluene (1 ml). The reaction was heated at 70 °C for 12 h. After cooling to room temperature, the solvent was reduced in vacuo, and the residue was purified by column chromatography (SiO₂, hexanes/EtOAc = 10/1 – 5/1) to provide the title compound 4a as a colorless solid.

**Data availability**

Additional data generated in this study have been available in the Supplementary Information file. For full characterization data of new compounds and experimental details, see Supplementary Methods, Notes and Figures in Supplementary Information file. For the energies and Cartesian coordinates, see Supplementary Data file. The X-ray crystallographic coordinates for structures 3i and 4b reported in this study have been available in the Supplementary Information.
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Author contributions

H.J. and A.S.K.H. conceived and designed the study; H.J. performed the experiments; H.J., M.R. and F.R. analyzed the experimental data; W.T. and S.Q. conducted the computational calculations; H.J., A.S.K.H. and S.Q. wrote the paper. J.Z. and X.S. checked the potential bioactivity and polished the words. All the authors contributed to scientific discussion.

Competing interests

The authors declare no competing interests.

Additional information

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