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Interrupting the [Au]-Catalyzed Nitroalkyne Cycloisomerization: Trapping the Putative α-Oxo Gold Carbene with Benzo[c]isoxazole

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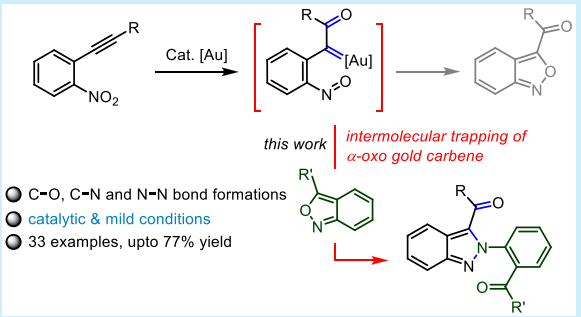
ABSTRACT: The [Au]-catalyzed nitroalkyne cycloisomerization of 2-alkynylnitrobenzenes leading to anthranils has been interrupted by possible trapping of the postulated intermediate α-oxo gold carbene with an external nucleophile such as benzo[c]isoxazole (anthranil). At the outset, this provides a simple synthesis of highly functionalized 3-acyl-(2-formylphenyl)-2*H*-indazoles with the sequential C−O, C−N, and N−N bond formations. This provides indirect support for the existence of α-oxo gold carbenes in the [Au]-catalyzed internal redox processes of nitroalkynes.



The 2*H*-indazole scaffold is one of the prominent pharmacophores well explored in medicinal chemistry with a good number of approved medicines spanning across a broad range of therapeutic applications.[1,2] The "Cadogan and Davis−Beirut reactions" that forge a 2*H*-indazole heterocyclic core via an intramolecular N−N bond formation are the two important reactions applied in the synthesis of this heterocyclic core.[3,4] In both the reactions, initially a nitro group undergoes either a reduction or an internal redox process leading to a reactive nitroso intermediate. In the case of the Davis−Beirut reaction, the intramolecular nucleophilic attack and/or a 5-centered 6π-electrocyclization of the nitroso intermediate results in an indazole *N*-oxide that undergoes either an internal redox reaction or deoxygenation. On the other hand, in the classical mechanism proposed for the Cadogan indazole synthesis, the nitroso intermediate further reduces to a nitrene that adds to the imine, though the possibility of the former process has also been established.[5] Despite their widespread utility, the harsh conditions/reagents employed for generating the reactive nitroso intermediates warrants the availability of milder reagents/conditions that are amicable for sensitive functional/protecting groups.

In this context, we speculated on the possibility of trapping the nitroso stabilized α-oxo gold carbene intermediates that are proposed in the catalytic cyclization of *o*-alkynylnitrobenzenes with *N*-centered nucleophiles.[6−9] The cycloisomerization of *o*-alkynylnitrobenzenes (trivially known as nitrotolans) leading to isatogens is one of the earliest redox neutral reactions, documented as early as in 1881 by Bayer during the course of his classic research on indigo.[6] In 2003, a seminal contribution by Yamamoto's group revealed the possibility of affecting this nitroalkyne cycloisomerization under gold catalysis.[7] Importantly, it has been revealed by Yamamoto's group that, depending upon the pendant substituent on the alkyne, the nitroalkyne cycloisomerization proceeds in complementary paths leading to either isatogen (when the substituent is aryl) and/or isomeric anthranil (exclusively with alky substituent). By isolating a nitroso-stabilized α-oxo alkyl iridium intermediate, Crabtree's group revealed that the overall process is a metal-mediated internal redox process leading to an α-oxo iridium carbene intermediate.[8] A similar mechanism even in gold(I\III)-catalyzed nitroalkyne internal redox processes with complementary regioselectivity during the initial oxygen transfer has been extended by Liu and our groups.[9]

These nitroso stabilized α-oxo gold carbene intermediates provide a handle for the carbene for exchange with N-centered nucleophiles[10] and also the reactive nitroso group in the proximity, for the subsequent N−N bond formation.[11] However, in this event, the carbene exchange process has to compete with the original intramolecular cyclization of the α-oxo gold carbene intermediate that leads to anthranil. As shown in Scheme 1, in the presence of anthranil **4** that is known to exchange with the goldcarbenes,[12] the reaction is expected to provide an imine that should undergo Davis-Beirut cyclization leading to the indazole **5** (or its *N*-oxide if it is sufficiently stable[13]) with simultaneous C−N and N−N bond formations.

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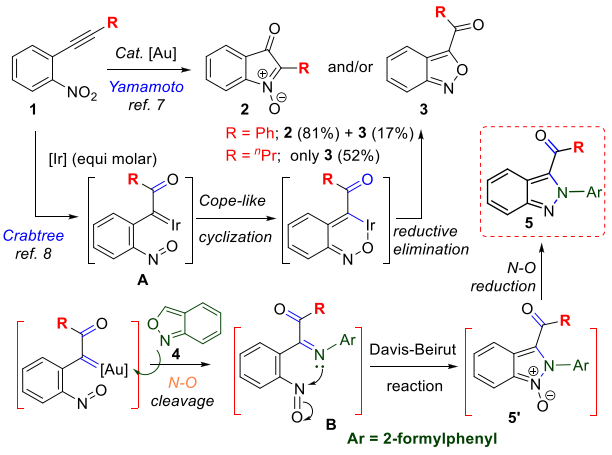
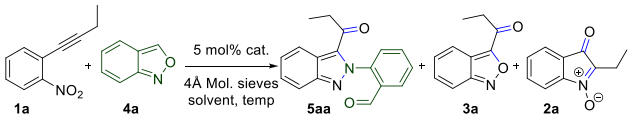
Scheme 1. Nitroalkyne Cycloisomerization and Associated Nitroso Stabilized α-Oxo Metal Carbene Intermediate and Possible Interruption with an External *N*-Based Nucleophile Leading to Indazoles



To examine these hypothetical possibilities, initially, employing 1-(but-1-yn-1-yl)-2-nitrobenzene (**1a**) as a substrate, we examined its cycloisomerization in the presence of anthranil **4a** following reported conditions using $AuBr_3$ (in toluene) and $Pd(CH_3CN)_2Cl_2$ (in acetonitrile) complexes. As shown in Table 1 (entries 1 and 2), with the palladium complex, isatogen **2a** was obtained exclusively.[14] On the other hand, with the $AuBr_3$,[7] the corresponding anthranil **3a** was mainly obtained with trace amounts of a new product, with the expected mass corresponding to the desired indazole **5aa**.

Table 1. Optimization of the Reaction Conditions[a]



Entry	Catalyst	Solvent	Yield (%) 5aa[b]	Yield (%) 2a or 3a[b]
1	$AuBr_3$	PhMe	trace	64 (**3a**)
2	$Pd(CH_3CN)_2Cl_2$	MeCN	–	69 (**2a**)
3	$AuCl_3$	$ClCH_2CH_2Cl$	–	trace (**3a**)
4	$AuCl_3$	PhMe	54	12 (**3a**)
5	$AuCl_3$	MeCN	–	–
6	$AuCl_3$	1,4-Dioxane	–	–
7	$AuCl_3$	$PhCF_3$	44	13 (**3a**)
8	$AuCl_3$	PhCl	49	10 (**3a**)
9	$PicAuCl_2$	PhMe	42	10 (**3a**)
10	AuCl	PhMe	35	24 (**3a**)
11	$PPh_3AuCl/AgSbF_6$	PhMe	26	38 (**3a**)
12	IPrAuCl/AgOTf	PhMe	20	46 (**3a**)
13	$(ArO)_3PAuCl/AgNTf_2$	PhMe	27	42 (**3a**)
14[c]	$AuCl_3$	PhMe	57	10 (**3a**)
15[d]	**$AuCl_3$**	**PhMe**	**69**	**trace (3a)**

[a]In general, the reactions were carried out with 0.2 mmol of **1a** and 0.22 mmol of **4a** in 2 mL of solvent and 5 mol % of catalyst at rt with a reaction time of 3−4 h. [b]Isolated yield. [c]Reaction was carried at 80 °C. [d]Slow addition of **1a** through syringe pump at rt for 4 h.

Next, we examined the reactions with $AuCl_3$, which had shown superior reactivity over $AuBr_3$ in nitroalkyne cycloisomerizations.[15] However, in the prescribed 1,2-dichloroethane solvent, we got a poor conversion, resulting mainly with the formation of the anthranil **3a** in small amounts. Gratifyingly, when we switched the solvent to toluene, the uncharacterized product **5aa** that was encountered with $AuBr_3$ was obtained in 54% yield along with the anthranil **3a** (12%). Gratifyingly, the spectral data and single crystal X-ray crystal structure analysis of compound **5aa** revealed that it was the desired indazole and, importantly, it proved the point that the intermolecular trapping of gold carbene that results during the nitroalkyne cycloisomerization was possible. With these results, we next proceeded further to improve the yield of the reaction. As shown in Table 1, our initial attempts with changing the solvent were not encouraging (entries 5−8). This prompted us to explore the other gold(III) and cationic gold(I)-complexes in this pursuit. As shown, in Table 1 (entry 9), with dichloro(2-pyridinecarboxylato)gold(III) ($PicAuCl_2$, entry 9) the requisite indazole was obtained as a major product in moderate yields. Similarly, with AuCl and with other cationic gold(I)-complexes, the results are not encouraging (entries 10−13). In the majority of the cases, the cycloisomerization leading to anthranil **3a** was the major event, along with the formation of the requisite **5aa**. Gratifyingly, with $AuCl_3$, in toluene, when the reaction was heated to 80 °C, the yield of **5aa** was improved to 57% and the anthranil **3a** was also obtained in 10% yield (entry 14). Finally, when the reaction was carried out by slow addition of **1a** to a solution of **2a** and $AuCl_3$ catalyst at rt, the yield of **5aa** was improved to 69%, and the formation of the cycloisomerization product **3a** was also minimized (entry 15).

As illustrated in Scheme 2, a wide range of substituted nitroalkynes have been employed to examine the scope of the reaction and to understand how the substituents influence the outcome. Initially, we employed the substrates having different pendant substituents on the alkyne unit. As shown, changing the length of the side chain did not alter the reaction outcome, and it was also found that the protecting groups such as O-acetyl and O-TBS placed on this alkyl chain were intact. Interestingly, with the cyclopropyl substituted alkyne, the intramolecular cyclization was successfully completed and resulted in the requisite indazole **5ha** as a minor product and the corresponding anthranil **4h** as the major product. For the substrates **5ia**−**5la** having different substituents placed para to the alkyne unit, the outcome of the reaction was influenced. For example, when a carboxylate as well as cyano was present, the yield was 72% (**5ka**) and 77% (**5la**) revealing that the presence of an electron-withdrawing group (EWG) at this position had a stabilizing effect on the intermediate gold carbene. In contrast, when the substituent was fluorine, the yield was reduced to 47% (**5ia**), which indicates that σ-acceptors at this position are not compatible. When a methyl group **5ja** was present at this position, the yield was only 56%. It is noteworthy that the good yield was retained even when the reaction was carried out on 500 mg scale (**5aa**, 65% yield).

Next, we varied the substituents on the anthranil ring. When halogen-substituted anthranils were employed as the substrates, the reactions in general resulted in the corresponding indazoles **5ab**−**5ad** in low to moderate yields depending upon the position of the halogen atom. The yields are poor when the halogen is placed para to the nitrogen. On the other hand, with 5-methyl and 5-carboxymethyl anthranils **4e** and **4f** respectively, the corresponding indazoles were obtained in good to moderate yields. Interestingly, when a methoxy group is placed on the anthranil ring, there was no interception of the original

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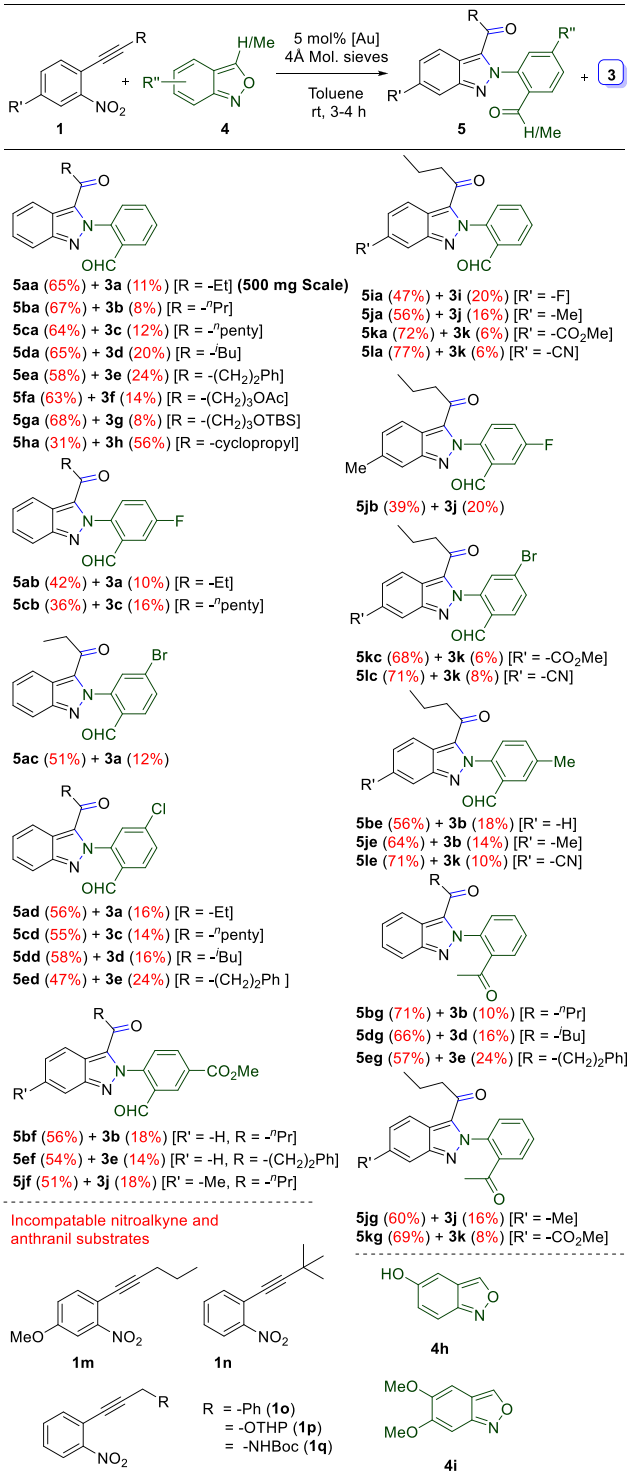
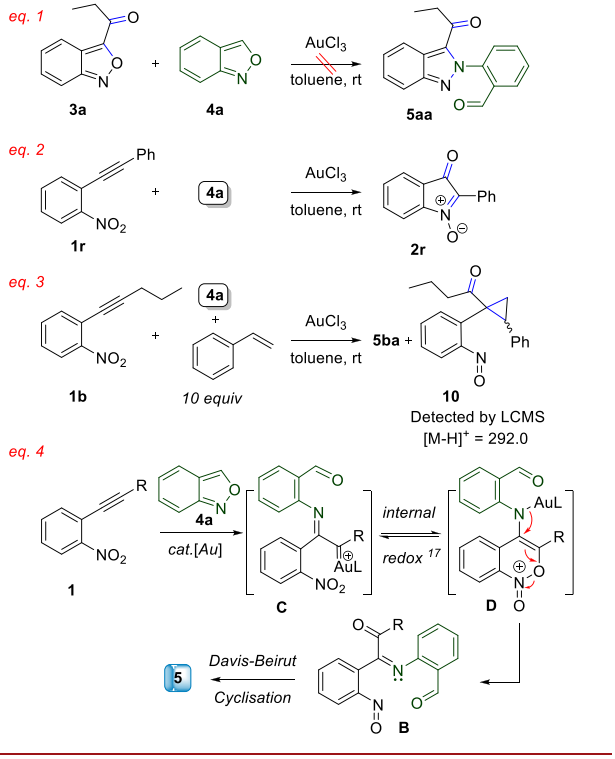
Scheme 2. Reaction Scope and Limitations



internal nitroalkyne redox process and the corresponding anthranil was obtained exclusively.[9a] Next, we examined the compatibility of a C3-methyl substituted anthranil **4g** employing different nitroalkynes. The results are encouraging, and the corresponding 2*H*-indazole containing an *o*-acyl group on the pendant aryl ring were obtained in moderate to good yields (**5bg**, **5cg**, **5dg**, **5jg**, and **5 kg**). In this case also, the nitroalkyne **1k** having the carboxylate group gave the best results. On the contrary, the nitroalkyne or the anthranil having methoxy or hydroxyl substitutes on the aryl ring were found to be incompatible and the reactions employing either of these substrates gave mainly the corresponding anthranil derivatives. In addition, when the alkyne end carries a bulky group or an alkyl chain having EWGs, the intramolecular cyclization is facile over the intermolecular carbene exchange, indicating that both steric and electronic factors play important roles. To show the utility, the selective homologation of the aldehyde group present in these products has been carried out employing the stable Wittig ylides (see Scheme S1, Supporting Information). The reactions are highly selective and proceed smoothly at rt to provide the corresponding *E*-olefins in excellent yields.

To probe whether this overall process involves the anthranil **3a** as an intermediate, control experiments have been carried out by employing **3a** as a substrate under the optimized conditions in the presence of **4a**. Even after prolonged reaction times, both **4a** and **3a** were intact, thus revealing that the internal redox cascade process was interrupted prior to the formation of **3a** and presumably by the carbene transfer from the intermediate α-oxo gold carbene to the nitrogen of anthranil **4a**. Next, the concern is about the possible intermolecular functionalization of alkyne with the anthranil **4** leading to an α-imino gold carbene[16] followed by oxygen transfer from the nitro group[17] (Scheme 3, eq 4) and finally

Scheme 3. Control Experiments to Support the Involvement of the α-Oxo Gold Carbene Intermediate (Eqs 1−3) and Alternative Possibility for the Formation of Indazole (Eq 4)



the N−N bond formation. As a control, the phenyl substituted nitroalkyne **1r**, when treated with **4a** under the optimized conditions (Scheme 3, eq 2), gave exclusively isatogen **2r** via 5-exo-dig cyclization. This indicated that the isomeric α-oxo gold carbene involved in this process prefers the intramolecular cyclization over the intermolecular carbene interception and importantly that the possibility of anthranil addition to the alkyne and subsequent α-imino gold carbene formation is not

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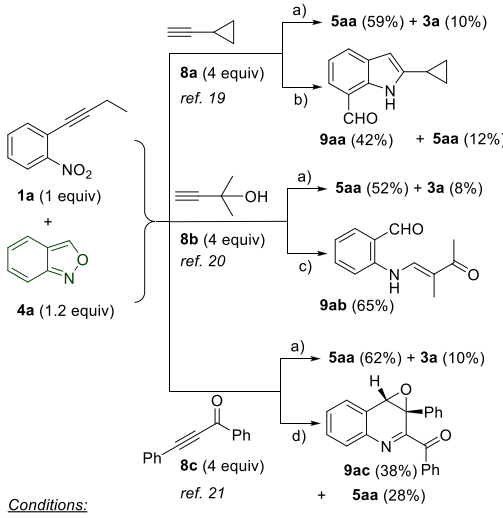
operational. An additional control experiment was conducted by carrying the reaction in the presence of excess styrene (known/used to trap the gold carbenes).[18] Although the expected cyclopropane product could not be isolated in reasonable amounts to characterize, the LCMS analysis showed its presence in the crude reaction mixture (Scheme 3, eq 3).

Further, competition experiments were done employing the alkynes **8a**–**8c**, which are known to be functionalized with the anthranil **4a** (leading to an α-imino gold carbene intermediate) under current conditions and also under the conditions\gold-complex reported for the same transformation.[19−21] As shown in Scheme 4, the reaction of **1a** and **4a** in the presence of

Scheme 4. Competition Experiments to Support the Involvement of the α-Oxo Gold Carbene Intermediate



ethynyl cyclopropane (**8a**) under the prescribed conditions and Au[I]-catalyst/Ag-additive catalysts resulted in a mixture of the reported product **9aa** (42%) and indazole **5aa** (12%).[19] When the same reaction was carried out under the current conditions, it provided mainly the indazole **5aa** along with the anthranil **3a**. Similar results were obtained in the competition experiments employing alkyne **8b** or **8c**.[20,21] In general, with the reported complexes, the reaction between the anthranil **4a** and the alkyne **8** is facile, and with $AuCl_3$, the nitroalkyne redox process seems to be operating exclusively. Thus, these competition experiments clearly indicate that, unlike with the other complexes, it appears that $AuCl_3$ selectively activates the nitroalkyne **1a** over the competing terminal alkyne, and this provides indirect evidence for an internal oxygen transfer leading to an α-oxo gold carbene intermediate, and subsequent carbene transfer to the nitrogen present in the anthranil **4**.

In summary, a novel synthesis of functionalized 2*H*-indazoles is described, employing easily accessible *o*-nitroalkynes and anthranils under gold catalysis. At the outset, the current results provide indirect support for the proposed nitroso-stabilized α-oxo gold carbene intermediate in the nitroalkyne cycloisomerization leading to anthranil. In addition, this also provides a mild and catalytic approach for the availability of the key nitroso intermediates required in the Davis–Beirut cyclization with, importantly, one of the nitrogens having been incorporated externally.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00539.

Characterization data ^{1}H, ^{13}C NMR/DEPT and HRMS spectra of all new compounds (PDF)

FAIR data, including the primary NMR FID files, for compounds **1a**, **1d**–**1f**, **1i**–**1m**, **2a**, **3a**, **3d**–**3g**, **3i**–**3m**, **5aa**–**5la**; **5ab**, **5cb**, **5jb**, **5kc**, **5lc**, **5ad**, **5cd**–**5ed**, **5be**, **5je**, **5le**, **5bf**, **5ef**, **5jf**, **5bg**, **5dg**, **5eg**, **5jg**, **5kg**, **7a**–**7c**, **8a**–**8c** (ZIP)

Accession Codes

CCDC 2050267 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Denya, I.; Malan, S.; Joubert, J. Indazole derivatives and their therapeutic applications: a patent review (2013–2017). *Expert Opin. Ther. Pat.* **2018**, *28*, 441–453. (b) Zhang, S. G.; Liang, C. G.; Zhang, W. H. Recent Advances in Indazole-Containing Derivatives: Synthesis and Biological Perspectives. *Molecules* **2018**, *23*, 2783. (c) Gaikwad, D. D.; Chapolikar, A. D.; Devkate, C. G.; Warad, K. D.; Tayade, A. P.; Pawar, R. P.; Domb, A. J. Synthesis of indazole motifs and their medicinal importance: An overview. *Eur. J. Med. Chem.* **2015**, *90*, 707–731.

(2) (a) Janardhanan, J. C.; Bhaskaran, R. P.; Praveen, V. K.; Manoj, N.; Babu, B. P. Recent Advances in the Transition Metal Catalyzed

Synthesis of Indazoles. *Asian J. Org. Chem.* **2020**, *9*, 1410−1431. (b) Hassan, A. A.; Aly, A. A.; Tawfeek, H. N. *Indazoles: Synthesis and Bond-Forming Heterocyclization in Advances in Heterocyclic Chemistry*, Vol. *125*,; Scriven, E. F. V., Ramsden, C. A., Eds.; Academic Press: Cambridge, 2018; pp 235−300. (c) Schmidt, A.; Beutler, A.; Snovydovych, B. Recent advances in the chemistry of indazoles. *Eur. J. Org. Chem.* **2008**, *2008*, 4073−4095.

(3) Kaur, M.; Kumar, R. C-N and N-N bond formation *via* Reductive Cyclization: Progress in Cadogan/Cadogan-Sundberg Reaction. *ChemistrySelect* **2018**, *3*, 5330−5340.

(4) Zhu, J. S.; Haddadin, M. J.; Kurth, M. J. Davis−Beirut Reaction: Diverse Chemistries of Highly Reactive Nitroso Intermediates in Heterocycle Synthesis. *Acc. Chem. Res.* **2019**, *52*, 2256−2265.

(5) Zhu, J. S.; Li, C. J.; Tsui, K. Y.; Kraemer, N.; Son, J.-H.; Haddadin, M. J.; Tantillo, D. J.; Kurth, M. J. Accessing Multiple Classes of 2H-Indazoles: Mechanistic Implications for the Cadogan and Davis−Beirut Reactions. *J. Am. Chem. Soc.* **2019**, *141*, 6247−6253.

(6) Baeyer, A. Uber dieVerbindungen der Indigogruppe. *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 1741−1746.

(7) Asao, N.; Sato, K.; Yamamoto, Y. $AuBr_3$-catalyzed cyclization of *o*-(alkynyl)nitrobenzenes. Efficient synthesis of isatogens and anthranils. *Tetrahedron Lett.* **2003**, *44*, 5675−5677.

(8) Li, X.; Incarvito, C. D.; Vogel, T.; Crabtree, R. H. Intramolecular Oxygen Transfer from Nitro Groups to C≡C Bonds Mediated by Iridium Hydrides. *Organometallics* **2005**, *24*, 3066−3073.

(9) (a) Jadhav, A. M.; Bhunia, S.; Liao, H.-Y.; Liu, R.-S. Gold-Catalyzed Stereoselective Synthesis of Azacyclic Compounds through a Redox/[2 + 2 + 1] Cycloaddition Cascade of Nitroalkyne Substrates. *J. Am. Chem. Soc.* **2011**, *133*, 1769−1771. (b) Patel, P.; Ramana, C. V. Divergent Pd(II) and Au(III) mediated nitroalkynol cycloisomerizations. *Org. Biomol. Chem.* **2011**, *9*, 7327−7334.

(10) For selected reviews on α-oxo gold carbenes: (a) Yeom, H.; Shin, S. Catalytic Access to α-Oxo Gold Carbenes by N-O Bond Oxidants. *Acc. Chem. Res.* **2014**, *47*, 966−977. (b) Zhang, L. A Non-Diazo Approach to α-Oxo Gold Carbenes *via* Gold-Catalyzed Alkyne Oxidation. *Acc. Chem. Res.* **2014**, *47*, 877−888. (c) Huple, D.; Ghorpade, S.; Liu, R. S. Recent Advances in Gold-Catalyzed N- and O-Functionalizations of Alkynes with Nitrones, Nitroso, Nitro and Nitroxy Species. *Adv. Synth. Catal.* **2016**, *358*, 1348−1367. (d) Zheng, Z.; Wang, Z.; Wang, Y.; Zhang, L. Au-Catalysed oxidative cyclisation. *Chem. Soc. Rev.* **2016**, *45*, 4448−4458. (e) Ye, L. W.; Zhu, X.; Sahani, R.; Xu, Y.; Qian, P. C.; Liu, R. S. Nitrene Transfer and Carbene Transfer in Gold Catalysis. *Chem. Rev.* **2020**, DOI: 10.1021/acs.chemrev.0c00348.

(11) For selected papers on the trapping of α-Oxo Gold Carbenes with N-centered nucleophiles, see: (a) Yeom, H.; Lee, J.; Shin, S. Gold-Catalyzed Waste-Free Generation and Reaction of Azomethine Ylides: Internal Redox/Dipolar Cycloaddition Cascade. *Angew. Chem., Int. Ed.* **2008**, *47*, 7040−7043. (b) Yeom, H. S.; Lee, Y.; Jeong, J.; So, E.; Hwang, S.; Lee, J. E.; Lee, S. S.; Shin, S. Stereoselective One-Pot Synthesis of 1-Aminoindanes and 5,6-Fused Azacycles Using a Gold-Catalyzed Redox-Pinacol-Mannich-Michael Cascade. *Angew. Chem., Int. Ed.* **2010**, *49*, 1611−1614. (c) Xiao, J.; Li, X. Gold α-Oxo Carbenoids in Catalysis: Catalytic Oxygen-Atom Transfer to Alkynes. *Angew. Chem., Int. Ed.* **2011**, *50*, 7226−7236. (d) He, W.; Li, C.; Zhang, L. An Efficient [2 + 2 + 1] Synthesis of 2,5-Disubstituted Oxazoles via Gold-Catalyzed Intermolecular Alkyne Oxidation. *J. Am. Chem. Soc.* **2011**, *133*, 8482−8485. (e) Xiao, Y.; Zhang, L. Synthesis of Bicyclic Imidazoles via [2 + 3] Cycloaddition between Nitriles and Regioselectively Generated α-Imino Gold Carbene Intermediates. *Org. Lett.* **2012**, *14*, 4662−4665. (f) Li, J.; Ji, K.; Zheng, R.; Nelson, J.; Zhang, L. Expanding the Horizon of Intermolecular Trapping of In-Situ Generated α-Oxo Gold Carbenes: Efficient Oxidative Union of Allylic Sulfides and Terminal Alkynes *via* C-C Bond Formation. *Chem. Commun.* **2014**, *50*, 4130−4133. (g) Mokar, B. D.; Huple, D. B.; Liu, R. S. Gold-catalyzed Intermolecular Oxidations of 2-Ketonyl-1-ethynyl Benzenes with *N*-Hydoxyanilines to Yield 2-Amino-indenones via Gold Carbene Intermediates. *Angew. Chem., Int. Ed.* **2016**, *55*, 11892−11896.

(12) (a) Mokar, B. D.; Jadhav, P. D.; Pandit, Y. B.; Liu, R. S. Gold-catalyzed (4 + 2)-annulations between α-alkyl alkenyl gold carbenes and benzisoxazoles with reactive alkyl groups. *Chem. Sci.* **2018**, *9*, 4488−4492. (b) Skaria, M.; Sharma, P.; Liu, R. S. Gold(I)-Catalyzed 1,3-Carbofunctionalizations of Anthranils with Vinyl Propargyl Esters To Yield 1,3-Dihydrobenzo[*c*]-isoxazoles. *Org. Lett.* **2019**, *21*, 2876−2879. (c) Kumar, R.; Singh, R.; Skaria, M.; Chen, L.; Cheng, M. J.; Liu, R. S. Gold-catalyzed (4 + 3)-annulations of 2-alkenyl-1-alkynylbenzenes with anthranils with alkyne- dependent chemoselectivity: skeletal rearrangement versus non-rearrangement. *Chem. Sci.* **2019**, *10*, 1201−1206.

(13) (a) Davies, I.; Guner, V.; Houk, K. Theoretical Evidence for Oxygenated Intermediates in the Reductive Cyclization of Nitrobenzenes. *Org. Lett.* **2004**, *6*, 743−746. (b) Pagar, V.; Jadhav, A.; Liu, R. S. Gold-Catalyzed Formal [3 + 3] and [4 + 2] Cycloaddition Reactions of Nitrosobenzenes with Alkenylgold Carbenoids. *J. Am. Chem. Soc.* **2011**, *133*, 20728−20731. (c) Schützner ová, E.; Krchňák, V. N-Oxide as an Intramolecular Oxidant in the Baeyer-Villiger Oxidation: Synthesis of 2-Alkyl-2*H*-indazol-3-yl Benzoates and 2-Alkyl-1,2-dihydro-3*H*-indazol-3-ones. *J. Org. Chem.* **2016**, *81*, 3585−3596. (d) Nykaza, T. V.; Harrison, T. S.; Ghosh, A.; Putnik, R.; Radosevich, A. T. A Biphilic Phosphetane Catalyzes N−N Bond-Forming Cadogan Heterocyclization via PIII/PV = O Redox Cycling. *J. Am. Chem. Soc.* **2017**, *139*, 6839−6842.

(14) Ramana, C. V.; Patel, P.; Vanka, K.; Miao, B.; Degterev, A. A Combined Experimental and Density Functional Theory Study on the Pd-Mediated Cycloisomerization of o-Alkynylnitrobenzenes − Synthesis of Isatogens and Their Evaluation as Modulators of ROS-Mediated Cell Death. *Eur. J. Org. Chem.* **2010**, *2010*, 5955−5966.

(15) (a) Liu, R. R.; Ye, S. C.; Lu, C. J.; Zhuang, G. L.; Gao, J. R.; Jia, Y. X. Dual Catalysis for the Redox Annulation of Nitroalkynes with Indoles: Enantioselective Construction of Indolin-3-ones Bearing Quaternary Stereocenters. *Angew. Chem., Int. Ed.* **2015**, *54*, 11205−11208. (b) Dhote, P. S.; Ramana, C. V. One-Pot Au[III]-/Lewis Acid Catalyzed Cycloisomerization of Nitroalkynes and [3 + 3]-Cycloaddition with Donor−Acceptor Cyclopropanes. *Org. Lett.* **2019**, *21*, 6221−6224.

(16) (a) Aguilar, E.; Santamaría, J. Gold-catalyzed heterocyclic syntheses through α-imino gold carbene complexes as intermediates. *Org. Chem. Front.* **2019**, *6*, 1513−1540. (b) Gao, Y.; Nie, J.; Huo, Y.; Hu, X. Q. Anthranils: Versatile Building Blocks in the Construction of C-N Bonds and N-heterocycles. *Org. Chem. Front.* **2020**, *7*, 1177−1196.

(17) (a) Yeom, H.; Lee, J.; Shin, S. Gold-Catalyzed Waste-Free Generation and Reaction of Azomethine Ylides: Internal Redox/Dipolar Cycloaddition Cascade. *Angew. Chem., Int. Ed.* **2008**, *47*, 7040−7043. (b) Yeom, H. S.; Lee, Y.; Lee, J. E.; Shin, S. Geometry-dependent divergence in the gold-catalyzed redox cascade cyclization of o-alkynylaryl ketoximes and nitrones leading to isoindoles. *Org. Biomol. Chem.* **2009**, *7*, 4744−4752. (c) Wetzel, A.; Gagosz, F. Gold-Catalyzed Transformation of 2-Alkynyl Arylazides: Efficient Access to the Valuable Pseudoindoxyl and Indolyl Frameworks. *Angew. Chem., Int. Ed.* **2011**, *50*, 7354−7358.

(18) (a) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002−18003. (b) Lopez, S.; Herrero-Gómez, E. H.; Pérez-Galán, P. P.; Nieto-Oberhuber, C. N.; Echavarren, A. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 6029−6032.

(19) Jin, H.; Huang, L.; Xie, J.; Rudolph, M.; Rominger, F.; Hashmi, S. K. Gold-Catalyzed C-H Annulation of Anthranils with Alkynes: A Facile, Flexible, and Atom-Economical Synthesis of Unprotected 7-Acylindoles. *Angew. Chem., Int. Ed.* **2016**, *55*, 794−797.

(20) Skaria, M.; More, S.; Kuo, T. C.; Cheng, M. J.; Liu, R. S. Gold-catalyzed Iminations of Terminal Propargyl Alcohols with Anthranils with A typical Chemoselectivity for C(1)-Additions and 1,2-Carbon Migration. *Chem. - Eur. J.* **2020**, *26*, 3600−3608.

(21) Sahani, R. L.; Liu, R. S. Gold-Catalyzed [4 + 2] Annulation/Cyclization Cascades of Benzisoxazoles with Propiolate Derivatives to

https://doi.org/10.1021/acs.orglett.1c00539
Org. Lett. 2021, 23, 2632−2637

Access Highly Oxygenated Tetrahydroquinolines. *Angew. Chem., Int. Ed.* **2017**, *56*, 12736−12740.

https://doi.org/10.1021/acs.orglett.1c00539
Org. Lett. 2021, 23, 2632−2637