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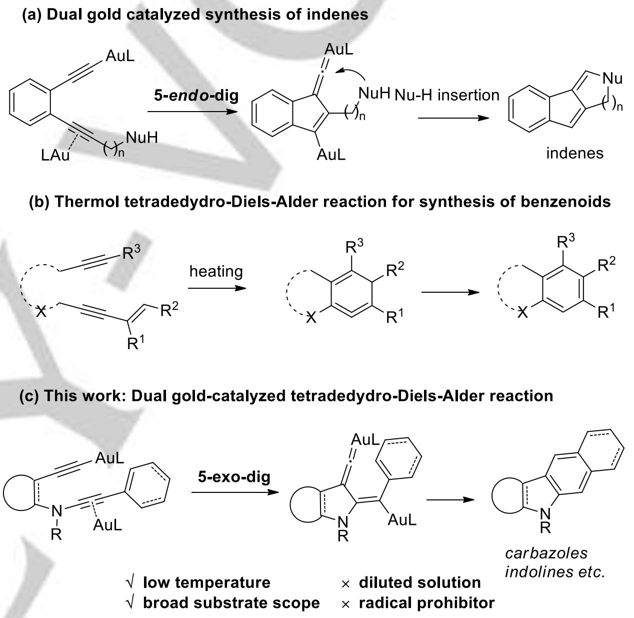
Dual Gold-Catalyzed Formal Tetradehydro-Diels-Alder Reactions for the Synthesis of Carbazoles and Indolines

Hong-Fa Wang, Shi-Yue Wang, Tian-Zhu Qin and Weiwei Zi*[a]

Abstract: We herein report a dual gold-catalyzed tetradehydro-Diels-Alder reactions for the synthesis of nitrogen-containing aromatic heterocycles. Under the catalysts system ($IPrAuNTf_2$/DIPEA), indolines and carbazoles as well as other N-containing aromatic heterocycles were prepared in high yields with good functional group tolerance. Unlike the traditional thermal tetradehydro-Diels-Alder reactions, diluted reaction concentration and radical prohibitors are not required for this protocol. Experimental data support a mechanism involving gold vinylidene species, which undergoes a 6π electrocyclization, followed with 1,2-hydrogen shift.

During the last few years, dual gold catalysis has attracted intensive study and tremendous success has been achieved in construction of aromatic compounds through this catalytic mode.[1] Mechanistic studies, as well as theoretical calculations, suggest gold vinylidene species from 5-*endo*-dig cyclization of dialkynes are incorporated in the mechanism.[1a,b] This intermediate could undergo facile C-H, N-H or O-H insertion to give a range of polycyclic arenes with an indene backbone (Scheme 1a).[1,2] Despite of these pioneering works, developing new reactions based on gold vinylidene chemistry via dual gold catalysis is still highly desirable.[1n]

A lot of fundamental studies on Thermal tetradehydro-Diels-Alder (TDDA) reactions[3] have been reported. These provided a powerfull strategy to de novo synthesis of benzenoids; however, the harsh reaction conditions, such as high temperature, diluted reaction concentrations and requirement of polymerization inhibitors, make them difficult to be used in practical synthesis (Scheme 1b).[3] Taking the advantages of the ability of Au complexes to activate alkynes in catalytic processes,[4] Liu recently reported a gold-catalyzed TDDA reaction[5] at mild reaction conditions. Widen substrate scope was achieved compared to Thermal tetradehydro-Diels-Alder (TDDA) reactions. Notably, terminal akyne substrate only gave low yield in that system. Inspired by recent dual gold catalysis, we hypothesized that if a ynamide tethered terminal enyne[6] was used, the n-*exo*-dig (n = 5, 6, 7) type of cyclization would be preferred due to the stabilization of carbocation by amine group. Then a trialkene type gold vinylidene would form, which could undergo a rapid cycloaromatization to afford nitrogen-containing aromatic heterocycles, such as carbazoles, indolines and tetrahydroquinolines (Scheme 1c), which represent important synthetic targets due to their prevalence in bioactive natural products and pharmaceuticals.[7]



(a) Dual gold catalyzed synthesis of indenes

(b) Thermol tetradedydro-Diels-Alder reaction for synthesis of benzenoids

(c) This work: Dual gold-catalyzed tetradedydro-Diels-Alder reaction

√ low temperature
√ broad substrate scope
× diluted solution
× radical prohibitor

Scheme 1. Dual gold-catalyzed tetradehydro-Diels-Alder reaction.

To test our hypothesis, substrate **1a** was chosen as the model substrate for the designed reaction (Table 1). $(PhO)_3PAuNTf_2$, Johnphos($AuNTf_2$) and bisphosphine-gold catalyst dppe$(AuNTf_2)_2$ were firstly investigated. Although the starting material **1a** was completely consumed in all three cases, only trace of desired tetradehydro-Diels-Alder cyclization product **2a** was detected, with large amount of unidentified polymers formed under these catalysts (entries 1-3). Further ligands screening revealed that strong electron-donating IPr (1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) ligand could largely improve the yield to 48% (entry 4). Encouraged by this result, additives were then investigated for the purpose to prohibit the polymerization side reaction. Lewis acids, $Fe(OTf)_3$ and $Zn(OTf)_2$ have no obvious effect to improve the yields (entries 5, 6) but pyridine base 2,6-tBu_2-Py would decrease the yield to 31%. Nevertheless, the addition of a catalytic amount of trialkyl amine could greatly enhance the formation of **2a** (entries 8, 9). For instance, when 10 mol% N,N-diisopropylethylamine (DIPEA) was adding, the yield of **2a** was increasing from 48% to 94%. Controlled experiments showed DIPEA itself could not catalyze this transformation (entry 10). In the absence of catalysts and additives, **1a** was recovered in 83% yield after heating for 24

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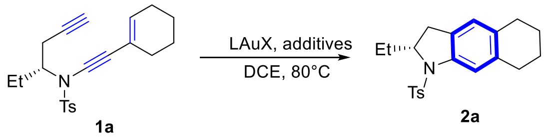
Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate)) hours at 80°C in dichloroethane (entry 11), without any cyclization **2a** being detected. This result revealed that no background thermal tetradehydro-Diels-Alder reaction took place.

Table 1. Optimization of the reaction conditions.[a]

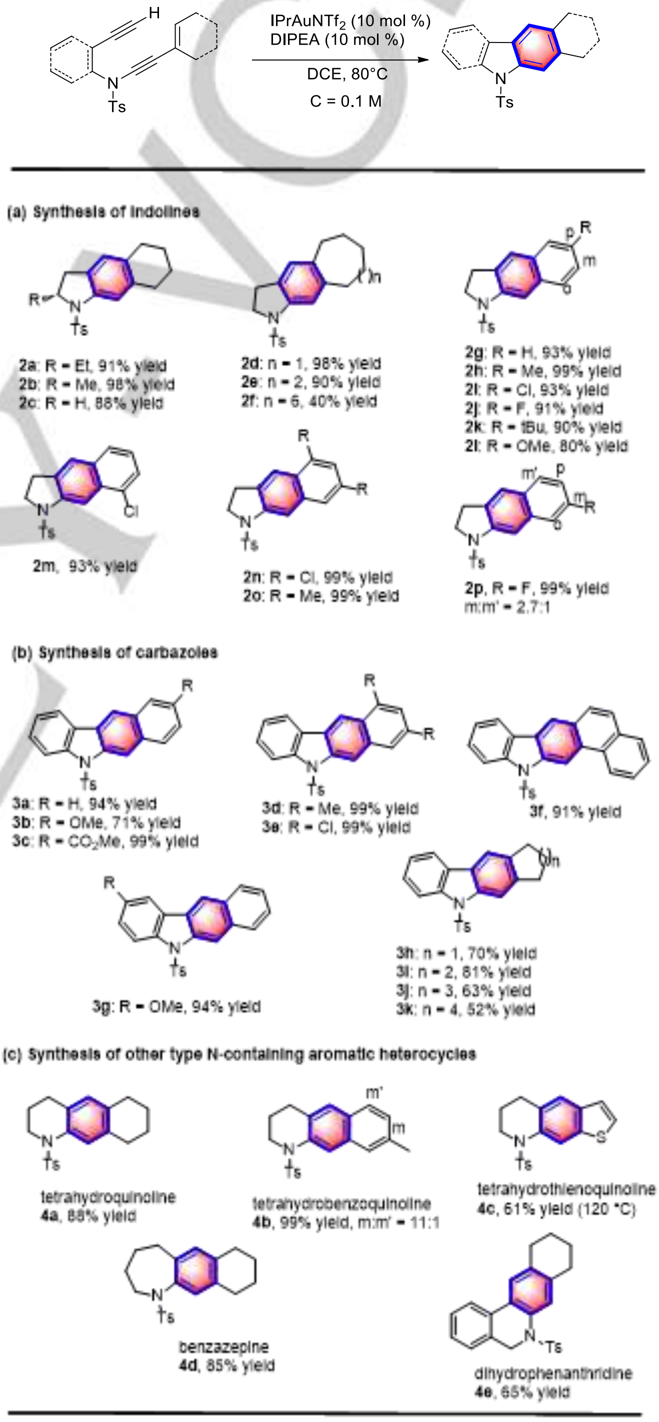


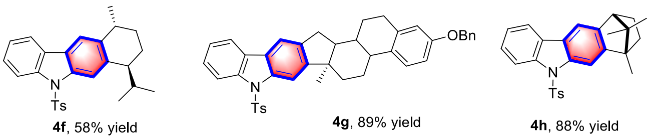
entry	LAuX	additives	Convertion (%)	Yield (%)
1	(PhO)$_3$PAuNTf$_2$	--	100	4
2	JohnphosAuNTf$_2$	--	63	4
3	dppe(AuNTf$_2$)$_2$	--	76	13
4	IPrAuNTf$_2$	--	100	48
5	IPrAuNTf$_2$	Fe(OTf)$_3$	100	39
6	IPrAuNTf$_2$	Zn(OTf)$_3$	100	50
7	IPrAuNTf$_2$	2,6-tBu$_2$-Py	100	31
8	IPrAuNTf$_2$	Et$_3$N	100	75
9	IPrAuNTf$_2$	DIPEA	100	94 (91)^b
10	--	DIPEA	<5%	--
11	--	--	17%	0

[a] Reaction conditions: 0.1 mmol 1a, 10 mol% gold catalyst, 10 mol% additives, 2 mL solvent, 80°C. Yields and conversions were determined by 1H NMR spectroscopic analysis using CH$_2$Br$_2$ as the internal standard. [b] Isolated yield.

Having established the optimized reaction parameters, we next tested the scope of this dual gold catalyzed tetradehydro-Diels-Alder reaction for the preparation of indolines (Table 2a). The R groups on the linker chain were first investigated (**2a-2c**) and comparable yields were obtained for methyl, ethyl and H. However, the yields dropped along with increasing the ring size of the cyclic olefin (**2d-2f**). For a twelve membered carbon ring fused indoline **2f**, only 40% yield could be obtained with a prolonged time (4 days). Substrates with a phenyl ring instead of the olefin moiety worked as well. Substitution at para- or ortho-positions with Me, Cl, F, tBu or OMe were well tolerated (**2g-2m**). However, regioselective cyclization products were observed for *meta*-substituted substrate (**2p**) with a ratio about 2.7:1. This reaction was competent to synthesis carbazole scaffolds without modification of the optimal conditions (Table 2b). In most cases, the reaction could be finished within 48 hours with the desired carbazoles being isolated with 52%-99% yields. Extension this method to access other nitrogen heterocycles was also possible (Table 2c). Tetrahydroquinoline **4a**, tetrahydrobenzoquinoline **4b**, tetrahydrothienoquinoline **4c**, benzazepine **4d** and dihydrophenanthridine **4e** were prepared with good to excellent yields. More importantly, this method could be used as a late-stage carbazole de Novo synthesis. As demonstrated in Scheme 2, we successfully constructed a carbazole moiety alongside natural products Menthone, Estrone, and Camphor, with the corresponding derivatives being isolated in good yields.

Table 2. Substrate scope

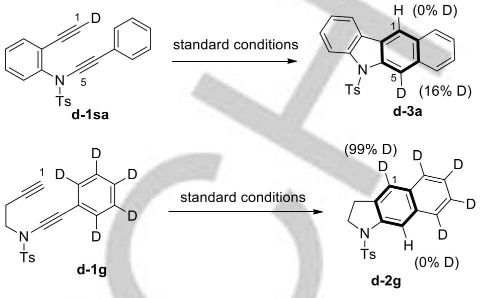




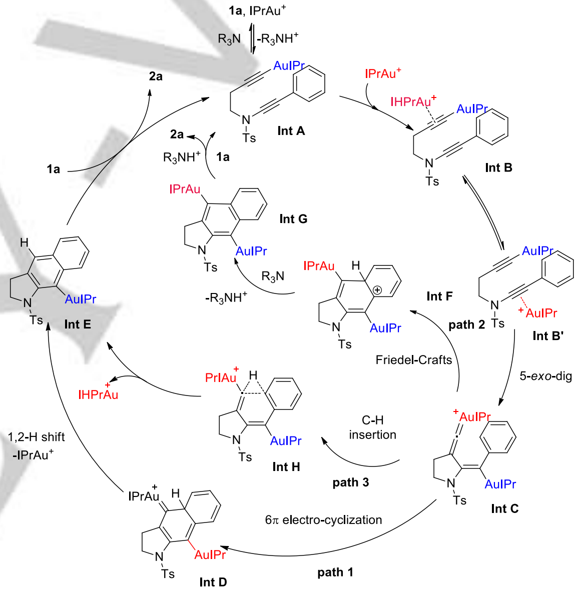
Scheme 2. Derivatization of natural products.

To get some insights into the mechanism, deuterium labelling experiments were conducted (Scheme 3). When deuterium labelling substrate **d-1sa** was subjected to the reaction, we observed the acetylenic-D was not maintained at C1 anymore after the reaction and 16% D atom was detected at C5 position in product **d-3a** (D-H exchange between the **d-1sa** with residual water in the solvent might explain the low ratio of D/H at C5).[8] This result ruled out the thermal tetradehydro-Diels-Alder mechanism. At the meantime, completely D atom transferring from benzene ring in **d-1g** to C1 position of **d-2g** was observed.

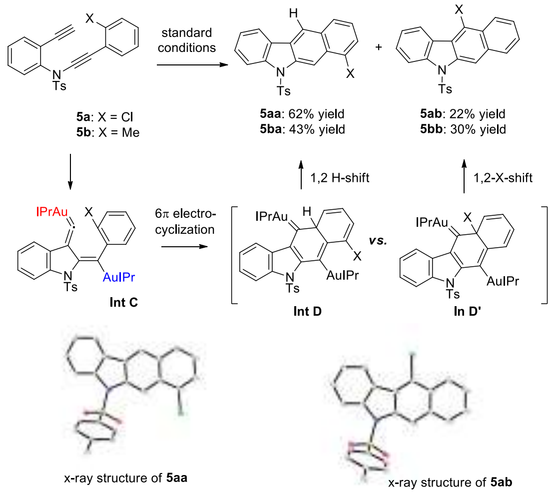
Based on the above results, together with previous studies from other groups,[1] a proposed mechanism was given in Scheme 4. Starting from a base-promoted equilibration, gold acetylide **Int A** is generated first to enter the catalytic cycle, and then the second cationic Au ion is coordinated to the alkyne moiety, forming a balance of σ，π-digold complex **Int B** and **Int B'**. A 5-*exo*-dig attack affords gold vinylidene **Int C**, which immediately undergoes a rapid 6π electrocyclization to give gold carbenoids **Int D**.[9] **Int D** is then transformed to aryl gold **Int E** via 1,2-hydrogen shift, and releasing one IPrAu ion at the same time. The second IPrAu catalyst was leaving the system to enter the next catalytic cycle by H-Au exchange between acetylenic-H in starting material **1a** and phenyl-Au in **Int E**.[10] A second possible pathway, involving Friedel-Crafts alkylation of gold carbenoid **Int C**[11] followed by a protodeauration step. We thought there should not be a big rate difference between the two phenyl-Au moiety in **Int G** during the protodeauration. Thus, the specifically deuterium atom transferring experiments ruled out this pathway. An alternative pathway **3** is directly C_{sp2}-H insertion to gold carbenoid **Int C**,[1l, 12] resulting intermediate **Int E**. This pathway is also consistent with deuterium labelling results. To distinguish these two mechanisms, we designed X (X = Cl and Me other than H) group migration experiments.[13] As showed in Scheme 5, when *ortho*-substituted **5a** (X = Cl) was tested in the reaction, regioselective cyclization products **5aa** and **5ab** was formed with 62%, 22% yields respectively.[14] Similar result was observed for substrate **5b**, in which the X group is methyl. Carbene insertion into C_{sp2}-Cl and C_{sp2}-C_{sp3} bond were considered unfavourable due to kinetically inert and thermodynamically stable property of C−Cl and C-C bonds.[15] Thus, **5ab** and **5bb** was not likely formed by this way. We rationalized that the intermediate **InC** undertake a 6π electrocyclization to give regioselective dearomative species Int D and Int D'. The latter followed with 1,2-chloro- or methyl-shift to furnish **5ab** and **5bb** respectively. Taken the above together, we believe the pathway 1 in Scheme 4 is a more reasonable process.



Scheme 3. Deuterium labelling experiments.



Scheme 4. Proposed mechanism.



Scheme 5. Regioselective cyclization experiments.

In conclusion, we have developed a dual gold-catalyzed tetradehydro-Diels-Alder reaction. Nitrogen-containing aromatic heterocycles including indolines and carbazoles are prepared highly efficiently by catalysts system IPrAuNTf$_2$/DIPEA. This reaction does not require diluted reaction concentration and radical prohibitors. Experiments support a mechanism involving gold vinylidene species, which undergoes a 6π electrocyclization followed with 1,2-hydrogen shift.

Acknowledgements ((optional))

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Keywords: dual gold catalysis • tetradehydro-Diels-Alder reactions • gold vinylidene • 6π electrocyclization

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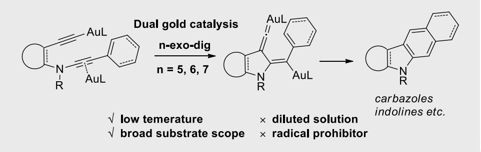

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Dual Gold-Catalyzed Tetradehydro-Diels-Alder Reactions for the Synthesis of Carbazoles and Indolines