Heterocycles

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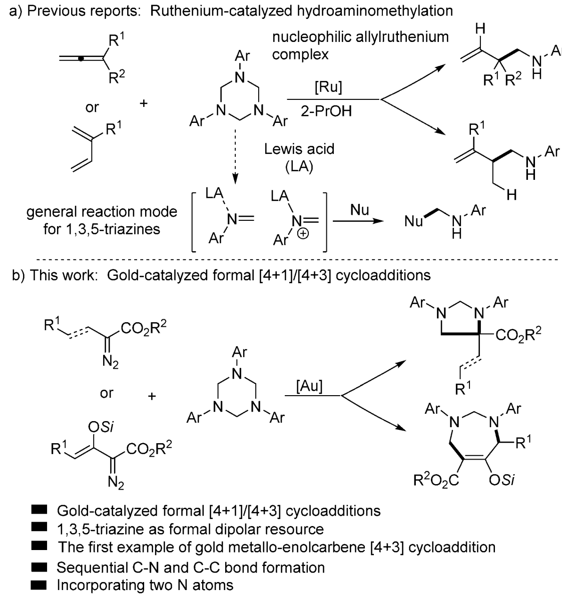
Gold-Catalyzed Formal [4+1]/[4+3] Cycloadditions of Diazo Esters with Triazines

*Chenghao Zhu, Guangyang Xu, and Jiangtao Sun**

Abstract: *Reported herein is the unprecedented gold-catalyzed formal [4+1]/[4+3] cycloadditions of diazo esters with hexahydro-1,3,4-triazines, thus providing five- and seven-membered heterocycles in moderate to high yields under mild reaction conditions. These reactions feature the use of a gold complex to accomplish the diverse annulations and the first example of the involvement of a gold metallo-enolcarbene in a cycloaddition. It is also the first utilization of stable triazines as formal dipolar adducts in the carbene-involved cycloadditions. Mechanistic investigations reveal that the triazines reacted directly, rather than as formaldimine precursors, in the reaction process.*

Transition-metal-catalyzed cycloadditions of diazocarbonyl precursors with dipolar adducts are powerful tools for the rapid construction of diverse scaffolds, and diazo compounds can serve as one- to three-carbon synthons in various [$n+m$] annulations.[1] In particular, the rhodium- and copper-catalyzed cycloadditions have been extensively studied by the groups of Doyle,[2] Davies,[3] and others.[4] In contrast, the use of gold complexes in such reactions remains less well investigated. Recently, the groups of Liu,[5] Davies,[6] and others[7] described several novel gold-catalyzed cycloadditions, thus demonstrating totally different reactivity and selectivity compared to other metals. Nevertheless, the unique catalytic activity of gold complexes prompted chemists to discover novel reactions which do not occur for others,[8,9] thus providing efficient ways towards molecular complexity.[10]

Recently, Krische and co-workers developed a series of novel ruthenium-catalyzed hydroaminomethylations by using hexahydro-1,3,5-triazines as precursors of N-aryl formaldimines (Scheme 1 a).[11] Just recently, following their efforts on developing novel aminations, Huang and co-workers described an elegant palladium-catalyzed formal insertion of carbenoids into aminals by C−N bond activation, thus affording an efficient approach towards diamino acid esters with quaternary carbon centers.[12] Inspired by these pioneering reports, and in continuation of our ongoing research interests in gold-carbene-mediated transformations,[13] we report herein the unprecedented formal [4+1]/[4+3] cycloadditions between diazo esters and hexahydro-1,3,5-triazines (Scheme 1 b). Notably, different from Krische's protocols, in which the triazines acted as active imine/iminium intermediates undergoing nucleophilic attack by a nucleophilic allylruthenium complex for various aminomethylations, we herein employ these triazines as formal dipolar adducts under gold catalysis to realize the synthesis of five- and seven-membered heterocycles.



Scheme 1. Previous reports and our approach. LA = Lewis acid, *Si* = silyl protecting group.

Initially, the triazine **1a** and phenyl diazoacetate (**2a**) were utilized as model substrates to achieve the optimal reaction conditions (Table 1). The application of gold complexes (5 mol %) as the catalyst was first examined. When the reactions were performed in dichloromethane at 60 °C, the use of IPrAuCl, PPh_3AuCl, $(C_6F_5)_3PAuCl$, Xantphos$(AuCl)_2$, XPhosAuCl, and JohnPhosAuCl all gave **3a** in quite low yield within 12 hours (entries 1–6). The use of *t*BuXPhosAuCl provided **3a** in 55 % yield (entry 7), which improves to 68 % yield in toluene (entry 8) and 81 % yield in tetrahydrofuran (entry 9). However, a reduced catalyst loading resulted in moderate yield (entry 10) and almost no **3a** was detected at room temperature (entry 11). Moreover, rhodium complexes such as [$Rh_2(Oct)_4$] and [$Rh_2(esp)_2$] were also examined, but gave low conversion (entries 12 and 13).

With the optimal reaction conditions in hand, we next set out to investigate the scope with respect to the substrates

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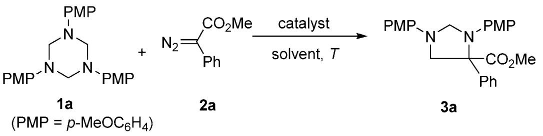
Table 1: Selected optimization.[a]



Entry	Catalyst (mol %)	Solvent	T [°C]	t [h]	Yield [%][b]
1	IPrAuCl (5)	CH_2Cl_2	60	12	< 5
2	Ph_3PAuCl (5)	CH_2Cl_2	60	12	< 5
3	$(C_6F_5)_3PAuCl$ (5)	CH_2Cl_2	60	12	< 5
4	Xantphos$(AuCl)_2$ (5)	CH_2Cl_2	60	12	< 5
5	XPhosAuCl (5)	CH_2Cl_2	60	12	< 5
6	JohnPhosAuCl (5)	CH_2Cl_2	60	12	15
7	*t*BuXPhosAuCl (5)	CH_2Cl_2	60	12	55
8	*t*BuXPhosAuCl (5)	toluene	60	12	68
9	*t*BuXPhosAuCl (5)	THF	60	12	81
10	*t*BuXPhosAuCl (2)	THF	60	24	57
11	*t*BuXPhosAuCl (5)	THF	25	24	< 5
12	$[Rh_2(OAc)_4]$ (1)	CH_2Cl_2	25	1	33
13	$[Rh_2(esp)_2]$ (1)	CH_2Cl_2	25	1	22

[a] Reactions were performed with **1a** (0.25 mmol) and **2a** (0.3 mmol) in solvent (5 mL) in the presence of either gold or rhodium complexes. [b] Yields of isolated products.

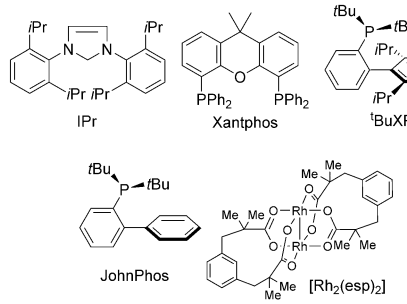
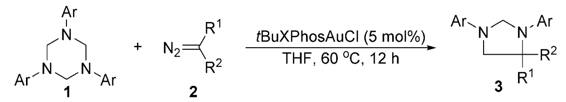
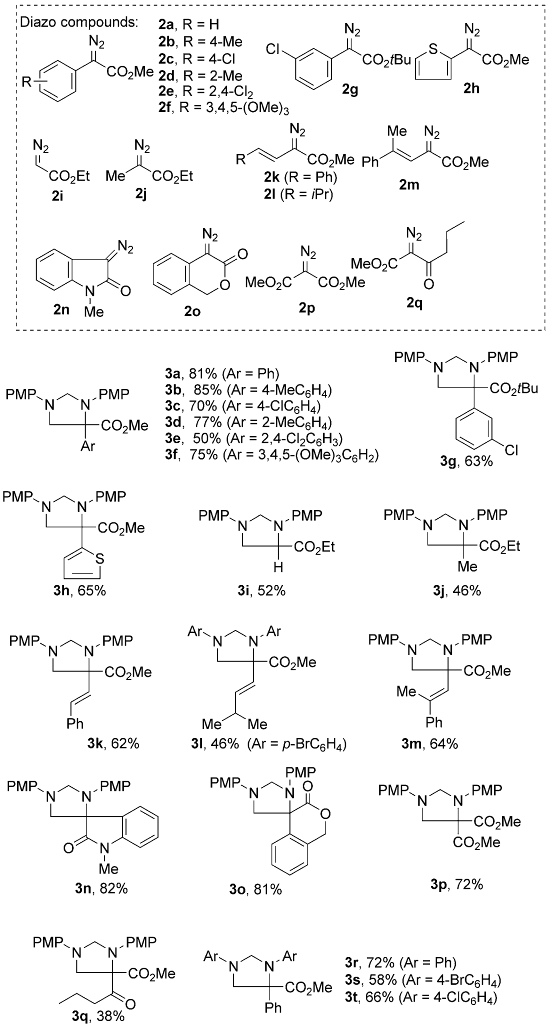


Table 2: Substrate scope for gold-catalyzed formal [4+1] cycloadditions.[a,b]

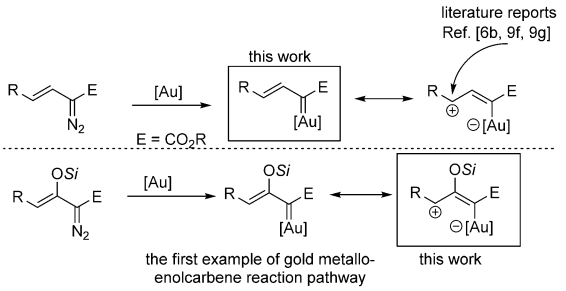




[a] Reactions were carried out with **1** (0.25 mmol), **2** (0.3 mmol), and *t*BuXPhosAuCl (5 mol %) in THF (5 mL) at 60 °C for 12 h. [b] Yields of isolated products.

(Table 2). A wide range of donor/acceptor diazo esters, including aryl diazoacetates (**2a**–**h**), alkyl diazoacetate (**2j**), vinyl diazoacetates (**2k**–**m**), cyclic diazo compounds (**2n** and **2o**), and acceptor/acceptor diazoesters (**2p** and **2q**) were evaluated. Generally, highly substituted imidazolidines bearing a quaternary carbon center were obtained in modest to excellent yields by a formal [4+1] cycloaddition for all cases. About the substituted phenyl diazoacetates, the phenyl ring bearing electron-rich groups gave higher yields than those bearing electron-poor ones (**3b**, **3d**, **3f** versus **3c**, **3e**). The thiophene diazoacetate **2h** was tolerated and afforded the corresponding product **3h** in 65 % yield. The use of the methyl diazoacetate **2j** gave **3j** in 46 % yield, and even the simple diazoacetate **2i** worked well to furnish **3i** in 52 % yield. It is noteworthy that when the vinyl diazoacetates were used, the catalytic system still worked well to provide the desired five-membered imidazolidines (**3k**–**m**) in modest yields. Also, the reaction of **1a** with cyclic diazo compounds furnished the spiro-imidazolidines **3n** and **3o** in 82 and 81 % yield, respectively. The diazo esters (**2p** and **2q**) with two acceptor groups were also examined and the corresponding products were obtained in 72 and 38 % yield, respectively. Moreover, the different aryl substituted 1,3,5-triazines were also examined, thus providing the corresponding products in moderate yields (**3r**–**t**). The structure of the products was determined by NMR analysis and additionally confirmed by X-ray analysis of **3g**.[14]

It is well known that the metallo-vinylcarbene and metallo-enolcarbene species have electrophilic character at both of the carbenic and vinylogous positions. Generally the nucleophilic addition occurs preferentially at the vinylogous position (Scheme 2).[15] Indeed, literature reports revealed that the activity of the vinylogous position for vinyl gold carbenes was dominant for most cases.[6b,9f,g] However, we found that the carbenic reactivity was preferred in this case (**3k**–**m** of Table 1). Moreover, for the enol diazoacetates, the electron-donating oxygen atom of the silyl ether group would

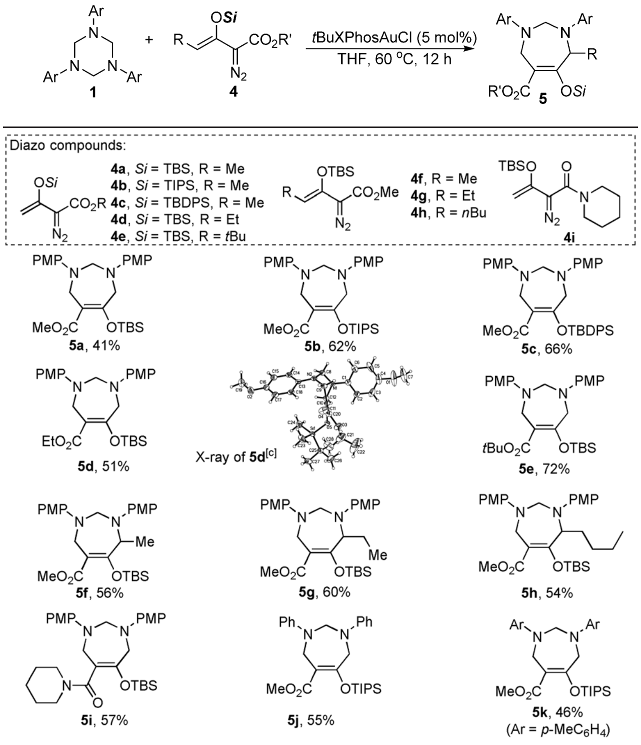


Scheme 2. Known reaction pathway and novel reaction modes (our work).

enhance the electrophilic character at the vinylogous position,[1c] and probably resulted in reaction modes different from those of linear vinyl diazoacetates. To our knowledge, no reports for the gold metallo-enolcarbene reaction have been described before.

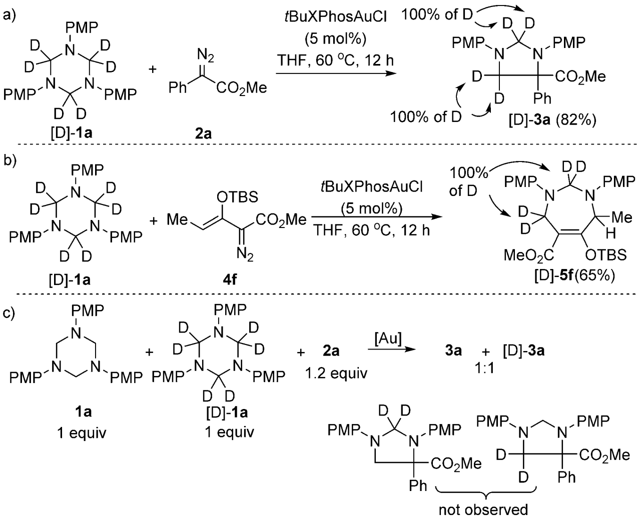
Next, to further evaluate the generality of this catalytic system, various enol diazo compounds (**4**) were employed (Table 3). Indeed, in contrast to the vinyldiazoacetates which gave the five-membered heterocycles as the sole products, the reaction of **1a** and the enol diazoacetates **4** proceeded smoothly through a formal [4+3] annulation to provide seven-membered heterocycles (**5**) with the C–N bond forming at the vinylogous position. All of the TBS (*tert*-butyldimethylsilyl), TIPS (triisopropylsilyl), and TBDPS (*tert*-butyldiphenylsilyl) protected enol diazoacetates were tolerated and gave the corresponding polysubstituted heterocycles in moderate to high yields. To further determine the structure of the products, the reaction between the enol diazoacetate **4d** and **1a** was performed and finally the single-crystal X-ray analysis of **5d** was obtained.[14] The substrate scope with respect to the diazo compounds was also investigated, and we found that the enol diazoacetates having substituents at the terminal alkene position furnished the corresponding products in moderate yields (**5f**–**h**). Moreover, the enol diazoacetamide **4i** also reacted well and gave **5i** in 57 % yield. Next, two different hexahydro-1,3,5-triazines were examined and also gave the corresponding products **5j** and **5k** in moderate yields.

Table 3: Gold-catalyzed formal [4+3] cycloadditions.[a,b]



[a] Reactions were carried out with **1** (0.25 mmol), **2** (0.3 mmol), and *t*BuXPhosAuCl (5 mol %) in THF (5 mL) at 60 °C for 12 h. [b] Yields of isolated products. [c] X-ray structure of **5d**.[14] Thermal ellipsoids shown at 30 % probability.

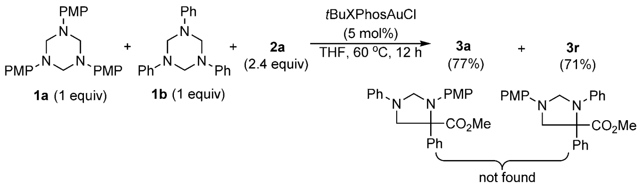
To gain insight into the reaction mechanism, deuterium-labeling experiments were conducted (Scheme 3). First, the reaction of [D]-**1a** and **2a** afforded the fully deuterated product [D]-**3a** (Scheme 3a). Moreover, [D]-**5f** was obtained in moderate yield, and indicated that the C–N bond formation occurred at the vinylogous position of the enol diazoacetates (Scheme 3b). Furthermore, upon treatment of 1 equivalent of **1a** and [D]-**1a** with 1.2 equivalents of **2a**, **3a** and [D]-**3a** were obtained almost in a 1:1 ratio. It is important to note that the cross-cyclization products were not observed (Scheme 3c).



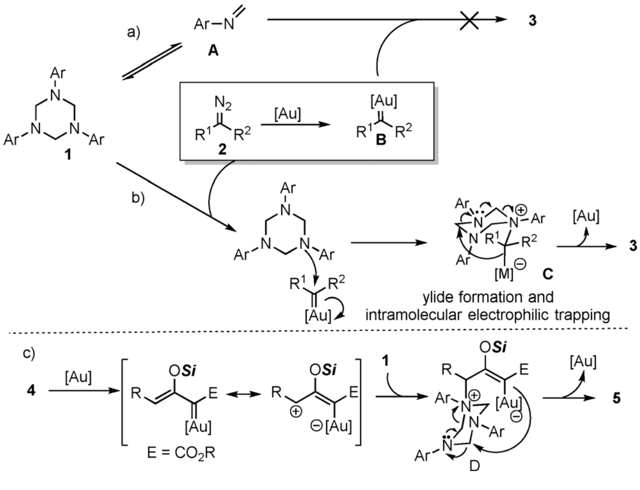
Scheme 3. Deuterium-labeling experiments. THF = tetrahydrofuran.

To further understand the reaction process, the reaction of **1a** and **1b** with **2a** was performed (Scheme 4). However, only **3a** and **3r** were cleanly isolated in 77 and 71 % yield, respectively. No cross-cyclization products were observed.

Since the cross-cycloaddition adducts were not detected (Schemes 3c and 4), the possible route by the formation the formaldimine **A** and subsequent cycloaddition with the metal-carbene **B** should be excluded (Scheme 5a).[16] Then a general mechanism for the formal [4+1] cycloaddition was proposed (Scheme 5b). First, the reaction of the triazine **1** with **B** provides the intermediate **C** by ylide formation.[17] The intramolecular electrophilic trapping associated with rear-



Scheme 4. Control experiments.



Scheme 5. Proposed mechanisms.

rangement, and subsequent reductive elimination affords the cycloaddition product **3**. For the formal [4+3] cycloaddition, the generation of a gold enolcarbene species is the key step. Then the nucleophilic addition of **1** at the vinylogous position of enolcarbene affords the intermediate **D**, which undergoes intramolecular cycloaddition and reductive elimination to provide the final product **5** and regenerates the gold catalysts (Scheme 5c).

In summary, we have developed unprecedented gold-catalyzed formal [4+1]/[4+3] cycloaddition reactions of diazo esters with hexahydro-1,3,5-triazines, thus affording five- and seven-membered N-containing heterocycles in moderate to high yields under mild reaction conditions with a broad substrate scope. This protocol features the first example of gold-catalyzed [4+1]/[4+3] cycloadditions using different diazo substrates, especially for the enol diazo compounds. Notably, mechanistic investigations offered strong evidence for the triazines reacting directly with the metal carbene.

Acknowledgments

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Keywords: cycloaddition · diazo compounds · gold · heterocycles · reaction mechanisms

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Communications

Heterocycles

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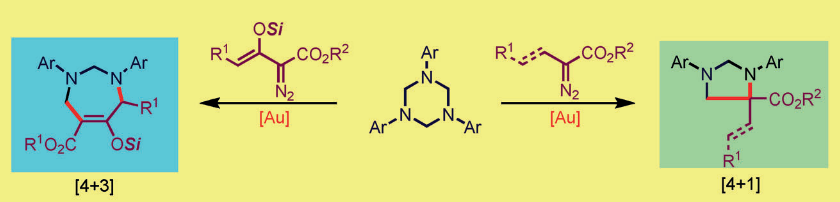
Gold-Catalyzed Formal [4+1]/[4+3] Cycloadditions of Diazo Esters with Triazines



Golden performance: The title reaction has been accomplished, thus providing five- and seven-membered heterocycles in moderate to high yields under mild reaction conditions. These reactions feature the use of a gold complex to accomplish the diverse annulations and serve as an example of the involvement of a gold metallo-enolcarbene in a cycloaddition. *Si* = silyl protecting group.