N-Heterocyclic Carbenes

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N-Heterocyclic Carbene Gold(I) Catalyzed Transformation of N-Tethered 1,5-Bisallenes to 6,7-Dimethylene-3-azabicyclo-[3.1.1]heptanes**

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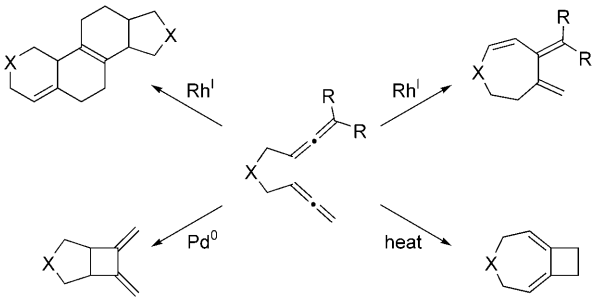
Transition-metal-catalyzed reactions of polyunsaturated systems have attracted a lot of attention because of their enormous synthetic potential in the preparation of a wide variety of carbo- and heterocyclic building blocks.[1] Among them, the chemistry of allenes has been recently developed into an established member of the synthetic arsenal.[2] Thus, transition-metal-catalyzed cycloaddition/cyclization of allenes is one of the most active branches of research on the formation of functionalized cyclic structures.[3]

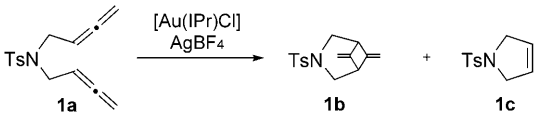
Compared to the advances of the chemistry of allenes and related compounds, the development of the chemistry of bisallenes is far behind,[4] presumably because of their high instability and difficulty of their synthesis. However, recent studies showed fascinating new properties of bisallenes.[5] For example, Ma and co-workers recently reported[6] the transition-metal-catalyzed cycloisomerization of 1,5-bisallenes (Scheme 1). Interestingly, the reaction patterns are highly varied, depending on the nature of the substrates and the catalyst systems, as is also observed in the cycloisomerization of enynes.[7]



Scheme 1. Transition-metal-catalyzed cycloisomerization of 1,5-bisallenes.

The use of metal complexes of N-heterocyclic carbenes (NHCs) has attracted a lot of attention.[8] However, the use of gold NHC complexes in catalytic reactions is quite rare.[9] Recently, we reported the gold NHC-catalyzed cycloisomerization of cyclohexadienyl alkynes.[10] Thus, we turned our attention to the use of gold NHC complexes in the chemistry of bisallenes.

The search for new catalytic reactions to generate nitrogen-containing heterocycles continues to be of immense importance to the pharmaceutical sciences for the synthesis of alkaloids and other nitrogen-containing heterocycles.[11] In the hope of finding new types of cycloisomerization reactions of bisallenes, we tested the cycloisomerization of a bisallene with an N–Ts tether (**1a**; Ts = *p*-toluenesulfonyl) in the presence of a catalytic amount of [Au(IPr)Cl] (IPr = *N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidene)/$AgBF_4$ [Eq. (1)]. To our delight, a new cycloisomerized product **1b** (6,7-dimethylene-3-azabicyclo[3.1.1]heptane) was obtained as a major product. Herein, we report our preliminary results.



(1)

We first screened the reaction conditions (Table 1). The reaction of **1a** was highly dependent upon the catalyst, the reaction medium, and the reaction temperature. The reaction is not catalyzed by Ag^I salts, $PtCl_2$, or [Au(IMes)Cl]/$AgBF_4$. Several years ago, Dixneuf and co-workers reported[12] the ruthenium-catalyzed intermolecular [2+2] cycloaddition of

Table 1: Reaction of **1a** under various reaction conditions[a] [see Eq. (1)].

Entry	mol% cat.	Solvent	*T* [°C]	*t* [h]	Yield [%][b] **1a**	**1b**	**1c**
1	5	CH_2Cl_2	25	24	87	6	2
2	5	benzene	25	24	0	67	0
3	5	benzene	75	0.5	0	93	0
4	5	toluene	25	18	13	65	22
5	5	toluene	75	0.8	0	90	10
6	5	toluene	100	24	42	51	0
7	7	toluene	75	0.5	0	87	6
8	10	toluene	75	0.5	0	96	0

[a] **1a** (0.3 mmol) was treated with [Au(IPr)Cl] and $AgBF_4$ in toluene. [b] Yield of product isolated after chromatography.

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allenyl boronate. However, the ruthenium catalyst [Cp*RuCl(cod)] (Cp* = pentamethylcyclopentadienyl; cod = 1,5-cyclooctadiene) did not give the expected product. A $[Au(PPh_3)Cl]/AgBF_4$ catalyst system gave the desired product with toluene as solvent but the yield was very low. When $[Au(IPr)Cl]/AgBF_4$ was used as a catalyst in dichloromethane (Table 1, entry 1),[13] **1b** was produced in only 6% and **1c** in 2% yield . The formation of **1b** was confirmed by X-ray diffraction analysis (Figure 1).[14] The carbon skeleton of bicyclo[3.1.1]heptanes is well established. However, as far as we are aware, this study reports the structural frame of azabicyclo[3.1.1]heptane for the first time.

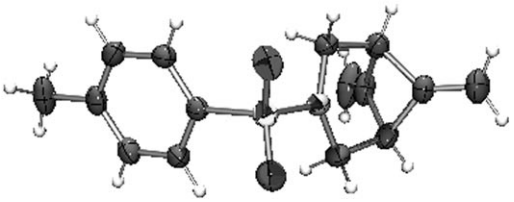
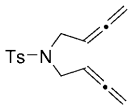
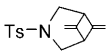
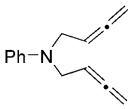
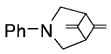
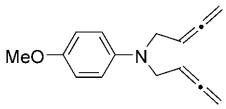
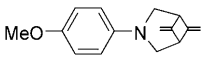
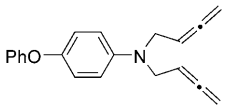
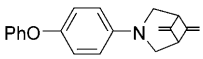
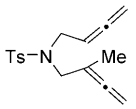
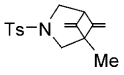
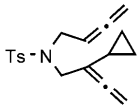
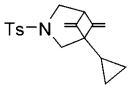
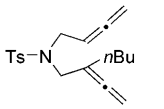
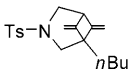
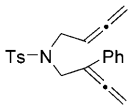
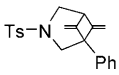
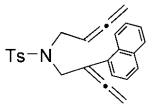
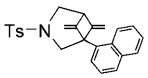
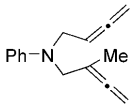
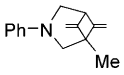
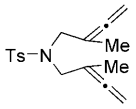
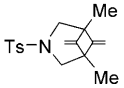
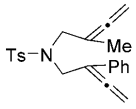
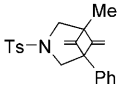
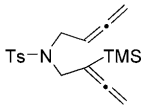


Figure 1. X-ray crystal structure of **1b**.

As the use of nonpolar solvents seemed to be significantly better than polar solvents, we focused our attention only on nonpolar solvents for further optimization. When the same reaction was carried out in benzene at room temperature for 1 day, the yield of **1b** dramatically increased to 67% (Table 1, entry 2). A 93% yield was obtained when the reaction performed at 75°C for 30 min (Table 1, entry 3). When the same reaction was carried out in toluene at room temperature, **1b** was obtained in 65% yield with concomitant formation of **1c** in 22% yield (Table 1, entry 4). When the reaction temperature was increased to 75°C, the yield of **1b** increased to 90% with a decrease in the yield of **1c** to 10% (Table 1, entry 5). A further increase of the reaction temperature was rather detrimental to the yield (Table 1, entry 6). A gradual increase of the amount of catalyst for the reaction at 75°C for 30 min gave **1b** in 87% and 96% for 7% and 10% catalyst, respectively (Table 1, entries 7 and 8). It is noteworthy that the reaction went to completion within 30 min with 5% of catalyst (93% **1b** and no **1c**) when benzene was used as the solvent. Thus, when we considered the proper balance between the amount of the catalyst used and the yield of the reaction, the optimized reaction conditions were as follows: 5 mol% $[Au(IPr)Cl]/AgBF_4$, benzene, at 75°C, and for 30 min. If the use of benzene as a solvent is unsuitable owing to its toxicity, the alternative reaction conditions might be 10 mol% $[Au(IPr)Cl]/AgBF_4$, toluene, at 75°C, and for 30 min.

We next studied the cycloisomerization of other bisallenes under the optimized reaction conditions (Table 2). Varying the substituent on the inner double bond did not harm to the yield of the reaction (Table 2, entries 5–9). Moreover, even having substituents on the inner double bonds of both allenyl groups did not inhibit the desired reaction (Table 2, entries 11 and 12). However, when TMS was introduced to this position (Table 2, entry 13), desilylated products **1b** and **1c** were isolated in 24% and 24% yields, respectively. Furthermore, cycloisomerization did not tolerate substitution at the terminal allenyl carbon atom.

Table 2: Au^I-catalyzed cycloisomerization of 1,5-bisallenes.[a]

Entry	Reactant		Product		Yield[b]
1		**1a**		**1b**	96
2		**2a**		**2b**	98
3		**3a**		**3b**	82
4		**4a**		**4b**	93
5		**5a**		**5b**	77
6		**6a**		**6b**	92
7		**7a**		**7b**	95
8		**8a**		**8b**	87
9		**9a**		**9b**	94
10		**10a**		**10b**	93
11		**11a**		**11b**	77
12		**12a**		**12b**	74
13[c]		**13a**	**1b** + **1c** (1:1)		48

[a] The reactant (0.3 mmol) was treated with 10 mol% of $[Au(IPr)Cl]/AgBF_4$ in toluene. [b] Yield of product isolated after chromatography. [c] 0.5 equiv catalyst was used.

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The cycloisomerization is sensitive to the tether. N–Ph tethered systems gave better yields than the well working N–Ts tethered systems (cf. Table 2, entry 1 vs 2 and 5 vs 10). When the system adopts *N*-(*p*-phenoxyphenyl) or easily removable *N*-(*p*-methoxyphenyl) tethers, the yields were still high (Table 2, entries 3 and 4). Unfortunately, however, no reaction was observed for 1,2,7,8-nonatetraene derivatives. Also, all of the reactant decomposed for bis(2,3-butadienyl)-ether derivatives, even at room temperature.

A number of different mechanistic pathways might be possible from the cationic [Au^{I}(bisallene)(NHC)] complex that include not only the twisted head-to-head [2+2] cycloaddition as in our case but also the head-to-head, the tail-to-tail, and the head-to-tail ones.[6c,15] To elucidate why the twisted head-to-head cycloaddition is more favorable than others, we performed DFT calculations. In the computational model, the NHC ligand (IPr) of the gold catalyst was represented by imidazol-2-ylidene and the substituent at the nitrogen atom in the bisallene substrate was replaced with hydrogen.

By the elaborate search for the possible reactive intermediates and transition states, we could construct a plausible mechanistic picture that explains the experimental results well. The result of these DFT calculations is shown in Figure 2. The major pathway for the formation of 6,7-dimethylene-3-azabicyclo[3.1.1]heptane is likely to be the stepwise **R1**→**I2**→**P2** route. The transition state between **R1** and **I2** (**TS-R1_I2**) is lower than that between **R1** and **I1** (**TS-R1_I1**) by 11 kcal mol^{-1}. Both **I1** and **I2** are formed by the nucleophilic attack of the C2′ atom in the pendant allenyl group to C1. The major difference between **I1** and **I2** is that the positive charge situated at C1′ is stabilized by the gold atom in **I2**, which facilitates the C2–C1′ bond formation. The pathway from **R1** to **P1** by a concerted mechanism necessitates a higher-barrier transition state **TS-R1_P1**, and thus is unfavorable.

When the C2′ atom in the pendant allenyl group attacks the C3 atom in the **R2** form, a reaction proceeds to the head-to-tail cycloaddition product **P3** through reactive intermediate **I3**. In this pathway, however, the reactive intermediate in which cationic carbon is stabilized by the gold atom was not identified and thus the reaction pathway follows the **R2**→**I3**→**P3** route exclusively. The reaction barrier for the first step (30.9 kcal mol^{-1}) is comparable to that between **R1** and **I2** (28.9 kcal mol^{-1}). However, the reaction barrier of the next step was 36.2 kcal mol^{-1}, which is more than 20 kcal mol^{-1} higher than that between **I2** and **P2**. As a result, the reaction favors the 6,7-dimethyleneazabicyclo[3.1.1]heptane.

The possibilities for the formation of the head-to-head and the tail-to-tail products were also considered. During the search for the possible reactant states, we could characterize a structure similar to that suggested by Ma et al.[6c] in which gold coordinated to the nitrgoen atom concomitantly with two allenyl moieties (**R3**, see the Supporting Information). Despite repeated attempts to locate a transition state that might lead to either the tail-to-tail or the head-to-head [2+2] cycloaddition products, we were not able to find one and thus tentatively concluded that those kinds of cycloaddition reactions are unfavorable under the conditions of the [(NHC)Au] catalyst.

From the results of the calculations described above, we propose that the Au-catalyzed cycloisomization reaction of bisallenes with an N tether to generate 6,7-dimethyleneazabicyclo[3.1.1]heptanes occurs by: 1) the nucleophilic attack of the pendant allenyl group to the gold-bound allene with a concomitant formation of a C1–Au–C2′ bridge (**I2**), and 2) C–C bond formation between C1 and C2′, which gives the final 6,7-dimethyleneazabicyclo[3.1.1]heptane skeleton (**P2**). The discovery by these DFT calculations of the intermediate state **I2**, which has not yet been suggested, is notable.

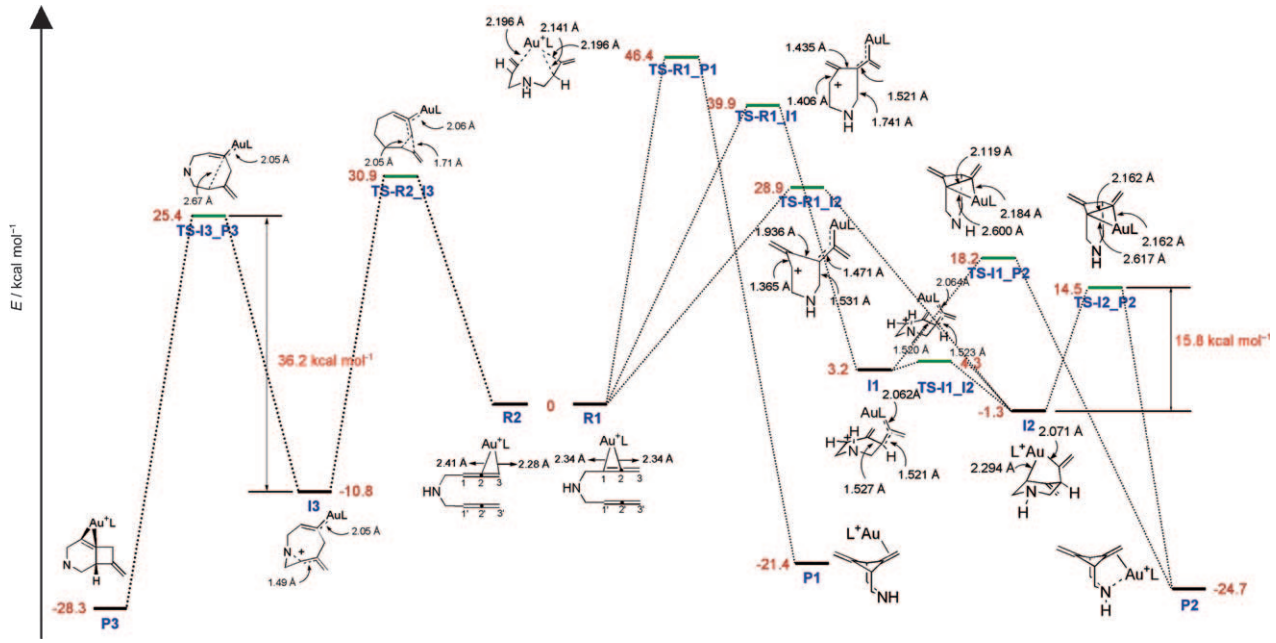

Figure 2. Proposed catalytic mechanism. Calculated ZPE-corrected energies are given in kcal mol^{-1} at the B3LYP/6-31G(d)-LANL2DZ level.

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In conclusion, the reaction described herein represents a new mode of gold NHC-catalyzed cycloisomerization of bisallenes with an N–R tether to generate 6,7-dimethyleneazabicyclo[3.1.1]heptanes. The newly synthesized compounds have two exocyclic double bonds, which could be modified in further reactions. Thus, the reaction studied herein should allow expeditious access to a diverse array of the 3-azabicyclo[3.1.1]heptane framework. The incorporation of a nitrogen atom in a carbocyclic cage compound frequently leads to pronounced changes in the chemical behavior. DFT calculations support a stepwise mechanism for the cycloisomerization by the initial formation of an η^1-allenyl gold(I) complex, followed by sequential C–C bond formations of C1–C2′ and C1′–C2 catalyzed by the gold–NHC complex. Further studies on the application of the new azabicyclo-[3.1.1]heptanes as molecular scaffolds and a comprehensive experimental and computational study will be reported in due course.

Experimental Section

General procedure (Table 2): [Au(IPr)Cl] (31 mg, 50 μmol), $AgBF_4$ (10 mg, 50 μmol), and toluene (3 mL) were added to a flame-dried Schlenk tube equipped with a stirring bar, and the mixture was stirred at room temperature for 3 min. Then 1,5-bisallene **a** (0.5 mmol) and toluene (2 mL) were added. The mixture was stirred at 75 °C until **a** disappeared completely (as checked by TLC). The mixture was purified by a flash chromatography to afford the desired 6,7-dimethylene-3-azabicyclo[3.1.1]heptane **b**.

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[14] The synthetic procedures and spectroscopic data of the new compounds are summarized in the Supporting Information. CCDC 708003 (**1b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[15] One of the referees suggested that C–C bond cleavage followed by re-formation could not be excluded as other mechanisms because of the existence of byproduct **1c**.

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