Cycloisomerization

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(N-Heterocyclic Carbene)Gold(I)-Catalyzed Cycloisomerization of Cyclohexadienyl Alkynes to Tetracyclo[3.3.0.0^{2,8}.0^{4,6}]octanes**

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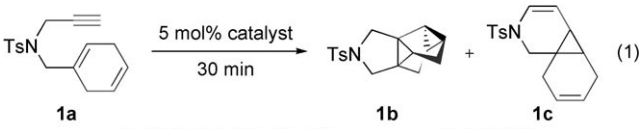
Transition-metal-catalyzed reactions of polyunsaturated systems have attracted much attention owing to their enormous synthetic potential in the preparation of a wide variety of carbo- and heterocyclic building blocks.[1] Among them, gold-catalyzed cycloisomerization is one of the hottest branches of research in the formation of functionalized cyclic structures.[2,3] In particular, the cycloisomerization of enynes producing novel modes is one of the most studied areas.[4] In research carried out in this field it must be taken into consideration that the reaction patterns vary widely, depending upon both the nature of the substrates and the catalyst systems. Minor changes in the substrate structures can lead to drastically different products. Thus, in many instances, some catalysts work only with a limited group of substrates bearing a particular tether. However, in some cases, substantial structural variations can be accommodated and different functional groups are found to be compatible.[5] We recently showed that the introduction of a cyclohexadienyl moiety to enynes influences the reaction pathway of cycloisomerization.[6]

Recently, the use of metal complexes of N-heterocyclic carbenes (NHCs) has attracted much attention.[7] However, the use of gold–NHC complexes in catalytic reactions is quite rare.[8] In our latest work we turned our attention to the synthesis of gold–NHC complexes and their use in catalytic reactions. Thus, in the hope of finding a new type of transformation, we tested a cycloisomerization of dienynes containing a cyclohexadiene unit in the presence of a catalytic amount of [Au(IPr)Cl]AgSbF$_6$ (IPr = *N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) [Eq. (1)]. To our great delight, a new cycloisomerized product formed as one of the two major products. According to its ^{1}H and ^{13}C NMR spectra, product **1b** contains no unsaturated C–C bonds. Compound **1b** is a biscyclopropanated product and a derivative of tetracyclo[3.3.0.0^{2,8}.0^{4,6}]octane.



[Au(IPr)]SbF$_6$, CH$_2$Cl$_2$, RT	(70%/30%)
[Au(IMes)]SbF$_6$, CH$_2$Cl$_2$, RT	(66%/34%)
[Au(PPh$_3$)]SbF$_6$, CH$_2$Cl$_2$, RT	(37%/ 7%)
PtCl$_2$, toluene, 80°C	(45%/55%)
GaCl$_3$, toluene, 60°C	(0%/ 0%)

(1)

Tetracyclo[3.3.0.0^{2,8}.0^{4,6}]octane derivatives have been known for some time.[9,10] However, there have been no reports on an intramolecular double-cyclopropanation reaction leading to this tetracyclic ring system. Thus, this is the first observation of their catalytic formation from dienynes. Herein we communicate our preliminary results.

As shown in Equation (1), the reaction of **1a** in the presence of a catalytic amount of [Au(IPr)Cl]AgSbF$_6$ in dichloromethane gave a mixture of **1b** and **1c** in 70% and 30% yields, respectively. The structure of **1b** was confirmed by X-ray diffraction analysis (Figure 1).[11] According to the X-ray diffraction study, two isomers (1:1) exist in the crystal. In structural terms, four carbon–carbon bonds are formed. Initially, this multiple reaction appeared to be rather complex, but it proved to be surprisingly general. Conversion of **1c** into **1b** in the presence or absence of the gold catalyst was not observed.

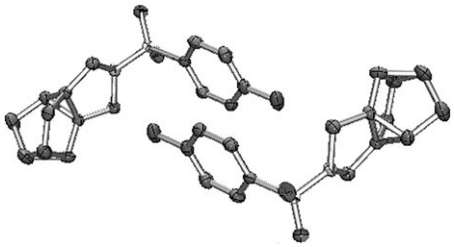


Figure 1. X-ray structure of **1b**.

Encouraged by these results, we screened reaction parameters such as the counter anion, solvent, reaction temperature, and reaction time (Table 1). When the reaction was conducted in dichloromethane (entries 1–5, Table 1), the effect of the counter anion on the yield of **1b** was negligible. However, the nature of the solvent (entries 5–8, Table 1) had a substantial effect on the efficiency of the reaction. The best yield (86%) was obtained in toluene solution. The temperature for the reactions in toluene (entries 8–11, Table 1) did not have a noticeable effect on the yield of **1b**. However, as

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

Entry	Cat. [mol%]	Additive	Solv.	*T* [°C]	*t*	Yield [%] (**1b**/**1c**)[a]
1	5	$AgSbF_6$	CH_2Cl_2	10–15	30 min	100 (70:30)
2	5	AgOTf	CH_2Cl_2	10–15	2 h	69 (60:9)
3	5	$AgClO_4$	CH_2Cl_2	10–15	30 min	79 (72:7)
4	5	$AgPF_6$	CH_2Cl_2	10–15	30 min	86 (71:15)
5	5	$AgBF_4$	CH_2Cl_2	10–15	30 min	79 (73:6)
6	5	$AgBF_4$	CH_3CN	10–15	18 h	100 (72:28)
7	5	$AgBF_4$	MeOH	10–15	18 h	45 (22:23)
8	5	$AgBF_4$	toluene	10–15	30 min	100 (86:14)
9	5	$AgBF_4$	toluene	−78	24 h	100 (87:13)
10	5	$AgBF_4$	toluene	0	30 min	100 (83:17)
11	5	$AgBF_4$	toluene	40	10 min	100 (89:11)
12	5	$AgBF_4$	toluene	10–15	10 min	100 (85:15)
13	2	$AgBF_4$	toluene	10–15	10 min	98 (82:16)

[a] Yield of product isolated after chromatography.

the reaction temperature was lowered, the reaction time increased. At 10–15 °C, the reaction time was shortened to 10 min with a high yield (entry 12, Table 1; 85%). Moreover, the amount of the catalyst could be reduced to 2 mol% and still lead to a high yield (entry 13, Table 1; 82%). A brief survey of different metal complexes such as [Au(IMes)Cl]$AgSbF_6$ (IMes = *N*,*N*′-bis(2,4,6-trimethylphenyl)-imidazol)-2-ylidene) (66%), [$AuCl(PPh_3)$]$AgBF_4$ (37%), and $PtCl_2$ (45%) indicated that [Au(IPr)BF_4] is the best catalyst of those examined for Equation (1).

We next investigated the cycloisomerization of various dienynes containing a cyclohexadienyl moiety (Table 2). Change of the tether group (or atom) from *N*-tosyl to oxygen and malonate (entries 2 and 3, Table 2) led to the isolation of **2b** and **3b** in 68% and 45% yields, respectively. Thus, variation of the tether group does not influence the reaction pattern. The introduction of a methyl group to the cyclohexadiene ring resulted in a mixture of two isomers (**4a** and **4a′**) in a ratio of 1:2. When this mixture was used as a substrate, the same ratio of two isomeric cyclized products (**4b** and **4b′**) was obtained in an overall yield of 67% (entry 4, Table 2). In the same way, treatment of **5a** and **5a′** yielded the same ratio of two products (**5b** and **5b′**) in an overall yield of 63% (entry 5, Table 2). The introduction of a methyl group at the position between the nitrogen atom and the cyclohexadiene moiety (entry 6, Table 2) did not change the reaction pathway. Thus the expected products were obtained in 75% yield. However, when two methyl groups were introduced to the cyclohexadiene ring (entries 8 and 10, Table 2), new cycloisomerized products (**7d** and **8d**) were formed.

The formation of **7d** was confirmed by ^1H and ^{13}C NMR spectroscopy and by X-ray diffraction analysis (Figure 2).[11] We first conjectured that prohibitively high strain would be generated when the two methyl groups are on the tetracyclo[3.3.0.$0^{2,8}$.$0^{4,6}$]octane ring. Alternatively, steric congestion between the NHC ligand and two methyl groups might prevent further reaction. Thus, the carbon–carbon bond-formation sequence stopped at **7d** to release the strain. However, when [Au(IMes)Cl]$AgBF_4$ was used as a catalyst (entries 7 and 9, Table 2), products **7b** and **8b** were obtained in 81% and 69% yields, respectively. Thus, it seems that a steric effect in the vicinity of the carbenoid moiety would be an important factor for the cyclopropanation to proceed. To examine the relation between **7b** and **7d**, **7d** was further reacted with and without the catalysts; however, no reaction was observed.

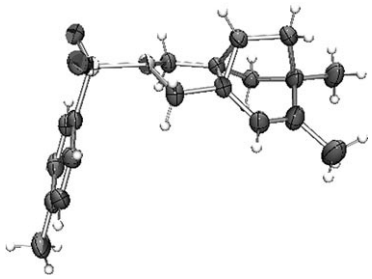
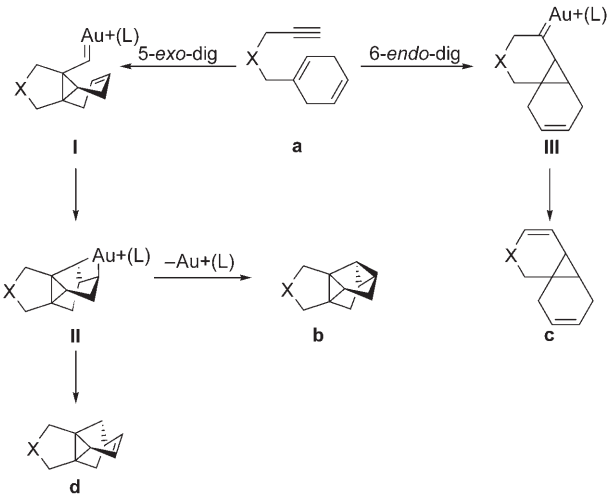


Figure 2. X-ray structure of **7d**.

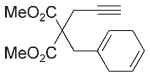
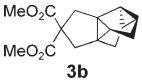
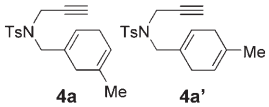
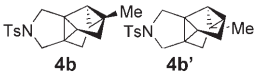
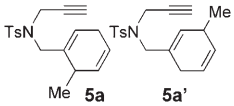
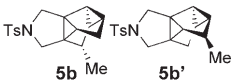
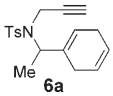
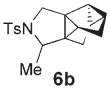
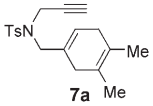
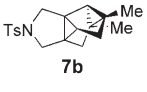
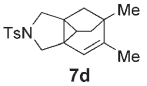
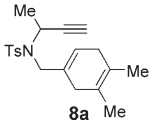
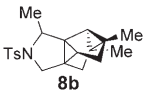
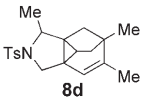
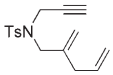
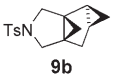
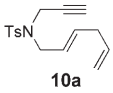
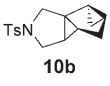
As an extension of the chemistry developed here, enynes bearing an open-chain diene, **9a** and **10a**, were treated with [Au(IPr)Cl]$AgBF_4$ under the same reaction conditions (entries 11 and 12, Table 2). Substrate **9a** was previously used by Shibata and Tahara[12] in the rhodium-catalyzed enantioselective intramolecular [2+2+2] cycloaddition reaction. After work-up, we obtained the tetracyclic compounds **9b** and **10b**, with two sides missing from the cage, in 77% and 70% yields, respectively. Thus, it seems that the biscyclopropanation is quite a general process provided the conformation and distances between bonds concerned are satisfied. However, in most entries except entries 2 and 3 shown in Table 2, minor amounts of the cyclopropanated products analogous to **1c** accompany the biscyclopropane derivatives formed as the major reaction products. Unfortunately, enyne substrates bearing an internal alkyne did not give the expected cage products.

A plausible reaction mechanism is outlined in Scheme 1.[13] The first step is the formation of the metal cyclopropyl carbene complexes **I** and (5-*exo*-dig) or **III** (6-*endo*-dig). A further reaction of **I** leads to the intermediate **II**. The interaction of **II** with the second C=C bond can take place



Scheme 1. Plausible mechanism of the biscyclopropanation.

Table 2: Gold-catalyzed cycloisomerization.[a]

Entry	Reactant	Product	*T* [°C]/ *t* [min]	Yield [%][b]
1	**1a**	**1b**	10–15/ 10	82
2	 **2a**	 **2b**	10–15/ 20	68
3	 **3a**	 **3b**	40/20	45
4	 **4a** **4a'**	 **4b** **4b'**	60/10	67 (22/45)
5	 **5a** **5a'**	 **5b** **5b'**	60/10	63 (12/51)
6	 **6a**	 **6b**	10–15/ 10	75
7	 **7a**	 **7b**	10–15/ 30	81
8	**7a**	 **7d**	60/10	86
9	 **8a**	 **8b**	60/10	69
10	**8a**	 **8d**	60/10	58
11	 **9a**	 **9b**	60/10	77
12	 **10a**	 **10b**	60/30	70

[a] Reaction conditions: 0.5 mmol of substrate was reacted with 2 mol% of [Au(IPr)]BF_4 in toluene. [b] Yield of isolated product. [c] [Au(IMes)]BF_4 was used.

according two ways. The first possibility is direct reductive elimination to form the second ring of **b**. In the other case, reductive elimination is not favored and β-H elimination forming new C=C double bond followed by reductive elimination would give **d**. When the carbenoid moiety in **II** is sufficiently close to react with the intramolecular olefin, **c** is produced by another cyclopropanation involving carbene transfer from the gold-carbenoid **II**.

In conclusion, we have developed a cycloisomerization reaction catalyzed by NHC–gold complexes which produces tetracyclo[3.3.0.$0^{2,8}$.$0^{4,6}$]octane derivatives from enynes bearing a cyclohexadiene group. The starting materials are readily prepared and the procedure is quite simple. Further studies on the properties of these analogues, an application of the methodology developed here to other substrates, and other reactions exploiting NHC–gold catalysts will be reported in due course.

Experimental Section

General procedure (Table 2): The enyne substrate (0.5 mmol) was added to a solution of [Au(IPr)Cl] (6 mg, 10 μmol) and $AgBF_4$ (2 mg, 10 μmol) in toluene (3 mL). The mixture was stirred until the starting material was completely consumed (as checked by TLC) at 10–60 °C. The mixture was purified by flash chromatography.

Substrates **1a**, **4a**, **4a′**, **7a**, **8a**, and **9a** were prepared by known methods.[6a,12] Other substrates were newly synthesized in this study (see the Supporting Information).

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[11] The synthetic procedures and spectroscopic data of the new compounds are summarized in the Supporting Information. CCDC- 645350 (**1b**) and CCDC-645351 (**7d**) contain 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.
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[13] For pioneering work on 1,6-enyne cycloisomerization involving cyclopropyl gold carbenoids, see: C. Nieto-Oberhuber, M. P. Muñoz, E. Buñuel, C. Nevado, D. J. Cárdenas, A. M. Echavarren, *Angew. Chem.* **2004**, *116*, 2456; *Angew. Chem. Int. Ed.* **2004**, *43*, 2402. The authors appreciate one of referees' suggestion (i.e., the involvement of intermediate **II** in Scheme 1) to explain the formation of **b** and **d**.

