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Gold(I)-catalyzed cycloisomerization of alkynyl hydroxyallyl tosylamides to 4-oxa-6-azatricyclo[3.3.0.0^{2,8}]octanes†

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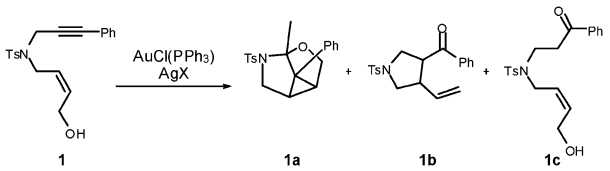
Reaction of alkyne allyl alcohols tethered with *N*-(*p*-tolylsulfonamide) in the presence of a cationic gold(I) catalyst gave new cycloisomerization products, 4-oxa-6-azatricyclo[3.3.0.0^{2,8}]octanes.

The transition metal-catalyzed cycloisomerization reactions have attracted much attention because they can provide many useful cyclized compounds from readily available starting materials.[1] The selective synthesis of different cyclic products from the same starting materials by subtle modifications of the catalytic conditions is an interesting but often troublesome topic for chemists.[2] In this regard, the gold-catalyst has widened its application by its versatile catalytic activities.[3,4]

Recently, Müller and coworkers have reported cycloisomerization reactions of alkyne allyl alcohols (AAAs) with rhodium,[5] iridium,[6] and palladium[7] catalysts. Nicolaou *et al.* also reported[8] a rhodium-catalyzed cycloisomerization using AAAs with terminal alkynes. In all cases, Alder-ene-type reaction products were isolated. The Montgomery group has reported a base-promoted, nickel-catalyzed cycloisomerization of AAAs and they also observed the formation of Alder-ene-type products.[9] We have studied the use of this substrate in an Au(I)-catalyzed cycloisomerization. While we were engaged in this study, Yeh *et al.* reported the result of such reactions.[10] The structure of the product in their work differs slightly from a typical Alder-ene-type product; 9-*endo-dig* cyclization was suggested as a plausible reaction pathway by the authors. Interestingly, however, we observed the formation of a new cycloisomerized product 5-methyl-6-tosyl-4-oxa-6-azatricyclo-[3.3.0.0^{2,8}]octane (eqn (1), **1a**) from the Au(I)-catalyzed cycloisomerization of a virtually same AAA starting material as that of Yeh's work yet under only subtly different reaction conditions. The structure of the 4-oxa-6-azatricyclo[3.3.0.0^{2,8}]-octane skeleton is exposed for the first time in this study as far as we are aware. We herein communicate our preliminary results.



(1)

When **1** was treated with 7 mol% of Au (7 mol% Au(PPh$_3$)Cl with 10 mol% of AgSbF$_6$) in THF at 50 °C, **1a** was obtained in 20% yield with a concomitant formation of **1b** and **1c** in 51% and 3% yields, respectively.[11] Compound **1b** was the product reported by Yeh *et al.* recently[10] and **1c** was a hydration product.[12] In contrast to Yeh's result where only *syn*-**1b** was formed, we obtained both *syn* and *anti* isomers of **1b**. We tentatively attribute the cause of this observed discrepancy to the reaction temperature; the reaction at elevated temperature might cause a loss of stereoselectivity. Hydration of alkynes to form the respective ketones by Au(I)-phosphine catalyst has been demonstrated.[13] The structure of **1a** was assigned based on a series of 1D and 2D NMR studies and was further confirmed by X-ray crystallography (Fig. 1).[11] According to the X-ray diffraction study, two isomeric (1 : 1) mixtures exist in crystals.

Encouraged by this observation, we began the optimization study to obtain a maximum yield of **1a**. Several parameters including counter-anion, solvent, temperature, and reaction time were examined. The most relevant results are presented in Table 1. It should be noted that the major difference in the

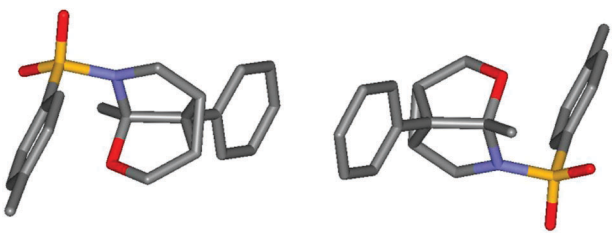


Fig. 1 X-Ray structure of **1a**. C, N, O, and S atoms are shown in gray, violet, red, and yellow, respectively. Hydrogen atoms are omitted for clarity.

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† Electronic supplementary information (ESI) available: CCDC 804791 (**1a**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc10907c

Table 1 Reaction of **1** under various reaction conditions[a]

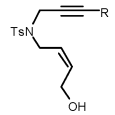
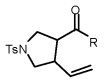
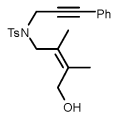
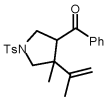
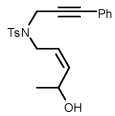
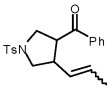
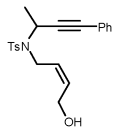
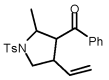
Entry	Au (mol%)	X (mol%)	T/°C	t/h	Yield[b] (%) 1a	1b	1c
1[c]	7	SbF_6 (10)	50	19	20	51	3
2[d]	5	SbF_6 (7)	40	5	45	22	10
3	5	SbF_6 (7)	50	4	42	12	12
4	5	PF_6 (7)	50	24	9	6	7
5	5	BF_4 (7)	50	3	31	20	18
6	5	ClO_4 (7)	50	24	14	28	17
7[e]	5	NO_3 (7)	50	24	0	0	0
8	5	OTf (7)	50	2	17	43	2
9	10	OTf (14)	85	1/6	12	68	0
10	5	SbF_6 (7)	85	0.5	55	15	0
11	10	SbF_6 (14)	85	1/6	72	11	0
12	10	SbF_6 (14)	115	1/12	60	13	0

[a] 0.15 mmol (or 0.3 mmol) of **1**, gold catalyst, and silver salt were reacted in 6.0 ml dichloroethane. [b] Isolated yield. [c] Solvent = THF. [d] Solvent = CH_2Cl_2. [e] 83% of the reactant recovered.

reaction conditions between Yeh's and ours was the reaction temperature. Therefore, we kept the reaction temperature at above the room temperature. We first tested the reaction in dichloromethane, THF, and 1,2-dichloroethane (DCE) solvents (entries 1–3). The yield was highly sensitive to the solvent (THF, 20%; CH_2Cl_2, 45%; DCE, 42%). Although the yield of **1a** was slightly higher in CH_2Cl_2 than in DCE, that of the side product **1b** was much lower in DCE. Thus DCE was our choice. With this solvent in hand, we screened the silver salts (entries 4–7). Reactions with $AgSbF_6$, $AgPF_6$, $AgBF_4$, and $AgClO_4$ salts produced **1a** in 55%, 9%, 31%, and 14% yields, respectively, and $AgSbF_6$ was thus the best. With $AgNO_3$, however, the reaction did not produce any products and 83% of the reactant was recovered. An interesting result was observed when AgOTf was used; the reaction produced **1b** as a major product (43%) with a minor formation of **1a** in 17% yield (entry 8). This result is reminiscent of the observation of Yeh's group.[10] Their [(PPh_3)AuCl]/AgOTf system at room temperature solely gave **1b** without producing **1a**. The observed difference strongly suggests that the reaction pathway is highly dependent upon the reaction temperature. Congruent with this, the yield of **1a** increased to 55% when the reaction temperature increased to 85 °C (entry 10) with a 30 min reaction time. Additional increase of the yield was achieved with the increase of the catalyst amount up to 10 mol% at the same temperature (72%, entry 11). With these reaction conditions, the reaction time was further shortened to 10 min. However, a reaction temperature higher than 85 °C was not helpful to enhance the yield of **1a**; at 115 °C (entry 12), for example, **1a** was isolated in 60% within 5 min. Likewise, the reaction with AgOTf at 85 °C gave rise to the decrease of the yield of **1a** with concomitant increase of **1b** (12% and 68% yields, respectively) relative to that at 50 °C. It is obvious that both temperature and counter anion play important roles in determining the reaction pathway. With the results described above, our optimized reaction conditions were established as follows: 10 mol% $Au(PPh)_3Cl$, 14 mol% $AgSbF_6$, DCE, 85 °C, and 10 min.

With the optimal conditions in hand, the substrate scope of the Au(I)-catalyzed cyclization reaction was investigated with a series of AAAs, and the results are summarized in Table 2.[11]

Table 2 Gold-catalyzed cycloisomerizations[a]

Entry	Reactant	Product[b] (%)	
	 **1-12**	 **1a-12a**	 **1b-12b**
1	R = phenyl	72	11
2	4-$C_6H_4OCH_3$	55	32
3	4-$C_6H_4CH_3$	65	18
4	3,5-$C_6H_3(CH_3)_2$	65	7
5	4-C_6H_4Cl	62	10
6	Naphthyl	65[c]	9
7	Methyl	48	0
8	Ethyl	50	9
9	*n*-Butyl	29	10
10	Cyclopropyl	62	10
11[d]	Cyclohexenyl	42	7
12[e]	Vinyl	30	Trace
13	 **13**	 **13a** 21	 **13b** 49
14	 **14**	 **14a** 19	 **14b** 48 (*syn*:*anti*=1:2)
15[f]	 **15**	 **15a** 35	 **15b** trace

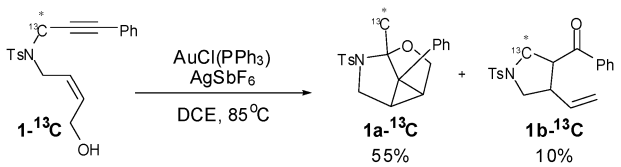
[a] Reaction conditions: 0.15 mmol of substrate, 10 mol% $AuPPh_3Cl$, and 14 mol % $AgSbF_6$ were reacted in 6 ml DCE at 85 °C for 10 min. [b] Isolated yields. [c] Two isomers are mixed. [d] 51% reactant recovered. [e] 28% of the reactant recovered and a trace amount of **b** was obtained. [f] 20 mol% catalyst used.

All the reactions were completed within 10 min. A certain type of substrates only gave the desired product in low yield with considerable amounts of reactants recovered (entries 11 and 12, 51% and 28% recovered) even under the prolonged reaction time. A variety of substrates with different substituents at the terminal alkyne have been proved to be useful candidates for the synthesis of 4-oxa-6-azatricyclo[3.3.0.$0^{2,8}$]octanes. In particular, substrates with all kinds of aryl groups tested in this study (entries 1–6) gave 4-oxa-6-azatricyclo[3.3.0.$0^{2,8}$]octanes in good yields (55–72%). It seems that the electronic or steric effect of the substituent(s) on the *para*-position of the arene ring was rather insensitive to the yield of the reaction. Substrates with alkyl substituents at the terminal alkyne afforded the corresponding 4-oxa-6-azatricyclo[3.3.0.$0^{2,8}$]octanes in moderate yields (42–62%, entries 7–10) except substrate **10** (29%). However, substrates with alkenyl–alkynyl (entries 11 and 12) gave a rather poor yield (30–42%). With a methyl substituent, in addition to **9a** (48%), a concomitant formation of **9c** (18%) was observed. When two methyl groups were introduced to an

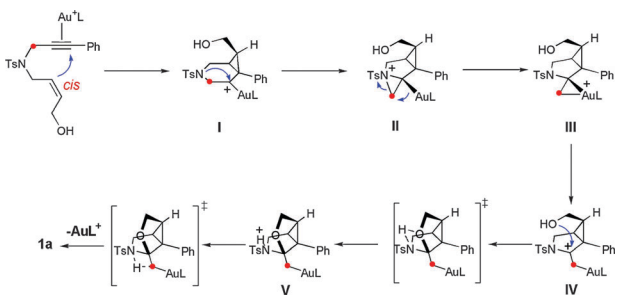
olefin group (entry 13), **13a** and **13b** were isolated in 21% and 49% yields, respectively. When an alkynyl tosylamide bearing a secondary alcohol was used as a substrate (entry 14), a mixture of **14a** and **14b** was isolated in 19% and 48% yields, respectively, and further purification of **14b** leads to separation of *syn* and *anti* isomers in a ratio of 1 : 2. When a methyl group was introduced to the 3-position of 1,6-enyne (**15**), a cyclization reaction was found not to take place in the presence of 10 mol% Au catalyst and the reactant was recovered; **15a** was isolated in 35% yield with a trace amount of **15b** only in the presence of 20 mol% of Au catalyst. Interestingly, when the protecting group on the *N* tether was changed from a tosyl to Ph group, the catalytic system was ineffective and the reactant was recovered. It seems that the electron-donating substituent further increased the coordinating ability of the amino group, which might block the alkyne from coordinating with the gold species. Therefore, no cycloisomerization product was observed with this substrate.

The formation of a new 4-oxa-6-azatricyclo[3.3.0.$0^{2,8}$]octane skeleton appeared to be quite interesting in terms of its reaction mechanism. In order to determine the position where the ^{13}C atom is located in the cycloisomerized product we performed a ^{13}C-labeling experiment using the simple enyne **1**-^{13}C. The reaction of **1**-^{13}C in the presence of $Au(PPh_3)Cl/AgSbF_6$ in DCE at 85 °C for 10 min gave **1a**-^{13}C in 55% yield, showing that the C3–N bond cleavage occurred during the reaction (Scheme 1). It is important to note that the C3–N bond remained intact in **1b**-^{13}C as the ^{13}C atom was found to be in the aza-5-membered ring.

On the basis of the above results and previous study,[14] a plausible reaction mechanism was proposed (Scheme 2). The first step is a gold(I)-catalyzed cycloisomerization of an enyne to a cyclopropanated compound (I), followed by a transannulation between the nitrogen atom and the carbon atom attached to the gold cation to give an intermediate II. The ring contraction through intermediate II is intriguing and might explain the different reactivity observed in this system. Shift of the gold leads to formation of an intermediate III which may



Scheme 1 Gold-catalyzed cycloisomerization of ^{13}C labelled enyne **1**.



Scheme 2 A plausible reaction mechanism.

equilibrate with an intermediate IV. Because of the significant carbocationic character at the alkynyl carbon adjacent to the *N*-Ts group in IV, a nucleophilic addition of the hydroxy oxygen occurs to give an intermediate V.[15] Proton transfer followed by protodemetalation in V affords the product and regenerates the gold(I) catalyst in the catalytic cycle.

In conclusion, we have reported a novel gold-catalyzed cycloisomerization of alkynyl hydroxyallyl tosylamides, leading to the synthesis of oxaazatricyclic compounds in a concise manner. Change in the reaction conditions completely alters the reaction pathway. On the basis of the experimental results, a possible reaction mechanism has been proposed. Further studies are needed to delineate the intimate mechanistic steps and expand the scope of this cyclization process.

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