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COMMUNICATION

Catalytic Dearomative Spirocyclization via Gold Carbene Species Derived from Ynamides: Efficient Synthesis of 2-Azaspiro[4.5]decan-3-ones

Mamoru Ito,[a] Ryosuke Kawasaki,[a] Kyalo Stephen Kanyiva,[b] and Takanori Shibata*[a,c]

Dedication ((optional))

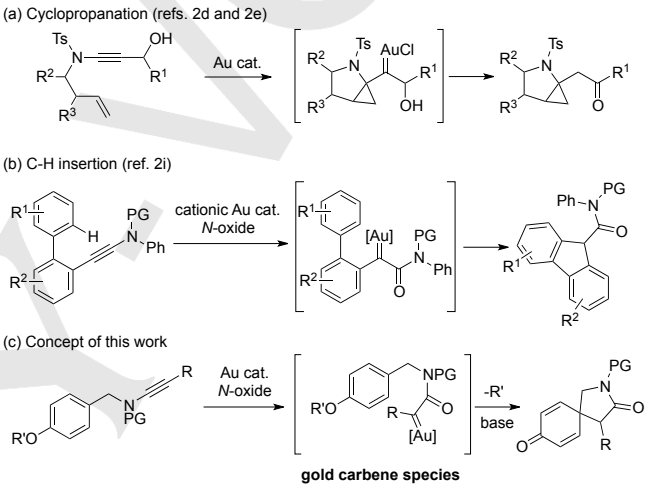
Abstract: An intramolecular catalytic dearomatization of phenols via gold carbene species proceeded to provide 2-azaspiro[4.5]decan-3-ones. The use of NHC ligand and water as a co-solvent was critical for achieving high reactivity. This reaction did not require hazardous diazo compounds as carbene sources and proceeded even under air. The obtained spirocyclic product could be readily transformed into a gabapentin derivative by hydrogenation and deprotection.

Introduction

Gold-catalyzed transformations can be used to realize the various facile syntheses of complex organic molecules generally under mild conditions.[1] In particular, gold carbene species exhibit unique reactivity in cyclopropanation (Scheme 1a) and X-H (X = C, O, N) insertion (Scheme 1b).[2] Therefore, it would be highly desirable to explore the reactivity of gold carbene species in organic synthesis. Among various protocols for the preparation of gold carbene species,[3] diazo compounds are the most conventional carbene source. To avoid the use of hazardous compounds, the oxidation of alkynes using a gold catalyst and *N*-oxide as an oxidant has been developed as an attractive alternative.[4]

The spirocyclic structure is a common skeleton in various natural products and biologically active compounds.[5] In particular, spirocyclohexadienones, which can be synthesized by the dearomatization of phenols, are attractive structures because of their biological activities.[6] Various strategies for the dearomatization of phenols have been developed:[7] oxidative spirocyclization using hypervalent iodine, Friedel-Crafts-type spirocyclization, and a radical-type reaction have been reported.

Against this background, we envisioned a catalytic dearomative spirocyclization of phenols by using gold carbene species generated from alkynes (Scheme 1c). There have been only a few previous reports of the dearomative spirocyclization of phenols via metal carbene species, and hazardous diazo compounds were used as carbene sources in all cases.[8]



Scheme 1. Reactivity of gold carbene species and concept of this work.

Results and Discussion

We chose 4-methoxybenzylamine derivative **1a** as a model substrate and subjected it to dearomative spirocyclization using a cationic gold catalyst prepared from chloro(triphenylphosphine)gold(I) and silver hexafluoroantimonate in a mixed solvent of 1,2-dichloroethane (DCE) and water (Table 1, Entry 1). As a result, the desired spirocyclic compound **2a** was obtained in moderate NMR yield. The major byproduct was diketone, which was probably generated by further oxidation of the gold carbene complex. To accelerate the desired spirocyclization, an electron-deficient phosphine ligand was examined, but the yield did not improve and formation of the diketone was observed (Entries 2 and 3). The counter anion did not affect the present reaction (Entries 4 and 5). While only a trace amount of product was obtained under gold complex-free conditions, a comparable yield was achieved under silver salt-free conditions (Entries 6 and 7). We further screened NHC ligands using neutral gold catalyst (Entries 8-13). Among them, IPr and SIPr suppressed the formation of diketone and the NMR yield reached ca. 80%. This results is probably due to the fact of that bulky NHC ligands prevented the attack of *N*-oxide to the gold carbene intermediate.[9] When the reaction was conducted in DCE as a sole solvent, the yield was drastically decreased and a significant amount of diketone was formed

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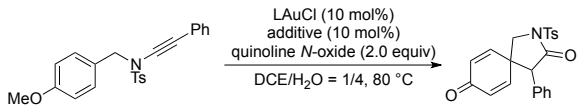
(Entry 9). These results mean that Cl of LAuCl was replaced by OH from water, and LAu(OH) would be an active catalyst.[10,11] We next added a catalytic amount of quinoline as a basic additive and the isolated yield improved to 85% (Entry 14).[12] The base probably captured the *in situ*-generated hydrogen chloride. The reaction could also be conducted on larger reaction scale (Entry 15). Finally, we conducted the reaction under air, and did not observe a significant decrease in the yield, which demonstrated the robustness of the present catalytic system (Entry 16).

Table 1. Screening of reaction conditions.[a]



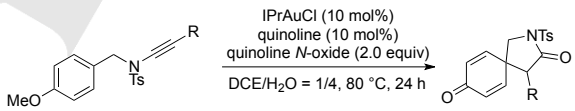
1a **2a**

Entry	Ligand (L)	Additive	Yield [%][b]
1	PPh_3	$AgSbF_6$	55
2	$P(C_6F_5)_3$	$AgSbF_6$	17
3	$P(p\text{-}CF_3C_6H_4)_3$	$AgSbF_6$	34
4	PPh_3	AgOTf	55
5	PPh_3	$AgBF_4$	56
6[c]	none	$AgSbF_6$	trace
7	PPh_3	none	51
8	IPr	none	81 (75)
9[d]	IPr	none	14
10	SIPr	none	82 (72)
11	ICy	none	32
12	IMes	none	63 (57)
13	SIMes	none	(63)
14	IPr	quinoline	(85)
15[e]	IPr	quinoline	(79)
16[f]	IPr	quinoline	81

[a] Reaction conditions: **1a** (0.05 mmol), Au cat. (10 mol%), additive (10 mol%), quinoline *N*-oxide (0.1 mmol), DCE (0.1 mL), H_2O (0.4 mL), 80 °C, 1 h (Entries 1-7) or 24 h (Entries 8-14, 16). [b] NMR yields were measured by using 1,1,2,2-tetrachloroethane as an internal standard. Isolated yield was shown in parentheses. [c] The reaction was conducted without gold complexes. [d] DCE (0.5 mL) was used as a sole solvent. [e] The reaction was conducted four times as much scale as other entries: **1a** (0.20 mmol), Au cat. (10 mol%), additive (10 mol%), quinoline *N*-oxide (0.2 mmol), DCE (0.4 mL), H_2O (7.6 mL), 80 °C, 24 h [f] The reaction was conducted under air. IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene, SIPr = 1,3-Bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene, ICy = 1,3-dicyclohexylimidazol-2-ylidene, IMes = 1,3-dimesitylimidazol-2-ylidene, SIMes = 1,3-dimesityl imidazolidin-2-ylidene.

Under the reaction conditions for Entry 14 in Table 1, various aryl-substituted ynamides were subjected to Au(I)-catalyzed dearomative spirocyclization (Table 2). A variety of halophenyl-substituted ynamides **1b**-**1e** provided spirocyclic compounds **2b**-**2e** in good to high yield (Entries 1-4). *Para*-, *ortho*-dihalo- and *para*-methoxycarbonyl-substituted phenyl groups could be used in this reaction, but more quinoline (20 mol%) was required (Entries 5 and 6). The reaction of *para*-trifluoromethyl-substituted phenyl group-substituted ynamide **1h** gave **2h** in the best yield of 98% (Entry 7). In contrast, an *ortho*-trifluoromethylphenyl group suppressed the reaction probably due to steric hindrance, and the yield of **2i** was low (Entry 8). The reactivities of electron-rich aryl group-substituted ynamides were low (Entries 9-12). In particular, *p*-tolyl-substituted ynamide **1j** required a higher reaction temperature with the use of Ph_3PAuCl as a catalyst and a moderate yield was achieved (Entry 9), but the yield of *p*-anisyl-substituted ynamide **1m** was low even under the same reaction conditions (Entry 12). Pyridyl-substituted ynamide **1n** was a good substrate (Entry 13). The spirocyclization of terminal alkyne **1o** was conducted with chloro(triphenylphosphine)gold(I) using 4-phenylpyridine *N*-oxide as an oxidant at room temperature to provide **2o** in a moderate yield (Entry 14). In all entries, ynamides were completely consumed, and the formation of diketones were ascertained as by-products.

Table 2. Scope of substituents on alkyne terminus.



1 **2**

Entry	R	Yield [%][a]
1	4-FC_6H_4 (**1b**)	68 (**2b**)
2	4-ClC_6H_4 (**1c**)	30, 79[b] (**2c**)
3	4-BrC_6H_4 (**1d**)	85 (**2d**)
4	3-ClC_6H_4 (**1e**)	82 (**2e**)
5	4-Br-2-FC_6H_3 (**1f**)	31, 69[b] (**2f**)
6	4-(CO_2Me)-C_6H_4 (**1g**)	86 (**2g**)
7	4-$CF_3C_6H_4$ (**1h**)	98 (**2h**)
8	2-$CF_3C_6H_4$ (**1i**)	27, 35[b] (**2i**)
9	4-MeC_6H_4 (**1j**)	37, 51[c] (**2j**)
10	3-MeC_6H_4 (**1k**)	52 (**2k**)
11	2-MeC_6H_4 (**1l**)	49 (**2l**)
12	4-$MeOC_6H_4$ (**1m**)	trace, 14[c] (**2m**)
13	3-pyridyl (**1n**)	67 (**2n**)
14	H (**1o**)	22, 53[d] (**2o**)

[a] Isolated yield. [b] Quinoline (20 mol%), DCE (0.2 mL) and H_2O (0.4 mL) were used. [c] Ph_3PAuCl (10 mol%), quinoline (20 mol%) and quinoline *N*-oxide (0.1

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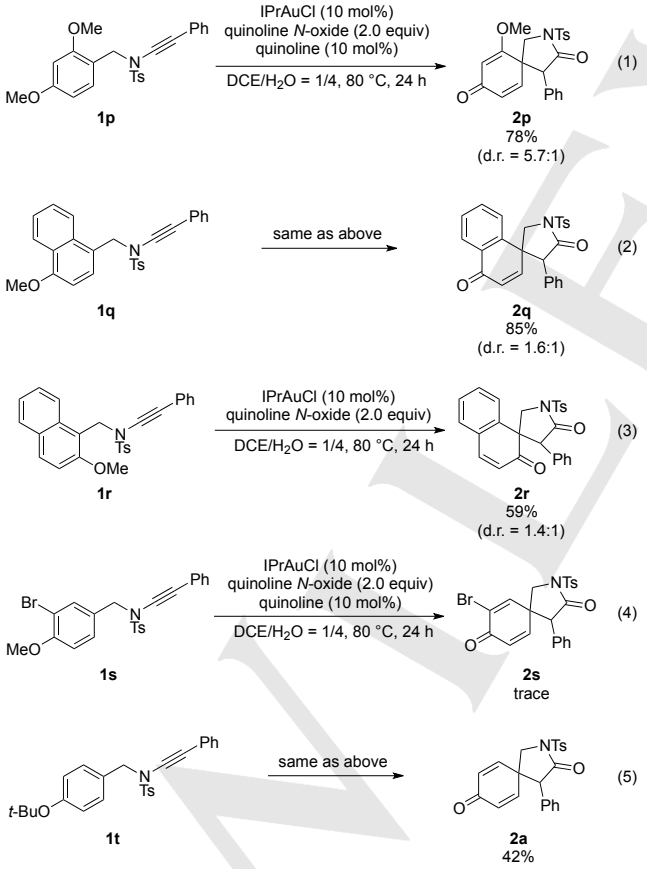
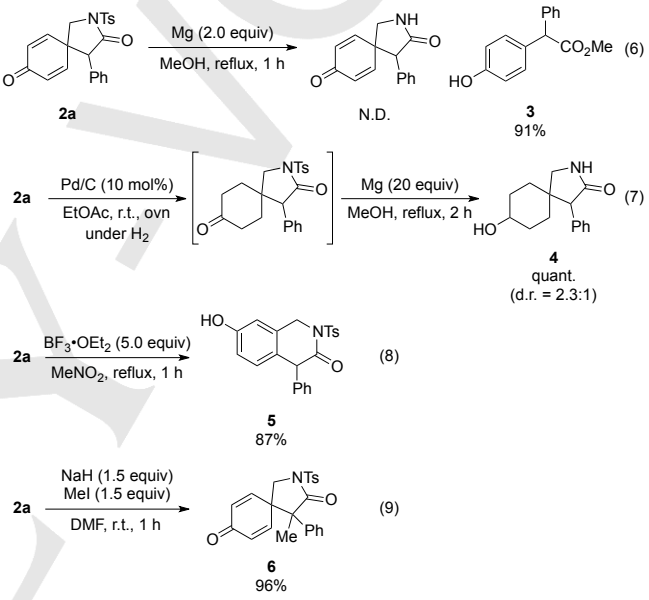
mmol) was used in a mixed solvent of PhCl (0.2 mL) and H_2O (0.8 mL) at 100 °C for 24 h. [d] **1n** (0.05 mmol), Ph_3PAuCl (10 mol%), 4-phenylpyridine *N*-oxide (0.1 mmol) in a mixed solvent of DCE (0.1 mL) and H_2O (0.4 mL) at rt for 5 h.

Next, we examined electron-rich arenes other than those with a *p*-anisyl group. The reaction of 2,4-dimethoxybenzylamine derivative **1p** gave spirocyclic compound **2p** in high yield and high diastereoselectivity [Scheme 2, Equation (1)]. Naphthol derivatives were subjected to the optimized conditions [Scheme 2, Equations (2) and (3)]. The reaction of 1-naphthol derivative **1q** provided spirocyclic compound **2q** in high yield as a mixture of diastereomers. On the other hand, the reaction of 2-naphthol derivative **1r** gave the desired spirocyclic compound **2r** in high yield without the addition of quinoline. 3-Bromo-4-methoxybenzylamine derivative **1s** was subjected to the optimized conditions, but only a trace amount of the desired spirocycle **2s** was obtained [Scheme 2, Equation (4)]. This result indicated that the electron-withdrawing group on the benzyl amine moiety decreased the nucleophilicity of the *ipso* position. When *tert*-butoxy-substituted **1t** was used as a substrate, the dearomatized product **2a** was obtained, albeit in lower yield than with methoxy-substituted substrate **1a** [Scheme 2, Equation (5)].



Scheme 2. Scope of arylmethylamino moiety.

Next, we examined deprotection of the tosyl group, but the reaction failed and diarylacetate **3** was obtained by rearomatization of the cyclohexadienone moiety via C-C bond cleavage [Scheme 3, Equation (6)].[13] To prevent this rearomatization, the diene moiety was reduced by Pd-catalyzed hydrogenation. Subsequent deprotection of the tosyl group proceeded smoothly with Mg, and synthetically important gabapentin lactam derivative **4** was obtained quantitatively in two steps [Scheme 3, Equation (7)].[14] In contrast, treatment of **2a** with a Lewis acid induced ring expansion to give isoquinolone **5** in high yield [Scheme 3, Equation (8)].[15] Alkylation of the α-position of the amide group under basic conditions proceeded smoothly to give **6** in high yield [Scheme 3, Equation (9)].



Scheme 3. Synthetic transformations of spirocyclic compound **2a**.

Regarding the mechanism, we propose the formation of acyl gold carbene species prepared from ynamide **1** and Au(I) complex with a NHC ligand as the initial step (Scheme 4, **A**).[16] This electron-deficient carbene species undergoes nucleophilic attack from the *ipso* position to give spirocycle **B**. The resulting spirocyclic compound **B** reacts with water to give **C**.[11] The presence of a catalytic amount of quinoline may promote this hydrolytic demethylation step by increasing the basicity.[12] Finally, protodemetallation of **C** provides desired spirocyclic compound **2** and regenerates the gold catalyst.

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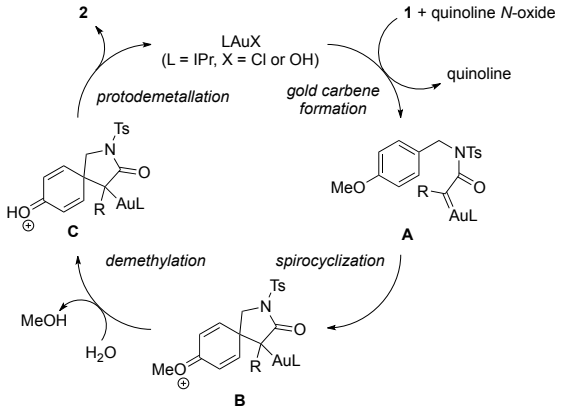

Scheme 4. Plausible reaction mechanism.

Conclusions

We have described an efficient synthesis of 2-azaspiro[4.5]decan-3-one derivatives by catalytic dearomative spirocyclization via a gold carbene intermediate generated from alkynes. This protocol was robust and did not require hazardous diazo compounds as carbene sources. The obtained spirocyclohexadienones could be transformed into synthetically useful compounds, such as a gabapentin lactam derivative and phenol derivatives. Further studies to explore the reactivity of the gold carbene intermediate are now underway in our laboratory.

Experimental Section

See supporting information.

Acknowledgements

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Keywords: gold • dearomatization • spirocyclohexadienones • carbene • aqueous media

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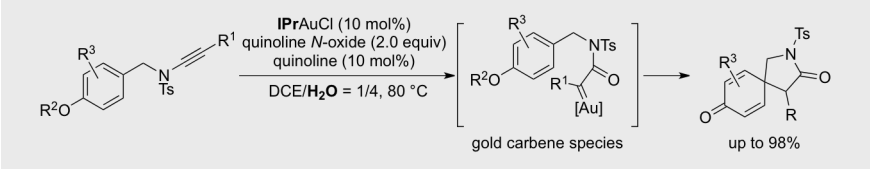

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