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Gold- and Silver-Catalyzed Intramolecular Hydroamination of Terminal Alkynes: Water-Triggered Chemo- and Regioselective Synthesis of Fused Tricyclic Xanthines

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Abstract: A simple, convenient and green synthetic approach to diverse fused tricyclic xanthines has been developed *via* gold(I) complex-catalyzed intramolecular hydroamination or silver(I)-catalyzed isomerization-hydroamination of terminal alkynes under microwave irradiation in water. The first synthesis of N9-annelated xanthines has also been reported.

Keywords: gold; hydroamination; silver; terminal alkynes; xanthines

Xanthines (**a**) – that belong to an important class of heterocyclic compounds – have gained significance in the synthesis of drugs and pharmaceutical products.[1] Various xanthine derivatives and other caffeine-based heterocycles have been suggested to be potential therapeutic agents for intervention in Alzheimer's disease,[2] asthma,[3] diabetes,[4] Parkinson's disease,[5] and cancer[6]. Fused tricyclic xanthines (**b**) (Figure 1) have been reported to be potent and selective antagonists of human A_{2A} adenosine receptors, and have potential activities as anticonvulsants to treat chemically induced seizures.[7] Although oxygen- or nitrogen-containing annelated xanthine derivatives have been synthesized by bromination of 8-unsubstituted xanthines and subsequent base-promoted cyclization,[8] it is important to develop a direct and efficient method featuring mild reaction conditions for the synthesis of fused tricyclic xanthines.

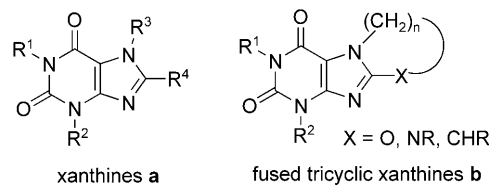
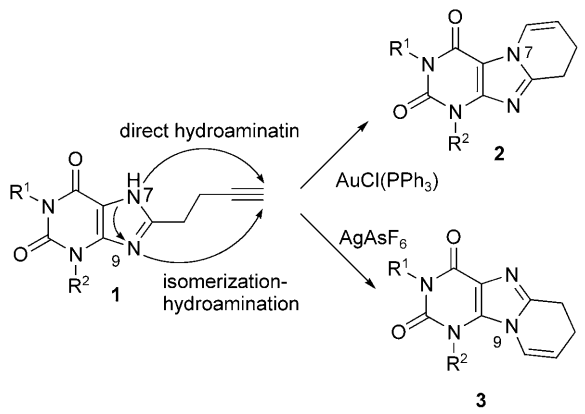


Figure 1. The structures of xanthines **a** and fused tricyclic xanthines **b**.

Recently, the transition metal-catalyzed intramolecular hydroamination of alkynes has been identified as an important synthetic reaction that can be used to synthesize various heterocycles in an efficient and atom-economic manner.[9] Among the numerous methods available for this reaction, Au-catalyzed synthesis of various five- and six-membered N-heterocycles such as indoles,[10] pyrroles,[11] quinolines,[12] and isoquinolines[13] has received considerable attention. We have previously developed an efficient and green method – Au(I)-catalyzed regioselective intramolecular hydroamination – for the synthesis of indoles under microwave irradiation in water.[14] In the light of our ongoing efforts to develop new methods for synthesizing heterocycles using transition metal catalysts,[15] in this study, we report the synthesis of fused tricyclic xanthines by microwave-assisted chemo- and regioselective cyclization of 8-(but-3-ynyl)-xanthines **1**[16] in water using an Au(I) complex or an Ag(I) catalyst. We found that the cationic Au(I) complex catalyzed the direct intramolecular hydroamination of **1** and a subsequent 6-*endo-dig* process afforded N7-annelated xanthines **2**; on the other hand, the Ag(I)-cat-

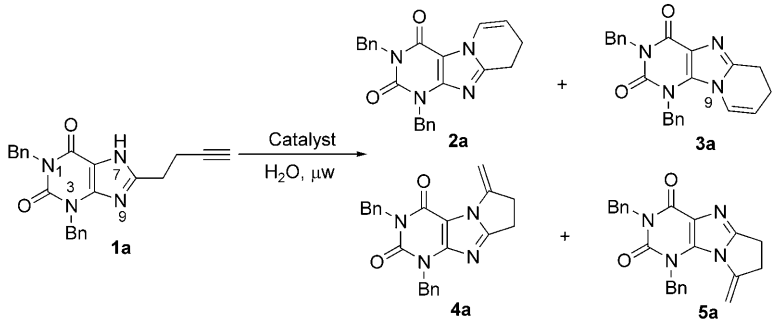


Scheme 1. Two different processes to diverse fused tricyclic xanthines **2** and **3**.

alyzed isomerization-hydroamination of **1** afforded N9-annelated xanthines **3** (Scheme 1). This catalytic method of synthesizing fused tricyclic xanthines is efficient and environmentally friendly. To the best of our knowledge, this is the first report of the synthesis of N9-annelated xanthines **3** by the aforementioned method.

Initially, we investigated the effectiveness of various combinations of catalysts and reaction conditions using 1,3-dibenzyl-8-(but-3-ynyl)-xanthine **1a** as the model substrate. The results of these experiments are shown in Table 1 (also see Table S1 in Supporting Information). Under catalyst-free conditions, the reaction could not proceed and only the starting material **1a** was recovered (Table 1, entry 1). However, under microwave heating for 30 min in the presence of 10 mol% $AuCl(PPh_3)$ in water at 120 °C, the desired N7-annelated product **2a** was formed in 27% yield; a small amount (3%) of the N9-annelated product **3a** was also isolated (Table 1, entry 2). The structures of **2a** and **3a** were confirmed by X-ray diffraction (XRD) studies (Figure 2).[17] Subsequently, we optimized the reaction conditions to obtain a single product in high yield. When the reaction was carried out using 10 mol% $AuCl(PPh_3)$ under microwave heating

Table 1. Optimization of the reaction conditions.[a]



Entry	Catalyst (mol%)	T [°C]	Yield [%][b]			
			2a	**3a**	**4a**	**5a**
1[c]	–	100	0	0	0	0
2	$AuCl(PPh_3)$(10)	120	27	3	0	0
3	$AuCl(PPh_3)$(10)	150	86	10	0	0
4[c]	$AuCl_3$ (10)	150	0	0	0	0
5	AuCl (10)	150	21	49	0	0
6[d]	Au catalyst X (10)	150	trace	0	0	0
7	$AuCl(PPh_3)$(10)/$AgSbF_6$ (10)	150	54	36	2	0
8	$AgSbF_6$ (10)	150	17	70	5	0
9	Ag_2CO_3 (10)	150	17	36	3	0
10[c]	AgI (10)	150	0	0	0	0
11	$AgNO_3$ (10)	150	11	44	2	0
12	$AgBF_4$ (10)	150	17	69	5	0
13	AgOTf (10)	150	17	69	5	0
14	$AgAsF_6$ (10)	150	18	72	5	0
15	$AuCl(PPh_3)$(5)	150	70	8	0	0
16	$AgAsF_6$ (5)	150	13	60	3	0

[a] *Reaction conditions:* **1a** (0.2 mmol), catalyst (0.02 mmol), H_2O (3 mL) for 10–30 min.
[b] Yield of isolated products based on **1a**.
[c] 100% of **1a** was recovered.
[d] Au catalyst X = [Tris(2,4-di-*tert*-butylphenyl)phosphite]gold chloride.

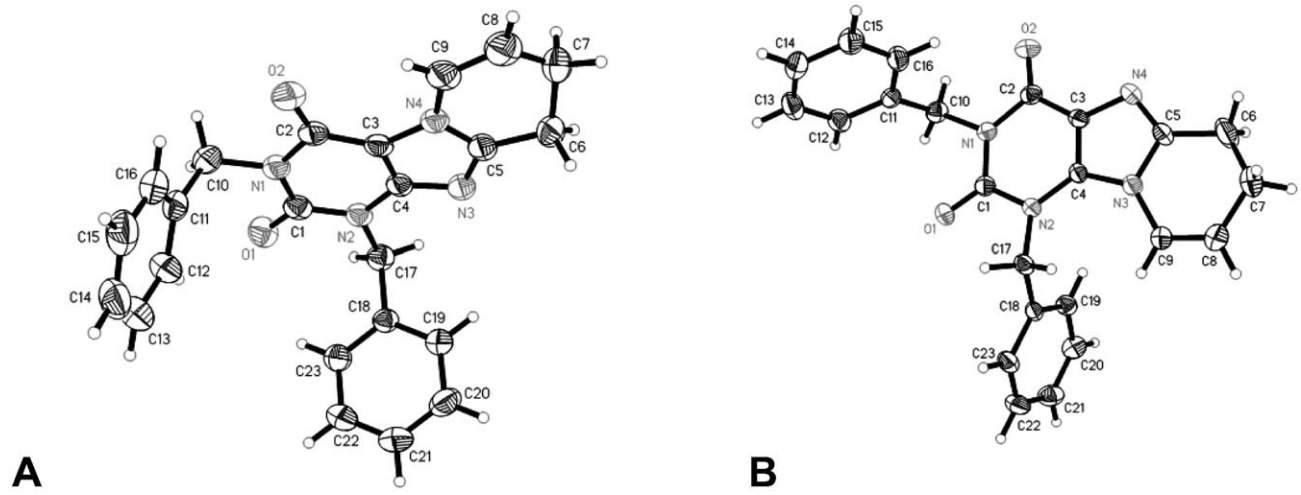


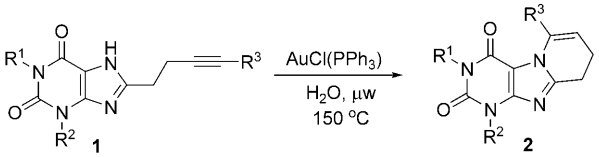
Figure 2. X-ray structures of **2a** (**A**) and **3a** (**B**).

for 10 min in water at 150 °C, **2a** was isolated in an excellent yield (86%) along with **3a** in 10% yield. No 5-*exo-dig* product **(4a** or **5a)** was detected in this reaction (Table 1, entry 3). The reaction carried out using a combination of 10 mol% $AuCl(PPh_3)$ and 10 mol% $AgSbF_6$ afforded **2a** and **3a** in 54% and 36% yields, respectively (Table 1, entry 7). In addition, the yield of **3a** increased to 72% when the reaction was carried out under microwave heating in water for 10 min at 150 °C using 10 mol% $AgAsF_6$ as the catalyst. However, a reduction of the catalyst [$AuCl(PPh_3)$ or $AgAsF_6$] concentration to 5 mol% resulted in incomplete consumption of **1a** (Table 1, entries 15 and 16). Furthermore, water was thought to play an important role in this reaction because the reaction did not proceed when toluene or absolute ethanol was used as the solvent (Supporting Information, Table S1, entries 11 and 12). This water-triggered reaction is similar to that reported in literature, in which water was found to play a key role to promote the gold- or silver-catalyzed reaction of terminal alkynes and aldehydes.[18,19]

To evaluate the scope of the proposed catalytic method, we attempted the cyclization of a variety of 8-(but-3-ynyl)-xanthines **1** under the above-mentioned optimized conditions. As shown in Table 2, the reaction proceeded smoothly to afford the corresponding N7-fused tricyclic xanthines **2** in good to excellent yields (Table 2, entries a–i). The bulky aliphatic substituents in **1b–d** ($R^1 = R^2 =$ cyclohexylmethyl, *n*-Bu, *n*-Pr) facilitated the efficient hydroamination, and hence, the desired products were obtained in excellent yields (up to 90%, Table 2, entries b–d). In contrast, when 8-(but-3-ynyl)-xanthine substrates with small substituents such as 1,3-dimethyl or 1,3-diethyl were used, the reaction proceeded slowly to afford the corresponding products **2f** and **2e** in 42% and 51% yields after 1 h, along with 40% of **1f** and 20% of **1e** (starting materials), respectively (Table 2, entries f and e). We also obtained the ketones **6f** and **6e** in 15% and 20% yields, respectively. The proposed reaction could also be extended to 8-(but-3-ynyl)-xanthines containing different R^1 and R^2 groups. For example, 1-methyl-3-benzyl-8-(but-3-ynyl)-xanthine **1g** (Table 2, entry g) afforded **2g** in 75% yield after 1 h. Upon replacing the 1-methyl moiety in **1g** with the 1-cyclohexylmethyl moiety, we obtained **1h**, which could be efficiently transformed into the target compound **2h** in 86% yield within 10 min (Table 2, entry h). A similar result was obtained when using 1-benzyl-3-cyclohexylmethyl-8-(but-3-ynyl)-xanthine **1i** as the substrate (85% yield, Table 2, entry i). However, no reaction occurred even under the optimized reaction conditions when an internal alkyne substrate like **1j** was used, and 100% of the starting material was recovered (Table 2, entry j).

Further experiments under the optimized reaction conditions (Table 1, entry 14) demonstrated that the proposed reaction could be extended to generate N9-fused tricyclic xanthines **3** (Table 3); however, the reaction was significantly affected by the nature of R^1 and R^2 (substituents on the xanthine ring). As observed during the synthesis of N7-fused tricyclic xanthines **2**, 8-(but-3-ynyl)-xanthines **1b–d** with bulky aliphatic substituents were tolerant to the isomerization-hydroamination and afforded the corresponding products **3b–d** in good yields (Table 3, entries b–d). However, the presence of small substituents on the xanthine scaffold decreased the reaction efficiency, and hence, the products **3e** and **3f** were obtained in low yields (Table 3, entries e and f). Interestingly, **1e** and **1f** were converted to **2e** and **2f** in 52% and 80% yields, respectively, in the presence of $AgAsF_6$. Furthermore, xanthines **1g–i** containing different R^1 and

Table 2. $AuCl(PPh_3)$-catalyzed synthesis of N7-fused tricyclic xanthines **2** in water.[a]



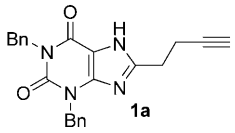
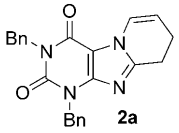
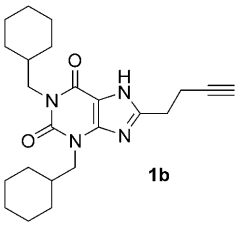
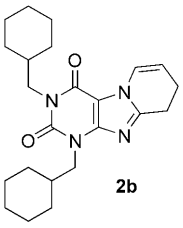
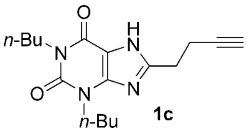
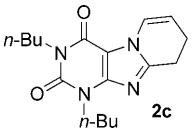
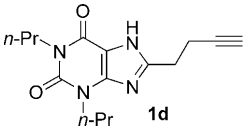
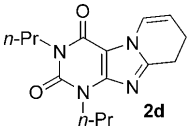
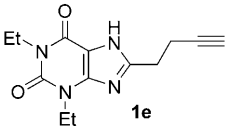
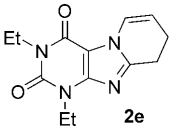
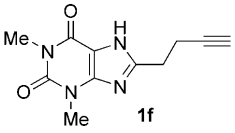
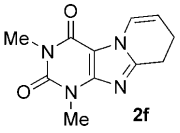
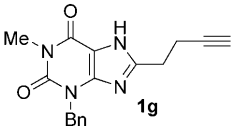
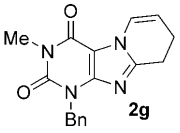
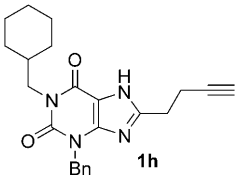
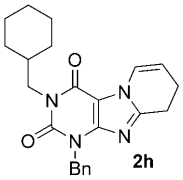
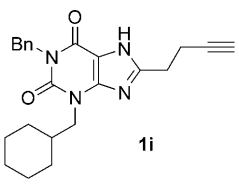
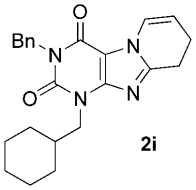
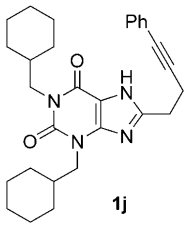
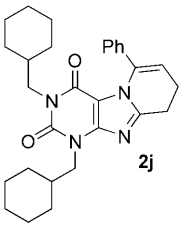
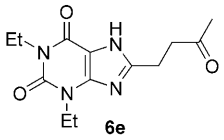
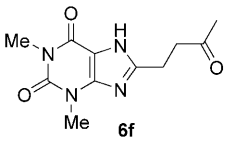
Entry	Substrate **1**	*t*	Product **2**	Yield [%][b]
a		10 min		86
b		10 min		91
c		10 min		93
d		30 min		90
e[c]		1 h		51
f[d]		1 h		42
g		1 h		75
h		10 min		86
i		10 min		85

Table 2. (Continued)

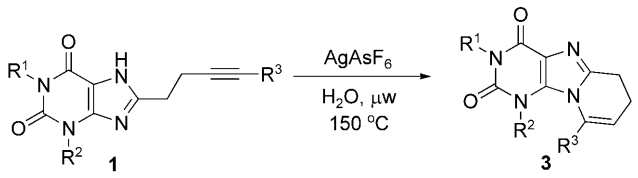
Entry	Substrate **1**	*t*	Product **2**	Yield [%][b]
j[e]	 **1j**	10 min	 **2j**	0

 **6e**

 **6f**

[a] *Reaction conditions:* **1** (0.2 mmol), $AuCl(PPh_3)$ (0.02 mmol), H_2O (3 mL), μw, 150 °C.
[b] Yield of isolated products based on **1**.
[c] 20% of **6e** along with 20% of starting material **1e** were obtained.
[d] 15% of **6f** along with 40% of starting material **1f** were obtained.
[e] 100% of **1j** was recovered.

Table 3. $AgAsF_6$-catalyzed synthesis of N9-fused tricyclic xanthines **3** in water.[a]



1 **3**

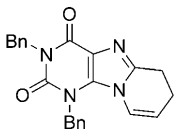
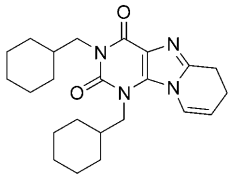
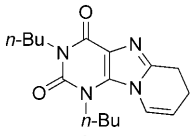
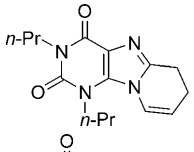
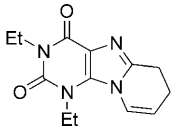
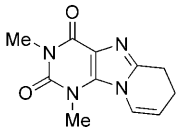
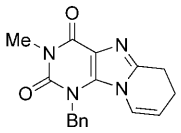
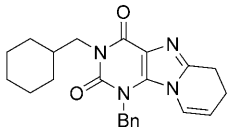
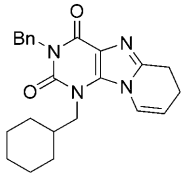
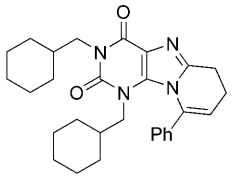
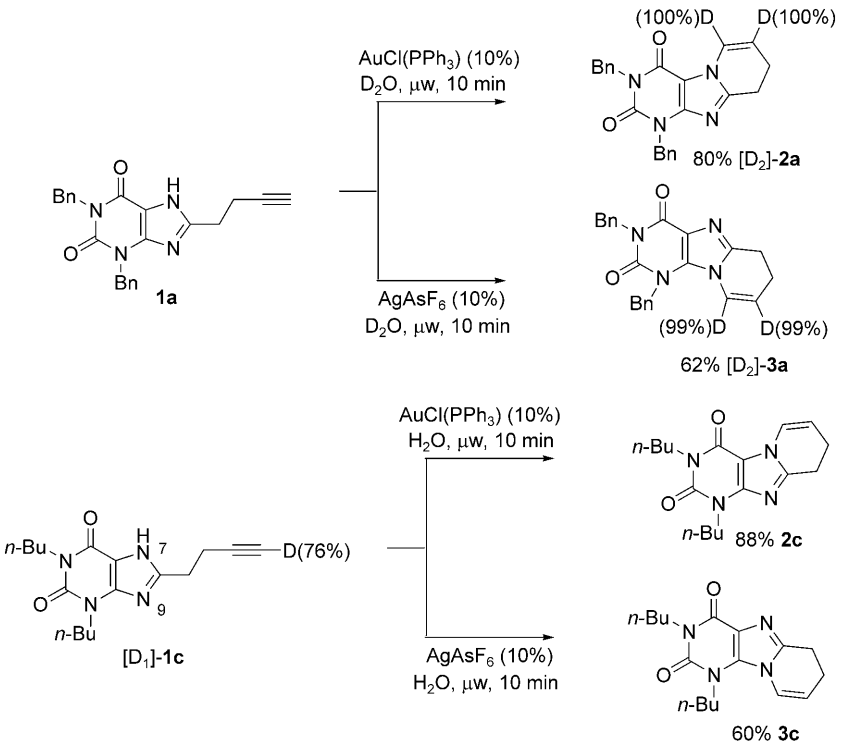
Entry	Substrate **1**	*t*	Product **3**	Yield [%][b]
a	**1a**	10 min	 **3a**	72
b	**1b**	10 min	 **3b**	72
c	**1c**	10 min	 **3c**	70
d	**1d**	1 h	 **3d**	60
e[c]	**1e**	1 h	 **3e**	26

Table 3. (Continued)

Entry	Substrate **1**	*t*	Product **3**	Yield [%][b]
f[d]	**1f**	1 h	 **3f**	trace
g	**1g**	1 h	 **3g**	57
h	**1h**	10 min	 **3h**	69
i	**1i**	10 min	 **3i**	70
j[e]	**1j**	10 min	 **3j**	0

[a] *Reaction conditions:* **1** (0.2 mmol), $AgAsF_6$ (0.02 mmol), H_2O (3 mL), μw, 150 °C.
[b] Yield of isolated products based on **1**.
[c] 52% of **2e** along with 10% of **6e** were obtained.
[d] 80% of **2f** along with 4% of **6f** were obtained.
[e] 100% of **1j** was recovered.



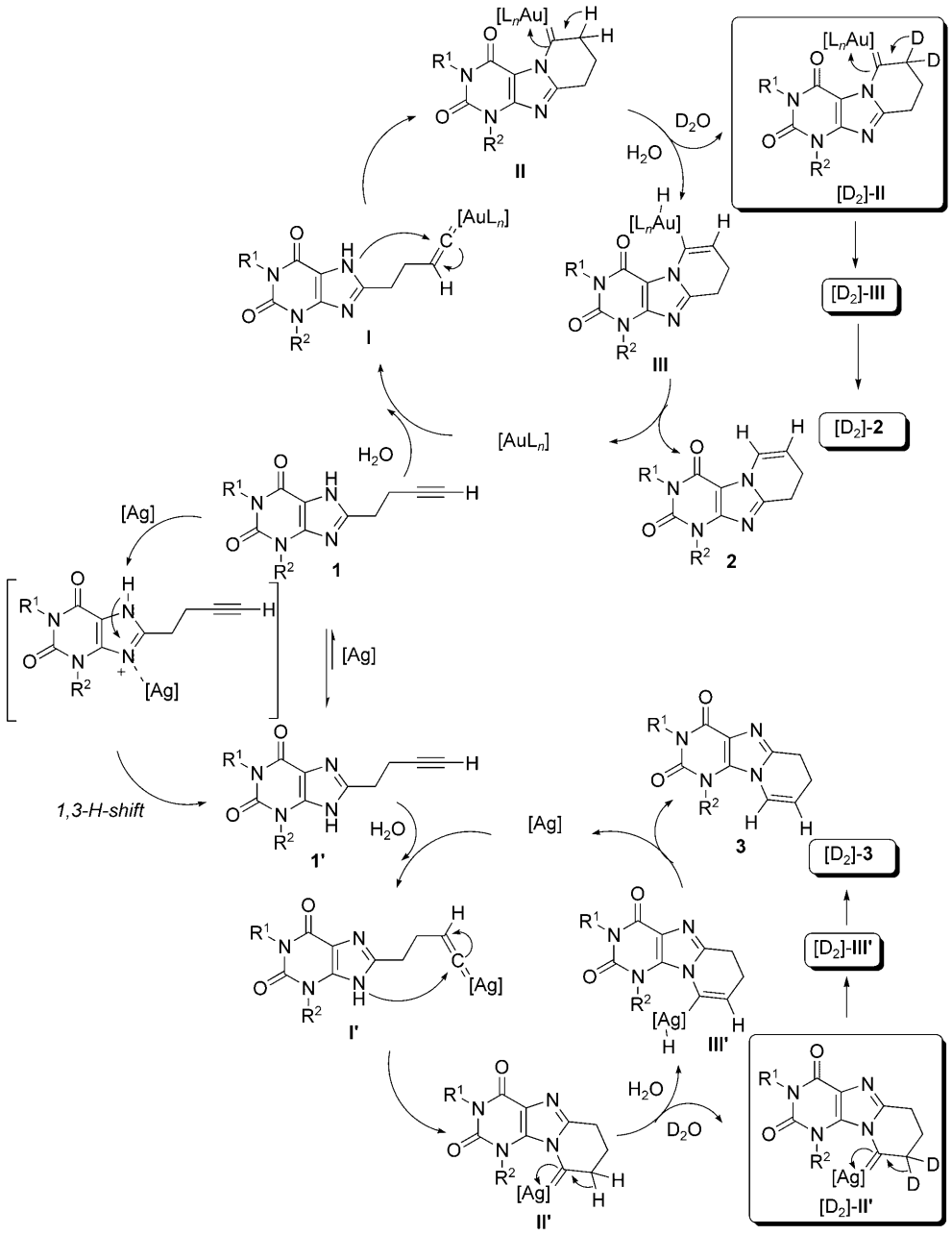
Scheme 2. Labeling studies with D_2O or deuterated starting materials.

R^2 groups also underwent the cyclization reaction smoothly, while no reaction was observed when the internal alkyne substrate **1j** was used as the substrate.

To understand the mechanism underlying the proposed cyclization reaction, we performed labeling studies using deuterated starting materials or solvents. The reaction of **1a** in D_2O under the two different conditions afforded 2,3-bideuterated compounds, namely, [D_2]-**2a** and [D_2]-**3a**. Reaction of the deuterated alkyne [D_1]-**1c** in water led to the formation of non-deuterated products **2c** and **3c** (Scheme 2).

On the basis of our previous knowledge and the results of our present study, we propose several potential mechanisms for the cyclization reaction studied herein (Scheme 3). One potential mechanism involving alkyne-vinylidene isomerization has been discussed previously for the transition metal-catalyzed synthesis of heterocycles.[20] In the presence of the Au(I) complex, the terminal alkyne **1** first coordinates with the cationic Au(I) complex. Then, a vinylidene intermediate **I** is formed *via* 1,2-H migration, and this adds to the N7 atom on the xanthine scaffold to afford a carbene complex **II**. Finally, tautomerization of **II** and reductive elimination of the metal hydride complex results in the formation of the desired product **2** and the active catalyst is regenerated. When using a ligand-free catalyst such as $AgAsF_6$, isomerization involving a 1,3-H-shift between N7 and N9 first occurs to afford the intermediate **I′**;[21] this step is facilitated by the cationic metal. Then, the intermediate **I′** undergoes alkyne-vinylidene isomerization and cyclization, as described above, to afford the desired product **3**. The aforementioned labeling experiments revealed that the vinyl protons of the products came from the solvent. The direct formation of [D_2]-**2a** or [D_2]-**3a** from D_2O is consistent with the results reported in the literature, according to which hydrogen atoms that occupy the α-position with respect to the carbene group can be exchanged with D_2O (Scheme 2).[19d,22,23] This proposed reaction mechanism can be further confirmed by comparing the products obtained from terminal and internal alkyne substrates (Table 2 and Table 3). An alternative mechanism has also been proposed for this reaction.[13,24] Accordingly, the catalyst coordinates with the alkyne to afford a π-complex; this triggers a nucleophilic attack by the amino group in the *endo* mode. However, this mechanism cannot explain the poor reactivity of internal alkynes.

In summary, we have developed a chemo- and regioselective approach for the synthesis of fused tricyclic xanthines *via* Au(I) complex-catalyzed intramolecular hydroamination or Ag(I)-catalyzed isomerization-hydroamination of terminal alkynes under microwave irradiation in water. This reaction is atom economical and has high functional group tolerance. Further studies for the synthesis of biologically impor-



Scheme 3. A proposed mechanism.

tant xanthine derivatives and understanding of its mechanism are currently in progress.

Experimental Section

General Procedure for the Preparation of Fused Tricyclic Xanthines 2 or 3

A mixture of **1** (0.2 mmol), $AuCl(PPh_3)$ (0.02 mmol) or $AgAsF_6$ (0.02 mmol) was stirred in water (3–5 mL) under an argon atmosphere. The vial was sealed and the mixture was then irradiated for 10 min at 150 °C. After the reaction had cooled to ambient temperature, the crude reaction mixture was extracted three times with ethyl acetate (15 mL × 3). The combined organic phase was washed with saturated $NaHCO_3$ solution, brine, dried with Na_2SO_4 and concentrated. The residue was purified by column chromatography on combiflash to provide the desired products.

2a: Compound **2a** was obtained after purification by flash chromatography (SiO_2, 300–400 mesh; ethyl acetate:petroleum ether, 1:9 to 1:4). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 2.461–2.528 (m, 2H, CH_2), 3.050 (t, 2H, $J = 8.7$ Hz , CH_2), 5.184 (s, 2H, CH_2), 5.262 (s, 2H, CH_2), 5.592–5.647 (m,1H, CH), 7.228–7.334 (m, 6H, CH, ArH), 7.402–7.475 (m, 5H,

ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.677 (CH_2), 22.314 (CH_2), 44.403, 46.635, 104.851, 113.213, 122.828, 127.432, 127.765, 128.361, 128.475, 128.676, 136.359, 137.293, 147.873, 148.775 (C=O), 151.220 (C=O), 154.586; ESI-MS: *m/z* = 385 $[M + H]^+$ 100%; HR-MS (ESI): *m/z* = 407.1406, calcd. for $C_{23}H_{20}N_4O_2Na$ $[M + Na]^+$: 407.1484.

3a: Compound **3a** was obtained after purification by flash chromatography (SiO_2, 300–400 mesh; CH_2Cl_2:MeOH, 50:1 to 40:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.350–2.367 (m, 2H, CH_2), 2.984 (t, *J* = 7.2 Hz, 2H, CH_2), 5.265 (s, 2H, CH_2), 5.345 (s, 2H, CH_2), 5.573–5.599 (m, 1H, CH), 6.611 (d, 1H, *J* = 7.8 Hz, CH), 7.111–7.514 (m, 10H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.659 (CH_2), 22.901 (CH_2), 44.945 (CH_2), 47.751 (CH_2), 115.896, 117.148 (CH), 121.857 (CH), 125.210, 127.220, 127.441, 128.106, 128.270, 128.908, 129.436, 134.788, 136.154, 137.088, 144.598 (C=O), 151.321 (C=O), 157.018; ESI-MS: *m/z* = 385.0 $[M+H]^+$ 100%; HR-MS (ESI): *m/z* = 407.1497, calcd for $C_{23}H_{20}N_4O_2Na$ $[M+Na]^+$: 407.1484.

Acknowledgements

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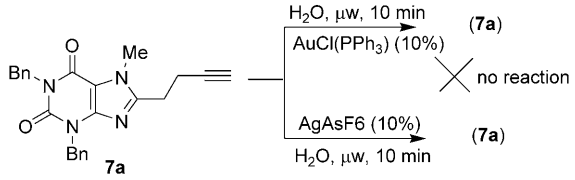
[21] In contrast with **1a**, no reactions occurred when heating substrate **7a** with $AuCl(PPh_3)$ or $AgAsF_6$ under optimal conditions.



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[23] An alternative process involving terminal alkyne H-D exchange to incorporate the first D, nucleophilic addition to the complexed alkyne, and deuteration (with D_2O) to incorporate the 2nd deuterium for the formation of [D_2]-**2a** or [D_2]-**3a** was also probable.

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