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Synthesis of 3-Aza-bicyclo[3.1.0]hexan-2-one Derivatives via Gold-Catalyzed Oxidative Cyclopropanation of *N*-Allylynamides

Kai-Bing Wang, Rui-Qiao Ran, Shi-Dong Xiu, and Chuan-Ying Li*

Department of Chemistry, Zhejiang Sci-Tech University, Xiasha West Higher Education District, Hangzhou 310018, China

licy@zstu.edu.cn

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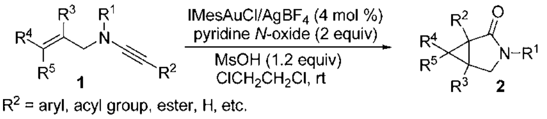
ABSTRACT



R^2 = aryl, acyl group, ester, H, etc.

***N*-Allylynamides with various functional groups and different substitution patterns can be converted into 3-aza-bicyclo[3.1.0]hexan-2-one derivatives in moderate to high yield using IMesAuCl/AgBF$_4$ as the catalyst and pyridine *N*-oxide as the oxidant. A noncarbene mediated approach is proposed as the mechanism.**

Metal carbenes are versatile intermediates in modern synthetic chemistry.[1] Recently, gold carbenes derived from alkynes and leaving-group-bearing nucleophiles have attracted considerable attention.[2] In 2007, Toste[3a] and Zhang[3b] reported that a gold activated alkyne could be trapped by a tethered sulfoxide to afford a gold carbene conveniently. On the basis of these pioneering works, many new transformations such as X–H (X = C, O, N) insertion,[3] cycloaddition,[4] β-hydride migration,[5] ylide formation,[6] and rearrangement[7] have been realized since then. In 2011, we reported an efficient process to oxidize alkynes to 1,2-dicarbonyl compounds using diphenyl sulfoxide as the mild oxidant.[8] During the reaction scope

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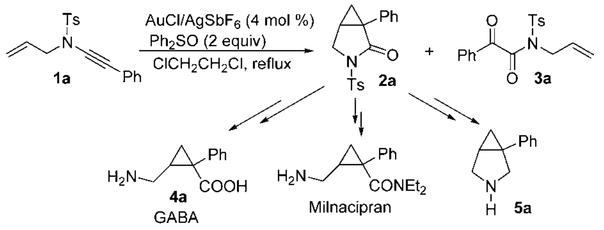
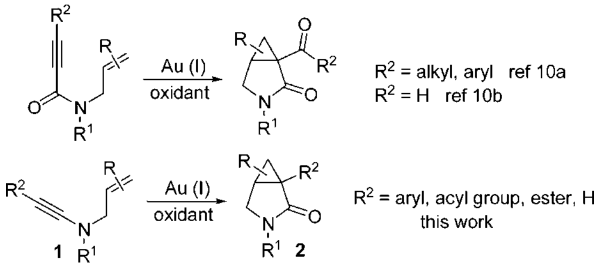
research, we synthesized *N*-allylynamide **1a** to see if the hypothetic gold carbene could be trapped by the intramolecular alkenyl group, which led to compound **2a** (Scheme 1). To our delight, **2a** was obtained in about 10% yield along with 50% of **3a**. **2a** is quite useful since it is the key intermediate for several bioactive molecules and pharmaceuticals. For example, milnacipran is a clinically useful antidepressant,[9a] conformationally restricted γ-amino butyric acid (GABA) **4a** is an analogue of the important inhibitory neurotransmitter,[9b] and 1-phenyl-3-azabicyclo-[3.1.0]hexane **5a** is a nonnarcotic analgesic agent.[9c] Similar products have been synthesized by gold-catalyzed oxidative cyclopropanation of propiolamide-tethered 1,6-enyne (Scheme 2).[10] Palladium-catalyzed oxidative cyclization of 1,6-enyne was also realized by Tse[11a] and Sanford.[11b] Noticeably, all the above-mentioned methods led to the formation of an acyl group substituted bicyclo[3.1.0]-hexane. In view of the importance of **2a**, a new strategy to achieve bicyclo[3.1.0]hexane with a variety of substituents is highly desired. Herein, we report a mild and efficient protocol to obtain the useful framework via gold-catalyzed oxidative cyclopropanation of *N*-allylynamides.

Scheme 1. Our Previous Results



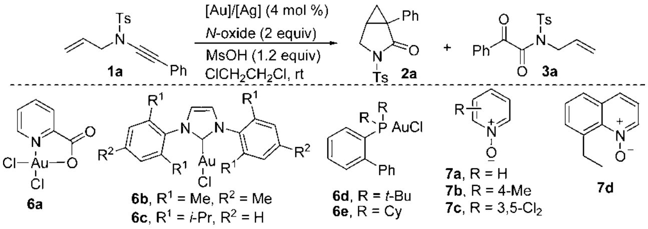
Scheme 2. Oxidative Cyclopropanation



In order to improve the yield of **2a**, various sulfoxides were tried first. 1,2-Dicarbonyl compound **3a** was obtained as a major product in all cases, so we turned our attention to pyridine *N*-oxide. Representative reaction conditions we investigated are summarized in Table 1. The gold catalyst was proven to strongly influence the yield of **2a** (entries 1−7); a bulkier ligand led to a lower yield (entries 4 vs 5, 6 vs 7). **2a** was formed in 76% yield at rt in 1.0 h with 4 mol % IMesAuCl/AgSbF$_6$ as the catalyst (entry 4). Silver catalysts were screened next, and the yield of **2a** was slightly improved to 78% when relatively cheaper AgBF$_4$ was used (entry 9). We also tested the reaction with different pyridine *N*-oxides and quinoline *N*-oxide (entries 11−13); the commercially available **7a** gave the best result (entry 9). Decreased loadings of **7a** led to lower yields (entries 14 and 15). Without AgBF$_4$, **2a** could be obtained in 20% yield after 24 h (entry 16). When no gold catalyst was added, **1a** decomposed completely in ∼20 h, a complex mixture was formed and no **2a** could be isolated (entries 17 and 18).

Under the optimized reaction conditions (Table 1, entry 9), various *N*-allylynamides with different functional groups and different substitution patterns were examined; the corresponding product **2** could be isolated in moderate to high yield (Table 2). Protecting groups such as Ms, Ns, SES, *p*-MeOC$_6$H$_4$SO$_2$, and *p*-BrC$_6$H$_4$SO$_2$ are compatible

Table 1. Optimization of Reaction Conditions[a]



				yield (%)	
entry	catalyst (4 mol %)	*N*-oxide (2 equiv)	time (h)	**2a**	**3a**
1	AuCl/AgSbF$_6$	**7a**	6.5	24	21
2	**6a**/AgSbF$_6$	**7a**	4.5	22	62
3	Ph$_3$PAuCl/AgSbF$_6$	**7a**	3.5	39	60
4	IMesAuCl (**6b**)/AgSbF$_6$	**7a**	1.0	76	21
5	IPrAuCl (**6c**)/AgSbF$_6$	**7a**	7.0	48	31
6	**6d**/AgSbF$_6$	**7a**	2.5	37	55
7	**6e**/AgSbF$_6$	**7a**	3.2	47	50
8	IMesAuCl/AgOTf	**7a**	4.5	71	28
9	IMesAuCl/AgBF$_4$	**7a**	1.0	78	20
10	IMesAuCl/AgNTf$_2$	**7a**	1.5	63	35
11	IMesAuCl/AgBF$_4$	**7b**	4.8	48	49
12	IMesAuCl/AgBF$_4$	**7c**	4.0	22	73
13	IMesAuCl/AgBF$_4$	**7d**	4.0	23	72
14[b]	IMesAuCl/AgBF$_4$	**7a**	1.5	68	30
15[c]	IMesAuCl/AgBF$_4$	**7a**	1.0	71	27
16	IMesAuCl	**7a**	24	20	64
17	AgBF$_4$	**7a**	16	0	0
18		**7a**	20	0	0

[a] [**1a**] = 0.1 M; the reaction was carried out in 2 mL of DCE in an open flask. [b] 1.2 equiv of **7a** was used. [c] 1.5 equiv of **7a** was used.

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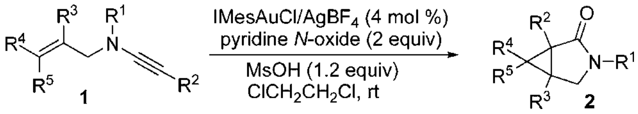
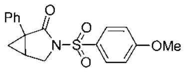
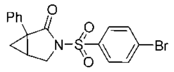
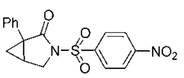
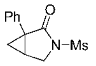
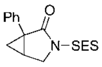
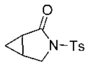
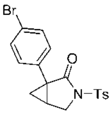
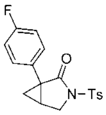
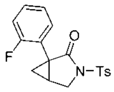
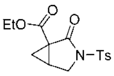
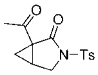
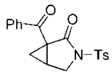
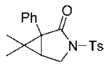
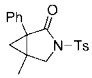
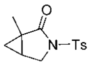
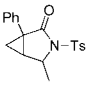
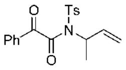
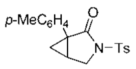
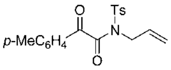
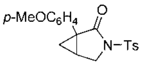
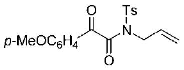
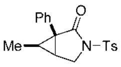
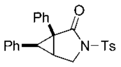
Table 2. Reaction Scope[a]



entry	product	entry	product	entry	product
1	 **2b**, 1.5 h, 64%	2	 **2c**, 1.5 h, 61%	3	 **2d**, 6.5 h, 69%
4	 **2e**, 8.0 h, 46%	5[b]	 **2f**, 1.0 h, 49%	6	 **2g**, R^2 = H, 1.0 h, 85%; R^2 = TMS, 1.0 h, 90%
7	 **2h**, 2.0 h, 66%	8	 **2i**, 2.0 h, 61%	9	 **2j**, 5.5 h, 99%
10	 **2k**, 1.5 h, 76%	11	 **2l**, 1.5 h, 73%	12	 **2m**, 4.5 h, 75%
13	 **2n**, 3.5 h, 71%	14	 **2o**, 2.5 h, 82%	15	 **2p**, 2 h, 43%
16	 **2q**, 1.0 h, 0% +  **3q**, 92%	17	 **2r**, 3.5 h, 26% +  **3r**, 59%	18	 **2s**, 4.0 h, 0% +  **3s**, 89%
19	 *trans*-**2t**, 2.0 h, 76%	20	 *trans*-**2u**, 4.0 h, 83%		

[a] [**1**] = 0.1 M; the reaction was carried out in 2 mL of 1,2-dichloroethane in open flask. [b] SES: 2-Trimethylsilylethanesulfonyl.

in this transformation, providing different opportunities to deprotect those groups (entries 1−5). Notably, terminal alkyne **1g** is a suitable substrate, which led to **2g** in 85% yield. When the alkyne terminus was substituted with TMS (trimethylsilyl), the TMS group was lost during the reaction and **2g** was isolated in 90% yield (entry 6). Bromide and fluoride are well tolerated in the transformation (entries 7−9). Electron-withdrawing-group substituted substrates **1k**, **1l**, and **1m** were synthesized smoothly by reacting deprotonated terminal ynamide with the corresponding acid chloride or anhydride, which led to the formation of carbonyl substituted products in high yield (entries 10−12). Substrates bearing an allyl unit with different degrees of substitution were then investigated; products with two vicinal quaternary carbon centers could be formed easily in high yield (entries 13 and 14). For the substrate with a methyl group at the allylic position, only 1,2-dicarbonyl compound **3q** was isolated (entry 16), presumably as a result of the steric bulk around the nucleophilic alkene partner. Noticeably, the substrate possessing a methyl group at the alkyne terminus led to alkyl substituted product **2p** in moderate yield (entry 15). The introduction of an electron-rich aromatic ring to the alkyne moiety resulted in 1,2-dicarbonyl compound **3** as the major product (entries 17 and 18), which may be because of the different reactivity of the intermediate. Significantly, only the *trans*-isomer could be isolated when substrates with a phenyl or methyl group at the terminal position of alkene were employed (entries 19 and 20).

The synthetic application of this transformation is demonstrated in Scheme 3. Substrate **1f** could be synthesized conveniently in two steps from allylamine via sulfonylation and a CuCl$_2$ catalyzed oxidative coupling reaction.[12] Under optimized reaction conditions, **2f** was obtained in 49% yield, which led to the formation of **2f′** in 70% yield in the presence of TBAF. Subsequent hydrolyzation afforded **4a′** in 66% yield.

In 2011, Liu et al. reported that benzene-tethered or alkene-tethered 1,5-enynes could undergo oxidative cyclization to afford bicyclo[3.1.0]hex-3-en-2-one derivatives.[7f] Based on the deuterated experiments and a formal C−H insertion reaction, they proposed that an α-oxo gold carbenoid was the key intermediate. However, in a later report,[7j] they focused on the formal C−H insertion reaction and found that gold carbenoids derived from diazo compounds could not afford the C−H insertion products in high yield, which excluded the intermediacy of the gold carbenoid. On the contrary, they proposed a 1,5-hydrogen shift procedure as the mechanism. In light of the above reports, diazo compound **8** was prepared to explore the mechanism. When **8** was treated with 4 mol % IMesAuCl/AgBF$_4$, only 10% of **2g** could be isolated, along with an unidentified polar mixture (Scheme 4A). When 1.2 equiv of MsOH were added, **8** decomposed completely in 30 min, with no **2g** detected, while mesylate **9** could be isolated in 84% yield. The formation of **9** indicated that a gold carbene could be obtained from a diazo compound and IMesAuCl/AgBF$_4$. Under the previous optimized reaction conditions, 16% of **2g** could be formed, but no **9** was detected. Considering the low yield of **2g** in the carbene-mediated transformation (Scheme 4A), the role of the gold carbene may be insignificant in the gold-catalyzed oxidative cyclopropanation of *N*-allylynamide. In a previous report by Gagosz et al.,[13] a bicyclic compound was

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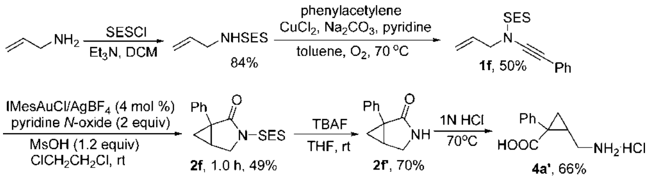
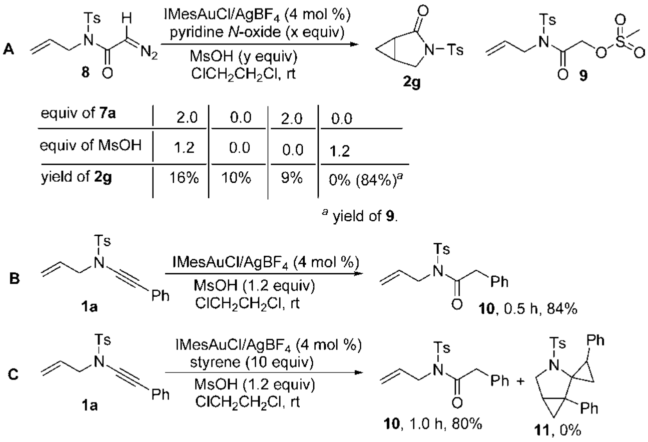
(12) For reviews on ynamides, see: (a) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064. (b) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840. (c) Evano, G.; Jouvin, K.; Coste, A. *Synthesis* **2013**, *45*, 17. Ynamides are very useful building blocks; for recent reports on oxidative intramolecular cyclopropanation of ynamides, see: (d) Couty, S.; Meyer, C.; Cossy, J. *Synlett* **2007**, 2819. (e) Al-Rashid, Z. F.; Hsung, R. P. *Org. Lett.* **2008**, *10*, 661. For selected examples on gold catalyzed activation of ynamides, see: (f) Couty, S.; Meyer, C.; Cossy, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6726. (g) Hashmi, A. S. K.; Salathé, R.; Frey, W. *Synlett* **2007**, 1763. (h) Istrate, F. M.; Buzas, A. K.; Jurberg, I. D.; Odabachian, Y.; Gagosz, F. *Org. Lett.* **2008**, *10*, 925. (i) Hashmi, A. S. K.; Rudolph, M.; Bats, J. W.; Frey, W.; Rominger, F.; Oeser, T. *Chem.—Eur. J.* **2008**, *14*, 6672.

(13) Buzas, A.; Istrate, F.; Goff, X. F. L.; Odabachian, Y.; Gagosz, F. *J. Organomet. Chem.* **2009**, *694*, 515.

Scheme 3. Synthesis of **4a′**



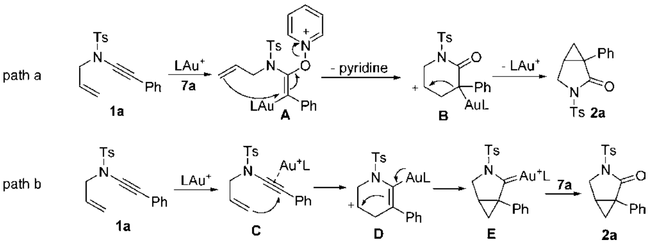
Scheme 4. Preliminary Study on Mechanism



equiv of **7a**	2.0	0.0	2.0	0.0
equiv of MsOH	1.2	0.0	0.0	1.2
yield of **2g**	16%	10%	9%	0% (84%)[a]

[a] yield of **9**.

Scheme 5. Proposed Mechanism



obtained when *N*-(hex-5-enynyl) *tert*-butyloxycarbamate was treated with a gold catalyst. They proposed a resonance between the gold carbene and gold-stabilized homoallylic carbocation. A similar intermediate has been proposed by Cossy[12f] and Shin.[10b] In addition, pyridine *N*-oxide in the reaction mixture can act as a nucleophile, which attacks the gold-activated ynamide. Based on these considerations, two pathways may be possible (Scheme 5). Gold-activated **1a** is attacked by pyridine *N*-oxide to afford intermediate **A**. Subsequent intramolecular nucleophilic addition of an alkenyl moiety and loss of pyridine lead to the formation of **B**, which undergoes release of the gold catalyst and formation of a C–C bond to obtain the final product **2a** (path a). Alternatively, intermediate **D** could be formed via 6-*endo*-dig cyclization of **1a**. Back donation of the gold catalyst results in highly reactive carbene **E**, which can be trapped by pyridine *N*-oxide to form **2a** (path b). We attempted the reaction without addition of pyridine *N*-oxide to see if hypothetic intermediate **E** could be trapped by MsOH. However, amide **10** was isolated in 84% yield after 0.5 h (Scheme 4B). We also used styrene to trap carbene **E**; no cyclopropane was detected. Although path b cannot be ruled out based on these experiments since hydrolysis of the starting ynamide may be favored in the absence of pyridine *N*-oxide, path a is thought to be the most possible approach.[14]

In summary, synthetically useful 3-aza-bicyclo[3.1.0]-hexan-2-one derivatives can be synthesized via gold-catalyzed oxidative cyclopropanation of *N*-allylynamide. The substrate is readily accessible, and various substituents such as an ester, aryl group, and acyl group are well tolerated. Moreover, the mechanism study excludes the gold carbenoid as the key intermediate, which reveals the complexity of the mechanism of the gold-catalyzed oxidative reaction.

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Supporting Information Available. Experimental procedures, characterization data, and NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[14] For more experiments about the mechanism, please see the Supporting Information.

The authors declare no competing financial interest.