

A New Route to Tricyclic 2-Pyridone Frameworks via Formation of Bicyclic *N*-Alkenyl Alkynylamides Followed by Gold-catalyzed Cycloisomerization

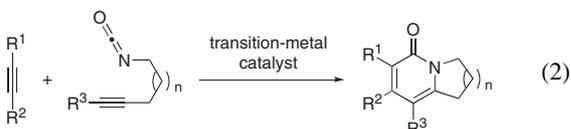
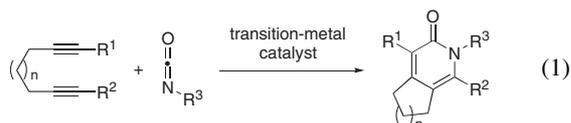
Hidetomo Imase and Ken Tanaka*

Department of Applied Chemistry, Graduate School of Engineering, Tokyo University of Agriculture and Technology, Koganei, Tokyo 184-8588

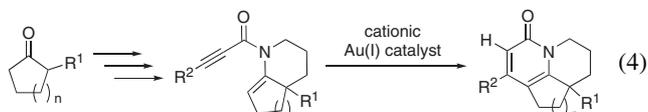
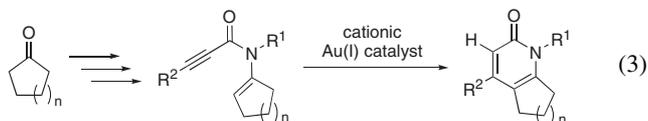
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A cationic gold(I)/PPh₃ complex catalyzes cycloisomerizations of bicyclic *N*-alkenyl alkynylamides leading to tricyclic 2-pyridone derivatives at room temperature in good yields. The bicyclic *N*-alkenyl alkynylamides are readily prepared starting from commercially available 2-substituted cycloalkanones.

As 2-pyridone frameworks are important core units in biologically active compounds and functional organic materials, their efficient synthesis has been extensively pursued to date.¹ For the synthesis of bicyclic 2-pyridones, transition metal mediated [2 + 2 + 2] cycloadditions of diynes with isocyanates (eq 1)² and alkynylisocyanates with alkynes (eq 2)³ are highly efficient and convergent methods.⁴



Recently, we have reported that a cationic gold(I)/PPh₃ complex catalyzes the cycloisomerization of *N*-alkenyl alkynylamides (amide-linked 1,5-enynes) that can be readily prepared starting from the corresponding cycloalkanones leading to 5–6 and 6–6 fused bicyclic 2-pyridones ($n = 1$ and 2, eq 3).^{5–7} In this letter, we describe the synthesis of tricyclic 2-pyridones (pyridoquinoline derivatives⁸) that cannot be synthesized by [2 + 2 + 2] cycloadditions via formation of bicyclic *N*-alkenyl alkynylamides starting from the corresponding 2-substituted cycloalkanones followed by the gold-catalyzed cycloisomerization (eq 4).



We first investigated the synthesis of bicyclic *N*-alkenyl alkynylamides **4** starting from the commercially available 2-substituted cycloalkanones **1**. After screening synthetic routes and optimization of reaction conditions, 1,5-enyne **4aa** was success-

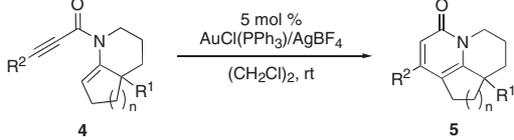
fully prepared starting from ketone **1a** in four steps without purification of each intermediate (Table 1, Entry 1). Intermediate azide **2a** was prepared via alkylation of ketone **1a** with 1-bromo-3-chloropropane followed by treatment with NaN₃. The azide **2a** was treated with PPh₃ to form the corresponding imine,¹⁰ which reacted with alkynoyl chloride **3a** to furnish the desired 1,5-enyne **4aa**. Various 1,5-enynes **4** were then prepared starting from 2-substituted cycloalkanones **1a–1d** by following the above optimized procedure. Both ethoxycarbonyl- (**1a** and **1b**, Entries 1–6) and phenyl-substituted cycloalkanones (**1d**, Entries 8 and 9) could be transformed to the corresponding 1,5-enynes in fair to good yields, while benzoyl-substituted cyclohexanone **1c** was transformed to the corresponding 1,5-enyne **4ca** in low yield due to the competitive aza-Wittig reaction in the benzoyl carbonyl group (Entry 7). With respect to alkynoyl chlorides, both aryl- (Entries 1–3 and 6–8) and alkyl-substituted alkynoyl chlorides (Entries 4, 5, and 9) could be employed.

Thus obtaining the bicyclic 1,5-enynes **4**, these were subjected to the cationic gold(I)/PPh₃ complex-catalyzed cycloisomerizations as summarized in Table 2. The cycloisomerizations of bicyclic 5–6 fused 1,5-enynes smoothly proceeded to give the desired tricyclic 2-pyridones in high yields (Entries 1–6). Not only 5–6 fused 1,5-enynes but also 6–6 fused 1,5-enynes (Entries 7–10) could participate in this reaction, although product yields were moderate and prolonged reaction times were required. With respect to the substituents (R¹) at the bridged carbon atom,

Table 1. Synthesis of bicyclic *N*-alkenyl alkynylamides **4**^a

Entry	Substrate 1	Substrate 3 ^b	Product 4 , Yield ^c /%
1	1a ($n = 1$, R ¹ = CO ₂ Et)	3a (R ² = Ph)	4aa , 35
2	1a ($n = 1$, R ¹ = CO ₂ Et)	3b (R ² = 4-MeOC ₆ H ₄)	4ab , 36
3	1a ($n = 1$, R ¹ = CO ₂ Et)	3c (R ² = 2-ClC ₆ H ₄)	4ac , 31
4	1a ($n = 1$, R ¹ = CO ₂ Et)	3d (R ² = Me)	4ad , 47
5	1a ($n = 1$, R ¹ = CO ₂ Et)	3e (R ² = Cy)	4ae , 57
6 ^d	1b ($n = 2$, R ¹ = CO ₂ Et)	3a (R ² = Ph)	4ba , 51
7 ^d	1c ($n = 2$, R ¹ = Bz)	3a (R ² = Ph)	4ca , 9
8	1d ($n = 2$, R ¹ = Ph)	3a (R ² = Ph)	4da , 45
9	1d ($n = 2$, R ¹ = Ph)	3d (R ² = Me)	4dd , 27

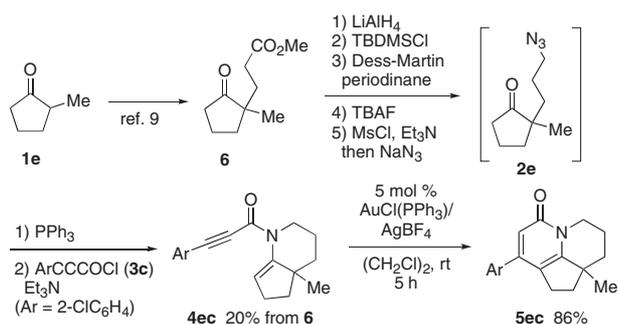
^aSee Supporting Information for detailed reaction conditions.⁹ ^bCarboxylic acid chloride **3** were prepared in situ by the reaction of the corresponding carboxylic acid and 1-chloro-*N,N*,2-trimethyl-1-propenylamine. ^cIsolated yield. ^d1-Chloro-3-iodopropane was used instead of 1-bromo-3-chloropropane.

Table 2. Gold-catalyzed cycloisomerizations of bicyclic *N*-alkenyl alkynylamides **4**^a


Entry	Substrate 4	Time/h	Product 5 , Yield ^b / %
1	4aa (<i>n</i> = 1, R ¹ = CO ₂ Et, R ² = Ph)	5	5aa , 82
2 ^c	4aa (<i>n</i> = 1, R ¹ = CO ₂ Et, R ² = Ph)	5	5aa , 81
3	4ab (<i>n</i> = 1, R ¹ = CO ₂ Et, R ² = 4-MeOC ₆ H ₄)	1	5ab , 87
4	4ac (<i>n</i> = 1, R ¹ = CO ₂ Et, R ² = 2-ClC ₆ H ₄)	4	5ac , 79
5	4ad (<i>n</i> = 1, R ¹ = CO ₂ Et, R ² = Me)	17	5ad , 71
6	4ae (<i>n</i> = 1, R ¹ = CO ₂ Et, R ² = Cy)	12	5ae , 86
7	4ba (<i>n</i> = 2, R ¹ = CO ₂ Et, R ² = Ph)	17	5ba , 71
8	4ca (<i>n</i> = 2, R ¹ = Bz, R ² = Ph)	30	5ca , 51
9	4da (<i>n</i> = 2, R ¹ = Ph, R ² = Ph)	15	5da , 64
10	4dd (<i>n</i> = 2, R ¹ = Ph, R ² = Me)	36	5dd , 60

^aAuCl(PPh₃)₃ (0.010 mmol), AgBF₄ (0.010 mmol), **4** (0.200 mmol), and (CH₂Cl)₂ (1.0 mL) were used. See Supporting Information in detail.⁹

^bIsolated yield. ^c(CH₂Cl)₂ (reagent grade) was used.

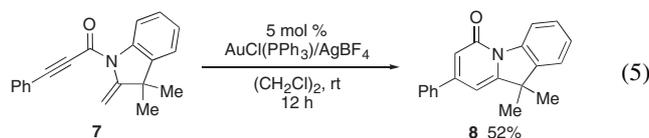
**Scheme 1.** Synthesis of tricyclic 2-pyridone **5ec** (See Supporting Information for detailed reaction conditions⁹).

the reactions of ethoxycarbonyl-substituted 1,5-enynes proceeded in higher yields than those of benzoyl- and phenyl-substituted 1,5-enynes (Entry 7 vs. Entries 8 and 9). With respect to the substituents (R²) at the alkyne terminus, the reactions of aryl-substituted 1,5-enynes proceeded at higher reaction rates than those of alkyl-substituted 1,5-enynes (Entries 1, 3, and 4 vs. 5 and 6; Entry 9 vs. 10). Importantly, the present cycloisomerization could be conducted using a reagent grade solvent without erosion of the product yield (Entry 2).

Although elaborate operations are required, tricyclic 2-pyridone **5ec**, bearing a methyl group at the bridged carbon atom, could also be synthesized as shown in Scheme 1. 1,4-Addition of methyl methacrylate to 2-methylcyclopentanone (**1e**) furnished ester **6** following the literature procedure.¹¹ The ester **6** was transformed into azide **2e** in five steps. The azide **2e** was treated with PPh₃ followed by reaction with alkynoyl chloride **3c** to furnish the desired 1,5-enyne **4ec**. The gold-catalyzed cycloisomerization of **4ec** proceeded to give the desired 2-pyridone **5ec** in high yield.

The cycloisomerization of 1,5-enyne **7** that can be readily prepared from phenylpropionic acid and 2,3,3-trimethylindole-nine in one step leading to tricyclic 2-pyridone **8** was also inves-

tigated. Fortunately, the desired cycloisomerization proceeded at room temperature by using the cationic gold(I)/PPh₃ complex (5 mol %) to yield the expected tricyclic 2-pyridone **8** in 52% yield (eq 5).



In conclusion, a new route to tricyclic 2-pyridone derivatives has been developed via formation of bicyclic *N*-alkenyl alkynylamides followed by the gold-catalyzed cycloisomerization. Future work will focus on application of this methodology to the total synthesis of natural products.

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References and Notes

- For recent reviews, see: a) M. Torres, S. Gil, M. Parra, *Curr. Org. Chem.* **2005**, *9*, 1757. b) I. Nakamura, Y. Yamamoto, *Chem. Rev.* **2004**, *104*, 2127. c) J. H. Rigby, *Synlett* **2000**, 1.
- a) K. Tanaka, A. Wada, K. Noguchi, *Org. Lett.* **2005**, *7*, 4737. b) Y. Yamamoto, K. Kinpara, T. Saigoku, H. Takagishi, S. Okuda, H. Nishiyama, K. Itoh, *J. Am. Chem. Soc.* **2005**, *127*, 605. c) H. A. Duong, M. J. Cross, J. Louie, *J. Am. Chem. Soc.* **2004**, *126*, 11438. d) L. V. R. Bonaga, H.-C. Zhang, D. A. Gauthier, I. Reddy, B. E. Maryanoff, *Org. Lett.* **2003**, *5*, 4537. e) T. Takahashi, F.-Y. Tsai, Y. Li, H. Wang, Y. Kondo, M. Yamanaka, K. Nakajima, M. Kotora, *J. Am. Chem. Soc.* **2002**, *124*, 5059, and references therein.
- R. A. Earl, K. P. C. Vollhardt, *J. Org. Chem.* **1984**, *49*, 4786.
- For recent reviews of synthesis of azaheterocycles including 2-pyridones by transition metal mediated [2 + 2 + 2] cycloadditions, see: a) B. Heller, M. Hapke, *Chem. Soc. Rev.* **2007**, *36*, 1085. b) P. R. Chopade, J. Louie, *Adv. Synth. Catal.* **2006**, *348*, 2307. c) J. A. Varela, C. Saà, *Chem. Rev.* **2003**, *103*, 3787.
- a) H. Imase, K. Noguchi, M. Hirano, K. Tanaka, *Org. Lett.* **2008**, *10*, 3563. b) H. Imase, T. Suda, Y. Shibata, K. Noguchi, M. Hirano, K. Tanaka, *Org. Lett.* **2009**, *11*, 1805.
- For selected recent examples of cycloisomerizations of 1,5-enynes to form six-membered compounds, see: a) J. Sun, M. P. Conley, L. Zhang, S. A. Kozmin, *J. Am. Chem. Soc.* **2006**, *128*, 9705. b) B. D. Sherry, L. Maus, B. N. Laforteza, F. D. Toste, *J. Am. Chem. Soc.* **2006**, *128*, 8132. c) M. Movassaghi, M. D. Hill, *J. Am. Chem. Soc.* **2006**, *128*, 4592. d) T. Shibata, Y. Ueno, K. Kanda, *Synlett* **2006**, 411. e) C. Nieto-Oberhuber, M. P. Muñoz, S. López, E. Jiménez-Núñez, C. Nevado, E. Herrero-Gómez, M. Raducan, A. M. Echavarren, *Chem.—Eur. J.* **2006**, *12*, 1677. f) C. M. Grisé, L. Barriault, *Org. Lett.* **2006**, *8*, 5905. g) S. Datta, A. Odedra, R.-S. Liu, *J. Am. Chem. Soc.* **2005**, *127*, 11606. h) C. Fehr, J. Galindo, *Angew. Chem., Int. Ed.* **2006**, *45*, 2901. i) H. Imagawa, T. Iyenaga, M. Nishizawa, *Org. Lett.* **2005**, *7*, 451. j) V. Mamane, P. Hannen, A. Fürstner, *Chem.—Eur. J.* **2004**, *10*, 4556, and references therein.
- For recent reviews of cycloisomerizations of 1,*n*-enynes, see: a) V. Michelet, P. Y. Toullec, J.-P. Genêt, *Angew. Chem., Int. Ed.* **2008**, *47*, 4268. b) L. Zhang, J. Sun, S. A. Kozmin, *Adv. Synth. Catal.* **2006**, *348*, 2271. c) C. Bruneau, *Angew. Chem., Int. Ed.* **2005**, *44*, 2328. d) L. Añorbe, G. Domínguez, J. Pérez-Castells, *Chem.—Eur. J.* **2004**, *10*, 4938.
- a) A. Padwa, A. C. Flick, H. Lee, *Org. Lett.* **2005**, *7*, 2925. b) A. Padwa, S. R. Harring, M. A. Semones, *J. Org. Chem.* **1998**, *63*, 44. c) C. H. Heathcock, M. H. Norman, D. A. Dickman, *J. Org. Chem.* **1990**, *55*, 798. d) D. A. Dickman, C. H. Heathcock, *J. Am. Chem. Soc.* **1989**, *111*, 1528.
- Supporting Information is available electronically on the CSJ-Journal Web site, <http://www.csj.jp/journals/chem-lett/index.html>.
- B. J. Neubert, B. B. Snider, *Org. Lett.* **2003**, *5*, 765.
- H. O. House, W. L. Roelofs, B. M. Trost, *J. Org. Chem.* **1966**, *31*, 646.