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Convergent and Rapid Assembly of Substituted 2-Pyridones through Formation of *N*-Alkenyl Alkynylamides Followed by Gold-Catalyzed Cycloisomerization

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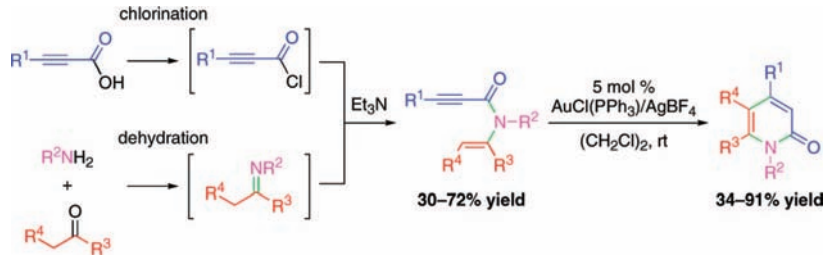
ABSTRACT



A new method for the convergent and rapid assembly of substituted 2-pyridones was developed through the formation of *N*-alkenyl alkynylamides (amide-linked 1,5-enynes) by N-acylation of imines with alkynoyl chlorides and the subsequent cationic Au(I)/PPh_3-catalyzed cycloisomerization.

2-Pyridones constitute important core units in a large number of pharmaceuticals, agrochemicals, and functional materials. The development of their efficient synthesis is, therefore, an important target in current organic synthesis.[1] Recent advances in transition-metal-catalyzed reactions allow development of new strategies for the synthesis of these compounds.[2] As such, the transition-metal-catalyzed [2 + 2 + 2] cycloaddition of two alkynes with an isocyanate has proven to be an efficient method for the convergent and rapid assembly of substituted 2-pyridones.[3,4] However, due to toxicity and instability of isocyanates, an alternative catalytic synthesis of 2-pyridones from nontoxic and stable starting materials would also be of great value.

In this respect, we anticipated that *N*-alkenyl alkynylamides (amide-linked 1,5-enynes) bearing an electron-rich

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(1) For recent reviews of the 2-pyridone synthesis, see: (a) Torres, M.; Gil, S.; Parra, M. *Curr. Org. Chem.* **2005**, *9*, 1757. (b) Rigby, J. H. *Synlett* **2000**, 1.

(2) For a recent review of the transition-metal-catalyzed synthesis of azaheterocycles including 2-pyridones, see: Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127.

(3) For recent reviews of the synthesis of azaheterocycles including 2-pyridones by transition-metal-catalyzed [2 + 2 + 2] cycloadditions, see: (a) Heller, B.; Hapke, M. *Chem. Soc. Rev.* **2007**, *36*, 1085. (b) Chopade, P. R.; Louie, J. *Adv. Synth. Catal.* **2006**, *348*, 2307. (c) Varela, J. A.; Saà, C. *Chem. Rev.* **2003**, *103*, 3787.

(4) For selected recent examples of the 2-pyridone synthesis by transition-metal-catalyzed [2 + 2 + 2] cycloadditions, see: (a) Yamamoto, Y.; Kinpara, K.; Saigoku, T.; Takagishi, H.; Okuda, S.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2005**, *127*, 605. (b) Duong, H. A.; Cross, M. J.; Louie, J. *J. Am. Chem. Soc.* **2004**, *126*, 11438. (c) Kondo, T.; Nomura, M.; Ura, Y.; Wada, K.; Mitsudo, T. *Tetrahedron Lett.* **2006**, *47*, 7107. (d) Tanaka, K.; Wada, A.; Noguchi, K. *Org. Lett.* **2005**, *7*, 4737. (e) Bonaga, L. V. R.; Zhang, H.-C.; Gauthier, D. A.; Reddy, I.; Maryanoff, B. E. *Org. Lett.* **2003**, *5*, 4537. For Zr-mediated reactions, see: (f) Takahashi, T.; Tsai, F.-Y.; Li, Y.; Wang, H.; Kondo, Y.; Yamanaka, M.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **2002**, *124*, 5059.

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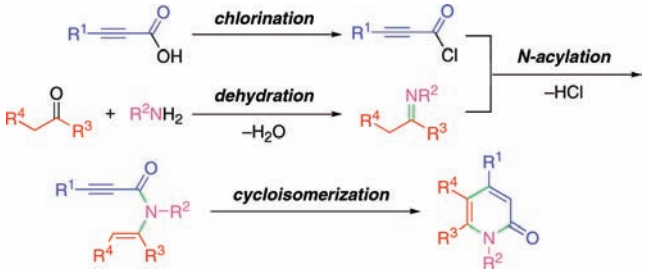
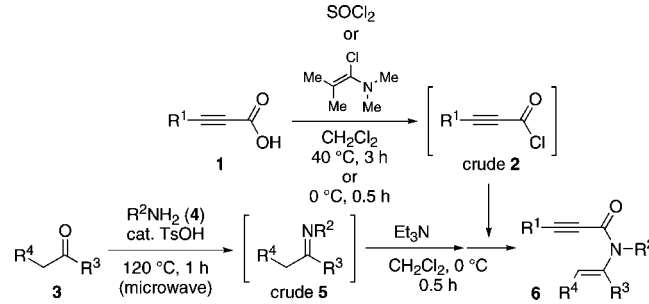
alkene moiety and an electron-deficient alkyne moiety, that might be available from the corresponding alkynoyl chlorides and imines, would cyclize to give substituted 2-pyridones by using a π-electrophilic transition-metal complex as a catalyst (Scheme 1).[5–10] Although several heterocycle syntheses through transition-metal-catalyzed cycloisomerizations of heteroatom-linked 1,5-enynes have been reported, application to the 2-pyridone synthesis has not been explored.[5–7] As alkynoyl chlorides can be readily prepared from the corresponding alkynoic acid and imines can be readily prepared from the corresponding carbonyl compounds and primary amines (Scheme 1), this protocol would serve as an attractive new method for the convergent and rapid assembly of substituted 2-pyridones.

Scheme 1. Our Plan for Convergent Synthesis of Substituted 2-Pyridones



The convergent synthesis of *N*-alkenyl alkynylamides **6** starting from the corresponding alkynoic acid **1**, carbonyl compounds **3**, and primary amines **4** was investigated to allow a high degree of structural diversity. The optimized reaction conditions for the synthesis of **6** are shown in Scheme 2. The reaction of crude imine **5**, prepared by dehydration between **3** and **4** under microwave heating, and crude alkynoyl chloride **2**, prepared by chlorination of **1**, at 0 °C in the presence of Et_3N furnished the desired amide **6**.[11]

Scheme 2. Optimized Reaction Conditions for the Synthesis of *N*-Alkenyl Alkynylamides **6**



Various *N*-alkenyl alkynylamides **6** were prepared in fair to good yields by the above optimized reaction conditions. Aryl- (entries 1−9), alkyl- (entry 10), and trimethylsilyl- (entry 11) substituted alkynoic acids, cyclic (entries 1−5 and 10) and acyclic (entries 6−9 and 11) carbonyl compounds, and benzylamine (entries 1−3 and 5−11) and neopentylamine (entry 4) could be used as summarized in Table 1.[12] The choice of the base is critical, and the use of pyridine instead of Et_3N did not furnish amide **6** at all (entries 1 vs 2). On the other hand, both thionyl chloride and 1-chloro-*N*,*N*-2-trimethyl-1-propenylamine could be employed as a chlorination reagent (entries 1 vs 3). All these reactions could be conducted using a reagent grade solvent and completed for 0.5−3 h, which might be attractive for the combinatorial synthesis.

Gratifyingly, the reaction of *N*-cyclopentenyl phenylethynylamide **6aaa** with a catalytic amount of π-electrophilic transition-metal complexes,[13] such as Rh(I), Pd(II), Pt(II), and Cu(II) complexes, at elevated temperature gave 4-phenyl-2-pyridone **7aaa** through endo cyclization (Table 2, entries 1−6).[14] A cationic Ag(I) complex is more active, which

(5) For the Au(I)-catalyzed cycloisomerization of *N*-propargyl silyl ketene amides leading to substituted dehydro-δ-lactams, see: Minnihan, E. C.; Colletti, S. L.; Toste, F. D.; Shen, H. C. *J. Org. Chem.* **2007**, *72*, 6287.

(6) For the Au(I)-catalyzed cycloisomerization of propargyl vinyl ethers leading to substituted dihydropyrans, see: Sherry, B. D.; Maus, L.; Laforteza, B. N.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 8132.

(7) For the Ru(II)-catalyzed cycloisomerization of 3-azadienynes leading to substituted pyridines via Ru−vinylidene intermediates, see: (a) Movassaghi, M.; Hill, M. D. *J. Am. Chem. Soc.* **2006**, *128*, 4592. Related recent azaheterocycle syntheses, see: (b) Movassaghi, M.; Hill, M. D. *J. Am. Chem. Soc.* **2006**, *128*, 14244. (c) Movassaghi, M.; Hill, M. D.; Ahmad, O. K. *J. Am. Chem. Soc.* **2007**, *129*, 10096. (d) Liu, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2008**, *130*, 6918.

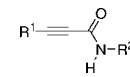
(8) For recent examples of π-electrophilic transition-metal-catalyzed cycloisomerizations of 1,5-enynes to form six-membered carbocycles by Au(I) catalysts, see: (a) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 11806. (b) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962. (c) Sun, J.; Conley, M. P.; Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2006**, *128*, 9705. (d) Shibata, T.; Ueno, Y.; Kanda, K. *Synlett* **2006**, 411. (e) Nieto-Oberhuber, C.; MuNunez, M. P.; Nevado, C.; Herrero-Gomez, E.; Raducan, M.; Echavarren, A. M. *Chem.−Eur. J.* **2006**, *12*, 1677. (f) Grise, C. M.; Barriault, L. *Org. Lett.* **2006**, *8*, 5905. By Cu(I) catalysts, see: (g) Fehr, C.; Galindo, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2901By Hg(II) catalysts, see: (h) Imagawa, H.; Iyenaga, T.; Nishizawa, M. *Org. Lett.* **2005**, *7*, 451. (i) Imagawa, H.; Iyenaga, T.; Nishizawa, M. *Synlett* **2005**, 703.

(9) For examples of Ru(II)-catalyzed cycloisomerizations of 1,5-enynes to form six-membered carbocycles via Ru−vinylidene intermediates, see: (a) Merlic, C. A.; Pauly, M. E. *J. Am. Chem. Soc.* **1996**, *118*, 11319. (b) Datta, S.; Odedra, A.; Liu, R.-S. *J. Am. Chem. Soc.* **2005**, *127*, 11606. (c) Odedra, A.; Wu, C.-J.; Pratap, T. B.; Huang, C.-W.; Ran, Y.-F.; Liu, R.-S. *J. Am. Chem. Soc.* **2005**, *127*, 3406.

(10) For recent reviews of cycloisomerization of 1,*n*-enynes, see: (a) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268. (b) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271. (c) Bruneau, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 2328. (d) Añorbe, L.; Domínguez, G.; Pérez-Castells, J. *Chem.−Eur. J.* **2004**, *10*, 4938.

(11) Although N-acylation of imines with alkynoyl chlorides has not been previously reported, N-acylation of imines with alkanoyl chlorides in the presence of a base was reported. See: (a) Saito, M.; Matsuo, J.; Uchiyama, M.; Ishibashi, H. *Heterocycles* **2006**, *69*, 69. (b) Lenz, G. R.; Lessor, R. A.; Rafalko, P. W.; Ezell, E. F.; Kosarych, Z.; Meyer, L.; Margaretha, P. *Helv. Chim. Acta* **2004**, *87*, 690.

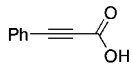
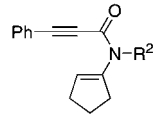
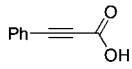
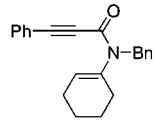
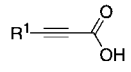
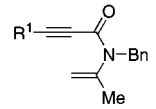
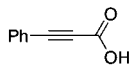
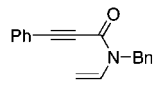
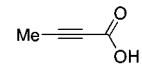
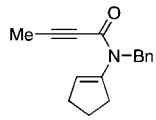
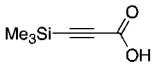
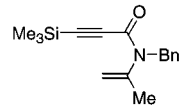
(12) Alkynyl-NH-amides, structures of which are shown below, were generated as byproducts.



(13) For a review of π-electrophilic Lewis acid catalysts, see: Yamamoto, Y. *J. Org. Chem.* **2007**, *72*, 7817.

(14) The NH-amide (R^1 = Ph, R^2 = Bn in ref 12) was obtained as a byproduct in ca. 35% yield (entry 2) and ca. 70% yield (entry 6). On the other hand, unidentified complex mixtures were generated other than the desired 2-pyridone in entries 1, 3, 4, 5, and 7.

Table 1. Synthesis of *N*-Alkenyl Alkynylamides **6**[a]

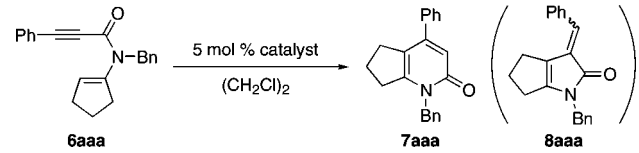
entry	substrates **1**, **3**, and **4**			product **6**
	1 (R^1)	**3**	**4** (R^2)	yield (%)[b]
			R^2–NH_2	
1	**1a**	**3a**	**4a** (Bn)	**6aaa** 66
2[c]	**1a**	**3a**	**4a** (Bn)	**6aaa** 0
3[d]	**1a**	**3a**	**4a** (Bn)	**6aaa** 66
4	**1a**	**3a**	**4b** (Me_3CCH_2)	**6aab** 72
			$BnNH_2$	
5	**1a**	**3b**	**4a**	**6aba** 53
			$BnNH_2$	
6	**1a** (Ph)	**3c**	**4a**	**6aca** 45
7[d]	**1b** (4-$MeOC_6H_4$)	**3c**	**4a**	**6bca** 56
8[d]	**1c** (4-$F_3CC_6H_4$)	**3c**	**4a**	**6cca** 30
			$BnNH_2$	
9	**1a**	**3d**	**4a**	**6ada** 32
			$BnNH_2$	
10[d]	**1d**	**3a**	**4a**	**6daa** 58
			$BnNH_2$	
11	**1e**	**3c**	**4a**	**6eca** 30

[a] **1** (5−10 mmol scale, 1.0 equiv), $SOCl_2$ (3.0 equiv), **3** (1.0 equiv), **4** (1.0 equiv), TsOH (ca. 2 mg), and CH_2Cl_2 (reagent grade) were used. See Supporting Information for details. [b] Isolated yield. [c] Pyridine was used instead of Et_3N. [d] 1-Chloro-*N*,*N*-2-trimethyl-1-propenylamine (1.1 equiv) was used instead of $SOCl_2$.

catalyzed the reaction at room temperature (entry 7).[14] A cationic Au(I)/PPh_3 complex showed the highest catalytic activity, which catalyzed the reaction at room temperature for only 0.5 h (entry 9), while a neutral Au(I)/PPh_3 complex showed no catalytic activity even at elevated temperature (entry 8). In all entries, the exo cyclization product **8aaa** was not generated at all.

The scope of the cationic Au(I)/PPh_3-catalyzed cycloisomerization of *N*-alkenyl alkynylamides **6**, leading to 2-pyridones **7**, was examined as summarized in Table 3. Both *N*-benzyl (entry 1) and *N*-neopentyl (entry 3) alkynylamides furnished the corresponding 2-pyridones in high yields. Alkynylamides bearing not only trisubstituted (entries 1−4 and 9) but also disubstituted (entries 5−7 and 10) and monosubstituted (entry 8) alkene moieties could participate in this reaction. With respect to the alkyne terminus, the reactions of aryl-substituted alkynylamides were rapid (entries 1−8), while the reactions of alkyl- and trimethylsilyl-substituted alkynylamides were slow (entries 9 and 10).[15]

Table 2. Screening of Catalysts for Cycloisomerization of *N*-Cyclopentenyl Phenylethynylamide **6aaa**[a]

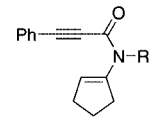
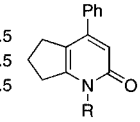
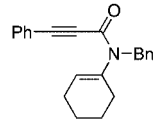
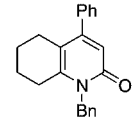
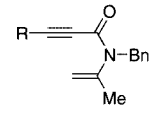
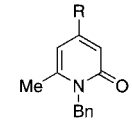
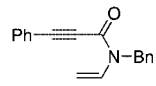
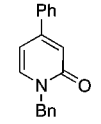
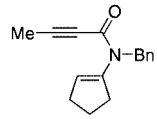
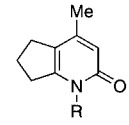
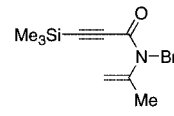
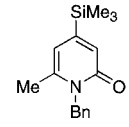


6aaa **7aaa** **8aaa**

				yield (%)[b]	
entry	catalyst	conditions	convn (%)	**7aaa**	**8aaa**
1	$[Rh(PPh_3)_2]BF_4$	80 °C, 3 h	85	49	0
2	$[Rh(P(OPh)_3)_2]BF_4$	80 °C, 3 h	50	13	0
3	$PdCl_2$	80 °C, 3 h	76	17	0
4	$[Pd(CH_3CN)_4](BF_4)_2$	80 °C, 1 h	100	68	0
5	$PtCl_2$	80 °C, 3 h	100	42	0
6	$Cu(OTf)_2$	80 °C, 3 h	100	18	0
7	$AgBF_4$	rt, 5 h	100	52	0
8	$AuCl(PPh_3)$	80 °C, 6 h	0	0	0
9	$AuCl(PPh_3)/AgBF_4$	rt, 0.5 h	100	82	0

[a] Catalyst (0.0050 mmol, 5 mol %), **6aaa** (0.10 mmol), and $(CH_2Cl)_2$ (1.0 mL) were used. [b] Isolated yield.

Table 3. Cationic Au(I)/PPh_3-Catalyzed Cycloisomerization of *N*-Alkenyl Alkynylamides **6** to Form 2-Pyridones **7**[a]

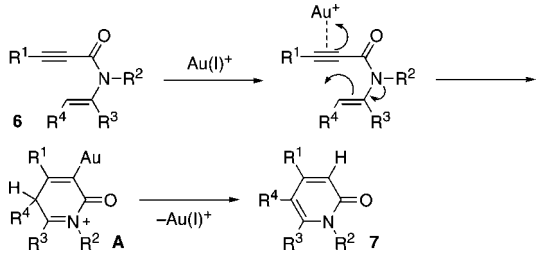
entry	substrate **6** (R)	time (h)	product **7**, yield (%)[b]
1	 **6aaa** (Bn)	0.5	 **7aaa** 89
2[c]	**6aaa** (Bn)	0.5	**7aaa** 87
3	**6aab** (Me_3CCH_2)	0.5	**7aab** 91
4	 **6aba**	4	 **7aba** 86
5	 **6aca** (Ph)	1	 **7aca** 70
6	**6bca** (4-$MeOC_6H_4$)	1	**7bca** 90
7	**6cca** (4-$F_3CC_6H_4$)	3	**7cca** 50
8	 **6ada**	3	 **7ada** 52
9	 **6daa**	13	 **7daa** 58
10	 **6eca**	12	 **7eca** 34

[a] Reactions were conducted using $AuCl(PPh_3)/AgBF_4$ (0.010 mmol, 5 mol %), **6** (0.20 mmol), and $(CH_2Cl)_2$ (2.0 mL: anhydrous) at rt. [b] Isolated yield. [c] $(CH_2Cl)_2$ (2.0 mL: reagent grade) was used.

The electronic nature of the aromatic substituents appears to have a high impact on yields [more electron-rich (entry 6), higher yield; more electron-poor (entry 7), lower yield].[16] Importantly, the present Au(I)-catalyzed cycloisomerization can be conducted using a reagent grade solvent without erosion of the yield (entry 2). The structure of the endo cyclization product **7**, not the exo cyclization product **8**, was unambiguously confirmed by X-ray crystallographic analysis of the crystalline 2-pyridone **7aca**.[17]

Scheme 3 depicts a possible mechanism for the present

Scheme 3. Possible Mechanism for Cationic Au(I)/PPh_3-Catalyzed Cycloisomerization of *N*-Alkenyl Alkynylamides **6**



cycloisomerization. We believe that the coordination of the catioinic Au(I) complex to the alkyne moiety of *N*-alkenyl alkynylamide **6** would induce the endo cyclization to generate the iminium intermediate **A**.[18–20] Subsequent deprotonation gives substituted 2-pyridone **7** and regenerates the Au(I) catalyst.

To intercept the cationic intermediate **A**, the reactions of **6aba** and **6cca** with MeOH (1 equiv) in 1,4-dioxane at room temperature were examined in the presence of the catioinic Au(I) complex (5 mol %). However, 2-pyridones **7aba** and **7cca** were obtained in almost identical yields (81% and 44%, respectively) as compared with entries 4 and 7 of Table 3, and the expected MeOH adducts **9aba** and **9cca** (Figure 1)

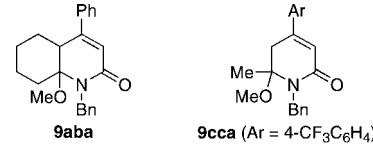


Figure 1. Expected MeOH adducts **9aba** and **9cca**.

were not obtained at all presumably due to the rapid deprotonation from the intermediate **A** and/or the rapid elimination of MeOH from the compounds **9** leading to the conjugated structures **7**.

In conclusion, we have established a new synthetic route to substituted 2-pyridones through the formation of *N*-alkenyl alkynylamides by *N*-acylation of imines with alkynoyl chlorides and the subsequent cationic Au(I)/PPh_3-catalyzed cycloisomerization. The present synthesis serves as a versatile new method for the convergent and rapid assembly of substituted 2-pyridones in pharmaceutical, agricultural, and material chemistry. Expansion of the substrate scope and an asymmetric variant of this reaction are underway in our laboratory.

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Supporting Information Available: Experimental procedures, compound characterization data, and an X-ray crystallographic information file (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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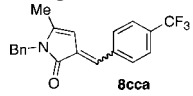
(15) Although the product yields were moderate in entries 8 and 9, the complete conversion of the starting material was observed, and the almost pure 2-pyridones were obtained after removal of the gold catalyst by a short silica gel column chromatography. Extremely polar decomposition products might be generated other than the desired 2-pyridones. On the other hand, an unidentified complex mixture was generated other than the desired 2-pyridone in entry 10.

(16) Exo cyclization product **8cca** was generated as a byproduct with ca. 25% yield in entry 7, although it could not be isolated in a pure form.



(17) See Supporting Information.

(18) Toste and co-workers proposed the formation of the oxocarbenium intermediate in their Au(I)-catalyzed synthesis of dihydropyrans from 1,5-enynes; see ref 6.

(19) Importantly, cyclopropane derivatives and alkyl migration products were not detected at all in the crude reaction mixtures of the present Au(I)-catalyzed cycloisomerization of amide-linked 1,5-enynes (Table 3). Therefore, cationic cyclopropylcarbene−gold intermediates may not play a role in this cycloisomerization. For examples, see: (a) Echavarren, A. M.; Nevado, C. *Chem. Soc. Rev.* **2004**, *33*, 431. (b) Gagosz, F. *Org. Lett.* **2005**, *7*, 4129. (c) See also ref 10.

(20) The electron-rich alkene moiety and the electron-deficient alkyne moiety of **1** are essential to promote the present cycloisomerization. The reaction of *N*-isopropenyl alkynylamide **6eca** furnished the corresponding pyridone **7eca** at room temperature (Table 3, entry 10), while no reaction was observed and the starting material remained unchanged in the reaction of *N*-alkynyl isopropenylamide even at elevated temperature as shown below.