ORGANIC LETTERS

2008
Vol. 10, No. 14
3137−3139

Gold-Catalyzed Synthesis of Polycyclic Enones from Carbon Tethered 1,3-Enynyl Carbonyls via Tandem Heteroenyne Metathesis and Nazarov Reaction

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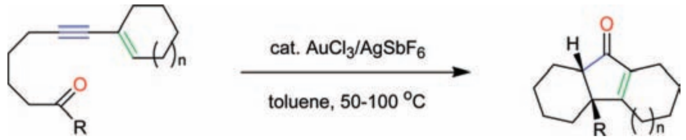
Received June 4, 2008

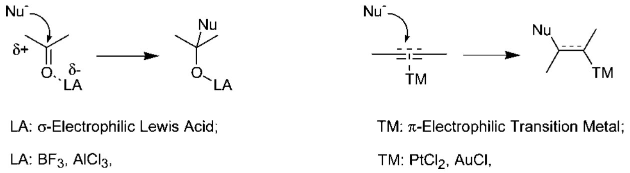
ABSTRACT



An efficient and general Au(III)-catalyzed tandem reaction, heteroenyne metathesis and Nazarov cyclization, of 1,3-enynyl ketones to produce fused tri- and tetracyclic enones has been developed. The products were formed with excellent regioselectivity of the double bond position and with very high diastereoselectivities. In this reaction, the Au(III) catalyst exhibits dual roles for activating both alkynes and carbonyls.

Lewis acid- and transition-metal-catalyzed transformations have been demonstrated to be powerful tools for synthetic organic chemistry.[1] Generally, the ordinary Lewis acids, such as BF_3, $AlCl_3$, etc., are known to activate carbonyl and imine groups by formation of a σ-complex by which the attack of nucleophiles is facilitated (Scheme 1).[1a,b,e] On the other hand, one of the representative roles of transition metal catalysts, such as AuCl, $PtCl_2$, etc., is the formation of a π-complex with C−C multiple bonds, which makes feasible the nucleophilic attack to an electron-deficient carbon to give an organometallic intermediate having a C−Nu bond (Scheme 1).[1c−e] It is thought that proper choice of a Lewis acid which may exhibit dual roles makes it possible to activate both C−C multiple bonds and C═X (X = O, N,...) unsaturated bonds in a single transformation.[2]

Scheme 1. Principal Role of a Lewis Acid and Transition Metal Catalyst[a]



[a] Nu = Nucleophiles.

We recently reported that cationic Au(III) catalyst brought about the intramolecular heteroenyne metathesis cyclization of the carbon-tethered alkynyl ketones **1**, leading to the formation of highly substituted cyclic enones **3** via the π-complex between Au catalyst and alkyne (Scheme 2).[3] We envisioned that when R′ was an alkenyl group the 1,3-enynyl

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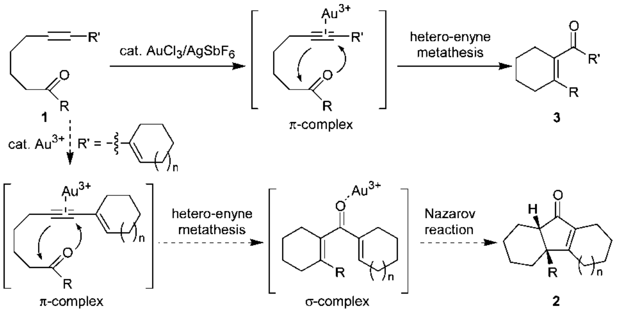
(1) For reviews, see: (a) *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, 2000; Vols. 1−2. (b) *Lewis Acid Reagents*; Yamamoto, H., Ed.; Oxford University Press: New York, 1999. (c) *Transition Matal Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley: New York, 2000. (d) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (e) Yamamoto, Y. *J. Org. Chem.* **2007**, *72*, 7817.

(2) (a) Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764. (b) Nakamura, I.; Bajracharya, G. B.; Mizushima, Y.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 4328. (c) Kamijo, S.; Yamamoto, Y. *J. Org. Chem.* **2003**, *68*, 4764.

10.1021/ol801265s CCC: $40.75

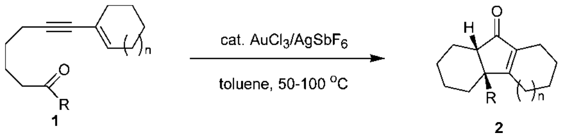
Scheme 2. Dual Roles of Au(III) Catalyst for the Tandem Cyclization of 1,3-Enynyl Carbonyls



carbonyls **1** would produce the divinyl ketones through a π-complex, which may undergo the sequential Nazarov reaction via σ-complex, affording the fused polycyclic enones **2** containing a cylopentenone ring.

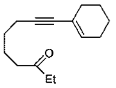
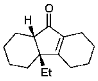
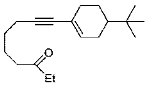
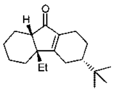
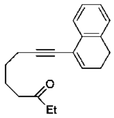
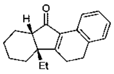
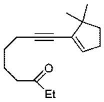
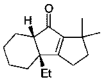
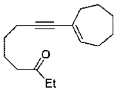
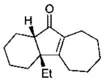
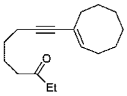
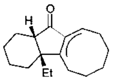
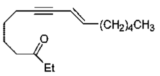
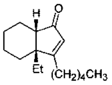
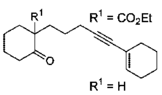
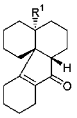
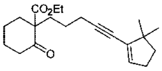
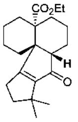
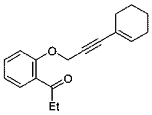
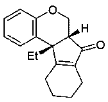
The Nazarov reaction, which is one of the most powerful methods for the construction of cyclopentenones, proceeds mostly by the use of a stoichiometric amount (or even more) of acid promoters, and a catalytic Nazarov reaction is very rare, especially for constructing tri- and tetracyclic carbocycles with various ring sizes,[4a–c,5] although the catalytic process is well-known for synthesizing simple cyclopentenones.[4] The earliest methods always required one or more equivalents of strong acids (polyphosphoric acid/100 °C), and the structural limitation of divinyl ketone starting materials or their precursors diminished the synthetic utility of the reaction.[6] More recently, two attractive strategies for the construction of polycyclic rings were reported: Denmark's silicon-directed Nazarov cyclization and West's interrupted Nazarov cyclization with alkenes and arenes were promoted by a stoichiometric amount of Lewis acids.[7]

Herein, we report an efficient and general synthetic method for various fused tri- and tetracyclic enones via the cationic Au(III)-catalyzed tandem heteroenyne metathesis and Nazarov cyclization (eq 1). The products were formed in good to high yields with excellent regioselectivity of the double bond position and with very high diastereoselectivities.



(1)

Table 1. Au-Catalyzed Tandem Cyclization of Various 1,3-Enynyl Carbonyls[a]

entry	substrate	1	time (h)	product	2	yield (%)[b]
1		**1a**	1		**2a**	80[c]
2		**1b**	2		**2b** dr	85[c] 6:1
3		**1c**	2		**2c**	60
4		**1d**	4		**2d**	70[c]
5		**1e**	4		**2e**	72
6		**1f**	3		**2f** **2f'**	52 33
7		**1g**	3		**2g**	50
8	 $R^1 = CO_2Et$	**1h**	4		**2h**	61[d]
9	$R^1 = H$	**1i**	2		**2i**	50
10		**1j**	3		**2j**	75[d]
11		**1k**	2		**2k**	40

[a] Reaction conditions: 2 mol % of $AuCl_3$ and 6 mol % of $AgSbF_6$, **1** (0.5 mmol), toluene (0.2 M), 100 °C. [b] Isolated yield. [c] 50 °C. [d] 5 mol % of $AuCl_3$ and 15 mol % of $AgSbF_6$ were used at 100 °C.

The reaction of **1a** using 2 mol % of $AuCl_3$ and 6 mol % of $AgSbF_6$ was performed at 50 °C for 1 h, giving the desired [6,5,6] linear tricycle **2a** having a cyclopentenone skeleton in 80% yield (Table 1, entry 1).[8] We then examined the scope of the polycycle synthesis. The enynyl ketone **1b**bearing a sterically bulky *tert*-butyl on the 4-position of the cyclohexene ring was subjected to the reaction condition affording a 6:1 mixture of diastereomers **2b** with the *cis-anti* isomer as a major

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(3) Jin, T.; Yamamoto, Y. *Org. Lett.* **2007**, *9*, 5259.

(4) For recent reviews, see: (a) Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193. (b) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479. (c) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577. For an efficient Au-catalyzed synthesis of cyclopentenones via tandem Nazarov reaction, see: (d) Zhang, L.; Wang, S. *J. Am. Chem. Soc.* **2006**, *128*, 1442.

(5) (a) Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671. (b) Liang, G.; Xu, Y.; Seiple, I. B.; Trauner, D. *J. Am. Chem. Soc.* **2006**, *128*, 11022.

(6) (a) Braude, E. A.; Coles, J. A. *J. Chem. Soc.* **1952**, 1430. (b) Braude, E. A.; Forbes, W. F. *J. Chem. Soc.* **1953**, 2208. (c) Eaton, P. E.; Giordano, C.; Schloemer, G.; Vogel, U. *J. Org. Chem.* **1976**, *41*, 2238. (d) Harding, K. E.; Clement, K. S. *J. Org. Chem.* **1984**, *49*, 3870. (e) Mehta, G.; Krishnamurthy, N. *J. Chem. Soc., Chem. Commun.* **1986**, 1319.

(7) (a) Denmark, S. E.; Wallace, M. A.; Walker, C. B. *J. Org. Chem.* **1990**, *55*, 5543. (b) Denmark, S. E.; Klix, R. C. *Tetrahedron* **1988**, *44*, 4043. (c) Bender, J. A.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 7443. (d) Browder, C. C.; Marmsater, F. P.; West, F. G. *Org. Lett.* **2001**, *3*, 3033.

(8) The reaction of **1a** in the presence of a protic acid, such as $HSbF_6$ or TfOH, gave a complex mixture of products, indicating that the use of $AuCl_3/AgSbF_6$ catalyst is essential for the present tandem reaction.

diastereomer (entry 2). The enynyl ketone with dihydronaphthalene **1c** afforded the tetracycle **2c** in a good yield, although a higher temperature was needed (entry 3). The enynyl ketones with various sizes of cyclic alkenes were tested. For example, the reaction with the enynyl ketones having cyclopentene and cycloheptene moieties gave the corresponding linear tricycles **2d** and **2e** in 70% and 72% yield, respectively (entries 4 and 5), while the enynyl ketone **1f** bearing a cyclooctene moiety afforded 52% of the corresponding tricycle **2f** along with 33% of an isomer **2f′**, in which the double bond was away from the ring-fused position. Perhaps the double bond migration took place to avoid ring strain (entry 6). In addition to the cyclic enynes, the reaction proceeded smoothly with the acyclic enynyl ketone **1g**, leading to the bicyclic cyclopentenone **2g** in 50% yield (entry 7). Furthermore, the *cis-anti* tetracyclic enones, **2h**, **2i**, and **2j**, were readily produced diastereoselectively from the Au-catalyzed tandem reaction of the corresponding cyclic enynes containing cyclic ketones, although a higher catalytic loading was necessary when R^1 was an ethoxycarbonyl group (entries 8, 9, and 10). The benzene tethered cyclic enynyl ketone **1k** underwent the tandem cyclization readily to give the corresponding tetracycle **2k** in 40% yield (entry 11).

The structure of **2k** was unambiguously determined by X-ray crystallography (Figure 1) which indicated that the ring-fusion stereochemistry of the ethyl and the proton groups was *cis*, and those of other products were assigned by analogy.[9]

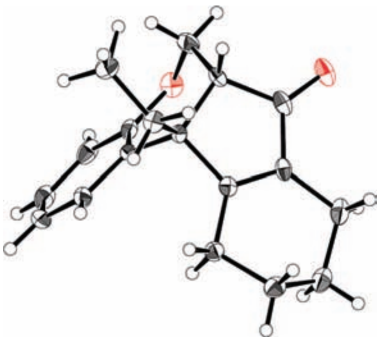
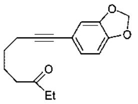
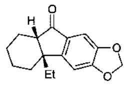
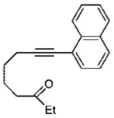
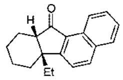
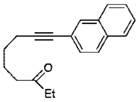
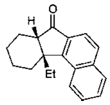


Figure 1. ORTEP drawings of **2k**.

Next, we investigated the Au-catalyzed tandem reaction with the aryl-substituted alkynes instead of enynes. The reaction of the alkynyl ketone **1l** substituted with a strong electron-donating 1,3-dioxoyl group on the aromatic ring produced the linear tetracyclic fluorenone derivative **2l** in 66% yield (Table 2, entry 1). Interestingly, the 1- and 2-naphthyl-substituted alkynyl ketones, **1m** and **1n**, were converted to the corresponding tetracyclic benzofluorenone derivatives **2m** and **2n** in 92% and 96% yields, respectively, and **2n** was obtained as a single regioisomer (entries 2 and 3).

Table 2. Au-Catalyzed Tandem Heteroenyne Metathesis and Aromatic Nazarov Reaction[a]

entry	substrate	1	product	2	yield (%)[b]
1		**1l**		**2l**	66
2		**1m**		**2m**	92
3		**1n**		**2n**	96

[a] Reaction conditions: 2 mol % of $AuCl_3$ and 6 mol % of $AgSbF_6$, **1** (0.5 mmol), toluene (0.2 M), 100 °C, 4 h. [b] Isolated yield.

In conclusion, we have developed an efficient method for constructing various fused tri- and tetracyclic enones via the Au-catalyzed tandem heteroenyne metathesis and Nazarov reaction. The Au(III) catalyst exhibits dual roles for activating both alkynes and carbonyls, and it should be noted that a catalytic Nazarov reaction proceeds very smoothly in this system.

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

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[9] CCDC-685029 contains the supplementary crystallographic data for **2k**. The detailed data can be obtained free of charge from The Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif. The stereochemistry of products, **2b**, **2f′**, **2h**, **2i**, and **2j**, was confirmed by measurement of various 1D, 2D, and NOE spectra. See Supporting Information for details.