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Gold-Catalyzed Cyclization–Cycloaddition Cascade Reactions of Allenyl Acetals with Nitrones

Dhananjayan Vasu and Rai-Shung Liu^{*[a]}

Gold-catalyzed cyclization-cycloaddition reactions^[1] of oxoalkynes,^[2] oxoallenes,^[3] oxoalkenes,^[4] and allenyl acetals^[5] are powerful tools for accessing complicated carboand oxacyclic frameworks. These reactions allow the simultaneous generation of two new rings and three chemical bonds. In the presence of gold complexes, such difunctional substrates undergo an initial cyclization to form reactive carbocation-like intermediates that can be trapped with suitable nucleophiles to achieve stereocontrolled cycloadditions.^[2-5] We recently reported^[5b] a gold-catalyzed cascade reaction between allenyl acetals and dinucleophilic phenols and one between allylsilanes and cyclic 1,3-diones, reactions that gave complex products stereoselectively. In those reports, allenyl acetals function as dication equivalents (Scheme 1). Herein, we report a different type of cyclization-cycloaddition cascade reaction of the same substrates (1): they react as 1,2-dipole equivalents with suitable nitrones in [3+2]-cycloadditions.^[6,7]. Although the new reactions afford two diastereomeric products 3, a subsequent HOAccatalyzed hydrolysis of this isomeric mixture gave tricyclic ketones 6 as single diastereomers.

Table 1 shows our efforts to realize a cyclization-cycloaddition cascade reaction between allenyl acetal 1a (1 equivalent) and nitrone 2a (1.2 equivalents) in dichloroethane (DCE, 25°C) by using various gold catalysts. Cationic gold species were selected and screened for their activity in promoting this cascade reaction because of their superior performance in the cyclizations of allenyl acetals with dinucleophilic molecules.^[5b] The use of [PPh₃AuCl]/AgNTf₂ resulted in complete consumption of starting material 1a to give cycloadducts 3a and 3a' in 54% and 28% yields, respectively, after their separation using silica-gel column chromatography (Table 1, entry 1). We obtained product **3a** exclusively in 80% yield when using bulky complex [LAuNTf₂] (L=(obiphenyl) $P(tBu)_2$; Table 1, entry 2). The use of [LAuSbF₆] led to a decrease in the yield of compound 3a (73%; Table 1, entry 3). The use of [IPrAuCl]/AgNTf₂ gave compound 3a and 3a' in 53% and 25% yields, respectively

[a] Dr. D. Vasu, Prof. Dr. R.-S. Liu Department of Chemistry National Tsing Hua University Hsinchu 30013, Taiwan (ROC) Fax: (+886) 3-5711082 E-mail: rsliu@mx.nthu.edu.tw

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Scheme 1. Different pathways for the cyclization-cycloaddition cascade reaction of allenyl acetals.

Table 1. The activities of various gold complexes in catalyzing the cascade reaction.

0 0 1a (1 equiv.)	$\overset{+}{\swarrow} \overset{\text{Ph}}{} \overset{\overset{+}{\bigvee} \overset{\text{Ph}}{} \overset{\text{Ph}}{} \overset{5 \text{ mol}\% [Au]}{\text{ solvent, 25 °C}}$ $\overset{10 \text{ min}}{} \overset{10 \text{ min}}{\overset{10 \text{ min}}} \overset{10 \text{ min}}{\overset{10 \text{ min}}{10 \text{ m$	OMe ON-H Ph 3a	$ \begin{pmatrix} & & & \\ & & & & \\ & & & \\ & & & & \\ & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\$
Entry ^[a]	Catalyst	Solvent	3 Yield [%] ^[b]
1	[PPh3AuCl]/AgNTf2	DCE	3a (54), 3a' (28)
2	[LAuCl]/AgNTf ₂	DCE	3a (80)
3	[LAuCl]/AgSbF6	DCE	3a (73)
4	[IPrAuCl]/AgNTf ₂	DCE	3a (53), 3a' (25)
5	[LAuCl]/AgNTf ₂	CH_2Cl_2	3a (77)
6	[LAuCl]/AgNTf ₂	THF	3a (32), 3a' (28)
7	AgNTf ₂	DCE	3a (35), 3a' (13)

[[]a] [1a] = 0.2 M. [b] Product yields were measured after purification. L= (o-biphenyl)P(tBu)₂, IPr=1,3-bis(diisopropylphenyl)imidazol-2-ylidene, Tf=trifluoromethanesulfonyl.

(Table 1, entry 4). The solvent was varied for the reaction catalyzed by $[LAuCl]/AgNTf_2$ and it was found that dichloromethane (CH₂Cl₂) was as effective as DCE, giving cycloadduct **3a** as the sole product; however, the use of THF gave compounds **3a** and **3a'** in 32 and 28% yields, respec-

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tively, (Table 1, entry 6). In a control experiment, we found that AgNTf₂ in DCE in the absence of a gold complex also afforded compounds **3a** and **3a'**, albeit in low yields (Table 1, entry 7). In its ¹H NMR spectrum, the signals associated with the hydrogen atoms on the isoxazolidine ring in compound **3a** showed a coupling constant indicative of a *trans* relationship ($J_{\rm H,H}$ =1.6 Hz) whereas those in **3a'** showed a coupling constant indicative of a *cis* relationship ($J_{\rm H,H}$ =8.8 Hz). The molecular structure of compound **3a** was confirmed by X-ray diffraction analysis of derivative **4c**.^[8]

Table 2 shows the results of cyclization–cycloaddition reactions of allenyl acetal **1a** with various nitrones **2b–2l**; for several of these reactions, we obtained the corresponding diastereomeric cycloadducts, which were separable using

OM.

OM-

Table 2. The reaction with various nitrones.

	$= \begin{pmatrix} {}^{+} R^{1} \stackrel{{\sim} N^{+}}{N} R^{2} & \frac{5 \operatorname{mol} \mathbb{W} [Au]}{DCE, 25 \circ C} \\ 0 \\ 2 \end{pmatrix}$	$ \begin{array}{c} $	$\begin{pmatrix} + & & & \\ & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & $
Entry ^[a]	Nitrone R^1, R^2 (2)	<i>t</i> [min]	3 Yield [%] ^[b]
1	Me, Ph (2b)	25	3b (65), 3b' (17)
2	$4-ClC_{6}H_{4}$, Ph (2 c)	15	3c (82)
3	$4-BrC_{6}H_{4}$, Ph (2d)	20	3d (61), 3d' (17)
4	$4\text{-MeOC}_6\text{H}_4$, Ph (2e)	10	3e (87)
5	2-furanyl, Ph (2 f)	25	3f (56), 3f ' (19)
6	3-furanyl, Ph (2g)	5	3g (58), 3g' (28)
7	2-thienyl, Ph (2h)	20	3h (67)
8	3-thienyl, Ph (2i)	10	3i (56), 3i' (23)
9	Ph, 4-BrC ₆ H ₄ (2j)	5	3j (43), 3j ' (41)
10	Ph, 4-MeC ₆ H ₄ $(\mathbf{2k})$	10	3k (43), 3k' (41)
11	Ph, 4-MeOC ₆ H ₄ (21)	5	31 (38), 31' (15)

[a] [1a] = 0.2 M. [b] Product yields were measured after purification.

silica-gel column chromatography. Using nitrone 2b, which bears a methyl group at the nitrone carbon atom, desired products 3b and 3b' were obtained in 65% and 17% yields, respectively (Table 2, entry 1). For nitrones 2c-2e, which contain electron-deficient and electron-rich imine moieties $(R^1 = 4 - XC_6H_4; X = Cl, Br, and OMe)$, the corresponding cycloadducts 3c, 3d/3d', and 3e were obtained in good yields (total yield of diastereomeric products; Table 2, entries 2-4). Nitrones 2 f-2i, which contain heteroaryl imine moieties $(\mathbf{R}^1=2$ - and 3-furanyl, and 2- and 3-thienyl), were also used as substrates in this cyclization-cycloaddition reaction and the corresponding cycloadducts 3 f/3 f', 3g/3g', 3h, and 3i/3i' with yields of greater than 67% (Table 2, entries 5-8). For nitrones 2j-2l, which contain alterable aniline moieties $(R^2=4-XC_6H_4; X=Br, Me, and OMe)$, cycloadducts 3j/3j', 3k/3k', and 3l/3l' were obtained in moderate to good yields (53-84%; Table 2, entries 9-11).

We examined the reactions of nitrone **2a** with various allenyl acetals **1b–1g** including both cyclic and acyclic compounds (Table 3). The cyclization–cycloaddition of substrates **1b** and **1c**, which both contain substituted cyclohex-



Table 3. The reaction with various allenyl acetals.



[a] [1]=0.2 M; reaction time of 15 min [b] Product yields were measured after purification. [c] Reaction time of 60 min.

ene moieties, gave the desired cycloadducts 4b/4b' and 4c in 76-79% yields. The structure of compound 4c was confirmed by X-ray diffraction analysis.^[8] The fact that species 4c was obtained with excellent diastereoselectivity is not surprising because it has a similar structure to that of allenyl acetal 1a. For substrate 1d, which contains a cycloheptenyl moiety, the gold-catalyzed reaction gave cycloadduct 4d and dienyl ester 5d in 41% and 35% yields, respectively (Table 3, entry 3). For allenyl acetal 1e, which was used as an isomeric mixture (Z/E=3.2:1), we obtained the desired [3+2]-cycloadducts 4e/4e' as two inseparable diastereomers in equal proportions; the yield (73%) was estimated based on the Z isomer of starting material 1e. We also prepared acyclic Z-configured allenyl acetals 1f and 1g and when they were used as substrates in the cyclization-cycloaddition reaction, the corresponding products 4 f/4 f' and 4g/4g' were obtained in 75-83% overall yields (Table 3, entries 5 and 6).

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In contrast, the use of E-configured acyclic substrate 1g' gave a complicated mixture of unknown species.

To our delight, the isomeric products of this reaction undergo Brønsted-acid-catalyzed hydrolysis to give the same product, an α -isopropylidene cyclopentanone. As shown in Table 4, treatment of major diastereomer **3a** with neat





[a] [Cycloadduct]=0.2 M. [b] Product yields were measured after purification.

HOAc at 25 °C (8 hours) afforded tricyclic ketone **6a** in 76% yield (Table 4, entry 1); ¹H NOE spectra and X-ray diffraction analysis^[8] confirmed its structure, which contains *trans*-related geminal hydrogen atoms on the isoxazolidine ring. Interestingly, a similar hydrolysis of its isomer, **3a'**, afforded the same ketone **6a** in 73% yield (Table 4, entry 2). We also subjected other diastereomeric mixtures to this acid-catalyzed hydrolysis: **4b/4b'** (d.r.=3.9:1) and **4e/4e'** (d.r.=1:1) were converted into bicyclic ketones **6b** (60%) and **6d** (76%), respectively, as the only products (Table 4, entries 3 and 5). Compound **4c** was converted into desired ketone **6c** in 71% yield (Table 4, entry 4).

This new nitrone-based cyclization—cycloaddition reaction is mechanistically interesting because the allenyl acetals function as 1,2-dipole equivalents. Scheme 2 shows a plausible mechanism for the nitrone-based cyclization–[3+2]-cy-



Scheme 2. A plausible reaction mechanism.

cloaddition reaction. In the presence of a cationic gold species, the acetal moiety of species **1** is converted into an oxonium ion moiety, thus giving intermediate **A**, which then undergoes an intramolecular cyclization to give allylic cation **B**. We envisage that the released Au–OMe species then assists in the deprotonation of species **B** to give highly nucleophilic 1-methoxyfulvene C,^[9–12] which reacts with nitrone through an *exo* cycloaddition reaction to afford diastereomeric cycloadducts **3** and **4** as the major products. The stereochemical outcome is consistent with a report on a [3+2]cycloaddition reaction of fulvene and nitrone.^[12] This reaction together with previous reports show that these allenyl acetal substrates can undergo two different cascade reactions catalyzed by similar gold catalysts.

The cyclization-cycloaddition cascade reaction described herein involves an attack of 1-methoxyfulvene C on nitrone whereas in the previously reported cascade reaction (Scheme 1) a nucleophilic attack of either 1,3-diketones or phenols at allylic cation **B** is involved.

We then attempted to obtain enantioenriched **3a** to understand the nature of its hydrolysis with HOAc. The treatment of substrate **1a** with a range of chiral bisphosphine–gold complexes, $[LAu_2Cl_2]/2AgX$, gave diastereomer **3a** exclusively in greater than 63 % yield, albeit with low *ee* values (5-18%).^[13] With $[LAu_2Cl_2]/2AgX$ (L=(*R*)-DM-Segphos and X=NTf₂), we obtained (+)-**3a** in 18% *ee* (Scheme 3). A further treatment of this sample with neat HOAc (25 °C, 8 h) gave desired **6a** (2% *ee*) with a large loss in optical purity. This observation suggests that Brønsted acid not only enables the hydrolysis of the enol ether of **3a** to ketone **6a**, but also leads to the racemization of **3a**, a process that presumably involves the two key steps, **6a** \rightarrow **D** and **F** \rightarrow *ent*-**6a**; this process causes the configurations of all three stereogenic centers to invert in a reversible manner.

In summary, we have developed a gold-catalyzed cyclization–cycloaddition cascade reaction between allenyl acetals^[14] and nitrones. A key intermediate in the cascade reaction is postulated to be a 1-methoxyfulvene species.^[12] These reactions reveal that the allenyl acetal substrates act as 1,2dipole equivalents, a behavior that is in contrast with the "dication behavior" described in our previous investigation.^[5b] Although we often obtained two diastereomeric products in this cascade reaction, HOAc-catalyzed hydroly-



Scheme 3. Loss of optical purity in HOAc-catalyzed hydrolysis.

sis of these isomeric mixtures afforded isopropylidene cyclopentanones as single products.

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Keywords: allenes • [3+2]-cycloaddition • gold homogeneous catalysis • nitrones

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Gold and silver: When allenyl acetals and nitrones are treated with a catalytic amount of a gold complex and a silver salt they react through a cyclization-cycloaddition cascade reaction to give a mixture of diastereomeric tri-



cyclic products. The mixture converges to a single product upon acid hydrolysis (see scheme). The key intermediate is postulated to be a 1-methoxyfulvene species.

Gold Catalysis

Gold-Catalyzed Cyclization-Cycload-dition Cascade Reactions of Allenyl Acetals with Nitrones

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