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## Catalytic cascade hydroalkoxylation/isomerization/ [4 + 2] cycloaddition using enyne alcohols as latent dienes or dienophiles†

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Enyne alcohols can react as precursors of either dienes or dienophiles with different substrates after hydroxylation and isomerization by gold catalysis. As such, oxa-bridged tricyclo[5.2.2.0<sup>2,6</sup>]undec-8-ene-3,5-dione derivatives have been obtained by the Diels-Alder reaction and tetrahydro-1*H*-furo[3,4-c]pyran derivatives could be accessed by the hetero-Diels-Alder cycloaddition.

Heterocyclic structural skeletons are prevalent in biologically active natural products, pharmaceuticals, and numerous functional molecules.<sup>1</sup> Therefore, the development of new synthetic methods to directly access heterocycles is of great importance. Indeed, a large number of synthetic methods have emerged for the synthesis of heterocycles.<sup>2</sup> Cascade or domino reactions, because they are able to build up structurally complex molecules from relatively simpler substrates, have received increasing attention.<sup>3</sup> In recent years, gold catalysis has allowed one to design a variety of cascade reactions, some of which are capable of efficiently preparing structurally complex heterocyles. For instance, Barluenga and co-workers<sup>4</sup> established a cascade cycloisomerisation/Diels-Alder reaction for the synthesis of polycyclic compounds, wherein the AuCl<sub>3</sub> was a catalyst for both the cycloisomerization of functionalized enynes to generate 1,3-butadiene derivatives and the subsequent Diels-Alder reaction with dienophiles (Scheme 1). Some other groups have also reported various cascade



Scheme 1 Au(III)-catalyzed cascade cyclization/Diels-Alder reaction

reactions by virtue of gold catalysis for the synthesis of structurally complex cyclic molecules.<sup>5</sup>

Very recently, we have found a variety of relay catalytic cascade reactions,<sup>6</sup> including the consecutive hydroamination/ transfer hydrogenation of alkynes<sup>6a</sup> and a cyclization of alkynols triggered addition of azlactones<sup>6b</sup> using a combined catalyst system consisting of a chiral phosphoric acid and a gold complex. In particular, the Au(1)/Brønsted acid binary catalyst enables enynes as latent 1,3-silyloxydienes to participate in an unprecedented alternative to traditional Diels–Alder reactions, providing an efficient route to highly enantioenriched polycyclic compounds.<sup>6d</sup>

Because of our continuous interest in this field, we envisaged that the 1,3-butadiene derivatives, generated from the cyclization of enyne alcohols 1 catalyzed by an appropriate gold complex, would principally participate in the subsequent cycloaddition reaction, which might presumably be catalyzed by chiral catalysts to afford enantioenriched bicyclic molecules.<sup>4,5</sup> Herein, we will demonstrate that the dienes catalytically generated from enyne alcohols 1 were able to undergo either the Diels–Alder or inverse-electron-demand hetero-Diels–Alder reaction, depending on the dienophiles and reaction conditions (Scheme 2).

At the outset of our study, the *N*-(4-nitrophenyl)-maleic diimine **2**, which could be activated by a Brønsted acid through formation of hydrogen bonds,<sup>7</sup> was used as a dienophile for the proposed cascade Diels–Alder reaction with enyne alcohols **1a** in the presence of combined catalysts of a



Scheme 2 The reactions investigated in this study.

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Table 1Optimization for gold-catalyzed cascade reaction of enyne alcohols 1awith N-(4-nitrophenyl)-maleic diimine  $2^a$ 



Entry	[Au]	Solvent	$\operatorname{Yield}^{b}(\%)$
1 <sup><i>c</i></sup>	PPh <sub>3</sub> AuTFA	CHCl <sub>3</sub>	60
$2^d$	PPh <sub>3</sub> AuTFA	CHCl <sub>3</sub>	80
3	PPh <sub>3</sub> AuTFA	CHCl <sub>3</sub>	78
4	AuCl <sub>3</sub>	$CHCl_3$	e
5	PPh <sub>3</sub> AuCl/AgSbF <sub>6</sub>	$CHCl_3$	e
6	PPh <sub>3</sub> AuCl/AgBF <sub>4</sub>	$CHCl_3$	e
7	PPh <sub>3</sub> AuCl/AgOTf	$CHCl_3$	e
8	PPh <sub>3</sub> AuCl/AgOTs	$CHCl_3$	e
9	PPh <sub>3</sub> AuCl/AgTFA	CHCl <sub>3</sub>	81
10	PPh <sub>3</sub> AuTFA	Toluene	Trace
11	PPh <sub>3</sub> AuTFA	THF	22
12	PPh <sub>3</sub> AuTFA	DCE	63
$13^f$	PPh <sub>3</sub> AuTFA	$\mathrm{CHCl}_3$	68

<sup>*a*</sup> Reaction was run as a 0.1 M solution of 2, TFA = CF<sub>3</sub>COO. <sup>*b*</sup> Isolated yield after purification by flash chromatography. <sup>*c*</sup> 4 (10 mol%) was added and the reaction was run at rt for 6 days. <sup>*d*</sup> 4 (10 mol%) was added and the reaction was run at 60 °C for 2 days. <sup>*e*</sup> A complicated reaction mixture was observed. <sup>*f*</sup> 5 mol% PPh<sub>3</sub>AuTFA.

gold complex and a chiral Brønsted acid.8 However, the reaction proceeded very slowly at room temperature. After the reaction proceeded for six days, the desired tricyclic product 3a was isolated in 60% yield, but with no stereoselectivity (Table 1, entry 1). When the temperature was elevated to 60 °C, the reaction could undergo completely within two days and the yield was improved to 80%, however, no stereoselection was observed (Table 1, entry 2). These results suggested that the chiral Brønsted acid might not act as an activator of the dienophile 2. Indeed, a control experiment to investigate the Diels-Alder reaction between diene 5a and 2 found that the diene 5a generated from the gold-catalyzed cyclization of enyne 1a was able to smoothly undergo the [4 + 2] cycloaddition with 2 even in the absence of any catalyst, furnishing the product 3c in 81% yield (eqn (1)), indicating that the Diels-Alder step was spontaneous and the Brønsted acid was therefore hard to control the stereochemistry. Moreover, the cascade reaction also proceeded cleanly in the presence of the gold complex alone (Table 1, entry 3). The commercially available gold trichloride, which was previously applied to catalyze the cascade cyclization/Diels-Alder reaction,<sup>4</sup> however afforded a complicated reaction, from which no desired product was observed (Table 1, entry 4). The counterions of gold complexes were found to exert considerable impact on the catalytic activity. Among the cationic gold complexes screened (Table 1, entries 5-9), only gold trifluoroacetate showed good catalytic activity (entries 3 and 9). The survey of solvents found that the halogenated solvents were basically better media for this cascade reaction whereas the reaction did not occur in a nonpolar solvent as exemplified by the case conducted in toluene (entries 10–12). The use of 5 mol% of the catalyst still provided a reasonable yield (entry 13).



With the optimized conditions in hand, the generality for a scope of enyne alcohols **1** was then explored. As shown in Scheme 3, a diverse spectrum of alkyl groups were tolerated, delivering **3** as a single diastereomer in good to high yields (65–83%). The enyne alcohols **1** bearing a linear alkyl substituent at C1 (R group) underwent the cascade reaction cleanly, furnishing the desired products (**3b**–**3c**) in high yields (74–78%). A slightly lower yield was obtained when a branched alkyl substituent was introduced into C1 (**3d**). Moreover, the  $\alpha$ -branched cyclopropyl group at C1 of the enyne alcohols was also allowed to provide product **3e** in an 83% yield. In addition, the presence of a aryl group at C1 of **1** was also tolerated to give **3f**–**3h** in good yields. The X-ray diffraction analysis of **3f** confirmed the structure and showed that the *endo*-selective products were favourably generated.<sup>9</sup>

However, the extension of the optimal conditions to the cascade hydroalkoxylation/cyclization reaction using (*E*)-dimethyl 4-oxo-pent-2-enedioate **6** as a dienophile with **1f** under gold catalysis failed. Thus, the re-optimization of reaction conditions was performed and found that the presence of catalytic amount of phosphoric acid **4** led to an unpredicted hetero-Diels–Alder reaction, to give a bicylic compound **7a**, as indicated by single-crystal X-ray diffraction analysis,<sup>10</sup> in a reasonable yield (Table 2, entry 1). Increasing the loading of the gold complex was beneficial to the reaction whereas the presence of more amounts of the phosphoric acid led to a sacrificed yield (Table 2, entry 2 *vs.* 3). The use of preformed Ph<sub>3</sub>AuTFA to replace that *in situ* generated from PPh<sub>3</sub>AuCl and AgTFA somehow eroded the yield (entry 4).<sup>11</sup> Elevating the reaction temperature also led to an unsatisfactory yield (entry



**Scheme 3** The scope of the cascade hydroalkoxylation/isomerization/Diels–Alder cycloaddition reaction of enyne alcohols **1** with N-(4-nitrophenyl)-maleic diimine **2**.

Table 2Optimization of reaction conditions for gold/Brønsted acid-catalyzedcascade reaction of enyne alcohols 1f with (E)-dimethyl 4-oxopent-2-enedioate $6^a$ 



2	10/10	2/1	$CH_2Cl_2$	62
3	10/20	2/1	$CH_2Cl_2$	46
$4^c$		2/1	$CH_2Cl_2$	48
$5^d$	10/10	2/1	$CH_2Cl_2$	44
6	10/10	4/1	CH <sub>2</sub> Cl <sub>2</sub>	68
7	10/10	4/1	CHCl <sub>3</sub>	63
8	10/10	4/1	THF	—
9	10/10	4/1	DCE	41
10	10/10	4/1	Toluene	22
11	10/10	4/1	Et <sub>2</sub> O	_

 $^a$  Reaction was run as a 0.05 M solution of 6.  $^b$  Isolated yield after purification by flash chromatography.  $^c$  PPh\_3AuTFA was used instead of PPh\_3AuCl/AgTFA.  $^d$  Reaction was run at 35 °C.

5). Tuning the ratio of **1f** to (*E*)-dimethyl 4-oxo-pent-2-enedioate (6) from 2/1 to 4/1 gave a much higher yield (68%, entry 6). A screening of solvents, including chloroform, 1,2-dichloroethane (DCE), and toluene, revealed that dichloromethane is the best media for this cascade reaction (entries 7, 9, and 10 *vs.* 5). However, no desired product was isolated when the reaction was conducted in THF and ether, indicating that the reaction was unable to occur in a solvent with coordinating heteroatoms (entries 8 and 11).<sup>12</sup>

The generality for 3-methylene-5-arylpent-4-yn-1-ols bearing an aryl substituent bonded to the carbon-carbon triple bond was then investigated (Scheme 4).<sup>13</sup> A variety of aryl substituents on the envne alcohols 1 were tolerated. Basically, electronically rich aryl substituents at C1 proceeded cleanly to give the desired products 7 in good yields ranging from 64% to 75% (7b-d and 7g). The variation of the para-substituent on the phenyl group at C1 of the enyne alcohols 1 showed that the less sterically hindered substituents were beneficial to the formation of the products (7b-7d). However, the introduction of an electron-withdrawing substituent such as 4-F or 3-OMe on the phenyl group at C1 would diminish the yields of bicyclic compounds 7e and 7h. The substrates with weakly electron-withdrawing substituents such as halides on the benzene ring at C1 also participated in a good reaction, affording the desired products in good yields, as exemplified by 7f and 7i (71-79%).

Although the presence of BINOL-based phosphoric acids and phosphoramides could accelerate the reaction, the enantioselectivity was disappointing (up to 18% ee, see ESI†). Previous findings indicated that chiral Lewis acids, such as copper complexes of chiral bis-(oxazoline), were excellent catalysts for the asymmetric hetero-Diels–Alder reactions of



**Scheme 4** The scope of the cascade hydroalkoxylation/isomerisation/Diels– Alder cycloaddition/hydrolysis/lactonization reaction of enyne alcohols **1** with (*E*)-dimethyl 4-oxopent-2-enedioate **6**.

carbonyl compounds.<sup>14</sup> Thus, we initially investigated the asymmetric cascade reaction using a chiral copper complex as the co-catalyst (Table 3). To our delight, the chiral cyclo-addition product was formed in 42% yield and 87% ee using 10 mol% of the chiral copper complex prepared *in situ* from Cu(OTf)<sub>2</sub> and bis-(oxazoline) **8a** (entry 1). Interestingly, the

Table 3Optimization for the asymmetric gold/Lewis acid catalyzed cascadereaction of enyne alcohols  $\mathbf{1f}$  with (E)-dimethyl 4-oxopent-2-enedioate  $\mathbf{6}^a$ 



<sup>*a*</sup> Reaction was run as a 0.05 M solution of **6**. <sup>*b*</sup> Isolated yield after purification by flash chromatography. <sup>*c*</sup> Determined by HPLC. <sup>*d*</sup> Reaction was run at 35 °C. <sup>*e*</sup> Trace product. <sup>*f*</sup> Not determined.

variation of the counter anion of the copper complex from triflate to hexafluoroantimonate was able to switch the stereochemistry and led to further enhanced results of 58% yield and 92% ee (entry 2 vs. 1). Although the yield was slightly improved, the enantioselectivity was significantly sacrificed upon conducting the reaction at an elevated temperature (entry 3). The use of other chiral Lewis acids with bis-(oxazoline) gave unsatisfactory results (entries 4-10). In comparison with dichloromethane, other solvents, including tetrahydrofuran, toluene and chloroform, always gave inferior results presumably due to the poorer solubility of the [Cu-box]- $(SbF_6)_2$  complexes (entries 11–13). Subsequently, some other substrates were examined using the combined catalyst system consisting of the gold complex and the chiral copper complex (Scheme 5). The presence of either an electron-donating or withdrawing substituent in the envne alcohols 1 was applicable to smoothly undergo the asymmetric relay catalytic cascade reaction, furnishing the products in acceptable yields and with high enantioselectivities of up to 90% ee. The absolute and relative configurations were determined by X-ray diffraction analysis.15

Interestingly, the cascade cyclization/Diels–Alder reaction of **1a** with **2** still proceeded in the presence of a non-poisoning base, 2,6-di-*tert*-butylpyridine (eqn (2)), which was used to scavenge the trifluoroacetic acid probably formed from the reaction.<sup>16</sup> The results suggested that the gold complex, rather than the Brønsted acid, promoted the *exo/endo* isomerization of the initially formed enol ether **I** (Scheme 6). On the other



Scheme 5 Representative examples for the asymmetric transformation.



Scheme 6 Gold-catalyzed cycloisomerization of 1.



Scheme 7 Proposed mechanism for the formation of the deuterated product.

hand, the hetero-Diels-Alder reaction between 1f and 6, in the presence of deuterium water  $(D_2O)$  showed that the product 7a' was formed with deuteration at C1-C3. As shown in Scheme 7, the gold complex first catalyzes the cyclization of the envne alcohols 1 to generate active intermediates 10. Subsequently, the proton formed by deprotonation of 10 was exchanged to deuterium ions by reacting with D<sub>2</sub>O, which participated in the protodemetalization of 10 to furnish deuterated intermediates 12 at C1. The re-coordination of the gold complex to the double bond outside the ring of 12 affords intermediates 13, which after deprotonation gave intermediates 14, as the deuteration occurred at both C2 and C3. By quenching with the deuterium ions, the intermediates 14 were subsequently transformed into the dienes 5' and the gold catalyst was regenerated. According to these controlled experiments and previous reports on related reactions,<sup>17</sup> a mechanism was proposed in Scheme 8. The dienes 5' could undergo Diels-Alder reaction with the dienophile 2 to yield the tricyclic compounds 3. On the other hand, the inverse-electrondemand hetero-Diels-Alder reaction between 5' and the (E)-dimethyl 4-oxo-pent-2-enedioate 6 occurred under the catalysis of the Brønsted acid 4<sup>18</sup> or Lewis acid to give bicyclic compounds 15, which were hydrolyzed to generate 17 promoted by the gold complex. After the proton transfer and lactonization, the intermediates 18 were converted to the final products 7.

In summary, we have developed an unprecedented cascade hydroalkoxylation/isomerization/Diels-Alder cycloaddition reaction, providing an efficient method to access tricyclo-[5.2.2.0<sup>2,6</sup>]undec-8-ene-3,5-dione derivatives and 1-0x0-3,3a,4,7a-tetrahydro-1*H*-furo[3,4-*c*]pyran derivatives, which are not easily accessible through traditional organic reactions. Interestingly, the key 1,3-butadiene intermediates generated from gold-catalyzed hydroalkoxylation isomerization of the enyne alcohols were able to function as either dienes or dienophiles, depending on the substrates and reaction conditions. The excellent stereoselectivity was also obtained in the cascade cycloisomerization/hetero-Diels-Alder reaction using



the combined gold complex and chiral copper Lewis acid (up to 92% ee).

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