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ARTICLE TYPE

Gold-catalysed cascade rearrangements of ynamide propargyl esters

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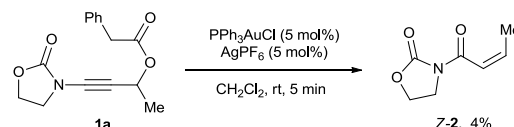
DOI: 10.1039/b000000x

5 The Au(I)-catalysed rearrangement of propargylic esters formed from an ynamide has been studied. The reaction is facile, and when conducted in the presence of a reactive indole nucleophile, leads to a cascade process whereby γ -indolyl α -acyloxyenamides are formed in good yield and
10 excellent *E*-stereoselectivity.

The development of many gold-catalysed transformations¹ in recent years has allowed rapid entries to a plethora of novel organic structural scaffolds.² Amongst these transformations, the Au(I)-catalyzed rearrangement of propargylic esters³ has attracted
15 a substantial level of interest in recent years.⁴ The mechanistic and regiochemical outcome of this reaction is known to be highly sensitive to the electronic and steric nature of the substrate alkynyl substituents. The prevailing consensus is that, though gold-mediated alkyne activation, either a 1,2-acyloxy migration
20 (I→II) or a 3,3-rearrangement (I→III) pathway can occur. Generally, an electron withdrawing substituent at position R³ promotes a 1,2-migratory pathway and in most other cases, a 3,3 rearrangement prevails. To the best of our knowledge, the effect of alkynyl heteroatom substituent (for example, an ynamide^{5,6}) on
25 the outcome of a Au-catalyzed [3,3]-rearrangement on propargylic ester substrate has not been studied.⁷ This communication reports our observations on such a class of substrate.

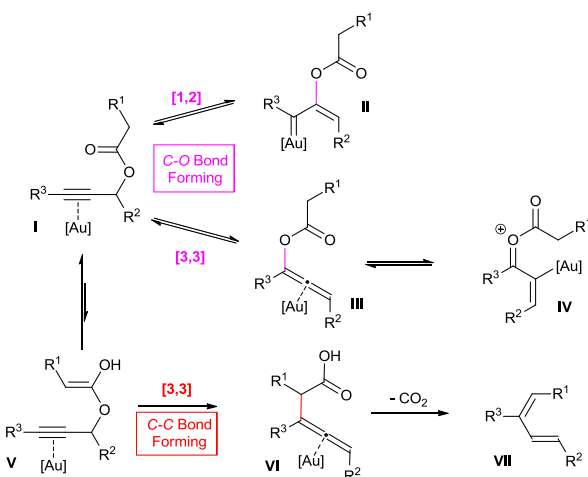
propargylic ester substrates, such as **1a** (Scheme 2).⁸ A facile rearrangement was observed in this study, attributed to both the
35 presence of the alkynyl oxazolidinone and aryl acetate moieties. In addition to studying the Au-catalysed reaction of ynamide esters, we also speculated whether the aryl acetate may promote the presence of the enol tautomer in turn leading to a potential C-C bond forming, [3,3]-sigmatropic rearrangement with
40 subsequent decarboxylation (V→VI→VII, Scheme 1).

Our study initially started by examining the effect of an *in situ* generated cationic Au(I) complex on ester **1a**. Initially, CH₂Cl₂ was chosen as solvent which is a common choice for similar [3,3]-sigmatropic transformations and the now familiar
45 combination of Au(I) and Ag(I) co-catalysts to generate a cationic gold species.⁹ Consumption of the starting ynamide was rapid, resulting in a complex reaction profile, with *Z*-**2** the only product readily isolable (Scheme 2).



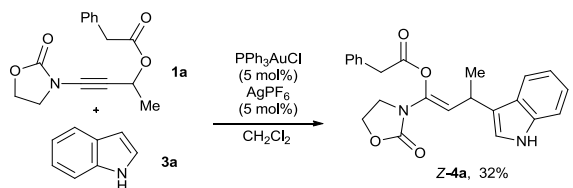
Scheme 2 Initial Reactivity Assessment

We initially postulated *Z*-**2** was formed through a Au-catalyzed hydrolytic degradation of an oxocarbenium intermediate (IV, Scheme 1, R¹=Ph, R²=Me, R³=oxazolidinone), generated after
55 3,3-rearrangement. It was hypothesised that the proposed α -acyloxyallenamide product III may be unstable in the presence of a Au(I) complex. Kimber has demonstrated that allenamides cleanly react with C-nucleophiles, such as indoles, under Au(I)-catalysis to form enamides.^{10,11} Accordingly, we chose to add indole in an attempt to trap III to form γ -indolyl α -
60 acyloxyenamide **4a**.¹² The addition of indole now allowed isolation of *Z*-**4a** in 59% (entry 1, Table 1) with no product consistent with a C-C bond formation observed. Initially, the nature of the Ag-additive was seen to effect the reaction with AgSbF₆ leading to a reduced reaction efficiency (entry 2),
65 however, temperature was found to significantly effect this cascade reaction. Cooling the reaction to -78 °C (entry 5) prevented a successful reaction, whilst reaction at either 0 °C or -30 °C did not improve the reaction (entries 3-4). It was the realisation, however, that a portion-wise addition of both metal salts, in combination with the utilisation of fresh AgPF₆, that led to the isolation of α -acyloxyenamide *Z*-**4a** as a single geometrical isomer in 93% yield (Table 1, entry 8).



Scheme 1 Ynamide Propargylic Ester Mechanistic Considerations

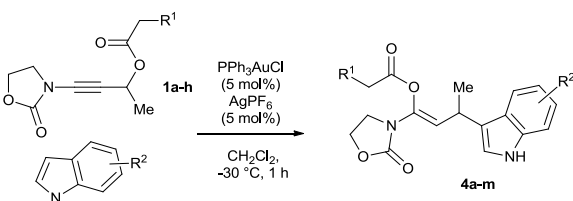
Recently, we reported the first LiHMDS-mediated Ireland-Claisen [3,3]-sigmatropic rearrangement reaction of ynamide

Table 1 Reaction Optimization


Entry	T (°C)	t (min)	Yield (%)
1	25	5	59
2 ^a	25	5	32
3	0	20	62
4	-30	45	63
5	-78	180	0
6	-30→25	45	52
7 ^b	-30	45	70
8 ^{b,c}	-30	45	93

^aAgSbF₆ used as additive. ^bBoth Ag and Au catalysts added in two portions. ^cFresh AgPF₆ used.

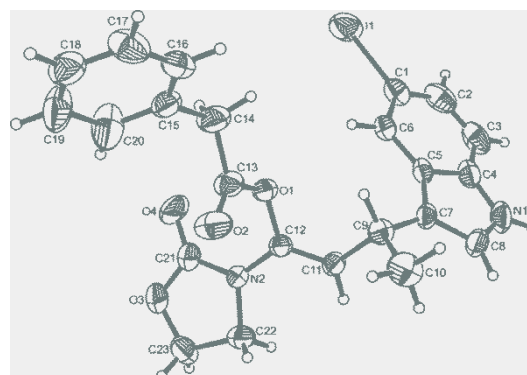
5 Having optimized the Au(I)-catalyzed cascade process between **1a** and **3a**, we have quickly assessed substrate scope with respect to both ester acyl and indole fragments (Table 2). Generally, the reaction is robust and can accommodate different functionality upon ester and indole. Alkyl esters also react without incident
10 (entry 8). However, the presence of an electron-withdrawing on the indole leads to a diminishing of reaction yield (entry 12) with concomitant isolation of *Z*-2.

Table 2 Substrate Scope


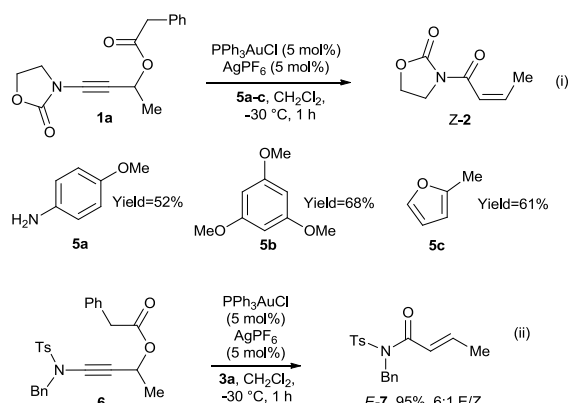
Entry	R ¹	R ²	Product	Yield (%)
1	Ph (1a)	H (3a)	4a	93
2	4-MeC ₆ H ₄ (1b)	H (3a)	4b	85
3	4-MeOC ₆ H ₄ (1c)	H (3a)	4c	74
4	4-Me ₂ NC ₆ H ₄ (1d)	H (3a)	4d	87
5	4-FC ₆ H ₄ (1e)	H (3a)	4e	79
6	4-IC ₆ H ₄ (1f)	H (3a)	4f	92
7	3,4-(OCH ₂ O) ₂ C ₆ H ₃ (1g)	H (3a)	4g	56
8	H (1h)	H (3a)	4h	89
9	Ph (1a)	5-Me (3b)	4i	82
10	Ph (1a)	5-I (3c)	4j	92
11	Ph (1a)	5-F (3d)	4k	99
12	Ph (1a)	5-CO ₂ Me (3e)	4l	53 ^a
13	Ph (1a)	6-OMe (3f)	4m	92

^a*Z*-**2** isolated in 24%.

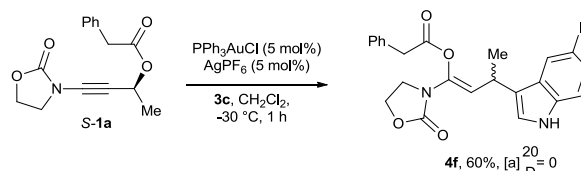
Iodoindole product **4f** was observed to form crystals suitable for X-ray analysis, with the structure displayed in Fig. 1. This analysis not only confirms the γ -indolyl α -acyloxyenamide structure but also the presence of the *Z*-stereoisomer.

**Fig. 1** X-ray structure of **Z-4f** (CCDC 918763)

In an attempt to further explore the scope of this chemistry, a selection of nucleophiles, which had been reported as effective in Kimber's report, have been examined (**5a-c**, Scheme 3). In contrast to the use of indoles, the aniline (**5a**), anisole (**5b**) and 2-methylfuran (**5c**) all failed to incorporate the nucleophile, furnishing *Z*-**2** in good yield (eq i, Scheme 3). The formation of the *Z*-product is particularly interesting as a recent report has highlighted the importance and difficulty of *Z*-selective enone
30 formation.¹³ A further point of contrast is now observed when sulphonamide **6** is reacted with **3a**, (eq ii, Scheme 3). In contrast to **1a-h**, no indole is incorporated into the isolated product. In this instance, enone *E*-**7** is formed with *E*-selectivity. This result may offer synthetic versatility to *N*-acyl sulfonamides; a medicinal
35 scaffold which has attracted recent interest.¹⁴

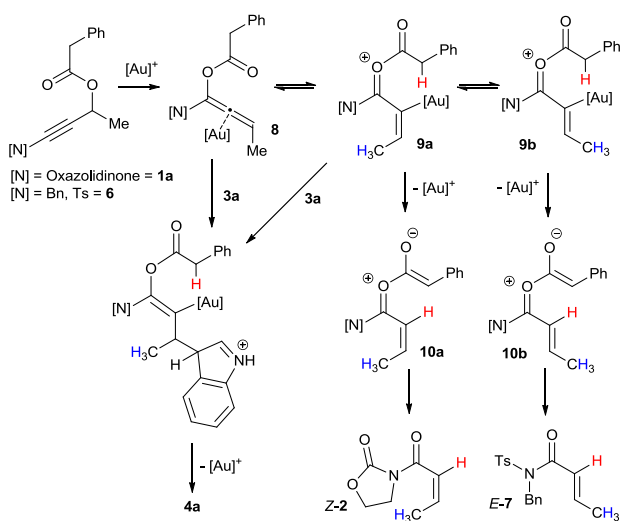
**Scheme 3** Effect of Nucleophile and Ynamide

Primarily as a mechanistic probe, *S*-**1a** has been examined when reacting with 5-iodoindole (Scheme 4). Under the same reaction
40 conditions as previously described, this enantioenriched ynamide furnished *rac*-**4f** in a reasonable yield of 60%.

**Scheme 4** Attempted Chirality Transfer

The experimental observations discussed in this communication, namely no chirality transfer and the sensitivity of the reaction
45 outcome to both ynamide and nucleophile structure, deserve

comment (Scheme 5). The complete absence of point→axial→point chirality transfer during the conversion of **5** **1a** to **4f** under the presently discussed mild conditions (-30 °C, 1 h, Scheme 4) strongly suggests the direct intermediacy of an achiral species. Accordingly, we feel chiral α -acyloxyallenamide **8** is in equilibrium with the achiral α -vinyl gold oxocarbenium complex **9**. A similar observation of 100% racemisation in a recent Au(I)-promoted rearrangement cascade of propargylic pivalates has supported the intermediacy of α -vinyl gold oxocarbenium species.¹⁵ The formation of **4a** can now occur through the addition of indole to either **8** or **9**. However, we feel the consideration of **9** may help in appreciating the sensitivity of reaction outcome. Depending on the nature of *N*-substitution and nucleophile, **9a** can either promote conjugate addition of **3a**, to form **4a**, or undergo *E*↔*Z* equilibration (**9a**↔**9b**) through vinylogous enolization, prior to proto-deauration and the formation of *Z*-**2** or *E*-**7**. The presence of the *O*-acyloxocarbenium moiety would be expected to significantly increase the acidity of both the enone γ -proton and the acyl α -methylene protons, thus assisting both *E*↔*Z* equilibration and intramolecular proto-deauration. The electron donating ability of the *N*-centre and the nucleophilicity will affect this subtle balance of acidities of these protons and the reactivity to the external nucleophile.



Scheme 5 Mechanistic Considerations

In conclusion, the presence of an alkynyl electron-donating group, in the form of an ynamide-based substrate, has been studied in the Au-catalyzed [3,3]-rearrangement of propargylic esters. Highly reactive 1,1'-substituted α -acyloxyallenamides are formed as the immediate product, existing in equilibrium with α -vinyl gold oxocarbenium complexes, can be trapped through the reaction with indole nucleophiles to form γ -indolyl α -acyloxyenamides in good to excellent yields and excellent *E*-stereoselectivity.

Notes and references

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† Electronic Supplementary Information (ESI) available: experimental details and NMR spectra of novel compounds. See DOI: 10.1039/b000000x/

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