Gold Catalysis

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Gold-Catalyzed Formal 1,6-Acyloxy Migration Leading to 3,4-Disubstituted Pyrrolidin-2-ones**

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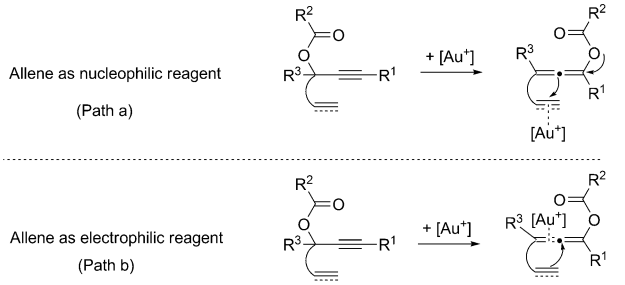
Homogeneous gold-catalyzed reactions involving the formation of carbo- or heterocycles have attracted much attention in the last decade.[1] Among the broad variety of gold-catalyzed reactions developed, gold-catalyzed migration reactions have been proven to be useful for the construction of natural products and complex molecules.[2] Noteworthy, these products often cannot easily be synthesized by conventional methods.

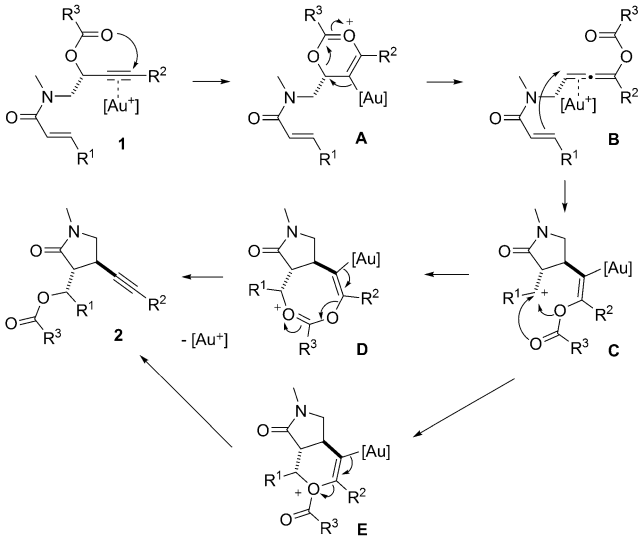
The most interesting and important rearrangement reactions are conducted with propargylic esters; the latter can undergo 1,2- or 1,3-acyloxy migration, providing the corresponding gold carbene or allene intermediate.[3] The research groups of Nolan, Toste, Zhang, Nevado, Gevorgyan, and others have intensively investigated this type of reaction.[3,4] In the case of an allene intermediate, there are two main alternative reaction pathways for the further transformation (Scheme 1): the allene moiety can act as a nucleophilic reagent by selective coordination of the Au catalyst to the neighbouring functional group (path a),[5] or it is activated by the Au species and can behave as a potential electrophilic reagent (path b).[6] So far, there have been no reports on long-range 1,*n*-acyloxy migrations.

We were interested in developing and expanding the scope of the 1,*n*-acyloxy migration. Here we report a novel rearrangement that includes a tandem 1,3-acyloxy migration and 1,5-acyloxy migration, overall leading to a formal 1,6-acyloxy migration. To our knowledge, such a migration is unprecedented. Furthermore, we can utilize this transformation to access butyrolactams, which are important building blocks for the total synthesis of natural products and the development of new pharmaceuticals.[7]



Scheme 1. Gold-catalyzed 1,3-acyloxy migration and subsequent further transformations.

As shown in Scheme 2, we envisioned that easily accessible substrates **1** after coordination to the gold catalyst would eventually undergo the known [3,3] sigmatropic rearrangement described above, and thus deliver **B**. A subsequent nucleophilic attack of the olefin at the activated allene should deliver **C**, and in **C** a 1,5-migration of the acyloxy group should provide the product **2**.



Scheme 2. Proposed mechanism of gold-catalyzed 1,6-acyloxy migration.

We began our investigation with an optimization of the reaction conditions for the conversion of this model substrate **1a**. The results obtained with various catalysts are summarized in Table 1. No reaction did occur even after 24 h when $Yb(OTf)_3$ or *p*-TsOH were employed (Table 1, entries 1 and

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[+] Crystallographic investigation.

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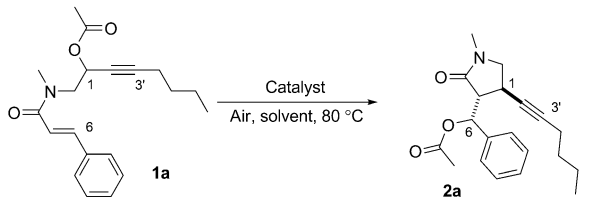
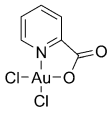
Table 1: Optimization studies on the 1,6-acyloxy migration of **1a**.[a]

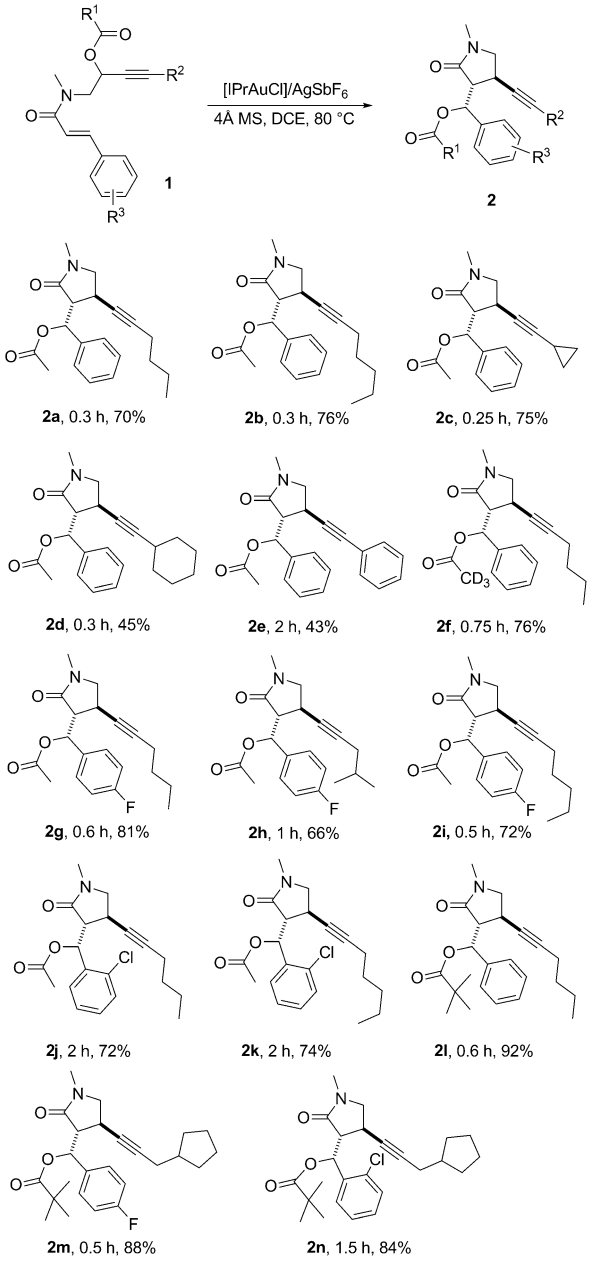


Entry	Catalyst	Solvent	Time [h]	Yield
1	$Yb(OTf)_3$	DCE	24	NR
2	*p*-TsOH	DCE	24	NR
3	$AgNTf_2$	DCE	24	trace
4	IPrAuCl	DCE	24	trace
5	$AgSbF_6$	DCE	24	trace
6	AuCl	DCE	24	unselective
7		DCE	24	unselective
8	[SPhosAuCl]/$AgSbF_6$	DCE	24	11%
9	[IPrAuCl]/$AgSbF_6$	DCE	0.5	45%
10[b]	[IPrAuCl]/$AgSbF_6$	DCE	0.3	70%
11[b]	[IPrAuCl]/$AgNTf_2$	DCE	1	66%
12[b]	[IPrAuCl]/AgOTs	DCE	24	15%
13[b,c]	[IPrAuCl]/$AgSbF_6$	DCE	12	61%
14[b,d]	[IPrAuCl]/$AgSbF_6$	DCE	24	NR
15[b]	[IPrAuCl]/$AgSbF_6$	CH_3CN	24	trace
16[b]	[IPrAuCl]/$AgSbF_6$	toluene	24	38%

[a] Reaction conditions: Substrate (100 μmol), solvent (2 mL), in air; entries 1–7: 5 mol% of the catalyst/entries 8–16: [Au] (5 mol%), [Ag] (5 mol%); the reaction was monitored by TLC; DCE = 1,2-dichloroethane, IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene, SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl; [b] reaction carried out in the presence of 4 Å MS; [c] 60 °C; [d] room temperature.

2). When we chose [IPrAuCl], $AgNTf_2$, or $AgSbF_6$ alone (Table 1, entries 3–5), these showed a very low activity under the same conditions. When switching to AuCl or dichloro(2-picolinato)gold(III),[8] in the thin-layer chromatogram (TLC) only an unselective conversion was visible (Table 1, entries 6 and 7). In the presence of 5 mol% of [SPhosAuCl]/$AgSbF_6$ in DCE at 80 °C, the expected 1,6-acyloxy migration indeed occurred to give **2a** in 11% yield (Table 1, entry 8). The use of [IPrAuCl] together with $AgSbF_6$ resulted in complete consumption of the starting material after 0.5 h, and the migration product could be isolated in 45% yield (Table 1, entry 9). Remarkably, when the reaction was carried out in the presence of 4 Å MS as an additive, the yield of **2a** increased to 70% (Table 1, entry 10). A similar result was obtained when [IPrAuCl]/$AgNTf_2$ was employed as catalyst and 4 Å MS as an additive in DCE (Table 1, entry 11). Somewhat surprisingly, change of the counterion to AgOTs under the same conditions resulted in a much lower yield of 15% even after 24 h (Table 1, entry 12). Decrease of the temperature to 60 °C led to **2a** in 61% within 12 h (Table 1, entry 13). No conversion was observed when the reaction was conducted at room temperature (Table 1, entry 14). Furthermore, an investigation of the solvent effect gave the best results in DCE (Table 1, entries 15 and 16).

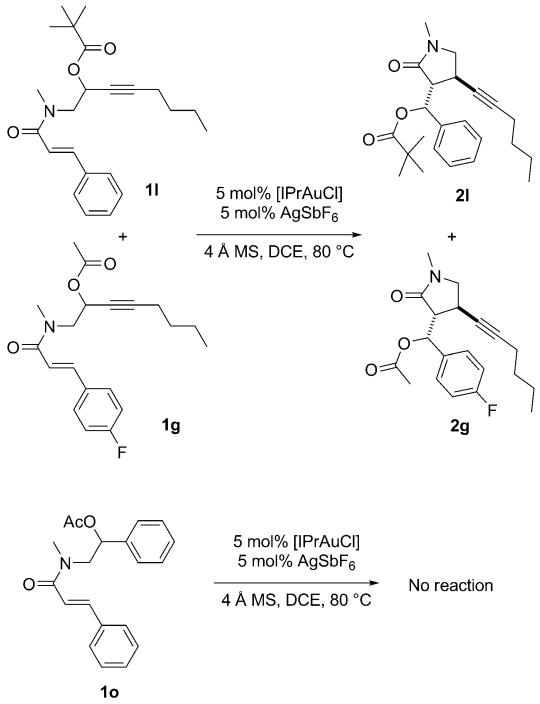
With the optimized conditions in hand, the scope of the gold-catalyzed 1,6-acyloxy migration was investigated with a variety of substrates **1**. Various substituents at the alkyne were tested (Scheme 3). *n*-Butyl, *n*-pentyl, and cyclopropyl gave a good yield (**2a**–**c**), only the more bulky cyclohexyl substitutent provided a low yield (**2d**). A phenyl group was also tolerated, but the yield decreased to 43% (**2e**). The structure of **2e** was further established by using an HMBC spectrum and an X-ray crystallographic analysis; the latter unambiguously proved the connectivity and the relative configuration of the three consecutive stereocenters.[9] A similar yield was observed with the substrate synthesized



Scheme 3. Scope of the Au^I-catalyzed formal 1,6-acyloxy migration (reaction conditions: substrate (100 μmol), [IPrAuCl] (5 mol%), $AgSbF_6$ (5 mol%), DCE (2 mL), 4 Å MS (100 mg); the reaction was monitored by TLC).

from deuterated acetic anhydride (**2f**). The reaction also readily proceeded to the migration products bearing fluoro and chloro substituents at the C4-or C2-position of the phenyl group (**2g–k**). When switching the acetyl to a pivaloyl functional group, we found that all the pivaloyl-substituted esters proceeded smoothly to give the corresponding products in high yields (**2l–2n**).

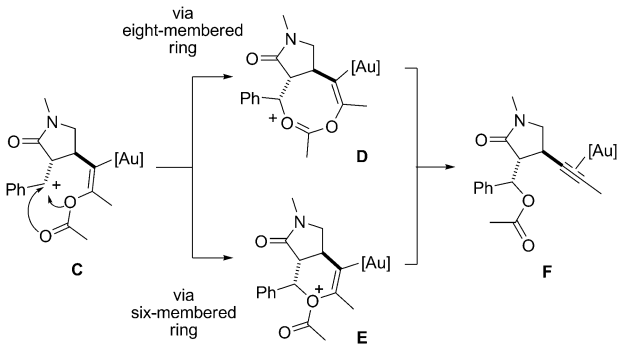
After having demonstrated a broad scope of the reaction with the NHC gold(I) complex as the catalyst, our attention turned to explore the mechanism of this formal 1,6-acyloxy migration. Initially, crossover experiments were carried out. Equimolar amounts of **1g** and **1l** were reacted (Scheme 4).



Scheme 4. Evidence for an intramolecular reaction and the importance of an initial propargylic rearrangement.

From the analysis of GC–MS and GC, no crossover products could be observed, but only the corresponding products **2g** and **2l** were detected. This clearly indicated that this novel 1,6-acyloxy migration is an intramolecular reaction, and no elimination of the acetoxy group occurs. To provide additional evidence for the exclusion of a fragmentation reaction, we also synthesized **1o** with a phenyl substituent instead of the alkynyl group. Then the acyloxy group can be easily eliminated, since the carbocation could be stabilized even better by the phenyl substituent and then induce the cyclization step. However, we could not observe any products from TLC monitoring. This highlighted the fact that the alkynyl group is necessary and important for the initial-stage 1,3-acyloxy migration.

Based on this evidence, the mechanism shown in Scheme 2 indeed seems to operate for the formation of the 3,4-disubstituted pyrrolidin-2-ones. The triple bond should be activated by the gold(I) complex, then an allene intermediate **B** could be formed in situ by a [3,3]-sigmatropic rearrangement via **A**. In **B** the gold(I) complex automatically (initially) would end up at the π face *anti* to the acetoxy group and subsequently triggers a direct nucleophilic attack of the alkene to provide **C**. This stereoselectivity would lead to the vinylgold intermediate with a *trans* arrangement of both substituents on the lactam ring and a *trans* configuration of the olefin. This olefin geometry would be essential for the possibility of an intramolecular migration of the acyloxy group. Two possible reaction pathways are conceivable for this acyloxy shift, either an eight-membered ring (**D**) or a six-membered ring (**E**). The facial selectivity at the benzylic cation correlates with the conformation depicted for **C**, with the group R^1 pointing away from the other substituents and towards the carbonyl group. Owing to the *trans* position of the side chains, the six-membered intermediate is geometrically unfavorable. Finally, the triple bond would be regenerated by elimination of the gold catalyst and the ester group. This is fully supported by computational chemistry (Scheme 5, Figure 1). The two pathways of lowest energy indeed proceed via the eight-membered intermediate and not the six-membered, which is significantly higher in energy. Within the error of the method it is not possible to decide which of the two minima **F1** or **F2** is more stable; since the gold fragment then is eliminated and **2** is the final product, this is not important.



Scheme 5. Reaction pathways for the final acetate shift. Pathways via six- and eight-membered intermediates are shown for the two diastereomers that lead to the observed product.

In conclusion, an unprecedented homogeneous gold-catalyzed formal 1,6-acyloxy migration has been developed, and the mechanistic investigation suggests that this novel transformation proceeds through tandem 1,3-acyloxy migration and a subsequent 1,5-acyloxy migration. This reaction can be utilized to access diastereomerically pure 3,4-disubstituted pyrrolidin-2-ones, which are very important structural motifs in natural products, in good to excellent yields.

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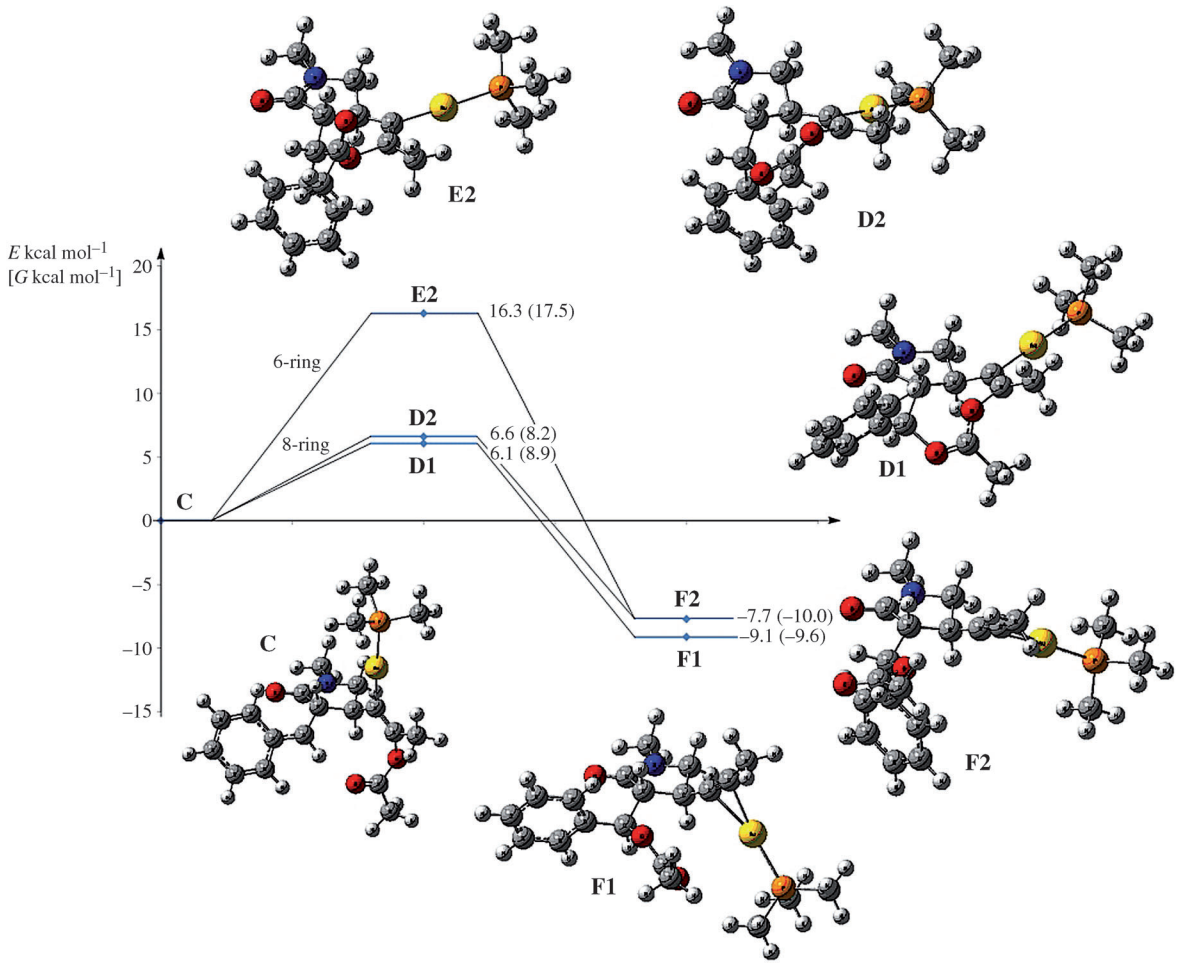

Figure 1. Reaction profile for the acetate shift. H white, C gray, O red, N blue, P orange, Au yellow.

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[9] CCDC 877495 (**2e**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

