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Gold catalyzed stereoselective tandem hydroamination–formal aza-Diels–Alder reaction of propargylic amino esters†

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A gold-catalyzed tandem intramolecular hydroamination–formal aza-Diels–Alder reaction of propargylic amino esters is described. The overall process leads to the formation of a tetracyclic framework as a single diastereoisomer, with the creation of four bonds and five stereocenters.

Cationic gold(I) and gold(III) complexes display unique behaviour towards unactivated multiple bonds such as alkenes, alkynes, allenes, 1,3-dienes or enynes, promoting the nucleophilic addition of a variety of functional groups both inter- and intramolecularly.[1] These complexes have shown an extraordinary ability to catalyze hydroamination reactions of alkynes.[2] The intramolecular version of this reaction is noteworthy since nitrogen heterocycles such as indoles, pyrroles, quinolines, pyridines or isoquinolines are formed in a very simple manner.[3]

On the other hand, one of the most effective ways of achieving synthetic efficiency is to implement a cascade reaction, thus enabling several bond-forming events to occur in a single synthetic operation. Gold complexes exhibit exceptional properties for promoting cascade or tandem reactions, thanks to their ability to activate alkyne, alkene or allene functionalities under mild conditions at low catalyst loadings.[4] Therefore, different types of gold-catalyzed tandem reactions have been successfully employed for the synthesis of densely functionalized polycyclic[5] and heterocyclic[6] structures. Many of these tandem processes involve a hydroamination reaction step.[7]

In the context of an ongoing project in our laboratory, we devised fluorinated α-substituted propargylic α-amino esters as suitable building blocks for the synthesis of several nitrogen-containing fluorinated heterocycles[8] by means of an intramolecular hydroamination reaction.[9] In the pursuit of this goal, a gold-catalyzed process was envisioned to effect the desired transformation. However, during the evaluation of this methodology, we found that these propargylic amino esters undergo a novel tandem hydroamination-formal aza-Diels–Alder reaction, giving rise to the formation of a tetracyclic intrincated framework. The scope of this process and its extension to non-fluorinated amino esters as well as a plausible mechanistic proposal are disclosed herein.

Our starting materials for the gold-catalyzed hydroamination reaction, *i.e.* amino esters **2**, were assembled by reacting propargyl bromide with imino esters **1** in the presence of zinc metal under Barbier-type conditions and DMF as solvent (see ESI†).[10] With substrates **2** in hand, we proceeded to study the behaviour of these propargylic amino esters in the presence of gold salts.

Compound **2a** was used as a model substrate on which different conditions were evaluated in order to perform the desired hydroamination reaction that would render fluorinated pyrrolines in a straightforward manner. An initial attempt was made in dichloromethane with gold(I) chloride; however, a complex reaction mixture was obtained (Table 1, entry 1). The use of gold(III) chloride or $Ph_3PAuOTf$ (*in situ* generated from Ph_3PAuCl and AgOTf) led to similar results (Table 1, entries 2 and 3). At this point, we found that the correct choice of the solvent was crucial in these reactions; while more polar solvents such as acetonitrile or methanol also afforded complex reaction mixtures (Table 1, entries 4 and 5), the use of toluene changed the situation dramatically since clean formation of two products was observed. The minor one, obtained in 13% yield, was identified as the intramolecular hydroamination product **4a**, while the structure of major product **3a**, isolated in 76% yield, had to be unambiguously determined by means of an X-ray experiment (Table 1, entry 6).[11] Besides $Ph_3PAuOTf$, gold(I) complexes **II–IV** were tested and comparable results were achieved (Table 1, entries 7–9). Additionally, other silver salts such as $AgNTf_2$, $AgSbF_6$ or $AgBF_4$ also gave comparable results to the ones obtained with AgOTf (Table 1, entries 10–12).

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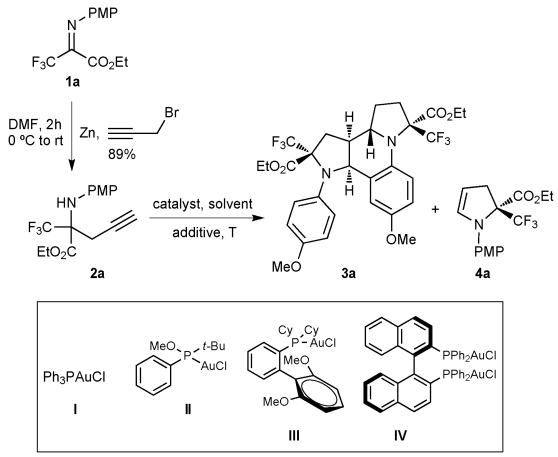
Table 1 Optimization of the reaction conditions



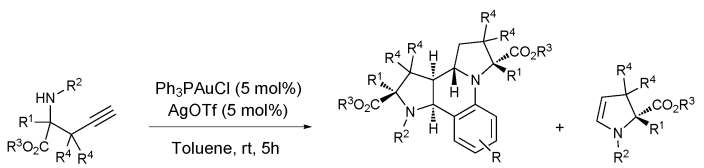
Entry	Catalyst	Additive	Solvent	**3a**[a] (%)	**4a**[a] (%)
1	AuCl	—	DCM	—[b]	—
2	$AuCl_3$	—	DCM	—[b]	—
3	I	AgOTf	DCM	—[b]	—
4	I	AgOTf	MeOH	—[b]	—
5	I	AgOTf	CH_3CN	—[b]	—
6	I	AgOTf	Toluene	76	13
7	II	AgOTf	Toluene	70	10
8	III	AgOTf	Toluene	78	12
9	IV	AgOTf	Toluene	68	20
10	I	$AgNTf_2$	Toluene	73	15
11	I	$AgSbF_6$	Toluene	70	16
12	I	$AgBF_4$	Toluene	72	18

[a] Isolated yields after column chromatography. [b] A complex mixture was formed. PMP = 4-Methoxyphenyl.

The formation of **3a** would involve a tandem process consisting of a hydroamination followed by a formal aza-Diels–Alder reaction. In this manner, the hydroamination product would undergo a [4+2] formal cycloaddition, acting both as diene and dienophile. In the formation of this product four new bonds were created (two C–C and two C–N bonds), giving rise to a fused tetracyclic structure containing five stereocenters. It is noteworthy that compound **3a** was obtained as a single diastereoisomer. With these optimized conditions in hand (Table 1, entry 6), the scope of this new transformation was explored with substrates **2a–n** affording the results shown in Table 2.

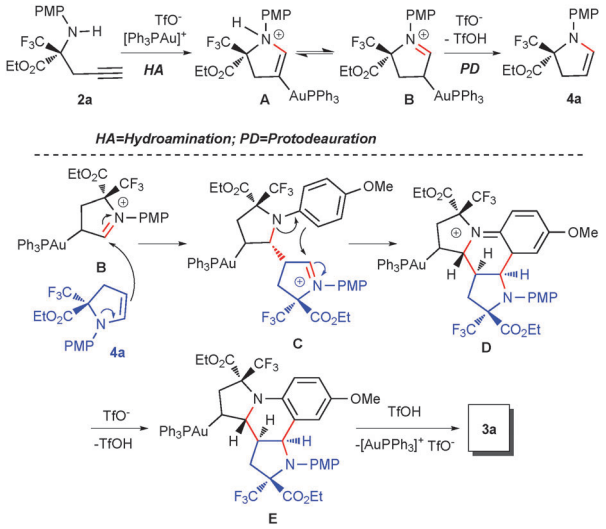
As expected, substitution at the ester group (R^3 position) had no influence on the process since ethyl, benzyl and trimethylsilyl esters afforded the final tetracyclic products **3a,b,e** respectively (Table 2, entries 1, 2 and 5). Likewise, several fluorinated substitutions (Table 2, entries 1–5) were allowed at the R^1 position. In all these cases, the tandem reaction took place in moderate to good yields. However, the nitrogen substitution (R^2 position) was crucial for the success of the tandem protocol. Propargyl amino esters **2** bearing a PMP group underwent the process efficiently, yielding the corresponding tetracyclic compounds **3a–e** (Table 2, entries 1–5). In contrast, when amino esters **2** containing less activated aromatic rings at the nitrogen atom were subjected to gold(I) catalysis, the hydroamination pathway leading to fluorinated pyrrolines **4** became more important. With a *p*-tolyl substituent, equimolecular amounts of tetracycle **3f** and hydroamination product **4f** were formed (Table 2, entry 6). Other substituents such as the phenyl group at the nitrogen atom produced a noticeable increase of the secondary product **4g** (Table 2, entry 7). The starting substrate bearing two aromatic methoxy groups (**2h**) failed in the tandem reaction and only gave the hydroamination adduct in low yield, which could be explained on the basis of steric requirements (Table 2, entry 8). Amino ester **2n** with two fluorine atoms at the propargylic position produced the corresponding tetracycle **3n** in excellent yield (90%) although as a 7 : 1 mixture

Table 2 Scope of the gold-catalyzed tandem reaction on α-amino esters **2**



Entry	**2**	R^1	R^2	R^3	R^4	R	**3** (yield %)[a]	**4** (yield %)[a]
1	**2a**	CF_3	PMP	Et	H	4-OMe	**3a** (76)	**4a** (13)
2	**2b**	CF_3	PMP	$(CH_2)_2TMS$	H	4-OMe	**3b** (52)	—
3[b]	**2c**	$ClCF_2$	PMP	Et	H	4-OMe	**3c** (60)	—
4[b]	**2d**	CF_3CF_2	PMP	Et	H	4-OMe	**3d** (51)	—
5	**2e**	$AllylCF_2$	PMP	Bn	H	4-OMe	**3e** (62)	—
6[b]	**2f**	CF_3	4-MeC_6H_4	Et	H	4-Me	**3f** (34)	**4f** (34)
7[b]	**2g**	CF_3	Ph	Et	H	H	**3g** (14)	**4g** (64)
8	**2h**	CF_3	3,5-$(MeO)_2C_6H_3$	Et	H	3,5-$(OMe)_2$	—	**4h** (34)
9	**2i**	Ph	PMP	Et	H	4-OMe	**3i** (60)	—
10	**2j**	Me	PMP	Me	H	4-OMe	**3j** (74)	—
11	**2k**	4-Cl-C_6H_4	PMP	Et	H	4-OMe	**3k** (70)	—
12	**2l**	PMP	PMP	Et	H	4-OMe	**3l** (72)	—
13	**2m**	2-Naphthyl	PMP	Et	H	4-OMe	**3m** (75)	—
14	**2n**	Allyl	PMP	Bn	F	4-OMe	**3n** (90)[c]	—

[a] Isolated yields after column chromatography. [b] In these cases, the reaction mixture was stirred for 12 h at rt. [c] Compound **3n** was obtained as a 7 : 1 mixture of diastereoisomers as determined by ^{19}F-NMR.



Scheme 1 Proposed mechanistic explanation.

of diastereoisomers (Table 2, entry 14). This result indicates that the triple bond in this substrate would be more activated than in the rest of the amino esters **2** towards the gold-catalyzed reaction, probably due to the increased electrophilicity produced by the two fluorine atoms at the α-position. This transformation was further extended to non-fluorinated amino esters **2i–m**. Either aliphatic substituents at the R^1 position or aromatic ones (bearing electron-donating or electron withdrawing groups) were tolerated in this gold catalyzed tandem process, affording the desired tetracycles **3i–m** in good yields (Table 2, entries 9–13).

It is important to note that compounds **3a–m** were obtained as single diastereoisomers and, according to the X-ray analysis of **3a**,[11] the same stereochemical outcome was assumed for all the tetracycles synthesized.

A mechanistic proposal, shown in Scheme 1, for this unprecedented tandem reaction involves the intramolecular addition of amine **2a** to the triple bond, activated by the gold catalyst, to render intermediate **A**, which is in equilibrium with its tautomer **B**. Subsequent protodeauration would afford the hydroamination product, namely pyrroline **4a**. A key step of the process is the formation of the cyclic intermediate **B**, bearing the gold catalyst. This intermediate is trapped for pyrroline **4a** by means of an enamine attack to render intermediate **C**.[12] This iminium intermediate is now prone to undergo the nucleophilic attack by the *ortho* position of the *N*-PMP group giving rise to the tetracyclic intermediate **D**, the overall sequence from **A** to **D**, resembling a stepwise aza-Diels–Alder reaction. The aromatization and protodeauration of the tetracyclic intermediate **E** would yield product **3a** and regenerate the catalytic species.

In conclusion, a new gold(I)-catalyzed tandem process has been described. It involves propargylic α-amino esters as starting materials and consists of an intramolecular hydroamination followed by a formal aza-Diels–Alder reaction. The overall sequence leads to nitrogen-containing tetracycles, as single diastereoisomers in most cases, through the creation of two C–C bonds, two C–N bonds and five stereocenters. Theoretical calculations are currently underway in order to elucidate the reaction mechanism.

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