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Gold-catalyzed intramolecular hydroamination of α-amino allenamides as a route to enantiopure 2-vinylimidazolidinones

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ABSTRACT

An efficient gold-catalyzed procedure for the preparation of 2-vinylimidazolidinones has been developed. The starting materials for the synthesis of these compounds are α-amino allenamides which undergo heterocyclization by means of nucleophilic attack of the amino group on the inside double bond of the 1,2-diene moiety. This is the first example of a gold-catalyzed cyclization on allene substrates bearing an amido group which, however, resulted inactive.

Intramolecular hydroamination, the formal addition of N–H group to carbon–carbon multiple bond, is a direct and efficient procedure for the synthesis of nitrogen-containing heterocycles.[1] Cyclization of allenes with tethered amines represents a fruitful route for this scope. Some alternative strategies based on basic[2] or transition-metal catalysis[3] have been used for this purpose. Among the latter palladium,[4] gold,[5] silver,[6] ruthenium,[7] copper,[8] cobalt,[9] mercury,[10] and titanium[11] warrant a wide range of procedures such as domino reactions, oxidative cyclizations, cyclocarbonylations, and cycloisomerizations which allow to achieve differently functionalized products.

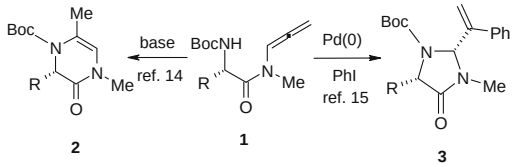
In recent years homogeneous catalysis using gold salts has emerged in organic synthesis as a powerful arm for interesting and useful transformations.[12] The success of the gold catalysis involving allene substrates is related to its ability to coordinate with C–C bonds, thereby allowing the attack of various nucleophiles in both inter- and intramolecular fashion.[13]

Taking into consideration recent works on heterocyclization of α-amino allenamides **1** under base-promoted[14] and domino palladium-catalyzed[15] conditions to give dihydropyrazinone and imidazolidinone derivatives **2** and **3**, respectively (Scheme 1), we thought to submit these substrates under a reaction in the presence of gold salts. This study was carried out with the double aim (i) to perform an alternative procedure to enter into optically active nitrogen-containing heterocycles, and (ii) to investigate the feasibility of gold-catalyzed heterocyclizations of compounds having amine and allene groups tethered on an amido group.

Herein, we report our results concerning gold-catalyzed intramolecular hydroamination of allenamides **1** leading to enantiopure 5-substituted 2-vinylimidazolidinones. The imidazolidinone derivatives are widespread in several natural products, many of them having biological activities.[16] Moreover, imidazolidinones have proved to be effective in organic catalysis as activators for α,β-unsaturated aldehydes through formation of an iminium ion.[17]

The starting materials were readily prepared as previously described.[15] Reaction conditions were optimized by using a variety of Au(I) and Au(III) catalysts in the reaction of allenamide **1a** arising from L-valine (Table 1).

First of all, in order to determine the need of a gold species for achieving the cyclization process, a control investigation was performed submitting the compound **1a** to a reaction catalyzed by protic acid. This procedure resulted in the formation of **4a** in 15%



2 **1** **3**

Scheme 1. Base- and palladium-catalyzed cyclization of allenamides **1**.

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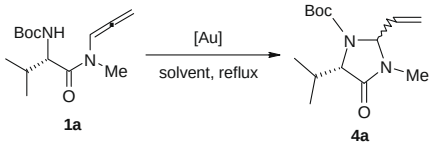
Table 1
Optimization of the cyclization conditions of **1a**



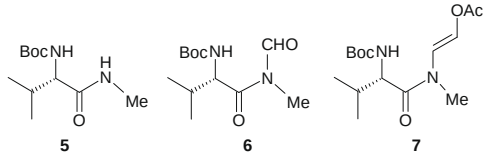
1a **4a**

Entry	Catalytic system[a]	Solvent	Reaction products[b] (%)				
			1a	**4a**	**5**	**6**	**7**
1	H_2SO_4[c]	MeCN	—	15	85	—	—
2	AuCl	Toluene	95	—	—	5	—
3	AuCl	MeCN	93	—	—	7	—
4	PPh_3AuCl, AgOTf	CH_2Cl_2	90	—	—	10	—
5	PPh_3AuCl, AgOTf, AcOH	CH_2Cl_2	92	—	—	8	—
6	$AuCl_3$	MeCN	—	90[d]	—	10	—
7	$AuCl_3$	Dioxane[e]	80	10	—	10	
8	$AuCl_3$	AcOH[f]	—	—	—	10	90
9	$AuCl_3$	CH_2Cl_2[g]	95	—	—	5	—
10	$AuCl_3$, $AgBF_4$	Toluene	95	—	—	5	—
11	$NaAuCl_4{\cdot}2H_2O$	MeCN	51	39	—	10	—
12	$NaAuCl_4{\cdot}2H_2O$	CH_2Cl_2[g]	95	—	—	5	—
13	$NaAuCl_4{\cdot}2H_2O$	Dioxane	95	—	—	5	—
14	$AuCl_3$, AgOTf	MeCN	90	—	—	10	—
15	$AuCl_3$, AgOTf	AcOH[f]	—	—	—	10	90

[a] Au catalyst is used in 5 mol %.
[b] Ratio determined by HPLC.
[c] 5 mol %.
[d] As a 2.5:1 cis/trans diastereoisomeric mixture.
[e] Working on DMF, MeOH, and toluene any conversion of **1a** was observed.
[f] At 70 °C.
[g] At room temperature.

yield besides a large amount of deallenylation byproduct **5** making its applicative interest of no value (entry 1). It should be outlined that $Yb(OTf)_3$ revealed a catalytic behavior similar to that of the sulfuric acid, while others Lewis acids such as $BF_3{\cdot}Et_2O$ and $Zn(OTf)_2$ afforded only tarry mixtures.

Treatment of α-amino allenamide **1a** with Au(I)-salts resulted only in the formation of small amounts of the degradation product **6** (entries 2 and 3). The same behavior was observed by using of PPh_3AuCl complex, also in addition to AgOTf and AcOH (entries 4 and 5).



5 **6** **7**

Working in the presence of $AuCl_3$ (5 mol %) in acetonitrile as the solvent at reflux, a mixture of imidazolidinones **4a** was obtained in a satisfactory yield (entry 6). Other solvents such as dioxane, DMF, MeOH, and toluene were tried without improvement in the cyclization outcome. By performing the reaction in AcOH as the solvent at 70 °C only the open-chain derivative **7** was recovered (entries 8 and 15). The use of $NaAuCl_4$ in acetonitrile instead of $AuCl_3$ afforded **4a** in lower yields (entry 11).

The presence of silver salts in addition to the Au(III) catalysts to form cationic gold species seems to inhibit the reaction (entries 10 and 14).

The cyclization ran in 5-*exo*-allylic manner leading to the imidazolidinones **4a** in 2.5:1 diastereoisomeric ratio.[18] The absolute stereochemistry of the *cis* and *trans* diastereoisomers **4a** was assigned by NOE measurements. In particular, NOE enhancement between Hb and Ha has been the determinant to identify the *cis*-configuration of the major diastereoisomer. The *trans*-configuration of the minor diastereoisomer was confirmed by the NOE interaction between Hb and Hc (Fig. 1).

HPLC analysis (Chiralcel ODH column) of *cis*- and *trans*-**4a**, performed in comparison to samples of the corresponding racemic mixture synthesized starting from the (±)-valine, proved an enantiomeric purity better than 99.5%.

Next we explored the scope of the reaction under the conditions of entry 6 of Table 1. Thus, a selection of the behaviors of allenamides **1** is collected in Table 2. The reactions were completed in 1–3.5 h, always providing the *cis*-imidazolidinones as the major products. Allenamides **1a–d** led to *cis* and *trans* products in very similar ratios and yields. The outcome of compound **1e** resulted in a tarry crude mixture that allowed to isolate *cis* diastereoisomer in only 22% yield. Allenamide **1f**, arising from L-phenylalanine, gave rise to cyclization in a higher diastereoselective level that led to the isolation of the sole *cis*-product in 65% yield.

The inertness of Au(I) catalysts prompted us to study the behavior of a substrate having a more nucleophilic amino group. So, the α-benzylamino allenamide **8** was submitted to a treatment with Au(I) and Au(III) catalysts. Although even in this case the latter resulted the most efficient catalyst, PPh_3AuCl was operative in the promotion of the 5-*exo*-allylic cyclization (Table 3). The reaction carried out in the presence of $AuCl_3$ was faster than the cyclizations tried on allenamide **1a** (0.20 h vs 2.5 h) giving the cis isomer as the

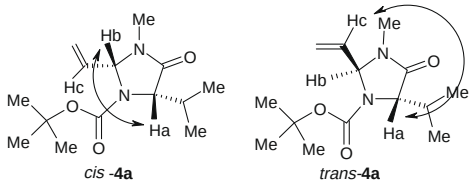


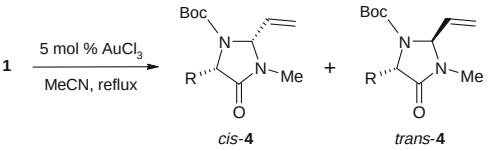
Figure 1. NOE enhancements observed in cis and trans diastereoisomers.

major product, although with a lower cis/trans ratio. The catalytic system $PPh_3AuCl/AgBF_4$ furnished the *cis* and *trans* imidazolidinones **9** with the same diastereoisomeric ratio found using $AuCl_3$ as the catalyst, although in lower yield.

A plausible mechanism for the gold-catalyzed heterocyclization is shown in Scheme 2. The inside C–C double bond of the 1,2-diene moiety is activated by the coordination of both Au(I) and Au(III) species (intermediate **A** or **A'**). The so-generated π-olefin complex undergoes intramolecular nucleophilic attack by the nitrogen atom of the amino group affording the cyclic vinyl-gold intermediate **B**. However, the development of the C–N bond can be achieved on the π-olefin-Au(III) complex by both Boc- and Bn-amino groups, whereas only the more reactive Bn-amino group can interact with π-olefin-Au(I) complex. Protonolysis of the gold-carbon bond of **B** gives imidazolidinone derivatives **4** and/or **9** and regenerates the gold catalyst.

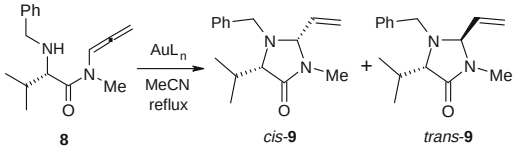
In summary, allenamides were proven to be efficient substrates for gold-catalyzed cyclization, increasing the range of their synthetic interests.[19] The procedure represents the first example of a gold-catalyzed cyclization on allenes bearing an amido group which, however, resulted inactive. Moreover, the obtained imidazolidinones bear a useful vinyl group in position 2 that allows further functionalizations in order to investigate their potential effectiveness as organocatalysts.

Table 2
Reaction scope

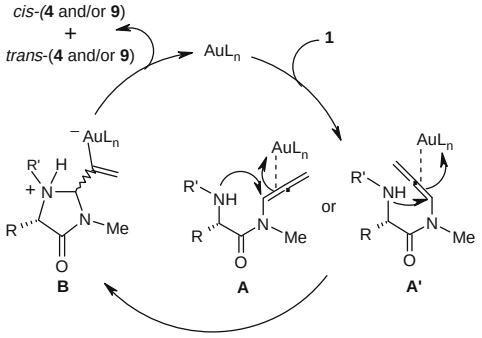


Entry	Allene	R	Time (h)	Yields of products (%)	
1	**1a**	*i*-Pr	2.5	*cis*-**4a** (41%)	*trans*-**4a** (12%)
2	**1b**	Me	1.5	*cis*-**4b** (50%)	*trans*-**4b** (12%)
3	**1c**	Et	1	*cis*-**4c** (50%)	*trans*-**4c** (12%)
4	**1d**	Ph	1.5	*cis*-**4d** (40%)	*trans*-**4d** (4%)
5	**1e**	*t*-Bu	3.5	*cis*-**4e** (22%)	*trans*-**4e** (10%)
6	**1f**	Bn	1.5	*cis*-**4f** (65%)	—

Table 3
Cyclization of α-benzylamino allenamide **8**



Entry	Catalytic system	Time (h)	Yields of products (%)	
1	$PPh_3AuCl/AgBF_4$	2.5	*cis*-**9** (21%)	*trans*-**9** (14%)
2	$AuCl_3$	0.20	*cis*-**9** (36%)	*trans*-**9** (24%)



Scheme 2. Proposed mechanism for the formation of 2-vinylimidazolidinones **4**.

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18. *General procedure for cyclization of* **1**: A 250 mL round-bottomed flask fitted with a magnetic stirrer was charged with **1** (4.2 mmol) and MeCN dry (75 mL) under argon atmosphere. $AuCl_3$ (0.063 g, 0.21 mmol) weighted under argon atmosphere was added to the solution and the mixture was refluxed for 1–3.5 h. After this time the mixture was cooled to room temperature and concentrated in vacuo to dryness. Purification and separation of the two diastereomers by flash column chromatography (toluene/AcOEt 7:3) afforded 5-substituted (2*S*,5*S*)- and (2*S*,5*R*)-3-methyl-1-terbutyloxycarbonyl-2-vinylimidazolidin-4-ones **4**.
Characterization of (2S,5S)-**4a**, *trans diastereoisomer*: Pale yellow oil. ^{1}H NMR (599.71 MHz, $CDCl_3$, T = 50 °C): δ 5.38–5.59 (m, 3H), 5.05–5.16 (m, 1H), 4.02–4.13 (m, 1H), 2.77 (s, 3H), 2.61–2.72 (1H, m), 1.46 (s, 9H), 1.16 (d, 3H, J = 7.1 Hz), 0.86 (d, 3H, J = 6.9 Hz). ^{13}C NMR (150.81 MHz, $CDCl_3$, T = 50 °C): δ 169.3 (C), 154.1 (C), 135.8 (CH), 121.2 (CH_2), 81.8 (C), 76.7 (CH), 63.2 (CH), 28.5 (CH_3), 28.5 (CH_3), 28.5 (CH_3), 26.6 (CH), 18.5 (CH_3), 16.3 (CH_3). IR (nujol): 1645, 1706 cm^{-1}. $[\alpha]_D^{23}$ +52.3 (*c* 0.69, $CHCl_3$).
Characterization of (2S,5R)-**4a**, *cis diastereoisomer*: Pale yellow oil. ^{1}H NMR (599.71 MHz, $CDCl_3$, T = 50 °C): δ 5.69 (ddd, 1H, J = 17.3, 9.9, 8.0 Hz); 5.50 (d, 1H, J = 17 Hz); 5.43 (d, 1H, J = 10.2 Hz); 5.16 (d, 1H, J = 7.7 Hz); 4.05 (br s, 1H); 2.79 (s, 3H); 2.17–2.30 (m, 1H); 1.46 (s, 9H); 1.08 (d, 3H, J = 7.1 Hz); 1.01 (d, 3H, J = 7.1 Hz). ^{13}C NMR (150.81 MHz, $CDCl_3$, T = 50 °C): δ 169.5 (C), 154.1 (C), 135.1 (CH), 121.1 (CH_2), 81.1 (C), 76.0 (CH), 64.0 (CH), 31.2 (CH_3), 28.3 (CH_3), 28.3 (CH_3), 28.3 (CH_3), 26.4 (CH), 18.6 (CH_3), 18.2 (CH_3). IR (nujol): 1648, 1714 cm^{-1}. $[\alpha]_D^{23}$ = +10.5 (*c* 0.91, $CHCl_3$).
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