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Synthesis of Substituted Pyrrolin-4-ones from Amino Acids in Mild Conditions via a Gold-Catalyzed Approach

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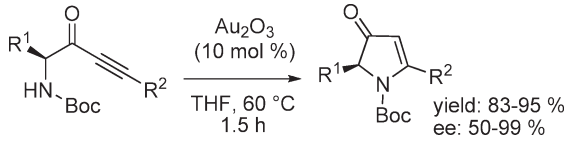

The gold-catalyzed cyclization of various α-amino-ynone derivatives gave the corresponding pyrrolin-4-ones in high yields. Moreover, the use of gold(III) oxide as catalyst allows a moderate to total stereocontrol during the cyclization. These pyrrolin-4-ones are highly useful intermediates for the synthesis of functionalized pyrrolidines and other natural products.

Functionalized pyrrolines and pyrrolidines are found in a broad array of biologically active natural products[1] and are used as excellent building blocks for the synthesis of a plethora of nitrogen-containing derivatives.[2] Furthermore, they are also used as useful chiral auxiliaries and ligands for asymmetric syntheses.[3]

Many methodologies have been reported for their syntheses over the years.[4] More recently, much work has been focused on metal-mediated approaches from unsaturated amines[5] or diazo compounds.[6] Nevertheless, the development of flexible strategies that would allow for a stereoselective construction of multisubstituted pyrrolidine derivatives employing versatile building blocks is still highly desirable. Therefore, although α-amino-ynones are easily accessible from α-amino acids, their use as intermediates for the synthesis of enantiopure pyrrolidine derivatives has remained largely unexplored. In a seemingly unique contribution, Overhand and Hecht[7] reported a mercury-promoted approach. Nevertheless their strategy required a stoichiometric amount of mercuric acetate to achieve the ring closure.

In this context, we decided to explore the use of the chiral pool of amino acids combined with the potential of gold for the synthesis of pyrrolin-4-ones that could be used for further transformations (Scheme 1). The above-mentioned approach reported by Overhand and Hecht did not allow the isolation of pyrrolin-4-one derivatives (**I**). Actually the use of mercuric salt afforded an intermediate organomercuric chloride that must be subjected to reductive demercuration with sodium borohydride leading to an hydroxypyrrolidine (**II**). Due to its ability to coordinate and activate carbon−carbon multiple bonds toward the intramolecular addition of a variety of nucleophiles, gold-catalysis emerged as the preferred choice.[8] Thus, the addition of various nucleophiles to alkynes offered a fascinating opportunity to build up several complex cyclic molecules under extremely mild conditions.

Initially, a series of α-amino-ynone derivatives **1a**−***l*** was generated from commercially available amino acids via Weinreb amide formation and subsequent addition of various lithium acetylides (Table 1). The enantiomeric purity of the intermediate **1a** was confirmed by chiral HPLC to be >99% ee, suggesting that minimal racemization had occurred during the process. Thus amino-ynones **1a**−***l*** could be produced in two steps with moderate to good overall yield from corresponding L-amino acids.

We then performed a catalyst screening to optimize the cyclization conditions. In this way, substrate **1a** was subjected to various catalysts and other activating agents in different conditions (Table 2).

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SCHEME 1. Synthetic Approach

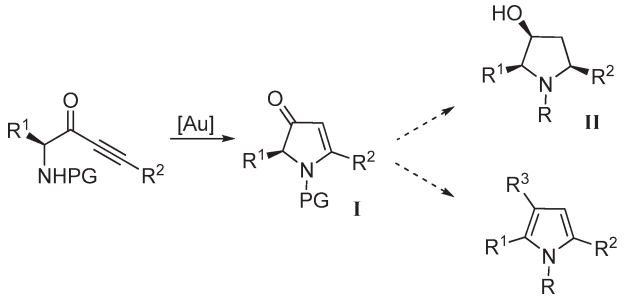
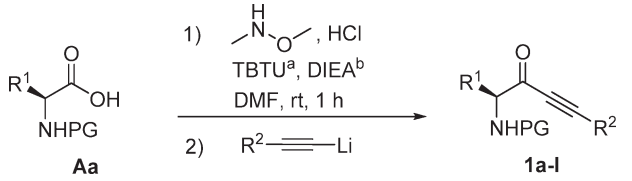


TABLE 1. Synthesis of the α-Amino-ynones 1a−*l*

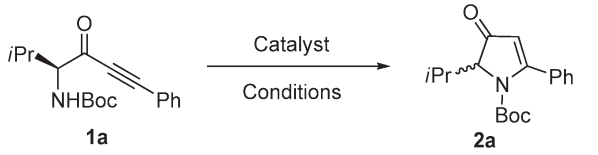


R^1 (Aa)	PG	R^2	1	yield (%)
*i*Pr (V)	Boc	Ph	**1a**	58
*i*Pr (V)	Boc	H[c]	**1b**	72
*i*Pr (V)	Boc	*n*Pr	**1c**	60
*i*Pr (V)	Boc	*p*MeO-Ph	**1d**	52
H (G)	Boc	Ph	**1e**	66
H (G)	Cbz	Ph	**1f**	58
H (G)	Ac	Ph	**1g**	63
Me (A)	Boc	Ph	**1h**	89
Bn (F)	Cbz	*n*Pr	**1i**	71
sec-Bu (I)	Boc	nPr	**1j**	56
sec-Bu (I)	Boc	Ph	**1k**	68
indol-3-ylmethyl (W)	Cbz	Ph	**1*l***	74

[a] *O*-(1*H*-Benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate. [b] Diisopropylethylamine. [c] Ethynyl magnesium bromide was used in this case.

We initially confirmed the highly catalytic activity of gold salt for this intramolecular cyclization (Table 2, entry 1). Actually, the use of 10 mol % of AuCl in THF at room temperature for 1 h cleanly afforded the corresponding pyrrolidin-4-one **2a** in an excellent yield (96%). The efficiency of this gold(I) salt was then compared to that of other catalytic systems. The ring closure did not proceed (or was not efficient) in the presence of 10 mol % of a variety of transition metal salts such as CuOAc,[9] AgOTf,[10] $PdCl_2$,[11] and $GaCl_3$[12] (entries 2−5). As a comparison, we also tested a Brønsted acid (PTSA,[13] entry 6), but no trace of compound **2a** has been detected even after 24 h. In a last set of experiments we decided to evaluate the potential of cyclization via 1,4-addition. The use of NaH[14] that should increase the nucleophilic character of nitrogen (entry 7) did not promote the present reaction at all. Decreasing the catalyst loading from 10 to 5 or 1 mol % only affected the reaction time without any change in yield (entries 8 and 9). In the absence of catalyst, the reaction did not occur (entry 10).

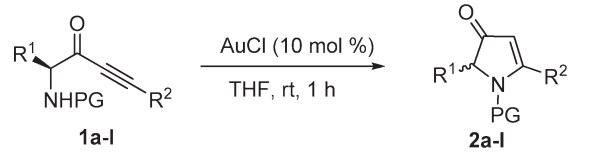
TABLE 2. Catalyst Screening for the Cyclization of 1a



entry	catalyst (mol %)	conditions	yield (%)
1	AuCl (10)	THF, rt, 1 h	96
2	$PdCl_2$ (10)	THF, rt, 4 h	deg[a]
3	CuOAc (10)	THF, rt, 24 h	(31)[b]
4	AgOTf (10)	THF, rt, 4 h	(8)[b]
5	$GaCl_3$ (10)	THF, rt, 24 h	nr[c]
6	PTSA[d](10)	DCM, rt, 24 h	nr[c]
7	NaH (100)	THF, rt, 24 h	nr[c]
8	AuCl (5)	THF, rt, 1.5 h	97
9	AuCl (1)	THF, rt, 4 h	94
10		THF, rt, 24 h	nr[c]

[a] Degradation of starting material. [b] Conversion determined by ^{1}H NMR on the crude material. [c] No reaction. [d] *p*-Toluenesulfonic acid.

TABLE 3. Screening of Substrates



entry	1	R^1	R^2	PG	2	→yield (%)
1	**1a**	*i*Pr	Ph	Boc	**2a**	96
2	**1b**	*i*Pr	H	Boc	**2b**	92
3	**1c**	*i*Pr	*n*Pr	Boc	**2c**	87
4	**1d**	*i*Pr	4-MeOPh	Boc	**2d**	94
5	**1e**	H	Ph	Boc	**2e**	95
6	**1f**	H	Ph	Cbz	**2f**	85
7	**1g**	H	Ph	Ac	**2g**	94
8	**1h**	Me	Ph	Boc	**2h**	83
9	**1i**	Bn	*n*Pr	Cbz	**2i**	95
10	**1j**	*sec*-Bu	*n*Pr	Boc	**2j**	90
11	**1k**	*sec*-Bu	Ph	Boc	**2k**	89
12	**1*l***	indol-3-ylmethyl	Ph	Cbz	**2*l***	85

To extend the generality of this reaction, the versatility of AuCl was then evaluated for other functionalized amino-ynone derivatives. As shown in Table 3, several structural variations were tolerated under these mild conditions, including substituent on the triple bond (entries 1−4), protecting group (entries 5−7), and choice of starting amino acid (entries 1, 5, 8−10). These intermediates **1a**−***l*** were efficiently converted to the corresponding pyrrolin-4-ones (**2a**−***l***) in good to excellent yields.

To further examine the scope of this gold-catalyzed cyclization, we then turned our attention to the synthesis of enantiopure pyrrolin-4-ones, since our strategy was developed from amino acids (Table 4). Using stereodefined substrate **1a** (ee > 99%), keeping the chirality of the stereogenic center after cyclization was evaluated by chiral HPLC.

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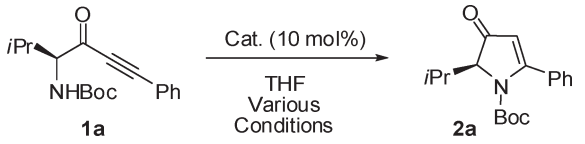
TABLE 4. Stereocontrol of the Cyclization of 1a



entry	catalyst	base (2 equiv)	temp (°C)	time (h)	yield (%)	ee (%)[a]
1	AuCl		rt	1	96	0
2	AuCl	K_2CO_3	rt	1	90	60
3	AuCl	DBP[b]	rt	1	85	70
4	AuCl	amylene	rt	1	82	10
5	$PPh_3AuCl\ AgSbF_6$		rt	1	90	10
6	Au_2O_3		rt	48	91	82
7	Au_2O_3		60	1.5	95	99
8	$Au(OH)_3$		rt	5	nr[c]	
9	$Au(OH)_3$		60	24	80	99
10	$Au(OAc)_3$		rt	5	nr[c]	
11	$Au(OAc)_3$		60	24	42	25

[a] Determined by chiral HPLC. [b] 2,6-Di-*tert*-butylpyridine. [c] No reaction.

SCHEME 2. Keto−Enol Equilibrium of 2a

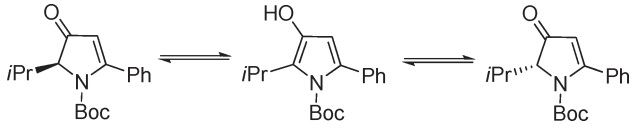
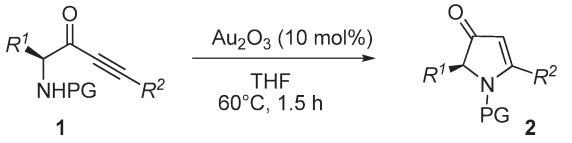


TABLE 5. Stereocontrolled Cyclization of 1



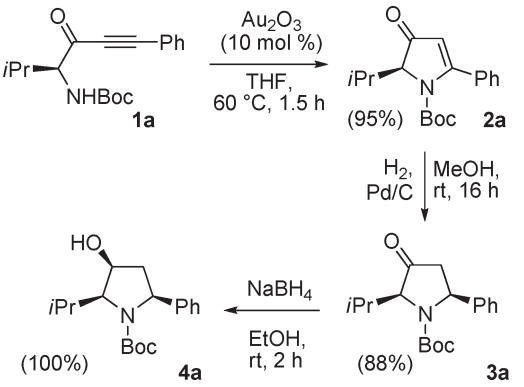
entry	1	R^1	R^2	PG	2	yield (%)	ee (%)[a]
1	**1a**	*i*Pr	Ph	Boc	**2a**	95	99
2	**1c**	*i*Pr	*n*Pr	Boc	**2c**	95	99
3	**1h**	Me	Ph	Boc	**2h**	85	60
4	**1i**	Bn	*n*Pr	CBz	**2i**	90	50[b]
5	**1j**	*sec*-Bu	*n*Pr	Boc	**2j**	92	99
6	**1k**	*sec*-Bu	Ph	Boc	**2k**	90	96

[a] Determined by chiral HPLC. [b] Enantiomeric excess determined by ^1H NMR experiment, using an europium complex.

The first attempt with the conditions previously described revealed disappointing results since epimerization occurred during the reaction (Table 4, entry 1). This could be explained by the keto−enol equilibrium[15] favored by acidic conditions (traces of HCl in the reaction medium) leading to a hydroxypyrrole (Scheme 2). This first result prompted us to investigate novel catalytic conditions. When the reaction was conducted in the presence of 2 equiv of base such as K_2CO_3 (entry 2) or 2,6-di-*tert*-butylpyridine (entry 3), the chirality was partially retained. The use of amylene as proton scavenger led to a loss of chirality (entry 4).

Therefore, we envisioned the use of other gold species that could avoid the generation of HCl in situ. We were pleased to observe the absence of epimerization when the reaction was carried out in the presence of a catalytic amount of gold(III) oxide or hydroxide (entries 7 and 9). For a complete conversion of **1a** at room temperature, the reaction time is longer (48 h) compared to the cyclization promoted with AuCl. On the other hand, the pyrrolin-4-one **2a** was isolated with a slight epimerization (entry 6) ee (82%). Performing the cyclization at 60 °C considerably decreased the reaction time (1 h instead of 48 h) without epimerization (ee ≥99%) (entry 7). No epimerization occurred also by substituting gold oxide with gold(III) hydroxide. Only a decrease in the yield was observed (entry 9). Gold(III) acetate displayed poor reactivity (entries 10 and 11).

SCHEME 3. Synthetic Approach to Hydroxypyrrolidine 4a



To expand the scope of this cyclization in a stereocontrolled manner, we investigated the reaction with other enantiopure substrates **1** (Table 5). The results indicate that no epimerization occurred with hindered substrates (Table 5, entries 1, 2, 5, and 6). The nature of the R^2 moiety (alkyl or aromatic) seemed to have no influence on the epimerization. However, less hindered substrates such as **1h** or **1i** were partially epimerized in the same conditions. This problem of epimerization of peptide aldehydes or related compounds has already been reported.[16]

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Finally, as shown in Scheme 3, this approach can be extented to the stereoselective formation of 3-hydroxypyrrolidine. Thus, hydrogenation of **2a** over Pd/C afforded stereospecifically **3a** in 88% yield. This compound was obtained as a single diastereoisomer (the other diastereoisomer was not detected by NMR) and NOESY experiment confirmed that **3a** has the cis stereochemistry (reduction from the less hindered face, i.e., opposite the isopropyl group). Furthermore ^{1}H NMR experiment with a europium complex[17] allowed the high enantiomeric purity of **3a** (ee $>98\%$) to be confirmed.

Lastly, reduction of **3a** with $NaBH_4$/EtOH gave **4a** stereospecifically in an excellent yield. The other diastereoisomer was not detected by ^{1}H NMR on the crude product and NOESY experiment confirmed that **4a** has the cis arrangement of substituants (hydride adds from the less hindered face). This final product was confirmed by chiral HPLC with DDL detector (light scattering detector) to be $>99\%$ ee, suggesting that no racemization occurred during the reductions steps.[18]

In conclusion, we have developed a gold-catalyzed cyclization of α-amino-ynones. This provides an efficient method for the synthesis of substituted pyrrolin-4-one derivatives. Moreover, the use of the chiral pool of amino acids in this process led to pyrrolin-4-ones with moderate to excellent stereocontrol during the cyclization. This approach provides a straightforward tool for further synthetic application.

(17) $Eu(hfc)_3$ was used for the ^{1}H NMR experiment.

(18) The two enantiomers were synthesized individually starting from L- and D-valine and analyzed with use of a Chiralpak AD-H column (compared to the racemic mixture).

Experimental Section

Representative Experimental Procedure for the Synthesis of (*S*)-2a. To the amino-ynone (*S*)-**1a** (prepared from (L)-Boc-valine) (50 mg, 0.166 mmol) in THF (1.5 mL) at rt under Ar atmosphere was added gold(III) oxide (7.3 mg, 10 mol %). After the resulting mixture was stirred at 60 °C for 1.5 h, Et_2O (5 mL) was added and the resulting mixture was filtered through Celite. After removal of solvents under reduced pressure, the crude product was purified by silica gel column chromatography by using a mixture of dichloromethane and ethyl acetate (98/2) as an eluant to give (*S*)-**2a** (47.5 mg) in 95% yield as a pale yellow solid. Mp 70−72 °C. The ee was 99% by HPLC (Chiralpak AD-H column, eluant: heptane/2-propanol 99/1; 1 mL/min); R_T = 10.6 min; $[\alpha]_D^{25}$ −4.0 (*c* 1, CH_2Cl_2); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.42−7.47 (m, 5H), 5.61 (s, 1H), 4.18 (d, J = 3.6 Hz, 1H), 2.54−2.67 (m, 1H), 1.25 (s, 9H), 1.18 (d, J = 7.2 Hz, 3H), 1.03 (d, J = 6.9 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 201.0, 173.0, 150.4, 133.3, 130.2, 128.1, 127.1, 113.7, 82.7, 71.6, 32.2, 27.7, 17.2, 17.1; IR (ATR) 2964, 1712, 1694, 1567, 1367, 1319, 1159, 972, 767, 695 cm^{-1}; HRMS (EI, m/z) calcd for $C_{18}H_{23}NO_3$ 301.1678, found $[M]^{+\bullet}$ 301.1681.

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Supporting Information Available: Representative experimental procedures, as well as chiral HPLC traces and NMR spectra for the novel cyclized products. This material is available free of charge via the Internet at http://pubs.acs.org.