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Synthesis of Enantioenriched Aza-Proline Derivatives through Gold(I)-Catalyzed Cyclization of Chiral α-Hydrazino Esters

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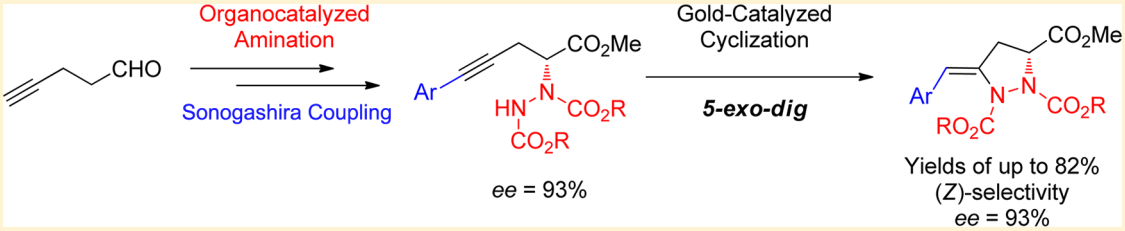
Supporting Information



ABSTRACT: A selective gold(I)-catalyzed synthesis of chiral aza-proline derivatives has been developed by ring closure of enantioenriched α-hydrazino esters bearing an alkyne group. These are easily prepared through a synthetic strategy involving two key steps: organocatalyzed electrophilic amination of pent-4-ynal with dialkyl azodicarboxylate promoted by L-proline and functionalization of the triple bond by Sonogashira cross-coupling. This strategy allowed the preparation of a range of enantioenriched α-hydrazino esters that underwent ring closure by using $Ph_3PAuCl/AgBF_4$ as a catalytic system. Under these conditions, 5-*exo*-*dig* cyclization was favored over 6-*endo*-*dig* and aza-proline derivatives were obtained in good yields without epimerization at the stereogenic center. Influence of the catalytic system, hydrazine protecting group and alkyne substitution on the cyclization step has also been investigated.

INTRODUCTION

The past decade has witnessed thriving advances within the realm of homogeneous gold catalysis.[1] The ability of cationic gold complexes to deprive carbon−carbon multiple bonds of a part of their electron density under smooth conditions has enabled the rapid development of a myriad of synthetic transformations. Activation of the carbon−carbon multiple bonds is based to a great extent on the preparation of cationic Au(I) complexes by treatment of Au(I) precatalyst with the corresponding silver salt. A tremendous area in this field of research involves the addition of X−H (e.g., X = C, N, O) bonds to alkynes and alkenes promoted by gold catalysts.[2] In particular, gold-catalyzed intramolecular cyclization has been a focal point for extensive research efforts, and recent methodology developments in this field have found fruitful applications in total syntheses of densely functionalized heterocycles.[3] Although a wide range of heteronucleophiles such as alcohols, amines, and thiols has been investigated, the use of hydrazine derivatives remains relatively unexplored.[4] Gold-catalyzed addition of hydrazines to alkynes and alkenes has enabled the synthesis of functionalized architectures such as hydrazones, indoles, indazoles, pyrroles, or pyrazole structures, but this is limited to the formation of nonchiral synthetic targets. In light of our recent work on the organocatalytic preparation of α-hydrazino esters,[5] we envisioned that these would be convenient substrates to investigate a novel route for preparing optically active aza-proline derivatives (Scheme 1), whose general synthesis is limited to a few synthetic strategies.[6] These are mainly based on dipolar diazo reactions,[7,8] palladium-catalyzed multicomponent strategies,[9] and intramolecular cyclization under kinetic resolution conditions.[10] Aza-proline derivatives are an interesting class of heterocycles that have applications in many facets of chemistry and biology. For instance, aza-proline derivatives have been used as building blocks for peptidomimetics.[11] Furthermore, they are convenient synthetic intermediates for the preparation of nitrogen-containing architectures of interest such as natural products.[12]

We describe herein a gold-catalyzed 5-*exo*-*dig* cyclization of enantioenriched α-hydrazino esters that allows a facile synthesis of aza-proline derivatives under mild reaction conditions.

RESULTS AND DISCUSSION

Racemic phenyl-substituted α-hydrazino esters **2a** (R = Bn) and **3a** (R = *t*Bu) were first prepared from readily available substrates to validate the synthetic strategy. The route started from the preparation of 5-phenylpent-4-ynal **1** easily obtained by a two-step sequence involving a Sonogashira cross-coupling of iodobenzene with pent-4-yn-1-ol followed by a Swern oxidation (Scheme 2). Under these conditions, aldehyde **1** was obtained in 59% overall yield after purification on silica gel.

According to our previous work and literature,[5,13−15] organocatalyzed electrophilic amination of aldehyde **1** with di-*tert*-butyl or dibenzyl azodicarboxylate promoted by DL-

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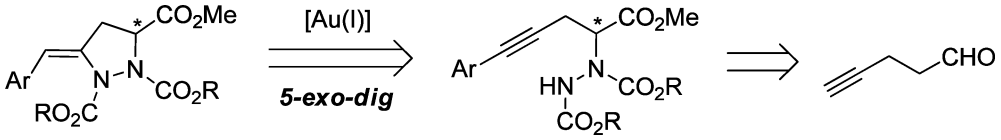
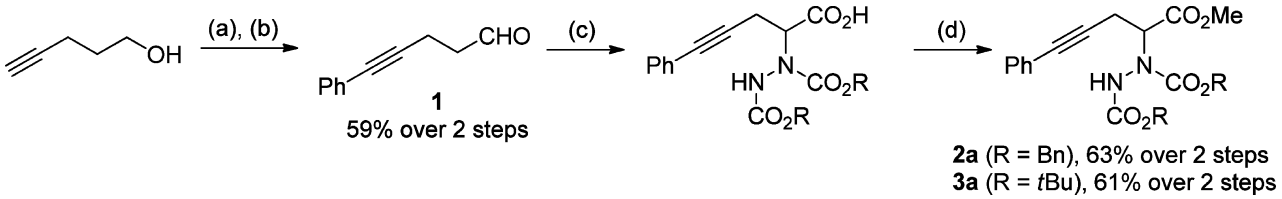
Scheme 1. Gold-Catalyzed Preparation of Aza-Proline Derivatives

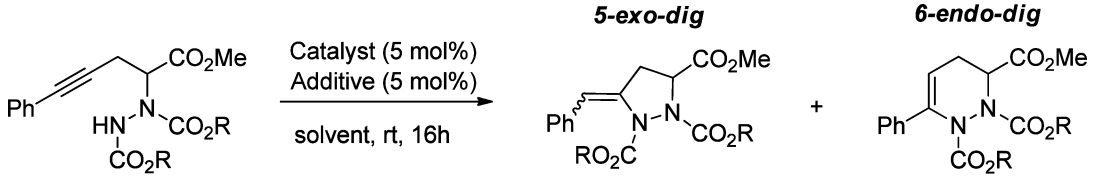


Scheme 2. Synthesis of α-Hydrazino Esters 2a and 3a[a]



[a]Reagent and conditions: (a) PhI (1.2 equiv), $PdCl_2(PPh_3)_2$ (2 mol %), CuI (1 mol %), Et_3N, 16 h, 60 °C; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt, 1 h; (c) $RO_2CN{=}NCO_2R$ (1.2 equiv), DL-proline (10 mol %), MeCN, rt, 16 h then KH_2PO_4, $NaClO_2{\cdot}H_2O$, 30% H_2O_2, MeCN/MeOH/H_2O, rt, 2 h; (d) $TMSCHN_2$ (1.5 equiv), toluene/MeOH (2:1), rt, 15 min.

Table 1. Optimization of the Cyclization of α-Hydrazino Esters 2a and 3a[a]



2a (R = Bn)
3a (R = *t*Bu)

4a (R = Bn)
6a (R = *t*Bu)

5a (R = Bn)
7a (R = *t*Bu)

entry	substrate	catalyst	additive	solvent	products (ratio)[b]	yield (%)[c]
1	**2a**	Ph_3PAuCl	$AgSbF_6$	CH_2Cl_2	(*Z*)-**4a**/(*E*)-**4a**/**5a** (13:67:20)	70
2	**2a**	Ph_3PAuCl	AgOTf	CH_2Cl_2	(*Z*)-**4a**	5
3	**2a**	Ph_3PAuCl	$AgBF_4$	CH_2Cl_2	(*Z*)-**4a**/**5a** (83:17)	66
4	**2a**	Ph_3PAuCl	$AgBF_4$	THF	(*Z*)-**4a**	25
5	**2a**	Ph_3PAuCl	$AgBF_4$	CH_3CN	(*Z*)-**4a**	5
6	**2a**	Ph_3PAuCl		CH_2Cl_2	nd	nr
7	**2a**	$AgBF_4$		CH_2Cl_2	nd	nr
8	**2a**	$Ph_3PAuNTf_2$		CH_2Cl_2	(*Z*)-**4a**/(*E*)-**4a**/**5a** (67:15:18)	50
9	**2a**	$PdCl_2$		CH_3CN	nd	nr
10	**2a**	CuI		CH_3CN	nd	nr
11	**2a**	PTSA[d]		CH_2Cl_2	nd	nr
12	**3a**	Ph_3PAuCl	$AgBF_4$	CH_2Cl_2	(*Z*)-**6a**/**7a** (95:5)	82[e]

[a]Unless otherwise noted, reaction conditions were **2a** or **3a** (1 equiv), catalyst (5 mol %), additive (5 mol %) in solvent for 16 h at room temperature. [b]Ratio determined by ^1H NMR spectroscopy of the crude. nd: not determined. [c]Combined yield of the different cyclized products after purification by chromatography on silica gel. nr: no reaction. [d]10 mol % of *p*-toluenesulfonic acid was used. [e]Yield of pure **6a**

proline was performed, and after 16 h the formed α-hydrazino aldehydes were *in situ* oxidized to the corresponding carboxylic acids. These were not purified and underwent esterification with trimethylsilyl diazomethane in a mixture of toluene and methanol at room temperature. After purification on silica gel, α-hydrazino esters **2a** and **3a** were obtained in 63% and 61% yields, respectively. With these substrates in hand, influence of the reaction conditions on the yield and selectivity of the intramolecular cyclization was investigated by screening various metal salts and solvents (Table 1). The cyclization of α-hydrazino esters **2a** and **3a** was studied at room temperature for 16 h as a model reaction.

Treatment of **2a** (R = Bn) with $Ph_3PAuCl/AgSbF_6$ (5 mol %) in dichloromethane at room temperature gave a mixture of cyclized products **4a** and **5a** in 70% yield (entry 1). (*Z*)-**4a**, (*E*)-**4a**, and **5a** were separated by a careful chromatography on silica gel, allowing the characterization of all the products.[16] Starting from **2a**, the use of AgOTf in combination with Ph_3PAuCl gave exclusively the cyclic compound (*Z*)-**4a** albeit with a very low yield (entry 2). Simply switching the silver salt to $AgBF_4$ successfully altered the reaction path to afford (*Z*)-**4a** along with a low amount of **5a** in 66% yield (entry 3), while lower yields were obtained by changing the solvent (entries 4 and 5).[17] Neither Ph_3PAuCl nor $AgBF_4$ were able to promote the intramolecular ring closure, and the starting material **2a** was fully recovered (entries 6 and 7). The use of the silver-free salt $Ph_3PAuNTf_2$ (5 mol %) in dichloromethane gave both lower selectivities and yield (entry 8).[18] The intramolecular cyclization did not proceed in the presence of 5 mol % of $PdCl_2$ or CuI or a Brønsted acid such as *p*-toluenesulfonic acid

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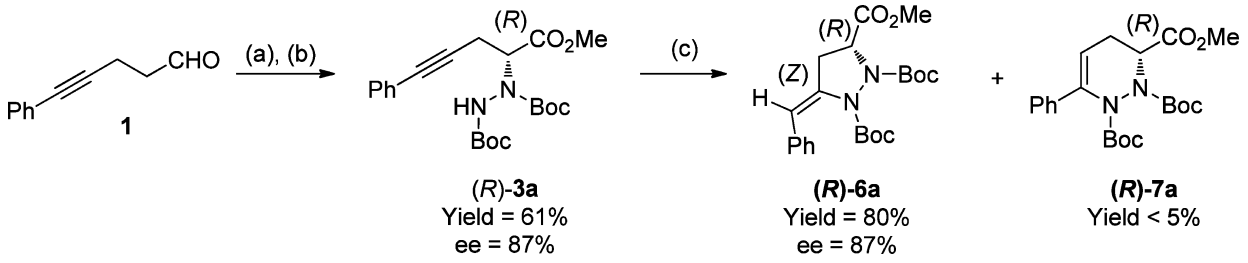
Scheme 3. Preparation and Ring Closure of Enantioenriched α-Hydrazino Ester (*R*)-3a[a]



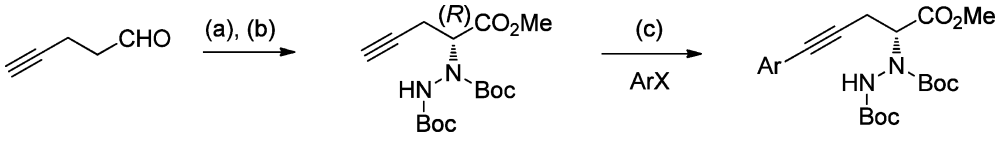
(*R*)-**3a**
Yield = 61%
ee = 87%

(*R*)-**6a**
Yield = 80%
ee = 87%

(*R*)-**7a**
Yield < 5%

[a]Reagent and conditions: (a) tBuO$_2$CN=NCO$_2t$Bu (1.2 equiv), L-proline (10 mol %), MeCN, 0 °C, 16 h then KH_2PO_4, $NaClO_2$·H_2O, 30% H_2O_2, MeCN/MeOH/H_2O, rt, 2 h; (b) $TMSCHN_2$ (1.5 equiv), toluene/MeOH (2:1), rt, 15 min; (c) $Ph_3PAuCl/AgBF_4$ (5 mol %), CH_2Cl_2, rt, 6 h.

Scheme 4. Synthesis of Various α-Hydrazino Esters (*R*)-3a–k[a]



(*R*)-**8**
Yield = 53%
ee = 93%

(*R*)-**3a-k**

[a]Reagent and conditions: (a) tBuO$_2$CN=NCO$_2t$Bu (1.2 equiv), L-proline (10 mol %), MeCN, −5 °C, 16 h then KH_2PO_4, $NaClO_2$·H_2O, 30% H_2O_2, MeCN/MeOH/H_2O, rt, 2 h; (b) $TMSCHN_2$ (1.5 equiv), toluene/MeOH (2:1), rt, 15 min; (c) ArX (1.2 equiv), $PdCl_2(PPh_3)_2$ (5 mol %), CuI (2 mol %), Et_3N, 2–16 h, 60 °C.

(entries 9–11). In order to study the influence of the hydrazine protecting group, the ring closure of α-hydrazino ester **3a** was tested in the presence of the catalytic system $Ph_3PAuCl/AgBF_4$ (5 mol %) in dichloromethane, and 5-*exo*-*dig* cyclization was highly favored leading to the (*Z*)-selective formation of **6a** in 82% yield (entry 12). Our interest then focused on the synthesis of enantioenriched α-hydrazino esters in order to study the effect of the gold-catalyzed reaction conditions on the stereogenic center. α-Hydrazino ester **3a** had given the best results in the cyclization step (Table 1, entry 12), and as a result, stereoselective synthesis of (*R*)-**3a** was considered following the synthetic strategy depicted in Scheme 2 (Scheme 3).

Mixing aldehyde **1** with di-*tert*-butyl azodicarboxylate in the presence of L-proline (10 mol %) at 0 °C for 16 h in acetonitrile turned out to be the best reaction conditions to afford after oxidation and esterification α-hydrazino ester (*R*)-**3a** in 61% yield and 87% enantiomeric excess.[19] It is worthwhile noting that decreasing reaction time for the amination (0 °C, 4 h) led (*R*)-**3a** in only 40% yield and a similar enantiomeric excess (ee = 88%), while increasing the temperature for the electrophilic amination step (rt, 4 h) led to lower yield and ee of (*R*)-**3a** (yield = 49%, ee = 72%). The influence of gold-catalyzed reaction conditions was investigated by comparing the enantiomeric excesses for the cyclized product (*R*)-**6a** and the starting material (*R*)-**3a**. As depicted in Scheme 3, no epimerization was observed with $Ph_3PAuCl/AgBF_4$ as a catalytic system, and conversion was complete after 6 h. We then embarked on the preparation of various α-hydrazino esters to diversify the scope of the gold-catalyzed reaction. The synthetic route depicted in Scheme 2 for the preparation of diverse α-hydrazino esters suffers from two drawbacks: (i) the synthetic pathway is lengthy because Sonogashira cross-coupling is the first step of the strategy and (ii) the organocatalyzed electrophilic amination would have to be optimized for every new aldehydic substrates. One approach in which these limitations can be circumvented is through the formation of the enantioenriched terminal alkyne (*R*)-**8**, which can further undergo Sonogashira cross-coupling to deliver different functionalized α-hydrazino esters (Scheme 4).

The α-hydrazino ester (*R*)-**8** was easily prepared by the three-step sequence electrophilic amination/oxidation/esterification from pent-4-ynal. The best yields and enantioselectivities for (*R*)-**8** were obtained by carrying out the electrophilic amination at −5 °C for 16 h (yield = 53%, ee = 93%).[20] The reactivity of (*R*)-**8** in Sonogashira cross-coupling was investigated by using 5 mol % of $PdCl_2(PPh_3)_2$ and 2 mol % of CuI in triethylamine at 60 °C (Table 2).

Regardless of the aromatic substitutions, cross-coupling of α-hydrazino ester (*R*)-**8** with aromatic iodides afforded (*R*)-**3** in good yields even if longer reaction times were required to ensure full conversion for (*R*)-**3d** and (*R*)-**3g** (entries 4 and 7). 4-Bromo trifluoromethylbenzene proved to be rather unreactive under these conditions, leading to (*R*)-**3j** in 17% yield (entry 10), while reaction of (*R*)-**8** with 2-bromopyridine gave rise to (*R*)-**3k** in 64% yield after 16 h reaction time (entry 11). No epimerization was observed, and therefore cross-coupling conditions did not impinge on the enantiopurity (entries 1, 4, and 7). With optically active (*R*)-**3a–k** in hand, gold-catalyzed cyclization was investigated , involving the use of 5 mol % of $Ph_3PAuCl/AgBF_4$ in dichloromethane at room temperature until completion of the reaction monitored by TLC (Table 3).

In all cases, 5-*exo*-*dig* cyclization led to the (*Z*)-selective formation of (*R*)-**6**, and no racemization was observed regardless of the reaction time (entries 1 and 4). Similar levels of yield and regioselectivity were obtained when alkyl- and fluoro-substituted aromatic derivatives were used as substrates (entries 1–6). In contrast, the cyclization outcome of (*R*)-**3g** and (*R*)-**3h** is highly dependent on the position of the methoxy group on the aromatic ring (entries 7 and 8). Gold-catalyzed

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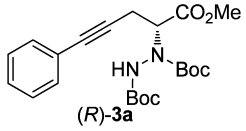
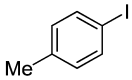
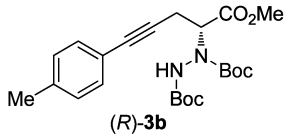
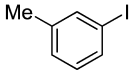
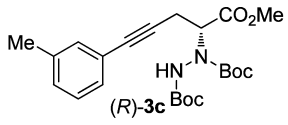
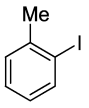
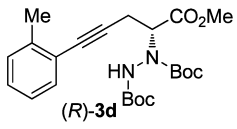
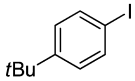
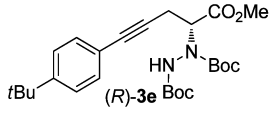
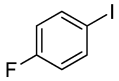
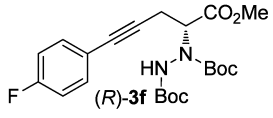
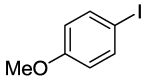
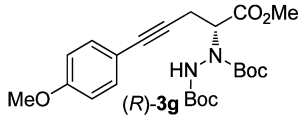
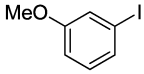
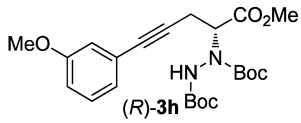
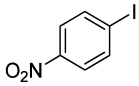
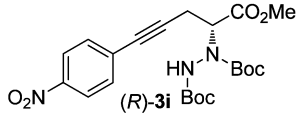
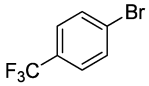
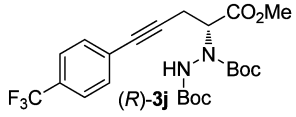
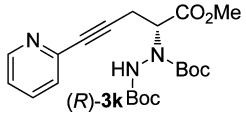
Table 2. Sonogashira Cross-Coupling[a]

Entry	Aromatic Halide	Time (h)	Product	Yield (%)
1		2	 (*R*)-**3a**	74[b]
2		2	 (*R*)-**3b**	67
3		2	 (*R*)-**3c**	87
4		16	 (*R*)-**3d**	53[b]
5		2	 (*R*)-**3e**	95
6		2	 (*R*)-**3f**	85
7		4	 (*R*)-**3g**	62[b]
8		2	 (*R*)-**3h**	71
9		2	 (*R*)-**3i**	83
10		16	 (*R*)-**3j**	17
11		16	 (*R*)-**3k**	64

[a]General reaction conditions: (*R*)-**8** (1 equiv), aromatic halide (1.2 equiv), $PdCl_2(PPh_3)_2$ (5 mol %), CuI (2 mol %) in triethylamine at 60 °C. [b]In this case, determination of the enantiomeric excess by chiral HPLC of the product showed no epimerization at the stereogenic center. See Supporting Information for further details.

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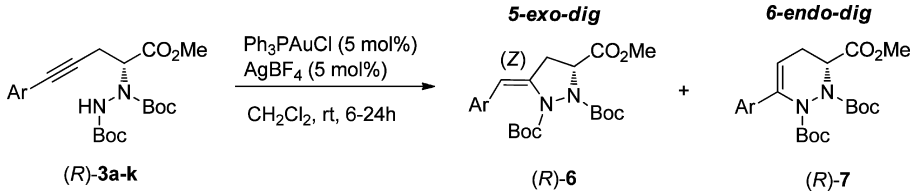
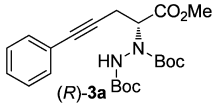
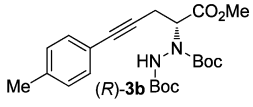
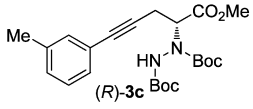
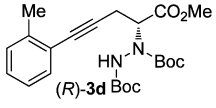
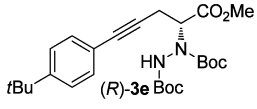
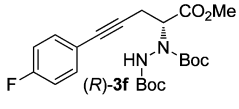
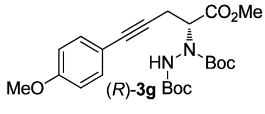
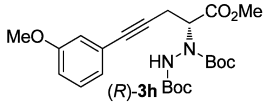
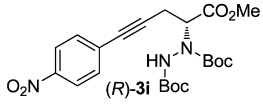
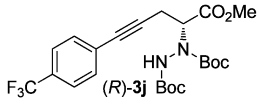
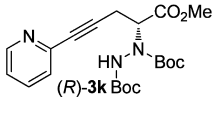
Table 3. Gold-Catalyzed Ring Closure of (*R*)-3a–k[a]



Entry	Substrate	Yield (*R*)-**6** (%)	**6**/**7** (ratio)[b]
1	 (*R*)-**3a**	82	**6a**/**7a** (95/5)[c]
2	 (*R*)-**3b**	71	**6b**/**7b** (86/14)
3	 (*R*)-**3c**	70	**6c**/**7c** (92/8)
4	 (*R*)-**3d**	62	**6d**/**7d** (95/5)[c]
5	 (*R*)-**3e**	67	**6e**/**7e** (85/15)
6	 (*R*)-**3f**	75	**6f**/**7f** (93/7)
7	 (*R*)-**3g**	64[d]	**6g**/**7g** (60/40)
8	 (*R*)-**3h**	64	**6h**/**7h** (95/5)
9	 (*R*)-**3i**	80	**6i**
10	 (*R*)-**3j**	77	**6j**
11	 (*R*)-**3k**	n.r.[e]	n.d.[f]

[a]General reaction conditions: (*R*)-**3** (1 equiv), Ph_3PAuCl (5 mol %), $AgBF_4$ (5 mol %) in CH_2Cl_2 at room temperature until completion of the reaction monitored by TLC. Unless otherwise stated, heterocycle **7** could not be isolated. [b]Ratio determined by ^1H NMR spectroscopy of the crude. [c]In this case, determination of the enantiomeric excess by chiral HPLC of the product showed no epimerization at the stereogenic center. See Supporting Information for further details. [d]Yield of **6g** and **7g**. [e]n.r.: no reaction. [f]n.d.: not determined.

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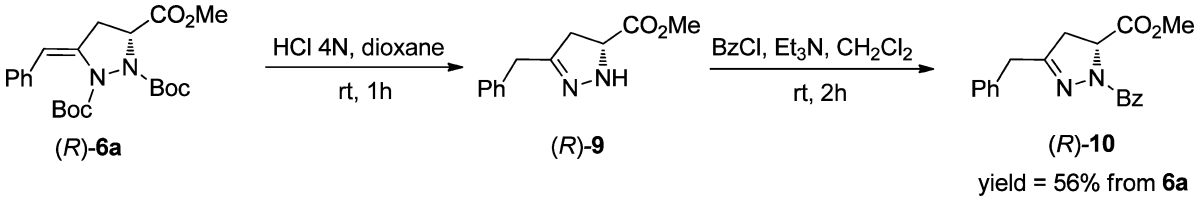
Scheme 5. Synthesis of 2-Pyrazoline 5-Carboxylic Acid Ester 10 from (*R*)-6a



ring closure of (*R*)-**3g** afforded a mixture of 5-*exo-dig* and 6-*endo-dig* cyclized products in 64% yield with a 60:40 ratio of (*R*)-**6g**/(*R*)-**7g**, while (*R*)-**6h** was obtained with an excellent selectivity in 64% yield. The lower regioselectivity for the cyclization of (*R*)-**3g** could be explained by a perturbation of the electronic density of the triple bond by the benzene ring substituent (i.e., OMe) when the alkyne and the substituent are in the para position on the phenyl ring. In contrast, marked improvements in selectivities were observed in the ring closure of α-hydrazino esters bearing an electron-withdrawing group on the aromatic ring. For instance, reaction of (*R*)-**3i** and (*R*)-**3j** allowed the selective formation of 5-*exo-dig* products in 80% and 77% yields, respectively, while 6-*endo-dig* compounds were not detected (entries 9 and 10). The reactivity of pyridine-containing α-hydrazino ester (*R*)-**3k** was also tested, but in this case cyclization did not take place and the starting material was fully recovered after 24 h reaction time (entry 11). In light of the experimental results described above, a competition between the two cyclization modes (5-*exo-dig* and 6-*endo-dig*) occurs during the ring closure of **3** catalyzed by 5 mol % of $Ph_3PAuCl/AgBF_4$. First, cationic gold complex would activate the alkyne via a π-complex, which would then undergo nucleophilic attack by the protected hydrazine to afford after protodeauration the desired cyclized products **6** and/or **7**. Furthermore, it is important to note that no *E*-isomer was formed for **6** under these conditions suggesting a nucleophilic attack to the gold-alkyne π-complex in a *anti*-fashion.

Additionally, aza-proline derivative (*R*)-**6a** was successfully transformed into chiral 2-pyrazoline 5-carboxylic acid ester (*R*)-**10**, which is a class of structure found in bioactive compounds (Scheme 5).[21]

Treatment of heterocycle (*R*)-**6a** with a hydrogen chloride solution in dioxane gave rise to pyrazoline (*R*)-**9**, which underwent benzoylation at room temperature to afford pyrazoline (*R*)-**10** in 56% overall yield.

In summary, we have reported a regioselective gold-catalyzed ring closure of enantioenriched α-hydrazino esters allowing a simple access to functionalized aza-proline derivatives with good yields. This strategy was applied to variously substituted α-hydrazino esters that were easily prepared by a three-step reaction sequence, organocatalyzed electrophilic amination/oxidation/esterification followed by a Sonogashira cross-coupling. Moreover, the results outlined herein demonstrate the importance of the nature of the silver salt, hydrazine protecting group, and alkyne substitution on the yield and selectivity of the gold-catalyzed cyclization. In the future, further functionalization of the aza-proline derivatives should deliver molecular structures with applications in catalysis and medicinal chemistry.

EXPERIMENTAL SECTION

General Experimental Methods. ^{1}H NMR (200 or 300 MHz) and ^{13}C NMR (50 or 75 MHz) spectra were recorded with 200 or 300 MHz spectrometers in chloroform-*d* with the residual peak solvent as an internal standard. Chemical shifts (δ) are given in parts per million, and coupling constants are given as absolute values expressed in hertz. Electrospray ionization (ESI) mass spectra were collected using a Q-TOF instrument. Samples (solubilized in ACN at 1 mg/mL and then diluted by 1000) were introduced into the MS via an UHPLC system while a Leucine Enkephalin solution was co-injected via a micro pump. Infrared spectra were recorded with a FT spectrometer. Optical rotation values were measured at room temperature. Melting points were determined in open capillary tubes and are uncorrected. Thin-layer chromatography (TLC) was carried out on aluminum sheets precoated with silica gel 60 F254. Column chromatography separations were performed using silica gel (0.040−0.060 mm). HPLC analyses were performed with a machine equipped with a UV−vis detector at 30 °C employing chiral AD-H or OD-H columns. HPLC grade heptane and isopropyl alcohol were used as the eluting solvents. Solvents were dried immediately before use by distillation from standard drying agents.

5-Phenylpent-4-ynal (1). A flame-dried Schlenk tube was charged with CuI (15.9 mg, 0.083 mmol), $PdCl_2(PPh_3)_2$ (117 mg, 0.166 mmol), and iodobenzene (1.11 mL, 10 mmol). The tube was evacuated and backfilled with nitrogen. This procedure was repeated three times. To this mixture was added Et_3N (45 mL, and the solution was stirred for 2 min at room temperature at which point pent-4-yn-1-ol (700 mg, 8.32 mmol) was added. After 16 h of reaction at 60 °C, the reaction vial was cooled, and the mixture was filtered over a pad of Celite by using diethyl ether as an eluent. The solvent was removed in vacuo, and ^{1}H NMR spectrum spectroscopy of the crude showed complete conversion. A CH_2Cl_2 (6 mL) solution of DMSO (1.4 mL) was added to a CH_2Cl_2 (45 mL) solution of $(COCl)_2$ (1.29 mL, 15 mmol) at −78 °C. The resulting mixture was stirred at −78 °C for 10 min, and then a CH_2Cl_2 (18 mL) solution of the unpurified alcohol was added at −78 °C. The mixture was stirred at −78 °C for 15 min. After stirring at −45 °C for 1 h, Et_3N (9.0 mL) was added. The reaction mixture was stirred at rt for 1 h, quenched by the addition of water, and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, concentrated, and purified by silica gel column chromatography (pentane/CH_2Cl_2 = 1:1 then 3:7 to collect the product) to afford the aldehyde **1** in 59% yield (785 mg) as a colorless oil. All physical and spectroscopic data were in complete agreement with the reported ones.[22]

General Procedure To Prepare α-Hydrazino Esters 2a, 3a, and 8 through a Three-Step Sequence: Electrophilic Amination/Oxidation/Esterification. To a stirred solution of aldehyde (1 mmol) in acetonitrile (0.2 mol/L) at the desired temperature (room temperature, 0 °C, or −5 °C) were successively added L- or DL-proline (11.5 mg, 0.1 mmol) and dialkyl azodicarboxylate (1.2 mmol). Once the reaction finished, the solution was then diluted with acetonitrile (6.5 mL), and a 1:1 mixture of MeOH/H_2O (4 mL/4 mL) was then added, followed by addition of KH_2PO_4 (350 mg, 2.6 mmol), $NaClO_2{\cdot}H_2O$ (346 mg, 3.2 mmol) and 30% H_2O_2 (3 mL). The reaction mixture was stirred at room temperature for 2 h (monitoring by TLC). The solution was acidified with a 1 M HCl aqueous solution until pH = 3. Saturated $Na_2S_2O_3$ aqueous solution (3.3 mL) was added at 0 °C, and the mixture was acidified with a 1 M HCl aqueous solution until pH = 3 if necessary. The aqueous phase was extracted three times with ethyl acetate, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. To a solution of the crude carboxylic acid in toluene/MeOH (3.3 mL/1.65 mL) was added dropwise a solution of $TMSCHN_2$ (2 M in hexanes, 750 μL, 1.5 mmol) at room temperature.

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The solution was stirred for 15 min (monitoring by TLC), and a solution of satd aq NH_4Cl was added to the reaction mixture. The aqueous phase was extracted with ethyl acetate, and the combined organic phases were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (pentane/ethyl acetate, 85:15) to furnish the desired product.

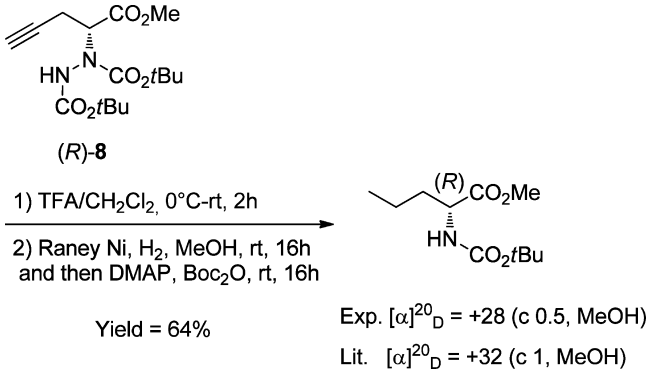
*Methyl 2-(1,2-Benzyloxycarbonylhydrazinyl)-5-phenylpent-4-ynoate (**2a**).* According to the general procedure, 1 mmol of aldehyde **1** (158 mg) and 1.2 mmol of dibenzyl azodicarboxylate (358 mg) afforded α-hydrazino ester **2a** (307 mg) as a white solid in 63% yield. Mp 110−112 °C; R_f 0.23 (pentane/ethyl acetate, 8:2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.43−7.10 (m, 15H), 6.88 (br s, 1H), 5.31−4.93 (m, 5H), 3.77 (br s, 3H), 3.24−2.91 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.1, 155.9 (2C), 135.6, 131.8 (2C), 128.6−127.9 (14C), 123.3, 84.8, 83.1, 68.7, 67.8, 58.9, 52.8, 20.7; FTIR (neat) cm^{-1} 3317, 2962, 1740, 1683, 1503, 1421, 1307, 1192, 1135, 1012, 751, 732; 686; HRMS (ESI) calcd for $C_{28}H_{27}N_2O_6$ $[M + H]^+$ 487.1869, found 487.1870.

*(R)-Methyl 2-(1,2-tert-Butyloxycarbonylhydrazinyl)-5-phenylpent-4-ynoate (**3a**).* According to the general procedure, 1 mmol of aldehyde **1** (158 mg) and 1.2 mmol of di-*tert*-butyl azodicarboxylate (276 mg) afforded α-hydrazino ester **3a** (255 mg) as a white solid in 61% yield. Mp 75−77 °C; R_f 0.33 (pentane/ethyl acetate, 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51−7.35 (m, 2H), 7.33−7.20 (m, 3H), 6.54 (br s, 0.65H), 6.27 (br s, 0.35H), 5.25−5.05 (m, 0.65H), 4.95−4.80 (m, 0.35H), 3.78 (s, 3H), 3.15−2.90 (m, 2H), 1.48 (br s, 9H), 1.45 (br s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 155.1, 154.7, 134.6 (2C), 127.7, 123.6, 85.4, 82.6, 82.2, 81.1, 58.5, 52.3, 28.12 (3C), 28.08 (3C), 20.6; FTIR (neat) cm^{-1} 3316, 2971, 2923, 1742, 1706, 1490, 1393, 1367, 1234, 1145, 1048, 1000, 755; HRMS (ESI) calcd for $C_{22}H_{30}N_2O_6Na$ $[M + Na]^+$ 441.2002, found 441.2001. Enantiomeric excess of **3a** has been determined by HPLC analysis employing a chiral AD-H column (heptane/2-propanol, 90/10, 1.0 mL/min), t_R = 8.14 min for the major enantiomer and t_R = 9.67 min for the minor enantiomer. $[\alpha]^{20}_D$ = −18.5 (*c* 1.0, $CHCl_3$) for 87% ee.

*(R)-Methyl 2-(1,2-tert-Butyloxycarbonylhydrazinyl)-pent-4-ynoate (**8**).* According to the general procedure, 1 mmol of pent-4-ynal (84.1 mg) and 1.2 mmol of di-*tert*-butyl azodicarboxylate (276 mg) afforded α-hydrazino ester **8** (181 mg) as colorless gum in 53% yield. R_f 0.41 (pentane/ethyl acetate, 85:15); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50−6.10 (m, 1H), 5.15−4.95 (m, 0.6H), 4.95−4.62 (m, 0.4H), 3.75 (s, 3H), 2.82−2.75 (m, 2H), 2.00 (br s, 1H), 1.46 (br s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 155.0 (2C), 82.6, 82.3, 81.6, 80.1 (0.5C), 70.5 (0.5C), 60.8 (0.5C), 58.4 (0.5C), 52.7, 28.28 (3C), 28.20 (3C), 19.8; FTIR (neat) cm^{-1} 3313, 3262, 2978, 2927, 1754, 1734, 1680, 1392, 1366, 1279, 1245, 1150; HRMS (ESI) calcd for $C_{16}H_{26}N_2O_6Na$ $[M + Na]^+$ 365.1689, found 365.1690. Enantiomeric excess of **3a** has been determined by HPLC analysis employing a chiral AD-H column (heptane/2-propanol, 90/10, 1.0 mL/min), t_R = 9.44 min for the major enantiomer and t_R = 10.58 min for the minor enantiomer. $[\alpha]^{20}_D$ = −0.8 (*c* 1.0, $CHCl_3$) for 93% ee.

Determination of the Configuration of (*R*)-8. The configuration of the stereogenic center was determined to be (*R*) by transforming **8** into (*R*)-2-*tert*-butoxycarbonylaminopentanoic acid methyl ester and by comparing the measured optical rotation with the reported one.[23]

To a solution of ester **8** (0.29 mmol, 100 mg) in dichloromethane (1 mL) was added trifluoroacetic acid (0.60 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2 h, and the volatiles were evaporated under reduced pressure. To a solution of the crude hydrazine in MeOH (1 mL) was added Raney Ni. The reaction mixture was stirred 16 h at room temperature under hydrogen atmosphere followed by the addition of DMAP (3.2 mg) and di-*tert*-butyldicarbonate (80 mg). The solution was stirred at room temperature overnight and then filtered through a pad of Celite, and the mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with the solvent mixture Et_2O/pentane, 20/80 to afford (*R*)-2-*tert*-butoxycarbonylaminopentanoic acid methyl ester (43 mg) in 64% overall yield.



General Procedure for the Sonogashira Cross-Coupling of 8 with Aromatic Halides: Preparation of α-Hydrazino Esters 3a−k. A flame-dried Schlenk tube was charged with CuI (0.75 mg, 0.004 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol), and aromatic halide (0.24 mmol). The tube was evacuated and backfilled with nitrogen. This procedure was repeated three times. To this mixture was added Et_3N (1.85 mL), and the solution was stirred for 2 min at room temperature at which point ester **8** (68 mg, 0.20 mmol) was added. The reaction was then stirred at 60 °C until completion of the reaction monitored by TLC. The reaction vial was then cooled, and the mixture was filtered over a pad of Celite by using a 1:1 mixture diethyl ether/dichloromethane as an eluent. The solvent was removed in vacuo and purified by chromatography on silica gel to afford the desired products.

*(R)-Methyl 2-(1,2-tert-Butyloxycarbonylhydrazinyl)-5-(4-methylphenyl)-pent-4-ynoate (**3b**).* According to the general procedure, reaction of ester **8** with 0.24 mmol of 4-iodotoluene (52 mg) afforded α-hydrazino ester **3b** (58 mg) as a colorless oil in 67% yield after purification on silica gel (pentane/ethyl acetate, 9:1). R_f 0.28 (pentane/ethyl acetate, 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (br d, *J* = 7.9 Hz, 2H), 7.05 (br d, *J* = 7.9 Hz, 2H), 6.62−6.15 (m,1H), 5.20−5.05 (m, 0.6H), 4.95−4.75 (m, 0.4H), 3.76 (s, 3H), 3.10−2.90 (m, 2H), 2.31 (s, 3H), 1.46 (br s, 9H), 1.44 (br s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 154.9, (2C), 137.9, 131.6 (2C), 128.9 (2C), 120.5, 84.7, 82.7, 82.2, 81.4, 60.9 (0.4C), 58.4 (0.6C), 52.6, 28.5 (3C), 28.2 (3C), 21.5, 20.8; FTIR (neat) cm^{-1} 3321, 2975, 2927, 1739, 1708, 1365, 1246, 1152, 1045; HRMS (ESI) calcd for $C_{23}H_{32}N_2O_6Na$ $[M + Na]^+$ 455.2158, found 455.2159. $[\alpha]^{20}_D$ = −17.7 (*c* 1.0, $CHCl_3$) for 93% ee.

*(R)-Methyl 2-(1,2-tert-Butyloxycarbonylhydrazinyl)-5-(3-methylphenyl)-pent-4-ynoate (**3c**).* According to the general procedure, reaction of ester **8** with 0.24 mmol of 3-iodotoluene (52 mg) afforded α-hydrazino ester **3c** (75 mg) as a colorless oil in 87% yield after purification on silica gel (pentane/ethyl acetate, 85:15). R_f 0.43 (pentane/ethyl acetate, 85:15); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21−7.10 (m, 3H), 7.09−7.04 (m, 1H), 6.60−6.36 (br s, 0.65H), 6.35−6.15 (br s, 0.35H), 5.20−5.05 (m, 0.65H), 4.92−4.71 (m, 0.35H), 3.76 (s, 3H), 3.10−2.90 (m, 2H), 2.29 (s, 3H), 1.46 (br s, 9H), 1.44 (br s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 154.9 (2C), 137.8, 132.4, 128.8 (2C), 128.1, 123.4, 85.1, 82.8, 82.2, 81.3, 60.9 (0.35C), 58.4 (0.65C), 52.6, 28.24 (3C), 28.20 (3C), 21.3, 20.8; FTIR (neat) cm^{-1} 3321, 2978, 2927, 1740, 1708, 1389, 1365, 1238, 1148, 1049; HRMS (ESI) calcd for $C_{23}H_{32}N_2O_6Na$ $[M + Na]^+$ 455.2158, found 455.2157. $[\alpha]^{20}_D$ = −20.2 (*c* 1.0, $CHCl_3$) for 93% ee.

*(R)-Methyl 2-(1,2-tert-Butyloxycarbonylhydrazinyl)-5-(2-methylphenyl)-pent-4-ynoate (**3d**).* According to the general procedure, reaction of ester **8** with 0.24 mmol of 2-iodotoluene (52 mg) afforded α-hydrazino ester **3d** (46 mg) as a colorless oil in 53% yield after purification on silica gel (pentane/diethyl ether,4:1). R_f 0.20 (pentane/diethyl ether,4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.2 Hz, 1H), 7.20−7.05 (m, 3H), 6.50 (br s, 1H), 5.22−5.05 (m, 0.7H), 4.96−4.75 (m, 0.3H), 3.78 (s, 3H), 3.13−3.00 (m, 2H), 2.40 (s, 3H), 1.48 (br s, 9H), 1.44 (br s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 154.9 (2C), 140.2, 132.1, 129.4, 127.9, 125.5, 123.4, 89.4, 82.3, 81.6, 81.4, 61.0 (0.3C), 58.6 (0.7C), 52.6, 28.2 (6C), 20.9, 20.7; FTIR (neat) cm^{-1} 3317, 2978, 2927, 1739, 1708, 1389, 1238, 1152, 1049; HRMS (ESI) calcd for $C_{23}H_{32}N_2O_6Na$ $[M + Na]^+$ 455.2158, found

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455.2157. Enantiomeric excess of **3d** has been determined by HPLC analysis employing a chiral AD-H column (heptane/2-propanol, 95:5, 1.0 mL/min), t_R = 12.52 min for the major enantiomer and t_R = 13.8 min for the minor enantiomer. $[\alpha]^{20}_D$ = −24.0 (*c* 1.0, $CHCl_3$) for 93% ee.

*(R)-Methyl 2-(1,2-tert-Butyloxycarbonylhydrazinyl)-5-(4-tertbutylphenyl)-pent-4-ynoate (**3e**).* According to the general procedure, reaction of ester **8** with 0.24 mmol of 1-*tert*-butyl 4-iodobenzene (62 mg) afforded α-hydrazino ester **3e** (90 mg) as a colorless oil in 95% yield after purification on silica gel (pentane/ethyl acetate, 85:15). R_f 0.27 (pentane/ethyl acetate, 85:15); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.29 (m, 4H), 6.60−6.20 (m,1H), 5.22−5.00 (m, 0.7H), 4.98−4.75 (m, 0.3H), 3.78 (s, 3H), 3.12−2.94 (m, 2H), 1.48 (br s, 9H), 1.46 (br s, 9H), 1.31 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 154.9, (2C), 151.1, 131.5 (2C), 125.2 (2C), 120.6, 84.7, 82.7, 82.2, 81.3, 60.9 (0.3C), 58.5 (0.7C), 52.6, 34.8, 31.3 (3C), 28.27 (3C), 28.23 (3C), 20.8; FTIR (neat) cm^{-1} 3321, 2967, 2904, 2868, 1740, 1708, 1365, 1235, 1152, 1045; HRMS (ESI) calcd for $C_{26}H_{38}N_2O_6Na$ $[M + Na]^+$ 497.2628, found 497.2627. $[\alpha]^{20}_D$ = −17.4 (*c* 2.0, $CHCl_3$) for 93% ee.

*(R)-Methyl 2-(1,2-tert-Butyloxycarbonylhydrazinyl)-5-(4-fluorophenyl)-pent-4-ynoate (**3f**).* According to the general procedure, reaction of ester **8** with 0.24 mmol of 4-fluoroiodobenzene (53 mg) afforded α-hydrazino ester **3f** (75 mg) as a colorless oil in 85% yield after purification on silica gel (pentane/ethyl acetate, 85:15). R_f 0.50 (pentane/ethyl acetate, 85:15); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (br dd, *J* = 8.4 Hz, *J* = 5.6 Hz, 2H), 6.94 (t, *J* = 8.4 Hz, 2H), 6.52 (br s, 0.75H), 6.26 (br s, 0.25H), 5.20−5.05 (m, 0.65H), 4.89−4.73 (m, 0.35H), 3.75 (s, 3H), 3.05−2.90 (m, 2H), 1.45 (br s, 9H), 1.42 (br s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 162.3, (1C, *J* = 249 Hz), 154.9 (2C), 133.5 (2C, *J* = 8.3 Hz), 119.6, 115.4 (2C, *J* = 22 Hz), 85.2, 82.2, 81.6, 81.2, 60.9 (0.35C), 58.4 (0.65C), 52.6, 28.23 (3C), 28.18 (3C), 20.7; FTIR (neat) cm^{-1} 3317, 2978, 2927, 1735, 1708, 1503, 1365, 1215, 1152, 832; HRMS (ESI) calcd for $C_{22}H_{29}N_2O_6FNa$ $[M + Na]^+$ 459.1907, found 459.1906. $[\alpha]^{20}_D$ = −16.8 (*c* 1, $CHCl_3$) for 93% ee.

*(R)-Methyl 2-(1,2-tert-Butyloxycarbonylhydrazinyl)-5-(4-methoxyphenyl)-pent-4-ynoate (**3g**).* According to the general procedure, reaction of ester **8** with 0.24 mmol of 4-iodoanisole (56 mg) afforded α-hydrazino ester **3g** (55 mg) as a with solid in 62% yield after purification on silica gel (pentane/ethyl acetate, 85:15). Mp 85−87 °C; R_f 0.17 (pentane/ethyl acetate, 85:15); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (br d, *J* = 8.7 Hz, 2H), 6.77 (br d, *J* = 8.7 Hz, 2H), 6.58−6.26 (br s, 1H), 5.15−5.00 (m, 0.65H), 4.90−4.72 (m, 0.35H), 3.76 (s, 3H), 3.74 (s, 3H), 3.07−2.87 (m, 2H), 1.44 (br s, 9H), 1.42 (br s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 159.3, 155.8, 154.9, 133.1 (2C), 115.7, 113.8 (2C), 83.9, 82.4, 82.1, 81.4, 60.9 (0.35C), 58.4 (0.65C), 55.3, 52.5, 28.22 (3C), 28.18 (3C), 20.7; FTIR (neat) cm^{-1} 3349, 2966, 2921, 1744, 1728, 1692, 1503, 1483, 1384, 1253, 1144, 824; HRMS (ESI) calcd for $C_{23}H_{32}N_2O_7Na$ $[M + Na]^+$ 471.2107, found 471.2104. $[\alpha]^{20}_D$ = −12.4 (*c* 1, $CHCl_3$) for 93% ee. Enantiomeric excess of **3g** has been determined by HPLC analysis employing a chiral AD-H column (heptane/2-propanol, 90:10, 1.0 mL/min), t_R = 11.9 min for the major enantiomer and t_R = 16.1 min for the minor enantiomer.

*(R)-Methyl 2-(1,2-tert-Butyloxycarbonylhydrazinyl)-5-(3-methoxyphenyl)-pent-4-ynoate (**3h**).* According to the general procedure, reaction of ester **8** with 0.24 mmol of 3-iodoanisole (56 mg) afforded α-hydrazino ester **3h** (64 mg) as a colorless oil in 71% yield after purification on silica gel (pentane/diethyl ether, 4:1). R_f 0.35 (pentane/diethyl ether, 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (br t, *J* = 7.8 Hz, 1H), 6.97 (br d, *J* = 7.8 Hz, 1H), 6.91 (app s, 1H), 6.97 (br dd, *J* = 8.3 Hz, *J* = 2.2 Hz, 1H), 6.60−6.22 (br s, 1H), 5.21−5.05 (m, 0.65H), 4.95−4.76 (m, 0.35H), 3.77 (s, 6H), 3.08−2.93 (m, 2H), 1.46 (br s, 9H), 1.44 (br s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 159.4, 155.0 (2C), 129.3, 124.7, 124.4, 116.7, 114.6, 85.4, 82.6, 82.2, 81.3, 60.9 (0.35C), 58.5 (0.65C), 55.4, 52.6, 28.27 (3C), 28.23 (3C), 20.8; FTIR (neat) cm^{-1} 3317, 2975, 2931, 1739, 1708, 1389, 1365, 1239, 1156; HRMS (ESI) calcd for $C_{23}H_{32}N_2O_7Na$ $[M + Na]^+$ 471.2107, found 471.2102, $[\alpha]^{20}_D$ = −22.9 (*c* 1, $CHCl_3$) for 93% ee.

*(R)-Methyl 2-(1,2-tert-Butyloxycarbonylhydrazinyl)-5-(4-nitrophenyl)-pent-4-ynoate (**3i**).* According to the general procedure, reaction of ester **8** with 0.24 mmol of 1-iodo-4-nitrobenzene (59 mg) afforded α-hydrazino ester **3i** (77 mg) as a colorless oil in 83% yield after careful purification on silica gel (pentane/ethyl acetate, 85:15). R_f 0.13 (pentane/ethyl acetate, 85:15); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.7 Hz, 2H), 7.50 (d, *J* = 8.7 Hz, 2H), 6.55−6.20 (br s, 1H), 5.24−5.05 (m, 0.7H), 4.94−4.72 (m, 0.3H), 3.76 (s, 3H), 3.04 (br d, *J* = 5.9 Hz, 2H), 1.45 (br s, 9H), 1.42 (br s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 154.8 (2C), 146.9, 132.5 (2C), 130.6, 123.5 (2C), 91.9, 82.4, 81.4, 81.1, 60.8 (0.3C), 58.4 (0.7C), 52.7, 28.24 (3C), 28.17 (3C), 20.9; FTIR (neat) cm^{-1} 3321, 2974, 2931, 2225, 1739, 1704, 1519, 1341, 1235, 1148; HRMS (ESI) calcd for $C_{22}H_{29}N_3O_8Na$ $[M + Na]^+$ 486.1852, found 486.1853. $[\alpha]^{20}_D$ = −11.2 (*c* 1, $CHCl_3$) for 93% ee.

*(R)-Methyl 2-(1,2-tert-Butyloxycarbonylhydrazinyl)-5-(4-trifluoromethylphenyl)-pent-4-ynoate (**3j**).* According to the general procedure, reaction of ester **8** with 0.24 mmol of 1-bromo-4-trifluoromethylbenzene (54 mg) afforded α-hydrazino ester **3j** (16 mg) as a white solid in 17% yield after careful purification on silica gel (pentane/ethyl acetate, 85:15). Mp 100−102 °C; R_f 0.64 (pentane/ethyl acetate, 85:15); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (br d, *J* = 8.2 Hz, 2H), 7.56 (br d, *J* = 8.2 Hz, 2H), 6.58−6.21 (br s, 1H), 5.23−5.02 (m, 0.7H), 4.95−4.75 (m, 0.3H), 3.73 (s, 3H), 3.10−2.95 (m, 2H), 1.46 (br s, 9H), 1.43 (br s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 154.9 (2C), 134.8−118.7 (7C), 88.6, 82.4, 81.4, 81.2, 60.9 (0.3C), 58.5 (0.7C), 52.7, 28.25 (3C), 28.20 (3C), 20.8; FTIR (neat) cm^{-1} 3347, 2979, 1736, 1709, 1705, 1480, 1323, 1155, 1123, 1067, 838; HRMS (ESI) calcd for $C_{23}H_{29}F_3N_2O_6Na$ $[M + Na]^+$ 509.1875, found 509.1876. $[\alpha]^{20}_D$ = −11.0 (*c* 1, $CHCl_3$) for 93% ee.

*(R)-Methyl 2-(1,2-tert-Butyloxycarbonylhydrazinyl)-5-(2-pyridyl)-pent-4-ynoate (**3k**).* According to the general procedure, reaction of ester **8** with 0.24 mmol of 2-bromopyridine (38 mg) afforded α-hydrazino ester **3k** (54 mg) as a colorless oil in 64% yield after careful purification on silica gel (pentane/ethyl acetate, 60:40). R_f 0.29 (pentane/ethyl acetate, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (br s, 1H), 7.59 (br t, *J* = 7.4 Hz, 1H), 7.42−7.30 (m, 1H), 7.22−7.10 (m, 1H), 6.67−6.27 (br s, 1H), 5.17−5.05 (m, 0.65H), 4.92−4.74 (m, 0.35H), 3.75 (s, 3H), 3.13−2.95 (m, 2H), 1.44 (br s, 9H), 1.42 (br s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 154.8 (2C), 149.7, 143.5, 136.2, 127.4, 122.6, 86.4, 82.9, 82.3, 81.3, 60.8 (0.35C), 58.5 (0.65C), 52.7, 28.22 (3C), 28.18 (3C), 20.7; FTIR (neat) cm^{-1} 3317, 2974, 2927, 1735, 1704, 1388, 1365, 1238, 1148, 773, 726; HRMS (ESI) calcd for $C_{21}H_{30}N_3O_6$ $[M + H]^+$ 420.2135, found 420.2136. $[\alpha]^{20}_D$ = −6.3 (*c* 1, $CHCl_3$) for 93% ee.

General Procedure for the Ring Closure. In an oven-dried Schlenk tube (wrapped with aluminum foil to keep light out) under argon, α-hydrazino ester (0.1 mmol) was dissolved in dry dichloromethane (0.5 mL) and treated with Ph_3PAuCl (2.5 mg, 0.005 mmol) and $AgBF_4$ (0.98 mg, 0.005 mmol). The reaction was stirred until completion of the reaction (monitored by TLC), and the mixture was diluted with diethyl ether and filtered over a pad of Celite (eluent = diethyl ether/dichloromethane, 1:1). The crude was concentrated under reduced pressure and analyzed by ^{1}H NMR to determine the selectivity of the cyclization. Purification of the crude mixture gave rise to the cyclized products. In cases where a mixture of five-membered and six-membered heterocycles was obtained, purification was carried out by preparative thin-layer chromatography to afford pure samples. When selectivity of **4a**/**5a** or **6**/**7** was superior to 85:15 in favor of the five-membered heterocycle (**4a** or **6**), the six-membered cyclic product (**5a** or **7**) was not isolated and only the yields of **4a** and **6** were reported.

*1,2-Dibenzyl 3-Methyl (5Z)-5-Benzylidenepyrazolidine-1,2,3-tricarboxylate (**Z-4a**).* The compound was purified by preparative thin-layer chromatography (pentane/ethyl acetate, 85:15) and was obtained as a gum. R_f 0.14 (pentane/ethyl acetate, 8:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.21 (m, 7H), 7.20−6.90 (m, 8H), 6.00 (s, 1H), 5.20 (d, *J* = 12 Hz, 1H), 5.14 (d, *J* = 12 Hz, 1H), 5.07 (d, *J* = 12 Hz, 1H), 4.95−4.86 (m, 1H), 4.92 (d, *J* = 12 Hz, 1H), 3.56 (s, 3H), 3.20−3.05 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 156.8, 153.8,

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135.4, 135.3, 132.2, 128.6−128.1 (15C), 127.2, 116.3, 68.9, 68.6, 57.4, 52.6, 36.1; HRMS (ESI) calcd for $C_{28}H_{26}N_2O_6Na$ $[M + Na]^+$ 509.1689, found 509.1692.

*1,2-Dibenzyl 3-Methyl (5Z)-5-Benzylidenepyrazolidine-1,2,3-tricarboxylate (**E-4a**).* The compound was purified by preparative thin-layer chromatography (pentane/ethyl acetate, 85:15) and was obtained as a colorless oil. R_f 0.25 (pentane/ethyl acetate, 85:15); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44−7.16 (m, 15H), 7.04 (s, 1H), 5.33 (d, J = 12.6 Hz, 1H), 5.27 (d, J = 12.6 Hz, 1H), 5.21 (d, J = 12.6 Hz, 1H), 5.17 (d, J = 12.6 Hz, 1H), 5.12 (dd, J = 7.0 Hz, J = 3.5 Hz, 1H), 3.62 (s, 3H), 3.33−3.20 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 156.5, 154.3, 136.2, 135.9, 135.5, 133.8, 128.7−128.0 (14C), 126.9, 114.7, 68.9, 68.4, 58.6, 52.8, 34.5; FTIR (neat) cm^{-1} 3061, 3032, 2951, 1715, 1486, 1387, 1286, 1210, 1067, 1025, 911, 751, 694; HRMS (ESI) calcd for $C_{28}H_{26}N_2O_6Na$ $[M + Na]^+$ 509.1689, found 509.1685.

*1,2-Dibenzyl 3-Methyl 6-Phenyl-3,4-dihydropyridazine-1,2,3-tricarboxylate (**5a**).* The compound was purified by preparative thin-layer chromatography (pentane/ethyl acetate, 85:15) and was obtained as a colorless oil. R_f 0.16 (pentane/ethyl acetate, 8:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−6.90 (m, 15H), 5.51 (t, J = 4.1 Hz, 1H), 5.30−5.20 (m, 5H), 3.64 (s, 3H), 2.90−2.55 (m, 2H); HRMS (ESI) calcd for $C_{28}H_{26}N_2O_6Na$ $[M + Na]^+$ 509.1689, found 509.1690.

*1,2-Di-tert-butyl 3-Methyl (5Z)-5-Benzylidenepyrazolidine-1,2,3-tricarboxylate (**6a**).* The compound was purified by preparative thin-layer chromatography (pentane/ethyl acetate, 85:15) and was obtained as a colorless oil. R_f 0.37 (pentane/ethyl acetate, 85:15); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, J = 7.4 Hz, 2H), 7.28 (app t, J = 7.4 Hz, 2H), 7.18 (t, J = 7.3 Hz, 1H), 6.02 (s, 1H), 4.89 (dd, J = 8.4 Hz, J = 4.6 Hz, 1H), 3.76 (s, 3H), 3.26−3.11 (m, 2H), 1.57 (s, 9H), 1.24 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 155.7, 152.1, 136.3, 133.1, 128.3 (2C), 128.0 (2C), 126.9, 114.8, 82.6, 82.1, 56.8, 52.7, 36.6, 28.2 (3C), 27.7 (3C); FTIR (neat) cm^{-1} 2977, 2931, 1731, 1711, 1363, 1304, 1151; HRMS (ESI) calcd for $C_{22}H_{30}N_2O_6Na$ $[M + Na]^+$ 441.2002, found 441.2003; $[\alpha]^{20}_D$ = −73 (c 1, $CHCl_3$) for 93% ee. Enantiomeric excess of **6a** has been determined by HPLC analysis employing a chiral OD-H column (heptane/2-propanol, 95:5, 1.0 mL/min), t_R = 7.23 min for the major enantiomer and t_R = 8.49 min for the minor enantiomer.

*1,2-Di-tert-butyl 3-Methyl (5Z)-5-(4-Methylbenzylidene)-pyrazolidine-1,2,3-tricarboxylate (**6b**).* The compound was purified by preparative thin-layer chromatography (pentane/ethyl acetate, 85:15) and was obtained as a colorless oil. R_f 0.29 (pentane/ethyl acetate, 85:15); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, J = 7.9 Hz, 2H), 7.06 (d, J = 7.9 Hz, 2H), 5.97 (s, 1H), 4.85 (dd, J = 8.7 Hz, J = 4.6 Hz, 1H), 3.74 (s, 3H), 3.30−3.12 (m, 2H), 2.32 (s, 3H), 1.54 (s, 9H), 1.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 155.9, 152.3, 136.7, 133.4, 132.3, 128.7 (2C), 128.3 (2C), 115.0, 82.5, 82.1, 56.8, 52.7, 36.6, 28.3 (3C), 27.8 (3C), 21.4; FTIR (neat) cm^{-1} 3056, 2986, 1744, 1711, 1421, 1368, 1266, 1147, 894, 739, 702; HRMS (ESI) calcd for $C_{23}H_{32}N_2O_6Na$ $[M + Na]^+$ 455.2158, found 455.2156; $[\alpha]^{20}_D$ = −61.3 (c 1, $CHCl_3$) for 93% ee.

*1,2-Di-tert-butyl 3-Methyl (5Z)-5-(3-Methylbenzylidene)-pyrazolidine-1,2,3-tricarboxylate (**6c**).* The compound was purified by preparative thin-layer chromatography (pentane/ethyl acetate, 85:15) and was obtained as a colorless oil. R_f 0.29 (pentane/ethyl acetate, 85:15); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.30 (m, 2H), 7.16 (t, J = 7.6 Hz, 1H), 7.00 (d, J = 7.6 Hz, 1H), 5.98 (s, 1H), 4.89 (dd, J = 8.7 Hz, J = 4.6 Hz, 1H), 3.75 (s, 3H), 3.24−3.10 (m, 2H), 2.32 (s, 3H), 1.56 (s, 9H), 1.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 155.9, 152.2, 137.3, 136.2, 132.9, 128.9, 127.9, 127.8, 125.6, 114.8, 82.5, 82.1, 56.7, 52.7, 36.7, 28.3 (3C), 27.8 (3C), 21.6; FTIR (neat) cm^{-1} 3047, 2974, 2931, 1736, 1712, 1365, 1298, 1242, 1148, 730, 694; HRMS (ESI) calcd for $C_{23}H_{32}N_2O_6Na$ $[M + Na]^+$ 455.2158, found 455.2156; $[\alpha]^{20}_D$ = −46.2 (c 1, $CHCl_3$) for 93% ee.

*1,2-Di-tert-butyl 3-Methyl (5Z)-5-(2-Methylbenzylidene)-pyrazolidine-1,2,3-tricarboxylate (**6d**).* The compound was purified by preparative thin-layer chromatography (pentane/ethyl acetate, 85:15) and was obtained as a colorless oil. R_f 0.27 (pentane/ethyl acetate, 85:15); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58−7.43 (m, 1H), 7.15−7.04 (m, 3H), 6.05 (s, 1H), 4.91 (dd, J = 8.7 Hz, J = 4.1 Hz, 1H), 3.74 (s, 3H), 3.34−3.07 (m, 2H), 2.29 (s, 3H), 1.56 (s, 9H), 1.14 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 155.8, 151.7, 135.5, 135.4, 133.2, 129.8, 127.7, 126.8, 125.4, 111.9, 82.5, 81.7, 56.8, 52.5, 36.5, 28.2 (3C), 27.5 (3C), 20.0; FTIR (neat) cm^{-1} 3047, 2974, 2931, 1736, 1712, 1365, 1298, 1242, 1148, 730, 694; HRMS (ESI) calcd for $C_{23}H_{32}N_2O_6Na$ $[M + Na]^+$ 455.2158, found 455.2155; $[\alpha]^{20}_D$ = −38.3 (c 0.5, $CHCl_3$) for 93% ee. Enantiomeric excess of **6d** has been determined by HPLC analysis employing a chiral OD-H column (heptane/2-propanol, 95:5, 1.0 mL/min), t_R = 6.36 min for the major enantiomer and t_R = 10.16 min for the minor enantiomer.

*1,2-Di-tert-butyl 3-Methyl (5Z)-5-(4-tert-Butylbenzylidene)-pyrazolidine-1,2,3-tricarboxylate (**6e**).* The compound was purified by preparative thin-layer chromatography (pentane/ethyl acetate, 85:15) and was obtained as a 85:15 mixture of colorless oils **6e**(A)/**7e**(B). R_f 0.30 (pentane/ethyl acetate, 85:15); ^{1}H NMR (300 MHz, $CDCl_3$) δ meaningful data: 7.45 (d, J = 8.4 Hz, 1H, A), 7.27 (d, J = 8.4 Hz, 1H, A), 5.98 (s, 1H, A), 5.45−5.35 (m, 1H, B), 5.28−5.20. (m, 1H, B), 4.85 (dd, J = 8.7 Hz, J = 4.9 Hz, 1H; A), 3.74 (s, 3H, A), 3.19−3.09 (m, 2H, A), 2.75−2.50 (m, 2H, B), 1.59 (s, 3H, A), 1.30 (s, 9H, A), 1.20 (s, 9H, A); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 155.7, 152.1, 149.8, 133.3, 132.4, 127.9 (2C), 124.8 (2C), 114.7, 82.4, 81.9, 56.7, 52.6, 36.4, 34.5, 31.2 (3C), 28.2 (3C), 27.5 (3C); FTIR (neat) cm^{-1} 2970, 2931, 2868, 1739, 1716, 1356, 1290, 1152; HRMS (ESI) calcd for $C_{26}H_{38}N_2O_6Na$ $[M + Na]^+$ 497.2628, found 497.2628.

*1,2-Di-tert-butyl 3-Methyl (5Z)-5-(4-Fluorobenzylidene)-pyrazolidine-1,2,3-tricarboxylate (**6f**).* The compound was purified by preparative thin-layer chromatography (pentane/ethyl acetate, 85:15) and was obtained as a colorless oil. R_f 0.24 (pentane/ethyl acetate, 85:15); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (dd, J = 8.5 Hz, J = 5.5 Hz, 2H), 6.94 (app t, J = 8.8 Hz, 2H), 5.97 (s, 1H), 4.85 (dd, J = 8.7 Hz, J = 4.6 Hz, 1H), 3.74 (s, 3H), 3.25−3.05 (m, 2H), 1.54 (s, 9H), 1.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 161.5 (1C, J = 247 Hz), 155.5, 152.0, 132.8 (J = 1.8 Hz), 132.3 (J = 3.4 Hz), 129.7 (J = 7.8 Hz, 2C), 114.8 (2C, J = 21 Hz), 113.7, 82.5, 82.2, 56.7, 52.8, 36.4, 28.2 (3C), 27.7 (3C); FTIR (neat) cm^{-1} 3056, 2982, 1740, 1715, 1503, 1364, 1262, 1221, 1151, 1017, 853, 740, 698; HRMS (ESI) calcd for $C_{22}H_{29}N_2O_6FNa$ $[M + Na]^+$ 459.1907, found 459.1908; $[\alpha]^{20}_D$ = −73.5 (c 1, $CHCl_3$) for 93% ee.

*1,2-Di-tert-butyl 3-Methyl (5Z)-5-(4-Methoxybenzylidene)-pyrazolidine-1,2,3-tricarboxylate (**6g**).* The compound was purified by preparative thin-layer chromatography (pentane/ethyl acetate, 8:2) and was obtained as a colorless oil. **6g** proves to be rather unstable and decomposes slowly in chloroform-d solution. R_f 0.23 (pentane/ethyl acetate, 85:15); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, J = 8.7 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 5.96 (s, 1H), 4.83 (dd, J = 8.7 Hz, J = 4.9 Hz, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 3.23−3.01 (m, 2H), 1.54 (s, 9H), 1.28 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 158.6, 152.4, 131.4, 130.8, 129.6 (2C), 128.9, 114.8, 113.5 (2C), 82.5, 82.1, 56.9, 55.4, 52.7, 36.5, 28.3 (3C), 27.9 (3C); FTIR (neat) cm^{-1} 3048, 2974, 2923, 2848, 1735, 1708, 1692, 1511, 1365, 1294, 1242, 1140, 1025; HRMS (ESI) calcd for $C_{23}H_{32}N_2O_7Na$ $[M + Na]^+$ 471.2107, found 471.2106.

*1,2-Di-tert-butyl 3-Methyl 6-(4-Methoxyphenyl)-3,4-dihydropyridazine-1,2,3-tricarboxylate (**7g**).* The compound was purified by preparative thin-layer chromatography (pentane/ethyl acetate, 85:15) to afford **7g** as a colorless oil which proves to be unstable in chloroform-d solution. R_f 0.35 (pentane/ethyl acetate, 8:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55−7.30 (m, 2H), 6.84 (app d, J = 8.7 Hz, 2H), 5.35 (t, J = 5.6 Hz, 1H), 5.25−5.15 (m, 1H), 3.81 (s, 3H), 3.74 (s, 3H), 2.77−2.63 (m, 1H), 2.55 (dt, J = 18.2 Hz, J = 3.6 Hz, 1H), 1.54 (s, 9H), 1.22 (s, 9H).

*1,2-Di-tert-butyl 3-Methyl (5Z)-5-(3-Methoxybenzylidene)-pyrazolidine-1,2,3-tricarboxylate (**6h**).* The compound was purified by preparative thin-layer chromatography (pentane/ethyl acetate, 85:15) and was obtained as a colorless oil. R_f 0.34 (pentane/ethyl acetate, 85:15); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19−7.13 (m, 2H), 7.07 (br s, 1H), 6.76−6.70 (m, 1H), 5.98 (s, 1H), 4.86 (dd, J = 8.7 Hz, J = 4.6 Hz, 1H), 3.78 (s, 3H), 3.73 (s, 3H), 3.25−3.05 (m, 2H), 1.54 (s, 9H), 1.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 159.6,

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155.7, 152.2, 137.8, 133.5, 128.9, 120.9, 114.8, 114.2, 112.5, 82.6, 82.1, 56.8, 55.4, 52.7, 36.6, 28.3 (3C), 27.8 (3C); FTIR (neat) cm^{-1} 2977, 2932, 1735, 1710, 1599, 1435, 1391, 1296, 1248, 1145, 1030, 751; HRMS (ESI) calcd for $C_{23}H_{32}N_2O_7Na$ $[M + Na]^+$ 471.2107, found 471.2104; $[\alpha]^{20}_D = -89.5$ (c 1, $CHCl_3$) for 93% ee.

*1,2-Di-tert-butyl 3-Methyl (5Z)-5-(4-Nitrobenzylidene)-pyrazolidine-1,2,3-tricarboxylate (**6i**).* The compound was purified by chromatography on silica gel (pentane/ethyl acetate, 7:3) and was obtained as a colorless oil. R_f 0.17 (pentane/ethyl acetate, 8:2); ^1H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, J = 9.0 Hz, 2H), 7.63 (d, J = 9.0 Hz, 2H), 6.07 (s, 1H), 4.91 (dd, J = 8.4 Hz, J = 4.1 Hz, 1H), 3.74 (s, 3H), 3.31−3.15 (m, 2H), 1.56 (s, 9H), 1.29 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 155.3, 151.4, 145.9, 143.3, 137.0, 128.5 (2C), 123.3 (2C), 112.1, 82.9, 82.8, 56.4, 52.7, 36.8, 28.2 (3C), 27.8 (3C); FTIR (neat) cm^{-1} 3049, 2978, 1739, 1712, 1515, 1365, 1341, 1262, 1148, 1022, 730, 698; HRMS (ESI) calcd for $C_{22}H_{29}N_3O_8Na$ $[M + Na]^+$ 486.1852, found 486.1851; $[\alpha]^{20}_D = -178$ (c 1, $CHCl_3$) for 93% ee.

*1,2-Di-tert-butyl 3-Methyl (5Z)-5-(4-Trifluoromethylbenzylidene)-pyrazolidine-1,2,3-tricarboxylate (**6j**).* The compound was purified by chromatography on silica gel (pentane/ethyl acetate, 85:15) and was obtained as a colorless oil. R_f 0.24 (pentane/ethyl acetate, 85:15); ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, J = 7.9 Hz, 2H), 7.50 (d, J = 7.9 Hz, 2H), 6.03 (s, 1H), 4.89 (dd, J = 8.6 Hz, J = 4.2 Hz, 1H), 3.74 (s, 3H), 3.30−3.10 (m, 2H), 1.55 (s, 9H), 1.27 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 155.4, 151.6, 140.0, 135.4, 130.2, 128.2 (2C), 124.7 (2C), 113.1, 82.7, 82.5, 56.5, 52.6, 36.6, 28.2 (3C), 27.6 (3C); FTIR (neat) cm^{-1} 2978, 2933, 1713, 1615, 1478, 1367, 1322, 1146, 1113, 1066, 1017, 849, 756; HRMS (ESI) calcd for $C_{23}H_{29}N_2O_6F_3Na$ $[M + Na]^+$ 509.1875, found 509.1874; $[\alpha]^{20}_D = -76.0$ (c 1, $CHCl_3$) for 93% ee.

1-Benzoyl-3-benzyl-4,5-dihydro-1*H*-pyrazole-5-carboxylic Acid Methyl Ester (10). A 4 N HCl dioxane solution (1.3 mL) was added to aza-proline derivative **6a** (33 mg, 0.079 mmol), and the reaction mixture was stirred at room temperature for 1 h. The volatiles were evaporated, and the crude product was dissolved in dichloromethane and washed with a saturated aqueous solution of $NaHCO_3$. The aqueous phase was extracted three times with dichloromethane, and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. ^1H NMR analysis of the crude showed clean formation of pyrazoline **9**, which was used without further purification in the subsequent step. In a round-bottom flask, benzoyl chloride (14 μL, 0.12 mmol) and triethylamine (21.5 μL, 0.158 mmol) were successively added to a solution of pyrazoline **9** in dichloromethane (0.9 mL). After 2 h of stirring at room temperature, water was added to the reaction mixture, and the aqueous phase was extracted three times with dichloromethane, dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the crude by silica gel column chromatography (pentane/EtOAc = 7:3) afforded **10** in 56% overall yield (14 mg) as a colorless oil. R_f 0.27 (pentane/ethyl acetate, 7:3); ^1H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J = 7.7 Hz, 2H), 7.56−7.20 (m, 8H), 5.03 (dd, J = 12.3 Hz, J = 6.1 Hz, 1H), 3.77 (s, 3H), 3.73 (s, 2H), 3.09 (dd, J = 18.2 Hz, J = 12.3 Hz, 1H), 2.79 (dd, J = 18.2 Hz, J = 6.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 166.7, 157.8, 135.5, 131.4, 130.1 (2C), 129.1 (2C), 128.9 (2C), 127.8 (2C), 127.4, 58.8, 52.8, 38.3, 36.7; FTIR (neat) cm^{-1} 3059, 3028, 2952, 2923, 2849, 1744, 1630, 1574, 1450, 1423, 1316, 1205, 1177, 1027, 790, 746, 697, 671; HRMS (ESI) calcd for $C_{19}H_{19}N_2O_3$ $[M + H]^+$ 323.1396, found 323.1392; $[\alpha]^{20}_D = 53.2$ (c 1, $CHCl_3$).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H, ^{13}C NMR and relevant NOE spectra as well as HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Hashmi, A. S. K.; Toste, F. D., Eds. *Modern Gold Catalyzed Synthesis*; Wiley-VCH: Weinheim, 2012.

(2) For reviews, see: (a) Lu, B.-L.; Dai, L.; Shi, M. *Chem. Soc. Rev.* **2012**, *41*, 3318−3339. (b) Pradal, A.; Toullec, P. Y.; Michelet, V. *Synthesis* **2011**, 1501−1514. (c) Boorman, T. C.; Larrosa, I. *Chem. Soc. Rev.* **2011**, *40*, 1910−1925. (d) Bandini, M. *Chem. Soc. Rev.* **2011**, *40*, 1358−1367. (e) Huang, H.; Zhou, Y.; Liu, H. *Beilstein J. Org. Chem* **2011**, *7*, 897−936. (f) Rudolph, M.; Hashmi, S. K. *Chem. Commun.* **2011**, *47*, 6536−6544. (g) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994−2009. (h) Alcaide, B.; Almendros, P.; Alonso, J. M. *Org. Biomol. Chem.* **2011**, *9*, 4405−4416. (i) Corma, A.; Leyva-Pérez, A.; Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657−1712. (j) Hashmi, A. S. K. *Pure Appl. Chem.* **2010**, *82*, 657−668. (k) Sengupta, S.; Shi, X. *ChemCatChem* **2010**, *2*, 609−619. (l) Hashmi, A. S. K.; Bührle, M. *Aldrichimica Acta* **2010**, *43*, 27−33. (m) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351−3378. (n) Kirsch, S. F. *Synthesis* **2008**, 3183−3204. (o) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326−3350. (p) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885−3903. (q) Skouta, R.; Li, C.-J. *Tetrahedron* **2008**, *64*, 4917−4938. (r) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266−3325. (s) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239−3265. (t) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395−3442. (u) Muzart, J. *Tetrahedron* **2008**, *64*, 5815−5849. (v) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410−3449. (w) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180−3211. (x) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333−346. (y) Widenhoefer, R. A.; Han, X. *Eur. J. Org. Chem.* **2006**, 4555−4563. (z) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896−7936.

(3) For reviews dealing with gold catalysis in total synthesis, see: (a) Rudolph, M.; Hashmi, S. K. *Chem. Soc. Rev.* **2012**, *41*, 2448−2462. (b) Krause, N.; Aksin-Artok, Ö; Asikainen, M.; Breker, V.; Deutsch, C.; Erdsack, J.; Fan, H.-T.; Gockel, B.; Minkler, S.; Poonoth, M.; Sawama, Y.; Sawama, Y.; Sun, T.; Volz, F.; Winter, C. *J. Organomet. Chem.* **2012**, *704*, 1−8. (c) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766−1775.

(4) For the use of hydrazines in gold-catalyzed transformations, see: (a) Naoe, S.; Suzuki, Y.; Hirano, K.; Inaba, Y.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2012**, *77*, 4907−4916. (b) Patil, N. T.; Lakshmi, G. V. V. P.; Sridhar, B.; Patra, S.; Bhadra, M. P.; Patra, C. R. *Eur. J. Org. Chem.* **2012**, 1790−1799. (c) Suzuki, Y.; Oishi, S.; Takei, Y.; Yasue, M.; Misu, R.; Naoe, S.; Hou, Z.; Kure, T.; Nakanishi, I.; Ohno, H.; Hirasawa, A.; Tsujimoto, G.; Fujii, N. *Org. Biomol. Chem.* **2012**, *10*, 4907−4915. (d) Suzuki, Y.; Naoe, S.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2012**, *14*, 326−329. (e) Capretto, D. A.; Brouwer, C.; Poor, C. B.; He, C. *Org. Lett.* **2011**, *13*, 5842−5845. (f) Kinjo, R.; Donnadieu, B.; Bertrand, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 5560−5563. (g) Hashmi, A. S. K.; Bührle, M.; Wölfle, M.; Rudolph, M.; Wieteck, M.; Rominger, F.; Frey, W. *Chem.—Eur. J.* **2010**, *16*, 9846−9854. (h) Patil, N. T.; Konala, A. *Eur. J. Org. Chem.* **2010**, 6831−6839.

(5) (a) Coeffard, V.; Desmarchelier, A.; Morel, B.; Moreau, X.; Greck, C. *Org. Lett.* **2011**, *13*, 5778−5781. (b) Desmarchelier, A.; Yalgin, H.; Coeffard, V.; Moreau, X.; Greck, C. *Tetrahedron Lett.* **2011**, *52*, 4430−4432. (c) Desmarchelier, A.; Marrot, J.; Moreau, X.; Greck,

C. *Org. Biomol. Chem.* **2011**, *9*, 994−997. (d) Kalch, D.; Ait-Youcef, R.; Moreau, X.; Thomassigny, C.; Greck, C. *Tetrahedron: Asymmetry* **2010**, *21*, 2302−2306.
(6) Küchenthal, C.-H.; Maison, W. *Synthesis* **2010**, 719−740.
(7) For a seminal report, see: Mish, M. R.; Guerra, F. M.; Carreira, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 8379−8380.
(8) For selected general catalyzed strategies, see: (a) Sibi, M. P.; Stanley, L. M.; Soeta, T. *Org. Lett.* **2007**, *9*, 1553−1556. (b) Sibi, M. P.; Stanley, L. M.; Soeta, T. *Adv. Synth. Catal.* **2006**, *348*, 2371−2375. (c) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2174−2175. (d) Sibi, M. P.; Stanley, L. M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 8276−8277. (e) Kanemasa, S.; Kanai, T. *J. Am. Chem. Soc.* **2000**, *122*, 10710−10711.
(9) (a) Yang, Q.; Jiang, X.; Ma, S. *Chem.—Eur. J.* **2007**, *13*, 9310−9316. (b) Ma, S.; Jiao, N.; Zheng, Z.; Ma, Z.; Lu, Z.; Ye, L.; Deng, Y.; Chen, G. *Org. Lett.* **2004**, *6*, 2193−2196.
(10) Maity, P.; Lepore, S. D. *Angew. Chem., Int. Ed.* **2011**, *50*, 8338−8341.
(11) (a) Lange, U. E. W.; Baucke, D.; Hornberger, W.; Mack, H.; Seitz, W.; Höffken, H. W. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2648−2653. (b) Liu, B.; Brandt, J. D.; Moeller, K. D. *Tetrahedron* **2003**, *59*, 8515−8523.
(12) For selected syntheses of natural products, see: (a) Tran, K.; Lombardi, P. J.; Leighton, J. L. *Org. Lett.* **2008**, *10*, 3165−3167. (b) Whitlock, G. A.; Carreira, E. M. *Helv. Chim. Acta* **2000**, *83*, 2007−2022. (c) Whitlock, G. A.; Carreira, E. M. *J. Org. Chem.* **1997**, *62*, 7916−7917.
(13) (a) Desmarchelier, A.; Coeffard, V.; Moreau, X.; Greck, C. *Chem.—Eur. J.* **2012**, *18*, 13222−13225. (b) Ait-Youcef, R.; Moreau, X.; Greck, C. *J. Org. Chem.* **2010**, *75*, 5312−5315. (c) Ait-Youcef, R.; Sbargoud, K.; Moreau, X.; Greck, C. *Synlett* **2009**, 3007−3010. (d) Ait-Youcef, R.; Kalch, D.; Moreau, X.; Thomassigny, C.; Greck, C. *Lett. Org. Chem.* **2009**, *6*, 377−380. (e) Kalch, D.; De Rycke, N.; Moreau, X.; Greck, C. *Tetrahedron Lett.* **2009**, *50*, 492−494. (f) Thomassigny, C.; Prim, D.; Greck, C. *Tetrahedron Lett.* **2006**, *47*, 1117−1119.
(14) For relevant reviews on organocatalyzed α-amination, see: (a) Vilaivan, T.; Bhanthumnavin, W. *Molecules* **2010**, *15*, 917−958. (b) Guillena, G.; Ramón, D. J. *Tetrahedron: Asymmetry* **2006**, *17*, 1465−1492. (c) Janey, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4292−4300. (d) Greck, C.; Drouillat, B.; Thomassigny, C. *Eur. J. Org. Chem.* **2004**, 1377−1385.
(15) For seminal works on organocatalyzed α-amination, see: (a) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656−5657. (b) Bøgevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1790−1793.
(16) Discrimination of the 5-*exo*-*dig* product (**4a**) and the 6-*endo*-*dig* heterocycle (**5a**) was performed by ^{1}H NMR analyses since the ethylenic proton in **5a** has a ^{3}J coupling constant with the adjacent $\underline{CH_2}CHCO_2Me$ fragment that is not present in **4a**. Furthermore, NOE experiments allowed us to determine the geometry of (*Z*)-**4a** and (*E*)-**4a**. See Supporting Information for further details.
(17) For a study about the influence of silver additives in gold(I) catalysis, see: Wang, D.; Cai, R.; Sharma, S.; Jirak, J.; Thummanapelli, S. K.; Akhmedov, N. G.; Zhang, H.; Liu, X.; Petersen, J. L.; Shi, X. *J. Am. Chem. Soc.* **2012**, *134*, 9012−9019.
(18) Mézailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133−4136.
(19) Enantiomeric excess of (*R*)-**3a** has been determined by chiral HPLC. See Supporting Information for further details.
(20) Enantiomeric excess of (*R*)-**8** has been determined by chiral HPLC. Transformation into (*R*)-2-*tert*-butoxycarbonylaminopentanoic acid methyl ester allowed us to determine the configuration of the stereogenic center. See experimental part for further details.
(21) (a) Hu, L.; Lan, P.; Song, Q.-L.; Huang, Z.-J.; Sun, P.-H.; Zhuo, C.; Wang, Y.; Xiao, S.; Chen, W.-M. *Eur. J. Med. Chem.* **2010**, *45*, 5943−5949. (b) Girgis, A. S.; Ismail, N. S. M.; Farag, H.; El-Eraky, W. I.; Saleh, D. O.; Tala, S. R.; Katritzky, A. R. *Eur. J. Med. Chem.* **2010**, *45*, 4229−4238. (c) Carrión, M. D.; López Cara, L. C.; Camacho, M. E.; Tapias, V.; Escames, G.; Acuña-Castroviejo, D.; Espinosa, A.; Gallo, M. A.; Entrena, A. *Eur. J. Med. Chem.* **2008**, *43*, 2579−2591. (d) Jun, M. A.; Park, W. S.; Kang, S. K.; Kim, K. Y.; Kim, K. R.; Rhee, S. D.; Bae, M. A.; Kang, N. S.; Sohn, S.-K.; Kim, S. G.; Lee, J. O.; Lee, D. H.; Cheon, H. G.; Kim, S. S.; Ahn, J. H. *Eur. J. Med. Chem.* **2008**, *43*, 1889−1902.
(22) Tanaka, K.; Hagiwara, Y.; Noguchi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7260−7263.
(23) Sasaki, N. A.; Hachimoto, C.; Potier, P. *Tetrahedron Lett.* **1987**, *28*, 6069−6072.