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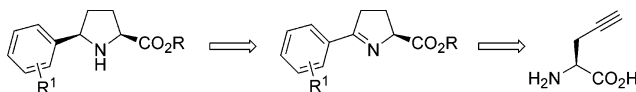
Novel Approach to 5-Substituted Proline Derivatives Using a Silver-Catalyzed Cyclization as the Key Step

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A novel synthetic approach to the synthesis of enantiomerically pure 2,5-disubstituted pyrrolines is described. The methodology involves a Ag-catalyzed 5-*endo-dig* cyclization of enantiopure aryl-substituted acetylene-containing amino acids. It has also been shown that the obtained pyrrolines can be efficiently transformed into the corresponding saturated 5-aryl-substituted proline derivatives.

Substituted prolines in general have gained considerable interest in recent years, which is reflected by the number of stereoselective syntheses of proline derivatives that have been reported in the literature.[1] These nonnatural substituted proline analogues can be considered as conformationally constrained amino acids and have actually been applied in biologically active peptidomimetics as tools for establishing structure–activity relationships.[2] Some of these proline analogues have also been recognized as privileged elements in medicinal chemistry among which the 5-aryl-substituted prolines are the most prominent examples.[3] Within this class of proline analogues, *cis*-5-phenylproline (**1**) has attracted special interest, being a key intermediate in the synthesis of the nonpeptide cholecystokinin antagonist (+)-RP 66803 (Chart 1).[4]

Consequently, a variety of synthetic approaches to *cis*-5-phenylproline (**1**) have been reported in recent litera-

CHART 1. *Cis*-5-phenylproline and (+)-RP 66803
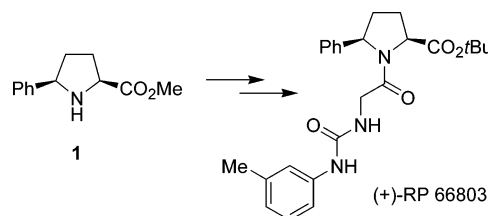
ture.[5] The most prominent synthetic pathway to *cis*-5-aryl-substituted proline analogues **2** relies on the selective ring opening of pyroglutamates such as **4** by organometallic reagents and subsequent ring closure of the resulting ketone,[6] leading to pyrrolines **3** (R = Et) which can then be selectively hydrogenated to the corresponding *cis*-5-aryl-substituted prolines (Scheme 1).[7]

Building on methodology that has recently been developed in our group,[8,9] we envisaged that the 2,5-disubstituted pyrrolines of type **3** will be accessible starting from optically active propargylglycine **6**.[10] In this approach, the pyrrolines **3** (R = Me) might be obtained

(1) For recent entries, see: (a) Del Valle, J. R.; Goodman, M. *J. Org. Chem.* **2003**, *68*, 3923. (b) Pellegrini, N.; Schmitt, M.; Bourguignon, J.-J. *Tetrahedron Lett.* **2003**, *44*, 6779. (c) Zhang, J.; Wang, W.; Xiong, C.; Hruby, V. J. *Tetrahedron Lett.* **2003**, *44*, 1413. (d) Del Valle, J. R.; Goodman, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 1600. (e) Xia, Q.; Ganem, B. *Tetrahedron Lett.* **2002**, *43*, 1597. (f) Flamant-Robin, C.; Wian, Q.; Chiaroni, A.; Sasaki, N. A. *Tetrahedron Lett.* **2002**, *43*, 10475. (g) Nevalainen, M.; Kauppinen, P. M.; Koskinen, A. M. P. *J. Org. Chem.* **2001**, *66*, 2061. (h) Kamenecka, T. M.; Park, Y.-J.; Lin, L. S.; Lanza, T., Jr.; Hagmann, W. K. *Tetrahedron Lett.* **2001**, *42*, 8571.

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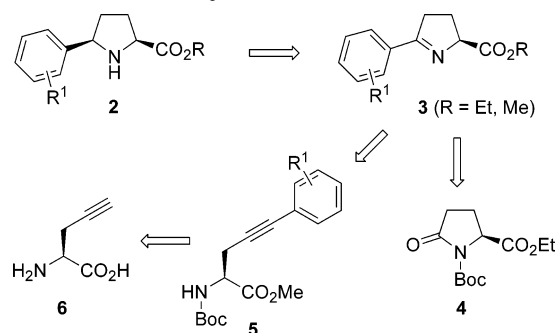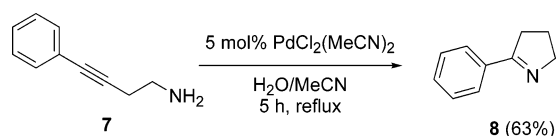
(4) Manfré, F.; Pulicani, J. P. *Tetrahedron: Asymmetry* **1994**, *5*, 235.

(5) (a) Severino, E. A.; Costenaro, E. R.; Garcia, A. L. L.; Correia, C. R. D. *Org. Lett.* **2003**, *5*, 305. (b) Davis, F. A.; Fang, T.; Goswami, R. *Org. Lett.* **2002**, *4*, 1599. (c) Momotake, A.; Togo, H.; Yokoyama, M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1193. (d) Haddad, M.; Imogaï, H.; Larchevêque, M. *J. Org. Chem.* **1998**, *63*, 5680. (e) van Betsbrugge, J.; van den Nest, W.; Verheyden, P.; Tourwé, D. *Tetrahedron* **1998**, *54*, 1753.

(6) (a) Molina, M. T.; Valle, C. D.; Escribano, A. M.; Ezquerra, J.; Pedregal, C. *Tetrahedron* **1993**, *49*, 3801. (b) Ezquerra, J.; Mendoza, J. D.; Pedregal, C.; Ramirez, C. *Tetrahedron Lett.* **1992**, *33*, 5589. (c) Rudolph, A. C.; Machauer, R.; Martin, S. F. *Tetrahedron Lett.* **2004**, *45*, 4895.

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SCHEME 1. Retrosynthetic Outline

SCHEME 2. Pd-Catalyzed Formation of Cyclic Imine 8

SCHEME 3. Pd-Catalyzed Pyrroline Formation[a]

[a] Key: (a) iodobenzene, $PdCl_2(PPh_3)_2$, CuI, Et_2NH, Et_2O, rt, 2 h. (b) i. HCl, EtOAc, rt, 3 h; ii. aq. NH_3, dioxane/H_2O (1:1 v/v), rt, 15 min. (c) $PdCl_2(MeCN)_2$, MeCN, reflux, 1 h.

TABLE 1. Evaluation of Several Metal-Catalysts

entry	catalyst[a]	time (h)	yield of 11 (%)[b]
1	$NaAuCl_4$	0.5	58
2	AgOTf	1	67
3	$Cu(OTf)_2$	1	48
4	$ZnCl_2$	6	65
5	$AlCl_3$	24	36
6	$Sn(OTf)_2$	>24	n.d.
7	$Sc(OTf)_3$	>24	n.d.
8	$Zn(OTf)_2$	>24	n.d.

[a] All reactions were conducted in refluxing MeCN using 10 mol % of the indicated catalyst. [b] Isolated yield calculated from precursor 10.

from the protected precursors 5 via cleavage of the Boc-group, followed by a metal-catalyzed intramolecular 5-*endo-dig* cyclization as the key step. Compounds 5, in turn, should be easily accessible from propargylglycine 6 by using a Pd-catalyzed Sonogashira coupling to introduce a range of aromatic groups.[11] Metal-catalyzed intramolecular additions of amines onto substituted acetylenes have already been reported in the literature using relatively simple (substituted) alkynylamines as the cyclization precursors.[12] A representative example is the intramolecular aminopalladation of alkyne 7, which upon treatment with $PdCl_2(MeCN)_2$ led to the five-membered cyclic imine 8 in a reasonable yield (Scheme 2).[12b]

This literature precedent, in combination with the facile access to enantiopure propargylglycine 6, inspired us to use it in the synthesis of the 2,5-disubstituted pyrrolines 3 (R = Me). This sequence might then eventually serve as a novel approach to *cis*-5-phenylproline (1) and related 5-aryl-substituted proline analogues.

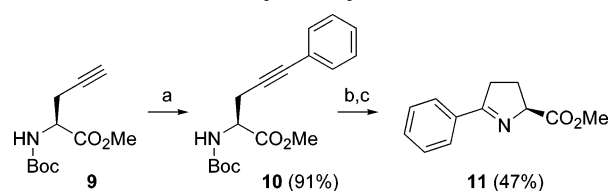To investigate the feasibility of pyrroline formation via a similar Pd-catalyzed cyclization, amino acid 10 was synthesized from the enantiomerically pure propargylglycine derivative 9[8a] via a Sonogashira-type coupling[13] with iodobenzene affording cyclization precursor 10 in 91% yield (Scheme 3).

Subsequent cleavage of the Boc-group of precursor 10 generated the corresponding free amino ester, which was immediately exposed to $PdCl_2(MeCN)_2$ in refluxing acetonitrile. We were pleased to find that these conditions led to the rapid formation of pyrroline 11 in 47% yield after column chromatography. Furthermore, we proved using chiral HPLC (Chiralcel OD) that no (partial) racemization had taken place during the whole synthetic sequence. Interestingly, the formation of pyrroline 11 could also be accomplished by refluxing the intermediate free amino ester in acetonitrile, without the presence of the Pd-catalyst, albeit that the reaction did not go to completion even after prolonged reaction times of over 24 h.

This observation prompted us to investigate the formation of pyrroline 11 more carefully to optimize the cyclization reaction. Therefore, several other Lewis acidic metal catalysts were used in this reaction and compared in terms of yield of 11 and reaction times. As can be inferred from Table 1, some of the investigated Lewis acids were very reactive catalysts, leading to the rapid formation of pyrroline 11 (entries 1−3). From this group of metal salts, $NaAuCl_4$ had previously been shown to be an excellent catalyst in similar cycloisomerizations.[12c] In our case, however, this catalyst gave a fast reaction, but turned out to be less effective affording 11 in a yield of 58% (entry 1). The use of AgOTf also led to a rapid formation of pyrroline 11, which was isolated in an even higher yield of 67% (entry 2).

Using $ZnCl_2$ as the catalyst, 11 was obtained in a similar yield of 65%, but the reaction required more time

(8) (a) van Esseveldt, B. C. J.; van Delft, F. L.; de Gelder, R.; Rutjes, F. P. J. T. *Org. Lett.* 2003, 5, 1717. (b) van Esseveldt, B. C. J.; van Delft, F. L.; Smits, J. M. M.; de Gelder, R.; Rutjes, F. P. J. T. *Synlett* 2003, 2354. (c) van Esseveldt, B. C. J.; van Delft, F. L.; Smits, J. M. M.; de Gelder, R.; Schoemaker, H. E.; Rutjes, F. P. J. T. *Adv. Synth. Catal.* 2004, 346, 823.

(9) (a) Wolf, L. B.; Tjen, K. C. M. F.; ten Brink, H. T.; Blaauw, R. H.; Hiemstra, H.; Schoemaker, H. E.; Rutjes, F. P. J. T. *Adv. Synth. Catal.* 2002, 344, 70. (b) Wolf, L. B.; Tjen, K. C. M. F.; Rutjes, F. P. J. T.; Hiemstra, H.; Schoemaker, H. E. *Tetrahedron Lett.* 1998, 39, 5081.

(10) This trifunctional amino acid (2-amino-4-pentynoic acid) is commercially available but in our group also readily prepared via a chemoenzymatic procedure that has been developed in collaboration with DSM Research (Geleen, The Netherlands): (a) Wolf, L. B.; Sonke, T.; Tjen, K. C. M. F.; Kaptein, B.; Broxterman, Q. B.; Schoemaker, H. E.; Rutjes, F. P. J. T. *Adv. Synth. Catal.* 2001, 343, 662. (b) Sonke, T.; Kaptein, B.; Boesten, W. H. J.; Broxterman, Q. B.; Kamphuis, J.; Formaggio, F.; Toniolo, C.; Rutjes, F. P. J. T.; Schoemaker, H. E. In *Stereoselective Biocatalysis*; Patel, R. N., Ed.; Marcel Dekker: New York, 2000; p 23.

(11) Rutjes, F. P. J. T.; Wolf, L. B.; Schoemaker, H. E. *J. Chem. Soc., Perkin Trans. 1* 2000, 4197.

(12) (a) Campi, E. M.; Jackson, W. R. *J. Organomet. Chem.* 1996, 523, 205. (b) Fukuda, Y.; Matsubara, S.; Utimoto, K. *J. Org. Chem.* 1991, 56, 5812. (c) Fukuda, Y.; Utimoto, K. *Synthesis* 1991, 975. (d) Jacobi, P. A.; Liu, H. *J. Org. Chem.* 2000, 65, 7676 and references therein.

(13) The Pd-catalyzed functionalization of propargylglycine derivatives with aromatic groups under Sonogashira-type conditions has already been described: Crisp, G. T.; Robinson, T. A. *Tetrahedron* 1992, 48, 3239.

to go to completion (entry 4). In addition, $Cu(OTf)_2$ appeared to be an equally effective catalyst compared to the initially used Pd(II)-catalyst (entry 3). In $AlCl_3$, a slow cycloisomerization was observed affording pyrroline **11** in a somewhat lower yield of 36% (entry 5). In all other cases, the reaction did not go to completion, even after prolonged reaction times of over 24 h (entries 6−8) so that the yield eventually was not determined.
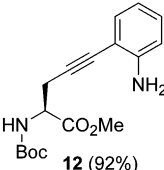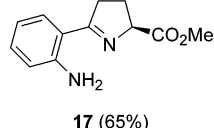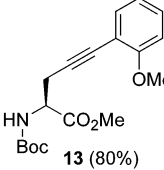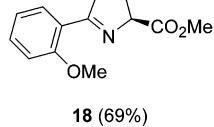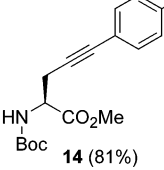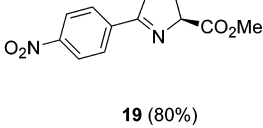
By analyzing these results, we concluded that AgOTf would be the catalyst of choice in the synthesis of other pyrrolines. Considering the high reactivity of the Ag-catalyst, we reasoned that lowering the reaction temperature might benefit the formation and thereby the yield of pyrroline **11**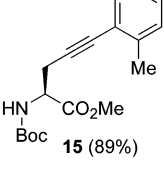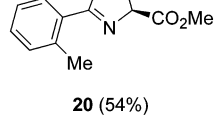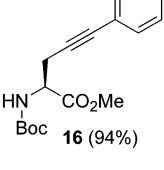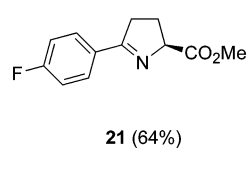. To verify this reasoning, we converted the Boc-protected precursor **10** in the corresponding free amino ester which was then subjected to 10 mol % of AgOTf in MeCN at room temperature. Indeed, these mild conditions resulted in the formation of **11** in an improved yield of 72%, although the reaction needed more time to go to completion. More importantly, a similar increase in yield upon lowering the temperature to room temperature was not observed using $NaAuCl_4$ as the catalyst.

These optimized conditions clearly have advantages over the initially proposed Pd-catalyzed reactions. First of all, the reaction proceeds readily at room temperature, thus providing mild reaction conditions. Furthermore, in comparison with our previous cyclization examples, there is no protection of the nitrogen atom necessary.[8,9] Pleased with this result, we set out to gain insight in the scope and limitations of the observed cycloisomerization. Therefore, we prepared a variety of cyclization precursors via Sonogashira couplings of propargylglycine derivative **9** with several substituted aryl iodides. The substituted acetylenes **12−16** were thus obtained in good yields and, after generation of the corresponding amino esters, subjected to the Ag-catalyst in MeCN at room temperature (Table 2). Subjection of the amino ester derived from precursor **12** to the Ag-catalyst led to the formation of the corresponding pyrroline **17** in 65% yield (entry 1).

Likewise, precursor **13**, substituted with an electron-donating *o*-methoxy group, could be conveniently converted into pyrroline **18** in 69% yield (entry 2). Acetylene **14** bearing an electron-withdrawing *p*-nitro substituent underwent, after generation of the amino ester, a smooth cyclization affording **19** in 80% yield (entry 3), indicating that the cyclization reaction is not very sensitive to electronic effects. The sterically more hindered precursor **15** underwent cyclization to pyrroline **20** in a somewhat lower yield of 54% (entry 4). Finally, acetylene **16** containing the pharmaceutically relevant *p*-fluorophenyl substituent could also be converted into pyrroline **21** in a reasonable yield of 64% (entry 5).

With the successful cyclization conditions in hand, we decided to extend this methodology to the synthesis of similar pyrrolines substituted with biologically interesting pyridyl moieties. Therefore, propargylglycine derivative **9** was first coupled under the Sonogashira conditions with 2- and 3-iodopyridine to afford the pyridyl-substituted precursors **22** and **23** in 85 and 91% yield, respectively (Scheme 4). First, precursor **22** was deprotected in a quantitative fashion, after which the initial liberation of the free amine using aqueous NH_3 turned out to be troublesome. Fortunately, this problem could be overcome by switching to other conditions, that is, Et_3N in chloro-

TABLE 2. Scope of Ag-Catalyzed Pyrroline Formation

| entry	precursor (yield)[a]	pyrroline (yield)[a]
1	**12** (92%)	**17** (65%)
2	**13** (80%)	**18** (69%)
3	**14** (81%)	**19** (80%)
4	**15** (89%)	**20** (54%)
5	**16** (94%)	**21** (64%)

[a] Isolated yield after column chromatography.

SCHEME 4. Ag-Catalyzed Formation of Pyridyl-Substituted Pyrrolines[a]

24: R = Me (38%)
25: R = H

22: X = N; Y = CH (85%)
23: X = CH; Y = N (91%)

26 (69%)
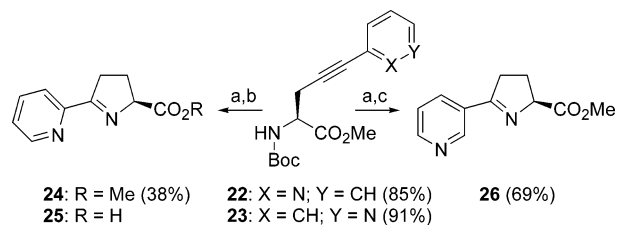
[a] Key: (a) *i*. HCl, EtOAc, rt, 3 h; *ii*. Et_3N, $CHCl_3$, rt, 30 min. (b) AgOTf, MeCN, reflux, 1 h. (c) AgOTf, MeCN, rt, 6 h.

form, leading to a smooth formation of the free amino ester of **22**. Subjection of this amino ester to the Ag-catalyst at room temperature did not give any reaction; however, heating at reflux temperature led to a rapid formation of pyrroline **24** in a somewhat lower yield of 38%. Interestingly, pyrroline **24** is an ester derivative of the natural product pyrimine (**25**), an Fe(II)-binding agent which has been isolated from the species *Pseudomonas* GH.[14]

Likewise, precursor **23** was deprotected and the resulting amino ester already underwent, in contrast to the

SCHEME 5. Ag-Catalyzed Cyclizations of Homologous Cyclization Precursors[a]
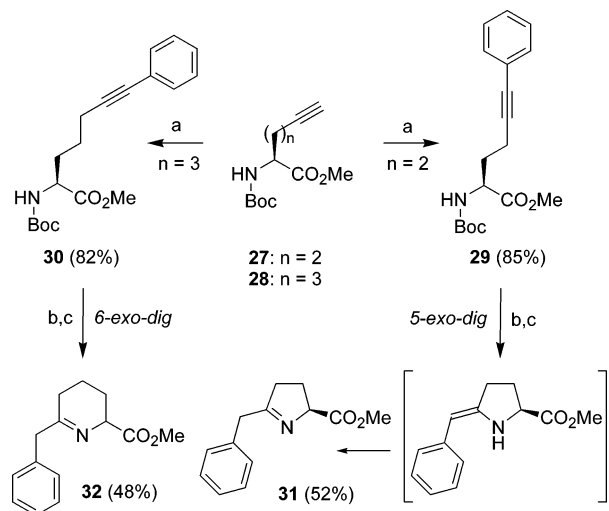
[a] Key: (a) iodobenzene, PdCl$_2$(PPh$_3$)$_2$, CuI, Et$_2$NH, Et$_2$O, rt, 2 h. (b) *i*. HCl, EtOAc, rt, 3 h; *ii*. aq. NH$_3$, dioxane/H$_2$O (1:1 v/v), rt, 15 min. (c) AgOTf, MeCN, reflux, 1 h.

2-pyridyl-substituted amino ester, cycloisomerization at room temperature affording pyrroline **26** in a yield of 69%.

Encouraged by the cyclization results, we started to investigate the feasibility of synthesizing homologous cyclic imines starting from the homo- and bishomopropargylglycine derivatives **27** and **28**, using the same synthetic pathway. Thus, the Pd-catalyzed Sonogashira coupling of the optically active homo- and bishomopropargylglycine derivatives **27** and **28** with iodobenzene afforded the cyclization precursors **29** and **30** in 85 and 82% yield, respectively (Scheme 5). First, the amino ester derived from precursor **29** was subjected to AgOTf at reflux temperature since we anticipated that the possible formation of a six-membered ring might require higher reaction temperatures. These conditions gave a rapid cyclization of the amino ester to pyrroline **31** as the sole product in 52% yield after purification by column chromatography. In contrast to the previously obtained pyrrolines, this benzyl-substituted pyrroline turned out to be a rather labile compound that slowly decomposed.

The formation of **31** can be explained by a Ag-mediated cyclization in an exclusive 5-*exo-dig* fashion giving the corresponding intermediate conjugated enamine, followed by isomerization of the exocyclic enamine double bond to the apparently thermodynamically more stable imine position (Scheme 5). Under the same conditions, the amino ester derived from the homologous precursor **30** cyclized in a similar manner exclusively in a 6-*exo-dig* manner affording the six-membered cyclic imine **32** as the sole product in an acceptable yield of 48%. In this case, the obtained imine proved to be a more stable compound, allowing a thorough analysis. During the analysis, it became clear that imine **32** showed no optical activity, which indicates a significant extent of racemization. The fact that racemization does not take place in the pyrroline systems might be due to the more basic

(14) Shiman, R.; Neilands, J. B. *Biochemistry* **1965**, *4*, 2233.

SCHEME 6. Hydrogenation to Give 5-Substituted Proline Analogues[a]
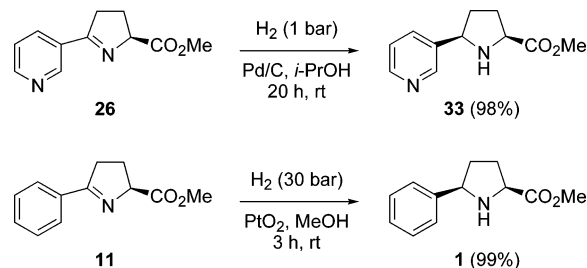
SCHEME 7. Formation of Pipecolic Acid Analogue 34
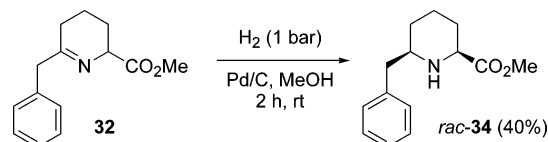
character of the nonconjugated imine, which can cause deprotonation at the α-position.

Having explored the cycloisomerization of differently substituted cyclization precursors, we turned our attention to the hydrogenation of some of the pyrrolines to complete the approach to 5-substituted proline analogues. First, the 3-pyridyl-substituted pyrroline **26** was subjected to straightforward hydrogenation conditions using Pd on carbon under an atmospheric hydrogen pressure (Scheme 6). These conditions[3a] led to a smooth and quantitative conversion of **26**, providing the *cis*-substituted proline analogue **33** as the sole product (indicated by ^{1}H NMR upon analysis of the crude reaction mixture). Interestingly, proline derivative **33** can also be regarded as a nicotine analogue which generally may have biological relevance as a ligand for the nicotinic acetylcholine receptor.[15]

The catalytic hydrogenation of pyrroline **11** under identical conditions led to the formation of the desired proline analogue **1**. However, in this case the reduction of the imine was severely hampered by partial hydrogenolysis at the benzylic position. This competitive reaction could be efficiently suppressed by using previously reported conditions,[16,3b] leading solely to the *cis*-substituted proline analogue **1** in a quantitative yield. In addition, the six-membered cyclic imine **32** was subjected to hydrogenation conditions but gave no clean formation of the corresponding pipecolic acid analogue **34**. Instead, imine **32** appeared to be moderately labile under these conditions giving also several unidentifiable side products. Luckily, pipecolic acid **34** could be isolated in pure form from this mixture by column chromatography in 40% yield as a single diastereoisomer according to ^{1}H and ^{13}C NMR (Scheme 7). By analogy to the stereochemistry in the reduction of the pyrrolines **11** and **26**, the relative configuration of the substituents of **34** was tentatively assigned to be cis.

(15) (a) Glennon, R. A.; Dukat, M. *Med. Chem. Res.* **1996**, 465. (b) McDonald, I. A.; Cosford, N.; Vernier, J.-M. *Annu. Rep. Med. Chem.* **1995**, *30*, 41.
(16) Petersen, J. S.; Fels, G.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 4539.

Conclusions

A novel approach to 5-substituted proline analogues is described. We have shown that the synthesis of 2,5-disubstituted pyrrolines can be achieved via a mild Ag-catalyzed 5-*endo-dig* cyclization of propargylglycine derivatives as the key step. We have also demonstrated that the developed methodology could also be applied to homologous acetylenic amino acids, leading to other proline and pipecolic acid derivatives. Finally, we have shown for two examples that the obtained pyrrolines can be easily converted into the corresponding 5-substituted proline analogues.

Experimental Section

General. All reactions were carried out under an atmosphere of dry nitrogen, unless stated otherwise. Infrared (IR) spectra were obtained using an FTIR spectrometer, and wavelengths (ν) are reported in cm^{-1}. Optical rotations were measured, using concentrations (c) in g/100 mL in the indicated solvents. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were determined in CDCl$_3$, unless indicated otherwise. Chemical shifts (δ) are given in ppm downfield from tetramethylsilane. Flash chromatography was performed with Acros Organics silica gel (0.035−0.070 nm) using the indicated solvent (mixture). R_f values were obtained by using thin-layer chromatography (TLC) on silica gel-coated glass plates (Merck silica gel 60 F$_{254}$) with the aforementioned solvent (mixture), unless noted otherwise. THF and Et$_2$O were distilled from sodium and benzophenone as indicator. Heptane, EtOAc, and CH$_2$Cl$_2$ were distilled from CaH$_2$. Et$_2$NH was distilled from and stored over KOH. If necessary, other solvents were distilled from the appropriate drying agents prior to use. Unless stated otherwise, all commercially available reagents were used as received.

Methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-5-phenyl-4-pentynoate (10). To a solution of **9** (364 mg, 1.60 mmol), iodobenzene (398 mg, 1.95 mmol) and Et$_2$NH (0.83 mL, 8.04 mmol) in Et$_2$O (18 mL), CuI (31 mg, 0.16 mmol), and PdCl$_2$-(PPh$_3$)$_2$ (58 mg, 0.08 mmol) were added and the resulting mixture was stirred for 2 h at room temperature. The reaction mixture was poured into a saturated aqueous solution of NH$_4$Cl (40 mL) and after a separation of the organic layer the aqueous layer was extracted with Et$_2$O (2 × 25 mL). The combined organic layers were washed with brine (25 mL), dried over MgSO$_4$, and concentrated in vacuo. The crude product was purified by chromatography (EtOAc/heptane = 1:6) to afford **10** (444 mg, 1.46 mmol, 91%) as a yellow oil. R_f 0.28 (EtOAc/heptane = 1:4); [α]$_D$ +71.3 (*c* 1.0, CH$_2$Cl$_2$); IR (neat) 3375, 2977, 1747, 1716, 1598; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.38 (m, 2H), 7.28 (m, 3H), 5.42 (d, J = 8.3 Hz, 1H), 4.56 (m, 1H), 3.79 (s, 3H), 2.95 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 171.1, 154.9, 131.5, 128.0, 127.6, 122.8, 83.7, 83.4, 79.8, 52.3, 52.1, 28.1, 23.6; HRMS (EI) calcd for C$_{17}$H$_{21}$NO$_4$ 303.1471, found 303.1471.

Methyl (2*S*)-5-phenyl-3,4-dihydro-2*H*-2-pyrrolecarboxylate (11). To a solution of precursor **10** (383 mg, 1.26 mmol) in EtOAc (5 mL), a ~3 M solution of HCl in EtOAc (2 mL) was added dropwise at room temperature. The mixture was

stirred at room temperature and monitored with TLC. After complete conversion of the starting material, the mixture was concentrated in vacuo to afford the corresponding HCl-salt. A solution of the HCl-salt in dioxane/water (15 mL, 1:1 v/v) was treated dropwise at room temperature with 25% aqueous NH$_4$OH until the mixture had reached pH 10. The aqueous solution was extracted with CH$_2$Cl$_2$ (3 × 25 mL) and the combined organic layers were dried over MgSO$_4$ and concentrated in vacuo. The remaining crude amino ester was subsequently dissolved in MeCN (10 mL), and AgOTf (32 mg, 0.13 mmol) was added. The mixture was stirred at reflux temperature and monitored by TLC. Upon completion, the reaction mixture was concentrated in vacuo and the crude product was purified by chromatography (EtOAc/heptane = 1:3) to afford **11** (185 mg, 0.91 mmol, 72%) as a light-yellow oil. The enantiopurity was confirmed by chiral HPLC analysis (Chiralcel OD, hexane/2-propanol 9:1). R_f 0.42 (EtOAc/heptane = 1:1); [α]$_D$ +104.1 (*c* 1.0, CH$_2$Cl$_2$); IR (neat) 2951, 1734, 1612, 1574, 1433; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.84 (dd, J = 1.5, 7.8 Hz, 2H), 7.31−7.41 (m, 3H), 4.89 (ddt, J = 8.8, 6.7, 1.7 Hz, 1H), 3.76 (s, 3H), 3.14 (dddd, J = 16.6, 10.1, 5.5, 2.1 Hz, 1H), 2.95 (dddd, J = 16.6, 8.7, 6.8, 2.0 Hz, 1H), 2.29 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 175.7, 173.0, 133.6, 130.8, 128.3, 127.9, 74.6, 52.4, 35.6, 26.6; HRMS (EI) calcd for C$_{12}$H$_{13}$NO$_2$ 203.0946, found 203.0948.

Methyl (2*S*,5*R*)-5-phenyltetrahydro-1*H*-2-pyrrolecarboxylate (1). To a solution of **11** (308 mg, 1.52 mmol) in MeOH (3 mL), PtO$_2$ (10 mg, 0.04 mmol) was added. The solution was subjected to hydrogen (30 bar) and stirred for 3 h at room temperature. The reaction mixture was filtered over Hyflo and concentrated in vacuo to afford **1** (308 mg, 1.50 mmol, 99%) as a light-yellow oil. An analytically pure sample was obtained after chromatography (EtOAc/heptane = 1:2). R_f 0.15; [α]$_D$ + 20.1 (*c* 1.0, CH$_2$Cl$_2$); IR (neat) 3356, 2950, 1731, 1610, 1502, 1459; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.40 (dd, J = 0.6, 7.5 Hz, 2H), 7.26 (m, 3H), 4.18 (dd, J = 5.7, 9.0 Hz, 1H), 3.92 (dd, J = 5.1, 8.1 Hz, 1H), 3.76 (s, 3H), 2.17 (m, 4H), 1.72 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 175.3, 143.2, 128.4, 127.1, 126.7, 63.7, 60.2, 52.3, 34.5, 30.8; HRMS (CI) calcd for C$_{12}$H$_{16}$NO$_2$ (MH$^+$) 206.1181, found 206.1179.

Methyl 6-benzyl-2-piperidinecarboxylate (34). To a solution of **32** (108 mg, 0.47 mmol) in MeOH (10 mL), 10% Pd/C (15 mg, 0.01 mmol) was added. The black suspension was subjected to hydrogen (1 atm) and stirred for 2 h at room temperature. The reaction mixture was filtered over Hyflo and concentrated in vacuo. Purification by chromatography (EtOAc/heptane = 1:1) afforded **34** (44 mg, 0.19 mmol, 40%) as a colorless oil. R_f 0.17; IR (neat) 3332, 2931, 2852, 2791, 1739, 1603, 1495, 1435; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.25 (m, 2H), 7.18 (m, 3H), 3.66 (s, 3H), 3.26 (dd, J = 2.7, 10.8 Hz, 1H), 2.70 (m, 3H), 2.03−1.84 (m, 3H), 1.64 (m, 1H), 1.48−1.14 (m, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 173.3, 138.7, 129.1, 128.4, 126.3, 59.5, 58.0, 52.1, 43.8, 32.1, 29.3, 24.7; HRMS (EI) calcd for C$_{14}$H$_{19}$NO$_2$ 233.1371, found 233.1374.

Supporting Information Available: Experimental procedures and characterization data for compounds **12−24**, **26**, **29**, and **30−34**. ^{1}H and ^{13}C NMR spectra for compounds **1**, **11**, **24**, **26**, and **31−34**. This material is available free of charge via the Internet at http://pubs.acs.org.