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Palladium-Catalyzed Synthesis of Novel Optically Active Tryptophan Analogues

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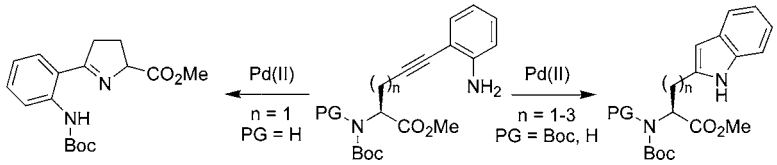
ABSTRACT



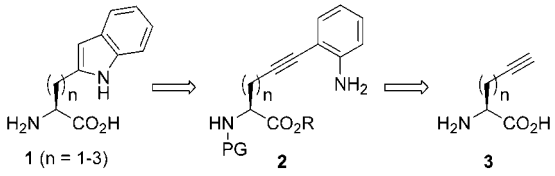
Both unsaturated proline derivatives and optically active tryptophan analogues have been obtained via Pd-catalyzed cyclization of aniline-containing acetylenic amino acids. The side chain length of the cyclization precursor determines which one of the two possible products will be formed.

Enantiomerically pure tryptophan analogues such as (*S*)-isotryptophan (**1**, $n = 1$), (*S*)-homoisotryptophan (**1**, $n = 2$), and (*S*)-bishomoisotryptophan (**1**, $n = 3$) are potentially biologically relevant α-amino acids[1] of which only isotryptophan itself has been previously prepared in an optically active form.[2] In that preparation, the synthesis proceeded via cyclization of an *ortho*-ethynylaniline moiety that was connected to a Schöllkopf chiral auxiliary. The key cyclization to the indole ring was promoted by copper, which has also been reported as the catalyst of choice for the synthesis of other indole systems.[3]

In addition to copper, palladium-catalysts have been frequently used in cyclization reactions of nitrogen nucleophiles[4] onto alkenes and alkynes to provide nitrogen heterocycles such as pyrroles[5] and indoles.[6] To the best of our knowledge, Pd-catalyzed syntheses of 2-substituted indoles have only been conducted using relatively simple 2-alkynylanilines as the cyclization precursors.[6]

We envisaged that the tryptophan analogues **1** might be readily synthesized from the corresponding protected anilines **2** via such a Pd-catalyzed cyclization as the key step. The anilines **2** should be easily accessible from the enantiopure acetylene-containing α-amino acids **3**[7] (Scheme 1). These trifunctional amino acids[8] are either commercially available (e.g., 2-amino-4-pentynoic acid)[9] or readily accessible via a chemoenzymatic procedure that has been developed in collaboration with DSM Research (Geleen, The Netherlands).[10]

Scheme 1. Retrosynthesis of (*S*)-Tryptophan Analogues



To investigate the feasibility of forming the 2-substituted indole ring via an intramolecular Pd-catalyzed reaction,

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(1) (a) Cady, S. G.; Sono, M. *Arch. Biochem. Biophys.* **1991**, *292*, 326. (b) Peterson, A. C.; Migawa, M. T.; Martin, M. J.; Hamaker, L. K.; Czerwinski, K. M.; Zhang, W.; Arend, R. A.; Fisette, P. L.; Ozaki, Y.; Will, J. A.; Brown, R. R.; Cook, J. M. *Med. Chem. Res.* **1994**, *3*, 531. (c) Southan, M.; Truscott, R.; Jamie, J.; Pelosi, L.; Walker, M.; Maeda, H.; Iwamoto, Y.; Tone, S. *Med. Chem. Res.* **1996**, *5*, 343.

(2) (a) Ma, C.; Yu, S.; He, X.; Liu, X.; Cook, J. M. *Tetrahedron Lett.* **2000**, *41*, 2781. (b) Ma, C.; Liu, X.; Li, X.; Flippen-Anderson, J.; Yu, S.; Cook, J. M. *J. Org. Chem.* **2001**, *66*, 4525.

(3) Hiroya, K.; Itoh, S.; Ozawa, M.; Kanamori, Y.; Sakamoto, T. *Tetrahedron Lett.* **2002**, *43*, 1277.

(4) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: New York, 1997.

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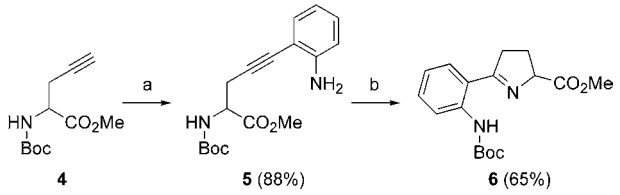
cyclization precursor **5** was synthesized starting from the racemic propargylglycine derivative **4**[7] (Scheme 1).

The Pd-catalyzed functionalization of propargylglycine derivatives with aromatic groups under Sonogashira-type coupling conditions has already been described by Crisp.[11] A slight modification of the reported conditions led to a smooth coupling of **4** with 2-iodoaniline at room temperature affording precursor **5** in 88% yield. Interestingly, subsequent subjection of **5** to previously reported cyclization conditions[6d] did not lead to the anticipated formation of the indole system. Instead, an unexpected product was formed as the sole product in 65%, which was unambiguously identified as the five-membered cyclic imine **6** through an X-ray crystal structure determination (Figure 1).[12]

Scheme 2. Synthesis of a Racemic Cyclization Precursor and Attempted Pd-Catalyzed Indole Formation[a]



[a] Conditions: (a) 2-iodoaniline, $PdCl_2(PPh_3)_2$, CuI, Et_2NH, Et_2O, rt, 2 h; (b) $PdCl_2(MeCN)_2$, MeCN, reflux, 3 h.

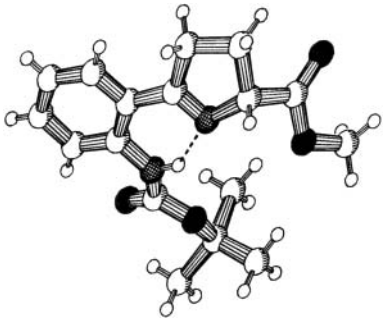
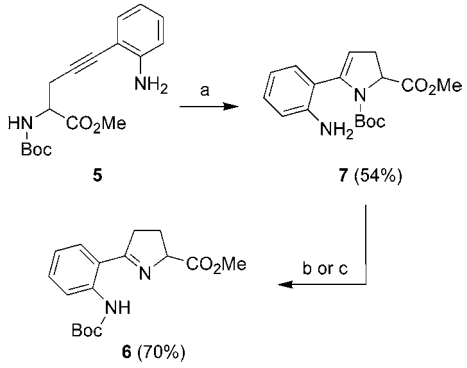


Figure 1. PLATON[13] drawing of the X-ray crystal structure of imine **6**.

After this surprising result, amino acid **5** was subjected to the same reagents at room temperature, resulting in the formation of the cyclic enamide **7** in 54% yield after chromatography (Scheme 3). Treatment of this enamide with the same Pd catalyst in refluxing acetonitrile led to a rapid conversion into the aforementioned imine **6** in 70% yield. The latter conversion could also be accomplished by refluxing **7** in acetonitrile without the Pd-catalyst present, however the reaction did not go to completion even after prolonged reaction times of over 24 h.

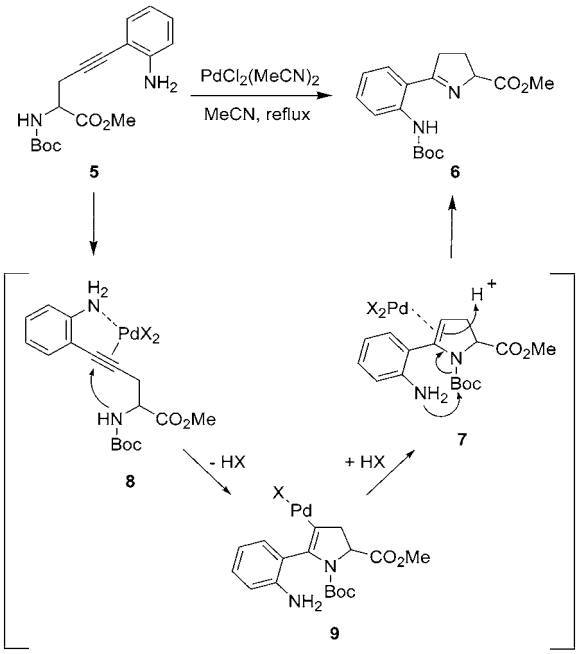
Scheme 3. Synthesis of Enamide **7** Followed by Conversion to Imine **6**[a]



[a] Conditions: (a) $PdCl_2(MeCN)_2$, MeCN, rt, 2 h; (b) $PdCl_2(MeCN)_2$, MeCN, reflux, 30 min; (c) MeCN, reflux.

A plausible mechanism involves complexation of the Pd(II) catalyst to the triple bond, possibly aided by coordination to the aniline nitrogen, giving rise to the π-complex **8** (Scheme 4).

Scheme 4. Mechanistic Aspects of the Pd-Catalyzed Formation of Imine **6** from Cyclization Precursor **5**



This renders the acetylene sufficiently electrophilic to undergo nucleophilic attack of the apparently more nucleo-

(5) (a) Gabriele, B.; Salerno, G.; Fazio, A.; Bossio, M. R. *Tetrahedron Lett.* **2001**, *42*, 1339. (b) Grigg, R.; Savic, V. *J. Chem. Soc., Chem. Commun.* **2000**, 873.

(6) (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc*. **1991**, *113*, 6689. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem* **1998**, *63*, 7652. (c) Cacchi, S.; Carcinelli, V.; Marinelli, F. *J. Organomet. Chem.* **1994**, *475*, 289. (d) Rudisill, D. E.; Stille, J. K. *J. Org. Chem.* **1989**, *54*, 5856.

(7) (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.

philic carbamate nitrogen to give the corresponding vinylpalladium intermediate **9**. This species will undergo protonolysis of the Pd−C bond (and regeneration of the Pd(II) catalyst) to give the cyclic enamide **7**, which under the circumstances immediately reacts further to provide the pyrroline **6** as the product. In the last step, the regenerated Pd-catalyst may possibly act as a Lewis acid by lowering the electron density of the double bond, thus facilitating intramolecular attack of the aniline nitrogen onto the Boc-group.

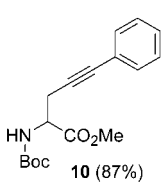
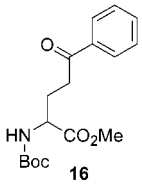
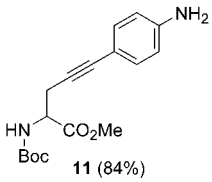
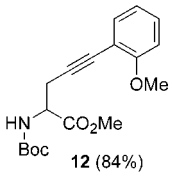
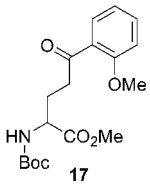
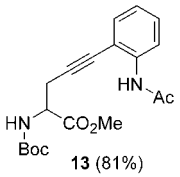
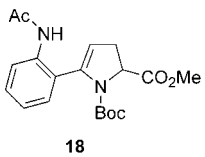
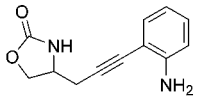
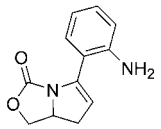
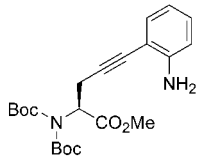
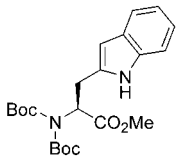
Having observed the mild and facile cycloisomerization of **5**, we set out to investigate this type of reaction somewhat further to gain insight into the scope and limitations of the observed cyclization. Therefore, we prepared several cyclization precursors via Sonogashira couplings between protected propargylglycine **4** and (substituted) aryl iodides. The racemic substituted acetylenes **10**−**13** were thus obtained in good yields and subjected to the cyclization conditions at different temperatures (Table 1).

Unfortunately, subjection of the substituted acetylenes **10**−**12** to the cyclization conditions did not lead to the formation of the corresponding cyclic enamides. In the case of **10**, a relatively clean reaction was observed affording hydrolysis product **16** as the sole product in a yield of 31%. With substrate **12**, a similar reaction was observed leading to the formation of ketone **17** as the major product in a somewhat lower yield of 19%. Presumably, in these cases the internal acetylene undergoes a Pd-catalyzed regioselective hydration leading to the corresponding ketone.[14] Cyclization precursor **11** did not give any reaction at room temperature, while heating at reflux temperature led to rapid decomposition of the starting compound.

The acetylated aniline **13** underwent cyclization at room temperature, resulting in the formation of the cyclic enamide **18** in 49% yield after column chromatography.

In addition, we converted cyclization precursor **5** into the more restricted oxazolidinone analogue **14** in two steps, i.e., ester reduction ($LiBH_4$, THF) followed by oxazolidinone formation (NaH, THF, reflux) in 52% yield. Subjection of the cyclic carbamate **14** to the Pd catalyst at reflux led to the formation of the corresponding bicyclic product **19** in a somewhat lower isolated yield of 32%. These preliminary results indicate that the presence of the *ortho*-aniline nitrogen atom in the precursor is crucial for the cycloisomerization

Table 1. Pd-Catalyzed Cyclizations of Several Functionalized Cyclization Precursors

entry	precursor	product	yield (%)[a]
1	 **10** (87%)	 **16**	31
2	 **11** (84%)	no cyclization	
3	 **12** (84%)	 **17**	19
4	 **13** (81%)	 **18**	49
5	 **14** (52%)	 **19**	32
6	 **15** (83%)	 **20**	52

[a] Isolated yield after column chromatography.

to occur. As shown before, cyclization precursor **5** could not be cyclized to the desired isotryptophan derivative. Therefore, we were pleased that subjection of the suitably protected biscarbamate **15** to the same Pd-catalyst in refluxing acetonitrile led to the formation of isotryptophan analogue **20** as the sole product without loss of enantiopurity according to chiral HPLC (Chiralcel OD).

Next, we investigated the feasibility of synthesizing optically active homologous isotryptophan derivatives starting from the homo- and bishomopropargylglycine derivatives **21** and **24**,[10a] respectively, using the same pathway. Thus, the Pd-catalyzed Sonogashira coupling of the optically active homo- and bishomopropargylglycine derivatives **21** and **24** with 2-iodoaniline afforded the cyclization precursors **22** and **25** in 79 and 78% yields, respectively (Scheme 5).

Subjection of **22** to the cyclization conditions led to a rapid conversion into homoisotryptophan analogue **23** in 60% yield

(8) For a review on applications of unsaturated amino acids, see: Rutjes, F. P. J. T.; Wolf, L. B.; Schoemaker, H. E. *J. Chem. Soc, Perkin Trans. 1* **2000**, 4197.

(9) In this article, referred to as propargylglycine; 2-amino-5-hexynoic acid is homopropargylglycine, etc.

(10) (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.

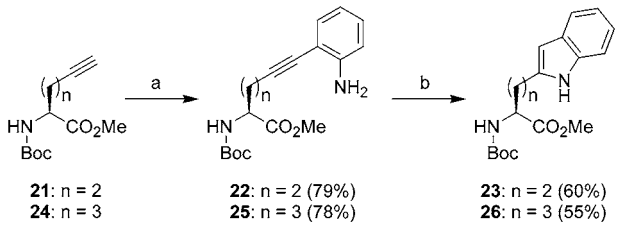
(11) Crisp, G. T.; Robinson, T. A. *Tetrahedron* **1992**, *48*, 3239.

(12) Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 203097.

(13) Spek, A. L. *PLATON, A Multipurpose Crystallographic Tool*; Utrecht University: Utrecht, The Netherlands, 2002.

(14) For similar regioselective Pd-catalyzed hydration of substituted acetylenes, see: Imi, K.; Imai, K.; Utimoto, K. *Tetrahedron Lett.* **1987**, *28*, 3127.

Scheme 5. Pd-Catalyzed Synthesis of Novel Optically Active Tryptophan Analogues[a]



[a] Conditions: (a) 2-iodoaniline, $PdCl_2(PPh_3)_2$, CuI, Et_2NH, Et_2O, rt, 3 h; (b) $PdCl_2(MeCN)_2$, MeCN, reflux, 30 min.

after chromatography. Under the same conditions, bishomoisotryptophan analogue **26** was also obtained in a reasonable yield of 55%. In both cases, we proved using chiral HPLC (Chiralcel OJ) that no (partial) racemization had taken place during the whole synthetic sequence.

In conclusion, we have developed a short and efficient synthesis of three novel tryptophan analogues in optically active forms using acetylene-containing α-amino acids as the starting materials. Furthermore, we demonstrated the possibility of constructing novel pyrroline derivatives in reasonable yields via an intramolecular Pd-catalyzed cycloisomerization. In addition, some insight was gained regarding the scope and limitations of the observed cycloisomerizations. Currently, we are further exploring the scope of these types of cyclization reactions.

Acknowledgment. T. Sonke (DSM Research, Geleen, The Netherlands) and R. P. M. Storcken (Department of Organic Chemistry, University of Nijmegen) are kindly acknowledged for conducting the enzymatic resolution of the amino acid amides.

Supporting Information Available: Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for compounds **5**−**7**, **13**−**16**, **18**−**20**, **22**, **23**, **25**, and **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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