Pergamon

Tetrahedron Letters 39 (1998) 5081–5084

TETRAHEDRON
LETTERS

Pd-Catalyzed Cyclization Reactions of Acetylene-Containing α-Amino Acids

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[+]Netherlands Institute for Research in Catalysis (NIOK) publication # UVA 98-4-01

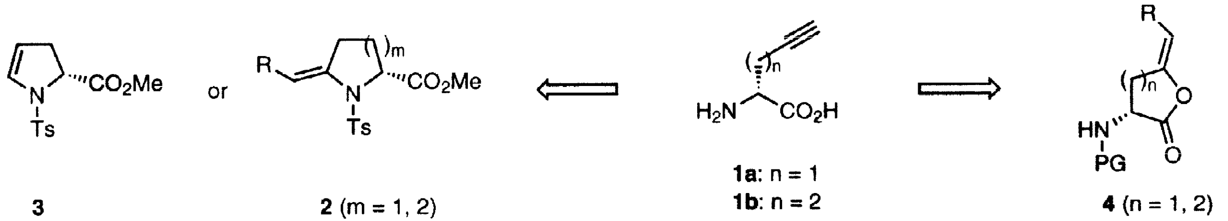
Received 12 February 1998; revised 29 April 1998; accepted 1 May 1998

Abstract

Acetylene-containing amino acids, obtained in enantiopure form via an enzymatic resolution process, serve as versatile intermediates in the synthesis of various highly functionalized heterocycles. The key transformations, intramolecular OC– and NC–bond formation, proceed via Pd-catalysis.

Keywords: amino acids and derivatives; Pd-catalysis; enamino esters, cyclization.

Small functionalized heterocyclic structures are important intermediates in the synthesis of pharmaceuticals and natural products [1] and may serve as ideal scaffolds for further functionalization via combinatorial techniques [2]. Intramolecular Pd-catalyzed cyclization of heteronucleophiles onto alkynes provides a convenient method for preparing such heterocycles [3]. Successful examples of nucleophiles include carboxylic acids [4–5] and amines [6]. In addition, further functionalization of the double bond might be achieved via cross-coupling with *in situ* formed organopalladium(II) species [7–12].



(1)

3 **2** (m = 1, 2) **1a**: n = 1 **1b**: n = 2 **1c**: n = 3 **4** (n = 1, 2)

Therefore, we reasoned that enantiopure acetylene-containing amino acids (**1a–c**), which contain both of these functionalities, might be ideal starting materials to arrive at highly functionalized heterocycles. This strategy should lead to *N*-heterocycles **2** or **3** if the nitrogen acts as the nucleophile, whereas lactones of type **4** should be formed in cases where the

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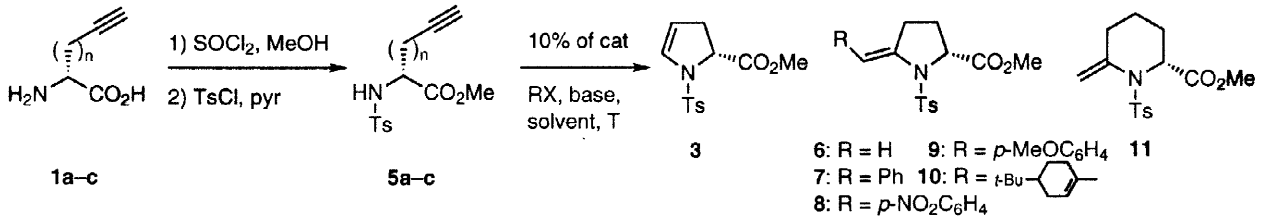
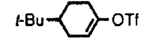
PII: S0040-4039(98)00910-1

carboxylic acid reacts with the triple bond (eq 1). Obviously, such an approach requires the facile preparation of acetylene-containing amino acids in enantiomerically pure form, for which we relied on a biocatalytic procedure [13,14].

Thus, the enantiopure D-amino acids **1a–c** were obtained via enantioselective hydrolysis of the corresponding racemic amino acid amides by an aminopeptidase produced by *Pseudomonas putida* in ee's higher than 99%.[1] Standard functional group protection (esterification, tosylation) of the amino acids **1a–c** yielded the cyclization precursors **5a–c** in yields ranging from 80% to 92% (Table 1).[2]

Table 1



entry	reactant	RX	cat	base	solvent	T (°C)	time (h)	product (yield)
1	**5a**		$Pd(PPh_3)_4$	K_2CO_3	DMF	80	3.5	**3** (76%)[a]
2	**5a**		$Pd(OAc)_2/PPh_3$	K_2CO_3	THF	60	4	**3** (64%)[b]
3	**5a**		$Pd(OAc)_2/PPh_3$	K_2CO_3	THF	40	48	**3** (48%)[c]
4	**5b**		$Pd(PPh_3)_4$	K_2CO_3	THF	60	1	**6** (87%)[d]
5	**5c**		$Pd(PPh_3)_4$	K_2CO_3	DMF	80	4.5	**11** (7%)
6	**5b**	PhI	$Pd(PPh_3)_4$	K_2CO_3/TBAC	MeCN	81	2.5	**7** (74%)[e]
7	**5b**	p-$NO_2C_6H_4I$	$Pd(PPh_3)_4$	K_2CO_3/TBAC	MeCN	81	0.6	**8** (59%)
8	**5b**	p-$MeOC_6H_4I$	$Pd(PPh_3)_4$	K_2CO_3/TBAC	MeCN	81	2	**9** (58%)
9	**5b**	p-$MeOC_6H_4Br$	$Pd(PPh_3)_4$	K_2CO_3/TBAC	MeCN	81	2	**9** (22%)
10	**5b**		$Pd(PPh_3)_4$	K_2CO_3/TBAC	THF	60	1	**10** (55%)

[a] The product was obtained in 33% ee (determined by chiral HPLC, Chiralpak OD; eluent: 20% *i*-PrOH/heptane); [b] 91% ee; [c] > 99% ee; [d] >99% ee; [e] > 99% ee.

A range of Pd-catalyzed reactions was carried out with the tosylamide function as the nucleophile (Table 1). In general, the best results were obtained by using a Pd(0)-catalyst (10 mol%) and K_2CO_3 (5 equiv) as a base. As an example, precursor **5a** (n = 1) cyclized in a 5-*endo*-fashion to give the pyrroline **3** in 76% yield (entry 1). Unfortunately, at 80 °C partial racemization occurred, which was circumvented by lowering the temperature and changing the solvent to THF (entries 2 and 3). In the case of a longer side chain (**5b**, n = 2) 5-*exo*-cyclization proceeded smoothly providing the enantiopure enamide **6** in 87% yield (entry 4). Upon further elongation of the side chain (**5c**, n = 3) the desired product **11** could only be obtained in low yield (entry 5). On the other hand, cyclizations in the presence of various aryl halides and an enol triflate led to the incorporation of organic substituents (entries 6–10). For

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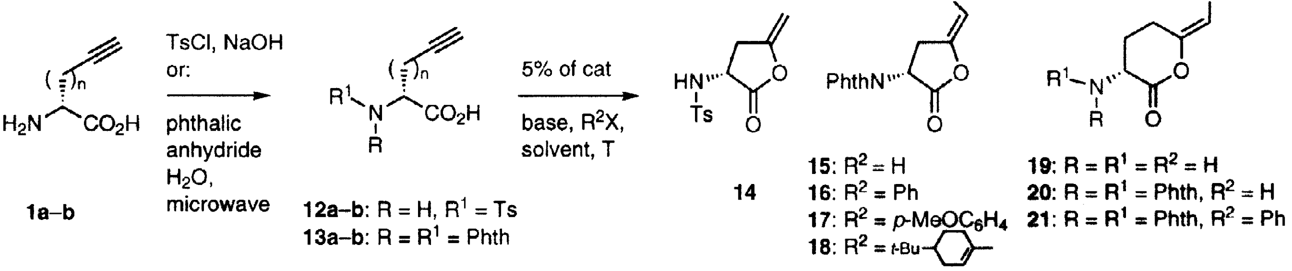
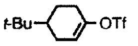
[1] Racemic propargylglycine (*rac*-**1a**) was obtained as described by Whitesides,[15] esterified ($SOCl_2$, MeOH) and converted into the corresponding amide (25% aqueous NH_3). Racemic 3-butynylglycine amide and 4-pentynylglycine amide were obtained via a Strecker reaction of 4-pentynal and 5-hexynal, respectively and subsequent partial hydrolysis of the nitrile function. Subjection of these amides to the enzymatic resolution conditions (aminopeptidase from *Pseudomonas putida*, pH 8.5, 37 °C, 60 h) provided the desired D-amino acids (after hydrolyis of the corresponding amides (2 M HCl, 90 °C, 2 h; or: amidase from *Rhodococcus erythropolis*,[16] pH 8, 38 °C, 24 h) and purification on a strongly acidic (Dowex 50W) ion exchange column) in >99% ee according to HPLC analysis.[17]

[2] All new compounds were appropriately characterized with IR, ^1H and ^{13}C NMR, HRMS data and rotational values.

example, reactions with aryl iodides (entries 6–8) proceeded in reasonable yields to the corresponding enantiopure cyclic amino esters **7**–**9**.[3] Addition of n-Bu_4NCl (TBAC) proved to give significantly higher yields in these cyclization reactions. A similar coupling with *p*-methoxyphenyl bromide (entry 9) proceeded in considerably lower yield. Moreover, the range of coupling reagents was extended to an enol triflate, which led to the desired cyclic adduct **10** in a satisfactory yield (entry 10). In all of these cases, the organic substituent was incorporated at the double bond in the (*E*)-geometry with respect to the heteroatom as was proven by NOE experiments on product **7** (entry 6).

Table 2



entry	reactant	R^2X	catalyst	base	solvent	T (°C)	time (h)	product (yield)
1	**12a**		$PdCl_2(MeCN)_2$	Et_3N	THF	80	16	**14** (66%)
2	**12a**		$Pd(OAc)_2$	Et_3N	THF	rt	1	**14** (66%)[a]
3	**13a**		$Pd(OAc)_2$	Et_3N	THF	rt	24	**15** (42%)[a]
4	**12b**		$PdCl_2(MeCN)_2$	Et_3N	MeCN	85	16	**19** (32%)
5	**13b**		$Pd(OAc)_2$	Et_3N	THF	60	5	**20** (24%)
6	**13a**	PhI	$Pd(OAc)_2/(PPh_3)_2$	Et_3N/TBAC	MeCN	60	5	**16** (41%)[b]
7	**13a**	PhI	$Pd(PPh_3)_4$	Et_3N/TBAC	MeCN	60	5	**16** (42%)
8	**13a**	p-$MeOC_6H_4I$	$Pd(PPh_3)_4$	Et_3N/TBAC	MeCN	60	24	**17** (41%)
9	**13a**	 t-Bu- -OTf	$Pd(OAc_2)/PPh_3$	Et_3N/TBAC	THF	60	16	**18** (23%)
10	**13b**	PhI	$Pd(OAc_2)/PPh_3$	Et_3N/TBAC	THF	60	5	**21** (31%)

[a] The product was obtained in > 95% ee (according to ^1H NMR using $Eu(hfc)_3$ as a shift reagent); [b] < 20% ee.

The cyclizations with the carboxylic acid as the nucleophile are shown in Table 2. In order to obtain suitable cyclization substrates, the nitrogen was either protected as a tosylamide to give precursors **12a**–**b** or as a phthalimide (*viz.* **13a**–**b**) in good yields [18]. Subjection of these precursors to various Pd-mediated cyclization conditions (10 mol% of a Pd(II)-catalyst, 15 mol% of Et_3N) led to different lactones. By using these conditions, carboxylic acid **12a** readily cyclized under the influence of 10 mol% of $PdCl_2(MeCN)_2$ or $Pd(OAc)_2$ under mild conditions to the five-membered lactone **14** in 66% yield (entries 1 and 2), while the

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[3] A typical cyclization experiment was carried out as follows: to a solution of the tosylated methyl ester **5b** (80 mg, 0.271 mmol), K_2CO_3 (187 mg, 1.35 mmol) and n-Bu_4NCl (79 mg, 0.271 mmol) in MeCN (2 mL) was added PhI (84 μl, 1.35 mmol) and $Pd(PPh_3)_4$ (32 mg, 27 μmol) and the solution was refluxed under a nitrogen atmosphere for 2.5 h. The mixture was poured into saturated aqueous $NaHCO_3$ (10 mL), extracted with ether (3 × 10 mL) and further purified by flash column chromatography (silica, 70% ether in petroleum ether) to give **7** as a light yellow solid (74 mg, 0.199 mmol, 74%). **7**: R_f 0.44 (70% ether in petroleum ether); $[\alpha]_D^{20}$ -73.6 (*c* 0.5, CH_2Cl_2); >99% ee (determined by chiral HPLC, Chiralpak OD; eluent: 20% *i*-PrOH/heptane) IR ($CHCl_3$) ν_{max} 2951, 2361, 1750, 1652, 1597, 1494, 1436, 1348, 1203, 1203, 1163, 1091 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.3 Hz, 2H, ArH), 7.23 (m, 5H, ArH), 7.12 (d, *J* = 7.3 Hz, 2H, ArH), 6.74 (s, 1H, =CH), 4.57 (dd, *J* = 6.7, 7.8 Hz, 1H, $NCHCO_2$), 3.32 (s, 3H, CO_2CH_3), 2.76 (m, 1H, $=CCH_2CH_2$), 2.42 (s, 3H, CH_3), 2.33 (m, 1H, $=CCH_2CH_2$), 2.12 (m, 1H, CH_2CH_2CH), 1.91 (m, 1H, CH_2CH_2CH); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.4, 144.2, 139.2, 136.9, 134.8, 129.5, 128.1, 128.1, 127.6, 126.0, 111.3, 62.5, 52.6, 28.8, 27.3, 21.5; HRMS (EI): calcd for $C_{20}H_{21}NO_4S$ (M) 371.1191, found 371.1178.

phthalimide-protected amino acid reacted to **15** in a somewhat lower yield (entry 3). In a similar manner, the homologous six-membered rings **19** and **20** were obtained, albeit in significantly lower yields (entries 4 and 5). Cross-coupling with aryl iodides proved to be possible after complete protection of the nitrogen atom as a phthalimide. A drawback of this protecting group, however, is that racemization occurs at the required temperatures. Nevertheless, treatment of the precursors **13a** and **b** with a Pd(0)-catalyst in the presence of an aryl iodide provided the corresponding lactones **16**, **17** and **21** in moderate yields (entries 6–8 and 10). In these cases, addition of 5 equiv of Et_3N in combination with 1 equivalent of TBAC was necessary to effect the required transformations. A similar type of reaction was achieved with a vinyl triflate (entry 9), but the yield of **18** still needs further optimization.

In general higher yields were obtained in the aminopalladation reactions. This might be partly due to the lower stability of the resulting enol esters in the oxypalladation reactions. Furthermore, it is surprising that the N-cyclizations only proceeded at a reasonable rate upon subjection to a Pd(0)-catalyst (Table 1), whereas generally Pd(II)-catalysts are used. A possible explanation is that the process starts with oxidative addition of Pd(0) into the NH-bond, after which insertion of the triple bond into this Pd(II)-species can take place (depending on the chain length an *endo-* or an *exo*-cyclic double bond will be formed) followed by reductive PdH-elimination [19].

Summarizing, we have described the use of enzymatically resolved acetylene-containing amino acids in Pd-catalyzed ring closure reactions to form enantiomerically pure highly functionalized *N*-and *O*-heterocycles. At present, we are further exploring the scope of these cyclization reactions and of the resulting products in the synthesis of natural products.

Acknowledgment: DSM Research is gratefully acknowledged for providing research grants to LBW and KCMFT. J. M. M. Boesten and dr A. L. L. Duchateau (DSM Research) are kindly acknowledged for carrying out some HPLC analyses.

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