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## Selective Azetidine and Tetrahydropyridine Formation via Pd-Catalyzed Cyclizations of Allene-Substituted Amines and Amino Acids

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By choosing the right substituents either highly functionalized unusual four-membered ring amino acids or the isomeric pipecolic acid derivatives are obtained in enantiomerically pure form. Starting material is a linear allene-containing amino acid that has been resolved via biocatalysis.

 $R = H, CO_2Me; R^1 = aryl, alkenyl$ 

Heteroannulation processes involving unsaturated functionality and Pd catalysis have been extensively studied over the past decade.<sup>1</sup> Beside the use of olefins and acetylenes as the

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electrophilic partners, allenes in particular have attracted the attention of organic chemists in recent years.<sup>2,3</sup> In all of these examples the heteronucleophile attacks one of the sp<sup>2</sup>-carbon atoms of the allene.<sup>4</sup> Recently, unprecedented alternative behavior was reported by our group, where a lactam nitrogen atom—with a two-carbon tether between the allene and the nitrogen atom— reacted at the sp carbon atom of the allene to form five-membered ring enamides.<sup>5,6</sup> In conjunction with this work and similar Pd-catalyzed reactions of acetylenic amino acids in our group,<sup>7</sup> we wish to present cyclizations

<sup>(1) (</sup>a) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: New York, 1995. (b) For a general review on metal-catalyzed amination, see: Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675.

<sup>(2)</sup> For nitrogen nucleophiles, see for example: (a) Larock, R. C.; Tu, C.; Pace, P. J. Org. Chem. **1998**, 63, 6859. (b) Desarbre, E.; Mérour, J. Y. Tetrahedron Lett. **1996**, 37, 43. (c) Larock, R. C.; He, Y.; Leong, W. W.; Han, X.; Refvik, M. D.; Zenner, J. M. J. Org. Chem. **1998**, 63, 2154. (d) Larock, R. C.; Zenner, J. M. J. Org. Chem. **1995**, 60, 482. (e) Kimura, M.; Tanaka, S.; Tamaru, Y. J. Org. Chem. **1995**, 60, 3764. (f) Davies, I. W.; Scopes, D. I. C.; Gallagher, T. Synlett **1993**, 85. (g) Kimura, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. J. Org. Chem. **1992**, 60, 6377. (h) Prasad, J. S.; Liebeskind, L. S. Tetrahedron Lett. **1988**, 29, 4257. (i) Shimizu, I.; Tsuji, J. Chem. Lett. **1984**, 233.

<sup>(3)</sup> For oxygen nucleophiles, see for example: (a) Ma, S.; Shi, Z. J. Org. Chem. **1998**, 63, 6387. (b) Jonasson, C.; Bäckvall, J. E. Tetrahedron Lett. **1998**, 39, 3601. (c) Walkup, R. D.; Guan, L.; Mosher, M. D.; Kim, S. W.; Kim, Y. S. Synlett **1993**, 88. (d) Walkup, R. D.; Guan, L.; Kim, Y. S.; Kim, S. W. Tetrahedron Lett. **1995**, 36, 3805. (e) Besson, L.; Bazin, J.; Goré, J.; Cazes, B. Tetrahedron Lett. **1994**, 35, 2881.

<sup>(4)</sup> Reference 1, p 166.

<sup>(5) (</sup>a) Karstens, W. F. J.; Rutjes, F. P. J. T.; Hiemstra, H. *Tetrahedron Lett.* **1997**, *38*, 6275. (b) Karstens, W. F. J.; Stol, M.; Rutjes, F. P. J. T.; Hiemstra, H. *Synlett* **1998**, 1126.

<sup>(6)</sup> More recently, similar regiochemistry was observed in lanthanidecatalyzed cyclizations of aminoallenes: Arredondo, V. M.; McDonald, F. E.; Marks, T. J. Am. Chem. Soc. **1998**, 120, 4871.

<sup>(7)</sup> Wolf, L. B.; Tjen, K. C. M. F.; Rutjes, F. P. J. T.; Hiemstra, H.; Schoemaker, H. E. Tetrahedron Lett. 1998, 39, 5081.

of the linear  $\beta$ -aminoallenes 4 (R = H, CO<sub>2</sub>Me; P = protecting group), where the allene and the amine are also separated by a two-carbon tether (Scheme 1).



In this case, four- and six-membered ring amines and amino acids are obtained with high selectivity.<sup>8</sup> Interestingly, attempts of the group of Yamamoto to cyclize such an unsubstituted  $\beta$ -aminoallene (viz., 4, R = H, P = Ts) failed, resulting in the isomerized diene product.<sup>9</sup> Very recently, the group of Kang presented a single example of the cyclization of this unsubstituted aminoallene, where in a moderate yield both the four- and six-membered heterocycle were obtained in a 2:1 ratio. The latter example, however, is rather limited in terms of selectivity, substitution pattern, and yield.<sup>10</sup> Our method, on the other hand, holds-in addition to the selective formation of four- and six-membered rings-a promising potential for introduction of various R<sup>1</sup> substituents and thus arrive at unique enantiopure amino acid derivatives.

The starting aminoallenes were synthesized as follows. The unsubstituted  $\beta$ -aminoallene 4 (R = P = H) was obtained via a literature procedure, involving a Crabbé reaction of 3-butyn-1-ol and conversion of the resulting alcohol into the

H. E.; Boesten, W. H. J.; Kaptein, B.; Roos, E. C.; Broxterman, Q. B.; van

den Tweel, W. J. J.; Kamphuis, J. Acta Chem. Scand. 1996, 50, 225-233.

amine.11 The enantiomerically pure allene-containing amino acid  $\mathbf{8}$  was prepared via an enzymatic resolution of the corresponding racemic amide 7 (Scheme 2).<sup>12</sup>



The latter compound was synthesized via (i) alkylation of the glycine-derived ketimine  $5^{13}$  with 4-bromo-1,2-butadiene (prepared from 2,3-butadienol<sup>14</sup> with Br<sub>2</sub>PPh<sub>3</sub> and imidazole), (ii) acid hydrolysis of the ketimine to give 6, and (iii) reaction with aqueous ammonia affording the amino acid amide 7.15 Subjection to the enzymatic resolution conditions (aminopeptidase produced by Pseudomonas putida ATCC 12633,16 pH 8.5, 37 °C, 60 h)<sup>17</sup> and separation of the resulting acid and amide<sup>15</sup> provided the (S)-acid **8** in 44% yield and 82% ee after purification by ion exchange chromatography.<sup>18</sup> The (R)-amide 7 was hydrolyzed by subjection to a nonspecific amidase produced by Rhodococcus erythropolis NCIB  $11540^{19}$  to afford (*R*)-8 in 35% yield (two steps) and >98% ee. 20

Functionalization to the cyclization precursors proceeded by using standard methodology leading to the desired precursors 9-10 and 21-24 in good yields and without detectable racemization. The cyclization results for the unsubstituted aminoallenes 9 and 10 are shown in Table 1. Application of the cyclization conditions (10 mol % Pd-(PPh<sub>3</sub>)<sub>4</sub>, 5 equiv of K<sub>2</sub>CO<sub>3</sub>, and 5 equiv of R<sup>1</sup>X, DMF, 80 °C)<sup>2f</sup> onto allene 9 (entry 1) led in 30 min to complete conversion, affording a 67:33 ratio of the four- and sixmembered rings 16a and b, respectively, which is in line with the result of Kang.<sup>10</sup> Upon prolonged reaction times, this ratio changed in favor of the six-membered ring (entry 2).<sup>21</sup> Use of the pyridine-derived iodide 13 gave a similar

<sup>(8)</sup> Similar three- vs five-membered ring formation of  $\alpha$ -amino allenes was reported recently: Ohno, H.; Toda, A.; Miwa, Y.; Taga, T.; Osawa, E.; Yamaoka, Y.; Fuji, N.; Ibuka, T. J. Org. Chem. 1999, 64, 2992.
(9) Meguro, M.; Yamamoto, Y. J. Org. Chem. 1998, 39, 5421.

<sup>(10)</sup> Kang, S.-K.; Baik, T.-G.; Kulak, A. N. Synlett 1999, 324.

<sup>(11) (</sup>a) Li, D.; Zhou, H.-Q.; Dakoji, S.; Shin, I.; Oh, E.; Liu, H.-W. J. Am. Chem. Soc. 1998, 120, 2008. (b) Hanack, M.; Haeffner, J. Chem. Ber. 1966, 99, 1077.

<sup>(12) 2-</sup>Amino-4,5-hexadienoic acid (homo-allenylglycine) is a naturally occurring amino acid of which several syntheses have been published. Isolation: Chilton, W. S.; Tsou, G.; Kirk, L.; Benedict, R. G. Tetrahedron Lett. 1968, 6283. Racemic synthesis: (b) Cazes, B.; Djahanbini, D.; Goré, J.; Genêt, J.-P.; Gaudin, J.-M. Synthesis 1988, 983. (c) Black, D. K.; Landor, S. R. J. Chem. Soc. (C) 1968, 281. (d) Black, D. K.; Landor, S. R. J. Chem. Soc. (C) 1968, 283. (S)-Enantiomer: (e) Baldwin, J. E.; Adlington, R. M.; Basak, A. J. Chem. Soc., Chem Commun. 1984, 1284. (S)-Enantiomer (benzyl ester): (f) Dunn, M. J.; Jackson, R. F. W.; Pietruszka, J.; Turner, D. J. Org. Chem. 1995, 60, 2210.

<sup>(13) (</sup>a) O'Donnell, M. J.; Polt, R. L. J. Org. Chem. 1982, 47, 2663. (b) O'Donnell, M. J.; Wojciechowski, K.; Ghosez, L.; Navarro, M.; Sainte, F.; Antoine, J.-P. Synthesis 1984, 313.

<sup>(14)</sup> Bailey, W. J.; Pfeifer, C. R. J. Org. Chem. 1955, 20, 1337.

<sup>(15)</sup> The amide was separated from residual acid via formation of the Schiff base (PhCHO,  $H_2O$ , pH ~9), extraction from the water layer, and precipitation upon hydrolysis in acetone using 1 equiv of HCl.

<sup>(16)</sup> The aminopeptidase was generously provided by DSM Research. (17) For related examples, see: (a) Schoemaker, H. E.; Boesten, W. H. J.; Broxterman, Q. B.; Roos, E. C.; Kaptein, B.; van den Tweel, W. J. J.; Kamphuis, J.; Rutjes, F. P. J. T. Chimia 1997, 51, 308-311. (b) Schoemaker,

<sup>(18)</sup> The ee was determined using chiral HPLC (Crownpak CR(+)) following a known protocol: Miyazawa, T.; Iwanaga, H.; Yamada, T.; Kuwata, S. Chem. Express 1991, 6, 887.

<sup>(19)</sup> Boesten, W. H. J.; Cals, M. J. H. U.S. Patent 4 705 752, 1987; Chem. Abstr. 1987, 105, 170617k.

<sup>(20)</sup> By using an aminopeptidase produced by a genetically modified Escherichia coli strain both enantiomers were produced in a single run in >98% ee. This experiment, however, has not yet been carried out on a preparative scale. Sonke, T.; Boesten, W. H. J.; Broxterman, Q. B.; Kamphuis, J.; Formaggio, F.; Toniolo, C.; Rutjes, F. P. J. T.; Schoemaker, H. E. In Stereoselective Biocatalysis Handbook; Patel, R. N., Ed.; Marcel Dekker, in press.

## Table 1



result, with the six-membered ring being the major isomer (entry 3). In contrast, reactions with the vinyl triflates **14** and **15** led to pleasing results. The azetidine **18a** was formed selectively by using triflate **14** (entry 4), while reaction with triflate **15** gave a selectivity of 95:5 in favor of the fourmembered ring **19a** (entry 5). On the other hand, subjection of aminoallene **10**—protected with the more easily removable *p*-nitrobenzenesulfonyl (Ns) group—to these reaction conditions provided the tetrahydropyridine **20b** selectively in 55% yield (entry 6).

To study the influence of the ester substituent, the enantiopure amino acid derivatives 21-24 were subjected to identical cyclization conditions (Table 2). Initially, 21 was

## Table 2

11	HN F		2Me	Pd(PPh <sub>3</sub> ), K <sub>2</sub> CO <sub>3</sub> , R solvent, <b>1</b>	<sup>4</sup> X R	P	R <sup>1</sup> ∽ + <sup>™</sup> CO₂Me	N CO <sub>2</sub> Me
<b>21</b> (P = Ts) <b>23</b> (P = CO <sub>2</sub> Me) <b>a b</b> <b>22</b> (P = Bn) <b>24</b> (P = Ac)								
е	ntry	allene	R <sup>1</sup> X	solvent	T (°C)	time	ratio ( <b>a:b</b> ) <sup>a</sup>	product (yield) <sup>b</sup>
	1	21	Phl	DMF	80	4 h	0:100	<b>25</b> (78%)
	2	21	PhI	DMF	rt	4 h	50:50	<b>25</b> (80%)
	3	21	PhI	DMF	80	10 min	70:30	<b>25</b> (84%)
	4	21	PhI	THF	60	1.5 h	88:12	<b>25</b> (45%)
	5	21	14	DMF	80	15 min	88:12	<b>26</b> (96%)
	6	21	15	DMF	80	10 min	95:5	<b>27</b> (77%)
	7	22	Phl	DMF	70	3 h	0:100	<b>28</b> (76%)
	8	23	PhI	DMF	80	16 h	42:58	<b>29</b> (33%)
	9	24	PhI	DMF	80	2 h	67:33	<b>30</b> (12%)

<sup>a</sup>Determined by analysis of the <sup>1</sup>H NMR data of the crude mixture. <sup>b</sup>Combined isolated yield of **20** and **21** after flash chromatography. In all entries, both products were obtained without loss of enantiopurity according to chiral HPLC (Chiralcel OD). treated under similar conditions as **9** for 4 h (entry 1), resulting selectively in the pipecolic acid derivative **25b** in 78% yield. Closer examination of the conditions revealed that with shorter reaction times a considerable amount of the four-membered ring **25a** was formed as a single *cis*-isomer.

The best example is shown in entry 3: the reaction was finished in 10 min, with 25a being the major product. Surprisingly, the reaction also proceeded at room temperature, but did not show any selectivity (entry 2). To improve the ratio in favor of the four-membered ring, different parameters (temperature, solvent, and reaction time) were varied, resulting in a maximum selectivity of 88:12 (THF, 60 °C), albeit the yield was moderate (entry 4). Again, interesting results were obtained by using the vinyl triflates 14 and 15. This led to fast reactions (finished in 10 min) and excellent yields of the four-membered amino acids 26a and 27a, with only a small degree of formation of the sixmembered rings (entries 5 and 6). The benzylated precursor 22 led in a clean reaction to the pipecolic ester 28b (entry 7). This result is in accord with previous reports on cyclizations of amines onto  $\pi$ -allylpalladium intermediates, where also complete conversion into the thermodynamic product was encountered.<sup>22</sup> Introduction of a methyl carbamate (entry 8) or an amide function (entry 9) did not lead to satisfactory results: the low yields did not encourage further investigations into optimization of the product ratio. Interestingly, the carbamate-functionalized azetidine ester 29a was the only product that gave crystals that could be subjected to an X-ray structure determination. Thus, the structure and absolute orientation of the substituents in the azetidine were unambiguously established (Figure 1).<sup>23</sup>



Figure 1. Crystal structure of 29a.

An explanation for these results can be found by considering the different pathways that play a role (Scheme 3). Initially, reaction of the allene with the in situ formed

<sup>(21)</sup> A similar ring expansion (from three- to five-membered rings) has been reported previously: Fugami, K.; Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 857.

<sup>(22)</sup> Review: Trost, B. M. Angew. Chem., Int. Ed. Engl. **1989**, 28, 1173. (23) X-ray data for **29a**:  $C_{15}H_{17}NO$ ;  $M_r = 227.3$ ; monoclinic; Cc; a = 12.994(2), b = 9.907(1), c = 10.371(2) Å;  $\beta = 111.36(1)^\circ$ ; V = 1243.4(3) Å<sup>3</sup>; Z = 4,  $D_x = 1.21$  g cm<sup>-3</sup>;  $\lambda$ (Cu K $\alpha$ ) = 1.5418 Å,  $\mu$ (Cu K $\alpha$ ) = 5.57 cm<sup>-1</sup>; F(000) = 488, -25 °C. Final R = 0.040 for 1064 observed reflections. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-114107.



organopalladium(II) species will give rise to the more stable *syn-π*-allylpalladium complex  $3^{24}$  which via  $\pi - \sigma - \pi$  isomerization can be converted to the more hindered *anti*-isomer.<sup>25</sup>

The *syn*-isomer can only cyclize in a 4-*exo-trig*-fashion to give the kinetic product **1**. The four-membered ring, however, can under the influence of Pd(PPh<sub>3</sub>)<sub>4</sub> undergo ring opening to regenerate the  $\pi$ -allylpalladium complex, which eventually via the equilibrium with the *anti*-complex under the reaction conditions can isomerize to the thermodynamically more stable six-membered ring **2**.<sup>26</sup> The rate of isomerization will depend on the substituents P and R<sup>1</sup>. For example, for R<sup>1</sup> = alkenyl, it is more difficult to form the intermediate complex so that isomerization does not rapidly occur and a relatively large amount of the four-membered ring is formed. On the other hand, improving the leaving group ability of the nitrogen (by going from Ts to Ns) enhances the isomerization process in such a way that the four-membered ring is no longer observed.

Thus, by changing different parameters either four- or sixmembered ring formation is observed resulting from attack of the nitrogen onto one of the sp<sup>2</sup>-allene carbon atoms. Remarkably, a slight substrate modification—ester reduction followed by oxazolidinone formation (viz., **31**, Scheme 4)— results in attack of the nitrogen on the central sp allene carbon atom under similar reaction conditions, providing the corresponding five-membered ring **32**.<sup>5b</sup>



In conclusion, we have shown that Pd-catalyzed cyclizations of  $\beta$ -aminoallenes can selectively lead to four- or sixmembered nitrogen heterocycles without loss of optical activity in high yields. In particular vinyl triflates show a promising selectivity in the cyclization processes leading to the four-membered rings. In addition, we have shown that via conversion into the more restricted oxazolidinone analogues, the corresponding five-membered rings are also accessible in both the (*R*)- and (*S*)-conformation. The mechanistic basis of this remarkable behavior is currently under further investigation.

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**Supporting Information Available:** A general procedure for the cyclization reactions and full characterization for compounds **7**, **8**, **18a**, **20b**, **25a**,**b**, **26a**, and **27a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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<sup>(24)</sup> An alternative cyclization mechanism-activation of the allene by the organopalladium(II) species as the  $\pi$ -complex followed by nucleophilic attack of the nitrogen, which has been proposed by Walkup (ref 3c,d) and Gallagher (ref 2f), cannot be ruled out.

<sup>(25)</sup> For a similar discussion, see: Ahmar, M.; Cazes, B.; Goré, J. Tetrahedron Lett. 1985, 26, 3795.

<sup>(26)</sup> The four- to six-membered ring isomerization was proven in a separate experiment via subjection of **25a** to the cyclization conditions, resulting in complete conversion into the tetrahydropyridine **25b**.