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

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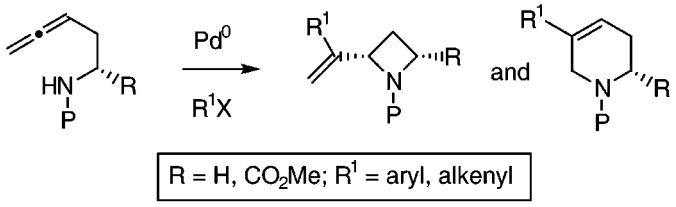
ABSTRACT



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.

Heteroannulation processes involving unsaturated functionality and Pd catalysis have been extensively studied over the past decade.[1] Beside the use of olefins and acetylenes as the electrophilic partners, allenes in particular have attracted the attention of organic chemists in recent years.[2,3] In all of these examples the heteronucleophile attacks one of the sp^2-carbon atoms of the allene.[4] 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.[5,6] In conjunction with this work and similar Pd-catalyzed reactions of acetylenic amino acids in our group,[7] we wish to present cyclizations

[†] DSM Research.

(1) (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.

(2) 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.

(3) 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.

(4) Reference 1, p 166.

(5) (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.

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

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

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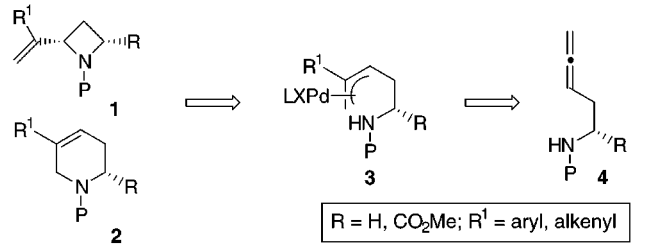
of the linear β-aminoallenes **4** (R = H, CO_2Me; P = protecting group), where the allene and the amine are also separated by a two-carbon tether (Scheme 1).

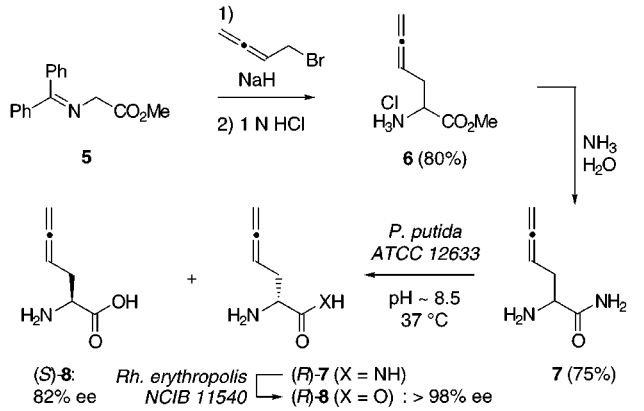
Scheme 1



In this case, four- and six-membered ring amines and amino acids are obtained with high selectivity.[8] Interestingly, attempts of the group of Yamamoto to cyclize such an unsubstituted β-aminoallene (viz., **4**, R = H, P = Ts) failed, resulting in the isomerized diene product.[9] 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.[10] 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^1 substituents and thus arrive at unique enantiopure amino acid derivatives.

The starting aminoallenes were synthesized as follows. The unsubstituted β-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 amine.[11] The enantiomerically pure allene-containing amino acid **8** was prepared via an enzymatic resolution of the corresponding racemic amide **7** (Scheme 2).[12]

Scheme 2



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[14] with Br_2PPh_3 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)[17] and separation of the resulting acid and amide[15] provided the (*S*)-acid **8** in 44% yield and 82% ee after purification by ion exchange chromatography.[18] 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-$(PPh_3)_4$, 5 equiv of K_2CO_3, and 5 equiv of R^1X, DMF, 80 °C)[2f] onto allene **9** (entry 1) led in 30 min to complete conversion, affording a 67:33 ratio of the four- and six-membered rings **16a** and **b**, respectively, which is in line with the result of Kang.[10] Upon prolonged reaction times, this ratio changed in favor of the six-membered ring (entry 2).[21] Use of the pyridine-derived iodide **13** gave a similar

(8) Similar three- vs five-membered ring formation of α-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.

(10) Kang, S.-K.; Baik, T.-G.; Kulak, A. N. *Synlett* **1999**, 324.

(11) (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.

(12) 2-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.

(13) (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.

(14) Bailey, W. J.; Pfeifer, C. R. *J. Org. Chem.* **1955**, *20*, 1337.

(15) 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.

(16) The aminopeptidase was generously provided by DSM Research.

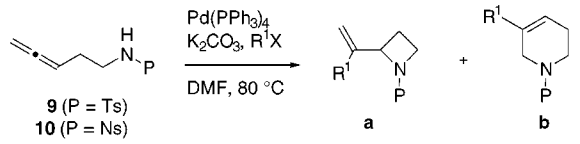
(17) For related examples, see: (a) Schoemaker, H. E.; Boesten, W. H. J.; Broxterman, Q. B.; Roos, E. C.; Kaptein, B.; van den Tweel, W. J. J.; Kamphuis, J.; Rutjes, F. P. J. T. *Chimia* **1997**, *51*, 308−311. (b) Schoemaker, H. E.; Boesten, W. H. J.; Kaptein, B.; Roos, E. C.; Broxterman, Q. B.; van den Tweel, W. J. J.; Kamphuis, J. *Acta Chem. Scand.* **1996**, *50*, 225−233.

(18) 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.

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

(20) 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



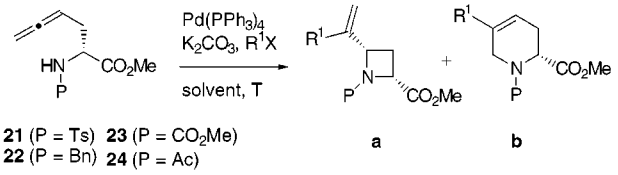
entry	substrate	R^1X	time	ratio (**a**:**b**)[a]	product (yield)[b]
1	**9**	PhI	0.5 h	67:33	**16** (67%)
2	**9**	PhI	40 h	10:90	**16** (34%)
3	**9**	**13**	4 h	25:75	**17** (55%)
4	**9**	**14**	10 min	100:0	**18** (34%)
5	**9**	**15**	15 min	95:5	**19** (41%)
6	**10**	PhI	4 h	0:100	**20** (55%)

[a]Determined by analysis of the ^{1}H NMR data of the crude mixture. [b]Combined isolated yield after column chromatography.

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 four-membered 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



entry	allene	R^1X	solvent	T (°C)	time	ratio (**a**:**b**)[a]	product (yield)[b]
1	**21**	PhI	DMF	80	4 h	0:100	**25** (78%)
2	**21**	PhI	DMF	rt	4 h	50:50	**25** (80%)
3	**21**	PhI	DMF	80	10 min	70:30	**25** (84%)
4	**21**	PhI	THF	60	1.5 h	88:12	**25** (45%)
5	**21**	**14**	DMF	80	15 min	88:12	**26** (96%)
6	**21**	**15**	DMF	80	10 min	95:5	**27** (77%)
7	**22**	PhI	DMF	70	3 h	0:100	**28** (76%)
8	**23**	PhI	DMF	80	16 h	42:58	**29** (33%)
9	**24**	PhI	DMF	80	2 h	67:33	**30** (12%)

[a]Determined by analysis of the ^{1}H NMR data of the crude mixture. [b]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 six-membered 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 π-allylpalladium intermediates, where also complete conversion into the thermodynamic product was encountered.[22] 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).[23]

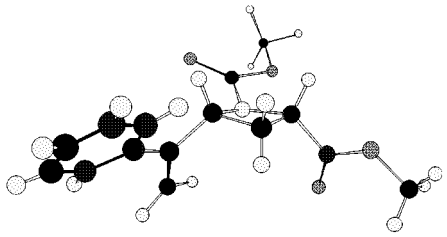


Figure 1. Crystal structure of **29a**.

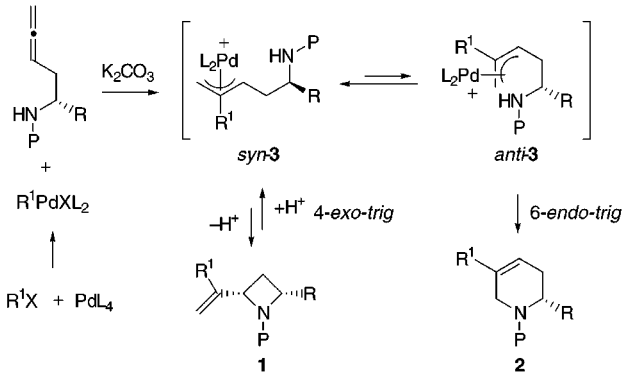
An explanation for these results can be found by considering the different pathways that play a role (Scheme 3). Initially, reaction of the allene with the in situ formed

(21) 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.

(22) 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; β = 111.36(1)°; V = 1243.4(3) Å^3; Z = 4, D_x = 1.21 g cm^{-3}; λ(Cu Kα) = 1.5418 Å, μ(Cu Kα) = 5.57 cm^{-1}; 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.

Scheme 3

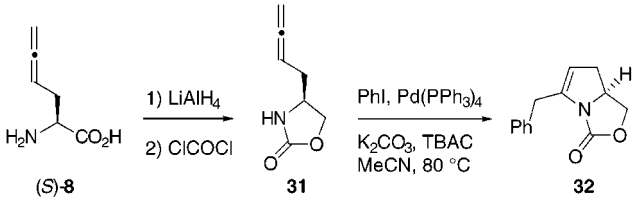


organopalladium(II) species will give rise to the more stable *syn*-π-allylpalladium complex **3**,[24] which via $\pi-\sigma-\pi$ isomerization can be converted to the more hindered *anti*-isomer.[25]

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 $Pd(PPh_3)_4$ undergo ring opening to regenerate the π-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**.[26] The rate of isomerization will depend on the substituents P and R^1. For example, for R^1 = 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 six-membered ring formation is observed resulting from attack of the nitrogen onto one of the sp^2-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**.[5b]

Scheme 4



In conclusion, we have shown that Pd-catalyzed cyclizations of β-aminoallenes can selectively lead to four- or six-membered 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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(24) An alternative cyclization mechanism—activation of the allene by the organopalladium(II) species as the π-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.

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

(26) 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**.