First Palladium-Catalyzed Aziridination Reaction of Amino Allenes

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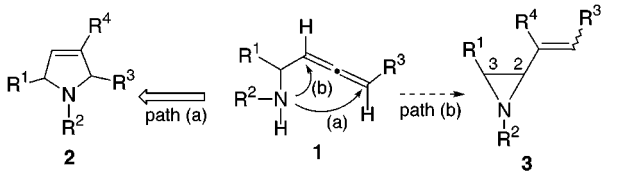
Received January 29, 1999

The transition-metal-catalyzed ring formation of hydroxy allenes in a highly regio- and stereoselective manner is a well-documented synthetic procedure.[1] Amino allenes, the aza-analogues of hydroxy allenes, also constitute an important class of molecules with interesting chemical properties due to their cumulated double bonds. Allenes bearing an amino group separated from the carbon atom by one to four carbon atoms have been attractive substrates for constructing five- and/or six-membered azacycles.[2−5] Transition-metal complexes such as Ag(I),[2] Pd(0 or II),[3] Hg(II),[4] and organolanthanides[5] have been reported to be effective catalysts for the cyclization reaction.[6]

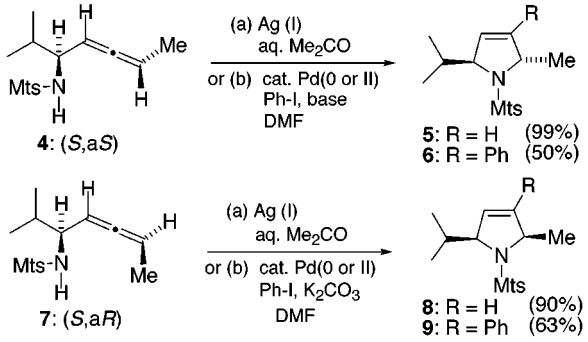
Currently, there is considerable interest in the synthesis and reaction of aziridines[7,8] since these compounds are often vital structural units of biologically active molecules and are frequently employed as key synthetic building blocks of natural products and elsewhere.[9] It was of considerable interest to determine whether amino allenes can be cyclized into substituted aziridines using a transition-metal-based catalytic system (Scheme 1). Although the intramolecular cyclization reaction of amino allenes of type **1** with transition-metal catalysts yielding pyrrolines such as **2** is known,[2a,b,3b] the ring-forming reaction for constructing

Scheme 1



R^1 = alkyl; R^2 = alkyl, acyl, etc.; R^3 = alkyl; R^4 = H, aryl, alkenyl, etc.

Scheme 2



thermodynamically less stable 2-alkenylaziridines **3** has no precedent as far as we are aware. Herein we report, for the first time, a simple method for converting amino allenes **1** to sterically congested aziridines **3** which are not readily accessible by other means.

The requisite enantiopure *N*-sulfonylated amino allenes bearing a methyl group at the terminal sp^2-carbon atom were prepared in high yields starting from natural α-amino acids by following the published procedure.[10]

To our disappointment, as shown in Scheme 2, initial experiments with the amino allene **4** by exposure to silver(I) salts such as $AgBF_4$ and $AgNO_3$−$CaCO_3$ yielded only the pyrroline derivative **5**. Gallagher and co-workers have developed effective transition-metal-catalyzed syntheses of five- and/or six-membered azacycles from amino allenes.[3a,4] Attempted palladium-catalyzed cyclization reaction under the Gallagher conditions[11] in the presence of an aryl halide and a base in DMF again resulted in the formation of five-membered azacycle **6** as the sole isolable product. Quite similar results were obtained by exposure of **7** to otherwise identical reaction conditions yielding **8** or **9** as the exclusive or major product. The structures of 3-pyrrolines **5** and **9** were unequivocally ascertained by single-crystal X-ray analyses. From the above results, we were initially apprehensive that the expected aziridine ring forming reaction could not be realized.

Fortunately, after considerable unsuccessful experimentation, our concerns were put to rest. Scheme 3 demonstrates how the chiral amino allenes were employed in a synthesis of the congested 2-alkenylaziridines. The most dominant factor in determining the site of intramolecular cyclization leading to aziridines was found to be the solvent employed. Although its exact role was unclear, dioxane was found to be the solvent of choice for the aziridination of amino allenes. Arylation takes place at the allenic central carbon to provide 2-alkenylaziridines in good yields. Some representative examples are listed in Table 1 and Scheme 3.

Typically, the aziridination reaction proceeded well when a dioxane solution of the allenic sulfonamide **4**, iodobenzene

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(1) (a) Marshall, J. A.; Pinney, K. G. *J. Org. Chem.* **1993**, *58*, 7180. (b) Walkup, R. D.; Guan, L. G.; Mosher, M. D.; Kim, S. W.; Kim, Y. S. *Synlett* **1993**, 88. (c) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31. (d) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 693.

(2) (a) Claesson, A.; Sahlberg, C.; Luthman, K. *Acta Chem. Scand.* **1979**, B*33*, 309. (b) Prasad, J. S.; Liebeskind, L. S. *Tetrahedron Lett.* **1988**, *29*, 4253. (c) Fox, D. N. A.; Gallagher, T. *Tetrahedron* **1990**, *46*, 4697.

(3) (a) Lathbury, D.; Vernon, P.; Gallagher, T. *Tetrahedron Lett.* **1986**, *27*, 6009. (b) Prasad, J. S.; Liebeskind, L. S. *Tetrahedron Lett.* **1988**, *29*, 4257. (c) Kimura, M.; Tanaka, S.; Tamaru, Y. *J. Org. Chem.* **1995**, *60*, 3764. (d) Imada, Y.; Vasapollo, G.; Alper, H. *J. Org. Chem.* **1996**, *61*, 7982. (e) Karstens, W. F. J.; Rutjes, F. P. J. T.; Hiemstra, H. *Tetrahedron Lett.* **1997**, *38*, 6275. (f) Karstens, W. F. J.; Stol, M.; Rutjes, F. P. J. T.; Hiemstra, H. *Synlett* **1998**, 1126. (g) Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 5421.

(4) Fox, D. N. A.; Lathbury, D.; Mahon, M. F.; Molloy, K. C.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1989**, 1073.

(5) Arredondo, V. M.; McDonald, F. E.; Marks, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 4871.

(6) For intermolecular palladium-catalyzed amination reactions of allenes, see: (a) Shimizu, I.; Tsuji, J. *Chem. Lett.* **1984**, 233. (b) Besson, L.; Goré, J.; Cazes, B. *Tetrahedron Lett.* **1995**, *36*, 3857. (c) Al-Masum, M.; Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* **1997**, *38*, 6071.

(7) (a) Vedejs, E.; Kendall, J. T. *J. Am. Chem. Soc.* **1997**, *119*, 6941. (b) Vedejs, E.; Moss, W. O. *J. Am. Chem. Soc.* **1993**, *115*, 1607.

(8) (a) Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 6844. (b) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328 and references therein. (c) Li, Z.; Quan, R. W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5889 and references therein. For reviews, see: (d) Rayner, C. M. *Synlett* **1997**, 11. (e) Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693. (f) Ibuka, T. *Chem. Soc. Rev.* **1998**, 27, 145.

(9) (a) Ibuka, T.; Mimura, N.; Ohno, H.; Nakai, K.; Akaji, M.; Habashita, H.; Tamamura, H.; Miwa, Y.; Taga, T.; Fujii, N.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 2982. (b) Toda, A.; Aoyama, H.; Mimura, N.; Ohno, H.; Fujii, N.; Ibuka, T. *J. Org. Chem.* **1998**, *63*, 7053.

(10) Ohno, H.; Toda, A.; Miwa, Y.; Taga, T.; Fujii, N.; Ibuka, T. *Tetrahedron Lett.* **1999**, *40*, 349. See also, Ohno, H.; Toda, A.; Fujii, N.; Ibuka, T. *Tetrahedron: Asymmetry* **1998**, *9*, 3929.

(11) Davies, I. W.; Scopes, D. I. C.; Gallagher, T. *Synlett* **1993**, 85.

10.1021/jo9901687 CCC: $18.00
Published on Web 04/07/1999

Scheme 3

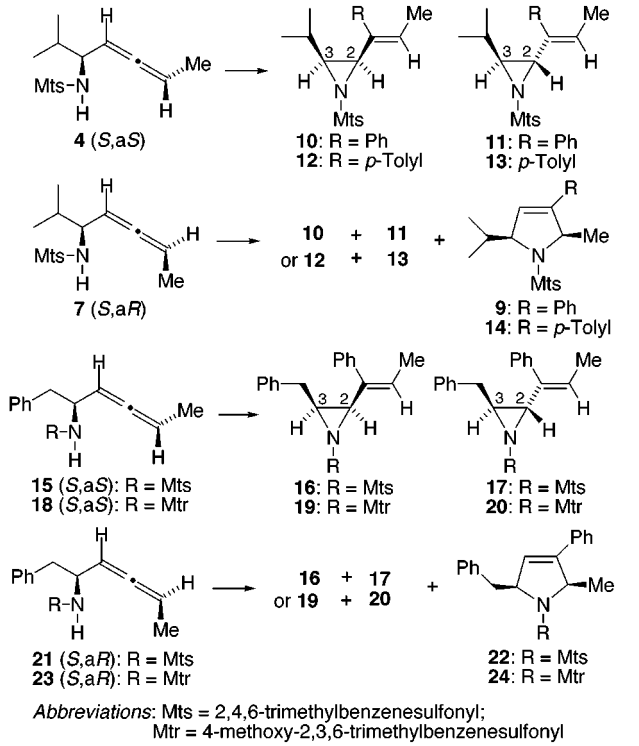


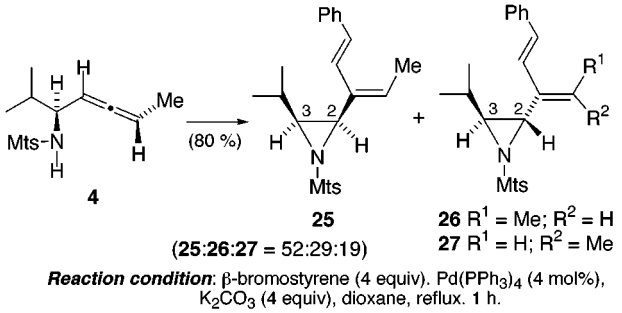
Table 1. Palladium(0)-Catalyzed Aziridination Reaction of Amino Allenes[a]

entry	substr	reactn time (h)	ArI	product ratio[b]	yield (%)[c]
1	**4**	6	PhI	**10**:**11** = 82:18	80
2[d]	**4**	2	PhI	**10**:**11** = 84:16	83
3	**4**	6	*p*-MePhI	**12**:**13** = 91:9	64
4	**7**	2.5	PhI	**10**:**11**: **9** = 2:90:8	79
5	**7**	3.5	*p*-MePhI	**12**:**13**:**14** = 12:85:3	44
6	**15**	4.5	PhI	**16**:**17** = 85:15	79
7	**18**	4	PhI	**19**:**20** = 80:20	79
8	**21**	4	PhI	**16**:**17**:**22** = 17:67:16	73
9	**23**	3.5	PhI	**19**:**20**:**24** = 17:78:5	77

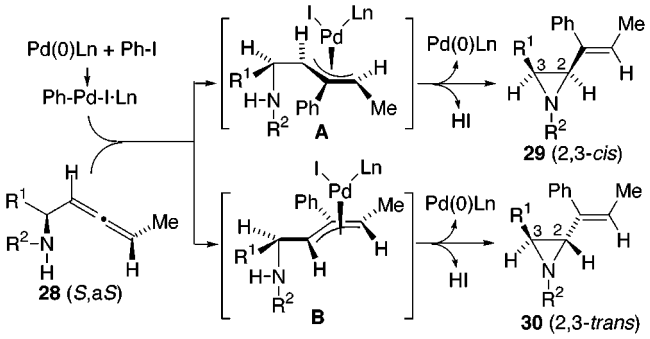
[a] All reactions were carried out in 1,4-dioxane under reflux using $Pd(PPh_3)_4$ (4−10 mol %), K_2CO_3 (4 equiv), and ArI (4 equiv) except for entry 2. [b] Ratios were determined by ^1H NMR (270 MHz). [c] Combined isolated yields. [d] $Pd(OAc)_2/4PPh_3$ (10 mol %) was used.

(4 equiv), potassium carbonate (4 equiv), and a catalytic amount of $Pd(PPh_3)_4$ (4−10 mol %) was refluxed under argon, yielding 2,3-*cis*- and 2,3-*trans*-2-alkenylaziridines **10** and **11** in an 82:18 ratio in a good combined yield (Scheme 3 and entry 1, Table 1).[12] There was no evidence of formation of any five-membered azacyclic compound. Although $Pd(PPh_3)_4$ proved to be the most convenient catalyst, $Pd(OAc)_2/4PPh_3$ was equally efficacious (entry 2, Table 1). Similarly, by using *p*-iodotoluene instead of iodobenzene, the expected aziridines **12** and **13** were obtained in 64% combined yield from **4** (entry 3, Table 1). On the other hand, exposure of the amino allene **7**, a diastereomer of **4**, to the otherwise identical conditions involving iodobenzene described above yielded the expected aziridines **10** and **11** bearing a phenyl group along with a small amount of the 3-pyrroline derivative **9** (entry 4, Table 1). In a similar manner, a 12:85:3 mixture of the *p*-tolylated aziridines **12** and **13** and 3-pyrroline **14** was obtained from **7** by the use of *p*-tolyl iodide in place of iodobenzene (entry 5, Table 1).

Scheme 4



Scheme 5



Quite similar results to those for the allenes **4** and **7** were obtained from the palladium-catalyzed cyclization reactions of amino allenes **15** and **18** with (*S*,a*S*)-stereochemistry and allenes **21** and **23** having (*S*,a*R*)-configuration. The results are shown in entries 6−9 in Table 1 and Scheme 3.

As an additional example, the (*S*,a*S*)-amino allene **4** was subjected to a palladium-catalyzed cyclization reaction in dioxane using *β*-bromostyrene. From this reaction, only 1,3-dienylaziridines **25**−**27** as a stereoisomeric mixture were obtained in 80% combined yield (Scheme 4).

A plausible rationale for the intramolecular aziridination reaction of amino allenes starting from (*S*,a*S*)-amino allene **28** is depicted in Scheme 5.[13] The phenylpalladium(II) iodide, formed in situ from iodobenzene and Pd(0), would generate η^3-allylpalladium complexes **A** and **B** by reaction with **28**.[6a,14] The η^3-allylpalladium moiety in **A** and **B** would be sufficiently electrophilic to undergo nucleophilic attack by the nitrogen, affording 2,3-*cis*- and 2,3-*trans*-aziridines **29** and **30**, respectively.

We are now undertaking extensive study on clarification of the scope of the present reaction under various reaction conditions.

Acknowledgment. This work was supported by The Japan Health Sciences Foundation and Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan. H.O. is grateful to Research Fellowships of the Japan Society for the Promotion of Science for Young Scientists.

Supporting Information Available: ORTEP drawings of **5**, **9**, and **10**, selected experimental procedures, and ^1H NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Confirmation of the structure and stereochemistry of the major aziridine **10** was based on single-crystal X-ray data. The consitution of the minor product **11** was deduced from ^1H NMR spectral data. All new compounds reported herein gave satisfactory spectroscopic and analytical results. The authors have deposited atomic coordinates for **5**, **9**, and **10** with the Cambridge Crystallographic Data Centre.

(13) Another possible organopalladium intermediate could not be ruled out. See refs 3e, 3f, and 11.

(14) Larock, R. C.; Zenner, J. M. *J. Org. Chem.* **1995**, *60*, 482.