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Potassium Carbonate-Promoted Stereospecific 5-*Endo*-*Trig* Cyclization of Unactivated Allenes in the Absence of Any Transition Metals

Hiroaki Ohno,*,† Yoichi Kadoh,‡ Nobutaka Fujii,† and Tetsuaki Tanaka*,‡

Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamadaoka, Suita, Osaka 565-0871, Japan, and Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan

hohno@pharm.kyoto-u.ac.jp; t-tanaka@phs.osaka-u.ac.jp

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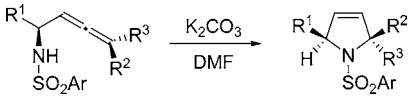
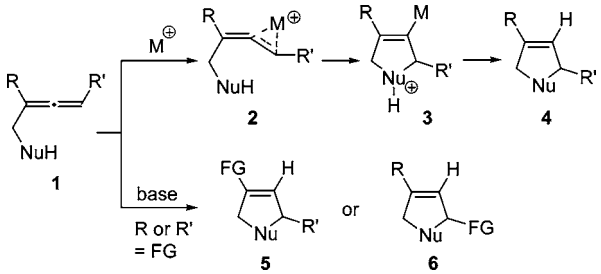
ABSTRACT



Formation of 3-pyrrolines from simple unactivated allenes bearing a protected amino group under basic conditions is described. Treatment of α-amino allenes with potassium carbonate in DMF under reflux in the absence of any transition-metal catalysts gave the corresponding 3-pyrrolines in good to excellent yields, by 5-*endo*-*trig* mode cycloisomerization. The reaction of internal allenes with an axial chirality afforded the corresponding 3-pyrrolines in a stereoselective manner.

Chiral 3-pyrrolines including 3,4-dehydroproline are known as useful synthetic intermediates for modified proline analogues,[1] conformationally restricted amino acid analogues,[2] antibiotic anisomycin,[3] and other related compounds.[4] Cycloisomerization of allenes through a 5-*endo*-*trig* mode is a powerful strategy for the construction of 3-pyrrolines[5] and other heterocycles such as dihydrofurans[6] and butenolides.[7] As shown in Scheme 1, this type of reaction generally proceeds through activation of the allenic moiety of **1** by coordination of transition metals such as Ag(I),[5−7] Pd(II),[8] Cu(I),[9] or Rh(I),[10] and subsequent attack by nitrogen or oxygen nucleophile onto the thus-activated allenic carbon of **2** leads to cyclized products **4** stereoselectively.[11] A recent contribution toward this area by Krause and Hashmi revealed that Au salts strongly catalyze the 5-*endo*-*trig* cycloisomerization of allenes **1** having a nitrogen or oxygen functional-

Scheme 1. Cycloisomerization of Allenes through 5-*Endo*-*Trig* Mode by Activation of Allenic Double Bond[a]



[a] FG = functional group.

† Kyoto University.
‡ Osaka University.

(1) (a) Baldwin, J. E.; Field, R. A.; Lawrence, C. C.; Lee, V.; Robinson, J. K.; Schofield, C. J. *Tetrahedron Lett.* **1994**, *35*, 4649−4652. (b) Robinson, J. K.; Lee, V.; Claridge, T. D. W.; Baldwin, J. E.; Schofield, C. J. *Tetrahedron* **1998**, *54*, 981−996. (c) Ishii, K.; Ohno, H.; Takemoto, Y.; Ibuka, T. *Synlett* **1999**, 228−230. (d) Ishii, K.; Ohno, H.; Takemoto, Y.; Osawa, E.; Yamaoka, Y.; Fujii, N.; Ibuka, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2155−2163.

(2) (a) Koskinen, A. M. P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1859−1866. (b) Chung, J. Y. L.; Wasicak, J. T.; Arnold, W. A.; May, C. S.; Nadzan, A. M.; Holladay, M. W. *J. Org. Chem.* **1990**, *55*, 270−275. (c) Holladay, M. W.; Lin, C. W.; May, C. S.; Garvey, D. S.; Witte, D. G.; Miller, T. R.; Wolfram, C. A. W.; Nadzan, A. M. *J. Med. Chem.* **1991**, *34*, 455−457.

(3) Jegham, S.; Das, B. C. *Tetrahedron Lett.* **1988**, *29*, 4419−4422.

(4) (a) Burley, I.; Hewson, A. T. *Tetrahedron Lett.* **1994**, *35*, 7099−7102. (b) Horikawa, M.; Shirahama, H. *Synlett* **1996**, 95−96. (c) Sibi, M. P.; Christensen, J. W. *Tetrahedron Lett.* **1995**, *36*, 6213−6216.

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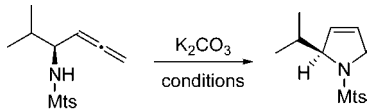
ity.[12,13] In contrast, only limited examples of the *endo*-mode cycloisomerization under basic conditions in the absence of any transition metals are reported to date, which used preactivated allenes **1** (R or R′ = functional group) such as methoxy allenes,[14,15] fluorinated allenes,[16] or allenyl sulfones and related compounds,[17] leading to functionalized cyclized products **5** or **6**.

As a part of our ongoing program directed toward economical and environmentally friendly cyclization of allenic compounds,[18−20] we investigated cycloisomerization of amino allenes without using any transition-metal catalysts. Herein, we describe K_2CO_3-mediated stereospecific cycloisomerization of α-amino allenes, which is the first example of base-induced 5-*endo*-*trig* mode cycloisomerization of simple unactivated allenes in the absence of any activating reagents toward the allenic π-bond.

We prepared α-amino allene **7** according to our reported procedure through the diethylzinc-mediated reductive synthesis of amino allenes catalyzed by palladium(0),[21] starting from L-valine. The choice of Mts as a protecting group was based primarily on its ease of deprotection.[22] First, cycloisomerization of **7** under various basic conditions (NaH/DMF, *t*-BuOK/DMF, or *n*-BuLi/THF, etc.) was investigated, and we found that treatment of **7** with K_2CO_3 in a polar solvent in high temperature afforded the desired cycloisomerized product **8** (Table 1). Among the solvents investigated (Table 1, entries 1−4), DMF has proven to be the solvent of choice for the desired transformation, leading to 3-pyrroline **8** in 84% yield (Table 1, entry 4). A catalytic amount of K_2CO_3 did promote the cycloisomerization (Table 1, entries 5 and 6) but required prolonged reaction time: the cyclization with 0.1 equiv of K_2CO_3 for 120 h yielded **8** (47%) with the recovered starting material (7%). Structure of **8** was unambiguously confirmed by comparison with the authentic sample.[23]

Table 1. Optimization of Reaction Conditions



7 **8**

entry	K_2CO_3 (equiv)	solvent	T (°C)	reaction time (h)	yield[a] (%)
1	1.0	DMSO	180	3	61
2	1.0	DMI	180	1	75
3	1.0	NMP	180	3	80
4	1.0	DMF	reflux	6	84
5	0.5	DMF	reflux	24	71
6	0.1	DMF	reflux	120	47

[a] Isolated yields. Mts = 2,4,6-trimethylphenylsulfonyl.

Next, K_2CO_3-promoted cyclization of other terminal allenes **9**−**12** was investigated (Table 2). The reaction of

(5) (a) Claesson, A.; Sahlberg, C.; Luthman, K. *Acta Chem. Scand.* **1979**, B*33*, 309−310. (b) Lathbury, D.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1986**, 114−115. (c) Kinsman, R.; Lathbury, D.; Vernon, P.; Gallapher, T. *J. Chem. Soc., Chem. Commun.* **1987**, 243−244. (d) Prasad, J. S.; Liebeskind, L. S. *Tetrahedron Lett.* **1988**, *29*, 4253−4256. (e) Fox, D. N. A.; Lathbury, D.; Mahon, M. F.; Molloy, K. C.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1989**, 1073−1075. (f) Ohno, H.; Toda, A.; Miwa, Y.; Taga, T.; Osawa, E.; Yamaoka, Y.; Fujii, N.; Ibuka, T. *J. Org. Chem.* **1999**, *64*, 2992−2993. (g) Dieter, R. K.; Yu, H. *Org. Lett.* **2001**, *3*, 3855−3858.

(6) (a) Olsson, L.-I.; Claesson, A. *Synthesis* **1979**, 743−745. (b) Fujisawa, T.; Maehata, E.; Kohama, H.; Sato, T. *Chem. Lett.* **1985**, 1457−1458. (c) Nikam, S. S.; Chu, K.-H.; Wang, K. K. *J. Org. Chem.* **1986**, *51*, 745−747. (d) Marshall, J. A.; Wang, X.-J. *J. Org. Chem.* **1990**, *55*, 2995−2996. (e) VanBrunt, M. P.; Standaert, R. F. *Org. Lett.* **2000**, *2*, 705−708. (f) Lepage, O.; Kattnig, E.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 15970−15971.

(7) (a) Gill, G. B.; Idris, M. S. H. *Tetrahedron Lett.* **1985**, *26*, 4811−4814. (b) Marshall, J. A.; Wolf, M. A.; Wallace, E. M. *J. Org. Chem.* **1997**, *62*, 367−371. (c) Yoneda, E.; Kaneko, T.; Zhang, S.-W.; Onitsuka, K.; Takahashi, S. *Org. Lett.* **2000**, *2*, 441−443.

(8) Hashmi, A. S. K.; Ruppert, T. L.; Knöfel, T.; Bats, J. W. *J. Org. Chem.* **1997**, *62*, 7295−7304.

(9) (a) Ma, S.; Yu, Z.; Wu, S. *Tetrahedron* **2001**, *57*, 1585−1588. (b) Kel′in, A. V.; Gevorgyan, V. *J. Org. Chem.* **2002**, *67*, 95−98.

(10) Marshall, J. A.; Robinson, E. D. *J. Org. Chem.* **1990**, *55*, 3450−3451.

(11) For a related cycloisomerizations, see: (a) Arseniyadis, S.; Sartoretti, J. *Tetrahedron Lett.* **1985**, *26*, 729−732. (b) Grimaldi, J.; Cormons, A. *Tetrahedron Lett.* **1986**, *27*, 5089−5090. (c) Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 5421−5424. (d) Arredondo, V. M.; Tian, S.; McDonald, F. E.; Marks, T. J. *J. Am. Chem. Soc.* **1999**, *121*, 3633−3639. (e) Ha, J. D.; Cha, J. K. *J. Am. Chem. Soc.* **1999**, *121*, 10012−10020.

(12) (a) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285−2288. (b) Hoffman-Röder, A.; Krause, N. *Org. Lett.* **2001**, *3*, 2537−2538. (c) Morita, N.; Krause, N. *Org. Lett.* **2004**, *6*, 4121−4123. (d) Lee, P. H.; Kim, H.; Lee, K.; Kim, M.; Noh, K.; Kim, H.; Seomoon, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 1840−1843.

(13) For HCl gas-mediated cyclization, see: Krause, N.; Laux, M.; Hoffmann-Röder, A. *Tetrahedron Lett.* **2000**, *41*, 9613−9616.

(14) (a) Gange, D.; Magnus, P. *J. Am. Chem. Soc.* **1978**, *100*, 7746−7747. (b) Hormuth, S.; Reissig, H.-U. *J. Org. Chem.* **1994**, *59*, 67−73. (c) Breuil-Desvergnes, V.; Compain, P.; Vatèle, J.-M.; Goré, J. *Tetrahedron Lett.* **1999**, *40*, 5009−5012. (d) Amombo, M. O.; Hausherr, A.; Reissig, H.-U. *Synlett* **1999**, 1871−1874. (e) Breuil-Desvergnes, V.; Goré, J. *Tetrahedron* **2001**, *57*, 1939−1950. (f) Flögel, O.; Amombo, M. G. O.; Reissig, H.-U.; Zahn, G.; Brüdgam, I.; Hartl, H. *Chem. Eur. J.* **2003**, *9*, 1405−1415.

(15) A methoxy group on the allenic carbon promotes single electron transfer from the dimsylate anion to give radical anion intermediate; see: Magnus, P.; Albaugh-Robertson, P. *J. Chem. Soc., Chem. Commun.* **1984**, 804−806.

(16) (a) Wang, Z.; Hammond, G. B. *J. Org. Chem.* **2000**, *65*, 6547−6552. (b) Lan, Y.; Hammond, G. B. *Org. Lett.* **2002**, *4*, 2437−2439.

(17) (a) Mukai, C.; Yamashita, H.; Hanaoka, M. *Org. Lett.* **2001**, *3*, 3385−3387. (b) Mukai, C.; Ohta, M.; Yamashita, H.; Kitagaki, S. *J. Org. Chem.* **2004**, *69*, 6867−6873. See also: (c) Pravia, K.; White, R.; Fodda, R.; Maynard, D. F. *J. Org. Chem.* **1996**, *61*, 6031−6032.

(18) For our recent contribution on [2 + 2] cycloisomerization of allenenes or allenynes without using any reagents or catalysts, see: Ohno, H.; Mizutani, T.; Kadoh, Y.; Miyamura, K.; Tanaka, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 5113−5115.

(19) For our recent contribution on tandem cyclization of allenenes and related compounds, see: (a) Ohno, H.; Miyamura, K.; Takeoka, Y.; Tanaka, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 2647−2650. (b) Ohno, H.; Miyamura, K.; Mizutani, T.; Kadoh, Y.; Takeoka, Y.; Hamaguchi, H.; Tanaka, T. *Chem. Eur. J.* **2005**, *11*, 3728−3741. (c) Ohno, H.; Yamamoto, M.; Iuchi, M.; Tanaka, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 5103−5106.

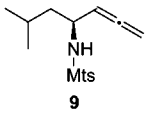
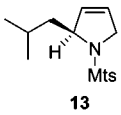
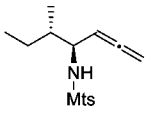
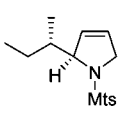
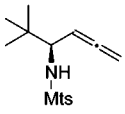
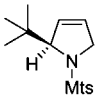
(20) For our recent contribution on tandem reaction of bromoallenes, see: (a) Ohno, H.; Hamaguchi, H.; Ohata, M.; Tanaka, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 1749−1753. (b) Ohno, H.; Hamaguchi, H.; Ohata, M.; Kosaka, S.; Tanaka, T. *Heterocycles* **2003**, *61*, 65−68. (c) Ohno, H.; Hamaguchi, H.; Ohata, M.; Kosaka, S.; Tanaka, T. *J. Am. Chem. Soc.* **2004**, *126*, 8744−8754. (d) Hamaguchi, H.; Kosaka, S.; Ohno, H.; Tanaka, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 1513−1517. (e) Ohno, H. *Chem. Pharm. Bull.* **2005**, *53*, 1211−1226. (f) Ohno, H. *Yakugaku Zasshi* **2005**, *125*, 899−925.

(21) (a) Ohno, H.; Toda, A.; Oishi, S.; Tanaka, T.; Takemoto, Y.; Fujii, N.; Ibuka, T. *Tetrahedron Lett.* **2000**, *41*, 5131−5134. (b) Ohno, H.; Miyamura, K.; Tanaka, T.; Oishi, S.; Toda, A.; Takemoto, Y.; Fujii, N.; Ibuka, T. *J. Org. Chem.* **2002**, *67*, 1359−1367.

(22) Unfortunately, treatment of *N*-Boc derivatives under the K_2CO_3-mediated cyclization conditions gave a mixture of unidentified products.

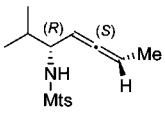
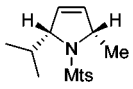
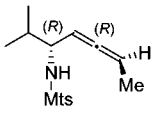
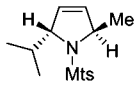
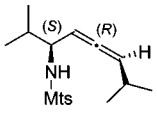
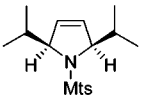
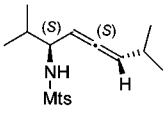
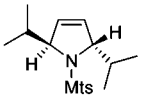
(23) Cyclized products **8**, **14**, and the enantiomers of **21** and **22** were previously prepared by our group, see refs 1c,d and 5f.

Table 2. K_2CO_3-Promoted Cycloisomerization of Terminal Allenes[a]

entry	substrate	time (h)	product	yield (%)[b]
1	 **9**	120	 **13**	61
2	 **10**	72	 **14**	60
3	 **11**	20	 **15**	78
4	 **12**	1	 **16**	77

[a] All reactions were carried out in the presence of K_2CO_3 (1 equiv) in DMF under reflux. [b] Isolated yields.

Table 3. K_2CO_3−Promoted Cycloisomerization of Internal Allenes[a]

entry	substrate	time (h)	product	yield (%)[b]
1	 **17**	18	 **21**	80
2	 **18**	102	 **22**	83
3	 **19**	24	 **23**	87
4	 **20**	312	 **24**	75

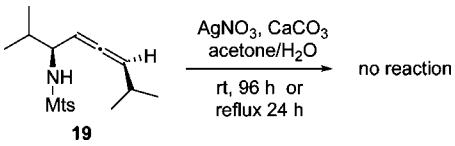
[a] All reactions were carried out in the presence of K_2CO_3 (1 equiv) in DMF under reflux. [b] Isolated yields.

amino allene **9** or **10** having an isobutyl group or a *sec*-butyl group, respectively, at the α-position of the allenic moiety with K_2CO_3 in DMF under reflux yielded the desired cyclized products **13** and **14** in 61% and 60% yields, respectively (Table 2, entries 1 and 2). Interestingly, both the allenes **11** with a bulky *tert*-butyl group and **12** without the α-substituent gave 3-pyrrolines **15** and **16** in slightly improved yields (77−78%). The required reaction time for this transformation is highly dependent on the α-substituent (1−120 h). Among the terminal allenes **7** and **9**−**12**, the α-unsubstituted amino allenes **12** showed the highest reactivity toward the K_2CO_3-mediated cycloisomerization: the reaction was completed within 1 h under the standard reaction conditions.

Then, the cycloisomerization of diastereomerically pure internal allenes bearing an α-amino group was investigated. The requisite chiral internal allenes **17**−**20** were easily prepared by organocopper-mediated stereospecific ring-opening reaction of 2-ethynylaziridines derived from L- or D-amino acids.[24] The results of the cycloisomerization reaction are summarized in Table 3. We were pleased to find that the reaction of all the internal allenes yielded 2,5-disubstituted 3-pyrrolines in a stereospecific manner and in good yields (75−87%). The reaction of (*R*,a*S*)- and (*S*,a*R*)-allenes **17** and **19**, respectively, completed within 24 h to give the 2,5-*cis*-3-pyrrolines **21** and **23**. In contrast, the reactivity of (*R*,a*R*)- and (*S*,a*S*)-allenes **18** and **20** was relatively low: the 2,5-*trans*-3-pyrrolines **22** and **24**, the latter having C_2-symmetry, were obtained after prolonged reaction time (102−312 h) but in good yields.[25] The relative configuration of the cyclized products **21** and **22** was determined by comparison with the authentic samples.[23]

It should be clearly noted that the internal allene **19** bearing an isopropyl group on the allenic carbon was completely inert toward the well-established silver(I)-mediated cyclization (Scheme 2). This result can be attributed to the steric

Scheme 2



crowding of the allenic moiety that inhibits access or coordination of silver to the allenic double bond. In contrast, K_2CO_3-induced reaction of **19** afforded the sterically congested *meso*-2,5-disubstituted 3-pyrroline **23** in 87% yield (Table 3, entry 3), presumably because these conditions activate the nitrogen atom of the amino allene **19**.

In conclusion, we have first demonstrated that cycloisomerization of unactivated allenes having a sulfonamide group can be promoted under simple basic conditions using

(24) (a) Ohno, H.; Toda, A.; Miwa, Y.; Taga, T.; Fujii, N.; Ibuka, T. *Tetrahedron Lett.* **1999**, *40*, 349−352. (b) Ohno, H.; Toda, A.; Fujii, N.; Takemoto, Y.; Tanaka, T.; Ibuka, T. *Tetrahedron* **2000**, *56*, 2811−2820.

(25) The lower reactivity of **18** and **20** will be an influence of the Mts group: the aryl group of Mts will direct the opposite side to the isopropyl group at the α position, which may cause an unfavorable steric interaction to the alkyl group on the allenyl carbon on cyclization. However, the exact reason for their lower reactivity is unclear.

K_2CO_3 in DMF. The present transformation is economical and applicable to the synthesis of a wide variety of 3-pyrrolines including highly congested ones. The scope and limitation of the reaction, as well as further transformation to complex nitrogen heterocycles, are currently under investigation.

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Supporting Information Available: Representative experimental procedure, as well as ^1H NMR spectra for the novel cyclized products. This material is available free of charge via the Internet at http://pubs.acs.org.

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