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Synthesis of Chiral Amino Allenes *via* an Organocyanocuprate-Mediated Ring-Opening Reaction of Enantiopure Ethynylaziridines

Hiroaki Ohno, Ayako Toda, Yoshihisa Miwa, Tooru Taga, Nobutaka Fujii, and Toshiro Ibuka*

Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan

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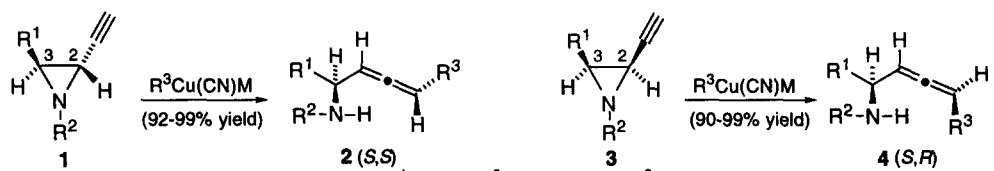
Abstract: Amino allenes have been synthesized from 2-ethynylaziridines *via* organocopper-mediated reactions. Whereas treatment of enantiomerically pure (2*R*,3*S*)-2,3-*trans*-3-alkyl-2-ethynylaziridines with RCu(CN)M (M = Li or MgX) yield exclusively (*S*,*S*)-allenylamines in high yields, isomeric (2*S*,3*S*)-2,3-*cis*-3-alkyl-2-ethynylaziridines afford (*S*,*R*)-allenylamines in comparable high yields.

The synthesis and reactions of mono- and di-substituted allenic compounds have attracted considerable attention in recent years.[1,2] Among various substituted allenes, amino allenes constitute an important class of molecules with interesting chemical properties due to their cumulated double bond.[3-5] The presence in allene compounds of a nitrogen functionality separated from the allenic carbon atom by one,[3] three,[4] and four[5] carbon atoms are attractive substrates for constructing five- and six-membered aza-heterocycles.[3d,4a-e,5] However, except for a few cases,[1c,2j,3f,3g,4b] relatively little synthetic work has been done on enantiomerically pure amino allenes. In connection with a programme directed towards the reaction of chiral amino allenes, we required a reliable procedure for the synthesis of amino allenes with high optical purity.

Until now, although the stereochemical course of an organocopper-mediated *anti*-S_N2' substitution[6] of alkynyloxiranes[7] and acetates[8] or sulfonates[9] of propargylic alcohols has been well documented, the ring-opening reaction of ethynylaziridines to form amino allenes is not known. It is of considerable interest to determine whether chiral ethynylaziridines can be transformed diastereoselectively into amino allenes with high optical purity. We wish to report a highly efficient ring-opening reaction of chiral 2,3-*trans*- and 2,3-*cis*-ethynylaziridines[10] affording the corresponding (*S*,*S*)- and (*S*,*R*)-amino allenes in both excellent isolated yields and high enantiomeric purities as illustrated in Scheme 1.



1 **2** (*S*,*S*) **3** **4** (*S*,*R*)

Abbreviations: M = Li or MgBr; R^1 = alkyl; R^2 = arylsulfonyl; R^3 = alkyl or tri-*n*-butylstannyl

Scheme 1. Synthesis of amino allenes *via* an organocopper–mediated reaction

The requisite activated 2,3-*trans*- and 2,3-*cis*-3-alkyl-2-ethynylaziridines for the present preliminary study were prepared in a straightforward manner from natural α-amino acids.[10] We initiated our study with investigation of the reactions of 2,3-*cis*-2-ethynylaziridine **5** with several organocopper reagents as shown in Scheme 2 and Table 1. The reaction of **5** in THF with Gilman-type reagent, $Me_2CuLi{\cdot}3LiI$, afforded a separable mixture of **6** (an *anti*-S_N2' product), **7** (a *syn*-S_N2' product), and **8** (a reduction product) in which the undesired product **8** predominated (entry 1, Table 1). In a similar manner, exposure of **5** to higher-order

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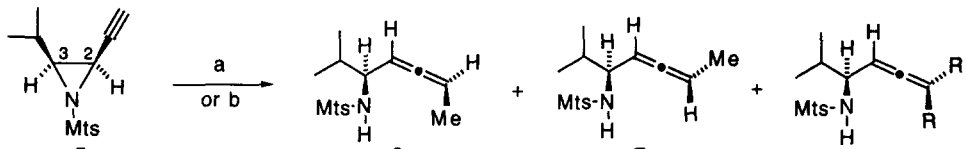
cyanocuprate, $Me_2Cu(CN)Li_2{\cdot}2LiBr{\cdot}2LiCl$,[11] led to the isolation of a mixture of **6**, **7**, and the dimethylated compound **9** (entry 2, Table 1). Claesson and Olsson had previously reported that certain allenes were racemized by treatment with organocuprates.[12] However, this was not to be the present case since exposure of the chiral allene **6** to $Me_2Cu(CN)Li_2{\cdot}2LiCl$ completely recovered the starting allene **6** unchanged. In the reactions of certain alkenyloxiranes[13] and propargylic substrates[14] with organocopper reagents, it has been frequently documented that small changes in the reaction conditions (solvents and reagents) and substrate structure can alter the course of reactions, but the reaction products such as **8** and **9** are particularly striking examples.



Reagents and *abbreviation*: a = $Me_2CuLi{\cdot}3LiI$; b = $Me_2Cu(CN)Li_2{\cdot}2LiBr{\cdot}2LiCl$; Mts = 2,4,6-trimethylbenzenesulfonyl

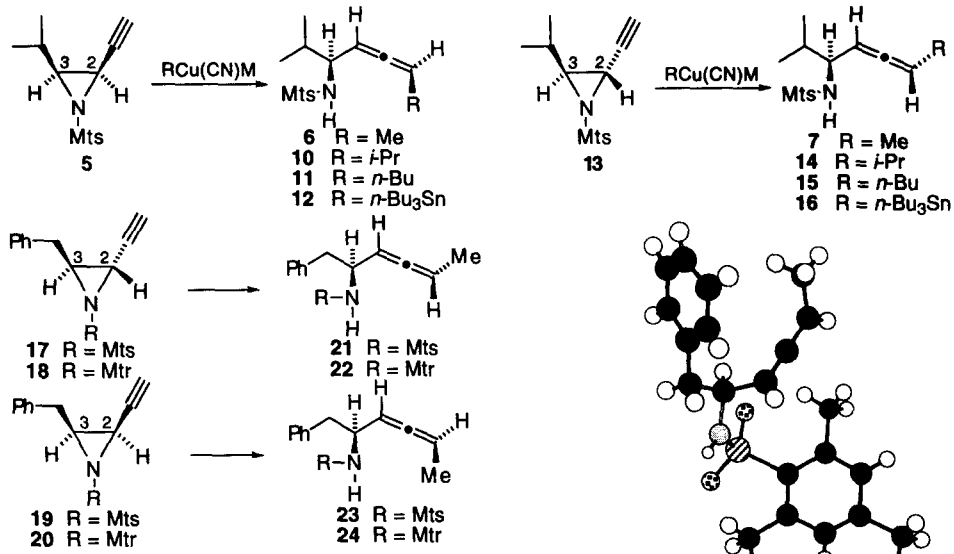
Scheme 2

Table 1. Reactions of 2-Ethynylaziridines with Organocopper Reagents[a]

entry	substr.	reagent	reaction time	product(s)	absolute config.	ratio[b]	yield[c]
1	**5**	$Me_2CuLi{\cdot}3LiI$	0.5 h	**6+7+8**		**6**:**7**:**8** = 25:2:73	78%
2	**5**	$Me_2Cu(CN)Li_2{\cdot}2LiBr{\cdot}2LiCl$	0.5 h	**6+7+9**		**6**:**7**:**9** = 45:18:37	72%
3	**5**	$MeCu(CN)Li{\cdot}LiBr{\cdot}2LiCl$	3.0 h	**6**	(*S*,*R*)	**6** = 100	93%
4	**5**	*i*-$PrCu(CN)MgCl{\cdot}2LiCl$	0.5 h	**10**	(*S*,*R*)	**10** = 100	99%
5	**5**	*n*-$BuCu(CN)Li{\cdot}2LiCl$	0.5 h	**11**	(*S*,*R*)	**11** = 100	97%
6	**5**	$Bu_3SnCu(CN)Li{\cdot}2LiCl$	0.5 h	**12**	(*S*,*R*)	**12** = 100	90%
7	**13**	$MeCu(CN)Li{\cdot}LiBr{\cdot}2LiCl$	0.5 h	**7**	(*S*,*S*)	**7** = 100	98%
8	**13**	*i*-$PrCu(CN)MgCl{\cdot}2LiCl$	0.5 h	**14**	(*S*,*S*)	**14** = 100	98%
9	**13**	*n*-$BuCu(CN)Li{\cdot}2LiCl$	0.5 h	**15**	(*S*,*S*)	**15** = 100	99%
10	**13**	$Bu_3SnCu(CN)Li{\cdot}2LiCl$	0.5 h	**16**	(*S*,*S*)	**16** = 100	92%
11	**17**	$MeCu(CN)Li{\cdot}LiBr{\cdot}2LiCl$	0.5 h	**21**	(*S*,*S*)	**21** = 100	99%
12	**18**	$MeCu(CN)Li{\cdot}2LiCl$	0.5 h	**22**	(*S*,*S*)	**22** = 100	97%
13	**19**	$MeCu(CN)Li{\cdot}LiBr{\cdot}2LiCl$	2 h	**23**	(*S*,*R*)	**23** = 100	96%
14	**20**	$MeCu(CN)Li{\cdot}2LiCl$	6 h	**24**	(*S*,*R*)	**24** = 100	99%
15	**ent-5**	$MeCu(CN)Li{\cdot}LiBr{\cdot}2LiCl$	1.2 h	**ent-6**	(*R*,*S*)	**ent-6** = 100	88%
16	**ent-5**	$EtCu(CN)MgBr{\cdot}2LiCl$	0.0 h	**25**	(*R*,*S*)	**25** = 100	89%
17	**ent-13**	$MeCu(CN)Li{\cdot}2LiCl$	0.5 h	**ent-7**	(*R*,*R*)	**ent-7** = 100	90%
18	**ent-13**	$EtCu(CN)MgBr{\cdot}2LiCl$	0.0 h	**26**	(*R*,*R*)	**26** = 100	97%

(a) All reactions were carried out in THF at –78 °C using 4 equiv of organocopper reagents. (b) Ratios were determined by isolation or HPLC. (c) Isolated yields.

After considerable experimentation, it was found that organocyanocuprates, $RCu(CN)M{\cdot}nLiX$ (M = Li or MgBr, X = Cl or Br), are the reagent of choice for the aziridine-ring opening reactions, giving excellent isolated yields of the corresponding *anti*-S_N2' products (Scheme 3). Typically, reaction of the aziridine **5** with $MeCu(CN)Li{\cdot}LiBr{\cdot}2LiCl$ in THF at - 78 °C for 30 min afforded the expected enantiomerically pure amino allene **6** (an *anti*-S_N2' product) as a single isomer in 93% isolated yield (entry 3, Table 1). While we cannot conclusively rule out the presence of trace quantities of isomeric- or reduction-product, the (*S*,*R*) product **6** was the only one detected by HPLC analysis. Similarly, exposure of **5** to *i*-$PrCu(CN)MgBr{\cdot}2LiCl$, *n*-$BuCu(CN)Li{\cdot}2LiCl$, and *n*-$Bu_3SnCu(CN)Li{\cdot}2LiCl$ yields the corresponding ring-opening products **10**, **11**, and **12** in excellent yields (entries 4-6, Table 1). The 2,3-*trans*-isomer **13** also gave exclusively the *anti*-S_N2' products **7**, **14**, **15**, and **16** (entries 7-10, Table 1).

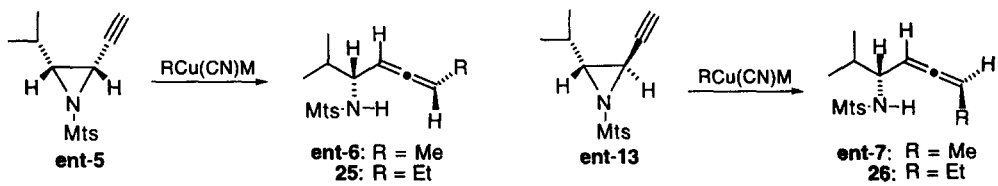


Abbreviations: Mts = 2,4,6-trimethylbenzenesulfonyl; Mtr = 4-methoxy-2,4,6-trimethylbenzenesulfonyl.

Solid-state conformation of **21**

Scheme 3

The ethynylaziridines **17-20** also gave the corresponding amino allenes **21-24** by treatment with organocyanocuprates (Scheme 3; entries 11-14, Table 1). Although the absolute configuration of all the amino allenes synthesized could be deduced from the well-established organocyanocuprate-mediated *anti* S_N2' pathway,[1c,6,7] the unambiguous structure assignment for **21** rested on X-ray analysis.[15] The X-ray data are consistent with a net S_N2' substitution reaction. For the purpose of synthetic transformation of amino allenes into bioactive compounds, the amino allenes **ent-6**, **ent-7**, **25**, and **26** have also been synthesized from the corresponding ethynylaziridines **ent-5** and **ent-13** (Scheme 4; entries 15-18,Table 1).



Abbreviations: Mts = 2,4,6-trimethylbenzenesulfonyl; Mtr = 4-methoxy-2,4,6-trimethylbenzenesulfonyl.

Scheme 4

In summary, chiral amino allenes with high optical puritiy have been synthesized from (2*R*,3*S*)-2,3-*cis*- or (2*S*,3*S*)-2,3-*trans*-2-ethynylaziridines via organocopper-mediated reactions. Work on synthetic transformations of amino allenes thus obtained is in progress and will be reported elsewhere in due course.

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References and Notes

1. For reviews, see (a) Smadja, W. *Chem. Rev.* **1983**, *83*, 263. (b) Brandsma, L.; Verkruijsse, H. D. In "Synthesis of Acetylenes, Allenes and Cumulenes", Elsevier, New York, 1981. (c) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31.

2. (a) Shimizu, I.; Tsuji, J. *Chem. Lett.* **1984**, 233. (b) Marshall, J. A.; Wang, X.-J. *J. Org. Chem.* **1991**, *56*, 960. (c) Larock, R. C.; Zenner, J. M. *J. Org. Chem.* **1995**, *60*, 482. (d) Besson, L.; Goré, J.; Cazes, B. *Tetrahedron Lett.* **1995**, *36*, 3857. (e) Desarbre, E.; Mérour, J.-Y. *Tetrahedron Lett.* **1996**, *37*, 43. (f) Al-Masum, M.; Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* **1997**, *38*, 6071. (g) Hiroi, K.; Kato, F.; Yamagata, A. *Chem. Lett.* **1998**, 397. (h) Ogawa, A.; Kudo, A.; Hirao, T. *Tetrahedron Lett.* **1998**, *39*, 5213. (i) Kamijo, S.; Al-Masum, M.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 691. (j) Marshall, J. A.; Liao, J. *J. Org. Chem.* **1998**, *63*, 5962. (k) Al-Masum, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 3809.
3. (a) Claesson, A.; Sahlberg, C. *Tetrahedron Lett.* **1978**, 1319. (b) Claesson, A.; Sahlberg, C. *J. Organomet. Chem.* **1979**, *170*, 355. (c) Sahlberg, C.; Claesson, A. *Acta Chem. Scand.* **1982**, B36, 179. (d) Claesson, A.; Sahlberg, C.; Luthman, K. *Acta Chem. Scand.* **1979**, B*33*, 309. (e) Xu, Z.; Lu, X. *J. Org. Chem.* **1998**, *63*, 5031. (f) D'Aniello, F.; Mann, A.; Taddei, M.; Wermuth, C.-G. *Tetrahedron Lett.* **1994**, *35*, 7775. (g) D'Aniello, F.; Schoenfelder, A.; Mann, A.; Taddei, M. *J. Org. Chem.* **1996**, *61*, 9631. (h) Imada, Y.; Vasapollo, G.; Alper, H. *J. Org. Chem.* **1996**, *61*, 7982.
4. (a) Arseniyadis, S.; Gore, J. *Tetrahedron Lett.* **1983**, *24*, 3997. (b) Fox, D. N. A.; Lathbury, D.; Mahon, M. F.; Molloy, K. C.; Gallagher, T. *J. Am. Chem. Soc.* **1991**, *113*, 2652. (c) Davies, I. W.; Scopes, D. I. C.; Gallgher, T. *Synlett* **1993**, 85. For related compounds, see (d) Kimura, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *J. Org. Chem.* **1992**, *57*, 6377. (e) Kimura, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **1991**, *32*, 6359.
5. (a) Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 5421. (b) Arredondo, V. M.; McDonald, F. E.; Marks, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 4871.
6. (a) Corey, E. J. ; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3059 and 3063. (b) Lipshutz, B. H.; Sengupta, S. In *Organic Reactions*; Paquette, L. A. Ed.; John Wiley & Sons: New York, **1992**; vol 41, pp 135-631. (c) Ibuka, T.; Yamamoto. Y. In *Organocopper Reagents*; Taylor, R. J. K. Ed.; Oxford University Press: Oxford, **1994**, 143. (d) Aoyama, H.; Mimura, N.; Ohno, H.; Ishii, K.; Toda, A.; Tamamura, H.; Otaka, A.; Fujii, N.; Ibuka, T. *Tetrahedron Lett*, **1997**, 38, 7383. (e) Toda, T.; Aoyama, H.; Mimura, N.; Ohno, H.; Fujii, N.; Ibuka, T. *J. Org. Chem.* **1998**, *63*, 7053. (f) Cantrill, A. A.; Jarvis, A. N.; Osborn, H. M. I.; Ouadi, A.; Sweeney, J. B. *Synlett* **1996**, 847.
7. (a) Marshall, J. A.; Pinney, K. G. *J. Org. Chem.* **1993**, *58*, 7180. (b) Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J.-F. *Tetrahedron* **1991**, *47*, 1677.
8. Spino, C.; Thibault, C.; Gingras, S. *J. Org. Chem.* **1998**, *63*, 5283.
9. (a) Marshall, J. A.; Wang, X.-J. *J. Org. Chem.* **1992**, *57*, 3387. (b) Elsevier, C. J.; Vermeer, P. *J. Org. Chem.* **1989**, *54*, 3726. (c) Buckle, M. J. C.; Fleming, I. *Tetrahedron Lett.* **1993**, *34*, 2383.
10. Ohno, H.; Toda, A.; Fujii, N.; Ibuka, T. *Tetrahedron: Asymmetry*, in print.
11. $Me_2Cu(CN)Li_2 \cdot 2LiBr \cdot 2LiCl$ may be better represented as $Me_2CuLi \cdot LiCN \cdot 2LiBr \cdot 2LiCl$. We are not concerned about the exact constitution, but watch the species as a reagent system. Lipshutz, B. H. In *Organocopper Reagents*; Taylor, R. J. K., Ed.; Oxford University Press: Oxford, 1994; 105. See also (a) Bertz, S. H.; Miao, G.; Eriksson, M. *J. Chem. Soc., Chem. Comm.* **1996**, 815. (b) Kronenburg, C. M. P.; Jastrzebski, J. T. B. H; Spek, A. L.; van Koten, G. *J. Am. Chem. Soc.* **1998**, 120, 9688. (c) Boche, G.; Bosold, F.; Marsch, M.; Harms, K. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1684.
12. Claesson, A.; Olsson, L.-I. *J. Chem. Soc., Chem. Commun.* **1979**, 524.
13. Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J.-F. *Tetrahedron Lett.* **1989**, *30*, 2387.
14. (a) MacDonald, T. L.; Reagan, D. R.; Brinkmeyer, R. S. *J. Org. Chem.* **1980**, *45*, 4740. (b) Oehlschlager, A. C.; Czyzewska, E. *Tetrahedron Lett.* **1983**, *24*, 5587. (c) Krause, N.; Handke, G. *Tetrahedron Lett.* **1991**, *32*, 7229. (d) Reich, H. J.; Eisenhart, E. K.; Whipple, W. L.; Kelly, M. J. *J. Am. Chem. Soc.* **1988**, *110*, 6432.
15. X-Ray crystallographic data, and the table of atomic coordinates have been deposited at the Cambridge Crystallographic Centre.