

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

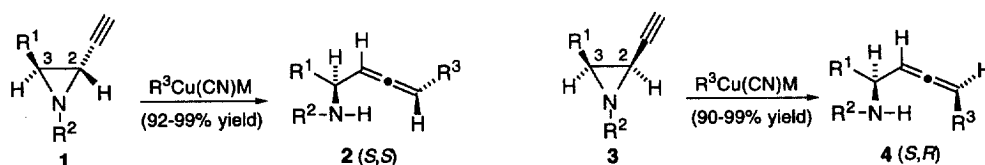
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Abstract: Amino allenes have been synthesized from 2-ethynylaziridines *via* organocopper-mediated reactions. Whereas treatment of enantiomerically pure (2*R*,3*S*)-2,3-*trans*-3-alkyl-2-ethynylaziridines with $\text{RCu}(\text{CN})\text{M}$ ($\text{M} = \text{Li}$ 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.
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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 four⁵ carbon atoms are attractive substrates for constructing five- and six-membered aza-heterocycles.^{3d,4a-c,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.

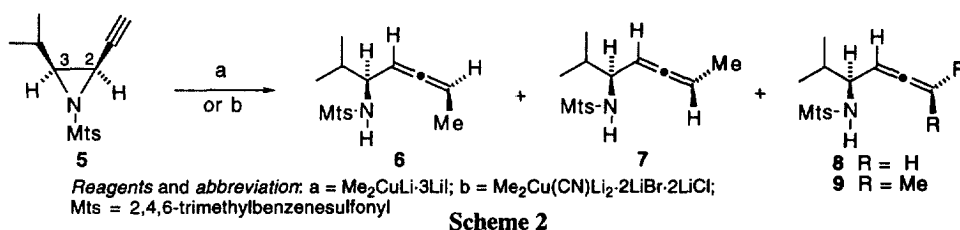
Until now, although the stereochemical course of an organocopper-mediated *anti*- $\text{S}_{\text{N}}2'$ substitution⁶ of alkynylloxiranes⁷ and acetates⁸ or sulfonates⁹ of propargylic alcohols has been well documented, the ring-opening reaction of ethynylaziridines to form amino allenes is not known. 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*-ethynylaziridines¹⁰ affording the corresponding (*S,S*)- and (*S,R*)-amino allenes in both excellent isolated yields and high enantiomeric purities as illustrated in Scheme 1.



Abbreviations: $\text{M} = \text{Li}$ or MgBr ; $\text{R}^1 = \text{alkyl}$; $\text{R}^2 = \text{arylsulfonyl}$; $\text{R}^3 = \text{alkyl}$ 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, $\text{Me}_2\text{CuLi} \cdot 3\text{LiI}$, afforded a separable mixture of **6** (an *anti*- $\text{S}_{\text{N}}2'$ product), **7** (a *syn*- $\text{S}_{\text{N}}2'$ 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

cyanocuprate, $\text{Me}_2\text{Cu}(\text{CN})\text{Li}_2\cdot 2\text{LiBr}\cdot 2\text{LiCl}$,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 $\text{Me}_2\text{Cu}(\text{CN})\text{Li}_2\cdot 2\text{LiCl}$ completely recovered the starting allene **6** unchanged. In the reactions of certain alkenyloxiranes¹³ and propargylic substrates¹⁴ 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.



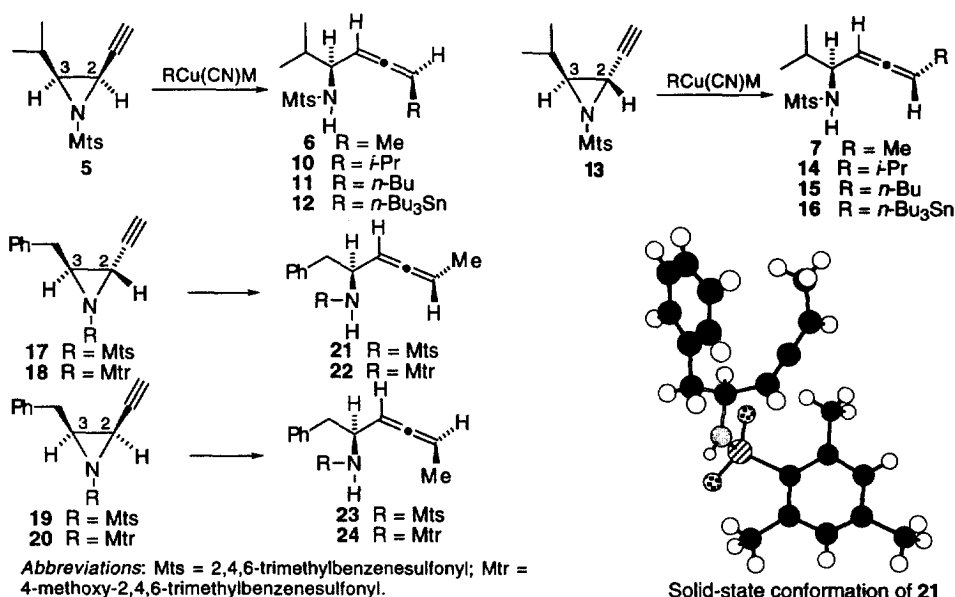
Scheme 2

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	$\text{Me}_2\text{CuLi}\cdot 3\text{LiI}$	0.5 h	6+7+8		6:7:8 = 25:2:73	78%
2	5	$\text{Me}_2\text{Cu}(\text{CN})\text{Li}_2\cdot 2\text{LiBr}\cdot 2\text{LiCl}$	0.5 h	6+7+9		6:7:9 = 45:18:37	72%
3	5	$\text{MeCu}(\text{CN})\text{Li}\cdot \text{LiBr}\cdot 2\text{LiCl}$	3.0 h	6	(<i>S,R</i>)	6 = 100	93%
4	5	<i>i</i> -PrCu(CN)MgCl·2LiCl	0.5 h	10	(<i>S,R</i>)	10 = 100	99%
5	5	<i>n</i> -BuCu(CN)Li·2LiCl	0.5 h	11	(<i>S,R</i>)	11 = 100	97%
6	5	$\text{Bu}_3\text{SnCu}(\text{CN})\text{Li}\cdot 2\text{LiCl}$	0.5 h	12	(<i>S,R</i>)	12 = 100	90%
7	13	$\text{MeCu}(\text{CN})\text{Li}\cdot \text{LiBr}\cdot 2\text{LiCl}$	0.5 h	7	(<i>S,S</i>)	7 = 100	98%
8	13	<i>i</i> -PrCu(CN)MgCl·2LiCl	0.5 h	14	(<i>S,S</i>)	14 = 100	98%
9	13	<i>n</i> -BuCu(CN)Li·2LiCl	0.5 h	15	(<i>S,S</i>)	15 = 100	99%
10	13	$\text{Bu}_3\text{SnCu}(\text{CN})\text{Li}\cdot 2\text{LiCl}$	0.5 h	16	(<i>S,S</i>)	16 = 100	92%
11	17	$\text{MeCu}(\text{CN})\text{Li}\cdot \text{LiBr}\cdot 2\text{LiCl}$	0.5 h	21	(<i>S,S</i>)	21 = 100	99%
12	18	$\text{MeCu}(\text{CN})\text{Li}\cdot 2\text{LiCl}$	0.5 h	22	(<i>S,S</i>)	22 = 100	97%
13	19	$\text{MeCu}(\text{CN})\text{Li}\cdot \text{LiBr}\cdot 2\text{LiCl}$	2 h	23	(<i>S,R</i>)	23 = 100	96%
14	20	$\text{MeCu}(\text{CN})\text{Li}\cdot 2\text{LiCl}$	6 h	24	(<i>S,R</i>)	24 = 100	99%
15	ent-5	$\text{MeCu}(\text{CN})\text{Li}\cdot \text{LiBr}\cdot 2\text{LiCl}$	1.2 h	ent-6	(<i>R,S</i>)	ent-6 = 100	88%
16	ent-5	$\text{EtCu}(\text{CN})\text{MgBr}\cdot 2\text{LiCl}$	0.0 h	25	(<i>R,S</i>)	25 = 100	89%
17	ent-13	$\text{MeCu}(\text{CN})\text{Li}\cdot 2\text{LiCl}$	0.5 h	ent-7	(<i>R,R</i>)	ent-7 = 100	90%
18	ent-13	$\text{EtCu}(\text{CN})\text{MgBr}\cdot 2\text{LiCl}$	0.0 h	26	(<i>R,R</i>)	26 = 100	97%

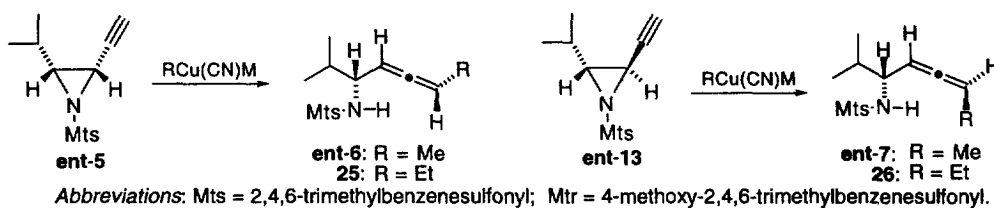
(a) All reactions were carried out in THF at -78°C using 4 equiv of organocopper reagents. (b) Ratios were determined by isolation or HPLC. (c) Isolated yields.

After considerable experimentation, it was found that organocyanocuprates, $\text{RCu}(\text{CN})\text{M}\cdot n\text{LiX}$ ($\text{M} = \text{Li}$ or MgBr , $\text{X} = \text{Cl}$ or Br), are the reagent of choice for the aziridine-ring opening reactions, giving excellent isolated yields of the corresponding *anti*- $\text{S}_{\text{N}}2'$ products (Scheme 3). Typically, reaction of the aziridine **5** with $\text{MeCu}(\text{CN})\text{Li}\cdot \text{LiBr}\cdot 2\text{LiCl}$ in THF at -78°C for 30 min afforded the expected enantiomerically pure amino allene **6** (an *anti*- $\text{S}_{\text{N}}2'$ 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·2LiCl, *n*-BuCu(CN)Li·2LiCl, and *n*-Bu₃SnCu(CN)Li·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*- $\text{S}_{\text{N}}2'$ products **7**, **14**, **15**, and **16** (entries 7–10, Table 1).



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).



Scheme 4

In summary, chiral amino allenes with high optical purity have been synthesized from (*2R,3S*)-2,3-*cis*- or (*2S,3S*)-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.

Acknowledgments

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