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Regio- and Stereoselectivity in Reactions of 2,3-*cis*- and *trans*-3-Alkyl-2-Vinylaziridines with Organocopper Reagents: Importance of 2,3-*cis*-Stereochemistry in Controlling Selectivity

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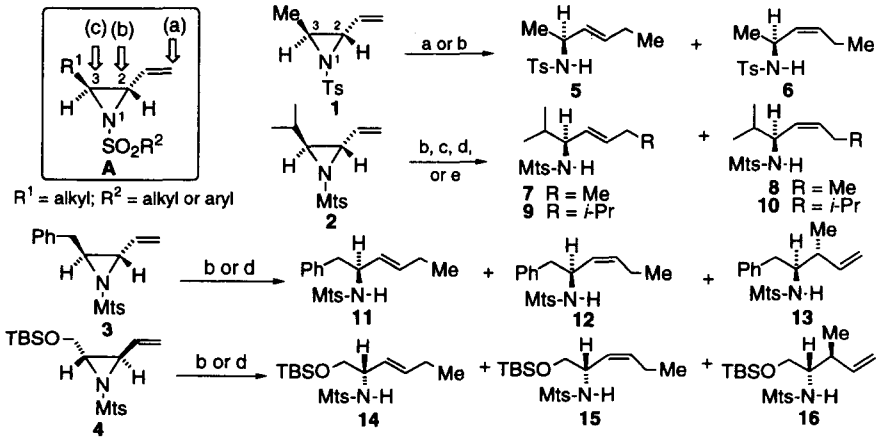
Abstract: By treatment with organocopper reagents, *N*-activated 2,3-*cis*-3-alkyl-2-vinylaziridines produced exclusively (*E*)-allyl amines in high yields, presumably via an *anti*-S_N2' reaction pathway. On the other hand, under otherwise identical conditions, *N*-activated 2,3-*trans*-3-alkyl-2-vinylaziridines gave an 85-96:15-4 mixture of (*E*)- and (*Z*)-allyl amines. In reactions of certain *N*-activated 2,3-*trans*-3-alkyl-2-vinylaziridines, S_N2 reaction products were obtained in only 2-3% yield.

Despite their potential usefulness for the synthesis of various compounds such as aza-heterocycles,[1] β-lactams,[2] alkaloids,[3] dipeptide isosteres,[4] and sphingoshines,[5] to date 2-vinylaziridines[6] have scarcely been studied from the view point of organocopper-mediated substitution reactions. We became interested in the question of how stereochemistry at the C-2 and C-3 positions of the aziridines influences stereochemistry of organocopper-mediated reaction products. Such reactions may provide a good testing ground to examine subtle steric effects of reactant stereochemistries of the aziridine ring, since the product mixture will be a fingerprint of the structure of the reaction intermediates.

While this work was in progress, an independent report by Sweeney and co-workers appeared.[7] Although it was our intention to defer publication until energy calculations of possible reaction intermediates were accomplished, the publication of Sweeney describing ring-opening reactions of 2,3-*trans*-*N*-diphenylphosphinyl-2-phenyl-3-vinylaziridines with nucleophilic reagents such as organocopper species prompts us to report our chemical results at this time.



Scheme 1 *Reagents:* a. MeCu·LiBr·LiI; b. MeCu(CN)Li·LiI; c. $Me_2CuLi·LiI·LiBr$; d. MeCu·2LiI; e. *i*-PrCu(CN)MgCl
Abbreviation: Mts = 2,4,6-trimethylbenzenesulfonyl

Since the regio- and (*E*)- and (*Z*)-stereoselectivity of the reaction may be controlled by a subtle balance of steric and electronic factors, it is not easy to predict with confidence whether the most reactive position toward

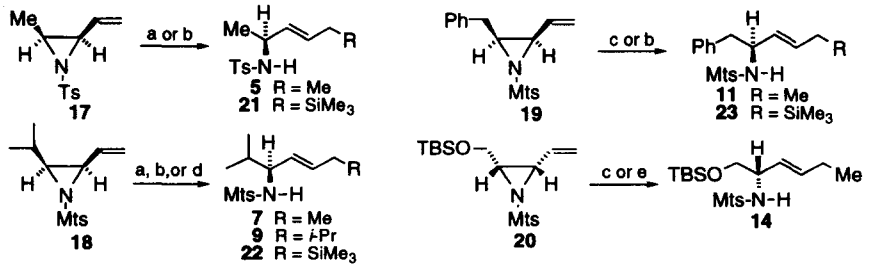
nucleophilic reagents would be (a) (S_N2' reaction), (b) (S_N2 reaction), or (c) (S_N2 reaction) (structure **A** in Scheme 1).

First, the scope of the organocopper-mediated reaction was determined by using the four 2,3-*trans*-substrates **1**- **4** (Scheme 1). As can be seen from Scheme 1 and Table 1 (Entries 1-10), regardless of the type of organocopper reagent, mixtures of two or three products were obtained from all reactions of 2,3-*trans*-vinylaziridines **1**- **4**. It is of particular interest, however, that these reactions exhibit high levels of regioselectivity and (*E*)-stereoselectivity (> 85%). In all cases examined in the 2,3-*trans*-series, 3-15% yields of (*Z*)-alkenes (**6**, **8**, **10**, **12**, and **15**) were isolated by flash chromatography and fully characterized spectrally.[8] In addition, minor products (**13** and **16**) (2 - 3% yields) which originated presumably *via* the S_N2 reaction pathway, were also isolated from the reaction products of vinylaziridines **3** and **4** with methylcopper reagents.

Table 1. Reaction of 2,3-*trans*- and *cis*-3-alkyl-2-vinylaziridines with organocopper reagents[a)]

Entry	Reactant	Reagent (mol. equiv.)	Product(s) (combined yield)	Ratio
1	**1**	MeCu(CN)Li·LiI (4)	**5** + **6** (99%)	**5** : **6** = 89 : 11
2	**1**	MeCu·LiI·LiBr (5)	**5** + **6** (99%)	**5** : **6** = 96 : 4
3	**2**	MeCu(CN)Li·LiI (5)	**7** + **8** (95%)	**7** : **8** = 85 : 15
4	**2**	Me_2CuLi·LiI·LiBr (5)	**7** + **8** (99%)	**7** : **8** = 93 : 7
5	**2**	MeCu·2LiI (5)	**7** + **8** (98%)	**7** : **8** = 92 : 8
6	**2**	*i*-PrCu(CN)MgCl (5)	**9** + **10** (99%)	**9** : **10** = 85 : 15
7	**3**	MeCu(CN)Li·LiI (5)	**11** + **12** + **13** (95%)	**11** : **12** : **13** = 95 : 3 : 2
8	**3**	MeCu·LiI·LiBr (5)	**11** + **12** + **13** (99%)	**11** : **12** : **13** = 93 : 4 : 3
9	**4**	MeCu(CN)Li·LiI (5)	**14** + **15** + **16** (89%)	**14** : **15** : **16** = 94 : 4 : 2
10	**4**	MeCu·2LiI (5)	**14** + **15** + **16** (93%)	**14** : **15** : **16** = 93 : 4 : 3
11	**17**	MeCu·LiI·LiBr (5)	**5** (91%)	**5** = 100
12	**17**	$Me_3SiCu(CN)Li$ (5)	**21** (98%)	**21** = 100
13	**18**	MeCu(CN)Li·LiI (5)	**7** (99%)	**7** = 100
14	**18**	*i*-PrCu(CN)MgCl (5)	**9** (99%)	**9** = 100
15	**18**	$Me_3SiCu(CN)Li$ (5)	**22** (99%)	**22** = 100
16	**19**	MeCu(CN)Li·LiI (5)	**11** (99%)	**11** = 100
17	**19**	$Me_3SiCu(CN)Li$ (5)	**23** (87%)	**23** = 100
18	**20**	MeCu(CN)Li·LiI (5)	**14** (98%)	**14** = 100
19	**20**	MeCu·2LiI (5)	**14** (87%)	**14** = 100

a) All reactions were carried out in dry THF under slight positive argon pressure. Product ratios were determined by reverse phase HPLC. All compounds were isolated by flash chromatography and fully characterized.



Scheme 2 *Reagents:* a. MeCu·LiBr·LiI; b. $Me_3SiCu(CN)Li$; c. MeCu(CN)Li·LiI; d. *i*-PrCu(CN)MgCl; e. MeCu·2LiI

In sharp contrast, upon exposure of the 3-alkyl-2-vinylaziridine **17**, in which the C-(3)-Me and the C-(2)-vinyl group are in a *cis* relationship, to either the MeCu·LiBr·LiI or $Me_3SiCu(CN)Li$ reagent, the (*E*)-alkenes **5** and **21** were exclusively produced in high yields (Scheme 2). The highly selective reactions were complete in a

few minutes at - 78 °C, but the reaction mixtures were usually stirred for 30 min. While we cannot conclusively rule out the presence of trace quantities (< 0.05%) of (*Z*)-alkenes or S_N2-products, the (*E*)-alkenes **5** and **21** were the only ones detected by reverse phase HPLC (Scheme 2 and Entries 11 and 12 in Table 1). In similar manners, other *N*-activated vinylaziridines **18**, **19**, and **20** were exclusively converted into the corresponding (*E*)-alkenes by treatment with organocopper reagents (Scheme 2; Entries 13-19, Table 1).

Although the ground state and the reactive conformer are not necessarily the same, the ground state conformations of various olefinic molecules containing the propene moiety play an important role in the stereochemical outcome of π-facial selectivity.[9] It is not, however, always reasonable to assume that reaction will occur only through the lowest energy conformer. The exclusive formation of (*E*)-alkenes from 2,3-*cis*-aziridines **17-20** may be rationalized by assuming the preferred conformation **24-A** as shown in Figure 1. The (*E*)- and (*Z*)-ratios of the S_N2' products may reflect the transition state energy difference related to the Ha/Hb staggered (**24-A**) and Ha/Hb eclipsed conformers (**24-B**). In conformation **24-A**, allylic 1,3-strain may be minimized. On the other hand, conformer **24-B**, which could lead to the (*Z*)-alkene **27** *via* the S_N2' pathway, should be highly disfavored by steric crowding between the alkyl (R^1) and the vinyl groups.[10] Consequently, the reactions of 2,3-*cis*-3-alkyl-2-vinylaziridines with organocopper reagents yield the corresponding (*E*)-alkenes most probably *via* the conformers of type **24-A**. On the other hand, the energy difference between possible conformers **25-A** and **25-B** would be smaller than that of **24-A** and **24-B**, yielding a mixture of (*E*)- and (*Z*)-alkenes **26** and **27**.

No doubt, the precise dihedral angle would not be exactly 180° (eg. **24-A**) or 0° (eg., **24-B**), either in the groud state or in the transition state, but in the absence of firm knowledge, the picture we use in Figure 1 is representative of our current level of understanding.

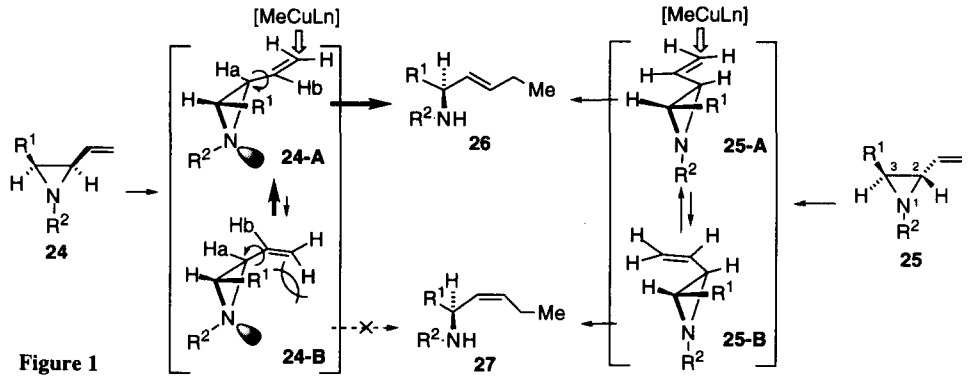
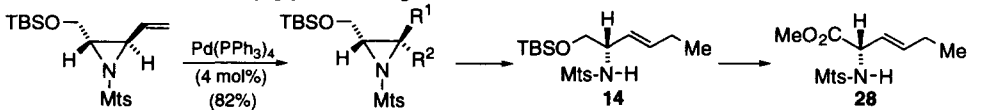


Figure 1

Unsaturated amino acids such as vinylglycines[11] are of particular biological interest as receptor antagonists[12] and enzyme inhibitors.[13] In this context, the above described organocopper chemistry has been applied to the synthesis of vinylglycine analogue **28**.



Scheme 3

Thus, the 2,3-*trans*-aziridine **4** was treated with 4 mol% of Pd(PPh3)4 in THF to afford a 1:9 equilibrium mixture of **4** and **20**.[14,15] Although **4** and **20** are separable by flash silica gel chromatography, the former material does not interfere with the subsequent use of the mixture for the preparation of **14**. The 1:9 mixture of **4** and **20** was treated with MeCu(CN)Li·LiI followed by the usual work-up and recrystallization to give analytically pure (*E*)-alkene **14** in 80% yield. L-Vinylglycine derivative **28** was obtained in a straight forward fashion by using a usual sequence of reactions. In conclusion, the organocopper reaction of 2,3-*trans*-3-alkyl-

2-vinylaziridine gives a mixture of two or three products, an (*E*)-alkene, a (*Z*)-alkene, and in certain case an S_N2-product. On the contrary, 2,3-*cis*-3-alkyl-2-vinylaziridine affords exclusively an (*E*)-alkene.

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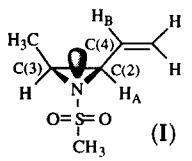
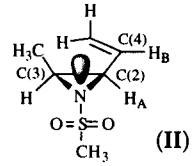
10. *Ab initio* calculations suggest that the energy difference between the conformers (**I**) and (**II**) of *N*-mesyl-3-methyl-2-vinylaziridine is ca. 19 kcal mol^{-1} at the RHF/6-31G** level. Details will be presented in a full paper.



(I)

∠ H_B - C(4) - C(2) - H_A = 188.8°
E. rel. = 0.00 kcal/mol



(II)

∠ H_A - C(2) - C(4) - H_B = ca. - 22°
E. rel. = ca. 19 kcal/mol

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