(*E*)-Stereoselective Synthesis of Vinylglycines from (*R*)-Serine *via* Organocopper–BF_3 and Related Reagents

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The stereoselective synthesis of biologically important vinylglycine derivatives by reaction of homochiral 4-methoxycarbonyl-5-vinyloxazolidin-2-ones with organocopper reagents is described; 4,5-*trans*-oxazolidin-2-one **6** yields (*E*)-vinylglycines as the major products by treatment with the 'higher order' cyanocuprate–BF_3 reagents or trialkylzincates in the presence of cuprous cyanide, 4,5-*cis*-oxazolidin-2-one **10** affords only the desired (*E*)-vinylglycines.

Recently, β,γ-unsaturated α-amino acids (vinylglycines) have received much attention as an important class of new α-amino acids.[1] Vinylglycine, the parent compound, has been isolated from mushrooms[2] and was considered as an intermediate in the enzymic transformation of homoserine into threonine[3] and α-ketobutyrate.[4] In addition, unsaturated amino acids are of particular interest as receptor antagonists,[5] enzyme inhibitors,[6] and synthetic intermediates.[7] Particularly, vinylglycines have been reported to act as 'suicide' substrates for pyridoxal phosphate dependent enzyme.[8] A number of methods for the synthesis of racemic and L- or D-vinylglycines have been published.[9] However, double bond isomerization to the α,β-position and racemization are two common problems during the syntheses of β,γ-unsaturated α-amino acids.[9a,9b,10]

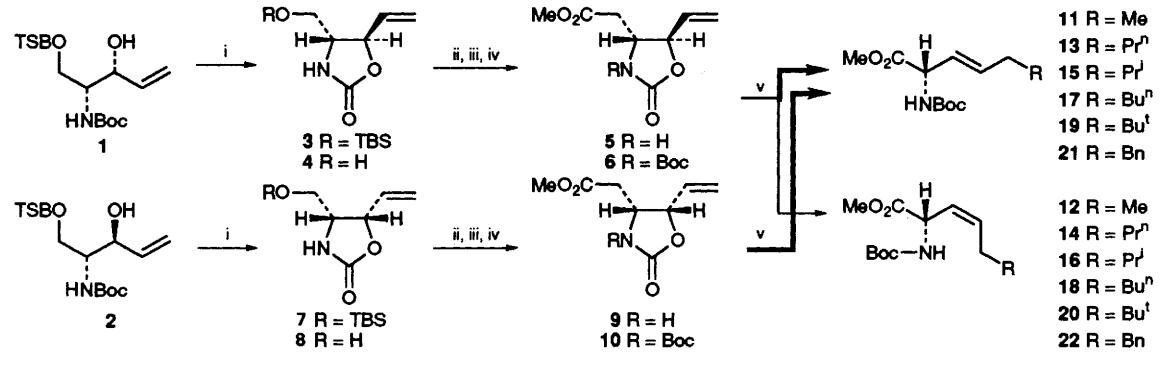
In connection with studies on peptide isosteres of biological importance,[11] we were interested in synthesizing (*E*)-β,γ-unsaturated α-amino acids (vinylglycines) from 5-vinyloxazolidin-2-ones in high chemical and optical yields.

Allylic alcohols **1** and **2**, which were used as starting materials for the present synthesis of vinylglycines, were conveniently prepared as a flash chromatographically separable 75:25 mixture in 60% combined overall yield from *N*-Boc-(*R*)-serine methyl ester using a procedure similar to that reported in the literature[12] *via* a sequence of reactions involving *tert*-butyldimethylsilylation, reduction of the ester group to an aldehyde group with DIBAL, and reaction with vinylmagnesium chloride in the presence of zinc chloride in THF.

As shown in Scheme 1, treatment of the alcohol **1** with sodium hydride yielded oxazolidin-2-one **3** in 78% yield, which upon exposure to hydrofluoric acid in MeCN afforded the alcohol **4** in 97% yield. Successive treatment of **4** with Jones' reagent and ethereal diazomethane furnished the methyl ester **5** in 38% yield, which can easily be converted into the *N*-Boc compound **6** by reaction with Boc_2O in the presence of sodium hydride in 99% yield. In a similar manner, the alcohol **2** was converted into the *N*-Boc 5-vinyloxazolidin-2-one **10** *via* **7**, **8** and **9** in comparable yields. With preparation of oxazolidin-2-ones **6** and **10** in hand, we set out to explore their utility in vinylglycine synthesis. The key step involves the organocopper-mediated S_N2' reaction, which serves to open the oxazolidin-2-one ring to generate the desired (*S*)-vinylglycine derivatives.

For the reactions of oxazolidin-2-one **6** with nucleophilic reagents, several organometallic reagents were investigated. The 4,5-*trans*-oxazolidin-2-one **6** was treated with 'lower order' methylcyanocuprate and after 30 min at −78 °C, a S_N2'-product **11** was obtained in only 18% yield. Use of the 'lower order' methylcyanocuprate–BF_3 reagent could not improve the yield of **11** (entries 1 and 2, Table 1). Exposure of **6** to the 'higher order' reagent, notably in the presence of BF_3, stereoselectivity provides **11** in excellent yield (entries 3 and 4, Table 1). The 'higher order' cyanocuprate–BF_3 reagents or trialkylzincates in the presence of copper(I) cyanide were found to give the most satisfactory results as shown in the Table 1. Reaction of **6** with dipropylcuprate gave rise to a chromatographically separable 91:9 mixture of *E*- and *Z*-products (**13** and **14**) in 89% yield (entry 5, Table 1). There was a similar trend of decreased *E*-selectivity with increased bulk of the alkyl group in organometallic reagents (entries 6–10, Table 1).

In sharp contrast, upon exposure of the oxazolidin-2-one **10**, in which the C(4)–CO_2Me and the C(5)-vinyl group are in a *cis* relationship, to either the 'higher order' cuprate–BF_3 reagents or trialkylzincates in the presence of CuCN exclusively produced the desired (*E*)-vinylglycines **11**, **15**, **17**, **19** and **21** in high chemical yields (entries 11–15, Table 1). While we cannot conclusively rule out the presence of trace quantities of (*Z*)-alkene, the (*E*)-isomer was the only one detected by ^1H NMR, capillary GC, and/or HPLC. The enantiomeric excess (e.e.) of these compounds were determined using chiral HPLC columns and found to be >96%. The absolute configuration of the α-position in both the (*E*)-vinylglycines (**11**, **13**, **15**, **17**, **19**, **21**) and (*Z*)-vinylglycines



Scheme 1 *Reagents and conditions*: i, NaH, THF, room temp., 8 h; ii, 48% HF/MeCN (1/3), 0 °C, 40 min.; iii, Jones oxidation, Me_2CO, 0 °C, 8 h, and then ethereal CH_2N_2; iv, NaH, THF, 0 °C, 1 h; v, see Table 1; abbreviation, TBS = *tert*-butyldimethylsilyl

Table 1 Synthesis of vinylglycines by reaction of oxazolidin-2-ones **6** and **10** with organocopper reagents[a]

Entry	Substrate	Reagent	Solvent	Product ratio[b] *E* : *Z*	Combined isolated yield (%)
1	**6**	MeCu(CN)Li·LiBr	THF–Et_2O (5 : 1)	**11** : **12** = >100 : 1	18
2	**6**	MeCu(CN)Li·LiBr·2BF_3	THF–Et_2O (5 : 1)	**11** : **12** = >100 : 1	<5
3	**6**	Me_2CuLi·LiCN·LiBr	THF–Et_2O (3 : 1)	**11** : **12** = >100 : 1	69
4	**6**	Me_2CuLi·LiCN·LiBr.3BF_3	THF–Et_2O (3 : 1)	**11** : **12** = >100 : 1	82
5	**6**	$Pr_2CuMgCl$·MgCl(CN)·2LiCl·3BF_3	THF	**13** : **14** = 91 : 9	89
6	**6**	$Pr_3Zn(MgCl)$·2$MgCl_2$ (30 mol% CuCN)[c]	THF–Et_2O (6 : 1)	**13** : **14** = 88 : 12	83
7	**6**	$^iPr_2CuMgCl$·MgCl(CN)·2LiCl·3BF_3	THF	**15** : **16** = 80 : 20	93
8	**6**	$^iPr_3ZnMgCl$·2$MgCl_2$ (30 mol% CuCN)[c]	THF–Et_2O (9 : 1)	**15** : **16** = 72 : 28	90
9	**6**	Bu_3ZnCl·2LiCl (30 mol% CuCN)[c]	THF–hexane-Et_2O (4 : 2 : 1)	**17** : **18** = 90 : 10	77
10	**6**	$^tBu_2CuLi$.LiCN·3BF_3	THF–pentane (3 : 1)	**19** : **20** = 87 : 13	91
11	**10**	Me_2CuLi.LiCN·3BF_3	THF–Et_2O (3 : 1)	**11** : **12** = 100 : 0	76
12	**10**	$^iPr_3ZnMgCl$.2$MgCl_2$·2LiCl (30 mol% CuCN)[c]	THF–Et_2O (6 : 1)	**15** : **16** = 100 : 0	96
13	**10**	$^nBu_3ZnLi$·2LiCl (30 mol% CuCN)[c]	THF–hexane-Et_2O (4 : 2 : 1)	**17** : **18** = 100 : 0	93
14	**10**	$^tBu_2CuLi$·LiCN·3BF_3	THF–pentane (3 : 1)	**19** : **20** = 100 : 0	92
15	**10**	$Bn_2CuMgCl$·MgCl(CN)·2LiCl·3BF_3	THF	**21** : **22** = 100 : 0	93

[a] All reactions were carried out at −78 °C for 30 min with 3 to 4 equiv. of organocopper reagents. Except for compounds **12** and **22**, all *E*- and *Z*-vinylglycines listed in Table 1 have been isolated by flash chromatography and/or HPLC and have been fully characterized. The stereochemistry of the double bond was readily ascertained by examination of the vicinal olefinic coupling constants (*ca.* 15.5 Hz and 11.0 Hz for *E*- and *Z*-vinylglycines, respectively). [b] All product ratios were determined by capillary gas chromatography (0.2 mm × 50 m) and/or HPLC. [c] Reaction was carried out by treatment of **6** or **10** with the indicated zincate in the presence of 30 mol% CuCN.

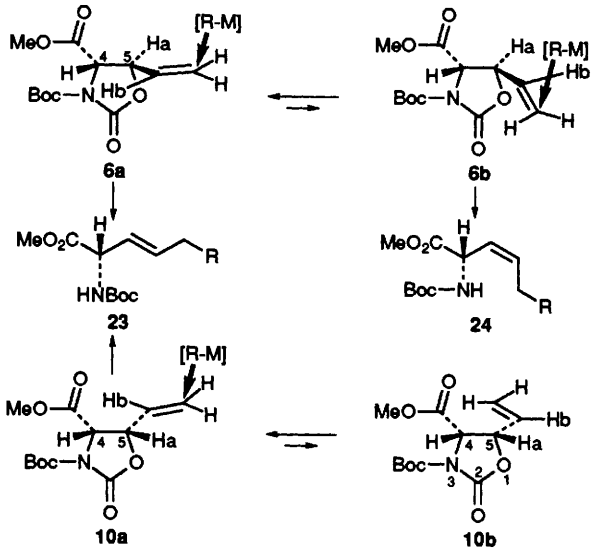


Fig. 1

(**14**, **16**, **18**, **20**) has been conveniently determined by a circular dichroism measurement[13] [(*E*)- and (*Z*)-vinylglycines show a positive n → π* Cotton effect near 220 nm].

The results may be rationalized by assuming the preferred conformations **6a** and **10a** for **6** and **10** as shown in Fig. 1. The (*E*)- and (*Z*)-ratios of the products may reflect transition-state energies related to the Ha/Hb staggered and Ha/Hb eclipsed conformers of the respective oxazolidin-2-ones.[14] In conformations **6a** and **10a**, allylic 1,3-strain would be minimized.[15] The conformer **6b**, which could lead to the (*Z*)-vinylglycine **24** by organocopper-mediated S_N2' reactions, is considerably disfavoured by the 1,3-allylic strain. Consequently, the reaction of **6** with organometallic reagents yields the desired (*E*)-vinylglycine **23** as the major products *via* the preferred conformer **6a**. On the other hand, with simple models, conformer **10b**, which would lead to **24**, is highly destabilized in comparison with **10a** owing to the 1,3-allylic strain as well as unfavourable interactions between the C(5)-vinyl group and the C(4)-methoxycarbonyl group. Therefore, the reaction of **10** with nucleophilic reagents would proceed through the conformer **10a** to give exclusively (*E*)-vinylglycine **23**.

In summary, the 4,5-*trans*-oxazolidin-2-one **6** yields (*E*)-vinylglycines as the major products by treatment with the 'higher order' cyanocuprate–BF_3 reagents or trialkylzincates in the presence of copper(I) cyanide. In contrast, the reaction of 4,5-*cis*-oxazolidin-2-one **10** affords only the desired (*E*)-vinylglycines. No common problems, *e.g.* double bond isomerization to the α,β-position and racemization were encountered.

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References

1 L. Havlícek and J. Hanus, *Collect. Czech. Chem. Commun.*, 1991, **56**. 1365.
2 G. Dardenne, J. Casimir, M. Marlier and P. O. Larsen, *Phytochemistry*, 1974, **13**, 1897.
3 M. Flavin and C. Slaughter, *J. Biol. Chem.*, 1960, **235**, 1112.
4 B. I. Posner and M. Flavin, *J. Biol. Chem.*, 1972, **247**, 6402.
5 G. E. Fagg, H. R. Olpe, M. F. Pozza, J. Baud, M. Steinmann, M. Schmutz, C. Portet, P. Baumann and K. Thedinga, *Br. J. Pharmacol.*, 1990, **99**, 791.
6 R. R. Rando, *Acc. Chem. Res.*, 1975, **8**, 281; R. H. Abeles and A. L. Maycock, *Acc. Chem. Res.*, 1976, **9**, 313–319; C. Walsh, *Tetrahedron*, 1982, **38**, 871; J. R. Sufrin, J. B. Lombardini and D. D. Keith, *Biochem. Biophys. Res. Commun.*, 1982, **106**, 251.
7 J. E. Baldwin, R. M. Adlington, N. P. Crouch, D. J. Drake, Y. Fujishima, S. W. Elson and K. H. Baggaley, *J. Chem. Soc., Chem. Commun.*, 1994, 1133.
8 R. R. Rando, *Science*, 1974, **185**, 320.
9 (*a*) A. Afzali-Ardakani and H. Rapoport, *J. Org. Chem.*, 1980, **45**, 4817; (*b*) S. Hanessian and S. P. Sahoo, *Tetrahedron Lett.*, 1984, **25**, 1425; (*c*) D. H. R. Barton, D. Crich, Y. Hervé, P. Potier and J. Thierry, *Tetrahedron*, 1985, **41**, 4347; (*d*) J. Clayden, E. W. Collington and, S. Warren, *Tetrahedron Lett.*, 1993, **34**, 1327.
10 R. M. Williams, W. Zhai, *Tetrahedron*, 1988, **44**, 5425.
11 M. Wada, R. Doi, R. Hosotani, T. Ibuka, H. Habashita, K. Nakai, N. Fujii and M. Imamura, *Pancreas*, in press.
12 T. Ibuka, K. Nakai, H. Habashita, Y. Hotta, N. Fujii, N. Mimura, Y. Miwa, T. Taga and Y. Yamamoto, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 652.
13 T. Ibuka, H. Habashita, S. Funakoshi, N. Fujii, K. Baba, M. Kozawa, Y. Oguchi, T. Uyehara and Y. Yamamoto, *Tetrahedron: Asymmetry*, 1990, **1**, 389.
14 B. M. Trost and T. P. Klun, *J. Org. Chem.*, 1980, **45**, 4257; J. A. Marshall, J. D. Trometer, B. E. Blough and T. D. Crute, *J. Org. Chem.*, 1988, **53**, 4274.
15 R. W. Hoffmann, *Chem. Rev.*, 1989, **89**, 1841; R. W. Hoffmann, *Angew. Chem., Int. Ed. Engl.* 1992, **31**, 1124.