Syn-S_N2' Pathway in the Reaction of Certain γ-(Mesyloxy) α,β-Enoates with RCu(CN)MgX·BF_3 Reagents. Importance of MgX and Bulky R Group upon the Diastereoselectivity

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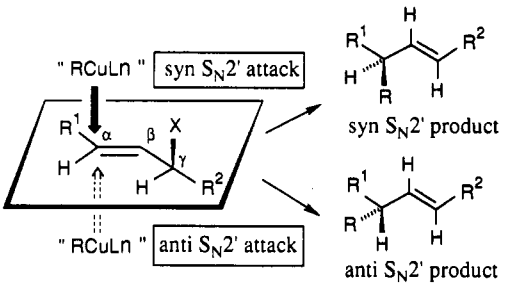
The reactions of protected serine- and threonine-derived γ-(mesyloxy) α,β-unsaturated esters with various magnesio organocyanocopper Lewis acid complexes have been investigated. The formation of syn-S_N2' products, in addition to the normally expected anti-S_N2' products, is taken as an indication that the reaction proceeds by a mechanism involving coordination of the magnesiocuprate with the C(δ)-N:C(γ)–O *syn*-γ-(mesyloxy) α,β-enoates.

The stereochemical course of organocopper-mediated S_N2' substitution of allylic compounds has been well documented to depend on the nature of the leaving group.[1] Allylic esters,[2] sulfonates,[3] oxiranes,[4] alcohols,[5] phosphates,[6] and halides[7] usually undergo highly stereoselective anti-facial reactions; i.e., the S_N2' displacement generally proceeds anti to the leaving group (anti-S_N2' reactions) (Scheme I).

Scheme I



On the other hand, allylic carbamates,[8] ammonium salts,[9] some oxiranes,[10] and (allyloxy)benzothiazoles[11] undergo stereospecific syn-facial attacks (syn-S_N2' reactions). Studies on the organocopper-mediated syn-S_N2' reactions of allylic carbamates suggested that directed intramolecular delivery of the alkyl nucleophile was responsible for the change in stereochemistry.[8b,f] However, except for a few cases,[1b,8e] syn-S_N2' reactions of allylic compounds with organocoppers have involved structurally rigid five- or six-membered cyclic compounds. In these cases, syn-S_N2' reactions are independent of the bulk alkyl group and of the salt involved in the organocopper reagents.

We have recently reported the results of a new synthetic study of (*E*) alkene dipeptide isosteres in which we achieved very high regio- and diastereoselectivity in the reaction of

(1) (a) Magid, R. M. *Tetrahedron* **1980**, *36*, 1901. (b) Marshall, J. A. *Chem. Rev.* **1989**, *89*, 1503. (c) Lipshutz, B. H. *Synlett* **1990**, 119. (d) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135.

(2) Trost, B. M.; Klun, T. P. *J. Org. Chem.* **1980**, *45*, 4257. Goering, H. L.; Kantner, S. S. *J. Org. Chem.* **1983**, *48*, 721. Goering, H. L.; Kantner, S. S. *J. Org. Chem.* **1984**, 49,422. Goering, H. L.; Kanter, S. S.; Seitz, E. P., Jr. *J. Org. Chem.* **1985**, *50*, 5495. Tseng, C. C.; Yen, S.-J.; Goering, H. L. *J. Org. Chem.* **1986**, *51*, 2892. Tseng, C. C.; Paisley, S. D.; Goering, H. L. *J. Org. Chem.* **1986**, *51*, 2884. Curran, D. P.; Chen, M.-H.; Leszezweski, D.; Elliott, R. L.; Rakiewicz, D. M. *J. Org. Chem.* **1986**, *51*, 1612. Underiner, T. L.; Goering, H. L. *J. Org. Chem.* **1988**, *53*, 1140.

(3) (a) Ibuka, T.; Nakao, T.; Nishii, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1986**, *108*, 7420. (b) Ibuka, T.; Tanaka, M.; Nishii, S.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1987**, 1596. (c) Ibuka, T.; Tanaka, M.; Nishii, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4864. (d) Ibuka, T.; Akimoto, N.; Tanaka, M.; Nishii, S.; Yamamoto, Y. *J. Org. Chem.* **1989**, *54*, 4055. (e) Ibuka, T.; Tanaka, M.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 967. (f) Ibuka, T.; Habashita, H.; Funakoshi, S.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 801. (g) Ibuka, T.; Habashita, H.; Otaka, A.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56*, 4370. (h) Chen, S.-H.; Horvath, R. F.; Joglar, J.; Fisher, M. J.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 5834. (i) Kempf, D. J.; Wang, X. C.; Spanton, S. G. *Int. J. Pept. Protein Res.* **1991**, *38*, 237. (j) Yamamoto, Y.; Tanaka, M.; Ibuka, T. *J. Org. Chem.* **1992**, *57*, 1024.

(4) (a) Marino, J. P.; Kelly, M. G. *J. Org. Chem.* **1981**, *46*, 4389. (b) Marino, J. P.; Jaén, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 3165. (c) Marino, J. P.; Fernández de la Pradilla, R.; Laborde, E. *J. Org. Chem.* **1987**, *52*, 4898. (d) Marshall, J. A.; Trometer, J. D. *Tetrahedron Lett.* **1987**, *28*, 4985. (e) Marshall, J. A.; Trometer, J. D.; Blough, B. E.; Crute, T. D. *Tetrahedron Lett.* **1988**, *29*, 913. (f) Marshall, J. A.; Trometer, J. D.; Cleary, D. J. *Tetrahedron* **1989**, *45*, 391. (g) Marshall, J. A.; Blough, B. E. *J. Org. Chem.* **1990**, *55*, 1540. (h) Marshall, J. A.; Blough, B. E. *J. Org. Chem.* **1991**, *56*, 2225. (i) Marshall, J. A.; Crute, T. D., III; Hsi, J. D. *J. Org. Chem.* **1992**, *57*, 115.

(5) (a) Tanigawa, Y.; Kanamaru, H.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1977**, *99*, 2361. (b) Tanigawa, Y.; Ohta, H.; Sonoda, A.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1978**, *100*, 4610. (c) Goering, H. L.; Kantner, S. S. *J. Org. Chem.* **1981**, *46*, 2144.

(6) Yanagisawa, A.; Noritake, Y.; Nomura, N.; Yamamoto, H. *Synlett* **1991**, 251. See also: Yanagisawa, A.; Nomura, N.; Yamamoto, H. *Synlett.* **1991**, 513. Yanagisawa, A.; Nomura, N.; Noritake, Y.; Yamamoto, H. *Synthesis* **1991**, 1130.

(7) Nakamura, E.; Sekiya, K.; Arai, M.; Aoki, S. *J. Am. Chem. Soc.* **1989**, *111*, 3091. Arai, M.; Nakamura, E.; Lipshutz, B. H. *J. Org. Chem.* **1991**, *56*, 5489.

(8) (a) Gallina, C.; Ciattini, P. G. *J. Am. Chem. Soc.* **1979**, *101*, 1035. Gallina, C. *Tetrahedron Lett.* **1982**, *23*, 3093. (b) Goering, H. L.; Kantner, S. S.; Tseng, C. C. *J. Org. Chem.* **1983**, *48*, 715. (c) Fleming, I.; Thomas, A. P. *J. Chem. Soc., Chem. Commun.* **1986**, 1456. (d) RajanBabu, T. V.; Nugent, W. A.; Taber, D. F.; Fagan, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 7128. (e) Greene, A. E.; Coelho, F.; Depres, J.-P.; Brocksom, T. J. *Tetrahedron Lett.* **1988**, *29*, 5661. (f) Underiner, T. L.; Goering, H. L. *J. Org. Chem.* **1989**, *54*, 3239. (g) Denmark, S. E.; Marble, L. K. *J. Org. Chem.* **1990**, *55*, 1984.

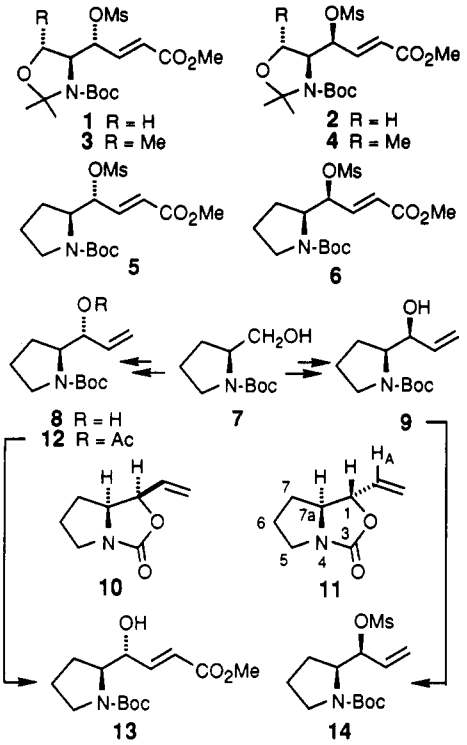
(9) Hutchinson, D. K.; Fuchs, P. L. *J. Am. Chem. Soc.* **1985**, *107*, 6137. Hutchinson, D. K.; Hardinger, S. A.; Fuchs, P. L. *Tetrahedron Lett.* **1986**, *27*, 1425. Hutchinson, D. K.; Fuchs, P. L. *Tetrahedron Lett.* **1986**, *27*, 1429. Pan, V.; Hutchinson, D. K.; Nantz, M. H.; Fuchs, P. L. *Tetrahedron* **1989**, *45*, 467. Berglund, R. A.; Braish, T. F.; Jakubowski, J. A.; Fuchs, P. L. *Bioorg. Med. Chem.* **1991**, *1*, 649.

(10) (a) Marshall, J. A.; Audia, V. H.; Jenson, T. M.; Guida, W. C. *Tetrahedron* **1986**, *42*, 1703. (b) Marshall, J. A.; Audia, V. H. *J. Org. Chem.* **1987**, *52*, 1106. (c) Ziegler, F. E.; Cady, M. A. *J. Org. Chem.* **1981**, *46*, 122.

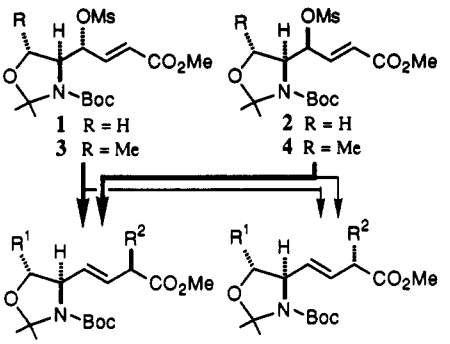
(11) Valverde, S.; Bernabé, M.; Garcia-Ochoa, S.; Gómez, A. M. *J. Org. Chem.* **1990**, *55*, 2294.

0022-3263/93/1958-1207$04.00/0

Scheme II



Scheme III



15 R^1 = H; R^2 = Me
16 R^1 = H; R^2 = Me
17 R^1 = H; R^2 = Et
18 R^1 = H; R^2 = Et
19 R^1 = H; R^2 = Pr
20 R^1 = H; R^2 = Pr
21 R^1 = Me; R^2 = Bu
22 R^1 = Me; R^2 = Bu
23 R^1 = H; R^2 = Pr^i
24 R^1 = H; R^2 = Pr^i
25 R^1 = Me; R^2 = Pr^i
26 R^1 = Me; R^2 = Pr^i
27 R^1 = H; R^2 = Bu^t
28 R^1 = H; R^2 = Bu^t
29 R^1 = Me; R^2 = Bu^t
30 R^1 = Me; R^2 = Bu^t
31 R^1 = Me; R^2 = Me
32 R^1 = Me; R^2 = Me
33 R^1 = H; R^2 = Bu^i
34 R^1 = H; R^2 = Bu^i

δ-aminated γ-(mesyloxy) α,β-enoates with organocyanocopper·BF_3 reagents prepared from the corresponding organolithium compounds.[3f,g] In these reactions, an anti-S_N2' pathway was observed irrespective of the steric bulk of RCu(CN)Li·BF_3 reagents. We wish to detail here new findings that some mesylates undergo a syn-S_N2' reaction with bulky magnesium reagents such as *i*-PrCu(CN)-MgCl·BF_3 and *t*-BuCu(CN)MgCl·BF_3 to yield protected dipeptide isosteres, e.g., Ser-ψ[(*E*)-CH=CH]-Val, in high diastereoselectivity.

Results and Discussion

The requisite serine- and threonine-derived γ-(mesyloxy) (*E*)-α,β-enoates (**1** and **2**) and (**3** and **4**) were readily prepared in acceptable yields by known methods from (*S*)-serine and (*S*)-threonine, respectively.[3g] Proline-derived substrates **5** and **6** were synthesized as follows. Reaction of Boc (*S*)-prolinol **7**[12] with SO_3–pyridine in CH_2Cl_2–DMSO followed by vinylmagnesium chloride[13] in THF (−40 to 0 °C) gave a mixture of *anti*- and *syn*-vinyl alcohols **8** and **9** in a ratio of 59:41 in 67% combined yield (Scheme II).

Stereochemical assignments for diastereomers **8** and **9** were made by convesion to oxazolidone derivatives **10** and **11** by treatment with sodium hydride in DMF and ^1H NMR analysis. The C-1 proton in **10** resonates at lower field (δ 5.14) than that of the isomer **11** (δ 4.70). The ^1H–^1H NOESY spectrum of **11** clearly indicated the presence of an NOE between one of the vinylic protons in δ 5.98 (H_A in structure **11**) and the C-7a proton at δ 3.65. Irradiation of the signal at δ 3.65 led to a 2.3% NOE enhancement of the signal of one of the vinylic protons at δ 5.98 (H_A in structure **11**). The data are in agreement with ^1H NMR data for related compounds.[14]

Acetylation of **8** gave the acetate **12**, which was successively treated with ozone at −78 °C in CH_2Cl_2, (carbomethoxymethylene)triphenylphosphorane, and sodium carbonate in methanol to yield the *anti*-γ-hydroxy (*E*)-α,β-enoate **13** in 40% overall yield after flash chromatographic purification. Mesylation of the alcohol **13** yielded the desired mesylate **5** in essentially quantitative yields. On the other hand, mesylate **14** derived from alcohol **9** was transformed into the *syn*-mesylate **6** by a sequence similar to that described for the synthesis of **5** (see Experimental Section).

We initiated our study to determine the influence of bulk in the alkyl group of the organocopper reagents derived from Grignard reagents, cuprous cyanide, and boron trifluoride etherate. As shown in Scheme III and Table I (entries 1–5), the γ-(mesyloxy) (*E*)-α,β-enoates **1** and **3**, in which the C(δ)–N and the C(γ)–O bonds are in an anti relationship (*anti*-mesylates), yielded the alkylated products via the expected anti-S_N2' pathway in high yield by treatment with RCu(CN)MgX·BF_3 reagents (R = primary alkyls). Clearly, organocopper additions to **1** or **3** occurred with a strong preference for approach from the less hindered side of the double bond anti to the mesyloxy group.

A significant observation with magnesiocuprate·BF_3 reagents was that a small amount of the syn-S_N2' product was formed by treatment with secondary or tertiary alkylcyanocuprate·BF_3 reagents such as *i*-PrCu(CN)-MgCl·BF_3 or *t*-BuCu(CN)MgCl·BF_3 (Table I, entries 6–9).

In contrast, exposure of the γ-(mesyloxy) (*E*)-α,β-enoates **2** and **4**, in which the C(δ)–N and the C(γ)–O bonds are in a syn relationship (*syn*-mesylates), to primary alkylcyanocopper·BF_3 reagents gave rise to a diastereoisomeric mixture of syn- and anti-S_N2' products. As shown in Table I (entries 12–17), increasing the size of the primary alkyl group in the organocyanocopper reagent decreased

(12) Miles, N. J.; Sammes, P. G.; Kennewell, P. D.; Westwood, R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2299.
(13) For a recent report, see: Coleman, R. S.; Carpenter, A. J. *Tetrahedron Lett.* **1992**, *33*, 1697 and references cited therein.
(14) (a) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Pedrine, P. *J. Org. Chem.* **1990**, *55*, 1439. (b) Sham, H. L.; Rempel, C. A.; Stein, H.; Cohen, J. *J. Chem. Soc., Chem. Commun.* **1990**, 904. (c) Patel, D. V.; R.-Gauvin, K.; Ryono, D. E. *Tetrahedron Lett.* **1990**, *31*, 5587. (d) Friesen, R. W.; Kolaczewska, A. E. *J. Org. Chem.* **1991**, *56*, 4888.

Table I. Reaction of Mesylates 1–4 with Organocyanocopper·BF_3 Reagents[a]

entry	substrate	reagent	products (yield,[b] %) anti-S_N2'		syn-S_N2'	anti-S_N2':syn-S_N2'
1	1	MeCu(CN)MgBr·BF_3	15 (93)	+	16 (trace)[c,f]	>99:1
2	1	EtCu(CN)MgBr·BF_3	17 (98)	+	18 (trace)	>99:1
3	1	*n*-PrCu(CN)MgBr·BF_3	19 (97)	+	20 (trace)	>99:1
4	3	*n*-BuCu(CN)MgCl·BF_3	21 (94)	+	22 (trace)	>99:1
5	3	*n*-BuCu(CN)MgBr·BF_3	21 (93)	+	22 (trace)	>99:1
6	1	*i*-PrCu(CN)MgCl·BF_3	23 (85)	+	24 (13)	87:13
7	3	*i*-PrCu(CN)MgCl·BF_3	25 (83)	+	26 (8)	91:9
8	1	*t*-BuCu(CN)MgCl·BF_3	27 (78)	+	28 (11)[d]	87:13
9	3	*t*-BuCu(CN)MgCl·BF_3	29 (79)	+	30 (14)[e]	85:15
10	4	MeCu(CN)Li·BF_3	32 (66)	+	31 (trace)[f,g]	>99:1
11	4	*n*-BuCu(CN)Li·BF_3	22 (90)	+	21 (ca. 2)	97:3
12	4	MeCu(CN)MgBr·BF_3	32 (41)	+	31 (11)[f,h]	80:20
13	2	EtCu(CN)MgBr·BF_3	18 (34)	+	17 (62)	36:64
14	2	*n*-PrCu(CN)MgBr·BF_3	20 (35)	+	19 (62)	37:63
15	4	*n*-BuCu(CN)MgCl·BF_3	22 (34)	+	21 (63)	35:65
16	4	*n*-BuCu(CN)MgBr·BF_3	22 (30)	+	21 (64)	32:68
17	2	*i*-BuCu(CN)MgCl·BF_3	34 (24)	+	33 (74)	25:75
18	2	*i*-PrCu(CN)MgCl·BF_3	24 (5.5)	+	23 (92)	6:94
19	4	*i*-PrCu(CN)MgCl·BF_3	26 (8)	+	25 (82)	9:91
20	2	*t*-BuCu(CN)MgCl·BF_3	28 (1.5)	+	27 (81.5)	2:98
21	4	*t*-BuCu(CN)MgCl·BF_3	30 (2.5)	+	29 (92.5)	3:97

[a] All reactions were carried out at −78 °C with 3–4 molar equiv of reagents. Diastereoselectivities (anti-S_N2':syn-S_N2') were determined by capillary VPC or HPLC. [b] All yields are isolated yields for chromatographically and spectroscopically pure syn-S_N2' and anti-S_N2' products. [c] Ca. 5.5% yield of reduction product was isolated. [d] Obtained along with ca. 6% yield of reduction product. [e] Obtained along with ca. 5.7% yield of reduction product. [f] The result of experiments from an earlier investigation of the cross-coupling reaction with RCu(CN)Li·BF_3 was included for comparison.[3f,g] [g] Obtained along with ca. 28% yield of reduction product. [h] Obtained along with ca. 32% yield of reduction product.

the ratio of the anti-S_N2' product. Except for entry 12, the diastereoselectivities were 63∼75:37∼25 favoring the syn-S_N2' isomers over the anti-S_N2' products (entries 13–17).

It should be noted that the diastereoselectivity varies dramatically depending upon the reagents used. Whereas reaction of the *syn*-mesylate **4** with a lithium alkylcyanocuprate·BF_3 reagent, MeCu(CN)Li·BF_3 or *n*-BuCu(CN)Li·BF_3, yielded predominantly anti-S_N2' products, **32** or **22** (Table I, entries 10 and 11), exposure of the same substrate **4** to a magnesio reagent, MeCu(CN)MgBr·BF_3 or *n*-BuCu(CN)MgBr·BF_3, gave rise to a diastereoisomeric mixture of syn- and anti-S_N2' products (**31** and **32**) or (**21** or **22**) (Table I, entries 12 and 16).

The reaction of **2** with *i*-BuCu(CN)MgCl·BF_3 yielded the syn-S_N2' product **33** in a rather low diastereoselectivity (Table I, entry 17). This result may be attributed to the primary alkyl group in the organocopper reagent.

The bulk of the alkyl group in organocyanocopper·BF_3 reagents strongly influences the level of the diastereoselectivity. Thus, the reaction between *i*-PrCu(CN)MgCl·BF_3 and the *syn*-mesylate **2** or **4** yielded predominantly the syn-S_N2' product **23** or **25** (Table I, entries 18 and 19). The preferred syn-S_N2' substitution to the mesylates **2** and **4** thus runs counter to the general anti-S_N2' trend seen for conformationally fixed and flexible systems. For example, it has been reported that both the *syn*- and *anti*-mesylates **35** and **36** afford exclusively anti-S_N2' products **37** and **38** by reaction with *t*-BuCu(CN)MgCl·BF_3 and *i*-PrCu(CN)MgCl·BF_3, respectively.[3f,g]

X-ray diffraction analysis of the syn-S_N2' product **23**, derived from **2**, confirmed the stereochemistry of the (*E*)-double bond and the alkylated carbon center as shown in Figure 1.

In a similar manner, exposure of the *syn*-mesylates **2** and **4** to *t*-BuCu(CN)MgCl·BF_3 gave rise to the syn-S_N2' products **27** and **29** preferentially (Table I, entries 20 and 21). The diastereoselection of the reaction of **2** with

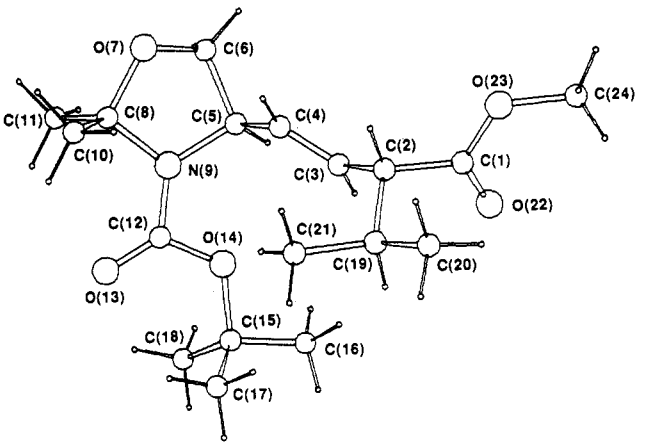
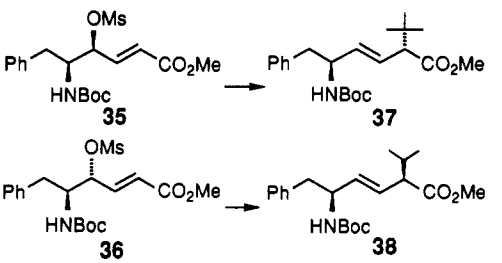


Figure 1. Crystal structure and solid-state conformation of **23**.

Scheme IV



t-BuCu(CN)MgCl·BF_3 was at least 98:2 favoring the syn-S_N2' addition product **27**.

The (*E*) geometry of the syn-S_N2' and the anti-S_N2' products listed in Table I was easily established from the coupling constant (ca. 15.5 Hz) of the two olefinic protons by ^1H NMR analysis. The strong preference for (*E*)-stereochemistry of the double bond in all *syn*-S_N2' addition products from γ-(mesyloxy) (*E*)-α,β-enoates is noteworthy. We have previously reported that the absolute configuration at the alkylated carbon center can be conveniently

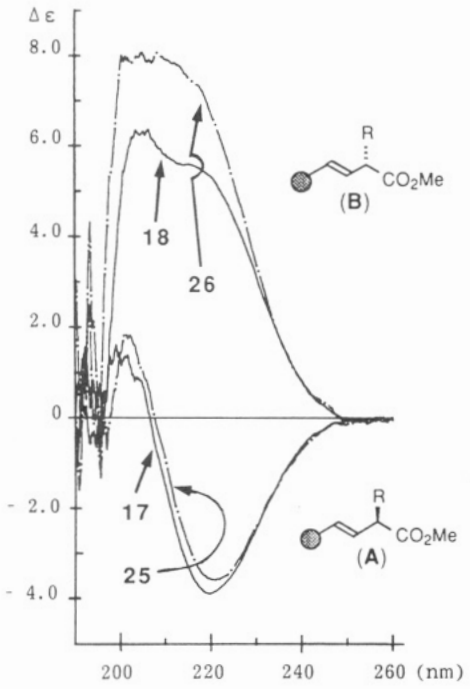


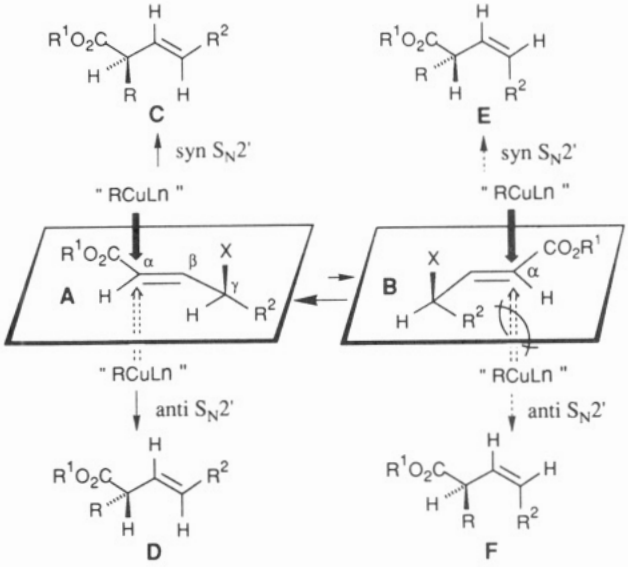
Figure 2. CD spectra of **17**, **18**, **25**, and **26** (in isooctane).

established by a circular dichroism measurement.[3g,15] Thus, whereas all compounds (**15**, **17**, **19**, **21**, **23**, **25**, **27**, **29**, **31**, and **33**) with a partial structure **A** (Figure 2) show a negative n → π* Cotton effect around 220 nm, compounds (**16**, **18**, **20**, **22**, **24**, **26**, **28**, **30**, **32**, and **34**) with a partial structure **B** (Figure 2) exhibited a positive n → π* Cotton effect near 220 nm. Thus, given the sign of the Cotton effect, one can determine the absolute configuration at the α-position in β,γ-unsaturated esters. There remains the question of why the syn-substrates **2** and **4** were transformed predominantly into syn-S_N2' products with an (*E*)-double bond such as **23**, **25**, **27**, and **29** upon exposure to *i*-PrCu(CN)MgCl·BF_3 or *t*-BuCu(CN)MgCl·BF_3.

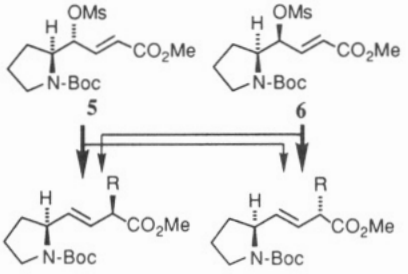
The mechanism of the S_N2' reaction has been a matter of some controversy since its discovery, and a number of arguments have been invoked to account for the results.[1,8-11] The acylic substrates, in principle, can react via either conformer **A** or **B** (Scheme V). Consequently, four possible different reaction products from (*E*)-α,β-enoates with a leaving group at the γ-position could be envisioned. Thus, whereas the syn-S_N2' reaction of conformer **A** would generate an α-alkylated product **C**, the anti-S_N2' reaction could provide an α-alkylated product **D**. Similarly, the syn-S_N2' reaction of conformer **B** would afford an α-alkylated product **E**, whereas the anti-S_N2' reaction could provide an α-alkylated product **F**.

In the present reactions, organocopper reagents attack γ-(mesyloxy) α,β-enoates to give overall syn- or anti-S_N2' products with an (*E*)-double bond, and the probable reason is that attack takes place in the more abundant conformation **A** on the face syn or anti to the mesyloxy group to yield **C** or **D**. For conformer **B**, unfavorable $A^{1,3}$ strain between the hydrogen at the α-position and the R^2 group

Scheme V



Scheme VI



39	R = Me	**40**	R = Me
41	R = benzyl	**42**	R = benzyl
43	R = Bu^i	**44**	R = Bu^i
45	R = Pr^i	**46**	R = Pr^i
47	R = Bu^t	**48**	R = Bu^t

would be present.[16] Thus, the reaction would proceed via the energetically more favorable conformer **A** to furnish product **C** and/or **D**, in agreement with the experimental result. Although all of the controlling factors in the present S_N2' reaction of **2** and **4** with *i*-PrCu(CN)MgCl·BF_3 and *t*-BuCu(CN)MgCl·BF_3 are not clear, the following reasoning concerning the syn-S_N2' selective pathway may be drawn:

(1) The configuration of the leaving group at the γ-position plays a significant role in the stereochemical consequences of the S_N2' reactions. [Compare entries 1–9 (Table I) (*anti*-mesylates **1** and **3**) with entries 12–21 (*syn*-mesylates **2** and **4**).]

(2) The *gem*-dimethyl group on the oxazolidine ring of **2** and **4** is indispensable for the predominant formation of syn-S_N2' products. For this purpose, we have examined the S_N2' diastereoselectivity of different substrates. As shown in Scheme VI and Table II, both proline-derived *anti*- and *syn*-mesylates **5** and **6** afforded predominantly

(15) Ibuka, T.; Habashita, H.; Funakoshi, S.; Fujii, N.; Baba, K.; Kozawa, M.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *Tetrahedron: Asymmetry* **1990**, *1*, 389. See also: Ibuka, T.; Taga, T.; Shingu, T.; Saito, M.; Nishii, S.; Yamamoto, Y. *J. Org. Chem.* **1988**, *53*, 3947.

(16) (a) Johnson, F.; Malhotra, S. K. *J. Am. Chem. Soc.* **1965**, *87*, 5492. See also: (b) Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162. (c) Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 666. (d) Chamberlin, A. R.; Mulholland, R. L.; Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 672. (e) Seebach, D.; Lamatsch, B.; Amstutz, R.; Beck, A. K.; Dobler, M.; Egli, M.; Fitzi, R.; Gautschi, M.; Herradón, B.; Hidber, F. C.; Irwin, J. J.; Locher, R.; Maestro, M.; Maetzke, T.; Mouriño, A.; Pfammatter, E.; Plattner, D. A.; Schickli, C.; Schweizer, W. B.; Seiler, P.; Stuckey, G.; Petter, W.; Escalante, J.; Juaristi, E.; Quintana, D.; Miravitlles, C.; Molins, E. *Helv. Chim. Acta* **1992**, *75*, 913.

Table II. Reaction of Mesylates 5 and 6 with Organocyanocopper·BF_3 Reagents[a]

entry	substrate	reagent	product (yield,[b] %) anti-S_N2'	syn-S_N2'	anti-S_N2':syn-S_N2'
1	5	MeCu(CN)MgBr·BF_3	39 (99)	40[c]	>99:1
2	6	MeCu(CN)MgBr·BF_3	40 (83)	39[c,d]	>99:1
3	5	BnCu(CN)MgCl·BF_3	41 (97)	42[c]	>99:1
4	5	*i*-BuCu(CN)MgCl·BF_3	43 (92)	44[c]	>99:1
5	6	*i*-BuCu(CN)MgCl·BF_3	44 (99)	43[c]	>99:1
6	6	BnCu(CN)MgCl·BF_3	42 (79)	41[c]	>99:1
7	5	*i*-PrCu(CN)MgCl·BF_3	45 (92)	46 (8)	92:8
8	6	*i*-PrCu(CN)MgCl·BF_3	46 (89)	45 (11)	89:11
9	5	*t*-BuCu(CN)MgCl·BF_3	47 (77)	48 (9)[e]	89:11

[a] All reactions were carried out at −78 °C with 3–4 molar equiv of reagents. Diastereoselectivities (anti-S_N2':syn-S_N2') were determined by capillary VPC or HPLC. [b] All yields are isolated yields for chromatographically and spectroscopically pure syn-S_N2' and anti-S_N2' products. [c] Could not be detected by capillary VPC. [d] Obtained along with ca. 7% yield of reduction product. [e] Obtained along with ca. 11% yield of reduction product.

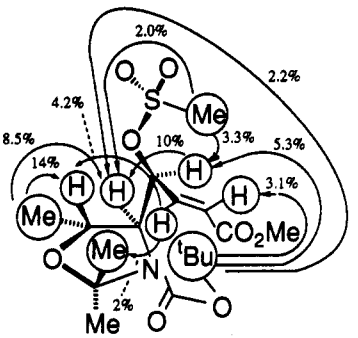


Figure 3. NOE data for **4** in THF-d_8 involving LiCl.

anti-S_N2' products upon exposure to Grignard-derived organocyanocopper·BF_3 reagents.[17]

(3) The ^1H NMR data (^1H–^1H COSY, ^1H–^1H NOESY, and selective decoupling experiments) for **4** (in THF-d_8 as well as in THF-d_8 containing lithium chloride) and the low-temperature (−70 °C) ^1H NMR data for **2** suggest that the preferred conformation of **4** could be drawn as depicted in Figure 3 (the relevant NOE data for **4** are presented by arrows in Figure 3).[18,19] The magnesio cuprate would

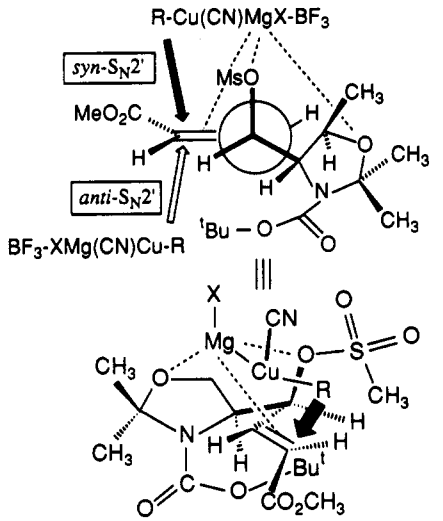


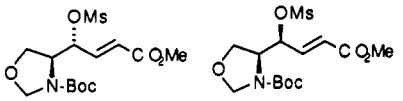
Figure 4.

precomplex with the oxygen of the mesyloxy group, the π-electrons of the double bond, and the oxygen of the oxazolidine ring of the substrate as shown in Figure 4. A similar mechanistic discussion for the coordination of the lithium cation of lithium dimethylcuprate has been reported by Marshall.[4d,e,10a]

In contrast, ^1H–^1H COSY and selective decoupling experiments in THF-d_8 for the γ-(mesyloxy) α,β-enoate **3** suggested that the preferred conformation of **3** could be depicted as shown in Figure 6 (for the relevant NOE data for **3**, see Figure 5). In the present reactions, organocopper reagents attack preferentially to give overall anti-S_N2' products, and the probable reason is that the attack takes place in the preferred conformation on the upper face anti to the electron-withdrawing mesyloxy group.

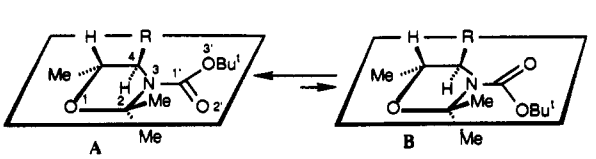
As is evident from the results shown in entries 12–21 (Table I), when the size of the alkyl group in the cuprate reagent is increased from the primary to secondary or tertiary, the amount of the anti-S_N2' product is decreased.

(17) We have also synthesized compounds **49** and **50** that lack a *gem*-dimethyl group in the oxazolidine ring for the purpose of comparing the stereochemical outcome. Unfortunately, products obtained by treatment with organocyanocopper–BF_3 reagents were unable to be separated by flash chromatography or HPLC.



49 **50**

(18) As shown in Figure 5, for the stereochemistry of the *tert*-butoxycarbonyl group, two stereoisomers (**A** and **B**) can be drawn. The carbon atoms (C-2, C-4, and C-1′), the nitrogen atom, and the oxygen atoms (O-2′ and O-3′) would lie nearly on the same plane. (see: Hondrelis, J.; Lonergan, G.; Voliotis, S.; Matsoukas, J. *Tetrahedron* **1990**, *46*, 565. See also: Shustov, G. V.; Kadorkina, G. K.; Varlamov, S. V.; Kachanov, A. V.; Kostyanovsky, R. G.; Rauk, A. *J. Am. Chem. Soc.* **1992**, *114*, 1616). Conformer **B** would be destabilized in comparison with **A** owing to unfavorable interactions between the bulky *tert*-butyl group and the *gem*-dimethyl group at the C-2 position. The NOESY spectrum and the selective decoupling experiment of **4** clearly indicated a NOE between the protons of the *tert*-butyl group and the proton on C-4 in Figure 5A. Furthermore, the crystal structure of **23** (Figure 1) shows that the stereochemistry of the Boc group in **23** is essentially the same as shown in structure **A**.



(19) Addition of an ethereal solution of magnesium dibromide to an ethereal solution of **2** or **4** resulted in a precipitate, presumably a coordinated complex. However, we were unable to find an appropriate solvent for the NMR measurement.

(20) Ibuka, T.; Chu, G.-N.; Yoneda, F. *Tetrahedron Lett.* **1984**, *25*, 3247. Ibuka, T.; Aoyagi, T.; Yoneda, F. *J. Chem. Soc., Chem. Commun.* **1985**, 1452. Takano, S.; Sekiguchi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1988**, 449. Fujii, N.; Habashita, H.; Shigemori, N.; Otaka, A.; Ibuka, T.; Tanaka, M.; Yamamoto, Y. *Tetrahedron Lett.* **1991**, *32*, 4969.

(21) Ruden, R. A.; Litterer, W. E. *Tetrahedron Lett.* **1975**, 2043. Wege, P. M.; Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 3144. Logusch, E. W. *Tetrahedron Lett.* **1979**, 3365.

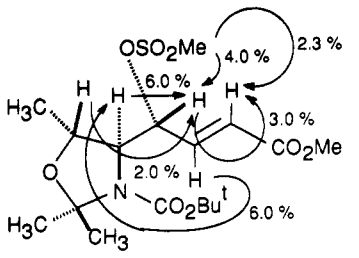


Figure 5. Selected NOE data for **3** in THF-d_8.

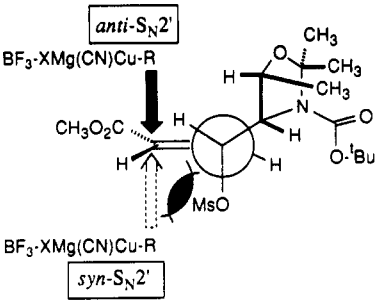


Figure 6.

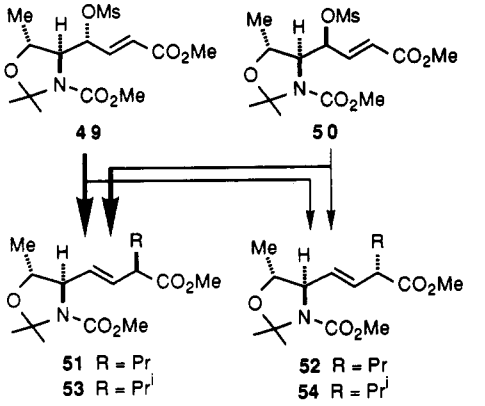
This may result from steric repulsion between the *tert*-butyloxy group of the substrate and the incoming reagent. In other words, in such a tris-coordinated complex, the bulky *tert*-butyl group of the substrate would block anti-S_N2' type attack by bulky organocoppers such as *i*-PrCu(CN)MgCl·BF_3 and *t*-BuCu(CN)MgCl·BF_3, and a coordinated intramolecular delivery of the alkyl nucleophile would be responsible for the formation of syn-S_N2' products.

The following experiment has been performed to substantiate the hypothesis of the effect of the bulky *tert*-butyl group in the substrate **2** or **4**. The required γ-(mesyloxy) (*E*)-α,β-enoates **49** and **50** were prepared in acceptable yields from (*S*)-threonine (see supplementary material). As we would expect, reaction of the *anti*-mesylate **49** with PrCu(CN)MgCl·BF_3 at −78 °C yielded only the propylated product **51** via the anti-S_N2' pathway (Table III, entry 1). Likewise, treatment of **49** with *i*-PrCu(CN)MgCl·BF_3 gave **53** predominantly (Table III, entry 3).

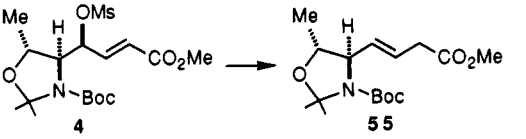
The *syn*-mesylate **50** gave two products (**51**:**52** = 58:42, 81% combined yield) upon treatment with PrCu(CN)MgCl·BF_3 with the syn-S_N2' product **51** predominating (Table III, entry 2) (the bulk of the propyl group is intermediate between a methyl group and an isopropyl group[22]). It is apparent from the following fact that the size of the alkyl group of the protective group on nitrogen also influences the level of the diastereoselectivity. The reaction between *i*-PrCu(CN)MgCl·BF_3 and **50** yielded a mixture of two products **53** and **54** with low diastereoselectivity [**53** (syn-S_N2' product):**54** (anti-S_N2' product) = 69:31] (Table III, entry 4). Thus, when the bulk of the alkyl group in the N-protective group is decreased from tertiary (*t*-Bu) to primary (Me), the amount of the unusual syn-S_N2' product is decreased. This indicates that the bulky *tert*-butyl group of the syn-substrate **2** or **4** blocks anti-S_N2' type attack by the bulky organocopper reagents such as *i*-PrCu(CN)MgCl·BF_3 and *t*-BuCu(CN)MgCl·BF_3. Needless to say, the exact structure is not known, either

(22) Jackson, R. F. W.; Standen, S. P.; Clegg, W.; McCamley, A. *Tetrahedron Lett.* **1992**, *33*, 6197.

Scheme VII



in the ground state or in the transition state; however, in the absence of firm knowledge, the model drawn in Figure 4 is conveniently simple at this stage in the development of our understanding.



Finally, it should be noted that the method stated above is not applicable to sp^2-copper reagents such as PhCu(CN)MgBr·BF_3, (vinyl)$_2$Cu(CN)(MgCl)$_2$, and $H_2C{=}C(Me)Cu(CN)MgBr$. As a typical example, reaction of the mesylate **4** with PhCu(CN)MgBr·BF_3 yielded only the reduction product **55** in 61% yield. In this reaction, we did not detect any arylation product by the TLC and ^1H NMR analyses. Similar reductions of simple cyclic and acyclic γ-oxygenated α,β-enoates[20] and γ-oxygenated α,β-enones[21] with organocopper reagents have been previously reported.

In summary, the *anti*-mesylate **1** or **3** reacts with alkylcyanocuprate·BF_3 reagents to yield mainly anti-S_N2' products. The *syn*-mesylate **2** or **4** affords a mixture of syn- and anti-S_N2' reaction products upon exposure to primary alkyl-Cu(CN)MgCl·BF_3. In addition, the *syn*-mesylate **2** or **4** yields a syn-S_N2' product by treatment with *i*-PrCu(CN)MgCl·BF_3 or *t*-BuCu(CN)MgCl·BF_3 with very high diastereoselectivity. The trend we observe for the *syn*-mesylates **2** and **4** runs counter to that reported for δ-HNBoc-γ-(mesyloxy) α,β-enoates.

Experimental Section

General Methods. All reactions were carried out under a positive pressure of argon. All glassware and syringes were dried in an electric oven at 100 °C prior to use. Ethereal MeLi (as complex with LiBr) was purchased from Aldrich. EtMgBr, *n*-PrMgBr, *n*-PrMgCl, *n*-BuMgCl, *n*-BuMgBr, *i*-BuMgCl, BnMgCl, and *i*-PrMgCl were prepared by reaction of EtBr, *n*-PrBr, *n*-PrCl, *n*-BuCl, *n*-BuBr, *i*-BuCl, BnCl, and *i*-PrCl with magnesium, respectively, in the usual way. *t*-BuMgCl was purchased from Kanto Chemicals. CuCN was obtained from Mitsuwa Chemicals and dried in an Abderhalden under vacuum at rt. All melting points are uncorrected. All NMR spectra were recorded at 200 MHz in $CDCl_3$ unless otherwise specified. Circular dichroism spectra were measured with a JASCO J-720A spectrometer at 20–30 °C. For flash chromatographies, silica gel 60 H (silica gel for thin-layer chromatography, Merck) or silica gel 60 (filter than 230 mesh, Merck) was employed. For HPLC, Cosmosil-5SL (10 × 250 mm, Nacalai Tesque) was employed.

Methyl (4*R*,2'*S*,2*E*)-4-[(Methylsulfonyl)oxy]-4-[*N*-(*tert*-butoxycarbonyl)pyrrolidin-2'-yl]-2-butenoate (5). To a stirred solution of 1.0 g (3.50 mmol) of alcohol **13** in a mixture of 4.25

Table III. Reaction of Mesylates 49 and 50 with Organocyanocopper·BF_3 Reagents[a]

entry	substrate	reagent	product (yield,[b] %) anti-S_N2'	syn-S_N2'	anti-S_N2':syn-S_N2'
1	49	PrCu(CN)MgBr·BF_3	51 (99)	52[c]	>99:1
2	50	PrCu(CN)MgBr·BF_3	52 (35)	51 (49)	42:58
3	49	*i*-PrCu(CN)MgCl·BF_3	53 (89)	54 (8)	92:8
4	50	*i*-PrCu(CN)MgCl·BF_3	54 (25.5)	53 (56)	31:69

[a] All reactions were carried out at −78 °C with 3–4 molar equiv of reagents. Diastereoselectivities (anti-S_N2':syn-S_N2') were determined by capillary VPC or ^1H NMR (300 MHz). [b] All yields are isolated yields for chromatographically and spectroscopically pure syn-S_N2' and anti-S_N2' products. [c] Could not be detected by capillary VPC.

mL (52.6 mmol) of pyridine, 43 mg (0.35 mmol) of 4-(dimethylamino)pyridine, and 5 mL of CH_2Cl_2 at −78 °C was added dropwise 2.71 mL of methanesulfonyl chloride, and the mixture was stirred for 18 h with warming to 0 °C. The mixture was poured into a cold solution of 25 mL of saturated $NaHCO_3$ and extracted with a mixed solvent of Et_2O–CH_2Cl_2 (4:1). The extract was washed successively with 1 N HCl, water, saturated $NaHCO_3$, and water and dried over $MgSO_4$. Concentration under reduced pressure below 25 °C yielded an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (3:1) to give a crystalline residue. Recrystallization from a mixed solvent of *n*-hexane–Et_2O (4:1) gave 980 mg (77% yield) of the title compound **5** as colorless crystals. **5**: mp 79 °C; $[\alpha]^{22}_D$ −82.6° (*c* 0.763, $CHCl_3$); IR ($CHCl_3$) 1730, 1685 cm^{-1}; ^1H NMR δ 1.47 (s, 9 H), 1.63–2.04 (m, 4 H), 2.97 (s, 3 H), 3.25–3.62 (m, 2 H), 3.76 (s, 3 H), 3.95 (m, 1 H), 5.50–5.85 (m, 2 H), 6.17 (dd, *J* = 15.6, 1.7 Hz, 1 H), 6.87 (dd, *J* = 15.6, 4.9 Hz, 1 H). Anal. Calcd for $C_{15}H_{25}NO_7S$: C, 49.57; H, 6.93; N, 3.85. Found: C, 49.44; H, 6.95; N, 3.63.

Methyl (2′*S*,4*S*,2*E*)-4-[(Methylsulfonyl)oxy]-4-[*N*-*tert*-butoxycarbonyl)pyrrolidin-2′-yl]-2-butenoate (6). To a stirred solution of 1.06 g (3.48 mmol) of mesylate **14** in 20 mL of CH_2Cl_2 was bubbled ozone at −78 °C until a blue color persisted. The solution was allowed to warm to 0 °C, and stirring was continued for 10 min. To the above solution at −78 °C were added 1.04 g (3.96 mmol) of PPh_3 and 3.61 g (10.80 mmol) of (carbomethoxymethylene)triphenylphosphorane, and the mixture was stirred for 3 h at 0 °C. The mixture was concentrated under reduced pressure to an oil which was flash chromatographed on a silica gel column. Elution with *n*-hexane–EtOAc (3:2) gave 962 mg (76% yield) of a crystalline mass, which was recrystallized from *n*-hexane–Et_2O (10:1). **6**: colorless crystals; mp 72 °C; $[\alpha]^{20}_D$ −76.9 ° (*c* 0.884, $CHCl_3$); IR ($CHCl_3$) 1720, 1680 cm^{-1}; ^1H NMR δ 1.49 (s, 9 H), 1.67–2.11 (m, 4 H), 3.08 (s, 3 H), 4.19 (m, 1 H), 5.65 (m, 1 H), 6.13 (d, *J* = 16.6 Hz, 1 H), 6.88 (dd, *J* = 15.6, 5.1 Hz, 1 H). Anal. Calcd for $C_{15}H_{25}NO_7S$: C, 49.57; H, 6.93; N, 3.85. Found: 49.56; H, 7.11; N, 3.84.

(2*S*)-*N*-[(*tert*-Butyloxy)carbonyl]pyrrolidine-2-methanol (7). To a stirred solution of LiCl (11.87 g, 280 mmol) in EtOH (140 mL) were successively added $NaBH_4$ (10.60 g, 280 mmol) in EtOH (140 mL) and the *N*-Boc-proline methyl ester (28.81 g, 126 mmol) in THF (140 mL) at −20 °C, and the stirring was continued for 16 h at rt. The mixture was made acidic with saturated citric acid (300 mL) at 0 °C followed by concentration under reduced pressure. The residue was extracted with AcOEt, and the extract was successively washed with saturated citric acid, saturated NaCl, saturated $NaHCO_3$, and saturated NaCl. The extract was dried over $MgSO_4$ and concentrated under reduced pressure to leave a crystalline residue, which was recrystallized from *n*-hexane (20.6 g, 81% yield). **7**: colorless crystals; mp 62 °C; $[\alpha]^{20}_D$ −49.8° (*c* 1.27, $CHCl_3$); IR ($CHCl_3$) 3400, 1670, 1460 cm^{-1}; ^1H NMR δ 1.47 (s, 9 H), 1.61 (m, 1 H), 1.70–1.88 (m, 2 H), 1.91–2.06 (m, 1 H), 3.25–3.49 (m, 2 H), 3.53–3.75 (m, 3 H), 3.93 (m, 1 H). Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.58; H, 9.52; N, 6.96. Found: C, 59.47; H, 9.61; N, 6.89.

(1′*R*,2*S*)-2-(1′-Hydroxypropen-2′-yl)-*N*-[(*tert*-butyloxy)carbonyl]pyrrolidine (8) and Its (1′*S*,2*S*)-Isomer 9. To a stirred solution of alcohol **7** (10.06 g, 50 mmol) in CH_2Cl_2 (30 mL) were added Et_3N (20.9 mL, 150 mmol) and SO_3–pyridine complex (23.87 g, 150 mmol) in 110 mL of DMSO at room temperature under argon. The brown solution was stirred for 10 min and was poured into ice–water. The mixture was extracted with Et_2O, and the organic layer was washed with saturated $NaHCO_3$, water, 5% citric acid, and water and dried over $MgSO_4$. The filtrate was concentrated in vacuo to leave a colorless oil. The oil in THF (30 mL) was added to a solution of vinylmagnesium chloride (150 mmol in 75 mL of THF) at −40 °C under argon. The mixture was stirred for 1 h at 0 °C and then poured into cold saturated citric acid. The mixture was extracted with AcOEt, and the extract was successively washed with saturated citric acid, saturated NaCl, saturated $NaHCO_3$, and saturated NaCl and dried over $MgSO_4$. Concentration under reduced pressure gave an oily residue which was flash chromatographed over silica gel. Elution with $CHCl_3$–AcOEt (10:3) gave 3.33 g (29% yield) of **9**, and further elution yielded 4.37 g (38% yield) of **8**. **9**: a colorless oil (Kugelrohr distillation, 135 °C/1 mmHg); $[\alpha]^{20}_D$ −86.2° (*c* 0.905, $CHCl_3$); IR ($CHCl_3$) 3350, 1680 cm^{-1}; ^1H NMR δ 1.48 (s, 9 H), 1.60–1.95 (m, 4 H), 3.32 (m, 1 H), 3.45 (m, 1 H), 3.85 (m, 1 H), 3.96 (m, 1 H), 5.15–5.36 (m, 3 H), 5.82 (ddd, *J* = 17.1, 10.0, 6.6 Hz, 1 H); MS *m/z* 227 (M^+), 170, 154, 70 (base peak), 57, 41; HRMS *m/z* calcd for $C_{12}H_{21}NO_3$ 227.1521, found 227.1501. **8**: a colorless oil (Kugelrohr distillation, 120 °C/1 mmHg); $[\alpha]^{20}_D$ −63.77° (*c* 0.853, $CHCl_3$); IR ($CHCl_3$) 3330, 1660, 1400 cm^{-1}; ^1H NMR δ 1.47 (s, 9 H), 1.55–2.10 (m, 4 H), 3.23 (m, 1 H), 3.48 (m, 1 H), 4.02–4.22 (m, 2 H), 5.15–5.36 (m, 3 H), 5.81 (ddd, *J* = 17.1, 10.3, 6.1 Hz, 1 H). Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.15; H, 9.45; N, 6.13.

(1*R*,7a*S*)-1-Ethenyl-3-oxotetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole (10). To a stirred suspension of NaH (120 mg, 5.0 mmol) in DMF (1 mL) was added alcohol **8** (227 mg, 1.0 mmol) in DMF (3 mL) at 0 °C under argon, and the mixture was stirred for 11 h at room temperature. The mixture was quenched by saturated NH_4Cl (4 mL) at 0 °C and was extracted with AcOEt (100 mL). The extract was washed with saturated NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel with AcOEt–hexane (1:2) to give **10** (52 mg, 34% yield) as a colorless oil. **10**: Kugelrohr distillation, 120 °C/1 mmHg; $[\alpha]^{20}_D$ −53.3° (*c* 0.560, $CHCl_3$); IR ($CHCl_3$) 1750 cm^{-1}; ^1H NMR δ 1.40–2.12 (m, 4 H), 3.19 (ddd, *J* = 11.5, 9.3, 3.9 Hz, 1 H), 3.66 (ddd, *J* = 11.5, 8.1, 7.6 Hz, 1 H), 3.90 (ddd, *J* = 10.3, 7.6, 5.6 Hz, 1 H), 5.14 (ddt, *J* = 7.6, 6.1, 1.2 Hz, 1 H), 5.36 (dt, *J* = 10.5, 1.2 Hz, 1 H), 5.449 (dt, *J* = 17.1, 1.2 Hz, 1 H), 5.85 (ddd, *J* = 17.1, 10.5, 5.9 Hz, 1 H). Anal. Calcd for $C_8H_{11}NO_2$: C, 62.72; H, 7.24; N, 9.14. Found: C, 62.73; H, 7.32; N, 9.01.

(1*S*,7a*S*)-1-Ethenyl-3-oxotetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole (11). By a procedure identical with that described for the preparation of **10** from **8**, 227 mg (1.0 mmol) of alcohol **9** was converted into the title compound **11** (13 mg, 8% yield) as a colorless oil. **11**: Kugelrohr distillation, 120 °C/1 mmHg; $[\alpha]^{20}_D$ −46.8° (*c* 0.692, $CHCl_3$); IR ($CHCl_3$) 1740 cm^{-1}; ^1H NMR δ 1.43–1.63 (m, 1 H), 1.81–2.17 (m, 3 H), 3.19 (ddd, *J* = 11.2, 8.8, 4.6 Hz, 1 H), 3.58–3.72 (m, 2 H), 4.70 (m, 1 H), 5.31 (dt, *J* = 10.3, 1.2 Hz, 1 H), 5.43 (dt, *J* = 17.1, 1.2 Hz, 1 H), 5.98 (ddd, *J* = 17.1, 10.3, 6.6 Hz, 1 H); MS *m/z* 153 (M^+), 125, 97, 69 (base peak), 54, 41; HRMS *m/z* calcd for $C_8H_{11}NO_2$ 153.0790, found 153.0787.

(1′*R*,2*S*)-2-(1′-Acetoxypropen-2′-yl)-*N*-[(*tert*-butyloxy)carbonyl]pyrrolidine (12). To a stirred solution of allyl alcohol **8** (2.74 g, 12.04 mmol) in CH_2Cl_2 (5 mL) were successively added pyridine (14.61 mL, 180.7 mmol), acetic anhydride (11.36 mL, 120.4 mmol), and 4-(dimethylamino)pyridine (147 mg, 1.20 mmol) at 0 °C. The mixture was stirred for 12 h at rt. Saturated $NaHCO_3$ (30 mL) was added to the mixture with vigorous stirring at 0 °C. The mixture was extracted with Et_2O–CH_2Cl_2 (4:1), and the extract was successively washed with water, 1 N HCl, water, saturated $NaHCO_3$, and water and dried over $MgSO_4$. Concen-

tration under reduced pressure gave a colorless oil which was purified by flash chromatography over silica gel with AcOEt–*n*-hexane (1:3) to give acetate **12** (3.29 g, 100% yield) as a colorless oil. **12**: Kugelrohr distillation, 120 °C/3 mmHg; $[\alpha]^{20}_D$ −47.3° (*c* 0.816, $CHCl_3$); IR ($CHCl_3$) 1730, 1670 cm^{-1}; ^1H NMR δ 1.48 (s, 9 H), 1.70–2.01 (m, 4 H), 2.07 (s, 3 H), 3.31 (m, 1 H), 3.48 (m, 1 H), 5.23 (m, 2 H), 5.65–5.81 (m, 2 H); MS *m/z* 269 (M^+), 196, 170, 154, 114, 70 (base peak), 58, 43; HRMS *m/z* calcd for $C_{14}H_{23}NO_4$ 269.1627, found 269.1635.

Methyl (4*R*,2′*S*,2*E*)-4-Hydroxy-4-[*N*-[(*tert*-butyloxy)carbonyl]pyrrolidin-2′-yl]-2-butenoate (13). To a stirred solution of 3.29 g (12.22 mmol) of acetate **12** in 20 mL of CH_2Cl_2 was bubbled ozone at −78 °C until a blue color persisted. The solution was warmed to 0 °C and stirred for 10 min. To the above solution were added 4.81 g (18.3 mmol) of PPh_3 and 12.26 g (36.67 mmol) of (carbomethoxymethylene)triphenylphosphorane at −30 °C, and the mixture was stirred for 3 h at 0 °C. The mixture was concentrated under reduced pressure to an oil which was flash chromatographed on a silica gel column. Elution with *n*-hexane–EtOAc (4:1) gave 3.03 g of a colorless oil. Powdered Na_2CO_3 (6.48 g) was added to a solution of 3.03 g of the above oil in 5 mL of MeOH under stirring at room temperature, and the mixture was stirred for 11 h. The mixture was filtrated. The filtrate was acidified with saturated citric acid and concentrated under reduced pressure to leave a slightly yellow oil which was extracted with AcOEt. The extract was washed with water, saturated $NaHCO_3$, and water and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography on a silica gel column with $CHCl_3$–EtOAc (10:3) gave 1.42 g (41% yield) of the title compound **13** as a colorless oil. **13**: Kugelrohr distillation, 160 °C/1 mmHg; $[\alpha]^{20}_D$ −71.9° (*c* 0.479, $CHCl_3$); IR ($CHCl_3$) 3300, 1710, 1650 cm^{-1}; ^1H NMR δ 1.45 (s, 9 H), 1.52–1.90 (m, 4 H), 2.07 (br s, 1 H), 3.25 (m, 1 H), 3.48 (m, 1 H), 3.74 (s, 3 H), 4.11 (m, 1 H), 4.41 (m, 1 H), 6.15 (dd, *J* = 15.4, 1.7 Hz, 1 H), 6.93 (dd, *J* = 15.4, 4.6 Hz, 1 H). Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.13; N, 4.91. Found: C, 58.96; H, 8.07; N, 4.92.

(1′*S*,2*S*)-2-[1′-[(Methylsulfonyl)oxy]propen-2′-yl]-*N*-[(*tert*-butyloxy)carbonyl]pyrrolidine (14). To a stirred solution of 1.0 g (4.40 mmol) of alcohol **9** in a mixture of pyridine (5.34 mL), 4-(dimethylamino)pyridine (53 mg), and CH_2Cl_2 (10 mL) at −78 °C was added dropwise 3.41 mL of methanesulfonyl chloride, and the mixture was stirred for 12 h at 0 °C. To the mixture was added 30 mL of saturated $NaHCO_3$ at 0 °C, and the mixture was stirred for 30 min. The mixture was extracted with a mixed solvent Et_2O–CH_2Cl_2 (4:1), and the extract was successively washed with water, 1 N HCl, water, saturated $NaHCO_3$, and water and dried over $MgSO_4$. Concentration under reduced pressure below 25 °C yielded a crystalline residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (4:1) to yield a crystalline mass. Recrystallization from *n*-hexane gave 1.11 g (82% yield) of the title compound as colorless crystals; mp 92 °C; $[\alpha]^{20}_D$ −56.5° (*c* 0.783, $CHCl_3$); IR ($CHCl_3$) 1685 cm^{-1}; ^1H NMR δ 1.49 (s, 9 H), 1.62–2.10 (m, 4 H), 3.02 (s, 3 H), 3.26 (m, 1 H), 3.46 (m, 1 H), 4.15 (m, 1 H), 5.36–5.48 (m, 3 H), 5.87 (ddd, *J* = 17.1, 10.5, 6.6 Hz, 1 H). Anal. Calcd for $C_{13}H_{23}NO_5S$: C, 51.13; H, 7.59; N, 4.59. Found: C, 50.90; H, 7.87; N, 4.61.

General Procedure Using RCu(CN)MgX·BF_3 (R = Me, Et, Pr, Bu, *i*-Bu, Bn, *i*-Pr, and *t*-Bu). The following procedure is representative for all reactions of δ-aminated γ-(mesyloxy) (*E*)-α,β-enoates with magnesiocuprate·BF_3 reagents.

Methyl (2*R*,3*E*)-2-Isopropyl-4-[(4*R*,5*R*)-*N*-[(*tert*-butyloxy)carbonyl]-2,2,5-trimethyl-4-oxazolidinyl]-3-butenoate (25) and Its (2*S*,3*E*)-Isomer 26. Reaction of γ-[(Methylsulfonyl)oxy] α,β-Enoate (4) with *i*-PrCu(CN)·MgCl·BF_3. To a stirred slurry of CuCN (81 mg, 0.9 mmol) in 5 mL of dry THF was added by syringe 0.5 mL (0.9 mmol) of 1.8 M *i*-PrMgCl in THF at −78 °C, and the mixture was allowed to warm to 0 °C and to stir at this temperature for 15 min. BF_3·Et_2O (0.093 mL, 0.9 mmol) was added to the above mixture at −78 °C, and the mixture was stirred for 5 min. A solution of α,β-enoate **4** (122 mg, 0.3 mmol) in dry THF (2 mL) was added dropwise to the above reagent at −78 °C with stirring, and the stirring was continued for 30 min followed by quenching with 2 mL of a 1:1 saturated NH_4Cl–28% NH_4OH solution. The mixture was extracted with Et_2O, and the extract was washed with water and dried over $MgSO_4$. Concentration under reduced pressure gave a mixture of products as a colorless oil. The mixture was separated by HPLC (Cosmosil-5SL). Elution with *n*-hexane–THF (98.2) gave 8.5 mg (8% yield) of **26**, and further elution gave 87 mg (82% yield) of **25**. **25**: a colorless oil (Kugelrohr distillation, 160 °C/1 mmHg); $[\alpha]^{20}_D$ −66.2° (*c* 0.70, $CHCl_3$); Δε −3.59 (221 nm, isooctane); IR ($CHCl_3$) 1732, 1692 cm^{-1}; ^1H NMR δ 0.93 (d, *J* = 6.6 Hz 6 H), 1.27 (d, *J* = 5.9 Hz, 3 H), 1.44 (s, 9 H), 1.50 (s, 3 H), 1.60 (s, 3 H), 2.02 (m, 1 H), 2.73 (t, *J* = 8.5 Hz, 1 H), 3.68 (s, 3 H), 3.75–3.90 (m, 2 H), 5.31–5.50 (m, 1 H), 5.65 (dd, *J* = 15.5, 8.5 Hz, 1 H). Anal. Calcd for $C_{19}H_{33}NO_5$: C, 64.20; H, 9.36; N, 3.94. Found: C, 64.47; H, 9.60; N, 3.72. **26**: a colorless oil (Kugelrohr distillation, 155 °C/1 mmHg); Δε +7.36 (217 nm, isooctane); ^1H NMR δ 0.88 (d, *J* = 6.8 Hz, 3 H), 0.92 (d, *J* = 6.6 Hz, 3 H), 1.29 (d, *J* = 5.9 Hz, 3 H), 1.39 (s, 9 H), 1.52 (s, 3 H), 1.60 (s, 3 H), 1.96 (m, 1 H), 2.72 (t, *J* = 8.8 Hz, 1 H), 3.67 (s, 3 H), 3.73–3.90 (m, 2 H), 5.38 (dd, *J* = 15.5, 7.5 Hz, 1 H), 5.59 (dd, *J* = 15.5, 8.5 Hz, 1 H). Anal. Calcd for $C_{19}H_{33}NO_5$: C, 64.20; H, 9.36; N, 3.94. Found: C, 64.38; H, 9.57; N, 4.06.

Methyl (3*E*)-4-[(4*R*,5*R*)-*N*-[(*tert*-Butyloxy)carbonyl]-2,2,5-trimethyl-4-oxazolidinyl]-3-butenoate (55). Reaction of γ-[(Methylsulfonyl)oxy] α,β-Enoate (4) with PhCu(CN)·MgBr·BF_3. To a stirred slurry of CuCN (180 mg, 2 mmol) in 8 mL of dry THF was added by syringe 1.82 mL (2 mmol) of 1.1 M PhMgBr in THF at −78 °C, and the mixture was allowed to warm to −30 °C and to stir at this temperature for 15 min. BF_3·Et_2O (0.25 mL, 2 mmol) was added to the above mixture at −78 °C, and the mixture was stirred for 15 min. A solution of α,β-enoate **4** (204 mg, 0.5 mmol) in dry THF (2 mL) was added dropwise to the above reagent at −78 °C with stirring, and the stirring was continued for 2 h followed by quenching with 2 mL of a 1:1 saturated NH_4Cl–28% NH_4OH solution. The mixture was extracted with Et_2O, and the extract was washed with water and dried over $MgSO_4$. Concentration under reduced pressure gave a mixture of products as a colorless oil which was purified by flash chromatography over silica gel with AcOEt–*n*-hexane (1:4) to give β,γ-unsaturated ester **55** (94 mg, 61% yield) as a colorless oil: Kugelrohr distillation, 140 °C/1 mmHg; $[\alpha]^{25}_D$ −7.1° (*c* 1.31, $CHCl_3$); IR ($CHCl_3$) 1732, 1688, 967, 860 cm^{-1}; ^1H NMR δ 1.28 (d, *J* = 5.9 Hz, 3 H), 1.42 (s, 9 H), 1.50 (s, 3 H), 1.60 (s, 3 H), 3.10 (m, 2 H), 3.69 (s, 3 H), 3.71–3.90 (m, 2 H), 5.41 (dd, *J* = 15.38, 7.56 Hz, 1 H), 5.71 (ddd, *J* = 15.38, 7.08, 7.08 Hz, 1 H). Anal. Calcd for $C_{16}H_{27}NO_5$: C, 61.32; H, 8.68; N, 4.47. Found: C, 61.31; H, 8.80; N, 4.49.

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Supplementary Material Available: Synthetic methods and spectral data [$[\alpha]_D$, Δε, IR, ^1H NMR, and MS] for **17–24**, **27–30**, **33**, **34**, **39–43**, **45–54**, **56–58**, **60**, **61**, and **64–67**, crystal data, atomic coordinates, bond lengths, bond angles, and torsion angles for **23**, and ^1H NMR spectra of **5**, **6**, **8–14**, **17–24**, **27–30**, **33**, **34**, and **39–48** (52 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.