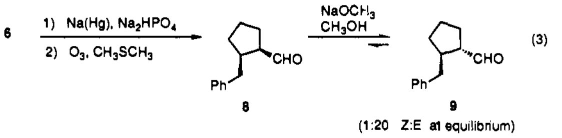
Table I. Dependence of Cyclization of **5a** on Experimental Parameters with $(dba)_3Pd_2{\cdot}CHCl_3$ as Catalyst

entry	ligand (mol %)	solvent	time, h	yield, %	*Z*	*E*
1[c]	$(iC_3H_7O)_3P$ (20)	THF	2.5	87	1	1.4
2[b,c]	$(iC_3H_7O)_3P$ (20)	THF	3.0	85	1	1.8
3	$(iC_3H_7O)_3P$ (15)	DMSO	5.0	91	6.9	1.0
4	$(iC_3H_7O)_3P$ (30)	DMSO	4.0	93	5.9	1.0
5[c]	Ph_3P (20)	THF	1.5	83	1.0	1.0
6	Ph_3P (30)	DMSO	2.0	89	5.5	1.0
7	$(o\text{-}CH_3C_6H_5)_3P$ (20)	THF	4.0	50	1.0	1.7
8	TTMPP[e] (30)	$PhCH_3$	0.3	89	1.0	1.1
9	TTMPP[e] (30)	THF	0.08	98	1.3	1.0
10	TTMPP[e] (30)	CH_3CN	0.4	91	1.2	1.0
11	TTMPP[e] (30)	DMSO	0.08	93	3.7	1.0
12	TTMPP[e] (10)	DMSO	0.3	87	4.5	1.0
13[d]	TTMPP[e] (5)	DMSO	1.0	73	4.5	1.0
14	$(C_4H_9)_3P$ (20)	THF	1.0	98	1.7	1.0
15	$(C_4H_9)_3P$ (20)	DMSO	1.0	97	2.7	1.0
16	$(iC_3H_7)_3P$ (30)	THF[f]	17.0	0		
17	$(iC_3H_7)_3P$ (30)	DMSO	1.0	93	3.0	1.0
18	none	DMSO[g]	12.0	44	2.3	1.0

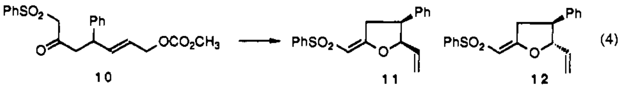
[a] Reactions were performed at approximately 0.1 M in the indicated solvent by using 1.25 mol % of $(dba)_3Pd_2{\cdot}CHCl_3$ and the indicated ligand at room temperature unless stated otherwise. [b] For this run, $Pd(OAc)_2$ was employed as the palladium source. [c] For this run, 2.5 mol % of $(dba)_3Pd_2{\cdot}CHCl_3$ was employed. [d] For this run, 0.125 mol % of $(dba)_3Pd_2{\cdot}CHCl_3$ was employed. [e] TTMPP = tris(2,4,6-trimethoxyphenyl)phosphine. [f] Reaction temperature = 70 °C. [g] Reaction temperature = 100 °C.

Most importantly, ring geometry proved sensitive to the reaction parameters. For the phosphite and triphenylphosphine ligands, solvent played a domineering role. The highest selectivities for the *Z* isomer were obtained with triisopropyl phosphite and TTMPP, two ligands that are diametrically opposite both in terms of electronic factors and steric bulk (cone angles of 130° and 184°, respectively).[11] The stereochemistry of **6a** and **7a** was established by an observed NOE between the methyl group and vinyl proton in **6** but between the methyl group and allylic methine proton in **7**.

The benzyl substrate **5b**[8] allowed dominance of either the *E* or *Z* isomers depending upon solvent with TTMPP as ligand. In dioxane, a 71% yield of a 1:3.1 *Z*:*E* ratio of **6b**:**7b**[8] was observed, whereas, in DMSO, an 82% yield of a 6.7:1 ratio of *Z*:*E* is observed with 10 mol % ligand. Triisopropyl phosphite was somewhat less *Z* selective (4.5:1 *Z*:*E*, 84% yield). Chemical equilibration of the aldehydes **8** and **9**[8] obtained as illustrated in eq 3 establishes the major cyclization product as *Z*.



Increasing the effective steric bulk of the substituent to isopropyl as in substrate **5c** enhances the *Z* selectivity of the cyclopentanes **6c** and **7c**[8] to 7.2:1 (94% yield) when TTMPP is used as ligand in DMSO at room temperature. Changing the nucleophile to the β-keto sulfone as in **10** generated the cyclization products derived from preferential O-alkylation, **11** and **12** (eq 4).[8,12] Under all



conditions studied, the *Z* isomer **11** dominated, the highest selectivity being observed with triphenylphosphine (20 mol %) in THF at 70 °C (*Z*:*E*, 6.2:1, 76% yield). Assignment of the *Z* stereochemistry derives from extensive NMR studies: NOE, solvent-induced shifts, and relative chemical shifts.[4]

Contrary to the general expectation to favor the thermodynamically favored *E* isomers in cyclizations, palladium-catalyzed cyclizations of the type generalized in eq 1 favor the *Z* product both for carbon and oxygen nucleophiles, regardless of the regioisomer or stereochemistry of the substrate. These results are in accord with the model presented in eq 1, wherein the steric demands associated with docking the substrate on the "template" dominate in spite of the generation of the product having the larger nonbonded interactions.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences, for their generous support of our programs. We are grateful for mass spectra kindly provided by the Mass Spectrometry Facility, University of California—San Francisco, supported by the NIH Division of Research Resources.

Supplementary Material Available: Characterization data for **5a–c**, **6a–c**, **7a–c**, and **10–12** (4 pages). Ordering information is given on any current masthead page.

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(10) Akermark, B.; Hansson, S.; Vitagliano, A. *J. Am. Chem. Soc.* **1990**, *112*, 4587.

(11) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313. Cf. cone angle of tris(2,6-dimethoxyphenyl)phosphine in ref 9.

(12) Small amounts of a byproduct tentatively identified as the 2-[(phenylsulfonyl)methylene]-4-phenyl-2,3,4,7-tetrahydrooxepine were detected.

Efficient, Complementary Binding of Nucleic Acid Bases to Diaminotriazine-Functionalized Monolayers on Water

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Received January 24, 1991

Intensive effort has been made recently to develop organic host molecules that specifically bind substrates by complementary hydrogen bonding.[1-5] The hydrogen bonding involved in these host–guest interactions is most effective in aprotic organic solvents, and it is usually supressed in aqueous environments.[6] Realization

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(1) Hamilton, A. D.; Van Engen, D. *J. Am. Chem. Soc.* **1987**, *109*, 5035.

(2) Chang, S.-K.; Hamilton, A. D. *J. Am. Chem. Soc.* **1988**, *110*, 1318.

(3) (a) Rebek, J., Jr. *Science* (*Washington, D.C.*) **1987**, *235*, 1478. (b) Rebek, J., Jr. *Acc. Chem. Res.* **1990**, *23*, 399.

(4) Aoyama, Y.; Tanaka, Y.; Sugahara, S. *J. Am. Chem. Soc.* **1989**, *111*, 5347.

(5) Kilburm, J. D.; Mackenzie, A. R.; Still, W. C. *J. Am. Chem. Soc.* **1988**, *110*, 5347.

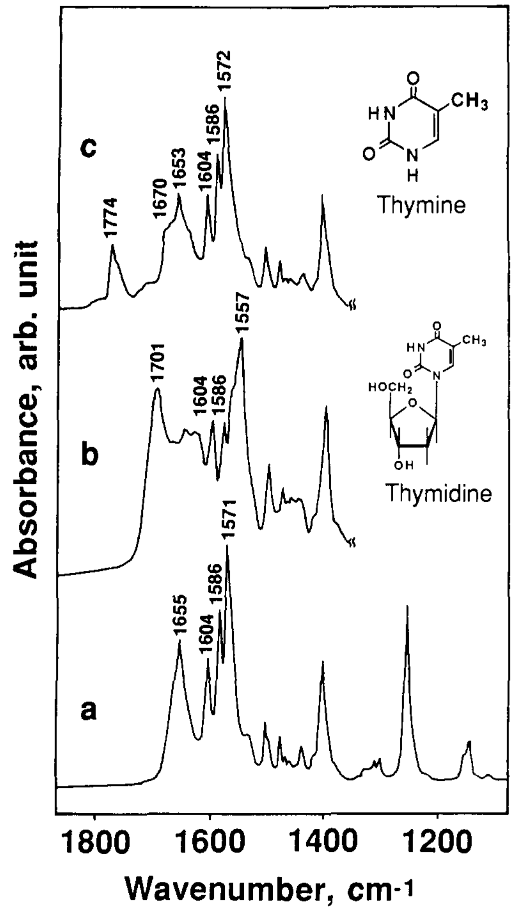

Figure 1. FT-IR reflection spectra of LB films of **1** transferred onto gold-coated glass slides: (a) from pure water; (b) from 0.01 M thymidine; and (c) from 0.01 M thymine. The films consist of 12 LB layers.

of effective hydrogen bonding *in water* is especially significant due to its relevance to biological molecular recognition. Surface monolayers provide a convenient molecular system to study host–guest interactions that remain exposed to water.[7-11] Surprisingly, we found that monolayers of a diaminotriazine amphiphile were capable of selective binding of nucleosides and nucleic acid bases in the aqueous environment.

A diaminotriazine amphiphile (2-[4-[[4-(decyloxy)phenyl]azo]phenyl]-4,6-diamino-1,3,5-triazine, **1**) forms a stable monolayer at the air–water interface.[11] Its surface pressure–area isotherm shows an expanded phase at 20.0 ± 0.2 °C. Thymidine and uridine dissolved in the aqueous subphase (0.01 M) only slightly expand the monolayer, and it is difficult to examine monolayer–substrate interactions from these isotherms. Subsequently, we employed FT-IR and X-ray photoelectron spectroscopies to study possible binding phenomena.

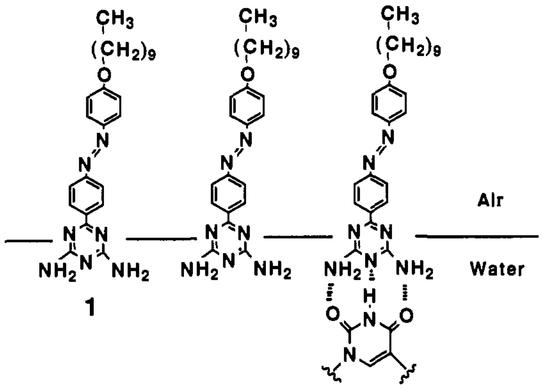

Figure 2. A schematic drawing of a monolayer of **1** at the air–water interface. Nucleic acid bases bearing the imide moiety bind to this monolayer through complementary hydrogen bonds.

An FT-IR reflection spectrum (Nicolet, Model 710) of an LB (Langmuir–Blodgett) film[12,13] of **1** transferred from pure water (Figure 1a) shows characteristic peaks of the triazine unit at 3506, 3313, and 3185 cm^{-1} (NH stretching), 1655 cm^{-1} (NH deformation), 1604 and 1586 cm^{-1} (phenyl breathing), and 1571 cm^{-1} (C=N stretching). For an LB film of **1** transferred from 0.01 M aqueous thymidine, a new peak at 1701 cm^{-1} (C=O stretching, thymidine) is found in addition to broadening of the peak at 1655 cm^{-1} and a shift of the C=N peak from 1571 to 1557 cm^{-1} (with a shoulder at 1571 cm^{-1}) (Figure 1b). The latter changes are caused by hydrogen-bond formation between the diaminotriazine unit and the imide group of thymidine. An LB film of **1** transferred from 0.01 M aqueous uridine displays similar IR changes. On the other hand, an LB film from 0.01 M aqueous adenosine exhibits a spectrum nearly identical with that from pure water. In the case of nucleic acid bases, 0.01 M thymine in the subphase also causes appearance of a new peak at 1774 cm^{-1} (C=O stretching, thymine) and broadening of the peak at 1653 cm^{-1}, though the location of the C=N peak remains the same at 1572 cm^{-1} (Figure 1c). Contrarily, 0.003 M adenine does not alter the spectrum.[14] LB films of octadecyl alcohol obtained from 0.01 M thymine or 0.003 M adenine demonstrate only traces of characteristic peaks of these substrates at 1757 cm^{-1} (thymine) and at 1670 cm^{-1} (adenine). Neither efficiency nor selectivity in substrate binding was observed with the alcohol monolayer.

X-ray photoelectron spectroscopy (XPS, Perkin-Elmer PHI 5300 ESCA system) provides quantitative binding data. The carbon:nitrogen:oxygen ratio of an LB film of **1** transferred from pure water onto a Au-coated glass slide was determined to be (81.4 ± 0.2):(14.7 ± 0.2):(3.9 ± 0.1) (%, at a takeoff angle of 45°), in close agreement with the theoretical ratio (81.7:15.0:3.3).[15] The C:N:O ratio of an LB film from 0.01 M thymidine is (75.5 ± 0.9):(14.1 ± 0.6):(10.4 ± 0.3) (%). This ratio is close to a computed atomic ratio of 1.1:1 for thymidine to **1**; i.e., C:N:O = 75.6:14.2:9.8.[17] Similarly, the molar ratio of bound substrate was estimated as 1.1, 1.1, 0.5,[18] and 0.2 for 0.01 M uridine, thymine, and adenosine and 0.003 M adenine, respectively.

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(6) Fersht, A. R. *Trends Biochem. Sci.* **1987**, *12*, 301.

(7) (a) Kurihara, K.; Ohto, K.; Tanaka, Y.; Aoyama, Y.; Kunitake, T. *Thin Solid Films* **1989**, *179*, 21. (b) Kurihara, K.; Ohto, K.; Tanaka, Y.; Aoyama, Y.; Kunitake, T. *J. Am. Chem. Soc.* **1991**, *113*, 444.

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(9) Ikeura, Y.; Honda, Y.; Kurihara, K.; Kunitake, T. *Chem. Lett.* **1990**, 169.

(10) Ikeura, Y.; Kurihara, K.; Kunitake, T., submitted to *J. Am. Chem. Soc.*

(11) Preparation of diaminotriazine monolayers and barbiturate binding have been reported elsewhere: Honda, Y.; Kurihara, K.; Kunitake, T. *Chem. Lett.* **1991**, 681.

(12) LB films of **1** were transferred in the vertical mode at a surface pressure of 25 mN/m and a transfer rate of 20 mm/min onto CaF_2 plates (for the transmission method) or Au-deposited glass slides (1000 Å vapor-deposited, for the reflection) from various subphases. The transfer ratio (±10%) was 1 in the up-stroke mode and 0 in the down-stroke mode.

(13) A transmission absorption spectrum of **1** is different from the corresponding reflection spectrum, because they emphasize vibration modes parallel and normal to the surface, respectively. Peaks ascribed to the diaminotriazine group are more clearly seen in reflection spectra; thus we used the reflection method to evaluate substrate–monolayer interactions.

(14) The solubility of thymine in water is 4 g/L (~0.03 M), and that of adenine is 0.5 g/L (~0.004 M) at room temperature: *The Merck Index*, 9th ed.; Merck & Co.: Rahway, NJ, 1976.

(15) The elemental composition of compound **1** is C:N:O = 76:21:3 (%). A theoretical value was calculated for an ideal Z-type LB film (four layers) by using an optimized mean free path of electron of 40 Å[16] for all C, N, and O. A slightly larger oxygen content was observed owing to adsorption of an unknown species to the LB film surface which broadens the oxygen peak.

(16) This value is close to the one reported for LB films of arachidic acid: Brundle, C. R.; Hopster, H.; Swalen, J. D. *J. Chem. Phys.* **1979**, *70*, 5190.

(17) The uncertainty in the computed ratios is 10–20%. The increase in the oxygen content by unknown adsorbed species is assumed to be the same as that in the film obtained from pure water (0.6%).

(18) This ratio appears unreasonably high because no appreciable changes were found in an FT-IR spectrum of the LB film obtained under identical conditions. The LB film was not uniform and showed an XPS peak of the substrate gold.

Equimolar amounts of thymidine, uridine, and thymine are bound to the host monolayer at 0.01 M.

The present results establish that thymidine, uridine, and thymine (substrates bearing the imide moiety) are bound to monolayer **1**, in preference to adenosine and adenine. Complementary hydrogen bonds between the diaminotriazine unit and the imide moiety (Figure 2) apparently caused the selective binding. The association constants of thymidine and thymine with monolayer **1** are estimated to be $(2 \pm 1) \times 10^2$ M^{-1}, by assuming the Langmuir adsorption. This value is comparable to the association constant reported for 1-butylthymidine with diamide pyridine receptors in $CDCl_3$,[19] in spite of very different microenvironments between the two systems. The hydrogen bonding with solvent molecules, albeit weak, produces a serious detrimental effect in this type of host-guest interaction.[20] Therefore, it is surprising to observe efficient hydrogen-bonding interactions at the air-water interface. This effectiveness may be attributed to unique macroscopic properties of the air-water interface and/or cooperative action of organized diaminotriazine units. We have found that other water-soluble substrates (monosaccharides and amino acids) were efficiently bound to host monolayers at the air-water interface.[7,10,11] These molecular recognitions should have important bearing on the related processes occurring at surfaces of the biological molecular system.

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[19] The association constants are 90 M^{-1} and 290 M^{-1}, depending on the receptor: Muehldorf, A. V.; Van Engen, D.; Warner, J. C.; Hamilton, A. D. *J. Am. Chem. Soc.* **1988**, *110*, 6561.

[20] Schneider, H.-J.; Juneja, R. K.; Simova, S. *Chem. Ber.* **1989**, *122*, 1211.

Stereoselective Formation of Carbon-Carbon Bonds through Metal Catalysis. The Zirconium-Catalyzed Ethylmagnesation Reaction

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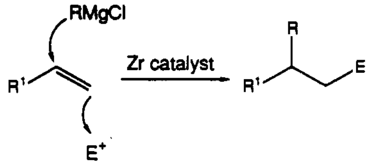
Received February 4, 1991

The design and development of stereoselective, catalytic reactions, especially those that effect formation of carbon-carbon bonds, is an important objective in chemical synthesis. In 1983, Dzhemilev reported that Cp_2ZrCl_2 catalyzes the addition of ethylmagnesium halides to simple alkenes (3-40%).[1] This transformation accomplishes a useful and unprecedented task: formation of a carbon-carbon bond by addition of an alkyl Grignard reagent to an unactivated olefin;[2] the initial product may then be employed in further bond-forming processes (eq 1). As part of a program aimed at the development of stereoselective metal-catalyzed reactions, we have examined the utility of the zirconium-catalyzed ethylmagnesation reaction.



(1)

Scheme I

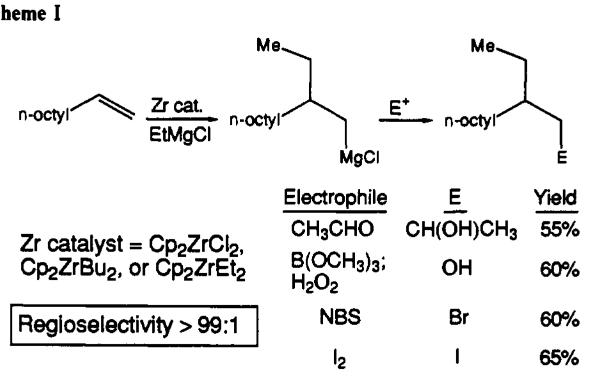
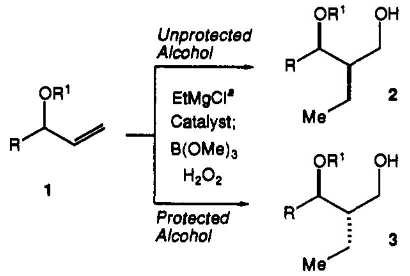


Table I. Diastereochemical Control in the Ethylmagnesation of Allylic Alcohols and Their Derivatives



substrate	R	R^1	catalyst (mol %)	2:3^b	% yield^c
1a	*n*-nonyl	H	Cp_2ZrCl_2 (5)	95:5	70
1b	cyclohexyl	H	Cp_2ZrCl_2 (5)	84:16	20^d
	cyclohexyl	H	Cp_2ZrBu_2 (25)^e	67:33	70
1c	*n*-nonyl	Me	Cp_2ZrCl_2 (5)	11:89	80
1d	*n*-nonyl	MEM	Cp_2ZrCl_2 (5)	10:90	53
1e	cyclohexyl	Me	Cp_2ZrBu_2 (5)	4:96	92
	cyclohexyl	Me	Cp_2ZrCl_2 (5)	4:96	60

[a] In all experiments, 3-4 equiv of freshly prepared EtMgCl was used. [b] Ratios were determined through GLC analysis of the corresponding acetonides or formals. [c] Isolated yields of purified products. [d] Sixty percent of the starting material was recovered. [e] Prepared at -78 °C in THF.

Carbometalations of simple monosubstituted alkenes by ethylmagnesium chloride can proceed more effectively than was reported previously.[1] Treatment of 1-decene with 3 equiv of Grignard reagent and 5 mol % Cp_2ZrCl_2 (12 h, 25 °C, Et_2O), followed by addition of 3-5 equiv of either acetaldehyde, $B(OMe)_3/H_2O_2$ (-78 °C), NBS, or iodine, results in the formation of the addition products in 55-65% yield after silica gel chromatography (Scheme I).[3] *Thus, by a simple one-pot procedure, double alkylation or hydroxyalkylation of an alkene is accomplished in good yield.* In addition, the carbometalation reaction proceeds with excellent levels of regiocontrol (>99:1).[4]

In contrast to earlier reports that electron-withdrawing substituents significantly retard the rate of carbomagnesation,[1b,c] we find a variety of allylic alcohols and ethers to be suitable substrates. As is illustrated in Table I, ethylmagnesation of allylic alcohol **1a** affords the syn diol **2a** with 95:5 diastereoselectivity (70% isolated yield). Reaction of cyclohexyl derivative **1b** is stereoselective but sluggish under these conditions. However, we find that 20 mol % Cp_2ZrCl_2 or Cp_2ZrBu_2 in 50% THF/Et_2O serves well in this case; the desired products are obtained in 70% yield, albeit with diminished diastereoselectivity (67:33, syn:anti). We subsequently discovered that in reactions of allylic alcohols use

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[1] (a) Dzhemilev, U. M.; Vostrikova, O. S.; Sultanov, R. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1983**, 218-220. (b) Dzhemilev, U. M.; Vostrikova, O. S.; Sulmanov, R. M.; Kukovinets, A. G.; Khalilov, A. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1983**, 2053-2060. (c) Dzhemilev, U. M.; Vostrikova, O. S. *J. Organomet. Chem.* **1985**, *285*, 43-51 and references cited therein. These workers report that ethylmagnesation of 1-octene (acid quench) proceeds in 30% yield at 25 °C (ref 1b), and in 52% yield, but with diminished regioselectivity (7:1), only when the reaction is heated not lower than 60 °C (ref 1a).

[2] For a nickel-catalyzed double alkylation where α,β-unsaturated acetals may serve as substrates, see: Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1989**, *111*, 366-368.

[3] The stereochemical identities of all compounds were determined through comparison with authentic materials. All compounds reported herein gave ^1H NMR (300 MHz), ^{13}C NMR (75 MHz), IR, and combustion analysis data consistent with the structures given. See the supplementary material for details.

[4] GLC analysis indicates that the zirconium-catalyzed carbomagnesation of 1-heptene (EtMgCl, $B(OMe)_3/H_2O_2$) proceeds with 556:1 regioselectivity. This is contrary to the previous reports that ethylmagnesation of 1-octene occurs with 10:1 regioselectivity (ref 1a).

0002-7863/91/1513-5079$02.50/0