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Rhodium-Catalyzed Heterocycloaddition Route to 1,3-Oxazoles as Building Blocks in Natural Products Synthesis

Richard D. Connell, Mark Tebbe, Anthony R. Gangloff, and Paul Helquist*

Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, Indiana 46556 USA

Björn Åkermark

Department of Organic Chemistry, Royal Institute of Technology, S-100 44 Stockholm, Sweden

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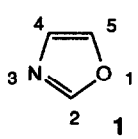
Abstract: Rhodium(II) acetate serves as a catalyst for the heterocycloaddition reaction of diazodicarbonyl compounds with nitriles to give functionalized 1,3-oxazole derivatives in a simple one-step procedure. In particular, dimethyl diazomalonate undergoes this reaction to give 2-aryl-, 2-alkenyl-, or 2-alkyl-4-carbomethoxy-5-methoxy-1,3-oxazoles, and ethyl formyldiazoacetate (diazomalonate half-ester half-aldehyde) gives 2-aryl-, 2-alkenyl-, or 2-alkyl-4-carboethoxy-1,3-oxazoles. These products are of potential importance as key intermediates in the synthesis of several oxazole-containing natural products and other heterocyclic systems.

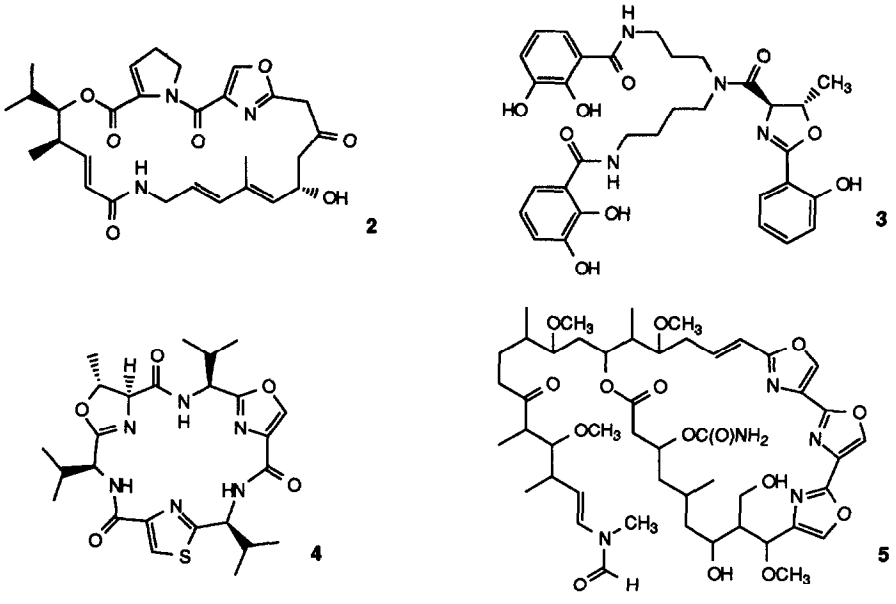
INTRODUCTION

1,3-Oxazoles (**1**) are very well-investigated compounds. The occurrence, the uses, and the synthesis of oxazole derivatives have been the subjects of extensive reviews.[1] Because of the many roles that these compounds play in natural products and synthetic organic chemistry, many methods have previously been developed for their preparation.[1,2] This heterocyclic unit is seen with various substitution patterns in a large number of naturally occurring compounds. Furthermore, 1,3-oxazoles serve as synthetic intermediates leading to many other systems.[1,3,4] In this context, 1,3-oxazoles have seen, for example, numerous applications as "2-azadiene" components in 4+2 cycloadditions, or hetero-Diels-Alder reactions, with several types of dienophiles. Further transformations of the products then lead to a number of other nitrogen- or oxygen-containing heterocyclic products.[4]



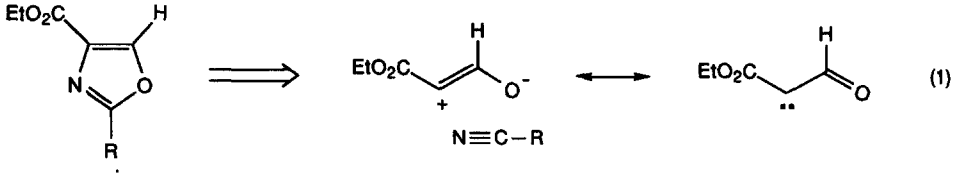
Of the many specific types of 1,3-oxazoles, those bearing a 4-carboxy-derived group, are of considerable importance. Among these compounds are several natural products, including many which contain this moiety, or the analogous thiazole moiety, as a repeating unit. A few examples include virginiamycin M_1 (**2**)[5], parabactin (**3**),[6] bistratamide C (**4**),[7] and kabiramide A (**5**).[8]

Several methods are available for the synthesis of 4-carboxy derivatives of 1,3-oxazoles.[1] A very well-established, classical method is the Cornforth oxazole synthesis (Scheme 1). This method has been shown to be widely applicable, although it employs a complex, multi-step pathway.[9]

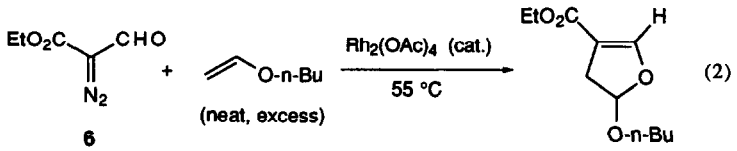


Scheme 1

In consideration of conceivable strategies for the more direct construction of these derivatives, nitriles can be regarded as simple starting materials with which the 3+2 cycloaddition of acylcarbenes would, in a *formal sense*, provide the desired oxazoles (eq 1). This approach follows directly from the ubiquitous 1,3-dipolar cycloadditions that have been developed by many groups of investigators during the past several decades.[10]



Obviously, free acylcarbenes themselves should probably not be regarded as appropriate synthetic intermediates for this type of transformation. However, this basic conceptual approach could, in principle, be implemented through use of the corresponding diazocarbonyl compounds. Carbene-like reactions of these compounds can be induced under thermal, photochemical, or metal-catalyzed conditions. Oxazoles, in fact, have previously been obtained by the reaction of diazocarbonyl compounds with nitriles through use of boron trifluoride etherate as a Lewis acid promoter or under photochemical conditions.[11] In order to develop a more general, synthetically useful version of this reaction, we considered the use of various metal species that have come into common use for reactions of diazo compounds. Among the metals used in this sense, copper and several of its compounds have most commonly been employed, although a large number of the transition metals and even many of the main-group metals have also been shown to be effective catalysts for diazocarbonyl reactions. In recent years, rhodium compounds have been shown to be particularly effective catalysts for many different types of reactions of diazo compounds.[12] Among others,[13] a recent example that is especially relevant to our studies is the rhodium-catalyzed reaction of ethyl formyldiazoacetate (**6**) with enol ethers to give dihydrofuroates (eq. 2) as reported by Professor Wenkert and co-workers.[14]



(2)

In this paper, we wish to report our investigations of the rhodium-catalyzed reactions of diazodicarbonyl compounds with nitriles. These reactions have indeed proven to be useful for the one-step preparation of 4-carboxy-1,3-oxazole derivatives.[15,16]

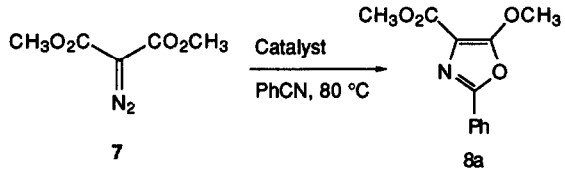
RESULTS

Applications of Dimethyl Diazomalonate

The studies of this approach to the desired oxazoles were begun with dimethyl diazomalonate (**7**) which is readily prepared from dimethyl malonate itself. Especially convenient is the use of diazo transfer reactions using reagents such as *p*-toluenesulfonyl azide.[17] Compared to simple diazoalkanes, diazocarbonyl and especially 2-diazo-1,3-carbonyl compounds are much more stable, but *appropriate precautions should still be taken as protection against possible explosion hazards.*

Although a number of rhodium compounds have come into use as catalysts for reactions of diazo compounds, one of the simplest and most readily available, rhodium(II) acetate, $Rh_2(OAc)_4$, is still the most commonly employed. Our attempts to use it as a catalyst for our proposed oxazole synthesis were successful right from the outset of these studies. In an initial test reaction, a solution of dimethyl diazomalonate (**7**) in benzonitrile was added dropwise to a solution of $Rh_2(OAc)_4$ in benzonitrile at 80 °C. The product, 2-phenyl-4-carbomethoxy-5-methoxy-1,3-oxazole (**8a**), was obtained in nearly quantitative yield. A number of other rhodium and copper compounds were also studied as possible catalysts in this reaction, but $Rh_2(OAc)_4$ ultimately proved to give the highest yield of the desired product (Table 1).

Table 1. Effect of the Catalyst on Oxazole Formation



7 8a

Catalyst	Addition Time (h)[a]	Reaction Time (h)[b]	Yield (%)[c]
$Rh_2(OAc)_4$	0.5	12	99
$Rh_2(NHAc)_4$	2	12	83
$Cu(OTf)_2$	2	36	65
$Cu(Et\text{-}acac)_2$	3	36	44
$Rh_2(O_2CC_3F_7)_4$	3.5	36	35
$Rh_3(CO)_{16}$	2.5	36	23

[a]Refers to the time for the addition of the solution of the diazo compound to the solution of the catalyst with neat benzonitrile as the solvent [b]Refers to the reaction time at 80 °C after completion of the addition [c]Isolated yield of pure product

The nitrile substrate can be used in neat form, or the reaction may also be done through use of various solvents. Halogenated solvents such as chloroform and 1,2-dichloroethane are particularly effective, whereas no reaction is observed when THF or diethyl ether is employed, and the use of benzene as solvent gives only low yields of the oxazole products. The highest yields of oxazoles are generally obtained by slow addition of a dilute solution of the diazomalonate to a solution of the nitrile and the rhodium catalyst. At these lower concentrations, there is a reduced tendency for the formation of dimeric materials from the diazo compound. Under these conditions, dimethyl diazomalonate reacts with a wide range of nitriles in the presence of catalytic quantities (0.005 to 0.01 mol-equiv) of $Rh_2(OAc)_4$ to give 2-substituted-4-carbomethoxy-5-methoxy-1,3-oxazoles (**8**) directly (eq 3) The summary of results in Table 2 shows that the highest yields of oxazoles are obtained when the nitrile substrate is conjugated with an alkenyl or an aryl group (see especially entries a, c, k, l, and p), whereas simple saturated alkyl-substituted nitriles typically give lower yields of the desired products unless they are used in neat form (entries d-i) Exceptions to this pattern are the case of 4-methoxybenzonitrile (entry m) which gives only a modest yield and the case of 4-nitrobenzonitrile which formed a very dark or black solution upon being mixed with the rhodium catalyst; upon workup of the reaction mixture, no oxazole was isolated, but unreacted diazomalonate was recovered. A non-conjugated, unsaturated nitrile (entry n) undergoes competitive

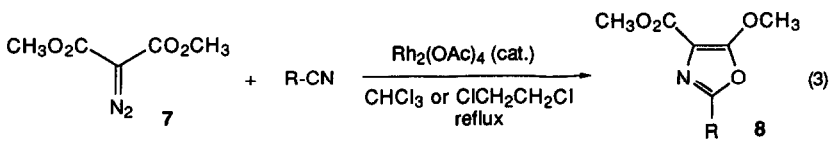


Table 2. Reaction of Dimethyl Diazomalonate (7) with Nitriles and $Rh_2(OAc)_4$ Catalyst to Give Oxazoles **8**

Entry	Nitrile[a]	mol-equiv. of 7	Yield of 8 (%)[b]
a	C_6H_5CN	1.5	95
	neat, 5.0 mol-equiv.	--	99
b	*E*-C_6H_5CH=CHCN	2.0	44
	neat, 4.0 mol-equiv.	--	68
c	*E*- and *Z*-CH_3CH=CHCN	1.0	74[c]
	neat, 4.0 mol-equiv.	--	88
d	n-$C_9H_{19}CN$	1.5	58
	neat, 3.6 mol-equiv.	--	77
e	CH_3CN	1.5	58
	8.0 mol-equiv.	--	75
f	$CH_3CH_2CH_2CN$	1.5	59
g	$(CH_3)_2CHCN$	1.5	51
h	$(CH_3)_3CCN$	1.5	46
i	$C_6H_5CH_2CN$	2.0	50
j	4-ClC_6H_4CN	2.0	90
k	3-ClC_6H_4CN	2.0	96
l	4-$CH_3C_6H_4CN$	2.0	93
m	4-$CH_3OC_6H_4CN$	2.0	47
n	H_2C=$CHCH_2CN$	1.0	45 (21)[d]
o	$HOCH_2CH_2CN$	1.0	O (96)[e]
p	EtOCH=CHCN	--	--
	neat, 6.0 mol-equiv.	--	97

[a]The reactions of these nitriles were normally done with chloroform or 1,2-dichloroethane as solvent Reactions that were run without solvent (neat nitrile) are specifically indicated [b]Isolated yield of pure product. [c]Obtained as a mixture of *E*- and *Z*-isomers [d]Yield of cyclopropane from addition to alkene double bond [e]Yield of the ether from O-H insertion

cyclopropanation of the alkene double bond, and the presence of a free hydroxy group (entry o) leads to preferential O-H insertion of the diazomalonate to give the corresponding ether.

Although many of the naturally occurring oxazoles of interest possess a 4-carboxy-derived substituent, very few of them bear a 5-alkoxy group. Therefore, methods were explored for removal of the 5-methoxy group from the oxazoles **8** obtained above. A number of reducing agents were investigated, including

$NaBH_3CN$, $NaBH_3CN/ZnCl_2$, LiB(sec-Bu)$_3$H (Aldrich L-Selectride®), KB(sec-Bu)$_3$H (Aldrich K-Selectride®), Na/EtOH, Na/t-BuOH, Mg/MeOH, H_2/Rh-C, H_2/Pd-$BaSO_4$, and (i-Bu)$_2$AlH/CuI/MeLi/HMPA, but none of them gave significant amounts of the desired reductive cleavage products. The only useful results were obtained with LiB(Et)$_3$H (Aldrich Super-Hydride®). When a THF solution of the oxazole is cooled to -116 °C, and the LiB(Et)$_3$H/THF solution is added dropwise, the mixture becomes green. This color fades when the solution is warmed to -90 °C, but if the reaction is quenched at -90 °C with methanol, only starting oxazole is obtained. When the reaction mixture is warmed to -78 °C, quenched with methanol, treated with 30% H_2O_2, and warmed to 25 °C, the desired oxazole products **9** are obtained (eq 4). If the required temperature constraints are not properly observed, other products are obtained, including the alcohol **10** from reduction of the 4-carbomethoxy group and the oxazoline **11** from reduction of the oxazole nucleus. Based upon the results summarized in Table 3, the reductive cleavage reaction is useful for only those substrates bearing an aryl or a cinnamyl group at the C-2 position of the oxazole (entries a-d), whereas the reaction fails for alkyl-substituted derivatives (entries e and f). In these latter cases, the starting oxazoles are recovered nearly quantitatively.

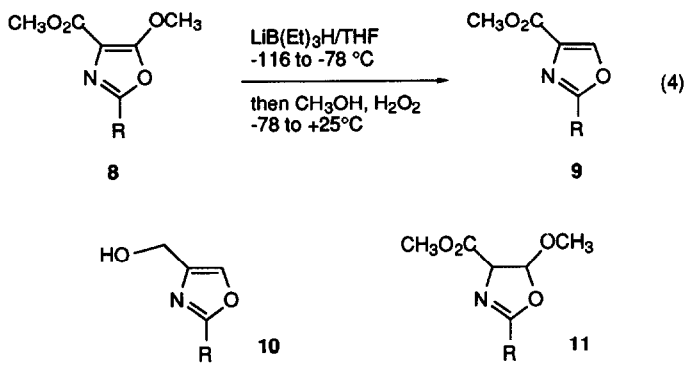


Table 3. Cleavage of the 5-Methoxy Group of Oxazoles **8** Using LiB(Et)$_3$H (eq 4)

Entry	R in **8** and **9**	Yield of **9** (%)
a	C_6H_5	81
b	$C_6H_5CH{=}CH$	84
c	3-ClC_6H_4	63
d	4-$CH_3C_6H_4$	89
e	CH_3	0
f	t-Bu	0

Applications of Ethyl Formyldiazomalonate

The above studies demonstrated that dimethyl diazomalonate (7) could be used to obtain oxazoles directly from a number of nitriles. However, removal of the 5-methoxy group from the initially obtained products proved to be problematic in many cases. Therefore, we sought to employ a mixed aldehyde ester system which, in principle, should give the desired 5-unsubstituted oxazoles directly in one step (see eq 1) without the need for a subsequent reduction step to remove the 5-alkoxy substituent.

The diazoaldehyde ester **6** is readily available by a Vilsmeier-Haack formylation (DMF/oxalyl chloride) of ethyl diazoacetate.[14,18] For the desired reaction of **6** with nitriles, a number of catalysts were investigated, including $Rh_2(OAc)_4$, $BF_3{\cdot}Et_2O$, Cu(ethyl-acac)$_2$, Cu(OTf)$_2$, and Pd(OAc)$_4$, but only $Rh_2(OAc)_4$ was found to be effective. The optimum conditions are use of excess nitrile as solvent at a temperature in the range of 65 to 95 °C (eq 5). As shown in Table 4, the desired oxazoles **12** are obtained in modest to low yields. The reaction most often gives the best results with conjugated nitriles, although acrylonitrile itself gave unsatisfactory results due to rapid polymerization. With other nitriles, a principal limitation of this method is the competitive formation of a formal carbene dimerization product. This product has not been characterized fully, but **13** or related structures as reported by others may be proposed.[19]

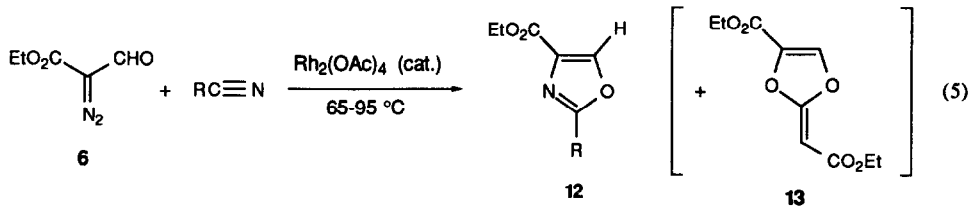
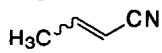
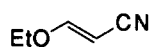
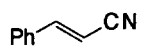


Table 4. Reaction of Diazoaldehyde Ester **6** to Give Oxazoles **12** (eq 5)

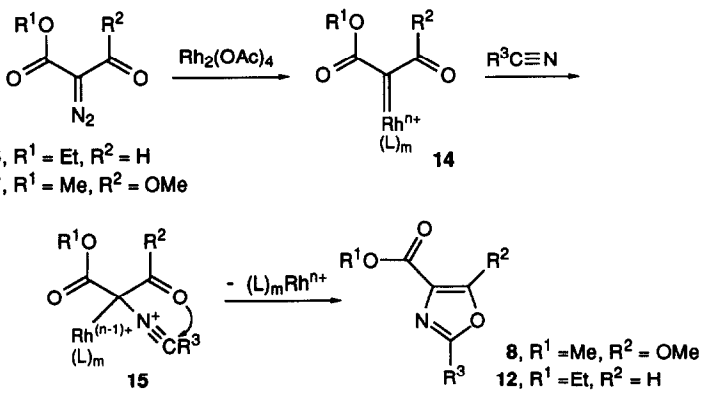
Entry	Nitrile	Temp. (°C)	Yield of **12** (%)
a	Ph-CN	70	45
b	p-Tol-CN	95	25
c		65	30[a]
d		65	36
e		80	24
f	CH_3CN	65	18
g	$BrCH_2CN$	75	65

[a]The starting crotononitrile was mainly *Z*. The product was a 63:37 mixture of *Z* and *E* isomers.

DISCUSSION

The rhodium-catalyzed reaction of diazo dicarbonyl compounds with nitriles provides very direct access to useful classes of functionalized 1,3-oxazoles. Dimethyl diazomalonate (**7**) gives a variety of these oxazoles through use of nitriles in neat form or in a simple chlorocarbon solvent. This reaction produces oxazoles **8** (eq 3) that bear a methoxy group at C-5. If desired, this substituent may be removed in some cases by reductive cleavage using $LiB(Et)_3H$ to give the 5-unsubstituted oxazoles **9** (eq 4). On the other hand, the same type of product can be obtained more directly through use of the diazoaldehyde ester **6**. It is best used with neat nitriles but gives only modest to low yields of the oxazoles **12** (eq 5). However, obtaining these products in just one simple step without the need for an additional reduction step to remove an undesired substituent is advantageous. Also, this method is more direct than the Cornforth synthesis (Scheme 1).

Several recent studies have indicated that many types of rhodium-catalyzed reactions of diazocarbonyl compounds proceed via formation of electrophilic rhodium carbene complexes as key intermediates rather than free carbenes or other types of reactive intermediates.[12] If this postulate holds for the reactions described herein, then the mechanism outlined in Scheme 2 may be proposed.[10c] The diazo compound **6** or **7** is assumed to react with the rhodium catalyst to generate a carbene complex **14** (L = other ligands, e.g. OAc, solvent, etc.) which in turn is subject to nucleophilic attack at its electrophilic carbon center by the nitrile. A nitrilium species **15** then undergoes internal attack by what is essentially an enolate oxygen to give the observed oxazole product **8** or **12**. To account for formation of the desired products **12** in the reaction of the diazoaldehyde ester **6** (eq 5), the more nucleophilic aldehyde carbonyl group (R^2 = H) must participate in the cyclization rather than the ester group of the intermediate **15**; the latter possibility would alternatively provide the regioisomeric 5-ethoxy-4-formyl-1,3-oxazoles. A less likely argument is that the regioisomeric products undergo an equilibration under the conditions of this reaction to give the desired oxazoles as the favored products.



Scheme 2

The oxazoles that are obtained from these rhodium-catalyzed reactions have many potential applications in synthesis. We have recently reported, for example, that the 2-bromomethyl derivative (**12**, R = CH_2Br; Table 4, entry g) undergoes a modified Reformatsky reaction[20] with a number of aldehydes and ketones.[21]

This reaction is potentially applicable to the synthesis of severally naturally occurring compounds mentioned in the introduction (e.g. virginiamycin M_1, **2**; bistratamide C, **4**; and kabiramide A, **5**) and many other oxazole-containing systems.[22]

CONCLUSIONS

The overall goals of this work have been reached Rhodium-catalyzed cycloaddition reactions of diazocarbonyl compounds with nitriles provide direct access to functionalized 1,3-oxazoles bearing a carboalkoxy group at the 4-position, a variety of alkyl, alkenyl, and aryl groups at the 2-position, and, in some cases, an alkoxy group at the 5-position These oxazole derivatives have a number of potential applications as key synthetic intermediates.

ACKNOWLEDGMENTS

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EXPERIMENTAL SECTION

General Procedure for Reaction of Dimethyl Diazomalonate with Nitriles. 4-Carbomethoxy-5-methoxy-2-phenyloxazole (8a). To a solution of rhodium (II) acetate dimer (0.021 g, 0 046 mmol) in $CHCl_3$ (1 mL) was added benzonitrile (0.402 g, 3 9 mmol) The solution was heated to reflux (68 °C) and became a deep purple color Dimethyl diazomalonate[17] (7, 0 930 g, 5 88 mmol) in $CHCl_3$ (5 mL) was placed in a 10-mL conical vial fitted with a septum, and the solution was transferred to the reaction flask by a double-ended needle over 29 h through use of a syringe pump to pressurize the vial. After the addition, the solution was cooled to 25 °C and concentrated The remaining oil was purified by flash chromatography (20% ethyl acetate in hexane) to yield 0 776 g (85%) of **8a** as white needles: mp 98-99 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ 7 94 (m, 2 H, Ar-H), 7.40 (m, 3 H, Ar-H), 4 22 (s, 3 H, C=COCH$_3$), 3 87 (s, 3 H, COOCH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161 55 and 161 68 (C00CH$_3$ and C-2), 150 61 (C-5), 130 23 (C-4'), 128 52 (C-2' and 6'), 126 31 (C-1'), 125 65 (C-3' and 5'), 107 23 (C-4), 59 63 (C=COCH$_3$), 51 63 (COOCH$_3$); IR ($CDCl_3$) 1716 (COOCH$_3$), 1625 (C=COCH$_3$) cm^{-1}; mass spectrum (CI, argon) m/e (rel intensity) 233 (M^+, 27), 173 (11), 146 (15), 105 (100), 77 (24). Anal Calcd for $C_{12}H_{11}NO_4$ C, 61 80, H, 4.75 Found C, 61.53, H, 4 75

4-Carbomethoxy-2-(E-cinnamyl)-5-methoxyoxazole (8b): 0 33 g (44%) as a white solid; mp 79-80 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ 7 43 (m, 5 H, Ar-H), 7 38 (d, J = 16 Hz, 1 H, ArCH=CH), 6 79 (d, J = 16 Hz, 1 H, ArCH=CH), 4 26 (s, 3 H, C=COCH$_3$), 3 91 (s, 3 H, COOCH$_3$), ^{13}C NMR (75 MHz, $CDCl_3$) §161 70 and 161 36 (C00CH$_3$ and C-2), 150 73 (C-5), 135 73, 135 08, 129 27, 128 85, 127 01, 112 90, 107 45 (C-4), 59 80 (C=COCH$_3$), 51 76 (COOCH$_3$), IR ($CDCl_3$) 1714 (COOCH$_3$), 1626 (C=COCH$_3$) cm^{-1}, mass spectrum (CI, argon) m/e (rel intensity) 260 (M+1, 14), 259 (M^+, 73), 200 (14), 199 (100), 155 (21) Anal Calcd for $C_{14}H_{13}NO_4$ C, 64 86, H, 5 05 Found C, 64 80, H, 5 18

Reaction with Crotononitrile. From **7** (1 411 g, 8 92 mmol, 1 0 eq) in 1,2-dichloroethane (5 mL), $Rh_2(OAc)_4$ (0.029 g, 0 065 mmol), and predominantly *Z*-crotononitrile (3 001 g, 44 71 mmol) in 1,2-dichloroethane (4 5 mL) was obtained 1 54 g (88%) of **8c** as a 86 14 2*Z* 2*E* mixture Pure fractions of each isomer could be obtained by an additional purification by radial chromatography (5% ethyl acetate in hexane)

4-Carbomethoxy-5-methoxy-2-(1Z-propenyl)oxazole (Z-8c): Rf on silica gel TLC = 0.08 with 20% ethyl acetate in hexane; mp 49-50 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6 11 (m, 2 H, HC=CHCH$_3$), 4.12 (s, 3 H, C=COCH$_3$), 3.88 (s, 3 H, COOCH$_3$), 2.15 (d, J = 5.6 Hz, 3 H, HC=CHCH$_3$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.97 and 160.77 (COOCH$_3$ and C-2), 150.60 (C-5), 134 89 and 115 06 (C=CHCH$_3$), 106 41 (C-4), 59.52 (C=COCH$_3$), 51.61 (COOCH$_3$), 15 36 (HC=CHCH$_3$); IR ($CDCl_3$) 1715 (COOCH$_3$), 1625 (C=COCH$_3$) cm^{-1}; mass spectrum (CI, argon) m/e (rel intensity) 198 (37, M+1), 197 (54, M$^+$), 166 (34), 165 (46), 138 (15), 137 (22), 110 (17), 69 (100) Anal Calcd for $C_9H_{11}NO_4$: C, 54 82, H, 5.62. Found: C, 54.83; H, 5.54

4-Carbomethoxy-5-methoxy-2-(1E-propenyl)oxazole (E-8c): Rf on silica gel TLC = 0 04 with 20% ethyl acetate in hexane, mp 91-92 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.55 (dq, J = 16.0 Hz, J = 6.9 Hz, 1 H, CH=CHCH$_3$), 6.10 (dd, J = 16.0 Hz, J = 1.7 Hz, 1 H, CH=CHCH$_3$), 4.14 (s, 3 H, C=COCH$_3$), 3 82 (s, 3 H, COOCH$_3$), 1.93 (dd, J = 6.9 Hz, J = 1 7 Hz, 3 H, CH=CHCH$_3$), ^{13}C NMR ($CDCl_3$) δ 161 13 and 161.82 (COOCH$_3$ and C-2), 150 43 (C-5), 134 99 and 116.99 (CH=CHCH$_3$), 106.63 (C-4), 59 61 (C=COCH$_3$), 51 63 (COOCH$_3$), 18 33 (CH=CHCH$_3$), IR ($CDCl_3$) 1715 (COOCH$_3$), 1627 (C=COCH$_3$) cm^{-1}, mass spectrum (CI, argon) m/e (rel intensity) 198 (M+1, 34), 197 (M$^+$, 54), 166 (29), 165 (25), 138 (17), 137 (26), 110 (20), 69 (100) Anal. Calcd for $C_9H_{11}NO_4$ C, 54.82, H, 5 62. Found· C, 54 63; H, 5.57

4-Carbomethoxy-5-methoxy-2-(n-octyl)oxazole (8d) 0.626 g (58%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4 15 (s, 3 H, C=COCH$_3$), 3.86 (s, 3 H, COOCH$_3$), 2 67 (t, J = 7.5 Hz, 2 H, CH$_2$(CH$_2$)$_6$CH$_3$) 1.74 (m, 2 H, CH$_2$CH$_2$(CH$_2$)$_5$CH$_3$), 1.31 (m, 10 H, (CH$_2$)$_5$CH$_3$), 0.87 (t, J = 6.5 Hz, 3 H, (CH$_2$)$_7$CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.93 and 161.61 (COOCH$_3$ and C-2), 154.23 (C-5), 105 71 (C-4), 59.64 (C=COCH$_3$), 51.66 (COOCH$_3$), 31.78 (CH$_2$(CH$_2$)$_7$CH$_3$), 29.09, 29.04, 28.16, 26 71, 22 69, 14 10 (CH$_2$)$_7$CH$_3$); IR ($CDCl_3$) 1714 (COOCH$_3$), 1639 (C=COCH$_3$) cm^{-1}, mass spectrum (CI, argon) m/e (rel intensity) 271 (17), 270 (100, M+1), 269 (40, M$^+$), 240 (15), 238 (41), 227 (20), 226 (50), 213 (54), 210 (58), 182 (40), 171 (50), 168 (18), 154 (26), 150 (29), 141 (54), 139 (42), 112 (29), 104 (54), 83 (27), 81 (32), 72 (23), 71 (54), 69 (50), 67 (28). Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62 43, H, 8.61. Found C, 62.51, H, 8 39

4-Carbomethoxy-5-methoxy-2-methyloxazole (8e) [11a,c,d] 0 68 g (58%) as a white solid; mp 119-120 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.15 (s, 3 H, C=COCH$_3$), 3.87 (s, 3 H, COOCH$_3$), 2.39 (s, 3 H, CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161 24 and 161 20 (COOCH$_3$ and C-2), 150.11 (C-5), 105 29 (C-4), 59.29 (C=COCH$_3$), 51.04 (COOCH$_3$), 13.34 (CH$_3$), IR ($CDCl_3$) 1716 (COOCH$_3$), 1642 (C=COCH$_3$) cm^{-1}, mass spectrum (CI, argon) m/e (rel intensity) 171 (46, M$^+$), 143 (54), 140 (49), 112 (31), 84 (100), 69 (25) Anal. Calcd for $C_7H_9NO_4$ C, 49.12, H, 5 30 Found: C, 49.07; H, 5 52

4-Carbomethoxy-5-methoxy-2-(n-propyl)oxazole (8f): 0.626 g (59%) as a colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4 16 (s, 3 H, C=COCH$_3$), 3 87 (s, 3 H, COOCH$_3$), 2 66 (t, J = 7.4 Hz, 2 H, CH$_2$CH$_2$CH$_3$), 1 78 (m, J = 7 4 Hz, 2 H, CH$_2$CH$_2$CH$_3$), 0 98 (t, J = 7 4 Hz, 3 H, CH$_2$CH$_2$CH$_3$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.94 and 161 76 (COOCH$_3$ and C-2), 154 12 (C-5), 105.90 (C-4), 59.76 (C=COCH$_3$), 51.59 (COOCH$_3$), 30 03 (CH$_2$CH$_2$CH$_3$), 20 24 (CH$_2$CH$_2$CH$_3$), 13 59 (CH$_2$CH$_2$CH$_3$); IR ($CDCl_3$) 1717 (COOCH$_3$), 1639 (C=COCH$_3$) cm^{-1}, mass spectrum (CI, argon) m/e (rel intensity) 199 (32, M$^+$), 168 (23), 112 (85), 86 (11), 71 (100). Anal Calcd for $C_9H_{13}NO_4$ C, 54.26; H, 6.58 Found C, 54.08; H, 6 50.

4-Carbomethoxy-2-isopropyl-5-methoxyoxazole (8g) 0.593 g (51%) as white needles; mp 52-54 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4 16 (s, 3 H, C=COCH$_3$), 3 87 (s, 3 H, COOCH$_3$), 3 00 (m, J = 7 2 Hz, 1 H, HC(CH$_3$)$_2$), 1 33 (d, J = 7 2 Hz, 6 H, HC(CH$_3$)$_2$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.96 and 161 57 (COOCH$_3$ and C-2), 158 03 (C-5), 105 58 (C-4), 59.58 (C=COCH$_3$), 51 67 (COOCH$_3$), 28 47 (C(CH$_3$)$_2$), 20.00 (C(CH$_3$)$_2$); IR ($CDCl_3$) 1714 (COOCH$_3$), 1638 (C=COCH$_3$) cm^{-1}, mass spectrum (CI, argon) m/e (rel intensity) 200 (21, M+1), 199 (41, M$^+$), 168 (32), 126 (26), 112 (40), 86 (26), 71 (100), 43 (57) Anal Calcd for $C_9H_{13}NO_4$· C, 54 26, H, 6 58. Found. C, 54 10, H, 6.63

4-Carbomethoxy-5-methoxy-2-(t-butyl)oxazole (8h). 0 582 g (46%) as a colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.17 (s, 3 H, C=COCH$_3$), 3 87 (s, 3 H, COOCH$_3$), 1 37 (s, 9 H, C(CH$_3$)$_3$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 161 65 and 161 30 (COOCH$_3$ and C-2), 159 87 (C-5), 105 28 (C-4), 59 27 (C=COCH$_3$), 51 29 (COOCH$_3$), 33.48 (C(CH$_3$)$_3$), 27 80 (C(CH$_3$)$_3$), IR ($CDCl_3$) 1708 (COOCH$_3$), 1640 (C=COCH$_3$) cm^{-1}, mass spectrum (CI, argon) m/e (rel intensity) 213 (6, M$^+$), 188 (11), 187 (25), 126 (57), 85(100), 80 (96), 70 (11), 69 (23) Anal Calcd for $C_{10}H_{15}NO_4$ C, 56 33, H, 7 09 Found C, 56 12; H, 7 32

2-Benzyl-4-carbomethoxy-5-methoxyoxazole (8i): 0.74 g (50%) as a white solid, mp 182-183 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5 H, Ar-H), 4.10 (s, 3 H, C=COC$\underline{H}_3$), 4.02 (s, 2 H, C$\underline{H}_2$-Ar), 3.87 (s, 3 H, COOC$\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161 84 and 161.66 (C$\underline{O}$OCH$_3$ and C-2), 151.93 (C-5), 128.63, 128.50, 127.12, 105.87 (C-4), 59.61 (C=CO$\underline{C}$H$_3$), 51.57 (COO$\underline{C}$H$_3$), 34.58 (Ar-$\underline{C}$H$_2$); IR ($CDCl_3$) 1716 ($\underline{C}$OOCH$_3$), 1637 (C=$\underline{C}$OCH$_3$) cm^{-1}, mass spectrum (CI, argon) m/e (rel intensity) 248 (24, M+1), 247 (44, M$^+$), 216 (13), 187 (12), 160 (25), 159 (25), 91 (100). Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63 15; H, 5.30 Found C, 63.12; H, 5.21.

4-Carbomethoxy-5-methoxy-2-(4'-chlorophenyl)oxazole (8j). 0.403 g (90%) as white needles; mp 111-113 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.92 (d, J = 8 6 Hz, 2 H, Ar-H), 7 42 (d, J = 8 8 Hz, 2 H, Ar-H), 4.28 (s, 3 H, C=COC$\underline{H}_3$), 3.92 (s, 3 H, COOC$\underline{H}_3$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.78 and 161.70 ($\underline{C}$OOCH$_3$ and C-2), 149.97 (C-5), 136 59 (C-4'), 129 06 (C-2' and 6'), 127 12 (C-3' and 5'), 124 83 (C-1'), 107 79 (C-4), 59.97 (C=CO$\underline{C}$H$_3$), 51 86 (COO$\underline{C}$H$_3$); IR ($CDCl_3$) 1716 ($\underline{C}$OOCH$_3$), 1630 (C=$\underline{C}$OCH$_3$) cm^{-1}; mass spectrum (CI, argon) m/e (rel intensity) 267 (23, M+), 207 (10), 141 (32), 139 (100), 111 (16), 75 (10) Anal Calcd for $C_{12}H_{10}ClNO_4$ C, 53.85, H, 3 77 Found· C, 53 86; H, 3 76.

4-Carbomethoxy-5-methoxy-2-(3'-chlorophenyl)oxazole (8k) 0 511 g (96%) as white needles; mp 134-136 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.98 (s, 1 H, Ar-H), 7.88 (m, 1 H, Ar-H), 7.40 (m, 2 H, Ar-H), 4 29 (s, 3 H, COOC$\underline{H}_3$), 3 93 (s, 3 H, OC$\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161 88 and 161 74 ($\underline{C}$OOCH$_3$ and C-2), 149.49 (C-5), 134.96 (C-3'), 130 43 (C-4'), 130.13 (C-2'), 127 95 (C-1'), 125.85 (C-5'), 123 92 (C-6'), 107.77 (C-4), 59 98 (C=CO$\underline{C}$H$_3$), 51 93 (COO$\underline{C}$H$_3$); IR ($CDCl_3$) 1715 ($\underline{C}$OOCH$_3$), 1628 (C=$\underline{C}$OCH$_3$) cm^{-1}; mass spectrum (CI, isobutane) m/e (rel intensity) 270 (35, M+3), 269 (29, M+2), 268 (1 00, M+1), 267 (31, M$^+$), 236 (25), 139 (15) Anal. Calcd for $C_{12}H_{10}ClNO_4$· C, 53 85, H, 3 77 Found. C, 53 82; H, 3.87

4-Carbomethoxy-5-methoxy-2-(4'-methylphenyl)oxazole (8l) 0 51 g (93%) as white needles, mp 133-134 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7 85 (d, J = 8 3 Hz, 2 H, Ar-H), 7 22 (d, J = 8 3 Hz, 2 H, Ar-H), 4 24 (s, 3 H, OC$\underline{H}_3$), 3.91 (s, 3 H, COOC$\underline{H}_3$), 2 38 (s, 3 H, Ar-C$\underline{H}_3$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.79 and 161 53 ($\underline{C}$OOCH$_3$ and C-2), 151 02 (C-5), 140 64 (C-4'), 129 28 (C-2' and 6'), 125 72 (C-3' and 5'), 123 51 (C-1'), 107 27 (C-4), 59 70 (C=CO$\underline{C}$H$_3$), 51 62 (COO$\underline{C}$H$_3$), 21 34 (Ar-$\underline{C}$H$_3$); IR ($CDCl_3$) 1714 ($\underline{C}$OOCH$_3$), 1631 (C=$\underline{C}$OCH$_3$) cm^{-1}, mass spectrum (CI, argon) m/e (rel intensity) 247 (30, M$^+$), 216 (5), 187 (16), 119 (100), 91 (25). Anal Calcd for $C_{13}H_{13}NO_4$ C, 63.15, H, 5.30 Found C, 63 15, H, 5 23.

4-Carbomethoxy-5-methoxy-2-(4'-methoxyphenyl)oxazole (8m) 0 21 g (47%) as a white solid, mp 121-123 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ 7 92 (d, J = 9 0 Hz, 2 H, Ar-H), 6 95 (d, J = 9.0 Hz, 2 H, Ar-H), 4 25 (s, 3 H, C=COC$\underline{H}_3$), 3 92 (s, 3 H, Ar-OC$\underline{H}_3$), 3 86 (s, 3 H, COOC$\underline{H}_3$), ^{13}C NMR (50 MHz, $CDCl_3$) δ 161 98, 161.56 and 161.40 (C-4', C-2, and $\underline{C}$OOCH$_3$), 151 07 (C-5), 127 56 (C-2' and C-6'), 119 00 (C-1'), 114 14 (C-3' and C-5'), 107.24 (C-4), 59 79 (C=CO$\underline{C}$H$_3$), 55 32 (Ar-O$\underline{C}$H$_3$), 51 75 (COO$\underline{C}$H$_3$), IR ($CDCl_3$) 1714 ($\underline{C}$OOCH$_3$), 1632 (C=$\underline{C}$OCH$_3$), 1612 (Ar-OCH$_3$) cm^{-1}, mass spectrum (CI, argon) m/e (rel intensity) 263 (30, M$^+$) , 176 (11), 135 (100) Anal Calcd for $C_{13}H_{13}NO_5$ C, 59.31, H, 4 98. Found C, 59 36, H, 4 93

Reaction with 3-Butenonitrile. 7 (1 907 g, 12 0 mmol, 1 02 eq) in $CHCl_3$ (4 mL) was added over 13 h to $Rh_2(OAc)_4$ (0 023 g, 0.065 mmol) and 3-butenonitrile (0 709 g, 11 8 mmol) in $CHCl_3$ (1 mL) The resulting brown slurry was passed through a 25-cm column of silica gel and eluted with methylene chloride The yellow solution was then purified by flash chromatography (20% ethyl acetate in hexane) to yield two products· 1 07 g (45%) of **8n** and 0 642 g (27%) of 1,1-dicarbomethoxy-2-(cyanomethyl)cyclopropane

4-Carbomethoxy 5-methoxy-2-(2'-propenyl)oxazole (8n) white solid, mp 55-57 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ 5 87 (m, 1 H, $CH_2C\underline{H}$=CH_2), 5 15 (dd, J1',2'-trans = 16 4 Hz, J1',3' = 1 5 Hz, 1 H, CH_2CH=C$\underline{H}$(H)), 5 13 (dd, J1',2'-cis = 10 4 Hz, J1',3' = 1 2 Hz, 1 H, CH_2CH=CH($\underline{H}$)), 4 08 (s, 3 H, C=COC$\underline{H}_3$), 3 79 (s, 3 H, COOC$\underline{H}_3$), 3 39 (dt, J = 3 9 Hz, 1 2 Hz, 2 H, C$\underline{H}_2$CH=CH_2), ^{13}C NMR (300 MHz, $CDCl_3$) δ 161 23 and 161 34 (C-2 and $\underline{C}$OOCH$_3$), 151.28 (C-5), 130 02 ($CH_2\underline{C}H$=CH_2), 118 31 (CH_2CH=$\underline{C}H_2$), 105 44 (C-4), 59 31 (C=CO$\underline{C}$H$_3$), 51 05 (COO$\underline{C}$H$_3$), 32 08 ($\underline{C}H_2CH$=CH_2), IR ($CDCl_3$) 1714 ($\underline{C}$OOCH$_3$), 1639 (C=$\underline{C}$OCH$_3$), 995 (CH2CH=CH2), 920 (CH2CH=CH2) cm^{-1}, mass spectrum (CI, argon) m/e (rel intensity) 198 (35, M+1), 197 (100, M$^+$), 168 (30), 166 (58), 138 (16), 137 (37), 111 (18), 110 (72), 109 (34), 78 (11), 69 (44), 68 (50), 66 (13) Anal Calcd for $C_9H_{11}NO_4$ C, 54 82, H, 5.62 Found C, 54 93, H, 5 69

1,1-Dicarbomethoxy-2-(cyanomethyl)cyclopropane: colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3 59 (s, 3 H, $COOCH_3$), 3.54 (s, 3 H, $COOCH_3$), 2.39 (dd, J = 7.1 Hz, 5 1 Hz, 2 H, CH_2CHCH_2CN), 1.99 (m, 1 H, CH_2CHCH_2CN), 1.34 (m, 2 H, CH_2CHCH_2CN); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.88 and 167 51 ($COOCH_3$), 117.13 (CH_2CN), 52 84 ($COOCH_3$), 33.08 ($CHCH_2CN$), 22 42, 20.28, 16 78; IR (neat) 2255 (CH_2CN), 17.22 ($COOCH_3$)cm^{-1}, mass spectrum (CI, argon) m/e (rel intensity) 198 (100, M+1), 166 (18) Anal. Calcd for $C_9H_{11}NO_4$. C, 54.82; H, 5 62. Found· C, 54.87, H, 5.74

3-[Bis(carbomethoxy)methyloxy]propanonitrile. From $Rh_2(OAc)_4$ (0.010 g, 0.023 mmol), 3-hydroxyproprionitrile (0.371 g, 5.22 mmol) in $CHCl_3$ (1 mL), and 7 (0 901 g, 5.70 mmol) in $CHCl_3$ (5 mL). Obtained after flash chromatography (methylene chloride) was 1.003 g (96%) of 3-[bis(carbomethoxy)methyloxy]-propanonitrile as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.65 (s, 1 H, $OCH(COOCH_3)_2$), 3 88 (t, J = 6 3 Hz, 2 H, OCH_2CH_2CN), 3.83 (s, 6H, $CH(COOCH_3)_2$), 2.76 (t, J = 6 3 Hz, 2 H, OCH_2CH_2CN); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.03 ($CH(COOCH_3)_2$) , 117 00 (OCH_2CH_2CN), 78 58 ($CH(COOCH_3)_2$), 65 45 (OCH_2CH_2CN), 52 91 ($CH(COOCH_3)_2$), 18 66 (OCH_2CH_2CN); IR ($CDCl_3$) 2255 (CN), 1768 ($COOCH_3$) cm^{-1}; HRMS (EI) calcd for $C_8H_{12}NO_5$ 202.0715, found 202 0715 (M+H)

4-Carbomethoxy-2-(2'-ethoxy-E-ethenyl)-5-methoxyoxazole (8p): 3 03 g (97%) as a white solid; mp 76-77.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7 38 (d, J = 13.01 Hz, 1 H, CH=CH), 5.58 (d, J = 12 98 Hz, 1 H, CH=CH), 4.18 (s, 3 H, OCH_3), 3 96 (q, J = 7.02 Hz, OCH_2CH_3), 3 85 (s, 3 H, CO_2CH_3), 1 38 (t, J = 7 0 Hz, 3 H, OCH_2CH_3 ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.73, 159 79, 153 72, 149.62, 105.46, 91.47, 65 42, 58 89, 50.32, 13.42, mass spectrum (EI) m/e (rel intensity) 227 (80, M^+), 170 (40), 139 (40), 99 (100) Anal Calcd for $C_{10}H_{13}NO_5$· C, 52.86; H, 5.72 Found. C, 52 83; H, 5 86.

General Procedure for the Reduction of 4-Carbomethoxy-5-methoxyoxazoles. 4-Carbomethoxy-2-phenyloxazole (9a). 8a (0.283 g, 1.21 mmol) and THF (10 mL) under nitrogen was cooled to -116 °C using an ethyl ether/liquid nitrogen bath The colorless solution was stirred vigorously as $LiBEt_3H$ (Aldrich Super-Hydride®, 1.33 mL of a 1 0 M solution in THF) was added dropwise down the side of the flask. After the addition, the lime green-colored solution was warmed up and became colorless at -83 °C The solution was maintained at -78 °C for 2 h and warmed to -65 °C before methanol (5 mL) was added The solution was warmed to -10 °C, and 30% H_2O_2 (0 5 mL) was added The solution was warmws to 20 °C and stirred for 2 h The solution was poured into chloroform (70 mL) and washed with satd aq solutions of $NaHSO_4$ (2 x 20 mL) and NaCl (20 mL). The solution was dried ($MgSO_4$), concentrated in vacuo, and purified by radial chromatography on silica gel (20% EtOAc/hexane) to provide **8a** (0 055 g, 19%) and 0 198 g (81%) of **9a** as a white solid: mp 86-87 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (s, 1 H, H-5), 8 11 (m, 2 H, Ar-H), 7 48 (m, 3 H, Ar-H), 3.96 (s, 3 H, $COOCH_3$), ^{13}C (75 MHz, $CDCl_3$) δ 162.42 and 161 68 (C-2 and $COOCH_3$), 143 72 (C-5), 134 33 (C-4), 131 13 (C-4'), 128.76 (C-2' and 6'), 126 81 (C-3' and 5'), 126 30 (C-1'), 52 20 ($COOCH_3$), IR ($CDCl_3$) 1725 cm^{-1} ($COOCH_3$), mass spectrum (CI, isobutane) m/e (rel intensity) 204 (100), 203 (30, M^+), 85 (28) Anal Calcd for $C_{11}H_9NO_3$ C, 65 02; H, 4 46 Found· C, 64 86, H, 4 63

4-Carbomethoxy-2-(E-cinnamyl)oxazole (9b) Obtained **8b** (0 063 g, 16%) and 0 198 g (84%) of **9b** as a white solid· mp 133-134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8 21 (s, 1 H, H-5), 7 63 (d, J = 16 4 Hz, 1 H, ArCH=CH), 7.54 (m, 2 H, Ar-H), 7.40 (m, 3 H, Ar-H), 6 95 (d, J = 16 4 Hz, 1 H, ArCH=CH), 3 95 (s, 3 H, $COOCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162 07 and 161.57 ($COOCH_3$ and C-2), 143 28 (C-5), 138 29, 134 82, 134 24, 129.26, 128 86, 127 29, 112 70 (C-4), 52 14 ($COOCH_3$); IR ($CDCl_3$) 1735 cm^{-1} ($COOCH_3$); mass spectrum (CI, isobutane) m/e (rel intensity) 230 (100, M+1), 229 (20, M+) Anal Calcd for $C_{13}H_{11}NO_3$ C, 68 11; H, 4 83 Found C, 68 23, H, 5 00

4-Carbomethoxy-2-(3'-chlorophenyl)oxazole (9c) Obtained **8k** (0 043 g, 25%) and 0 108 g (63%) of **9c** as a white solid mp 128-129 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8 30 (s, 1 H, H-5), 8 13 (s, 1 H, Ar-H), 8 00 (d, J = 8 0 Hz, 1 H, Ar-H), 7 48 (m, 2 H, Ar-H), 3 96 (s, 3 H, $COOCH_3$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 161 49 and 161 10 ($COOCH_3$ and C-2), 143 03 (C-5), 134 98 (C-4), 134 47 (C-3'), 131 17 (C-4'), 130 21 (C-2'), 127 84 (C-1'), 126 64 (C-5'), 124 82 (C6'), 52 27 ($COOCH_3$), IR ($CDCl_3$) 1726 cm^{-1} ($COOCH_3$), mass spectrum (CI, isobutane) m/e (rel intensity) 240 (30, M+2), 238 (100, M^+) Anal Calcd for $C_{11}H_8ClNO_3$ C, 55 60, H, 3 74 Found C, 55 69, H, 3 25

4-Carbomethoxy-2-(4'-methoxyphenyl)oxazole (9d) Obtained **8m** (0 010 g, 9%) and 0 801 g (89%) of **9d** as a white solid mp 115-117 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8 24 (s, 1 H, H-5), 8 04 (d, J = 9 0 Hz, 2 H, Ar-H), 6 96 (d, J = 9 0 Hz, 2 H, Ar-H), 3 94 (s, 3 H, Ar-OCH_3), 3 86 (s, 3 H, $COOCH_3$), ^{13}C NMR (75

MHz, $CDCl_3$) δ 162.92, 161.89 and 161.84 (C-4', C-2 and COOCH3), 143.29 (C-5), 134.00 (C-4), 126.94 (C-2' and 6'), 118 98 (C-1'), 114.19 (C-3' and 5'), 59.33 (Ar-OCH3), 52.13 ($COOCH_3$); IR ($CDCl_3$) 1714 cm^{-1} ($COOCH_3$), mass spectrum (CI, isobutane) m/e (rel intensity) 234 (70, M+1), 233 (1 00, M^+) Anal Calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75. Found: C, 62.00; H, 4.72

Ethyl α-Formyldiazoacetate (6).[18] Into a 1-L Schlenk flask was added DMF (14.2 mL, 13.4 g, 184 mmol) and anhyd ethyl ether (800 mL) under nitrogen. The flask was placed in a cold bath at -78 °C. Oxalyl chloride (15 1 mL, 22.0 g, 175 mmol) was added, and a fluffy white precipitate formed. The CO_2 was vented. After the addition, the mixture was stirred at 24 °C for 2 h. The flask was transferred to a glove box and filtered The fluffy white solid was transferred into a clean 1-L flask fitted with a septum and removed from the glove box. The flask was placed under nitrogen, and chloroform (500 mL) was added. The solution was stirred at 24 °C for 10 min The flask was cooled to -78 °C. The nitrogen inlet was replaced with a drying tube as ethyl diazoacetate (39.6 g, 346 mmol) was added. After the addition, the flask was warmed to 24 °C. (Caution. nitrogen gas evolution may become brisk upon warming. The -78 °C bath should be kept close by in case gas evolution becomes too brisk). After being stirred at 24 °C for 2 h, the solution was concentrated at ca 10 torr at <30 °C. The yellow residue was treated with anhyd ethyl ether (100 mL), and the heterogeneous solution was placed in a -20 °C freezer for 1 h. The ether was decanted off, and 5% aq acetic acid (100 mL) and ethyl ether (200 mL) were added. The solution was stirred at 24 °C for 1 h. The solution was poured into a separatory funnel, and the ether layer was isolated The aq layer was extracted with ether (5 x 40 mL). The combined ether extracts were washed with 1 N aq $NaHCO_3$ (30 mL) and satd aq NaCl (30 mL), dried ($MgSO_4$), and concentrated at ca. 10 torr at <30 °C), and the resulting yellow-orange oil was distilled at reduced pressure to provide 10 5 g (42%) of **6** as a bright yellow liquid (Caution: distillation should be carried out behind a safety shield in a well-ventilated hood.). bp 75-80 °C (9-10 torr; lit.[18] bp 35-36 °C, 0 7 torr); ^1H NMR (300 MHz, $CDCl_3$) δ 9.68 (s, 1 H, HC(O)), 4 33 (q, J = 7.11 Hz, 2 H, OCH_2CH_3), 1 33 (t, J = 7 12 Hz, 3 H, OCH_2CH_3); ^{13}C (75 MHz, $CDCl_3$) δ 180.83 (HC(O)), 160.79 ($CO_2CH_2CH_3$), 103.55 ($C=N_2$), 61 48 (OCH_2CH_3), 13.81 (OCH_2CH_3); IR (neat) 2149 ($C=N_2$), 1725 ($COOCH_2CH_3$), 1715 cm^{-1} (C=O)

General Procedure for the Synthesis of Oxazoles from Ethyl α-formyldiazoacetate (6). 4-Carboethoxy-2-phenyloxazole (12a). **6** (0.546 g, 3 84 mmol) in benzonitrile (20 mL) was added to $Rh_2(OAc)_4$ (0.023 g, 0.06 mmol) in benzonitrile (20 mL) over a 4-h period. After the addition, the solution was stirred at 65-70 °C for 6 h. The excess nitrile was distilled off under reduced pressure, and the residual brown oil was purified by radial chromatography on silica gel (10 % ethyl acetate in hexane) to provide 0.35 g (45%) of **12a** which was recrystallized from ether as white needles mp 69-71 °C, ^1H NMR (300 MHz, $CDCl_3$) δ 8 25 (s, 1 H, H-5), 8.10 (m, 2 H, Ar-H), 7.45 (m, 3 H, Ar-H), 4.40 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 1.39 (t, J = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C (75 MHz, $CDCl_3$) δ 162.36 and 161.27 (C-2 and $COOCH_2CH_3$), 143 58 (C-5), 134.58 (C-4), 131.08 (C-4'), 128.73 (C-2', 6'), 126.84 (C-3', 5'), 126.33 (C-1'), 61.26 (OCH_2CH_3), 14 30 (OCH_2CH_3), IR ($CDCl_3$) 1736 cm^{-1} ($COOCH_2CH_3$ str), mass spectrum (CI, isobutane) m/e (rel intensity) 219 (20, M+2), 218 (1 00, M+1), 217 (42, M^+). Anal. Calcd for $C_{12}H_{11}NO_3$ C, 66.35; H, 5.10. Found C, 66.49; H, 5.31

4-Carboethoxy-2-(4'-methylphenyl)oxazole (12b). 0.321 g (25%) as white needles, mp 93-94 °C, ^1H NMR (300 MHz, $CDCl_3$) δ 8.14 (s, 1 H, H-5), 7 87 (d, J = 8 17 Hz, 2 H, Ar-H), 7 14 (d, J = 7 94 Hz, 2 H, Ar-H), 4 32 (q, J = 7.10 Hz, 2 H, $COOCH_2CH_3$), 2 28 (s, 3 H, Ar-CH_3), 1 29 (t, J = 7 17 Hz, 2 H, $COOCH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162 61 and 161.30 ($COOCH_2CH_3$ and C-2), 148 24 (C-5), 141.44 (C-4'), 134.98 (C-4), 129.39 (C-2' and 6'), 126 79 (C-3' and 5'), 123.77 (C-1'), 61.06 ($COOCH_2CH_3$), 21.39 (Ar-CH_3), 14 22 ($COOCH_2CH_3$); IR ($CDCl_3$) 1726 cm^{-1} ($COOCH_2CH_3$); mass spectrum (CI, isobutane) m/e (rel intensity) 232 (86, M+1), 231 (100, M^+), 203 (22, $M^+ - C_2H_4$). Anal Calcd for $C_{13}H_{13}NO_3$ C, 67 52; H, 5.66 Found. C, 67 51; H, 5.70

4-Carboethoxy-2-(1'-propenyl)oxazole. Mixture of Z and E Isomers. Purification of the crude product from predominantly *Z*-crotononitrile by radial chromatography on silica gel (5% ethyl acetate in hexane) gave 0.801 g (30%) of **12c** as a 63.37 *Z*:*E* mixture. The first fractions gave the pure *Z*-isomer, and the last fractions gave the pure *E*-isomer. *Z*-**12c**: ^1H NMR (300 MHz, $CDCl_3$) δ 8 24 (s, 1 H, H-5), 6.35 (d, $J_{1',2'}$ = 11.71 Hz, 1 H, $CH_3CH=CH$), 6.22 (dq, $J_{1',2'}$ = 11 78 Hz, $J_{2',3'}$ = 6.69 Hz, 1 H, $CH_3CH=CH$), 4.40 (q, J = 7.15 Hz, 2 H, OCH_2CH_3), 2.20 (dd, $J_{2',3'}$ = 6 43 Hz, $J_{1',3'}$ = 0.54 Hz, 3 H, $CH_3CH=CH$), 1.38 (t, J = 7.14 Hz, OCH_2CH_3); ^{13}C (75 MHz, $CDCl_3$) δ 161.29, 160.68, 142 25, 136 98, 133.43, 114 68, 60 47 (OCH_2CH_3), 15 01, 13.67; mass spectrum (El) m/e (rel intensity) 181 (40, M^+), 136 (24), 135 (100), 69 (48)

Anal. Calcd for $C_{10}H_{13}NO_4$: C, 59.60; H, 6.07 Found: C, 59.69; H, 6.17. ***E*-12c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (s, 1 H, H-5), 6.85 (dq, $J_{1',2'}$ = 15.96 Hz, $J_{2',3'}$ = 6.90 Hz, 1 H, $CH_3C\underline{H}$=CH), 6.37 (dq, $J_{1',2'}$ = 15.97 Hz, $J_{1',3'}$ = 1.77 Hz, 1 H, CH_3CH=C$\underline{H}$), 4.40 (q, J = 7 13 Hz, 2 H, O$\underline{CH_2}CH_3$), 1.95 (dd, $J_{2',3'}$ = 6.91 Hz, $J_{1',3'}$ = 1.75 Hz, 3 H, $\underline{CH_3}CH$=CH), 1.38 (t, J = 7.13 Hz, $OCH_2\underline{CH_3}$); ^{13}C (75 MHz, $CDCl_3$) δ 161.45, 161 07, 142.66, 137.23, 133.84, 116.91, 60.85 (O$\underline{CH_2}CH_3$), 18.21, 14.02; IR $CDCl_3$) 1726 cm^{-1} ($COOCH_2CH_3$); mass spectrum (El) m/e (rel intensity) 181 (78, M^+), 153 (100, M^+ - C_2H_4), 136 (44), 135 (70), 69 (100); mass spectrum (EI) m/e (rel intensity) 181 (35, M^+), 153 (55, M^+- C_2H_4), 136 (22), 135 (38), 69 (100), 56 (44), 44 (78). Anal. Calcd for $C_{10}H_{13}NO_4$: C, 59.60; H, 6 07. Found: C, 59.46; H, 6.18.

4-Carboethoxy-2-(2'-ethoxy-E-ethenyl)oxazole (12d): 1.47 g (36%) as a white solid; mp 51-52 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.079 (s, 1 H, H-5), 7.58 (d, J = 12.93 Hz, 1 H, CH=CH), 5.72 (d, J = 12.93 Hz, 1 H, CH=CH), 4.40 (q, J = 7.07 Hz, 2 H, $CO_2\underline{CH_2}CH_3$), 3.94 (q, J = 7.06 Hz, 2 H, O$\underline{CH_2}CH_3$), 1.39 (m, 6 H, $CH_2\underline{CH_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.78, 161.15, 156.05, 141.74, 133.57, 92.22, 66 29, 60.17, 14.18, 13 99, IR ($CDCl_3$) 1730 cm^{-1} ($\underline{COO}CH_2CH_3$); mass spectrum (CI, isobutane) m/e (rel intensity) 212 (20, M+1), 211 (64, M^+), 183 (27), 166 (30), 155 (42), 137 (100), 99 (58), 71 (42). Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.16 Found: C, 57.00; H, 6 28.

4-Carboethoxy-2-(E-cinnamyl)oxazole (12e): 0.846 g (24%) as a white solid; recrystallized as white needles from ethyl ether; mp 110-112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) d 8.20 (s, 1 H, H-5), 7.62 (d, J = 16.46 Hz, 1 H, ArCH=CH), 7 52 (m, 2 H, Ar-$\underline{H}$), 7.38 (m, 3 H, Ar-$\underline{H}$), 6 96 (d, J = 16.44 Hz, 1 H, ArCH=CH), 4.42 (q, J = 7.15 Hz, 2 H, O$\underline{CH_2}CH_3$), 1.40 (t, J = 7.16 Hz, 3 H, $OCH_2\underline{CH_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.98 and 161.11 ($\underline{C}OOCH_2CH_3$ and C-2), 143.13 (C-5), 138 10, 134.85, 134.55, 129.52, 128.80, 127.3, 112.79 (C-4), 61.11 ($COO\underline{CH_2}CH_3$), 14 18 ($COOCH_2\underline{CH_3}$); mass spectrum (CI, isobutane) m/e (rel intensity) 244 (100, M^+). Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5 38. Found: C, 69.08; H, 5.46.

4-Carboethoxy-2-methyloxazole (12f). 0.397 g (18%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1.H, H-5), 4.31 (q, J = 7.40 Hz, 2 H, O$\underline{CH_2}CH_3$), 2.45 (s, 3 H, $\underline{CH_3}$), 1 31 (t, J = 7.14 Hz, 3 H, $OCH_2\underline{CH_3}$) (lit.[23] ^{1}H NMR), IR ($CDCl_3$) 1736 cm^{-1} ($\underline{COO}CH_2CH_3$ str); mass spectrum (EI) m/e (rel intensity) 156 (10, M+1), 155 (50, M^+), 127 (100, M^+ - C_2H_4), 110 (60), 99 (20).

4-Carboethoxy-2-(bromomethyl)oxazole (12g): 2.21 g (67%) as a white solid; recrystallized from hexane; mp 43-44 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8 21 (s, 1 H, H-5), 4 45 (s, 2 H, $\underline{CH_2}$Br), 4.36 (q, J = 7 1 Hz, 2 H, $CH_3\underline{CH_2}O$), 1.35 (t, J = 7 1 Hz, 3 H, $\underline{CH_3}CH_2O$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 160.64, 159 99 ($\underline{C}O_2Et$, C-2), 144.84 (oxazole C-5), 134.26 (oxazole C-4), 61 44 ($CH_3\underline{CH_2}O$), 19.35 ($\underline{CH_2}$Br), 14.24 ($\underline{CH_3}CH_2O$); IR (neat) 3034 (aromatic C-H stretch), 2980, 2934 (aliphatic C-H str), 2253 (C=N str), 1738 (C=O str), 1579 (C=C-O str), 1468 ($CH_2OC(O)$ bend), 1447 (CH_2Br scissoring bend), 1371 (CH_3 bend), 1315, 1245 (CH_2Br wagging bend), 1110 cm^{-1}, mass spectrum (EI) m/e (rel intensity) 233 (2 35, M^+ - 1), 154 (14 0, M^+ - Br), 149 (30 1), 126 (18 5), 119 (3 6, $BrCH_2CN^+$), 94 (25.3, CH_2Br^+ + H^+), 81 (19 4, isotope Br^+), 79 (6 6, Br^+), 73 (10 5, $C_3H_5O_2^+$), 71 (46.3, $C_3H_3O_2^+$), 69 (36.9), 45 (17 3, $C_2H_5O^+$), 43 (100, $C_2H_3O^+$) Anal Calcd for $C_7H_8BrNO_3$ 36 06% C, 3 46% H Found· 36 17% C, 3 34% H

REFERENCES AND NOTES

1 For a review on the occurrence and the chemistry of oxazoles, see. "Oxazoles", Turchi, I. J., Ed., Wiley New York, 1986, and other reviews cited therein

2. For some additional, more recent preparations of 1,3-oxazole derivatives, see (a) Hamada, Y , Shioiri, T *J. Org. Chem.* **1986**, *51*, 5489-5490 (b) Takeuchi, H , Yanagida, S ; Ozaki, T ; Hagiwara, S , Ehuchi, S *J. Org. Chem.* **1989**, *54*, 431-434. (c) Freeman, F., Kim, D. S. H. L. *Tetrahedron Lett.* **1989**, *30*, 2631-2632. (d) Dow, R. L *J. Org. Chem.* **1990**, *55*, 386-388 (e) Zhao, Z.; Scarlato, G. R , Armstrong, R W *Tetrahedron Lett.* **1991**, *32*, 1609-1612 (f) Smith, A B ; Salvatore, B A ; Hull, K G.; Duan, J. J.-W. *Tetrahedron Lett.* **1991**, *32*, 4859-4862 (g) Yokoyama, M.; Sujino, K , Irie, M.; Togo, H *Tetrahedron Lett.* **1991**, *32*, 7269-7272. (h) Yokoyama, M , Irie, M ; Sujino, K ; Kagemoto, T.; Togo, H.; Funabashi, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2127-2134 (i) Evans, D. A., Gage, J R , Leighton, J. L ; Kim, A S *J. Org. Chem.* **1992**, *57*, 1961-1963 (j) Cunico, R F ; Kuan, C. P *J. Org. Chem.* **1992**, *57*, 3331-

3336. (k) Yokokawa, F ; Hamada, Y ; Shioiri, T. *SynLett* **1992**, 153-155 (l) Williams, E. L *Tetrahedron Lett.* **1992**, *33*, 1033-1036.

3 Wasserman, H H.; McCarthy, K E ; Prowse, K S. *Chem. Rev.* **1986**, *86*, 845-856.

4 (a) Jacobi, P A. Bis-Heteroannulation: Total Synthesis of Furanoterpenes, Butenolides, Lactones and Related Materials. In *Advances in Heterocyclic Natural Product Synthesis*; Pearson, W. H Ed.; JAI Press: Greenwich, CT, Vol. 2, 1992; Chap 3. (b) Subramanyam, C.; Noguchi, M , Weinreb, S M *J. Org. Chem.* **1989**, *54*, 5580-5585

5 (a) Cocito, C In "Antibiotics"; Corcoran, J W., Hahn, F E , Eds ; Springer: Berlin, Vol. VI, 1983, pp. 296-332 (b) Di Giambattista, M., Chinali, G., Cocito, C J. Antimicrob Chemoth. **1989**, 24, 485-507.

6. Nagao, Y.; Miyasaka, T ; Hagiwara, Y ; Fujita, E *J. Chem. Soc., Perkin Trans. I* **1984**, 183-.

7 Foster, M. P ; Concepción, G. P ; Caraan, G. B , Ireland, C. M *J. Org. Chem.* **1992**, *57*, 6671-6675.

8 Matsunaga, S.; Fusetani, N ; Hashimoto, K , Koseki, K ; Noma, M.; Noguchi, H ; Sankawa, U. *J. Org. Chem.* **1989**, *54*, 1360-1363.

9 Cornforth, J. W.; Cornforth, R. H *J. Chem. Soc.* **1947**, 96-102.

10 (a) Huisgen, R. In "1,3-Dipolar Cycloaddition Chemistry"; Padwa, A , Ed , Wiley New York, 1984; Chap. 1, pp. 1-176. (b) *Advances in Cycloaddition*; Curran, D. P., Ed , JAI Press Greenwich, CT, Vol 1, 1988. (c) Padwa, A.; Hornbuckle, S F *Chem. Rev.* **1991**, *91*, 263-309

11. For related oxazole syntheses, see: (a) Buu, N T ; Edward, J T. *Can. J. Chem.* **1972**, *50*, 3730-3737. (b) Moniotte, Ph G ; Hubert, A J., Teyssié, Ph. *J. Organomet. Chem.* **1975**, *88*, 115-120. (c) Ibata, T., Sato, R. *Chem. Lett.* **1978**, 1129-1130. (d) Ibata, T.; Sato, R. *Bull. Chem. Soc. Japan* **1979**, *52*, 3597-3600. (e) Doyle, M P , Buhro, W. E.; Davidson, J. G , Elliott, R C.; Hoekstra, J W., Oppenhuizen, M *J. Org. Chem.* **1980**, *45*, 3657-3664 (f) Mashraqui, S. H ; Keehn, P. M. *J. Am. Chem. Soc.* **1982**, *104*, 4461-4465 (g) Nagayoshi, K.; Sato, T. *Ibid.* **1983**, 1355-1356. (h) Ibata, T.; Isogami, Y. *Bull. Chem. Soc. Japan* **1989**, *62*, 618-620 (i) Vedejs, E , Piotrowski, D W. *J. Org. Chem.* **1993**, *58*, 1341-1348

12 (a) Doyle, M P. *Chem. Rev. 1986*, **86**, 919 (b) Adams, J ; Spero, D M *Tetrahedron* **1991**, *47*, 1765-1808

13. (a) Alonso, M E , del Carmen García, M., Chitty, A W. *J. Org. Chem.* **1985**, *50*, 3445-3449 (b) Davies, H M. L.; Romines, K R. *Tetrahedron* **1988**, *44*, 3343-3348.

14. Wenkert, E.; Ananthanarayan, T. P , Ferreira, V. F ; Hoffmann, M G ; Kim, H -S. *J. Org. Chem.* **1990**, *55*, 4975-4976

15. For preliminary accounts describing portions of this work, see: (a) Connell, R D.; Scavo, F ; Helquist, P ; Åkermark, B *Tetrahedron Lett.* **1986**, *27*, 5559-5562 (b) Connell, R. D., Tebbe, M , Helquist, P., Åkermark, B *Tetrahedron Lett.* **1991**, *32*, 17-20 (c) Connell, R. D *New and Selective Transformations Directed Toward the Synthesis of Griseoviridin and Virginiamycin;* Ph D Dissertation, University of Notre Dame 1989

16. For other recent reports of the use of these reactions, see (a) Shi, G ; Xu, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 607-608. (b) Pirrung, M. C , Zhang, J ; McPhail, A. T *J. Org. Chem.* **1991**, *56*, 6269-6271. (c) Yoo, S -K. *Tetrahedron Lett.* **1992**, *33*, 2159-2162

17. Regitz, M. *Synthesis* **1972**, 351-357

18 Strojanovic, F M , Arnold, Z *Coll. Czech. Chem. Commun.* **1967**, *32*, 2155-2160

19 Pomerantz, M ; Levanon, M *Tetrahedron Lett.* **1991**, *32*, 995-998.

20. Retherford, C , Yeh, M.C P.; Schipor, I.; Chen, H G , Knochel, P *J. Org. Chem.* **1989**, *54*, 5200-5202

21 Gangloff, A R.; Åkermark, B , Helquist, P. *J. Org. Chem.* **1992**, *57*, 4797-4799.

22 For other approaches to the oxazole unit seen in **2**, see (a) Meyers, A I , Lawson, J. P , Walker, D G.; Linderman, R. J *J. Org. Chem.* **1986**, *51*, 5111-5123 (b) Nagao, Y , Yamada, S , Fujita, E. *Tetrahedron Lett.* **1983**, *24*, 2287-2290, 2291-2294 (c) Wood, R. D ; Ganem, B *Tetrahedron Lett.* **1983**, *24*, 4391-4392 See also· (d) Lipshutz, B H ; Hungate, R W *J. Org. Chem.* **1981**, *46*, 1410-1413

23 Brown, D. J.; Ghosh, P B *J. Chem. Soc. B* **1969**, 270-276.