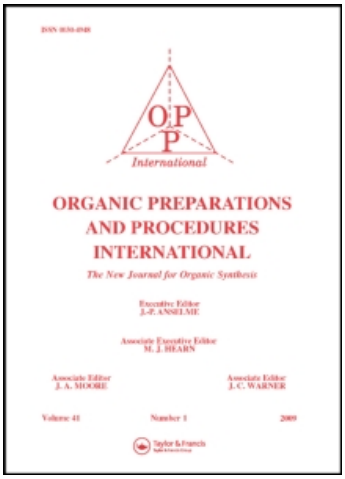

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THE LATERAL METALATION OF ISOXAZOLES. A REVIEW

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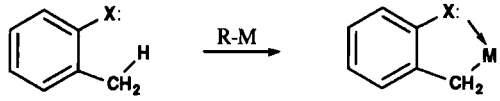
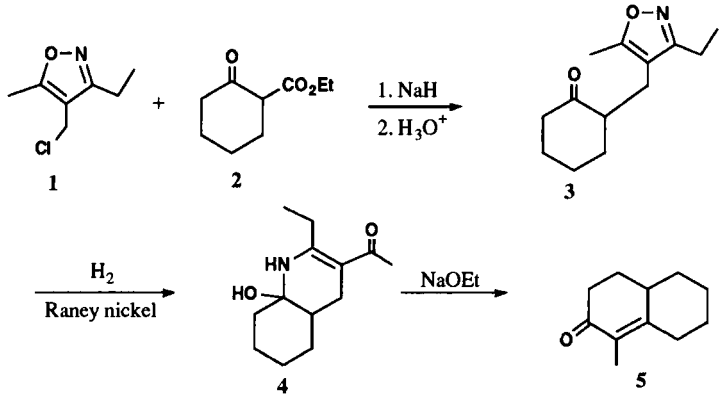
INTRODUCTION

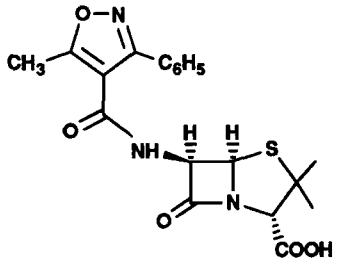
Lateral metalation, as illustrated in the Gschwend and Rodriguez review on heteroatom facilitated metalations,[1] is the deprotonation of a C-H bond adjacent or "lateral" to an aromatic ring.



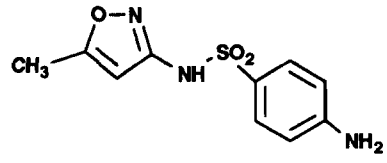
Lateral metalation in the above landmark paper was cited as an example of a "side-reaction". However, this is a quite important and general side-reaction and this review focuses on lateral metalation of a particularly interesting type of heterocycle, the isoxazoles. Lateral metalation of carbocycles continues to find numerous applications.[2,3] The lateral metalation of pyridine and other nitrogen containing heterocycles is quite selective and an excellent review by Kaiser has appeared.[4] The present review covers the literature to mid-1992. The use of isoxazoles is widespread.[5] The isoxazole ring often represents a tool to the synthetic chemist as a masked form of 1,3-diketones.[6] The elegant isoxazole annulation method developed by Stork illustrates this application.[7] After the isoxazole ring is used as alkylating agent, its latent potential is unveiled in a ring opening and cyclization sequence that now is a standard synthetic tactic.[7d]



New examples continue to appear almost daily of isoxazole compounds with valuable biological activity.[8] Often in biology the isoxazole moiety is a pro-drug and is ultimately unmasked *in vivo*. A classic example is the isoxazole ß-lactams, including oxacillin, which were an early pro-drug form of the antibiotic, which could be administered orally.[9a]



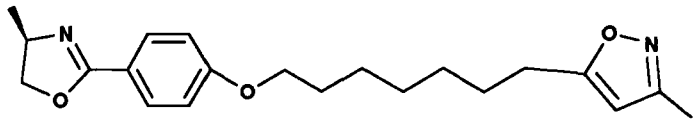
Oxacillin



Sulfamethoxazole

A second major use of isoxazole is found when the isoxazole is substituted for another π-deficient aromatic ring, also known as bioisosteric replacement. A familiar and now generic example of bioisosteric replacement is the antibiotic sulfamethoxazole.[9b] Both of these examples are used in general medical practice.

A recent and exciting development is the antirhinoviral isoxazole WIN 51711, an example where the isoxazole itself is known to play a valuable role in the drug-receptor interaction.[10]



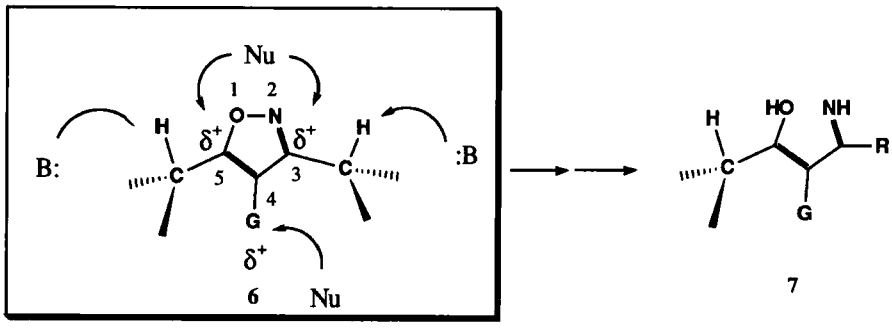
WIN 51711

With the current interest in isoxazole synthesis, methods for their selective and efficient preparation are in demand. This review will highlight the lateral metalation approach to isoxazole synthesis as well as related chemistry of organometallic reagents in the presence of the isoxazole ring. We continue to be intrigued by the possibilities of functionalized isoxazoles,[11] and while interest continues to grow, we feel that the real potential of this heterocycle has yet been only partially revealed.

I. POTENTIAL FATES OF THE ISOXAZOLE RING

The synthetic utility of isoxazoles depends upon one's ability to select and control the functional groups on demand. Advances have been made in applications towards natural products,[6] where in many cases the isoxazole acts as a latent or masked functional equivalent.

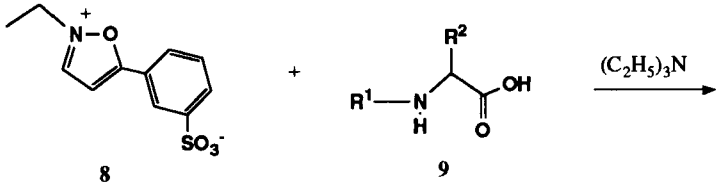
Thus, the isoxazole, after serving as an important intermediate, is absent from the final target molecule. Direct deprotonation on the isoxazole ring usually leads to ring opening, thus, lateral metalation represents an alternative approach to synthetic transformation about an intact isoxazole.



For the purpose of this review, lateral metalation refers to the deprotonation of an acidic proton on a carbon α- to the heteroaromatic ring. When the carbon adjacent to the isoxazole ring in molecule **6** bears a hydrogen, lateral metalation may proceed at either the C-3 or C-5 lateral position. In general terms, several reactions compete with lateral metalation; therefore, they will be surveyed in the course of considering the scope and limitations. An isoxazole which bears an electron withdrawing functional group (EWG) in the C-4 position should increase the rate at which lateral metalation proceeds. The C-4 EWG. should, in principle at least, render the isoxazole ring more susceptible to nucleophilic attack at (a) the C-3 and (b) C-5 ring positions, as well as at (c) the C-4 functional group itself. Finally, strong bases are also known to undergo electron transfer chemistry. While the isoxazole as a protecting group is relatively robust under conditions of hydrolysis or mild oxidation, it is labile under reductive conditions leading to cleavage of the oxygen nitrogen bond, i.e. to produce **7**. Given such potential problems, however, the selectivity which is possible to achieve is often remarkable.

1. Direct Ring Deprotonation

Deprotonation of an isoxazole at the C-3 or C-5 ring position leads to ring opening. This reaction has proven quite valuable in a number of applications. The classic example is peptide coupling using the N-alkyl-isoxazolium sulfonate commonly known as Woodward's Reagent K (**8**).[12] Deprotonation of the isoxazole ring of N-alkylisoxazolium salts is the first step in the cascade which activates the carboxylate moiety and has been used as a tactic in peptide synthesis. Even difficult peptide couplings proceed in excellent yields, the by-products are water soluble and easily removed from the peptide derivative and racemization is minimal.



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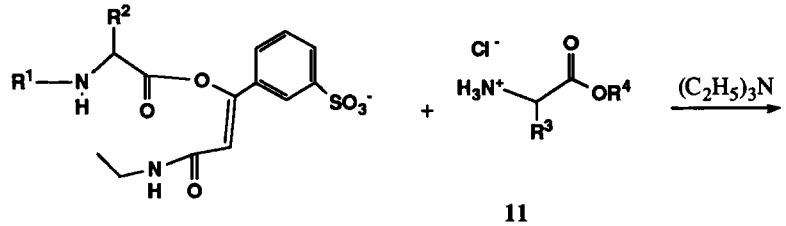
Woodward's Reagent K has been used to inactivate enzymes with nucleophilic side chains and thus serve as a spectrophotometric probe for imidazole, lysine, cysteine and tyrosine residues.[12b]



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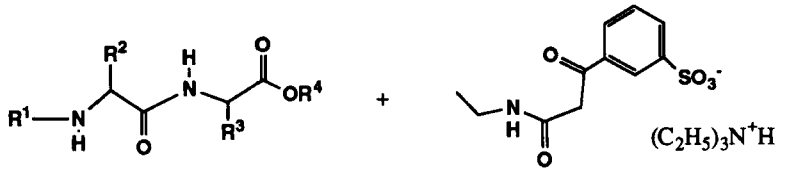
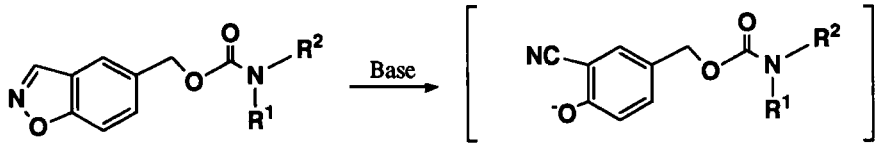


12 13

Kemp and Hoyng[13] used C-3 deprotonation initiated ring opening as a key tactic in developing the 5-benzisoxazolylmethyleneoxycarbonyl (Bic) protecting group. The Bic group withstands most conventional manipulations in peptide synthesis, including treatment with trifluoroacetic acid. It is selectively cleaved in a two-step sequence, consisting of treatment with a base in polar aprotic solvent, followed by solvolysis at pH 7.



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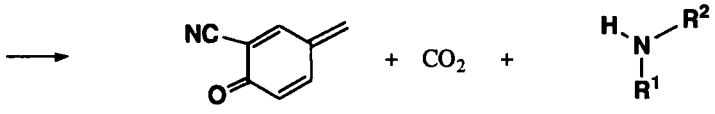
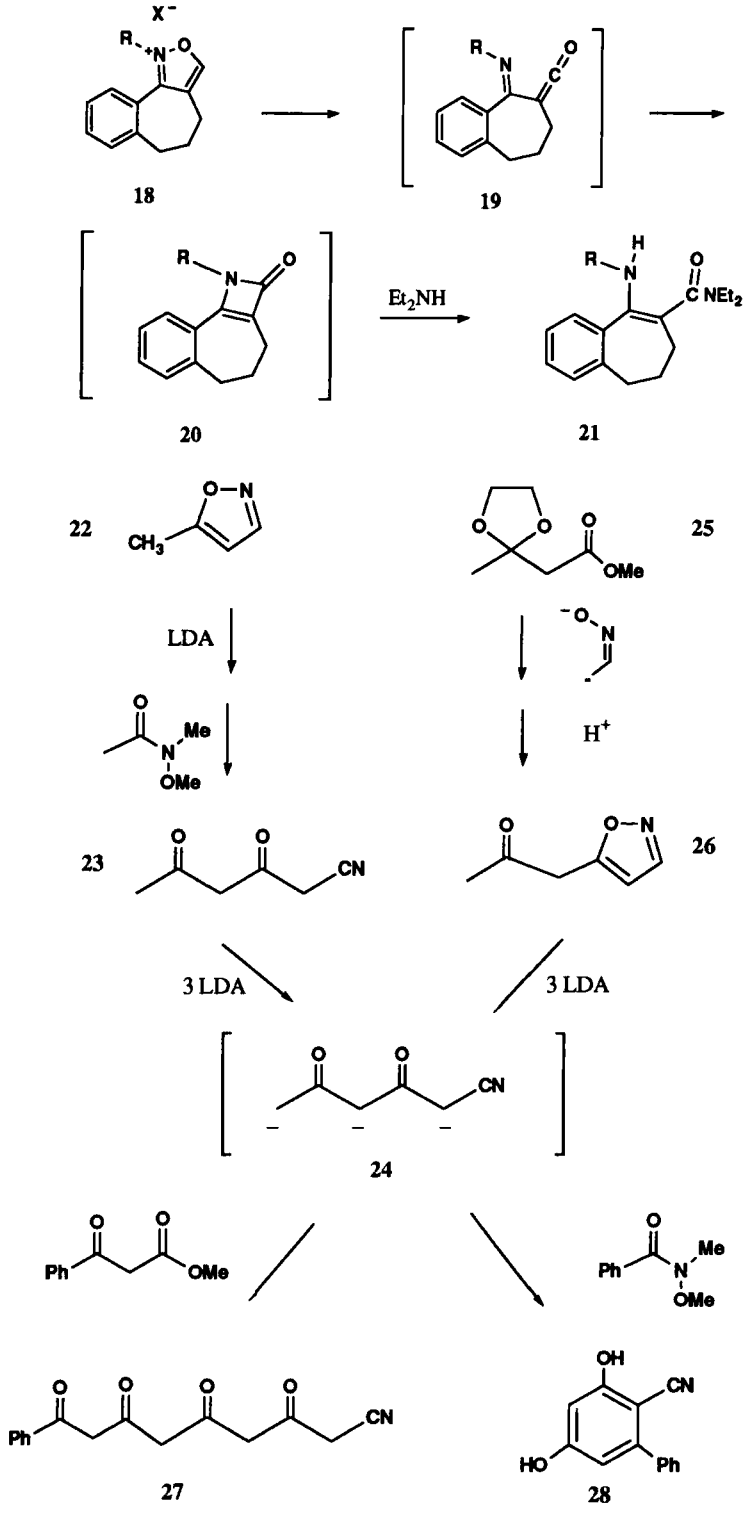


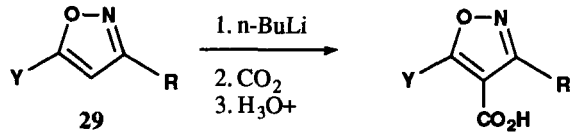
16 17

Olofson and co-workers[14] have used the facile C-5 deprotonation of N-isoxazolium salts to prepare and characterize the ephemeral azetinone, **20**. Treatment of the N-adamantyl salt **18** at low temperature with base, led to the putative iminoketene **19** which then cyclized to **20** (lifetime of *ca.* 20 minutes at 5°). Proof for the azetinone structure rested upon the strong FT-IR C=O absorption at 5.56 mm and the ^{13}C NMR signals at δ177.0 (C=O) and 170.5 and 144.6 (C=C); nucleophiles add quickly to the azetinone. For example, diethylamine produced the corresponding amide **21**.



An innovative simultaneous use of a combination of ring deprotonation/ring opening and lateral metalation is found in the work of Harris[15] who described two approaches to the synthetically useful nitrile trianion **24**, both employing the above tactic. In the first approach, 5-methylisoxazole (**22**) was treated with two equivalents of base to produce the ring opened dianion, followed by C-acylation to produce the 3,5-dioxohexane nitrile **23**, finally, triple deprotonation provided the nitrile trianion **24**. The second parallel approach involved the construction of the acetonyl isoxazole **26** *via* the oxime dianion method.[16] Ring opening/deprotonation provided the same nitrile trianion **24**. The nitrile trianion **24** was found to be an effective intermediate in the synthesis of polyketides **27** and, of highly functionalized aromatic systems **28**.

Ring deprotonation at C-4 proceeds smoothly when C-3 and C-5 lack acidic α -hydrogens.[17]

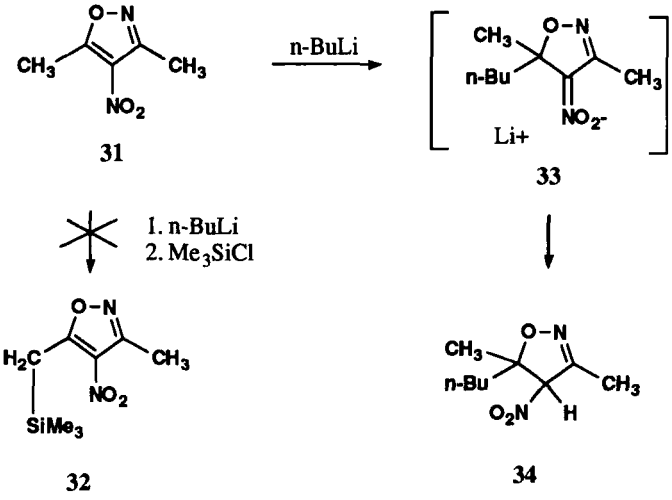


29 **30**

When acidic α -hydrogens are present, lateral metalation is a competing reaction and will be discussed in more detail below. The method of choice for C-4 metalation, when acidic α-hydrogens are present, is halogen metal exchange from the C-4 iodide at low temperature.

2. Nucleophilic Attack on the Heterocyclic Ring

Alkyllithium reagents attack C-4 nitro isoxazole **31** at the C-5 position,[18] in a Michael addition with respect to the EWG at C-4 to produce the 4,5-dihydroisoxazole **34**.

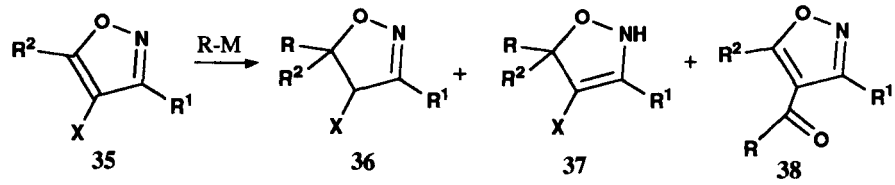


31 **33**

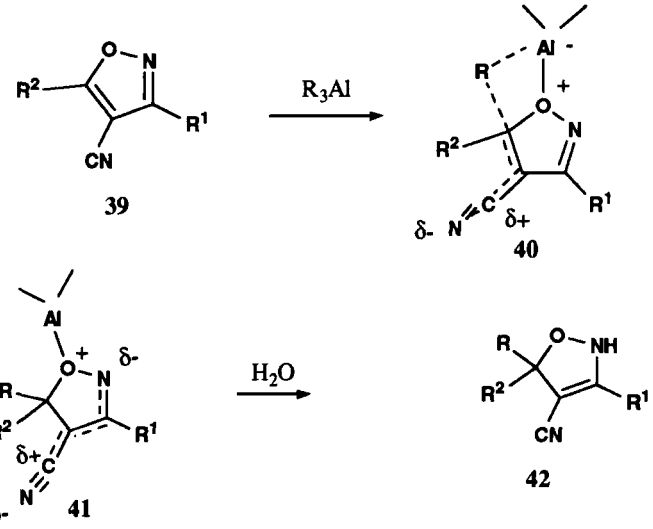
32 **34**

Albertola and co-workers have reported a systematic investigation into the nucleophilic addition of organometallic reagents to isoxazole and N-isoxazolium salts.[19] They confirmed that, for C-4 nitro isoxazoles **35**, nucleophilic attack at C-5 is the major product with organolithium or Grignard reagents, to produce the 4,5-dihydroisoxazoles **36**.[20] The stereochemistry of the products was not

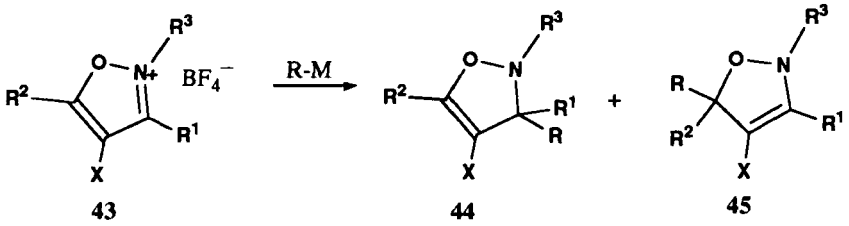
assigned. However, when the C-4 group is a nitrile, nucleophilic addition with organolithium and Grignard reagents was observed at the C-4 nitrile group, which after hydrolysis, produced the ketone **38**.



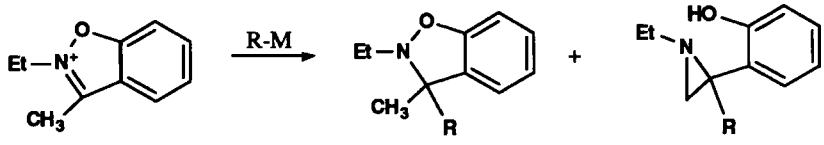
In contrast organoaluminum reagents gave C-5 ring addition to the 2,5-dihydroisoxazoles **37** when X = CN. The authors attributed the regioselectivity observed to HSAB principles, based on the assumption that the nitrile carbon in the conjugated 4-cyanoisoxazole is harder than C-5 and that the alkyllithium and alkylmagnesium iodides are harder than the trialkylaluminum reagents. The relative softness of the organoaluminum reagent and its affinity for the coordination of the isoxazole oxygen with the organoaluminum *via* complex **40** directs formation of 2,5-dihydroisoxazoles, as illustrated below.



The reaction of C-4 chloro or bromo N-isoxazolium salts **43** with organolithium or Grignard reagents produced C-3 ring addition **44**. In contrast, reaction of C-4 benzoyl or ester N-isoxazolium salts **43** with organolithium or magnesium reagents produced C-5 addition **45**. Interest in 2,3-dihydroisoxazoles (Δ^4-isoxazolines) has focused on the dazzling array of rearrangement reactions this ring system has produced and this topic has been reviewed.[21]

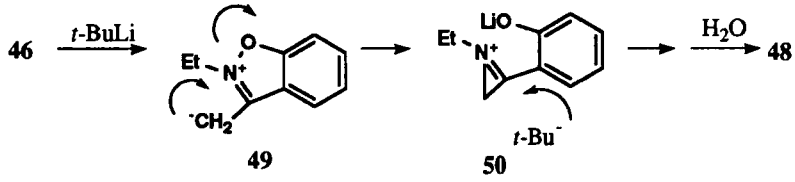


Benzisoxazolium salts **46** behave similarly to isoxazolium salts; thus, reaction with methyllithium, methylmagnesium iodide or sodium borohydride resulted in nucleophilic addition leading to the dihydrobenzisoxazole **47**. The reaction of **46** with *t*-butyllithium, however, produced the aziridine



46 **47** **48**

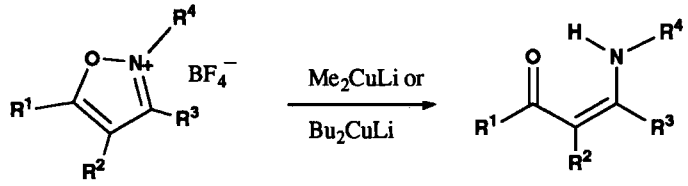
48 as the major product. The authors suggested that the formation of **48** could be explained by lateral metalation of **46** to produce anion **49**, which fragments to the azirinium ion **50**, followed by nucleophilic attack to provide **48**.



49 **50**

3. Ring Opening

N-Alkylisoxazolium salts **51** undergo reductive cleavage of the oxygen-nitrogen bond on treatment with lithium dialkylcuprates to give ß-enaminones **52**.[22]



51 **52**

II. REGIOSELECTIVITY

1. Ring *vs* Lateral Metalation

Bowden[23] found that metalation of 3-methoxy-5-methylisoxazole **53** produces a mixture of products arising from deprotonation at the ring **54** and lateral **55** positions. The selectivity for this process was explained by the relative facility of formation of the complexes **56** and **57**, which directs the metalation to adjacent sites.

Gainer and co-workers[24] reported on a study of the influence of different C-3 groups on ring *versus* lateral metalation. When the C-3 group was hydroxyl (Table 1, Entry 1), two equivalents of *n*-butyllithium produced exclusive C-5 lateral metalation. With methoxymethyl (Entry 2) or dimethylaminomethyl (Entry 4) and *n*-butyllithium as base, C-4 ring metalation **60** competed with C-3 lateral metalation **59**. With LDA as the base, only C-5 lateral metalation **61** resulted in both cases (Entries 3 and 5). The authors invoked the formation of an initial complex of **58** with *n*-butyllithium to explain the results.

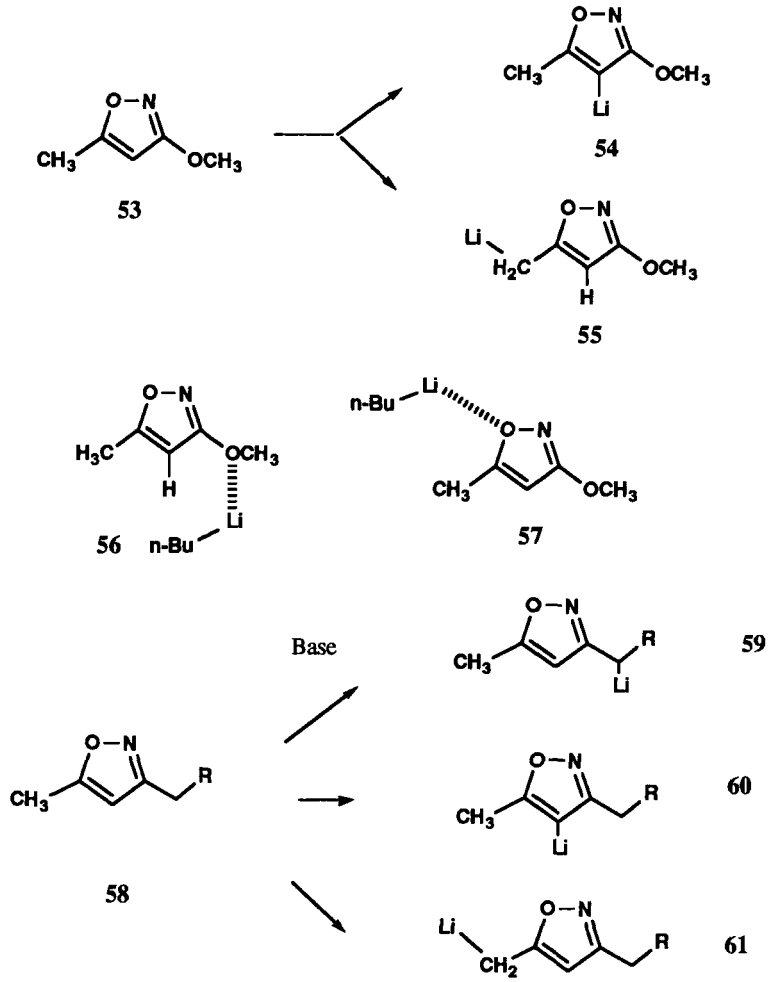
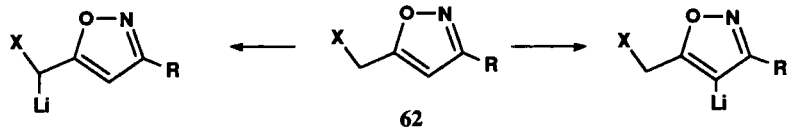


TABLE 1. Ring *versus* Lateral Metalation Study of Gainer.[24]

Entry	R	Base	Product (Ratio)		
			59 C-3	**60** C-4	**61** C-5
1	OH	2 n-BuLi	0	0	100
2	OCH_3	n-BuLi	80	20	0
3	OCH_3	LDA	0	0	100
4	$N(CH_3)_2$	n-BuLi	50	50	0
5	$N(CH_3)_2$	LDA	0	0	100

Micetich[25] studied the effect of 5-alkoxymethyl, alkylthiomethyl and dialkylaminomethyl groups on the course of lateral *versus* ring metalation of isoxazole **62**. With 5-alkoxymethyl or 5-alkylthiomethyl, only lateral metalation **63** was observed, with 5-dialkylamino methyl, the ring C-4 position was metalated exclusively to give **64**.

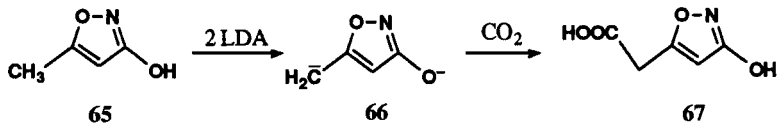


63 X= -OR' or -SMe

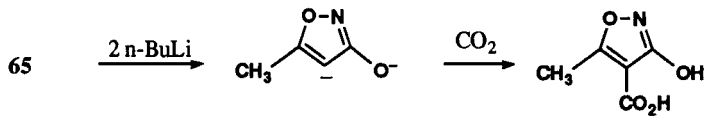
62

64 X = -N(Me)$_2$

Oster and Harris[26] reported that treatment of 3-hydroxy-5-methyl isoxazole **65** with lithium diisopropylamide gave the lateral dianion **66**, which gave carboxylic acid **67** on addition of carbon dioxide. The use of *n*-butyllithium gave a 7:3 mixture of lateral and C-4 ring metalation, **66** and **68** and after quenching with carbon dioxide, led to the corresponding acids **67** and **69**.



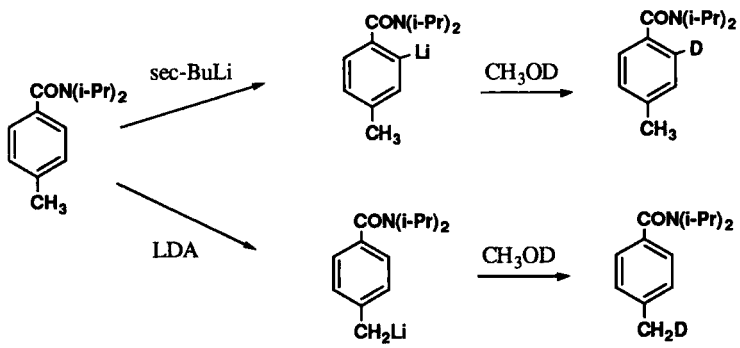
65 **66** **67**



68 **69**

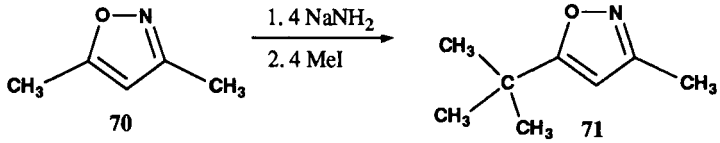
A recent study by Albertola and co-workers addressed the role of base in ring *versus* lateral metalation.[17c] With n-BuLi, mixtures of products alkylated at the C-4 and C-3 methyl group were obtained, whereas with lithium isopropylcyclohexylamide (LICA)-TMEDA regioselective reaction at C-3 was observed.

In summary, the observations to date on the isoxazole system are, for the most part, in agreement with the conclusion of Beak[2a] concerning ring *versus* methyl deprotonation in the carbocyclic series: for the coordinatively unsaturated alkyllithium reagents, kinetic metalation on the ring is expected while thermodynamic lateral metalation is observed with the less basic dialkylamides.



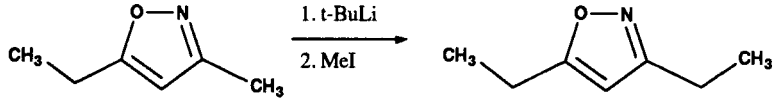
2. Kinetic *vs.* Thermodynamic Deprotonation

Micetich had reported that subsequent lateral metalation of isoxazole proceeded at the C-5 position.[25] Kashima reported that reaction of 3,5-dimethyl isoxazole **70** with four equivalents of sodamide and methyl iodide the 5-t-butyl isoxazole **71** was obtained.[27] Rate studies of deuterium incorporation by Kashima indicated exchange at the C-5 methyl at least two orders of magnitude faster than that at the C-3 methyl group. Kashima concluded, based on theoretical calculations, that the selectivity observed could be attributed to the lower energy of the corresponding carbanion formed at the C-5 lateral position.



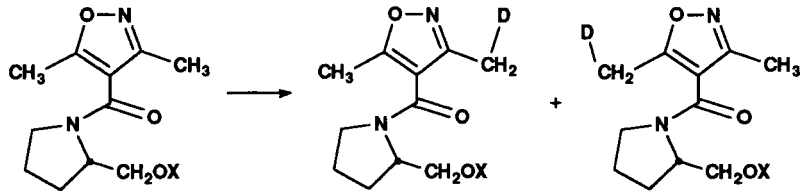
70 **71**

Brunelle reported that kinetic deprotonation of 5-ethyl-3-methyl isoxazole **72** followed by quenching produced C-3 electrophile incorporation **73**.[28]



72 **73**

When the dianion of the C-4 carboxamide isoxazole **74** (X=H) was quenched with deuterium, only C-5 deprotonation **76** was indicated Table 2, Entries 1 and 2). For the prolinol O-methyl ether ($X=CH_3$), however, shorter reaction times or inverse addition gave rise to deuterium incorporation in the C-3 position **75**, (Table 2, Entries 4 and 5).[29]

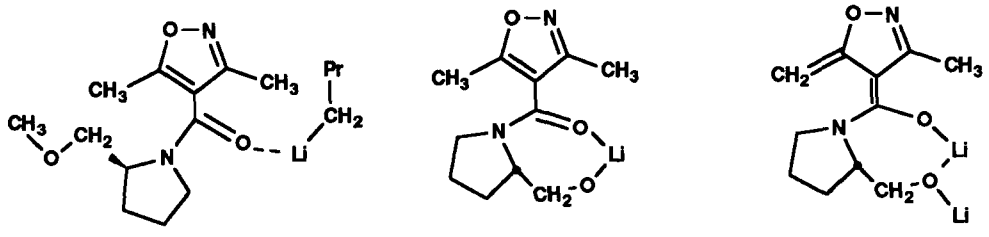


74 X = H; X = CH_3 **75**, C-3 **76**, C-5

TABLE 2. Kinetic *versus* Thermodynamic Deprotonation of Isoxazolyl Carboxamide **74**[29]

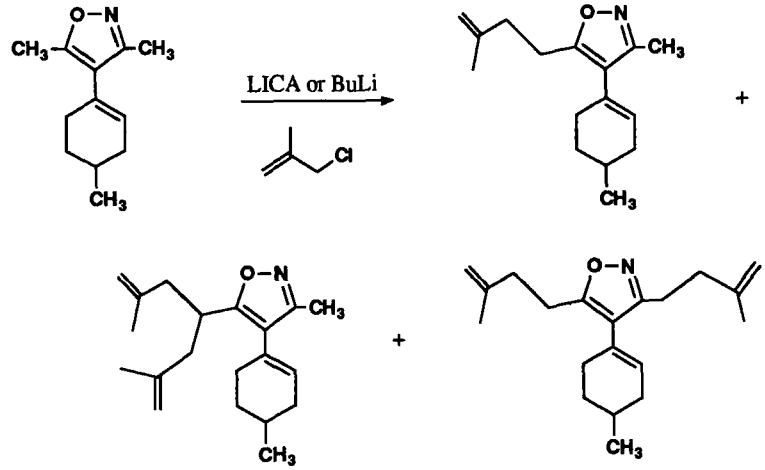
Entry	X	Time (hr)	Deuterium Incorporation **75**, C-3	**76**, C-5	Conditions
1	H	2	< 5	> 95	Thermodynamic
2	H	2	< 5	> 95	Kinetic
3	Me	2	< 5	> 95	Thermodynamic
4	Me	1	45	55	Thermodynamic
5	Me	1	93	7	Kinetic

The authors rationalized this reactivity by extending the Ireland-Evans model for stereoselective deprotonation to this vinylogous imidate system. In conformation (i), the carbonyl may direct the alkyl lithium reagent into proximity with the C-3 methyl protons. In the case of the dianion, the initial deprotonation produces the alkoxide (ii) in which the carbonyl may be involved in chelation. The greater thermodynamic stability of the more stabilized imidate (iii) could then determine the regioselectivity.

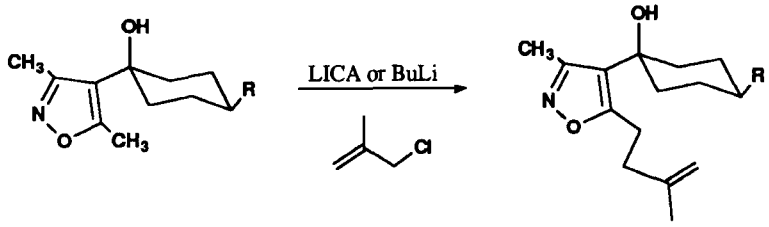


i ii iii

Torroba and Marcaccini,*et al*, reported that the reaction of C-4-cycloalkenyl isoxazoles with two equivalents of BuLi or lithium isopropylcyclohexylamide (LICA), produced C-3/C-5 bis alkylation as the major product in 45% yield. With one equivalent of either base, monoalkylaytion at C-5 was the major product in 65% yield.[30a]



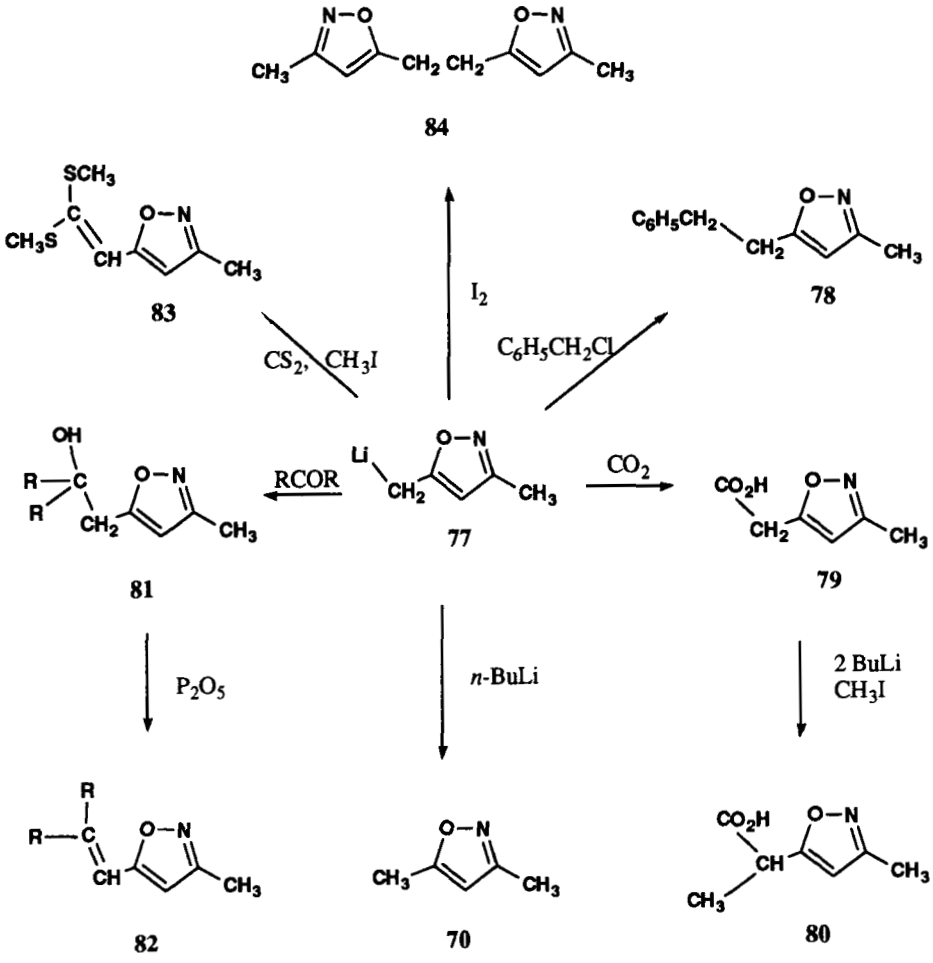
In contrast the dianion of the hydroxycycloakyl isoxazole produced predominantly C-5 monoalkylation (85-33% yields).[30a]



Further evidence for C-3 kinetic deprotonation has been provided by Cherton's group who observed the usual C-5 metalation and electrophilic quenching at -78°, but found that when the reaction was performed at lower temperature (-105°) the products from C-3 alkylation could also be isolated, the C-3 to C-5 alkylation ratios varied from 79:21 to 34:66.[30b]

III. LATERAL METALATION AND ELECTROPHILIC QUENCHING

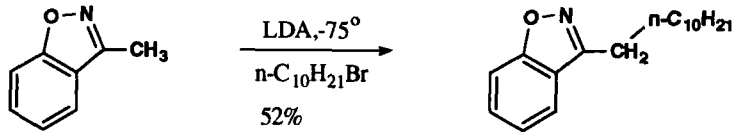
Micetich studied the lateral metalation of 3,5-dimethyl isoxazole **70** and provided systematic information on the potential scope of this process.[31] The lithio isoxazole **77** could be alkylated by a variety of electrophiles.



Reaction of **77** with benzyl chloride provided **78**, carbon dioxide produced carboxylic acid **79**. Subsequent metalation of acid **79** with two equivalents of base and alkylation with iodomethane provided **80**. Reaction with ketones gave **81** and dehydration of **81** produced the α,β-unsaturated isoxazole **82**. Quenching with carbon disulfide and S-alkylation with iodomethane produced the ketene

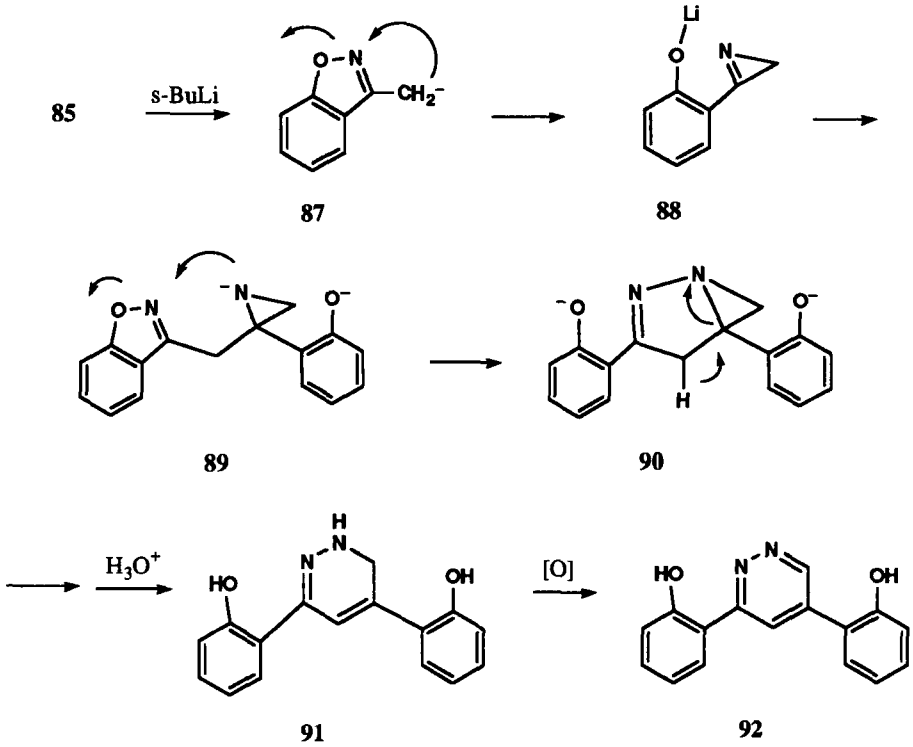
dithioacetal isoxazole **83**. Reaction of the lithio isoxazole **77** with iodine produced dimerization to bisisoxazole **84**.

1,2- Benzisoxazoles **85** react with LDA in the presence of electrophiles to give the product of lateral metalation and electrophilic quenching **86**.[32]



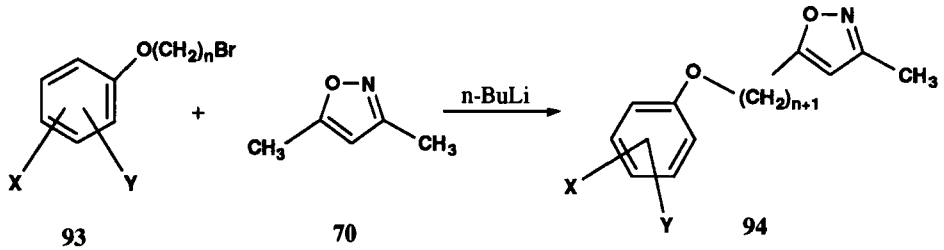
85 **86**

However, the reaction of **85** in the absence of an external electrophile produced a mixture of diaryl dihydropyridazine **91** and diaryl pyridazine **92**. The authors envisioned the rearrangement starting with the expected product of lateral metalation, lithio benzisoxazole **87**. Ring opening to the azirine **88**, followed by nucleophilic addition of **87** produces dimer **89**. Intramolecular phenoxide displacement of **89** forms the fused aziridine **90**, which ring opens to the diaryl dihydro pyridazine **91**. This result refutes an earlier claim[33] that metalation of 1,2-benzisoxazoles **85** gives rise to dimerization without rearrangement.



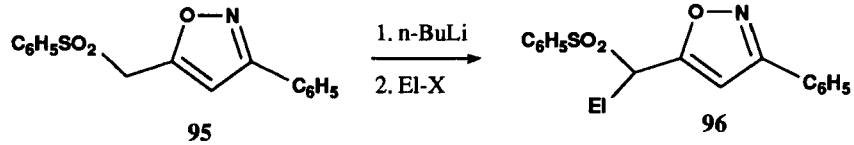
1. Alkyl Halides

Diana and co-workers have used the lateral metalation method in their preparation of antiviral isoxazoles **94**.[34]



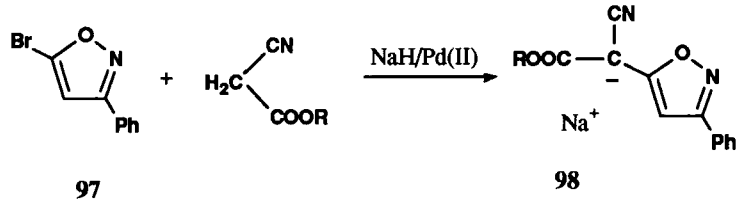
93 70 94

Sulfonylmethyl isoxazoles **95** are metalated and produce good yields of **96** upon quenching with alkyl halides.[30] The sulfonyl group could be selectively removed by reduction with sodium mercury amalgam without disturbing the isoxazole ring.

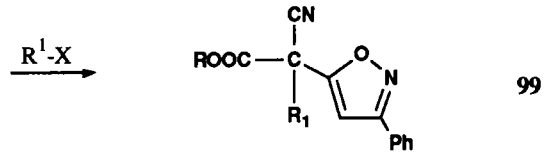


95 96

Palladium catalyzed reaction of 4-bromo isoxazole **97** with stabilized malononitrile anions gave the intermediate **98** which could be alkylated directly to give **99**.[36]

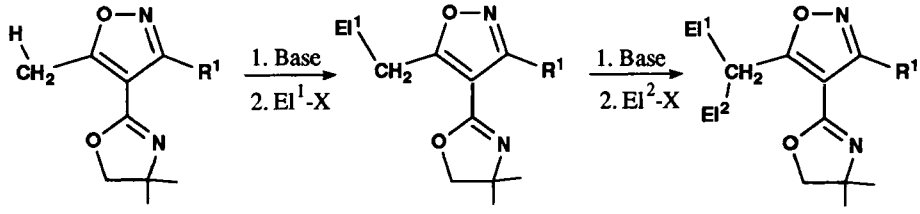


97 98



99

The metalation and electrophilic quenching of isoxazoles functionalized in the C-4 position has been the subject of study by our own group.[37-40] The reaction of isoxazolyl oxazolines **100** to produce alkylated products **101** is summarized in Table 3.



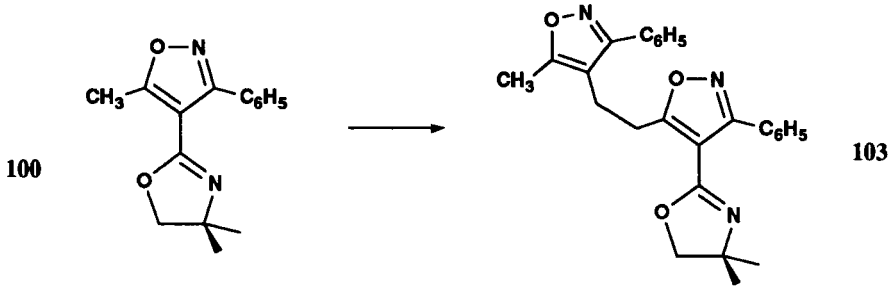
100 101 102

Deprotonation of isoxazolyl oxazoline **100** was effected with either Lithium diisopropyl amide (-5°, 30 min, Entry 1) or n-butyl lithium (-78°, 2 hrs, Entry 2) , the latter method was usually more effective for the C-3 phenyl isoxazoles (compare Entries 5 and 6). Primary Iodides (Entries 1,2 and 6) and bromides (Entries 3,4,7,8 and 9) were suitable electrophiles. An aliphatic primary bromide was displaced selectively in the presence of primary chloride (Entry 7). Aryl halides (Cl, Br) were incorporated without reduction (Entries 8 and 9).

TABLE 3. Lateral Metalation of **100** to **101**[37,38]

Entry	R^1	Base	El-X	Yield (%)
1	CH_3	LDA	CH_3-I	92
2	CH_3	n-BuLi	CH_3-I	78-86
3.	CH_3	LDA	n-octyl-Br	82
4.	CH_3	n-BuLi	$C_6H_5CH_2$-Br	91
5.	C_6H_5	LDA	CH_3-I	36
6	C_6H_5	n-BuLi	CH_3-I	86-92
7	C_6H_5	n-BuLi	$Cl(CH_2)_3$-Br	61
8	C_6H_5	n-BuLi	o-$BrC_6H_4CH_2$-Br	98
9	C_6H_5	n-BuLi	2,6-$Cl_2C_6H_3CH_2$-Cl	89

Isoxazolylmethyl chlorides also could be used as electrophiles without electron transfer reductive ring opening to produce diisoxazole **103**.



Subsequent deprotonation and quenching produced dialkylated product cleanly in synthetically useful yields (Table 4). Using this approach the highly branched triisoxazole **104** was prepared from **103** in 89% yield.

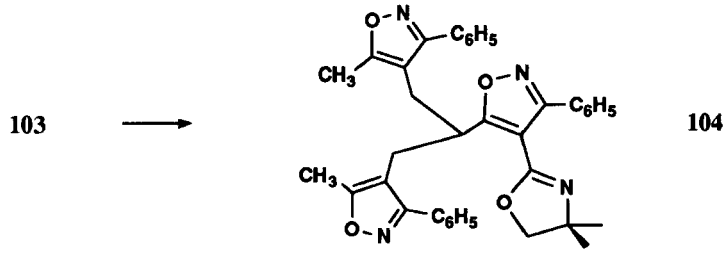
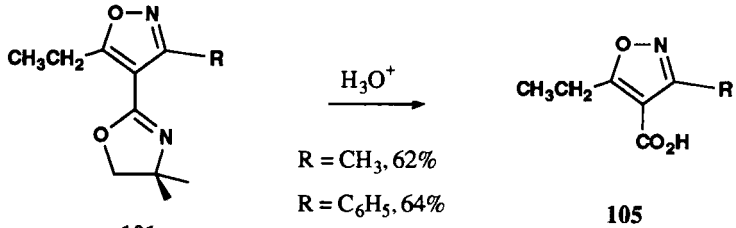


TABLE 4. Subsequent Metalation of **101** to Produce Dialkylated **102**

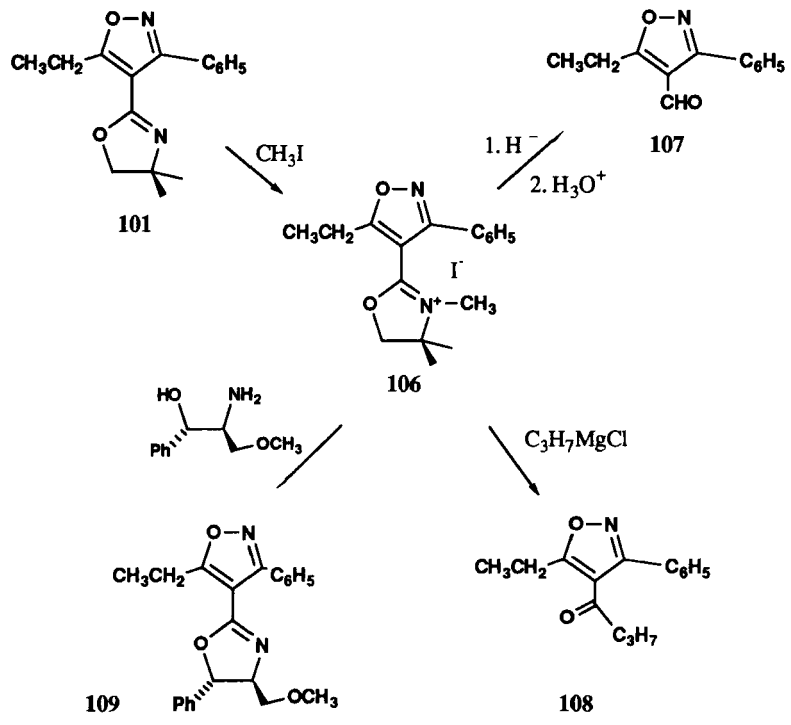
Entry	R	El[1]	El[2]	Yield (%)
1	CH_3	CH_3	CH_3	73
2	CH_3	$CH_2C_6H_5$	CH_3	70
3	C_6H_5	CH_3	CH_3	93
4	C_6H_5	$CH_2C_6H_5$	CH_3	74

The oxazolines **101** could be hydrolyzed in the presence of the isoxazole to produce the carboxylic acids **105**.



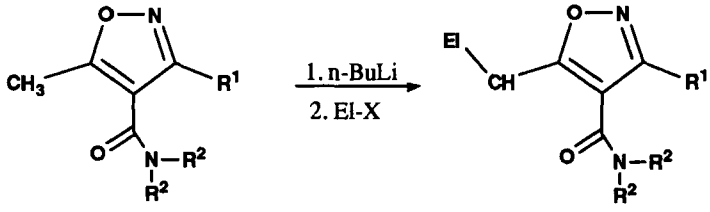
101 **105**

The oxazoline nitrogen of **101** could also be selectively quaternized with iodomethane and the resulting oxazolidium salt **106** served as a useful precursor for nucleophilic addition of hydride which after hydrolysis provided the aldehyde **107**, Grignard reagents produced isoxazolyl ketone **108** and amino alcohols produced the chiral isoxazolyl oxazoline **109**.



101 **107** **106** **109** **108**

A critical comparison of the use of isoxazole oxazolines **100** to isoxazole carboxamides **110** and isoxazole carboxylate dianions **112** was reported.[39] A series of isoxazoles carboxamides **110** were prepared and evaluated (Table 5).



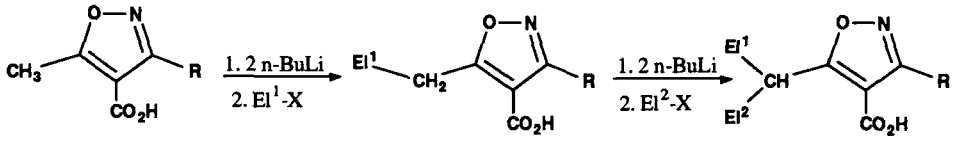
110 **111**

TABLE 5. Lateral Metalation of Isoxazole Carboxamides **110**[39]

Entry	R^1	R^2	Temp (°C)	El-X	Yield (%)
1	CH_3	i-C_3H_7	-78	CH_3-I	63-65
2	C_6H_5	i-C_3H_7	-40	CH_3-I	70
3.	C_6H_5	$(CH_2)_4$-	-40	CH_3-I	66
4.	C_6H_5	$(CH_2)_2O(CH_2)_2$-	-40	CH_3-I	72
5.	C_6H_5	$CH_2C_6H_5$	-78	CH_3-I	62

Higher temperature (i.e., -40°) was required for the deprotonation of most C-3 phenyl carboxamides (Entries 2,3 and 4). The N,N-dibenzyl carboxamide (Entry 5) could be deprotonated under the usual conditions (-78°).

Dianions of isoxazole carboxylic acids **112** are the most direct entry into alkyl substituted products **113** and **114** (Table 6)[33], since the extra steps for protection and deprotection of the C-4 functional group are not required.



112 **113** **114**

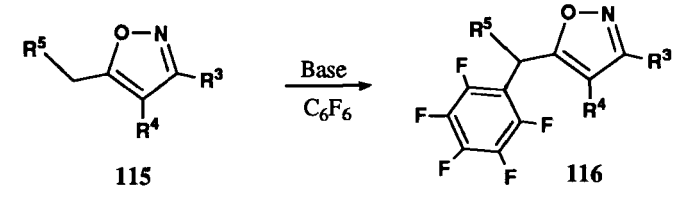
TABLE 6. Lateral Metalation *via* Carboxylate Dianion of **112**[38]

Entry	R	El^1-X	El^2-X	Yield (%)
1	CH_3	CH_3-I	H	91
2	CH_3	$C_6H_5CH_2$-Br	H	88
3	CH_3	n-C_8H_{17}-Br	H	69
4	C_6H_5	CH_3-I	H	81
5	CH_3	CH_3-I	CH_3-I	92
6	C_6H_5	CH_3-I	CH_3-I	89

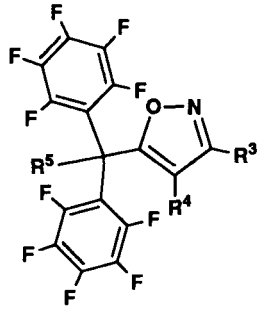
Although the dianion technique is most direct, the scope of the reaction appeared to be limited. The carboxamides **110** were intermediate in both efficiency of overall yield and number of steps required for protection-deprotection. The methods have also been evaluated for the facility of scale-up beyond the three to five millimoles typically used for exploratory reactions. The dianion technique required rapid stirring of the insoluble slurry during alkylation, it has been observed that on addition of the alkylating agent should the mixture precipitate as an oil, that subsequent di- and tri-alkylation by-products are observed. The isoxazolyl oxazoline system **100** appeared most amenable of the three methods to scale-up. For the C-3 methyl cases it was found that although larger scale alkylation could be effected cleanly in high yield, the optimum solubility of the lithio anion was only approximately 0.1 M in THF at -78°.[40] The C-3 phenyl lithio anion was found to much more soluble, approximately 0.4 M.[8b] Overall, the conclusion of our group is that the isoxazolyloxazoline system **100** represents the method of choice, which combines facility and versatility.

2. Hexafluorobenzene *via* Nucleophilic Aromatic Substitution

Lithioalkylisoxazoles derived from **115** were observed to react with hexafluorobenzene to produce perfluoroaryl isoxazoles **116-119**.[41] Yields of monoperfluoroarylation product **116** were best for C-4 electron withdrawing groups (Table 7, Entries c and d).



115 **116**



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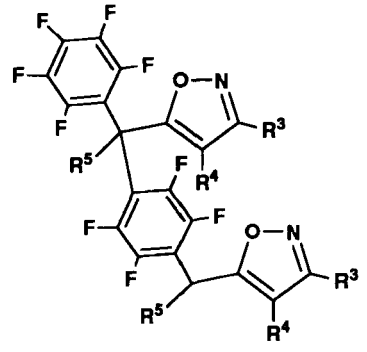

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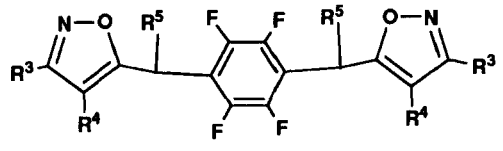
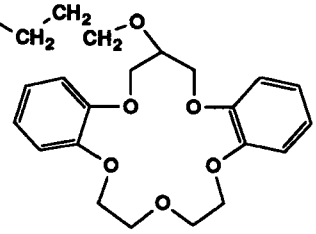


119

TABLE 7. Products of Nucleophilic Aromatic Substitution

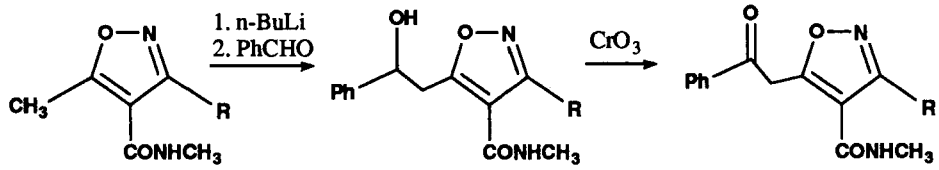
Entry	R^3	R^4	R^5	Products (% Yield)			
				116	**117**	**118**	**119**
a	CH_3	H	H	20	31	10	3
b	CH_3	H	COOH	18			
c	CH_3	$CON(iPr)_2$	H	42	7		
d	C_6H_5	$CON(iPr)_2$	H	39	24		
e	CH_3	[a]	H	20	4		
f	CH_3	$(CH_2)_3OCH_3$	H	9	7		

[a] R^4 =



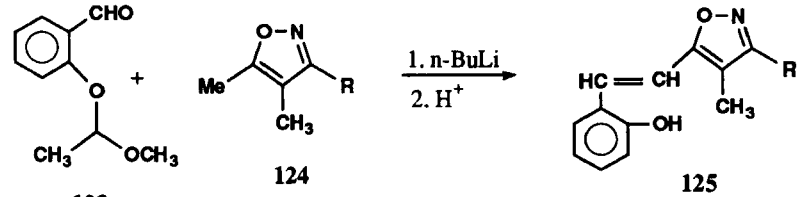
3. Carbonyl Derivatives, including RCOZ Reagents

Nadelson reported the reaction of aldehydes with dianions of isoxazole C-4 secondary carboxamides **120**.[42] Subsequent oxidation of the products **121** provided ß-keto-isoxazoles **122**, which were intermediates for ring opening/ ring closure synthesis.



120 **121** **122**

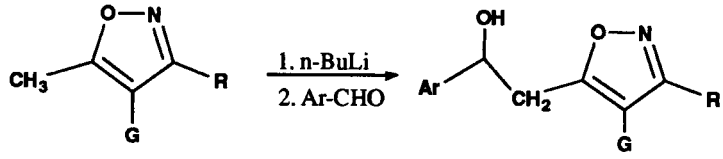
Schlecker's group[43] reported that deprotonation of 4,5-dimethyl-3-chloroisoxazole **124a** or 3,4,5-trimethylisoxazole **124b** followed by quenching with an aryl aldehyde **123** and deprotection provided the corresponding unsaturated isoxazolyl phenols **125**.



123 **124** **125**

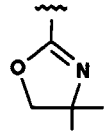
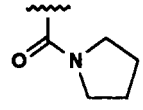
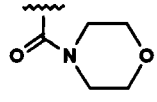
Our group has examined the reaction of substituted aromatic aldehydes with C-4 functionalized isoxazoles **126**, shown in Table 8. Several functional groups which produce addition with organolithium reagents survived in the presence of the vinylogous imidates, such as nitrile (Entries 5

and 10) and pyridyl (Entries 8 and 12) and gave moderate to good yields of adducts **127**. Functional groups which can react *via* halogen metal-exchange (i.e., chloro: Entry 3; and bromo: Entries 6, 9 and 14-16) or reduction (i.e., nitro, Entries 7 and 11) pathways could be incorporated.



126 **127**

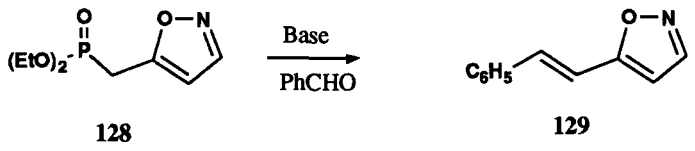
TABLE 8. Reaction of Lithio Vinylogous Imidates **126** with Aryl Aldehydes to give **127**[37-39]

Entry	R	Ar	G	%
1	CH_3	C_6H_5		97
2	C_6H_5	C_6H_5	"	81
3	C_6H_5	o-ClC_6H_4	"	50
4	C_6H_5	2,5-$(CH_3O)_2C_6H_3$	"	77
5	C_6H_5	p-NCC_6H_4	"	40
6	C_6H_5	p-BrC_6H_4	"	66
7	C_6H_5	o-$NO_2C_6H_4$	"	50
8	C_6H_5	3-Pyridyl	"	66
9	CH_3	p-BrC_6H_4	-CON(i-Pr)$_2$	43
10	CH_3	p-NCC_6H_4	"	48
11	CH_3	o-NO2C_6H_4	"	37
12	CH_3	3-Pyridyl	"	62
13	CH_3	2-Furanyl	"	70
14	C_6H_5	p-BrC_6H_4	"	40
15	C_6H_5	p-BrC_6H_4		48
16	C_6H_5	p-BrC_6H_4		60

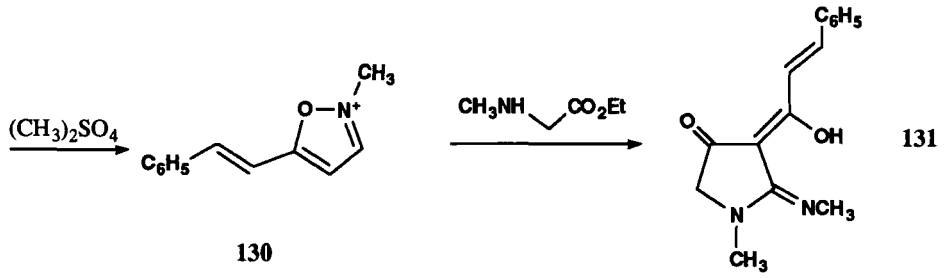
The isoxazolyl oxazolines gave superior yields to the isoxazolyl carboxamides (compare Entry 6 to Entries 9 and 14-16).

Isoxazole Wittig and Horner-Emmons reagents have been used to enhance the acidity of hydrogens α to the isoxazole ring.[5] A recent application of this tactic is found in DeShong's report[44]

of the isoxazole phosphonate **128**, which could be deprotonated and condensed with aldehydes to give the unsaturated isoxazole **129**. Intermediates of type **129** were N-alkylated and the resulting isoxazolium salt **130** reacted with α-amino esters to form amidines **131**.

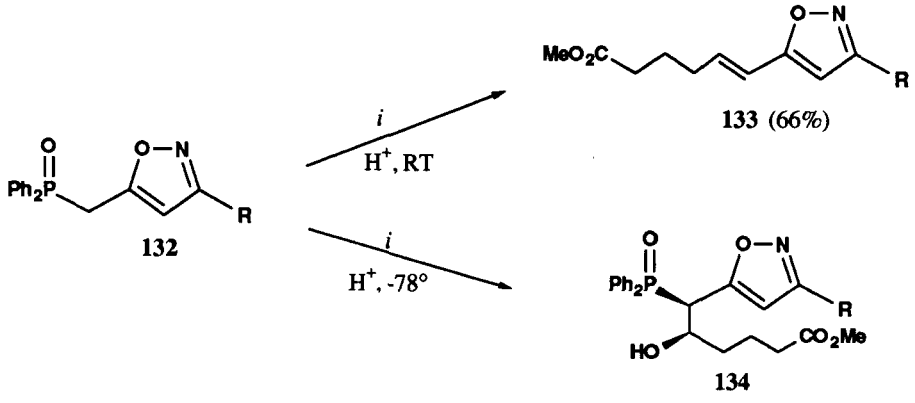


128 **129**



130 **131**

Olefination using phosphorus containing isoxazoles **132** has been used by Warren,[45] in his preparation of leukotriene analogues. In most cases, simple addition of the aldehyde to the lithio isoxazole derivative produces the E-alkenyl isoxazoles **133** in reasonable yield, after warming to room temperature. The ß-hydroxy phosphine oxides **134** could be isolated when the reaction was quenched at low temperature. Treatment of the erythro adduct **134** with sodium hydride gave rise to the E-alkene **133** and starting material **132**, emphasizing that the E-alkenes arise by reversible addition.



132 **133** (66%)

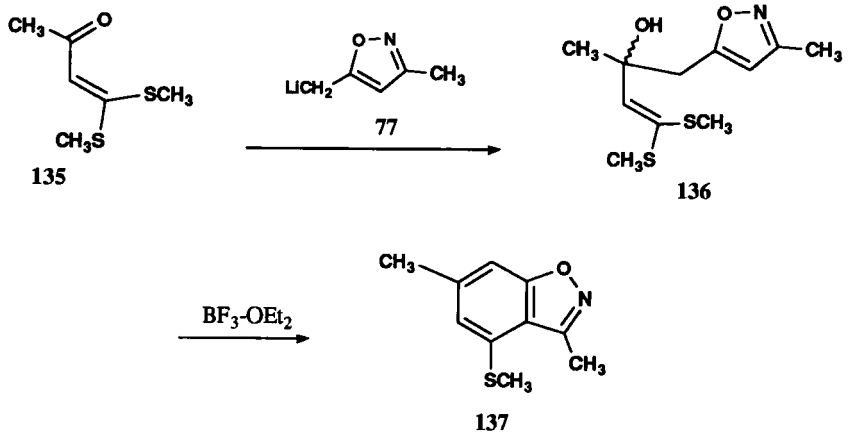
134

erythro, 26% + E-**133**, 24%

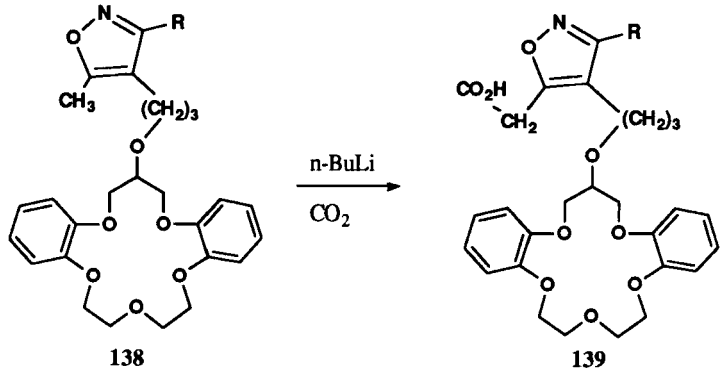
i) BuLi, $MeO_2C(CH_2)_3CHO$

R = $-(CH_2)_{10}CH_3$

Unsaturated ketones usually react with lithioalkyl isoxazoles to give predominant 1,2-addition in modest yield.[27] A recent example is the addition of **77** to **135**, which affords the 1,2-adduct **136**. Cyclization to annulated **137** with boron trifluoride-etherate proceeds in very good to excellent overall yields.[46]

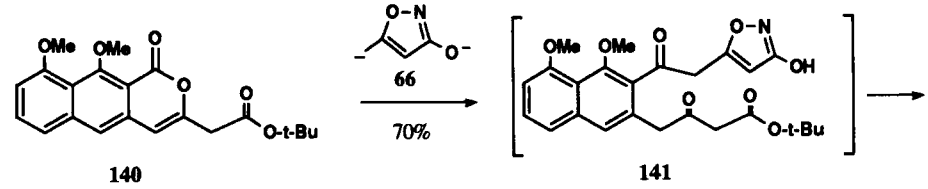


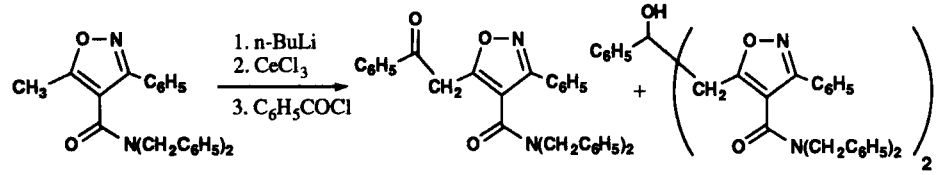
Metalation in the presence of a C-4 crown ether moiety **138** and quenching with carbon dioxide produced the lariat crown ether derivative **139**.[47] This lariat crown ether showed high efficiency in the liquid-liquid extraction of lanthanide and actinide elements into organic solvents.



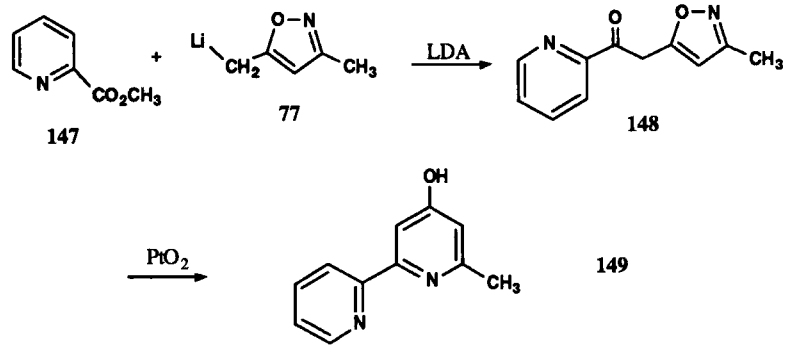
In their biomimetic route to the polyketide pretetramide **143**, Harris and co-workers[48] used their dilithio salt of 3-hydroxy-5-methyl isoxazole **66** as a synthetic equivalent of the inaccessible N,2,4-trianion of acetamide. Acylation of the dianion using the enol-lactone **140** produced an adduct, **141**, which spontaneously cyclized to the anthracene isoxazole **142** in 70% yield. Direct conversion of the anthracene isoxazole **142** to pretetramide **143** was achieved in 74% yield. This synthesis of pretetramide **143** is biomimetic to the extent that the naphthalene was assembled by aldol and Claisen cyclizations of carbonyl compounds and the rings are formed in the same sequence as in the biosynthesis.

Direct preparation of functionalized ß-ketoisoxazoles **145** can be accomplished using lithioalkyl isoxazoles of **144**. The yield of ketone **145** was higher - and the production of tertiary alcohol **146** lower- when the reaction was performed in the presence of cerium trichloride.[49]



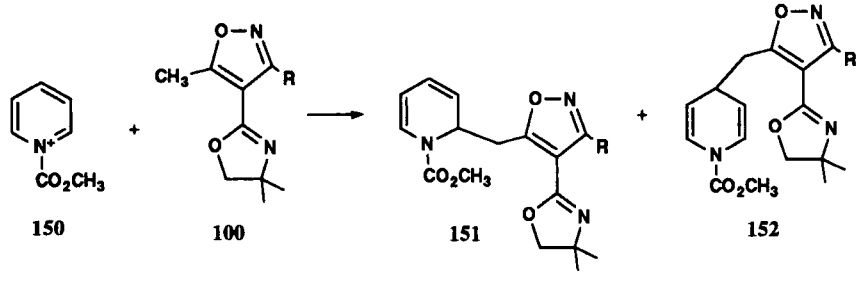


Selective addition of **77** to the ester function of **147** to give ketone **148** was a key step in the preparation of caerulomycin intermediate **149**.[50]



4. Imines and Related Systems

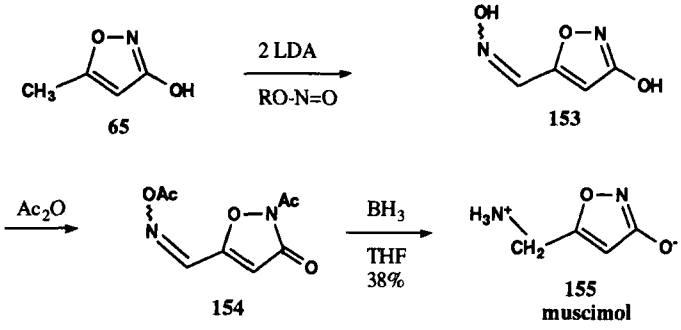
Addition of lithiomethylisoxazole to imines and nitriles has been reported.[27] Usually pyridines are relatively inert to addition, however, N-acyl-pyridinium salts **150** react to give 1,2- and 1,4-addition products, **151** and **152**, respectively.[38]



5. Nitrogen

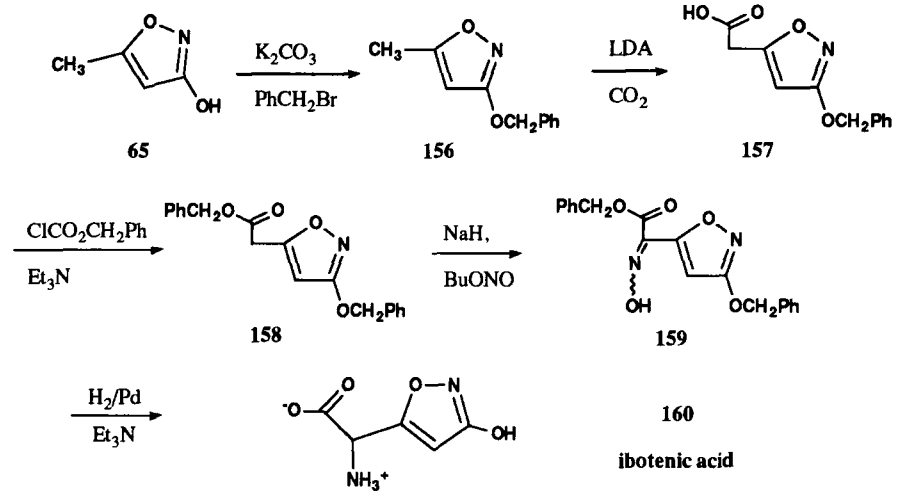
A useful method for the introduction of electrophilic nitrogen is the use of alkyl nitrites,[27] followed by selective reduction. This two step process has been applied by Harris in his synthesis of muscimol **155** and by Madsen in the preparation of ibotenic acid **160**.

Harris[26] utilized his dianion methodology to prepare oxime **153** from **65**. They found that selective reduction to muscimol **155** was best effected from the acetylated **154** with borane - THF.



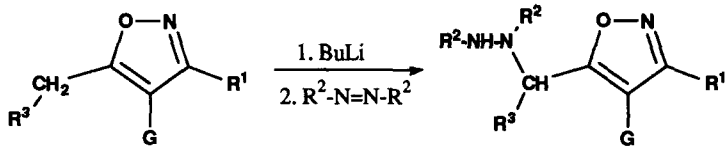
65 153 154 155 muscimol

Ibotenic acid **160** was prepared using a route which used two lateral metalation steps.[51] Compound **65**, after protection as the benzyl ether **156**, was deprotonated and treated with carbon dioxide to afford acid **157**. The acid was protected as the benzyl ester **158** and again deprotonated at the now active methylene and reaction with *n*-butyl nitrite afforded the oxime **159**. The reduction step is noteworthy in that it established that benzyl ethers, benzyl esters and oximes can be selectively hydrogenated in the presence of the isoxazole ring of **160**.



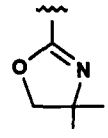
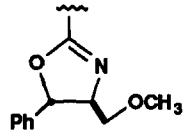
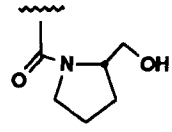
65 156 157 158 159 160 ibotenic acid

Reaction of lithioalkylisoxazoles of **161** with diethyl azodicarboxylate (DEAD) provided direct entry into carbon nitrogen bond formation and produced the hydrazinoalkyl isoxazole derivatives **162** in excellent yields (Table 9).[52]

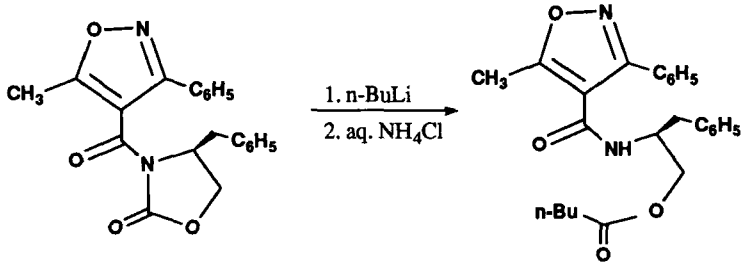


161 162

TABLE 9. Direct Incorporation of Hydrazino Groups on **161** to **162**[52]

Entry	R^1	R^2	R^3	G	%
1	CH_3	CO_2Et	H		75
2	CH_5	CO_2Et	H	"	80
3	CH_5	CO_2Et	H		95
4	CH_3	CO_2Et	H	"	74
5	CH_3	CO_2Et	H	$-CON(i\text{-}Pr)_2$	96
6	CH_3	CO_2-t-Bu	H	"	81
7	CH_3	CO_2Et	CH_3	"	84
8	CH_3	CO_2Et	H		78

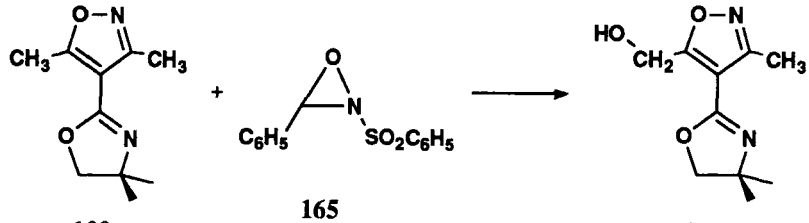
One limitation to this method was encountered with the isoxazole oxazolidone **163**, which was found to react at the C-4 group with butyl lithium to produce the isoxazole carboxamide **164**.



163 164

6. Electrophilic Oxygen

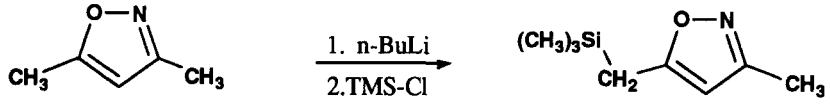
Our group has compared the use of MOOPh and N-sulfonyl oxaziridine **165** (a.k.a., Davis reagent[53]) as sources of electrophilic oxygen. Davis reagent **165** is the method of choice for the transformation of the lithio isoxazoles of **100** to alcohol **166**.[38]



100 165 166

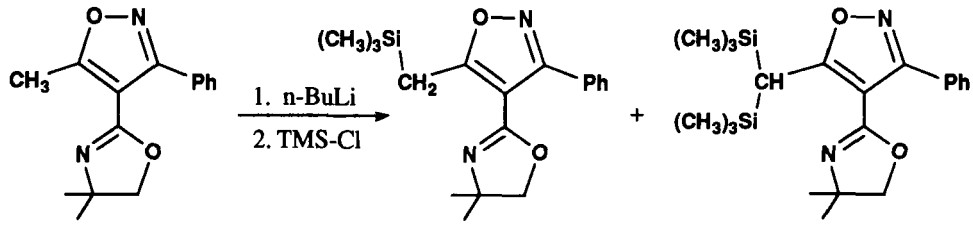
7. Silicon Electrophiles

Reaction of lithio derivative ofisoxazole **70** with chloro trimethyl silane gave the trimethylsilyl methyl isoxazole **167**.[54] As previously cited, however, when the group in the C-4 position was nitro, nucleophilic addition was observed which gave rise to 4,5-dihydroisoxazoles such as **34** (Section I.2).[18]



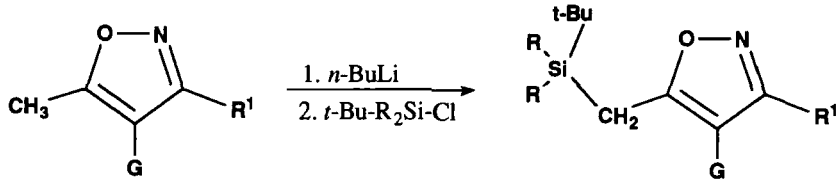
70 167

Reaction of lithioalkylisoxazole oxazoline of **100** with chlorotrimethylsilane gave rise to a mixture of mono- **168** and disilyl **169** products.[38]



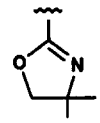
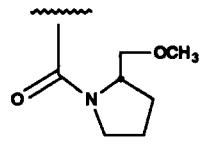
100 168 169

This problem could be circumvented by the use of sterically hindered silanes and clean monosilation to **171** can be obtained (Table 10).[55]



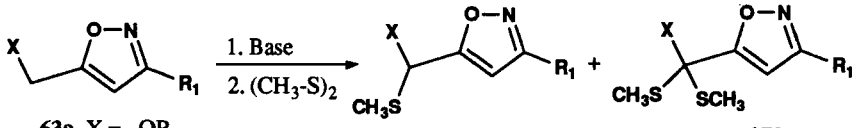
170 171

TABLE 10. Use of Hindered Silanes as Electrophile[55]

Entry	R1	R^2	G	%
1	CH_3	C_6H_5		78
2	C_6H_5	CH_3	"	34
3	CH_3	C_6H_5	$-CON(CH_2C_6H_5)_2$	63
4	CH_3	C_6H_5	$-CON(i\text{-}C_3H_7)_2$	41
5	CH_3	CH_3		32

8. Sulfur Electrophiles

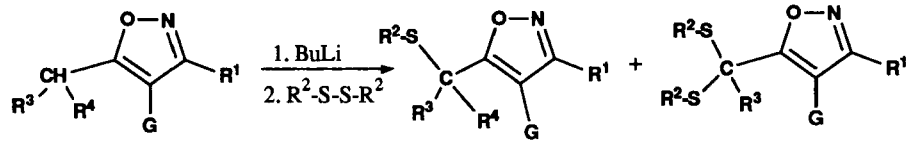
Micetich reported[25] that dimethyldisulfide could be effectively used as an electrophile and that sulfides **63**, thioacetals **172** and trithioorthoesters **173** could be readily produced.



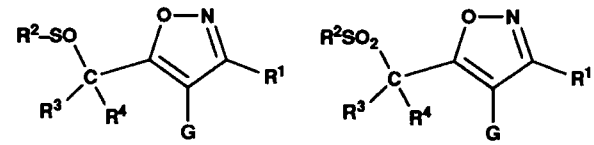
63a, X = –OR
63b, X = $-SCH_3$

172 **173**

For the C-4 functionalized analogues **174** ,we have found that thioalkyl isoxazoles **175** were readily prepared in moderate yield by metalation and quenching with disulfides (Table 11).[56]



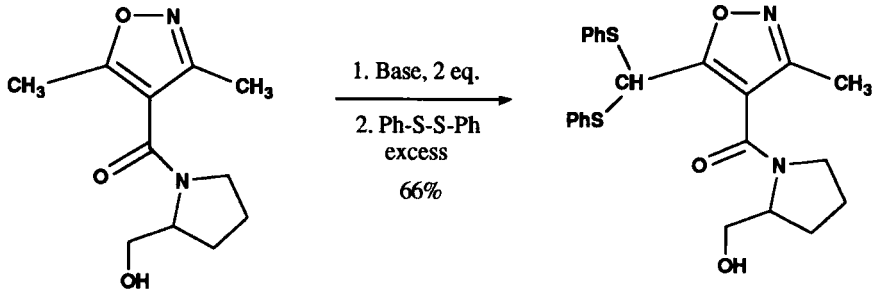
174 **175** **176**



177 **178**

The thio group so introduced should increase the acidity of the remaining protons on the lateral position. Consistent with this expectation, the monothioalkyl products **175** were accompanied

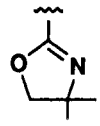
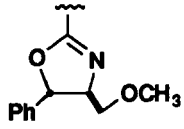
in several cases by minor amounts by dithioacetals **176**. Oxidation of the thioalkyl isoxazole oxazoline **175** proceeded selectively at sulfur in the presence of both isoxazole and oxazoline nitrogens to produce the sulfoxide **177**, n=1 or sulfone **178**, n=2, respectively, dependent upon stoichiometry.



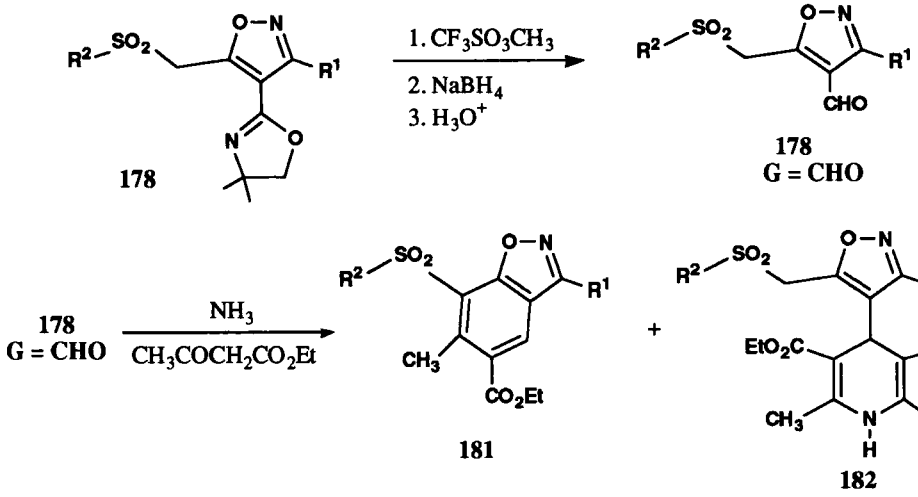
179 **180**

In the case of the dianion of isoxazolyl prolinol carboxamide **179**, the dithioacetal **180** was the major product isolated in 66% yield.

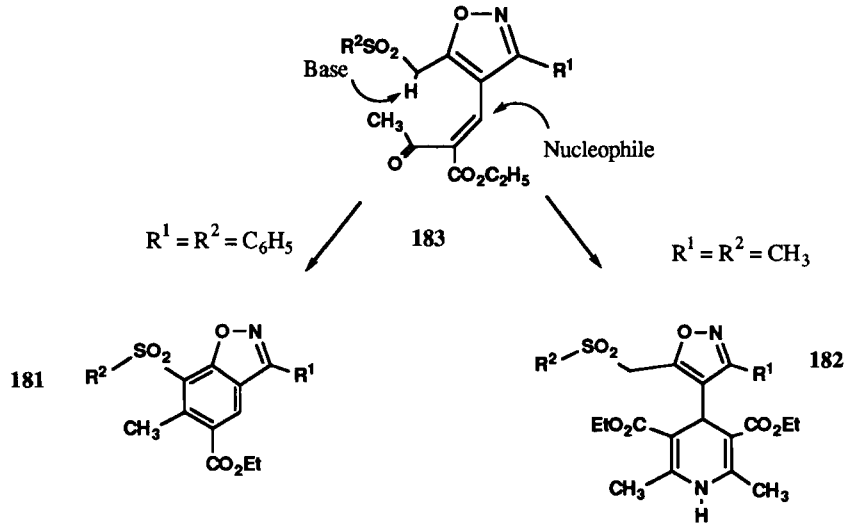
TABLE 11. Metalation and Electrophilic Quenching with Disulfides[56]

Entry	R^1	R^2	R^3	R^4	G	%
1	Ph	Ph	H	H		55-60
2	CH_3	2-Pyridyl	H	H	"	55
3	CH_3	Ph	H	H	"	50
4	Ph	CH_3	H	H	"	60-65
5	Ph	Ph	CH_3	CH_3	"	73
6	CH_3	Ph	H	H		65
7	Ph	Ph	H	H	"	55
8	CH_3	Ph	H	H	-CON(i-Pr)$_2$	65
9	CH_3	CH_3	CH_3	H	"	82

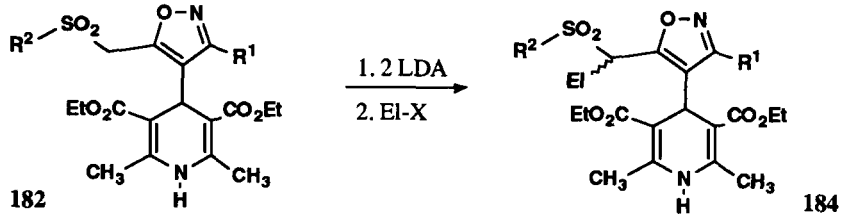
It was subsequently observed that sulfonylmethyl isoxazole oxazoline, **178**, could be deprotected to the corresponding aldehyde **178** (G =CHO) and that this ambident compound reacted with ethylacetoacetate in the presence of ammonia to produce the benzisoxazole **181** and 4-isoxazolyl-1,4-dihydropyridine, **182**.



When $R^1 = R^2 = Ph$, the benzisoxazole **181** was found to be the major product (7:1 ratio), whereas in contrast, when $R^1 = R^2 = Me$ the 4-isoxazoly-1,4-dihydropyridine **182** was the major product (60% yield). The authors rationale was based on the fate of the common intermediate α,β-unsaturated keto ester **183**, in which for the $R^1 = R^2 = Ph$ case Michael addition would be inhibited *via* steric factors and acidity of the C-5 methylene would be increased, hence benzisoxazole **181** formation predominates.



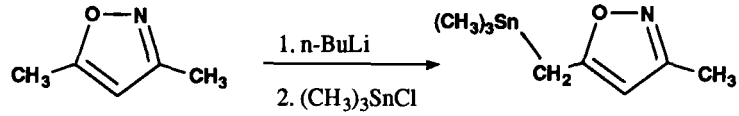
The 4-isoxazolyl-1,4-dihydropyridine **182** was found to readily form N,C-5-dianions. When the base was LDA, electrophilic quenching of the lithio dianion of **182** produced C-5 alkylation **184** in good to excellent yields. The potassium dianion of **182** was found to give N,C-5 *di* methylation upon quenching with iodomethane in good yield.



182 184

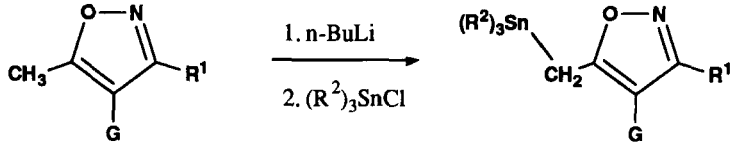
9. Tin.

Reaction of simple isoxazole **70** with chlorotrimethyl tin provided the stannyl isoxazole **185**.[54]



70 **185**

We have recently extended our study of more functionally complex systems to prepare the tin derivatives **186**.[57] We have not encountered any meaningful production of stannyl isoxazoles from isoxazolyloxazolines **100**. However, satisfactory results have been achieved with isoxazole carboxamides **110** (Table 12).



110 **186**

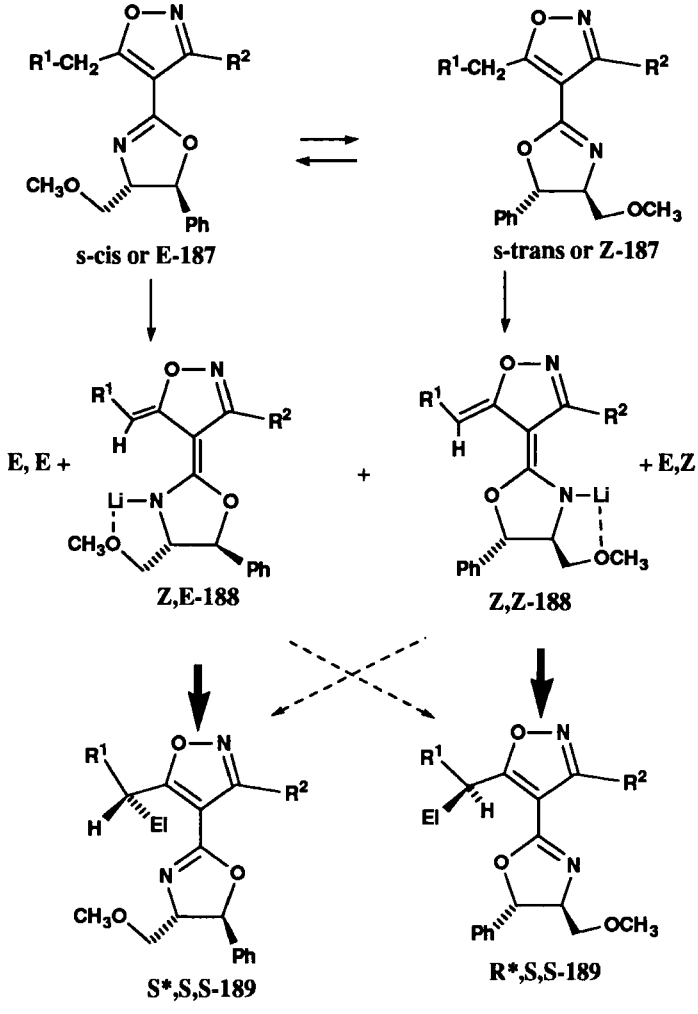
TABLE 12. Electrophilic Quenching with Tin Halides to Produce **186**

Entry	R^1	R^2	G	Yield(%)
1	CH_3	n-C_4H_9	CON(i-C_3H_7)$_2$	70
2	CH_3	CH_3	CON(i-C_3H_7)$_2$	68
3	CH_3	C_6H_5	CON(i-C_3H_7)$_2$	50
4	C_6H_5	n-C_4H_9	CON(i-$CH_2C_6H_5$)$_2$	75

IV. Diastereoselectivity

Chirality plays an important role in biological activity, yet among the numerous reports concerning the biology of the isoxazoles,[5,8] only a few address this critical issue.[59a,b] Given the importance of isoxazoles in many synthetic transformations and our interest in the lateral metalation of isoxazoles, we have initiated a study of the diastereoselectivity of the latter process.[59c] Since the pioneering observations of useful asymmetric induction by Meyers,[60] chiral enolate equivalents have developed into a standard tool for synthetic organic chemists. The success in asymmetric induction

has been usually attributed to the formation of a geometrically defined enolate equivalent, which incorporates some rigidity into the diastereotopic transition states, in turn resulting in meaningful differences in energy of activation between these transition states and thus translating into the high diastereomeric selectivity observed. Often the rigidity involves the metal counter ion, thus the concept has been termed chelate enforced intraannular chirality transfer.[61] Fewer examples exist of vinylogous systems. One notable example is the elegant vinylogous urethane work of Schlessinger,[62] which consistent with the concept referenced above, fortuitously adopts a single geometric isomer. The major complicating factor encountered in the present study arises from the fact that a conformationally mobile ring juncture resides between the chiral auxiliary group and the site of lateral metalation and electrophilic quenching. The problem is illustrated in the scheme below.

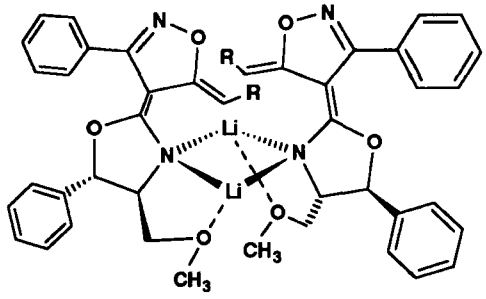


Rotation about the ring juncture between isoxazole and oxazoline moieties gives rise to an infinity of conformations, with the extremes being represented by the E-187 and Z-187 ring juncture

conformations illustrated. Upon metalation both Z and E geometric isomers are possible for the lithio-vinylogous imidate **188**, but the E conformations would appear to be excessively hindered and are not shown. In the electrophilic quenching step, available precedent would lead to the expectation that the Z,E-**188** would lead to S,S,S-**189** as the major product and that Z,Z-**188** would give rise to R,S,S-**189**.

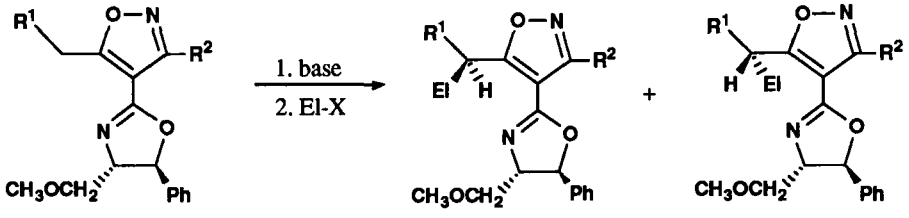
In the event, excellent chemical yields of isoxazolyloxazoline **189** are obtained upon metalation and electrophilic quenching with a variety of electrophiles. While, the diastereoselectivities obtained to date have been modest, the diastereomers are usually separable by HPLC, providing ready entry to chiral isoxazoles. We have attempted variation of temperature, base, order of addition and counterion (Table 13).[58]

Butyllithium as base produced d.e.'s comparable to those originally reported by Meyers for the simple enolate equivalent (on the order of 46-48% d.e., Table 13, Entries 1 and 11), however, no significant improvement was observed for either LDA (Entry 14) or LiHMDS (Entries 3 and 15). No improvement was noted for NaHMDS (Entry 4), Cp_2ZrCl_2 (Entry 12) and the d.e. was actually lower for KHMDS (Entry 5). Similarly, lowering the temperature during electrophilic quenching gave no corresponding rise in d.e. (Entry 13). These observations suggest the possibility that the isoxazole moiety is too large sterically to aggregate to form the dimeric lithioazaenolate **190** which appears to contribute to higher diastereoselectivity.[63]



190

Another possibility for the modest ratios observed is the conformation at the ring juncture. Molecular mechanics calculations suggest that there is not a large intrinsic difference in energy between E and Z conformation about the single bond connecting the heterocyclic rings in **187**.



187 R*,S,S-**189** S*,S,S,-**189**

a) $R^1 = CH_3, R^2 = Ph$ b) $R^1 = CH_2Ph, R^2 = Ph$ c) $R^1 = R^2 = CH_3$
d) $R^1 = CH_2Ph, R^2 = CH_3$ e) $R^1 = SPh, R^2 = CH_3$

TABLE 13. Diastereoselectivity in Lateral Metalation of Isoxazoles

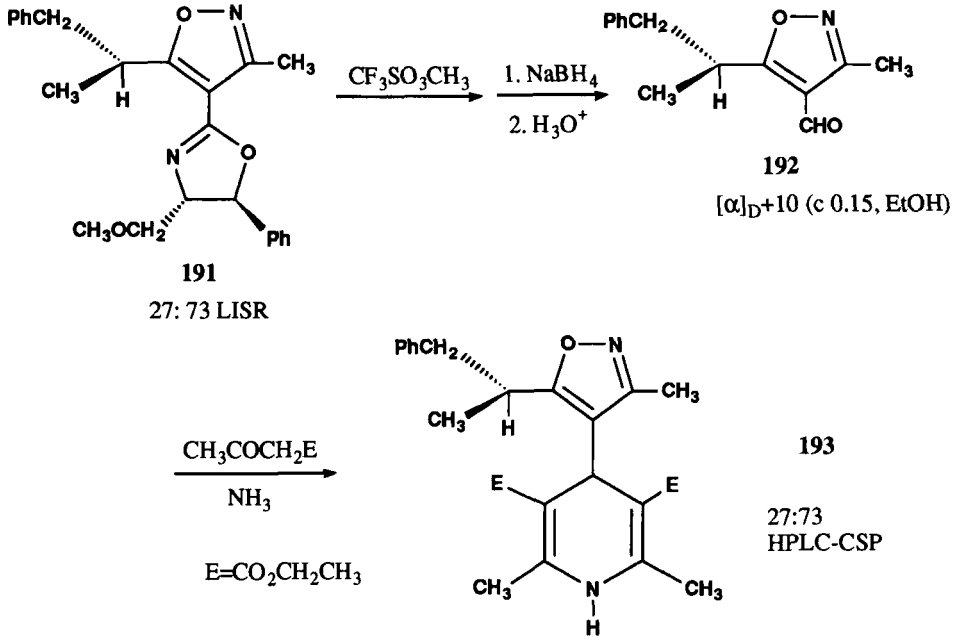
Entry	R^1	R^2	El-X	Base	D.E.	α
1	CH_3	C_6H_5	$C_6H_5CH_2Br$	n-BuLi	33:67	1.21
2	$C_6H_5CH_2$	C_6H_5	CH_3I	n-BuLi	62:37	*ibid.*
3	CH_3	C_6H_5	$C_6H_5CH_2Br$	LiHMDS	25:75	*ibid.*
4	.CH_3	C_6H_5	$C_6H_5CH_2Br$	NaHMDS	23:77	*ibid.*
5	CH_3	C_6H_5	$C_6H_5CH_2Br$	KHMDS	34:66	*ibid.*
6	CH_3	C_6H_5	$CH_3(CH_2)_3Br$	n-BuLi	39:61	1.126
7	CH_3	C_6H_5	CH_3OCH_2Cl	n-BuLi	37:63	1.21
8	CH_3	C_6H_5	C_6H_5COCl	n-BuLi	53:47	*n.d.*
9	CH_3	C_6H_5	(OH)[a]	n-BuLi	40:60	1.146
10	CH_3	C_6H_5	(E-NH-N-E)[b]	n-BuLi	46:54	*n.d.*
11	CH_3	CH_3	$C_6H_5CH_2Br$	n-BuLi	27:73	*n.s.*
12	CH_3	CH_3	$C_6H_5CH_2Br$	n-BuLi Cp_2ZrCl_2	29:71	*n.s.*
13	CH_3	CH_3	$C_6H_5CH_2Br$	n-BuLi -100°	27:73	*n.s.*
14	CH_3	CH_3	$C_6H_5CH_2Br$	LDA	27:73	*n.s.*
15	CH_3	CH_3	$C_6H_5CH_2Br$	LiHMDS	27:73	*n.s.*
16	$C_6H_5CH_2$	CH_3	CH_3I	n-BuLi	63:37	*n.s.*
17	CH_3	CH_3	$CH_3(CH_2)_2I$	n-BuLi	34:66	*n.d.*
18	CH_3	CH_3	$CH_3(CH_2)_3I$	n-BuLi	23:77	1.12
19	CH_3	CH_3	CH_3OCH_2Cl	n-BuLi	25:75	1.07
20	CH_3	CH_3	C_6H_5COCl	n-BuLi	53:47	*n.d.*
21	CH_3	CH_3	(OH)[a]	n-BuLi	40:60	*n.d.*
22.	CH_3	CH_3	(E-NH-N-E)[b]	n-BuLi	30:70	*n.d.*
23	CH_3	CH_3	$C_6H_5SSC_6H_5$	n-BuLi	47:53	*n.d.*
24.	C_6H_5S	CH_3	CH_3I	n-BuLi	59:41	*n.d.*
25.	C_6H_5S	CH_3	CH_3I	LDA	52:48	*n.d.*
26	C_6H_5S	CH_3	CH_3I	n-BuLi $CeCl_3$	66:34	*n.d.*
27	CH_3	CH_3	2-PyridylS-S-2-Pyridyl	n-BuLi	44:56	*n.d.*

a) Electrophile was N-phenylsulfonyloxaziridine, as described in Section III.6. b) Electrophile was diethylazodicarboxylate, as described in Section III.5. (ref. 52) *n.d.* separable, however, a value not determined *n.s.* not separable, baseline separation could not be effected under the conditions studied, see text.

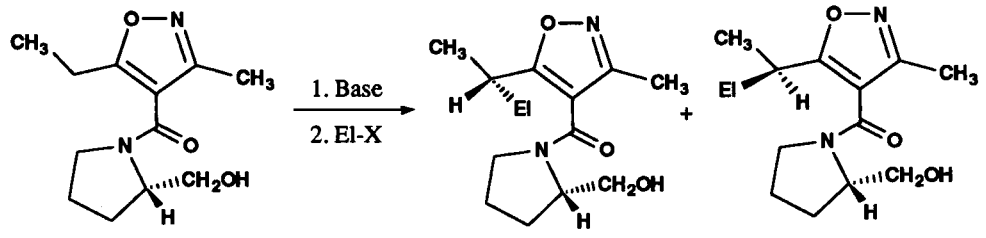
2D nOesy spectroscopy provides evidence for an average Z-conformation of **187** at room temperature, however, at -78° both conformations are in evidence. A Z-conformer of **187** would place the prochiral

C-5 position of the isoxazole 5.2 Å from the C-4 position of the oxazoline (according to the molecular mechanics calculation coordinates), further than the distance between the latter chiral center in more successful applications of this auxiliary. In most cases, the diastereomers are separable by preparative HPLC and enantiomerically pure isoxazolyloxazolines **189** can be obtained. The one exception, Table 13, Entry 11, could be readily transformed to the isoxazolyl-dihydropyridine, *vide infra*, which could be resolved by HPLC using a chiral stationary phase (HPLC-CSP).

Deprotection of the oxazoline **191** in the presence of the isoxazole can be effected by quaternization with methyl trifluoromethyl sulfonate, followed by reduction with sodium tetrahydridoborate. The aminal is hydrolyzed to the isoxazole aldehyde **192** in excellent yield. The aldehyde was then transformed *via* Hantzsch pyridine synthesis to the crystalline isoxazolyl-dihydropyridine, **193**. The major isoxazolyl-oxazoline diastereomer **191**(27:73 ration by LIS) correlated with the slow moving (-)- isoxazolyl-dihydropyridine **193**, 27:73 by HPLC-CSP.



The absolute configuration the (-)-isoxazolyldihydropyridine **193** was assigned by chemical degradation. Optically pure (-)-isoxazolyl dihydropyridine **193**, obtained by chromatographic resolution, was subjected to ring opening and hydrolysis to (S)-(+)-2-methyl-3-phenyl-propionic acid. The structure of (-)-isoxazolyldihydropyridine **193** was confirmed by single crystal x-ray diffractometry.
Finally, we have briefly examined an alternate chiral auxiliary group, the carboxamide of (S)-prolinol **194** (Table 14).



S-194 S*,S-195 R*,S-195

TABLE 14. Diastereoselectivity Using Carboxamidol Dianions of (S)-**194**

Entry	El -X	Yield	D.E.	α
1	n-C_4H_9-Br	42	13:87	1.224
2	C_6H_5S-SC_6H_5	54	39:61	1.098
3	(E-NH-N-E)	85	38:62	1.157

While the isoxazole-C-4-carboxamide of S-prolinol **194** gives rise to slightly higher d.e. in the case of n-butyl-iodide (Compare Table 13, Entry 18, with Table 14, Entry 1) and diphenyldisulfide (Compare Table 13, Entry 23 to Table 14, Entry 2) the process is complicated by lower chemical yield. For diazodicarboxylate the d.e. is lower (compare Table 13, Entry 22 and Table 14, Entry 3) and the chemical yield comparable for the two methods.

This expeditious route to enantiomerically pure isoxazoles should prove to be useful as a general tool for the study of the enantioselectivity of biological action of the numerous isoxazole containing agricultural and medicinal agents already reported and for those that await discovery.

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