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THE SYNTHETIC UTILITY OF OXAZOLINES IN AROMATIC SUBSTITUTION

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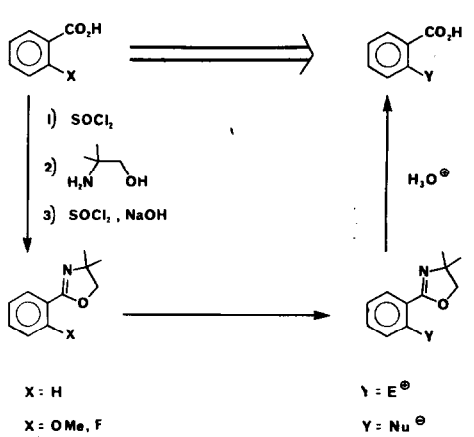
CONTENTS

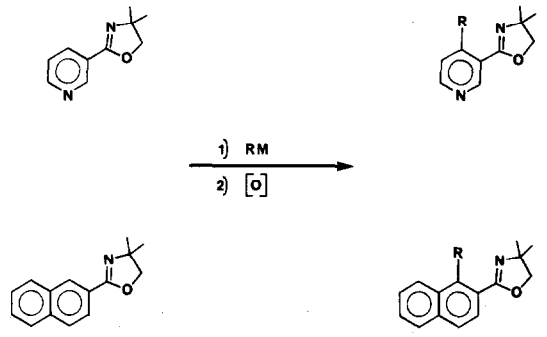
I. INTRODUCTION

Since they were reviewed in 1976,[1] the synthetic potential of 2-oxazolines has continued to provide efficient and novel routes to various organic molecules. This review will describe advances since that time.

In particular, the synthetic utility has been most notable for aromatic systems where the oxazoline is an efficient director for *o*-lithiation of the benzene nucleus. The *o*-lithiooxazoline can then be treated with electrophilic reagents and hydrolyzed to afford the *ortho*-substituted benzoic acids (Scheme 1). If metalation is repeated and another electrophile added, ready access to 2,6-disubstituted benzoic acids can be realized. In addition to its ability to direct *o*-lithiation, the oxazoline is a remarkably efficient director for nucleophilic aromatic substitution. When the oxazoline is derived from an *o*-methoxy or an *o*-fluoro benzoic acid, the methoxy or fluoro group can be displaced by a wide array of nucleophilic groups. The reaction is generally regiospecific and thus allows elaboration of the aromatic ring in a complimentary fashion (Scheme 1).



Scheme 1.

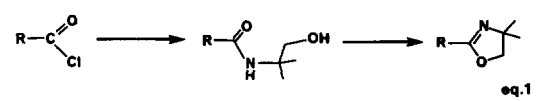


Scheme 2.

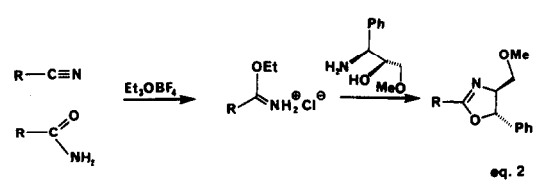
In other aromatic systems (pyridines, naphthalenes and quinolines) the aromatic nucleus is also subject to conjugate addition when treated with certain nucleophilic reagents to give, after aromatization, the *ortho*-substituted oxazoline (Scheme 2).

II. RECENT PREPARATION OF OXAZOLINES

Oxazolines are usually prepared by treatment of the acid chloride with the appropriate amino alcohol followed by cyclization of the amide with thionyl chloride (Eq. 1).[2] Alternatively, oxazolines can be prepared from the amide or nitrile *via* the imidate (Eq. 2).



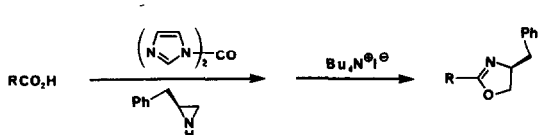
eq.1



eq. 2

The preparation of oxazolines from carboxyl derivatives may be less than desirable in the presence of other labile functionality. Treatment of carboxylic acids, in the presence of amino alcohols and triethylamine or DBU with Ph_3P–CCl_4 afforded good yields of the oxazolines in one step under mild conditions (Table 1).[3] This method of oxazoline synthesis can prove to be satisfactory when other methods may fail (entries 5 and 6, Table 1).

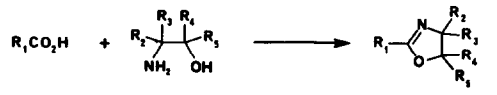
A mild one-pot method for oxazoline preparation from carboxylic acid was recently reported which proceeds through the acyl aziridine (Eq. 3).[4] It was suggested that enantiomeric mixtures of carboxylic acids might easily be resolved by preparation and separation of the diastereomeric oxazolines.

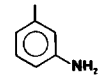


eq. 3

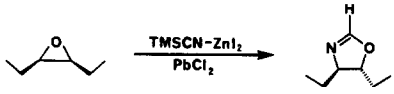
Treatment of epoxides with TMSCN–ZnI_2 followed by KF affords isonitrile alcohols as intermediates which are readily converted into oxazolines simply by treatment with a catalytic

Table 1. Preparations of oxazolines by Ph_3P–CCl_4

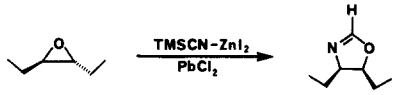


Entry	R_1	R_2	R_3	R_4	R_5	% Yield
1	Ph	H	H	H	H	72
2	Ph	Ph	H	H	H	64
3	Ph	H	H	Ph	H	
4	Ph	CH_2OH	CH_2OH	H	H	73
5		Me	Me	H	H	67
6		H	H	H	H	63
7		Me	Me	H	H	74
8	$PhCH_2$–	Me	Me	H	H	69
9	$PhCH_2$–	H	H	H	H	52

amount of $PdCl_2$.[5] This method is stereospecific as *cis*-3-hexene oxide gives only the *trans*-4,5-diethyloxazoline and the corresponding *trans*-epoxide gives only the *cis*-oxazoline (Eqs 4a and b).



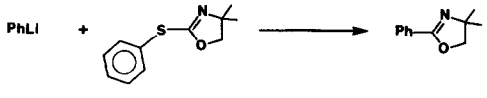
eq. 4a



eq. 4b

New methodology has been developed which now allows aromatic halides to be transformed into the oxazoline accompanied with a one carbon homologation. Treatment of Grignard reagents with 2-(methylthio)-4,4-dimethyl-2-oxazoline in the presence of palladium or nickel phosphine complexes gives good yields of the corresponding aromatic oxazolines[6] (Table 2). Application of this reaction to aliphatic Grignard reagents gave poor results.

A similar reaction was observed by Chenard using 2-(thiophenyl)-4,4-dimethyl-2-oxazoline and phenyllithium (Eq. 5).[7] In this case, no transition metal catalyst is required. Work from the authors' laboratory suggests that the displacement of the phenylthio group by phenyllithium is general and will work with other aryllithium reagents.[8]



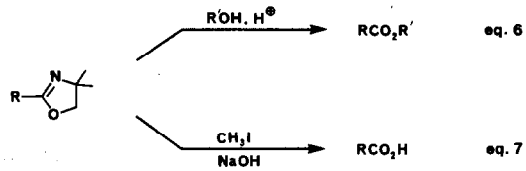
eq. 5

III. TRANSFORMATION OF OXAZOLINES INTO OTHER FUNCTIONAL GROUPS

Oxazolines, as masking groups for carboxylic acids,[9] are relatively inert toward a variety of synthetic manipulations. Attack at the C=N link by organometallic reagents is slow, likewise, it is resistant toward reduction by a variety of common reducing agents such as $NaBH_4$, $LiAlH_4$ or BH_3.

The oxazoline can be hydrolyzed to the carboxylic acid or ester in aqueous or alcoholic HCl[9] (Eq. 6). In cases where acidic hydrolysis is not desirable, the oxazoline can be removed by alkaline

hydrolysis of the oxazolinium salt[10] (Eq. 7).

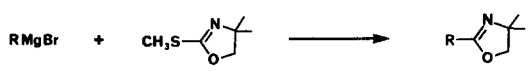


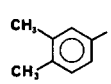
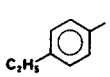
Methods for cleaving the oxazoline to the carboxylic acid under mild conditions other than the usual hydrolysis were explored by Weinreb.[11] When the oxazoline is treated with NaOCl under phase transfer conditions followed by NaOH–MeOH, the corresponding acid can be obtained in good yield (Scheme 3) as shown in Table 3.

Aromatic oxazolines can be converted directly into nitriles by treatment with $POCl_3$–pyridine.[12] The reaction is satisfactory except when the aromatic ring contains a 4-nitro group or if dehydration is competitive (Table 4).

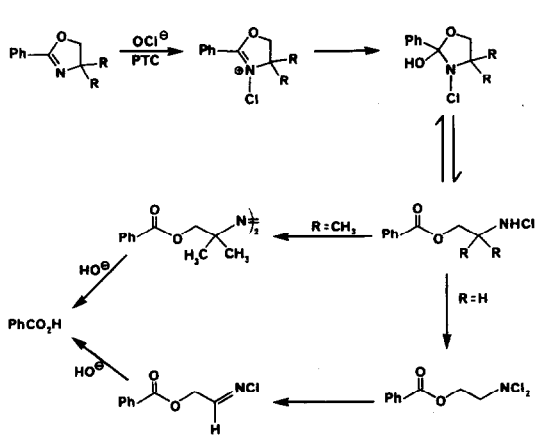
Oxazolines can be readily converted into the oxazoles by oxidation with NiO_2[13] (Table 5). The oxidation is slow, requiring several hours to several days at reflux in a hydrocarbon solvent, but gives synthetically useful yields of the 1,3-oxazole. This reaction was recently utilized by Weinreb in

Table 2. Conversion of aromatic Grignards to oxazolines



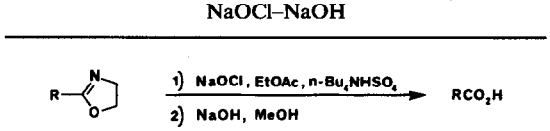
R	% Yield	$NiCl_2$ (dppp)	$PdCl_2$ (dppf)
Ph		77	84
p-Tolyl		65	94
p-Anisyl		46	73
		71	93
		72	90

* Reactions using the Ni catalyst were run in Et_2O–THF at 50–60°C. Reactions using the Pd catalyst were run in Et_2O at ambient temperature.



Scheme 3.

Table 3. Conversion of oxazolines to carboxylic acids: NaOCl–NaOH



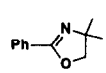
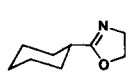
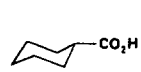
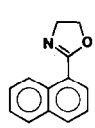
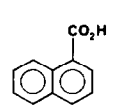
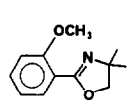
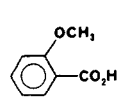
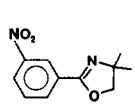
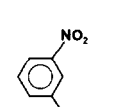
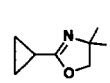
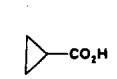
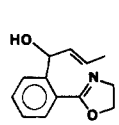
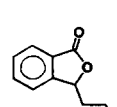
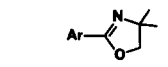
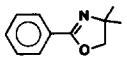
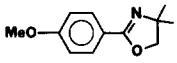
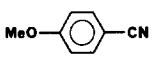
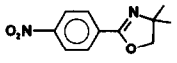
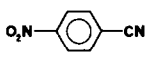
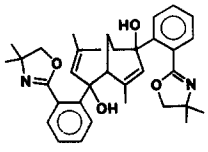
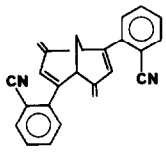
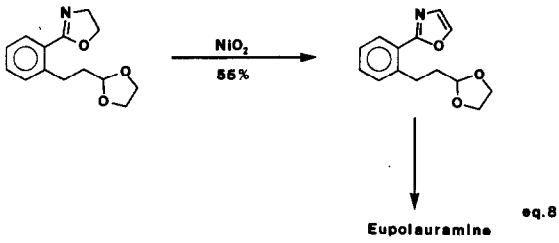
Oxazoline	Product	% Yield
	PhCO2H	89
	PhCO2H	92
		76
		79
		84
		93
		60
		80

Table 4. Conversion of oxazolines to nitriles



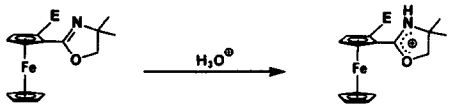
Oxazoline	Product	% Yield
		80
		63
		0
		66

an elegant Diels–Alder approach to Eupolauramine[14] (Eq. 8).



eq. 8

Attempted hydrolysis of 2-ferrocenyl-2-oxazolines under acidic conditions resulted either in no hydrolysis due to the stability of the ferrocenyl carbonium ion (Eq. 9), or decomposition through

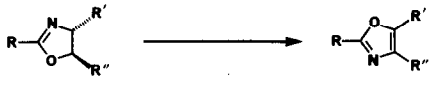


eq. 9

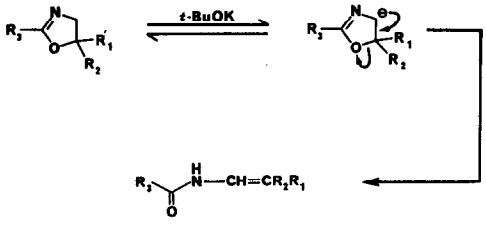
rupture of the organometallic system. Studies directed toward a basic hydrolysis led to the discovery of the rearrangement of the 2-oxazoline to N-vinylamides (Table 6). This proceeds via deprotonation at C-4 and subsequent isomerization to give the amide on workup (Scheme 4).[15]

Oxazolines can also be opened up to the corresponding β-phenethylamides under Friedel–Crafts

Table 5. NiO_2 oxidation of oxazolines to oxazoles

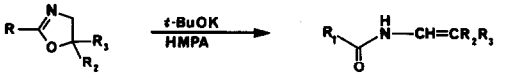


R	R′	R″	Solvent	% Yield
Me	H	CO_2Et	Hexane	50–53
n-Pr	H	CO_2Me	Benzene	58
Ph	H	CO_2Me	Cyclohexane	69
Me	Me	CO_2Et	Me-cyclohexane	22
$ClCH_2$	H	CO_2Et	Cyclohexane	19
Et	Ph	CH_2OCH_3	Me-cyclohexane	2
Et	H	CH_2OCH_3	Hexane	35
p-$NO_2C_6H_4$	H	H	Benzene	28



Scheme 4.

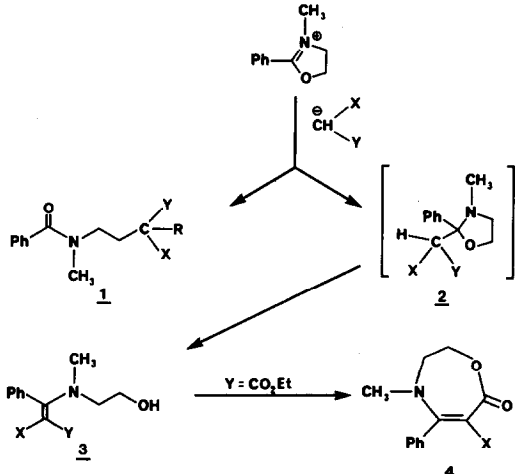
Table 6. Rearrangement of 2-oxazolines to N-vinylamides



R	R_2	R_3	Time	Temp (°C)	% Yield
Me	H	Me	16	80	Not isolated
Me	Me	Me	18	80	Not isolated
t-Bu	H	Me	18	80	25
t-Bu	Me	Me	18	80	30
Ph	H	Me	1.3	110	76
Ph	H	Ph	1.5	100	70
Ph	Me	Me	18	80	86
2-(NH_2)Ph	H	Me	17	80	67
p-Ph	H	Me	7	110	90
Ferrocenyl	H	Me	16	80	70
Ferrocenyl	Me	Me	4	80	83

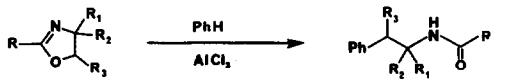
conditions (Table 7). Thus, treatment of a variety of oxazolines with $AlCl_3$ in benzene at reflux (16 hr) afforded good yields of these products, derived from electrophilic substitution at C-5 of the oxazoline.[16]

In addition to opening the oxazoline ring under Friedel–Crafts conditions, the oxazoline can be quaternized and treated with stabilized carbanions[17] to give the substituted alkylamides **1**, from attack at C-5 or products from attack at C-2 (Table 8). The choice of reaction pathways seems to depend partially upon the steric crowding in the transition state as only very encumbered nucleophiles result in alkylamide formation (Scheme 5). When attack occurs at C-2, the oxazoline intermediate **2**, opens up to form the enamine alcohol **3**. This is isolated as a final product except when intramolecular transesterification is possible to give the 1,4-oxazepine **4**.



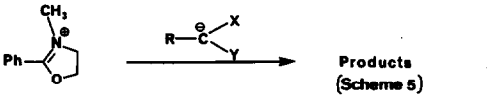
Scheme 5.

Table 7. Conversion of oxazolines to β-phenethylamides



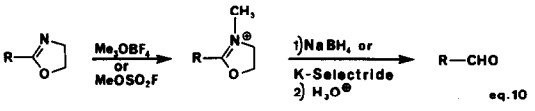
R	R_1	R_2	R_3	% Yield
Me	H	H	H	85
n-C_7H_5	H	H	H	90
$PhCH_2$	H	H	H	98
Ph	H	H	H	68
Ph	H	H	Me	98
$PhCH_2$	Me	Me	H	0

Table 8. Reaction of oxazolinium salts with stabilized carbanions

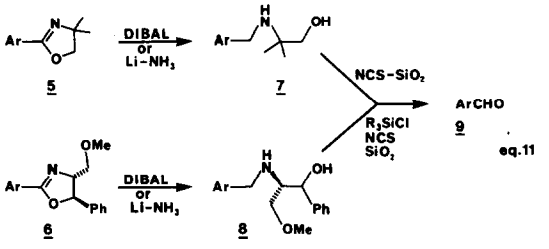


R	X	Y	1	Products (Scheme 5) 3	4
H	CN	CO_2Et			85
H	CN	CN		85	
Me	CN	CO_2Et	50		
Me	CN	CN	75		
H	SO_2Ph	SO_2Ph	85		
H	CO_2Et	CO_2Et	63		

When conversion of the oxazoline to the aldehyde is required, the most common method is usually by reduction of the oxazolinium salt with $NaBH_4$.[18] The oxazoline salts are generally obtained by treatment of the oxazoline with methyl iodide, neat or in nitromethane, and when this is not successful, $MeOSO_3F$ or Me_3OBF_4 can be advantageous.[19] The oxazolinium salt, when treated with $NaBH_4$, gives the aldehyde *via* the oxazolidine after hydrolysis. In some cases, $NaBH_4$ is reported to give over reduction to the amino alcohol and in these cases the use of K-selectride overcomes this problem[20] (Eq. 10).



A new method for the reduction of aromatic oxazolines to benzaldehydes and methyl compounds have recently been reported.[21] It was found that, in most instances, the oxazoline can be readily reduced to the corresponding amino alcohols with DIBAL from 0° to room temperature. While DIBAL is successful in the reduction of unusually hindered oxazolines (entry **5k**, Table 9), it was found that such hindered systems can be reduced in minutes with Li–NH_3 (entries **5k**, **5l**, Table 9). The amino alcohols obtained could be readily oxidized to the aldehyde by chlorination with NCS, followed by elimination on alumina and hydrolysis on silica gel. This sequence is essentially a one-pot procedure and can be completed in times ranging from a few minutes to *ca* 24 hr depending on the structure of the amino alcohol (Table 10). When applied to amino alcohols **8** derived from *trans*-(4*S*,5*S*)-aryl-4-(methoxymethyl)-5-phenyl-2-oxazolines **6**, a competitive Grob fragmentation was observed giving rise to a mixture of the desired aldehyde plus benzaldehyde. The Grob pathway was blocked when the amino alcohol was silylated with t-$BuMe_2SiCl$, chlorinated and dehydrohalogenated with KO_2. Oxalic acid hydrolysis was carried out giving only the desired aldehydes (Eq. 11).



It was also found that the amino alcohols could be hydrogenated using Pd–C to give the toluene derivatives (Table 11). In some cases where the debenzylation did not proceed, a catalytic transfer hydrogenation using formic acid–methanol was advantageous. It is clear that the reduction is limited to substrates which are not very heavily substituted (e.g. amino alcohol **7k** was completely resistant to reduction).

Pridgen has pointed out the general lack of methods available to effect reduction of the oxazoline to the amino alcohol and reported that this can be carried out using BH_3 in THF at reflux (Table 12). The intermediate N-(β-hydroxyethyl)arylalkylamines were used in the preparation of tetrahydroisoquinolines and tetrahydro-1H-3-benzazapines[22] (Table 13).

IV. REACTIONS OF ARYL OXAZOLINES

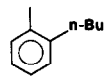
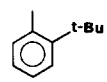
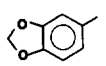
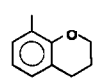
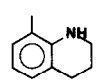
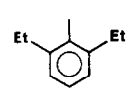
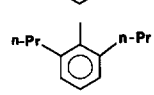
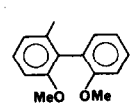
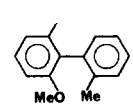
A. *Nucleophilic substitution*

It was demonstrated earlier (Scheme 1) that *o*-methoxy and *o*-fluoro[phenyl-2-(4,4-dimethyl-2-oxazolines)] undergo facile nucleophilic substitution with a variety of reagents such as organolithiums, Grignards, lithium amides, alkoxides and silyllithium reagents.[23a,b,c]

The substitution reaction with aromatic Grignard reagents has provided ready access to a variety of substituted biaryl derivatives.[23a] The more classical approaches to unsymmetrical biaryls such as the Ullman coupling are usually not satisfactory.[24]

i. *Synthesis of binaphthyl derivatives.* Unsymmetrical binaphthyl derivatives were prepared by the

Table 9. Reduction of oxazolines to amino alcohols by DIBAL or Li–NH_3

Oxazoline	Aryl	Method	Time (hr)	% Yield	Amino alcohol
5a	Ph	DIBAL	2.5	91	**7a**
		Li–NH_3	0.5	100	**7a**
5b		DIBAL	15	95	**7b**
5c		Li–NH_3	2	100	**7c**
5d	*p*-$MeOC_6H_4$	DIBAL	3.5	90	**7d**
5e	*m*-ClC_6H_4	DIBAL	3.5	100	**7e**
5f		DIBAL	3.5	90	**7f**
5g	*o*-PhC_6H_4	DIBAL	21	90	**7g**
5h		DIBAL	24	70	**7h**
5i		DIBAL	12	92	**7i**
5j	α-Naphthyl	DIBAL	24	88	**7j**
5k		DIBAL	18	78	**7k**
		Li–NH_3	0.33	97	**7k**
5l		Li–NH_3	0.25	91	**7l**
6a	*o*-BrC_6H_4	DIBAL	18	95	**8a**
6b	*o*-MeC_6H_4	DIBAL	12	91	**8b**
6c		DIBAL	5	90	**8c**
6d		DIBAL	4	90	**8d**

addition of organometallic reagents to 1-methoxy naphthyl oxazoline[25] (Eq. 12). Moreover, chiral binaphthyl derivatives in high enantiomeric excess can be obtained by this reaction.[26,27]

eq.12

In one approach,[26] the requisite chiral *o*-methoxyoxazolines were prepared from the available 1-methoxynaphthoic acid and (+)-(1*S*,2*S*)-1-phenyl-2-amino-3-methoxy-1-propanol. Treatment of the chiral oxazolines with various naphthyl Grignard reagents gave the diastereomeric binaphthyl oxazoline derivatives which were converted into the benzyl alcohols (Table 14). Fortuitously, during

Table 10. Oxidation of amino alcohols to aldehydes

Amino alcohol	Method*	Chlorination time (min)	Elimination time (hr)	% Yield **9**
7a	A	8	0.2	83
7b	A	15	3	76
7c	A	15	12	84
7d	A	10	0.33	78
7e	A	22	0.1	68
7f	A	6	0.33	67
7g	A	43	2	84
7k	A	10	8	73
7l	A	39	24	63
8a	B	—	—	75
8b	B	—	—	72
8c	B	—	—	70
8d	B	—	—	70

* Methods A: NCS–Al_2O_3–SiO_2. Method B: t-$BuMe_2$-SiCl–NCS–KO_2–oxalic acid.

Table 11. Reduction of amino alcohols to aromatic methyl compounds

Amino alcohol	Reduction method*	Time (hr)	% Yield
7b	A	19	29
7d	A	12	81
7e	A	0.25	†
7f	A	6	91
7g	A	21	87
7i	A	12	78
7j	A	8	88
7k	A	12	‡
8c	B	96	71
8d	B	120	75

* Method A: H_2, Pd–C at 50 psi in methanol with Ph buffer. Method B: formic acid–methanol with Pd–C at room temp.

† This gave primarily dichlorination to amino alcohol **7a**.

‡ Only starting material was recovered.

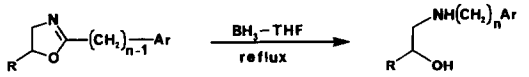
the transformation of the oxazoline to the alcohol (*via* reduction of the amino ester hydrochloride with $LiAlH_4$) some enrichment of the *R* enantiomer had occurred.

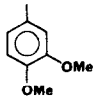
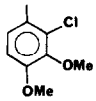
In a somewhat different approach,[27] Cram employed a chiral alkoxide (Table 15) leaving group to give the asymmetric induction and the achiral oxazoline as the activating group. With the *l*-methoxy leaving group, the greatest chiral reaction efficiency was obtained.

While both approaches give important and potentially useful chiral binaphthyl derivatives[28] in good to excellent enantiomeric excess, equally important is the demonstration that the transformation of the oxazoline to benzyl alcohols,[26] amines and phenols,[27] in hindered aromatic systems is possible.

ii. *Synthesis of biaryl derivatives.* A superior approach to cannabinol and cannibifuran[29] was developed using the displacement reaction on *ortho*-methoxyaryl oxazolines to prepare hindered biphenyl oxazolines (Scheme 6). An alternate approach using transition metal catalyzed cross coupling of Grignard reagents gave only poor yields of the required biphenyls.[30] The conversion of

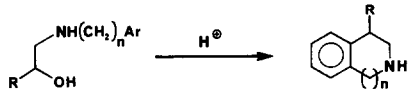
Table 12. Reduction of oxazolines to amino alcohols by BH_3–THF

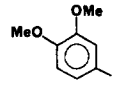
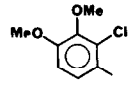
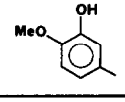


Ar	R	n	Time (hr)	% Yield
Ph	H	1	5	96
	H	1	6	70
	Ph	2	8	94
	Ph	2	16	80
	p-Anisyl	2	3	56
Ph	Ph	1	4	95*
p-Anisyl	Ph	1	3	63

* This reduction was carried out using $LiAlH_4$.

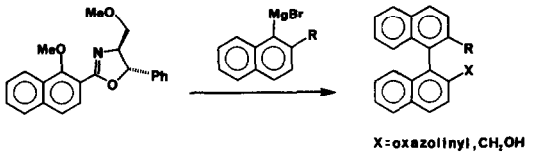
Table 13. Cyclization of N-(β-hydroxyethyl)arylalkylamines



Ar	R	n	% Yield
Ph	Ph	1	78
p-Anisyl	Ph	1	82
	Ph	2	—
	4-MeOPh	2	85
	4-HOPh	1	79*

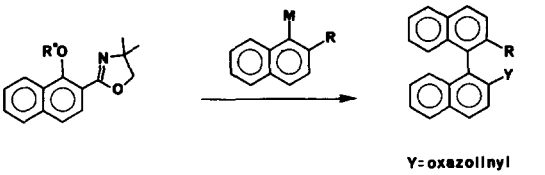
* Cyclization performed under basic conditions.

Table 14. Synthesis of chiral binaphthyls: methoxide displacement



R	% Yield	Diastereomeric ratio	% Yield	% ee	Configuration
H	80	87:13	56	90	*R*
Me	67	76:23	46	87.4	*R*
OMe	71	92:9	65	96	*R*

Table 15. Synthesis of chiral binaphtyls: *l*-menthoxy displacement*



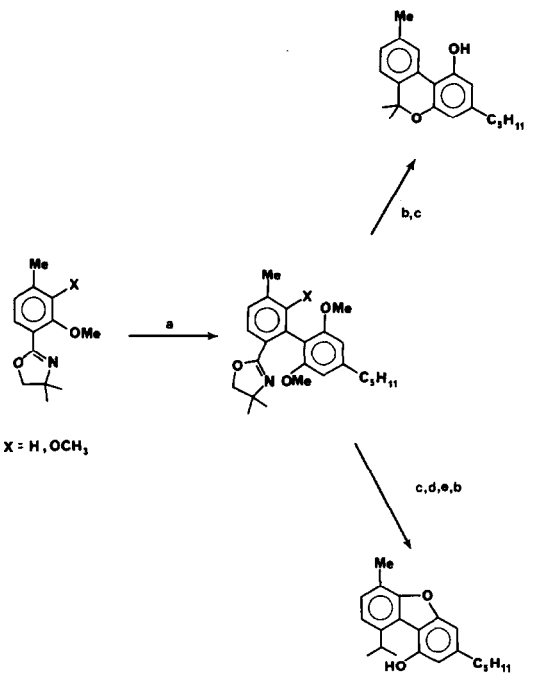
R	M	% Yield	% ee	Configuration
H	Li	80	67	*S*
OMe	MgBr	53	78	*S*
OMe	Li†	68	95	(+)‡

*The *l*-menthoxy leaving group gave the highest chiral reaction efficiency.

†Metalation of α-bromo-β-methoxynaphthalene gives predominantly γ-lithio-β-methoxynaphthalene.

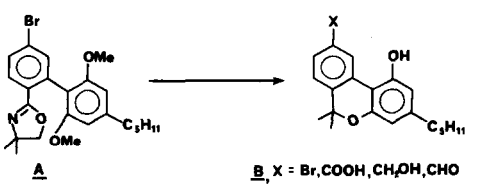
‡Configuration was not determined.

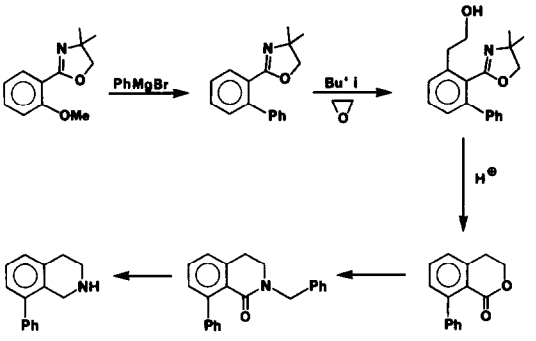
the biphenyl oxazolines into the lactone or furan was accomplished in a straightforward manner as shown in Scheme 6.



Scheme 6. a—$C_6H_2(OMe)_2C_5H_{11}MgBr$; b—HI, Ac_2O, reflux; c—MeMgI; d—CF_3CO_2H; e—H_2PtO_2.

These authors also described the synthesis of the cannabinol metabolites: 11-hydroxycannabinol, the corresponding aldehyde, and the acid (B) using the same substitution reaction shown in Scheme 6 to give the analogous biaryl derivatives (A).[30]

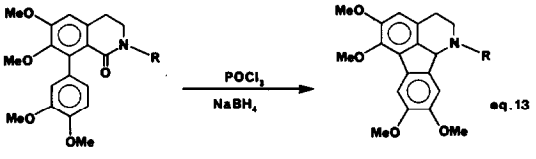




Scheme 7.

An efficient entry into 8-aryl-1,2,3,4-tetrahydro isoquinolines was reported[32] using nucleophilic substitution on *o*-methoxy phenyloxazolines to give biaryl intermediates (Scheme 7). The *β*-phenethylalcohol was obtained by treatment of the *o*-lithiooxazoline with ethylene oxide and subsequent hydrolysis to give the lactone. The lactam was prepared from the lactone and reduced directly to the desired isoquinolines. Other attempts to prepare these derivatives such as the Pomeranz–Fritsch or Bischler–Napieralski were unsuccessful.

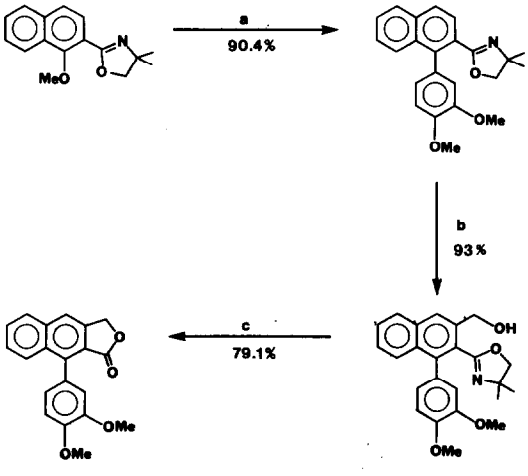
This same approach was used in a recently reported synthesis of indeno[1,2,3-ij]isoquinolines.[31] In this synthesis the lactam is cyclized under Vilsmeier conditions to give the iminium salt which is reduced to the desired isoquinoline with $NaBH_4$ (Eq. 13).



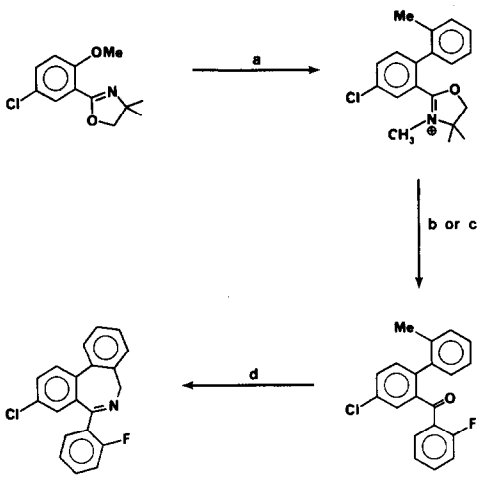
eq. 13

The use of aromatic oxazolines has provided access to lignan lactone derivatives illustrated in Scheme 8 for a Chinesin analog.[33] Nucleophilic substitution afforded the biaryl derivative in high yield. This was taken on to the benzyl alcohol *via* the *o*-lithio derivative and subsequent hydrolysis gave the desired lactone.

In the preparation of 9-chloro-7-(*o*-fluorophenyl)-5H-dibenz[c,e]azepine[34] (Scheme 9) the biphenyl oxazoline, prepared in the usual fashion, was quaternized to generate the oxazolinium salt



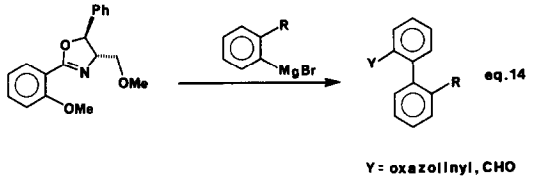
Scheme 8. a—$C_6H_3(OMe)_2Li$; b—*s*-BuLi–TMEDA; DMF; $NaBH_4$ done as a one-pot procedure; c—6 N HCl.



Scheme 9. a—*o*-tolyl magnesium bromide, MeI; b—$NaBH_4$, *o*-fluorophenyllithium, CrO_3; c—*o*-fluorophenyllithium, H_3O^+; d—NBS, NH_3.

which served as a key intermediate. Reduction with $NaBH_4$ furnished the aldehyde while subsequent treatment with *o*-fluorophenyllithium and oxidation gave the benzophenone which was converted into the desired benzazepine. Alternatively, treatment of the oxazolinium salt with *o*-fluorophenyllithium and hydrolysis also gave the same benzophenone.

Following the successful preparation of chiral binaphthyl derivatives (Tables 14 and 15), this important aryl–aryl bond forming reaction was extended to the biphenyl series[35] (Eq. 14).

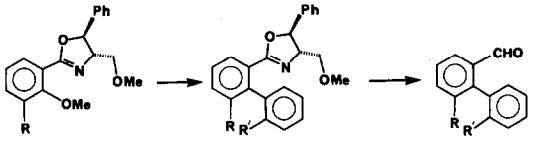


eq.14

Y = oxazolinyl, CHO

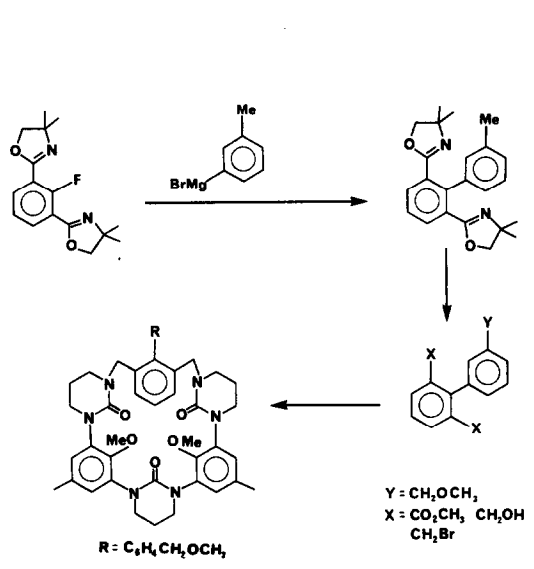
The biphenyl oxazolines were prepared in good diastereomeric excess (Table 16). These, however, required a mild method for removal of the oxazoline. To avoid racemization, reduction of the oxazoline to the amino alcohol using DIBAL followed by oxidation to the aldehyde (Table 10) proved to be the method of choice.[21]

Table 16. Synthesis of chiral biphenyls

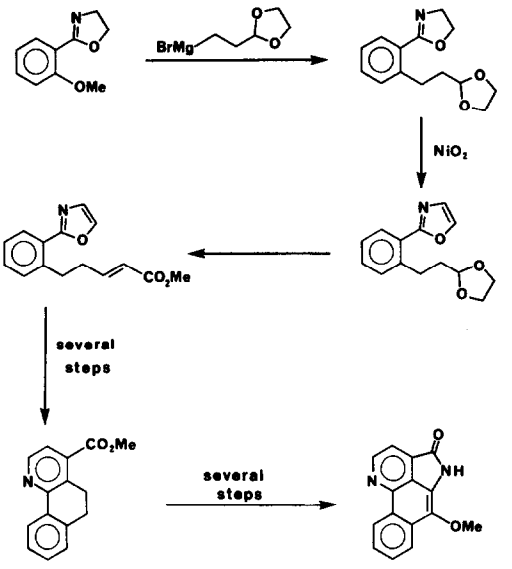


			Oxazoline		Aldehyde	
Entry	R	R′	DE %	$t_{1/2}$ (hr)	ee %	$t_{1/2}$ (hr)*
1	Me	Me	35	∞	35	∞
2	Me	OMe	92	2.3	0	5 min
3	OMe	Me	60	40	60	3
4	OMe	OMe	0	†	0	†
5	Me	CH_2OSiMe_2t-Bu	62	†	‡	
6	OMe	CH_2OSiMe_2t-Bu	58	73	52	5
7	CH=CHMe	Me	33	†	‡	
8	CH=CHMe	OMe	84	1.5	0	†

* Half-life measured at 110°.
† Not measured.
‡ Not prepared.



Scheme 10.

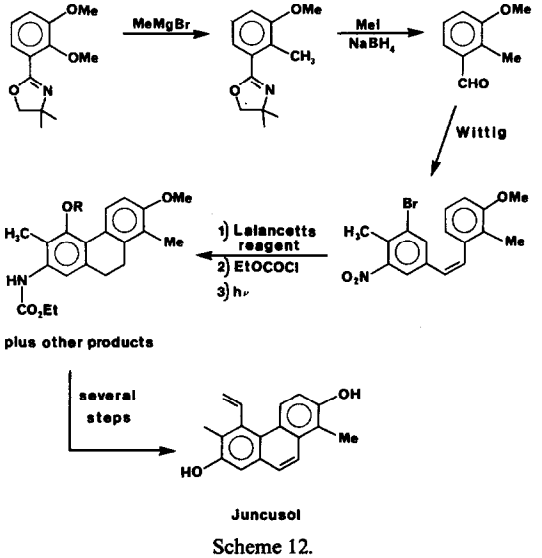


Scheme 11.

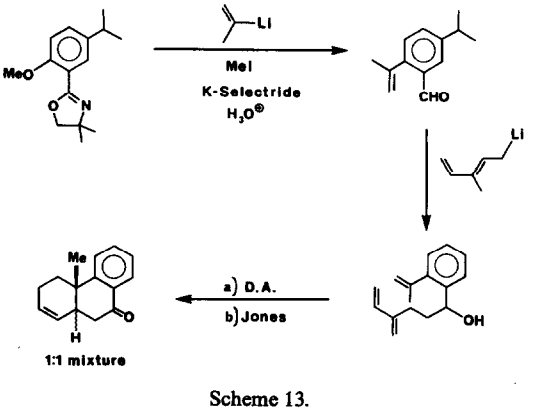
Nucleophilic substitution followed by further transformation of the oxazoline provided a straightforward entry into serine protease mimics (Scheme 10). The 1,3-bisoxazolinyl-2-fluorobenzene was converted to the *m*-toluyl derivative *via* the Grignard reagent. The toluene methyl was transformed to the methoxymethyl and the oxazolines were converted into the benzyl bromides by routine transformations. The dibromide obtained was coupled with the urea (NaH, high dilution) to give the desired cycle.

iii. *Other nucleophilic substitution.* Weinreb's synthesis of eupolauramine[14] used the nucleophilic substitution reaction to prepare the masked *β*-phenyl propanal derivative (Scheme 11). The oxazoline was oxidized to the oxazole (NiO_2 in benzene), the aldehyde deprotected and homologated to the unsaturated ester *via* the Horner–Emmons reaction. The key step, the intramolecular Diels–Alder reaction with the oxazole, was carried out in good yield giving the dihydroazaphenanthrene which was converted to eupolauramine in several steps.

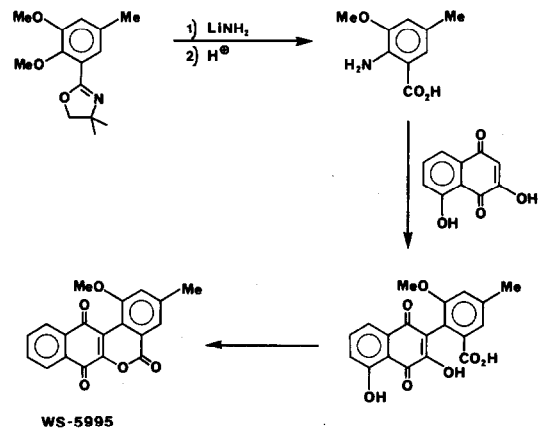
An approach to phyloalexins such as juncusol (Scheme 12) was explored by Ganem.[38] Substitution of the 2,3-dimethoxyphenyl oxazoline gave the methyl compound which was transformed into the aldehyde in excellent yield. A Wittig coupling on the aldehyde and further



Scheme 12.



Scheme 13.



Scheme 14.

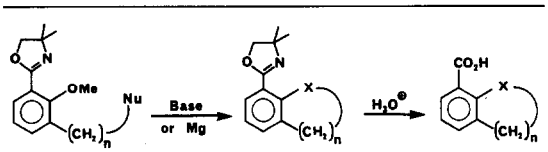
transformations gave the requisite fused ring system. This material was obtained in low yield as a mixture of products and has yet to be carried on to juncusol.

In a Diels–Alder approach to diterpenes (Scheme 13), the synthesis of the *o*-isopropylidenebenzaldehyde derivative was achieved *via* substitution of the *o*-methoxyoxazoline with 2-lithiopropene[39] and reduction to the aldehyde.[20] Conversion of the aldehyde to the hydroxydiene set the molecule up for the Diels–Alder reaction. The cyclization followed by Jones oxidation gave a 1 : 1 mixture of adducts in 77% yield.

The pigment, WS 5995, from *Streptomyces auranticolor* was synthesized as shown in Scheme 14 from the *o*-methoxy phenyl oxazoline.[40] Displacement of the methoxide with lithium amide and hydrolysis gave the requisite anthranilic acid derivative. This was coupled *via* the diazonium salt with 3-hydroxy juglone to give the hydroxy acid which was converted directly to WS 5995.

Recently, an extension of the nucleophilic substitution reaction to include the synthesis of a variety of benzo-fused ring systems was described[41] (Table 17).

Table 17. Synthesis of benzo-fused ring systems

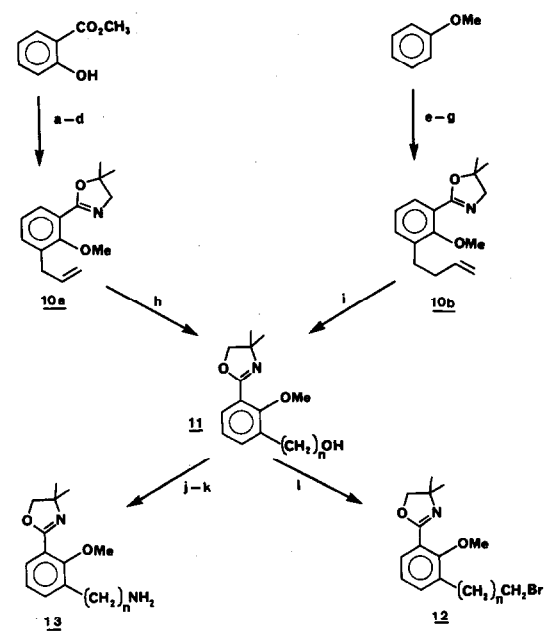


Oxazoline	Nu	n	% Yield	X	% Yield
12a	CH_2MgBr	2	80	CH_2	67
12b		3	84	CH_2	72
11a	O^-Na^+	2	82	O	49
11b		3	72	O	65
11c		4	54	O	64
13a	NH^-Li^+	2	83	NH	68
13b		3	78	NH	61*
13c		4	48	NH	45
13d		5	†	NH	‡

* Hydrolysis resulted in decarboxylation to give only tetrahydrohydroquinolin.

† Annulation attempt gave the 16-membered product from dimerization.

‡ Hydrolysis not attempted.



Scheme 15. (a) AllylBr, NaH; (b) heat; (c) MeI, NaH; (d) H^+, $SOCl_2$, 2-amino-2-methyl-1-propanol; (e) BuLi, 1,4-diiodobutane; (f) BuLi, CO_2; (g) $SOCl_2$, 2-amino-2-methyl-1-propanol; (h) O_3–Me_2S; (i) BH_3, H_2O_2; (j) MsCl, Et_3N; (k) K-phthalmide, NH_2NH_2; (l) LiBr–DMF.

The precursors for the annulations were all prepared in a straightforward manner as shown in Scheme 15. Methylsalicylate or anisole were transformed to the olefins **10a** or **10b** which served as key intermediates from which all the ring systems were derived.

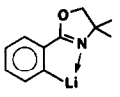
This simple annulation procedure shows not only a novel entry into a variety of benzo-fused ring systems, but also the wide array of synthetic manipulations to which the oxazoline is stable.

B. *Metalation and electrophilic substitution*

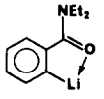
Scheme 1 illustrated the complimentary modes of reactivity available with aromatic oxazolines. Metalation *ortho* to an activating group is a powerful tool in synthetic organic chemistry.[42] In 1975, both Gschwend and Meyers reported[43] that aromatic oxazolines could be metalated and treated with electrophilic reagents to give, after hydrolysis, *o*-deutero or other *o*-substituted benzoic acids.

A comparative study of the ability of different groups to direct *o*-lithiation was reported by Meyers and Beak. The Beak[44] study used N,N-diethylbenzamide as an anchor group and studied its ability to direct lithiation relative to other groups on the aromatic nucleus. In the Meyers study,[45] the oxazoline was compared to other common directing groups in a series of intermolecular competition experiments. Both studies found that the benzamide is superior to the oxazoline in its ability to direct *o*-lithiation.

It is believed that the slower rate of lithiation exhibited by the oxazoline may be due to the greater degree of strain in the lithiated products. In the *o*-lithiooxazoline, the lithio species contains two five-membered rings fused to the benzene ring (C). This is not the case with the benzamide (D).

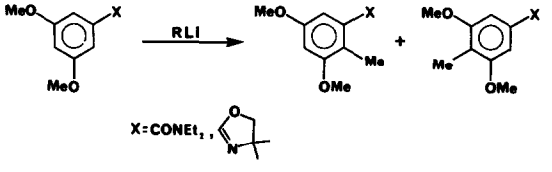


C



D

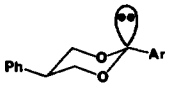
Metalation studies[46] on 3,5-dimethoxyphenylbenzamides and the corresponding oxazolines below, indicate that the benzamide is more effective in its ability to direct *o*-lithiation. With the diethylbenzamide as the activating group, only *o*-lithiation occurred and an 80% yield of the *o*-methyl compound was isolated. The oxazoline gave a 90:10 mixture of *p*- to *o*-methyl products with DME–*s*-BuLi. This serves to illustrate that with a judicious choice of activating groups and reaction conditions, the aromatic nucleus can be rather selectively elaborated.



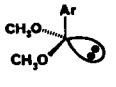
Aryl acetals, when substituted in the *p*-position by the oxazoline, can serve as acyl anion equivalents rather than undergo the usual fragmentation to the carboxylate[47] (Scheme 16).

The 1,3-dioxolane or the dimethoxy acetal, when used as the aldehyde masking group, resulted in complete metalation only at the acetal hydrogen. Treatment of these anions with electrophilic reagents gave excellent yields of the alkylated products. When the acetal is derived from 2-phenyl-1,3-propanediol, metalation occurs *ortho* to the oxazoline permitting the usual *ortho* substitution (Scheme 17). Furthermore, it is possible to choose conditions where either the oxazoline (Et_3O^+ BF_4^- followed by alkaline hydrolysis), or the acetal (Me_3SiI), can be selectively removed.

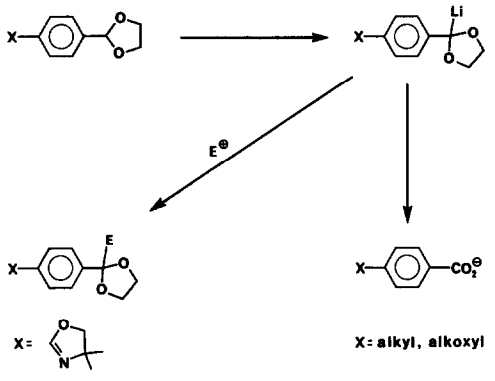
This unusual pattern of selectivity is most probably derived from destabilization of the axial acetal carbanion (E) in the case of the 6-membered acetal, which is not possible with the 5-membered acetal or the dimethoxy acetal (F).[48]



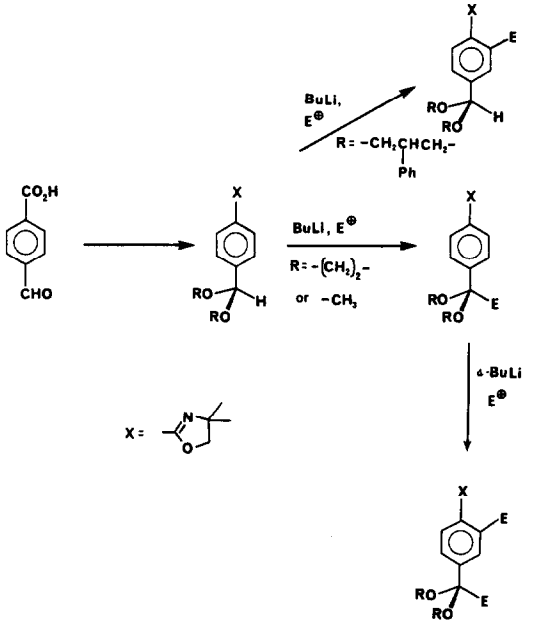
E



F



Scheme 16.



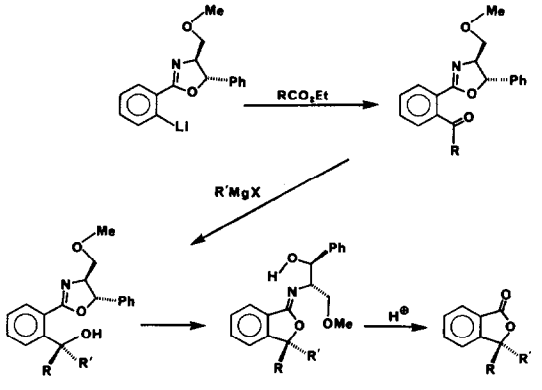
Scheme 17.

Some applications of the *ortho*-lithiation of oxazolines have been discussed earlier in this review in connection with lignan lactones and 8-aryltetrahydroquinolines.[31–33] In these cases both activation modes of the oxazoline, nucleophilic substitution and *ortho*-lithiation, were used to gain access to key intermediates in the synthesis.

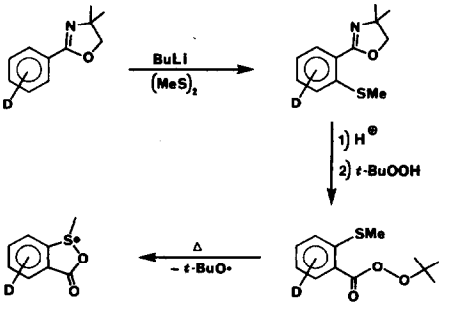
Chiral *o*-lithiophenyloxazolines provide access to chiral phthalides[49] *via* the diastereomeric iminolactone intermediates as shown (Scheme 18). Direct preparation of the iminolactones by addition of aldehydes or ketones to the lithiated oxazoline resulted in poor diastereomeric ratios (51:49 to 64:33). These intermediates, however, were readily separated by recrystallization to give enantiomerically pure phthalides after hydrolysis (oxalic acid–THF). Acylation of chiral *o*-lithio phenyloxazolines to give ketones followed by the addition of organometallic reagents also afforded excellent yields of the iminolactones. Direct hydrolysis of the mixture gave the phthalides in 40–80% ee.

In connection with work on σ-sulfuranyl radicals it became necessary to prepare specifically ring deuterated benzoic acid derivatives as radical precursors. This was easily accomplished by oxazoline lithiation as shown in Scheme 19 below. The appropriate deuterated aryloxazoline was lithiated and treated with dimethyldisulfide, and was then converted *via* the acid chloride into the perester.[50]

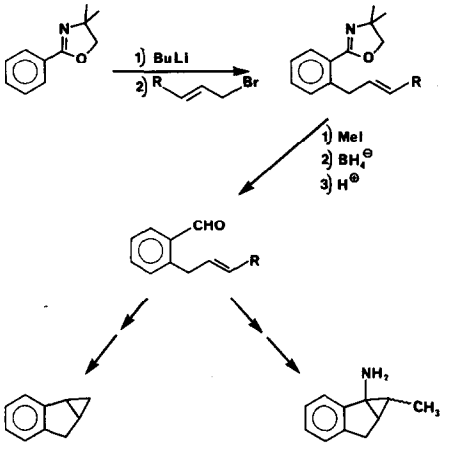
Padwa used the *o*-lithiation reaction of aryl oxazolines to gain access to *o*-allyl benzaldehydes[51] (Scheme 20). These aldehydes were used to study the cycloaddition of tosylhydrazones and nitrile ylids.



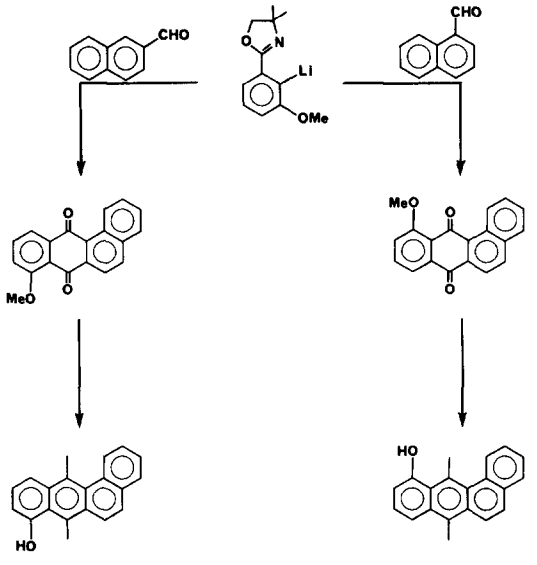
Scheme 18.



Scheme 19.



Scheme 20.



Scheme 21.

The synthetic utility of *o*-lithiophenyloxazolines was exploited by Newman in several syntheses of benzanthracene and benzopyrene derivatives.[52a–d] An example is illustrated in Scheme 21 for 8-hydroxy- and 11-hydroxy-7,12-dimethylbenz[a]anthracene. Thus, it was demonstrated, for many other examples, the wide variation of substitution patterns available on the benzanthracene nucleus is limited only by the availability of the appropriate aldehyde and benzoic acid derivatives.

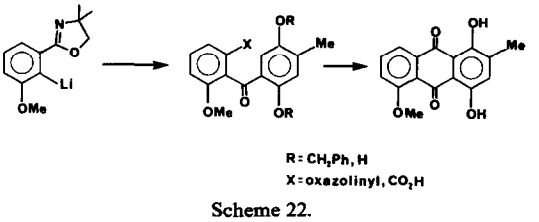
Witiak has also used the same synthetic approach in an attempted synthesis of 5-fluoro-7,12-dimethylbenz[a]anthracene,[53] except that the oxazoline was used as a masking group for preparation of the *ortho*-Grignard in place of lithiation.

The acylation of *o*-lithiooxazolines was used in the preparation of the intermediate islandicine methyl ester, for anthracycline synthesis (Scheme 22).[54]

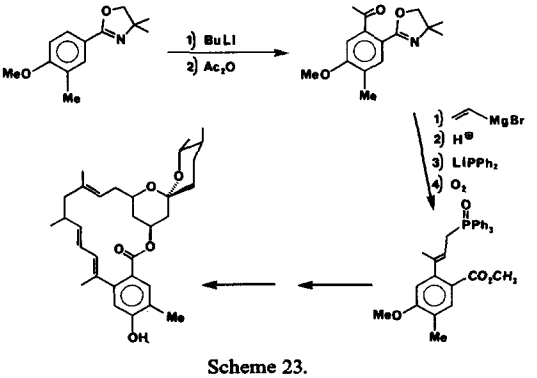
Similarly, lithiooxazolines were acylated to give acetophenone derivatives which were converted into the phosphine oxide. Subsequent coupling of this key intermediate with the Northern zone gave Milbemycin-β_3 (Scheme 23). Noteworthy is the preparation of only one acetophenone derivative after lithiation and acylation of the oxazoline. This selectivity may be due to steric inability of the BuLi to deprotonate between the methyl and the oxazoline when a more accessible site is available.[55]

In a recent berberine synthesis[56] (Scheme 24), the oxazoline facilitated the introduction of a trimethylsilylmethyl group and was then reduced to the aldehyde. Reductive aminationo and formylation provided the precursor for a Bischler–Napieralski ring closure. The iminium ion obtained was then treated with CsF which gave only the desired berberine derivative.

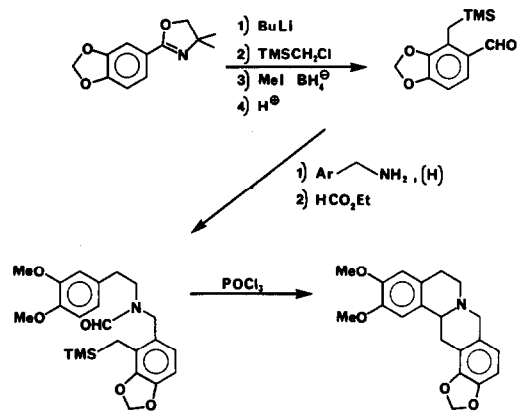
The authors suggest that this result supports a betaine mechanism rather than one involving an



Scheme 22.



Scheme 23.

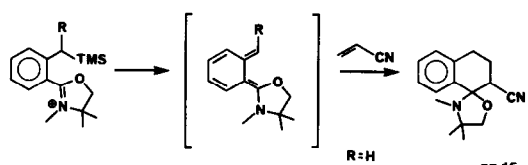


Scheme 24.

unsymmetrical *o*-quinodimethane since the berberine shown above was the only product obtained.

The quaternization of the oxazoline, which makes the CN double bond more susceptible to nucleophilic attack, is generally used to facilitate either hydrolysis under alkaline conditions (Eq. 7) or reduction (Eq. 10) to the aldehyde. N-Alkyl oxazolinium salts can also be used to generate *o*-quinodimethane intermediates.[57]

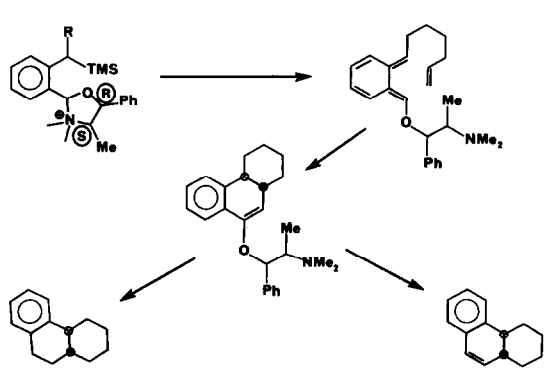
Methylation of *o*-trimethylsilylmethylphenyloxazoline followed by treatment with CsF in the presence of acrylonitrile gave the Diels–Alder adduct in 89% yield (Eq. 15) as a mixture of diastereoisomers. The structure of this adduct was confirmed by hydrolysis to the cyanotetralone. The attempted intramolecular cyclization [R = $(CH_2)_4CH{=}CH_2$] was not successful.



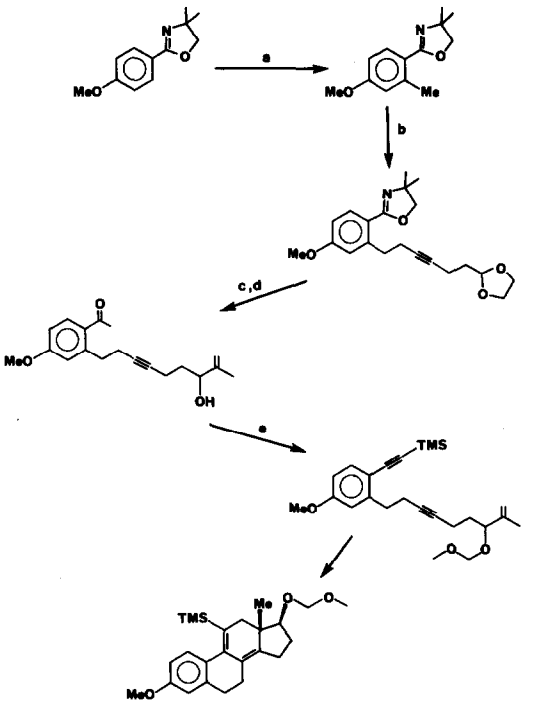
When the aldehyde is transformed into the oxazolidine and quaternized, the intramolecular cycloaddition proceeded smoothly. In particular, the use of a chiral amino alcohol for the preparation of the oxazolidine results in an asymmetric Diels–Alder reaction to give polycyclic compounds in 28–55% enantiomeric excess (Scheme 25).

In addition to the regiochemistry possible in these Diels–Alder reactions with the heterosubstituted quinodimethane and the potential for a novel, elegant asymmetric synthesis, it should be emphasized that the ability to efficiently lithiate and manipulate the oxazoline played a key role in the development of this chemistry.

The elegant cobalt mediated cyclizations of enediynes, which provides access to polycyclic dienes, has now been extended to include a synthesis of the 11-(trimethylsilyl)-3-methoxyestra-



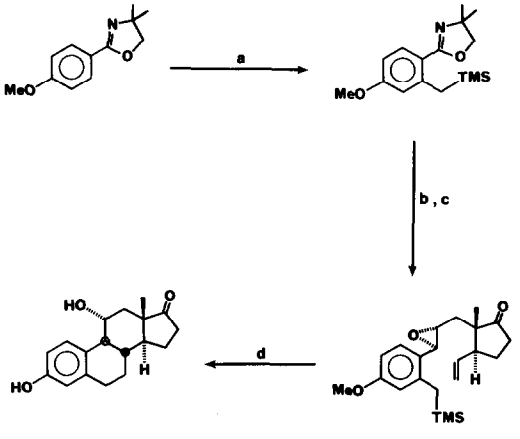
Scheme 25.

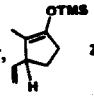


Scheme 26. a—n-BuLi, MeI; b—n-BuLi, 6-chloro-4-hexynal ethylene acetal; c—HCO_2H, propenyl magnesium bromide; d—MeI, MeMgCl, HCl; e—$ClCH_2OCH_3$, LDA, $ClP(O)(OEt)_2$, LDA, TMSCl; f—$CpCo(CO)_2$, oxidation.

1,3,5(10),8(14),9(11)-pentane nucleus[58] (Scheme 26). The enediyne precursor for this steroid intermediate was prepared by alkylation of *o*-lithio-*p*-methoxy phenyloxazoline. The *o*-methyl group was then metalated and alkylated followed by conversion of the oxazoline into the silyl acetylene *via* the benzophenone. Cyclization in the presence of $CpCo(CO)_2$ followed by oxidative removal of the cobalt gave a 24% overall yield of the steroid nucleus from the starting acid chloride.

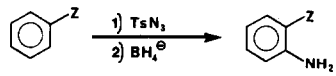
The utility of the oxazoline was important in developing an efficient synthesis of 11-α-hydroxyesterone methyl ether (Scheme 27).[59] Regiospecific lithiation of the oxazoline was used to



Scheme 27. a—n-BuLi, MeI, n-BuLi, TMS–Cl; b—MeI, $NaBH_4$; c—vinyl MgBr,  $ZnBr_2$, MCPBA; d—CsF.

incorporate the trimethylsilylmethyl group. Reduction of the oxazoline to the aldehyde and addition of the vinyl Grignard gave the allylic alcohol. Coupling with the silyl enol ether in the presence of $ZnBr_2$ followed by epoxidation set the molecule up for generation of the *o*-quinodimethane. Treatment with CsF led to the desired estrone derivative.

Snieckus has recently reported that several groups which facilitate *o*-lithiation, including the oxazoline and diethylbenzamide, can be aminated thus extending the scope of the *o*-lithiation reactions.[60a] The amination is accomplished by treatment of the *o*-lithio derivative with tosyl azide followed by reduction with $NaBH_4$ (Eq. 16).



eq.16

Z = oxazolinyl, OCH_2OMe, $CONEt_2$

A similar study was also reported[60b] using phenyllithium and other groups which facilitate *ortho*-lithiation (Z = OMe, CH_2NMe_2, and CONHMe in Eq. 16). The amination was accomplished using tosyl azide followed by reduction using Ni—Al alloy, in place of $NaBH_4$, to give 34–85% yields of the amines.

An efficient entry into 2,3-disubstituted thiophenes was realized by lithiation of the 3-position in 2-oxazolinylthiophenes.[61a] More recently furans[61b] and N-substituted pyrroles[61b,c] have also been transformed into the 2,3-disubstituted derivatives by the same method (Table 18).

The 2,3-substitution pattern on thiophenes, furans and pyrroles is particularly difficult to achieve emphasizing the importance of these results.

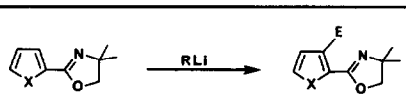
Ziegler reported that organolithium reagents generally add to the CN bond of pyridines to give dihydropyridines.[62] Direct metalation of the pyridine nucleus, without such competing side reactions, has only recently been achieved. The oxazoline has proved successful in activating the pyridine nucleus toward regiospecific lithiation. The 4-pyridyl oxazoline is metalated with MeLi (Table 19), and the 3-pyridyloxazoline with LiTMP (Table 20). In most cases, these lithiated intermediates gave good to excellent yields of alkylated products when treated with a variety of electrophilic reagents.

C. *Addition of organometallics to aryloxazolines*

Attempts to lithiate 3-pyridyloxazoline with MeLi under conditions which worked best for the 4-pyridyloxazoline, gave none of the lithiated product but rather addition by the lithium reagent to the 4-position of the pyridine ring (Table 21). Addition of a wide variety of organolithium or Grignard reagents gave good yields of the dihydropyridine which may be oxidized to the corresponding pyridine. Giam reported a similar study[64] on the addition of organolithium reagents to 3-pyridyloxazolines and also obtained good yields of the dihydropyridines and pyridines.

Addition of organometallic reagents to chiral pyridyl oxazolines afforded good yields of the

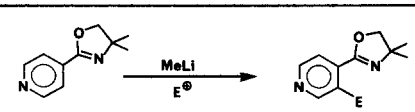
Table 18. Lithiation of 5-membered heterocycles



X	Solvent	Electrophile (E^+)	% Yield	Ref.
S	Et_2O	PhCHO	91	59*a*
O	DME	PhCHO	87*	59*b*
NMe	DMe	CO_2	56*	59*b*
NC_6H_5	THF	PhCHO	32†	59*c*

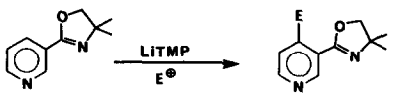
* 9% of the 5-substituted isomer was also obtained.
† 5% of the 5-substituted isomer and 33% recovered starting material was obtained.

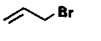
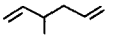
Table 19. Lithiation and alkylation of 4-pyridyloxazoline



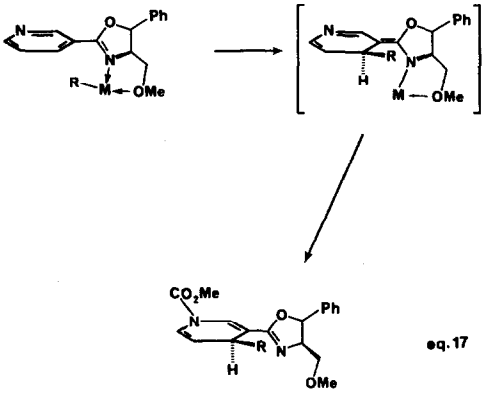
Electrophile (E^+)	% Yield	Structure of E
D_2O	79	D
MeI	63	Me
EtI	56	Et
	54	
PhCHO	83	PhCHOH
Et_2CO	76	Et_2COH
DMF	52	CHO
O_2	27	OH

Table 20. Lithiation and alkylation of 3-pyridyloxazoline



Electrophile (E^+)	% Yield	Structure of E
D_2O	70	D
MeI	80	Et
	72	
PhCHO	50	PhCHOH
Et_2CO	52	Et_2COH

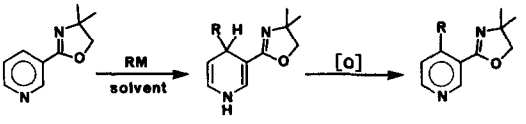
diastereomeric dihydropyridines in high diastereomeric excess[65] (Table 22). The absolute configuration was determined by X-ray analysis of the amide obtained from hydrogenation of the 4-methyl adduct and indicates that organometallic entry occurs from the topside of the ring as shown in Eq. 17.



eq. 17

In addition to the conjugate addition reaction observed with pyridyl oxazolines, an analogous reaction was observed with naphthalene derivatives.[66] Thus, treatment of 1-naphthyl-4,4-dimethyl-2-oxazoline with organolithium reagents followed by alkyl halides gave good to excellent yields of

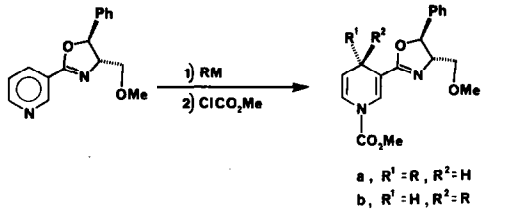
Table 21. Addition of organometallics to 3-pyridyloxazoline



Organometallic	Solvent	Yield	Oxidation method	% Yield	Ref.
MeLi	THF	100	Chloranil	73	62
BuLi	THF	99	Chloranil	90	62
EtMgBr	THF	99	Air	99	62
PhLi	THF	100	Chloranil	88	62
PhMgBr	THF	56		88	62
$LiCH_2CN$	THF	32	Chloranil	71	62
t-BuLi	THF	13*			62
PhLi	Et_2O	78.6	DDQ	50.3	63
MeLi	Et_2O	69.3	O_2	52.3	63
n-BuLi	Et_2O	78.5	$KMnO_4$	83.2	63
s-BuLi	Et_2O	74.2	$KMnO_4$	55.3	63
t-BuLi	Et_2O	75.7	$KMnO_4$	71.1†	63
t-BuLi	THF	53.3‡			63

* 87% 1,6-addition was observed.
† Recovered 27.4% of starting 3-pyridyl oxazoline.
‡ 34.5% 1,6-addition was observed.

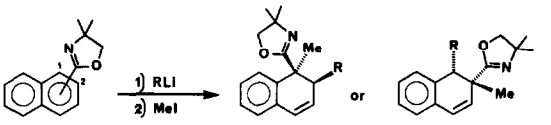
Table 22. Synthesis of chiral dihydropyridines



RM	Temp (°C)	Diastereomeric ratio a:b	% Yield*
MeLi	−40	93:7	79
	−78	94:5	79 (63)
MeMgCl	0	91:9	88
n-BuLi	−78	97:3	(92)
n-BuMgCl	0	95:5	98
EtMgBr	0	92:8	63
PhLi	−78	92:8	94

* Yield in parentheses represents purified yield of a.

Table 23. Addition of organolithium reagents to naphthyl oxazolines



Oxazoline	R	Conditions	% Yield
1-	n-Bu	−45°, 1.5 hr	90
1-	s-Bu	−45°, 1.5 hr	94
1-	t-Bu	−45°, 1.5 hr	100
1-	Me	−45° to RT, 3.5 hr	65
2-	n-Bu	−45°, 1 hr	90
2-	s-Bu	−45°, 1 hr	91
2-	t-Bu	−45°, 1 hr	90

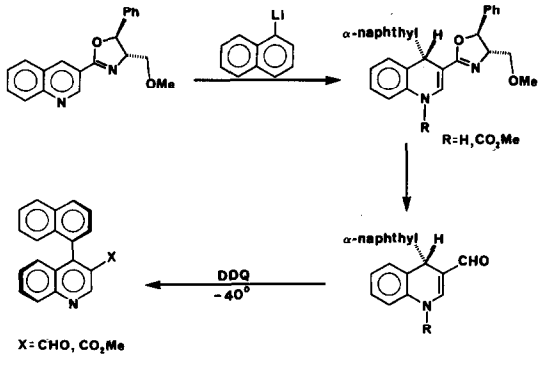
the dihydronaphthaline derivatives (Table 23). The product is the result of a net *trans* addition to the double bond of the incoming lithium reagent and the electrophile. The isomeric 2-naphthyloxazolines give the same excellent results.

Work is currently in progress on the addition of organometallic reagents to chiral naphthyl oxazolines and preliminary results indicate that these additions go in high diastereomeric excess.[19]

The addition of 1-lithionaphthalene to the chiral 3-quinoline oxazoline gives the *S*-dihydroquinoline shown in Scheme 28.[67] When the oxazoline is reduced to the aldehyde, oxidation of the dihydroquinoline gives the optically active *S*-4-naphthylquinoline derivative. The *R* enantiomer was obtained by addition of 1-naphthyl magnesium bromide to the oxazoline, followed by oxazoline reduction and DDQ oxidation. It should be noted that the oxidation proceeds with complete (>95%) transfer of a central chiral element to an axial chiral element in the absence of any chiral auxiliary.

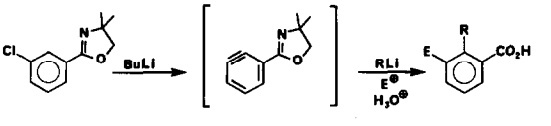
Lithiation of 2-(*m*-chlorophenyl)-4,4-dimethyl-2-oxazoline at −78° with warming to −15° results in generation of the benzyne (Table 24). The addition of organometallic reagents to this intermediate occurs primarily at the *ortho*-position to give the *ortho*-substituted oxazoline after protonation. Sequential treatment of the benzyne with organometallic reagents followed by other electrophiles provides access to 1,2,3-trisubstituted benzoic acid derivatives.[68] In Table 24, this is shown for R = n-Bu and a variety of electrophilic reagents, the yields for the overall transformation are quite good.

The regiochemistry of addition to the benzyne is determined by coordination of the organolithium reagent to the oxazoline. Organolithium reagents which are more encumbered or



Scheme 28.

Table 24. Synthesis of 2-n-butyl-3-substituted benzoic acids



R	E^+	E in product	% Yield
n-Bu	EtOH	H	70
n-Bu	MeI	Me	68
n-Bu	$(CH_2O)_n$	CH_2OH	58
n-Bu	DMF	CHO	57*
n-Bu	PhCHO	PhCHOH	57*
n-Bu	PhCOCl	PhCO	53

* Isolated as the methyl ester.

contain groups which would compete for coordination to the oxazoline on the benzyne result in an increasing proportion of addition at the *meta* position.

V. CONCLUSION

This review has shown a number of examples involving the synthetic utility of aryloxazolines based on their ability to specifically activate the *ortho* position of an aromatic ring toward deprotonation or nucleophilic substitution. While other groups have been shown to activate aromatic rings toward these reactions,[4,2] the oxazoline proves to be stable toward a wide array of other synthetic transformations. This unique stability of the oxazoline, coupled with a number of new, mild conditions for preparing and removing this activating group suggest that in years to come, many more synthetic applications of aromatic oxazolines will appear.

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