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Nucleophilic Aromatic Substitution on *o*-(Methoxy)aryloxazolines. A Convenient Synthesis of *o*-Alkyl-, *o*-Alkylidene-, and *o*-Arylbenzoic Acids

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Reaction of *o*-(methoxy)aryloxazolines **1** with organolithium or Grignard reagents results in methoxy displacement to the *o*-(alkyl)-, *o*-(aryl)-, and *o*-(vinyl)aryloxazolines **3**. A variety of organometallics were employed and only those considered to be delocalized anions failed to displace the methoxy group. Various poly(methoxy)aryloxazolines (**1a–e**) were investigated, and the reactions proceeded with general success, the yields dropping off in the 2,6-(dimethoxy)aryloxazoline **1d** due to steric factors. The method describes a facile synthesis of unsymmetrically substituted biphenyls and terphenyls by merely choosing the appropriate aryl metallic and methoxyaryloxazolines. Hydrolysis of the *o*-(substituted)aryloxazoline gave the corresponding benzoic acid derivatives **4** in good yield. In the case of 2,6-(disubstituted)aryloxazolines, hydrolysis to the benzoic acid proved difficult and led only to partially hydrolyzed amides.

Nucleophilic aromatic substitution has long been recognized as an important synthetic process, but has been limited to aromatic substrates with so-called "activating groups".[1] In recent years a number of elegant synthetic techniques have evolved which do not require the traditional activating groups and nucleophiles for substitution. Among these are the nickel-catalyzed reaction of aryl halides with Grignard reagents,[2] arene chromium derivatives reacting with carbanions,[3] the nickel-catalyzed reaction of enolates and aryl halides,[4] displacement on aryl halides[5] by alkoxide in powerful ion-solvating media, the copper-catalyzed substitution of *o*-bromobenzoic acids with enolates,[6] and the [2,3]sigmatropic rearrangements of sulfur ylides to ortho-substituted anilines.[7] The extensive studies by Bunnett,[8] which provided a variety of substituted benzenes, involve radical and radical ion intermediates and electron-transfer processes ($S_{RN}1$ mechanism). In effect, the overall transformation is that of nucleophilic substitution on aryl halides with traditional carbanions (enolates, thiolates, amide ions, etc.).

This report describes an aromatic substitution process which involves an activating group, but not in the traditional sense since it "activates" only toward nucleophilic reagents that are possessed of metal ions capable of chelation and transfer of the nucleophile from a tight ion pair to the electrophilic site.

In 1975, a preliminary report appeared[9] which described the overall process (eq 1) as a nucleophilic displacement of the *o*-methoxy group by several organometallics. This report will provide, in greater detail, the scope and limitations of this useful transformation and offer some evidence that the reaction is most probably occurring by an addition–elimination sequence and not by a free-radical mechanism.

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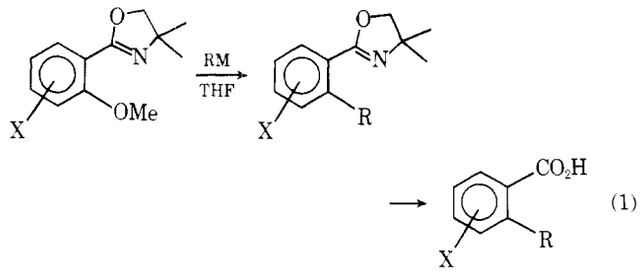
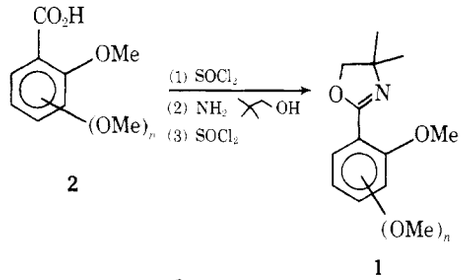


(1)

X = H, MeO; RM = alkyl or aryl lithium or Grignard

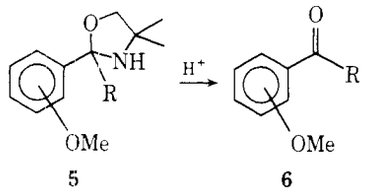
Since the appearance of the earlier report, a large number of examples have been investigated using five different methoxy-substituted aryloxazolines (**1a–e**) obtained in a simple



2 **1**

a, n = 0
b, n = 1 (3-methoxy)
c, n = 1 (4-methoxy)
d, n = 1 (6-methoxy)
e, n = 2 (4,5-dimethoxy)

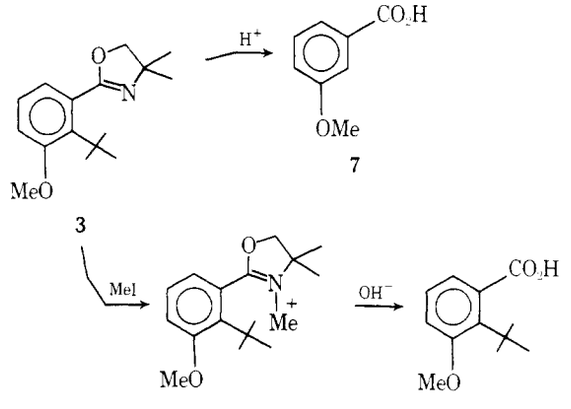
transformation from the corresponding methoxy-substituted benzoic acids (**2**).[10] Reaction of these methoxyaryloxazolines with a wide variety of organometallic reagents led to ortho-substituted derivatives as outlined in eq 1 and tabulated in Table I. The treatment of **1** with organolithium reagents was performed at −30 to −45 °C and in many cases proceeded smoothly. At higher temperatures (>−20 °C) organolithium reagents added slowly to the C=N link of the oxazoline, leading to **5**. This was verified by hydrolysis to the ketones **6**



(2)

5 **6**

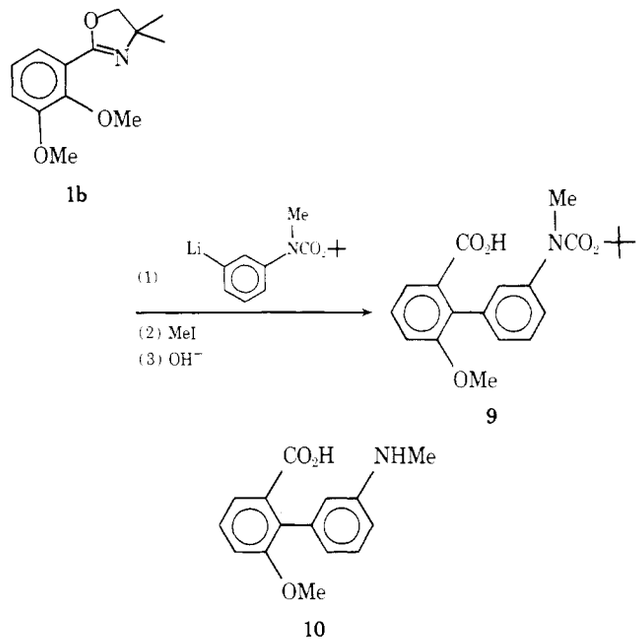
(eq 2). For those cases (Table I, entries 1, 3, 18) where the methoxy displacement with organolithium was inefficient at −40 °C, the corresponding Grignard reagents were employed (entries 2, 4, 17) and gave excellent yields of products. The Grignard reagents could be introduced at 25 °C or, if necessary, heated without any addition to the oxazoline moiety. The resistance of 2-oxazolines to Grignard reagents and, hence, its use as a suitable protecting group have already been described.[10] The versatility of this process can be appreciated by examining the large variation in organometallic structures present in Table I. Prominent among these examples is the introduction of the *o-tert*-butyl group (entry 20) in high yield. However, removal of the oxazoline activating group under acidic conditions gave only *m*-methoxybenzoic acid **7**. The acid lability of the *tert*-butyl group in this instance could have valuable synthetic implications by selectively demethoxylating an *o*-methoxy group from an aromatic ring, a process without precedent. However, the *o-tert*-butylbenzoic acid **4** could be retrieved from **3** by conversion to the methiodide **8** and removal of the oxazolinium moiety by alkaline hydrolysis. Another example which took advantage of the alkaline removal of the oxazoline was that furnishing the biphenyl de-



7

3 **8** **4**

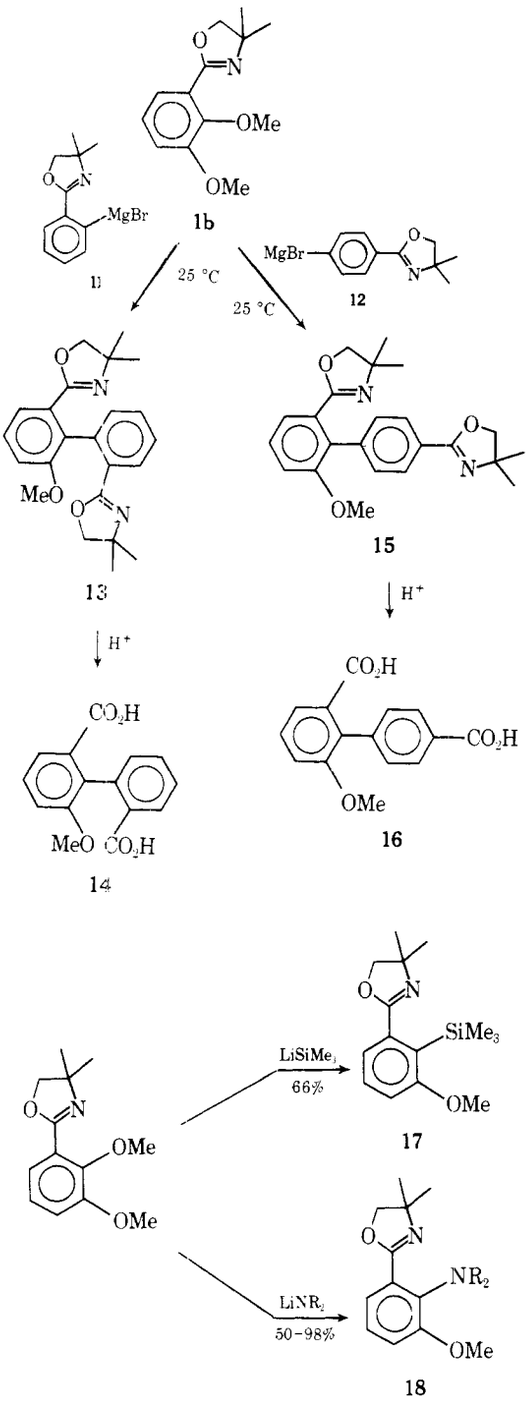
rivative **9** containing the acid sensitive Boc group. Whereas alkaline hydrolysis of the adduct gave **9** without event, acid hydrolysis led to the aminobiphenic acid **10.**

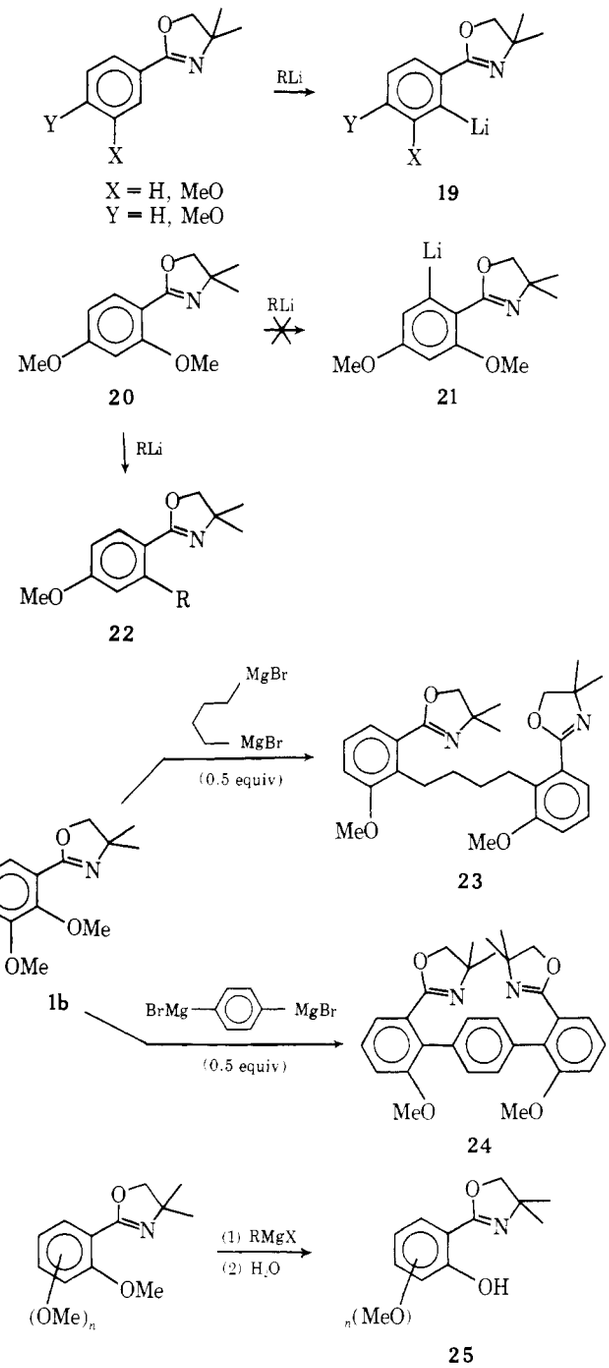


1b **9**

10

The use of aryl metallics has proven to be a most convenient route to unsymmetrical biaryl derivatives, a synthetic challenge of long standing. Recent progress in biphenyl syntheses[2,11,12] has improved greatly on the classical Ullmann reaction,[13] but most suffer from chemospecificity and/or limitations leading only to symmetrical biaryls. Although several efficient biaryl preparations are listed in Table I (entries 4, 14–17, 25), an additional study was performed using both an electrophilic and a nucleophilic aryloxazoline. The conversion of *o*-bromobenzoic acid to its oxazoline and then its Grignard reagent **11** gave after treatment with **1b** an 88% yield of the biaryl **13.** Hydrolysis of **13** gave the unsymmetrical biphenic dicarboxylic acid **14** in 93% yield. Similar treatment of **1b** with the Grignard reagent **12** (from *p*-bromobenzoic acid) gave **15** (90%) and the isomeric biphenic acid **16** in 85% yield. This sequence illustrates the versatility of the oxazoline ring as an activating group in nucleophilic aromatic substitution as well as the ability of oxazolines to protect carboxyl functions toward Grignard formation. The process, by virtue of its nature, precludes any isomeric products and is truly a chemospecific route to biaryls containing a number of ortho substituents. Other metal derivatives also appear to behave similarly in this substitution process. Thus, lithiotrimethylsilane gave the *o*-(trimethylsilyl)aryloxazoline **17,** while a variety of lithioamines smoothly displaced the methoxy group, affording the *o*-amino derivatives **18.**[14] The facile introduction



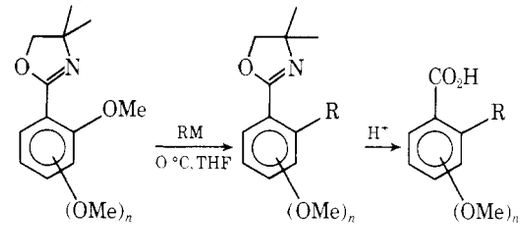


of the silyl group (**17**) provides a useful precursor for further substitution,[15] and a recent report by Dervan[16] has also opened new pathways for aryl silanes.

Metallation of aryloxazolines to **19** has been reported[17,18,19] to occur specifically ortho to the oxazoline activating group; however, if a methoxy group occupies an ortho position (**20**), no metallation occurs (to **21**) and only methoxy substitution takes place (**22**) (Table I, entries 21, 22). The absence of ortho lithiation was confirmed by quenching the reaction product of **20** with D_2O after addition of butyllithium (entry 22). In this instance undeuterated starting material was recovered in 51% yield. Grignard reagents derived from dihalides were also successfully employed, transforming **1b** into the 1,4-diarylbutane **23** and the terphenyl **24.** A general side reaction that was observed in these substitutions, particularly when Grignard reagents were employed, was the formation of the phenol **25** in 5–50% yields. The phenolic product, starting materials, and the substitution product were routinely separated using either column or preparative layer chromatography.

Introduction of organolithium reagents or Grignard reagents to the 2,6-(dimethoxy)aryloxazoline **1d** proceeded with less efficiency than the other aryloxazolines, presumably due to steric effects imparted by the two *o*-methoxyl groups (Table I, entries 23–25). For example, when 1 equiv of organometallic was added to **1d,** the substituted product **4** was isolated in moderate yield only after 40–90 h of reaction, thus indicating the slowness of the process. This may be attributed to the fact that the two *o*-methoxy substituents inhibit the oxazoline from achieving coplanarity with the aromatic nucleus. On the other hand, 2 equiv of phenyl Grignard reagent (after 76 h at 25 °C) gave a 93% yield of mono- and diarylated product **26** and **27** in equal amounts. An interesting facet of this reaction arose when it was found that the monoaryl product **26** when treated with phenyl Grignard reagent (excess, 126 h) gave no visible trace of the *m*-terphenyl derivative **27.** Thus, the biphenyl system (**26**) is not a precursor to the terphenyl system

Table I. Nucleophilic Substitution of 2-(o-Methoxyarl)oxazolines



1 3 4

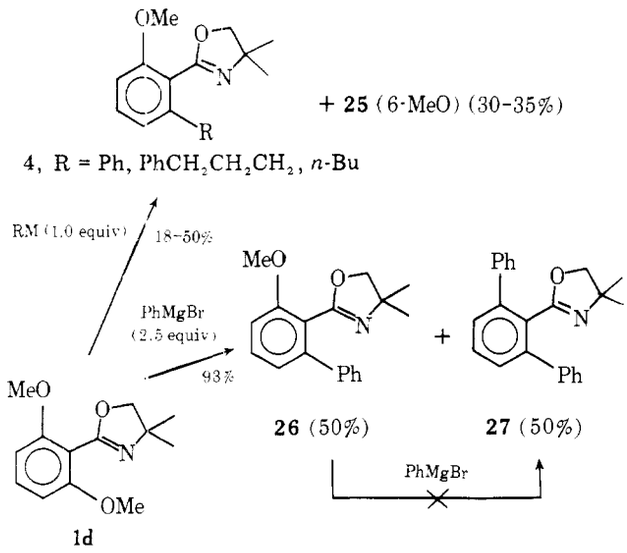
Entry	1	n	Posn	RM	Temp, °C	3,[a] %	Registry no.	4, %	Mp, °C	Registry no.
1	1a	0		n-BuLi	−35	22		74	39-40[b]	
2				n-BuMgBr	25	85				
3				PhLi	0	45		75	113-114[c]	
4				PhMgBr	25	95				
5	1b	1	3	n-BuLi	−45	98		93	101-102[d]	
6				MeMgBr	25	84		92	148-150[e]	
7				$Ph(CH_2)_2MgBr$	25	88		91	118-119[f]	65000-01-3
8				$Ph(CH_2)_3MgBr$	25	94		71	107-108[g]	64957-77-3
9				$PhCH_2MgBr$	25	6		[h]	69.0-69.5	
10				PhC≡CMgBr	25	31[i]	64957-79-5	67	146-148[j]	64957-78-4
11				CH_2=CHMgBr	25	66		90	125-127[k]	64957-80-8
12				CH_2=CHLi	−45	64				
13				(E)-PhCH=CHMgBr	25	61		87	128-130[l]	64957-81-9
14				4-(Ph)PhLi	−45	73		71	201-202[m]	57598-45-5
15				PhLi	−45	95		70	176-177[d]	
16				$4-(Me_2N)PhLi$	−45	66[n]	57598-37-5	69	253-254[o]	57598-46-6
17				2-(MeO)PhMgBr	25	95[p]	57598-39-7	78	196-197[q]	57598-49-9
18				2-(MeO)PhLi	−45	13				
19				EtLi	−45	88		75	120-121[r]	
20				t-BuLi	−45	95		45[t]	123-124[s]	57598-52-4
21	1c	1	4	EtMgBr	25	50[u]	64957-63-7			
22				n-BuLi	−22	47[v]	64957-64-8			
23	1d	1	6	n-BuLi[w]	−25	49[x]	64957-65-9			
24				$Ph(CH_2)_3MgBr$	25	18[y]	64957-66-0			
25				PhMgBr	25	50[z]	64957-67-1			
26	1e	2	4,5	n-BuMgBr	25	49		71	132-133[aa]	64957-69-3
27				EtMgBr	25	57[bb]	64957-68-2	[h]		

[a] Crude product unless otherwise noted. [b] C. D. Gutsche, G. L. Bachman, and R. S. Coffey, *Tetrahedron*, **18**, 617 (1962). [c] "Handbook of Chemistry and Physics", 47th ed, The Chemical Rubber Co., Cleveland, Ohio. [d] H. Richtzenhain and P. Nippus, *Chem. Ber.*, **77**, 566 (1944). [e] R. A. Barnes and R. W. Faessinger, *J. Org. Chem.*, **26**, 4544 (1961). [f] Anal. Calcd: C, 74.98; H, 6.38. Found: C, 74.78; H, 6.31. [g] Anal. Calcd: C, 75.52; H, 6.72. Found: C, 75.48; H, 6.94. [h] Not hydrolyzed to benzoic acid derivative; melting point is that of the 2-benzyl derivative (registry no., 65000-00-2). Anal. Calcd: C, 77.26; H, 7.17. Found: C, 76.92; H, 6.94. [i] Reaction stirred at 25 °C for 7 days; mp 93.5-94.5 °C. [j] Anal. Calcd: C, 73.55; H, 5.02. Found: C, 73.21; H, 5.30 ($0.5H_2O$). [k] Anal. Calcd: C, 67.41; H, 5.66. Found: C, 67.55; H, 5.88. [l] Anal. Calcd: C, 75.57; H, 5.55. Found: C, 75.65; H, 5.61. [m] Anal. Calcd: C, 78.93; H, 5.30. Found: C, 78.88; H, 5.15. [n] Mp 110-110.5 °C. [o] Isolated as hydrochloride. Anal. Calcd: C, 62.44; H, 5.90. Found: C, 62.41; H, 5.77. [p] Mp 129-131 °C. Anal. Calcd: C, 70.07; H, 8.65. Found: C, 69.74; H, 8.79. [q] Anal. Calcd: C, 69.76; H, 5.46. Found: C, 69.46; H, 5.51. [r] H. Richtzenhain, *Chem. Ber.*, 77, 1 (1944). [s] Anal. Calcd: C, 69.21; H, 7.74. Found: C, 68.94; H, 8.00. [t] Hydrolysis performed on methiodide salt (Experimental Section). [u] Oil; bulb-to-bulb distillation at 55 °C (0.06 mm). Anal. Calcd: C, 72.07; H, 8.21. Found: C, 71.90; H, 8.06. [v] Oil; distilled at 60 °C (0.04 mm). Anal. Calcd: C, 73.53; H, 8.87. Found: C, 73.89; H, 9.04. [w] A 1.0-1.1 equiv amount of organometallic introduced. [x] Anal. Calcd: C, 73.53; H, 8.87. Found: C, 72.95; H, 8.72. [y] Oil; distilled bulb-to-bulb, 135 °C (0.05 mm). Anal. Calcd: C, 77.98; H, 7.79. Found: C, 77.85, H, 8.00. [z] Mp 95.0-95.5 °C. Anal. Calcd: C, 76.84; H, 6.81. Found: C, 77.05; H, 6.75. [aa] Anal. Calcd: C, 65.53; H, 7.61. Found: C, 66.00; H, 8.00. [bb] Oil; bulb-to-bulb distillation at 100 °C (0.05 mm). Anal. Calcd: C, 68.42; H, 8.04. Found: C, 68.82; H, 8.26.

(**27**). This is not surprising in view of the large ortho substituents present in **26**. Thus, the terphenyl system must have arisen from some intermediate during the reaction.

If it is assumed that these reactions proceed via an addition–elimination sequence (Scheme I), then the σ complex B allows the oxazoline to align itself in a coplanar fashion with the aromatic ring while the metal (Mg^{2+} or Li^+) forms a strong complex with the methoxy group. The transition state leading to B may be envisioned as forming from A, where the R group of the organometallic enters from the side almost perpendicular to the aromatic ring (to the π cloud). This is consistent with the lack of steric inhibition to addition by large groups (*tert*-butyl, phenyl, etc.). However, if there are two ortho substituents, complex A and ultimately B become difficult to form and the reaction is slow or unable to occur. Thus, the failure of **26** to form the terphenyl **27** is understandable.

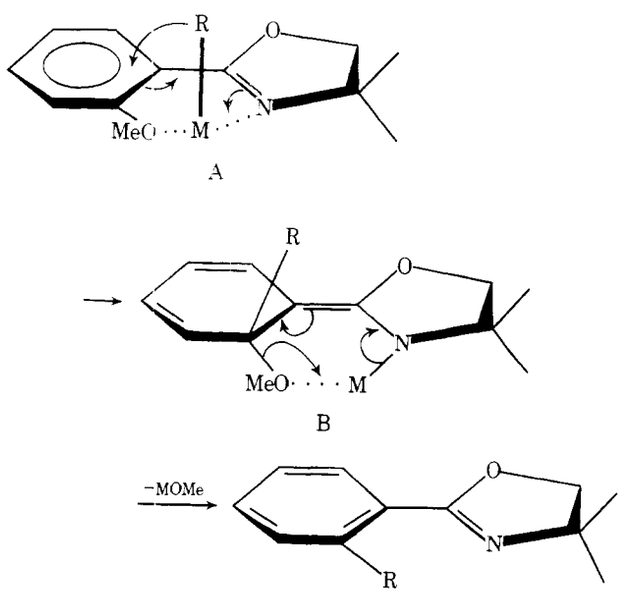
However, if the second phenyl group enters after the initial phenyl group is still in the σ complex C (Scheme II), complexation of phenyllithium may occur to the oxazoline sandwiched between the initial phenyl and methoxy group and addition may ensue with expulsion of the 2-methoxyl group. In effect, the second phenyl is introduced in a 1,8 addition to C. The relative rates of addition (C, k_2) and elimination (**26**, k_1) therefore determine the 1:1 mixture which results.[23] In those instances where 2,6-(disubstituted)aryloxazolines are formed, hydrolysis to the benzoic acids by removal of the ox-



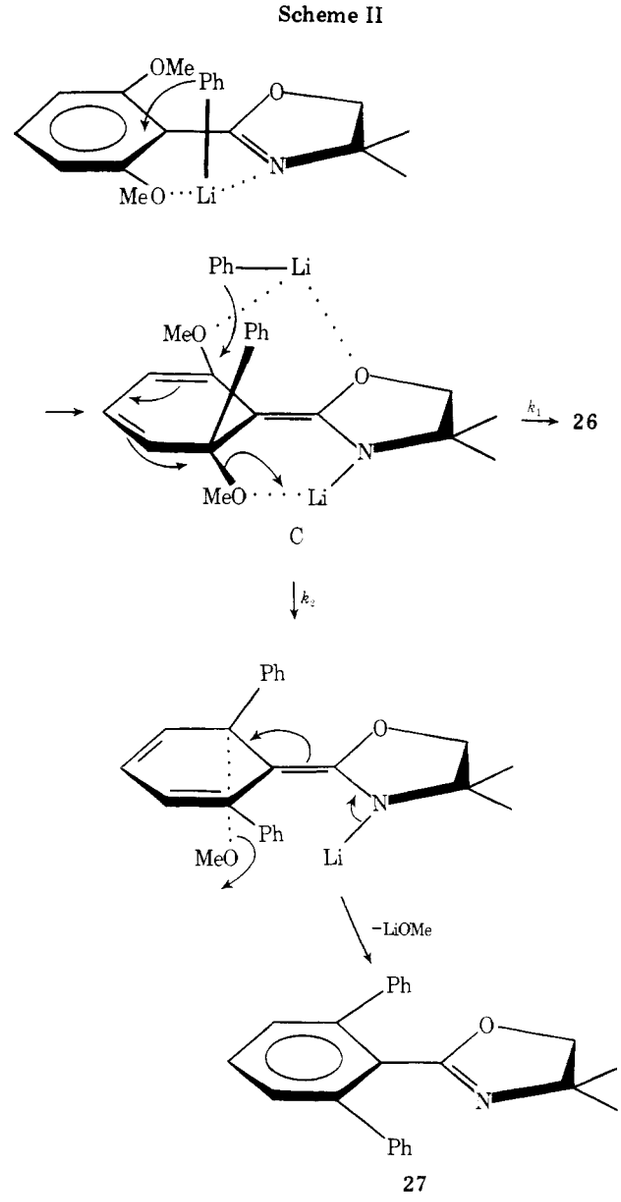
azoline has thus far proved to be unsatisfactory. The usual steric effects toward hydrolysis are obviously in play, and further efforts in this regard are in progress.

The importance of organometallic (RM) complexation to the *o*-(methoxy)aryloxazolines 1 (A in Scheme I) cannot be overstated since a number of organometallic reagents failed to substitute the methoxy group. Grignard and lithium reagents which gave no substitution are listed in Table II. Benzyl Grignard reagent gave 5–6% of the substitution products, but all of the others listed gave only starting material or demethylation (10–50%) to the phenol **25**. A glance at the structures in Table II indicates that all are delocalized or intramolecularly chelated anions. It would therefore seem that failure to add to the aromatic ring is due to (a) the complex A generating an anion sufficiently delocalized to allow its addition or (b) the intramolecular complexation already present in the organometallic precluding any complexation with the methoxyaryloxazoline. For lithium ethanethiolate, the high nucleophilicity of the sulfur results in rapid and complete demethylation of the *o*-methoxy group, affording **25** in quantitative yield. The failure of LiSEt to displace methoxy also enhanced the assumption that the substitution reactions were not occurring by an electron-transfer (ET) process since sulfides are known to be excellent ET reagents.[20] In order to assess further the possibility of an ET mechanism

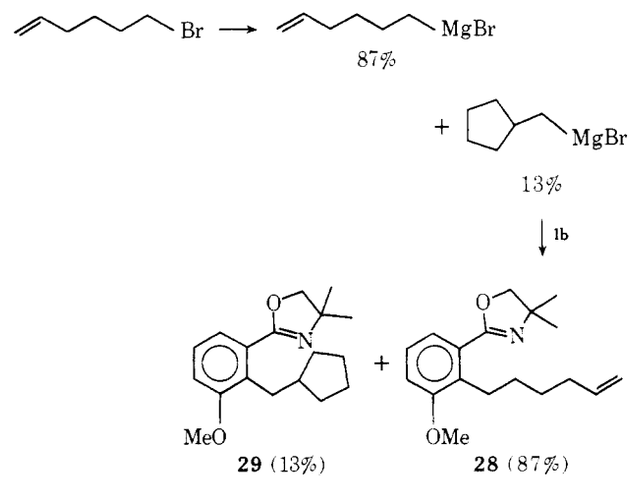
Scheme I



Scheme II



for this reaction, 1-bromohexene and its Grignard reagent were examined as an alkylating agent. It is well-known[21] that hexenylmagnesium bromide in a radical reaction rearranges rapidly ($k_{cycln} = 10^5\ s^{-1}$) to cyclopentylmethylmagnesium bromide. Therefore, reaction with **1b** should give a large amount of **29** as a byproduct in the formation of **28** if alkyla-



tion proceeded by an ET route. Hexenyl bromide was transformed[22] into its Grignard reagent (THF), and prior to reaction with **1b** it was quenched and analyzed (VPC) for the ratios of *n*-hexene and methylcyclopentane. The ratio of several runs was 87 ± 3% of the former and 13 ± 3% of the latter, in agreement with the literature.[22] Reaction with **1b** gave **28** and **29** in 73% yield, and NMR analysis indicated that 87% of **28** and 13% of **29** was present. Thus, there was virtually no change in the composition of the products compared to the composition of the starting Grignard reagents. It therefore may be concluded that if the alkylation of methoxyaryloxazoline is an ET process, its rate constant must be considerably faster than 10^5 s^{-1}, the rate constant for the rearrangement of hexenyl to cyclopentylmethyl radical. In view of the efficiency of lithioamides[14] in this reaction and the unlikelihood of their ability to proceed by ET mechanisms, it can be assumed at this time that this highly useful synthetic process is occurring through an addition–elimination sequence.

Further studies on polynuclear aromatics and heteroaromatics are in progress, and results of these efforts will be reported in due course.

Experimental Section

2-(2-Methoxyphenyl)-4,4-dimethyl-2-oxazoline (1a). A mixture of 50 g (330 mmol) of *o*-anisic acid and 117.3 g (980 mmol) of thionyl chloride was stirred at 25 °C for 24 h. The excess thionyl chloride was removed in vacuo, and the residue was distilled (bp 68 °C, 0.05 mm), yielding 51.4 g of the acid chloride as a colorless oil. A solution of the acid chloride in 75 mL of methylene chloride was added dropwise to 53.7 g (600 mmol) of 2-amino-2-methyl-1-propanol in 125 mL of methylene chloride at 0 °C. After stirring for 2.5 h at 25 °C, the solution was filtered and the filtrate evaporated to give 68.3 g of the crystalline amide. The latter (25 g) was treated dropwise with 40.2 g of thionyl chloride and magnetically stirred. The solution was then poured into 150 mL of dry ether, and the oxazoline hydrochloride precipitated and was removed by filtration. The salt was neutralized with 20% sodium hydroxide, and the alkaline solution was extracted with ether, dried ($MgSO_4$), and concentrated to give an oil (21 g, 83%), which crystallized on standing, mp 66–68 °C. An analytical sample was purified by recrystallization from hexane, mp 68–69.5 °C; IR (KBr) 1635 cm^{-1}; NMR (CCl_4) δ 7.75 (m, 1), 7.33 (m, 1), 6.94 (m, 2), 3.96 (s, 2), 3.86 (s, 3), 1.33 (s, 6).

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37. Found: C, 70.47; H, 7.47.

2-(2,3-Dimethoxyphenyl)-4,4-dimethyl-2-oxazoline (1b). In a manner similar to the preparation of **1a**, 12 g of 2,3-dimethoxybenzoic acid gave 10.44 g (70%) of **1b**, mp 49–50 °C; IR (film) 1642 cm^{-1}; NMR (CCl_4) δ 6.8–7.4 (m, 3), 3.96 (s, 2), 3.83 (s, 3), 3.78 (s, 3), 1.33 (s, 6).

Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28. Found: C, 66.31; H, 7.54.

2-(2,4-Dimethoxyphenyl)-4,4-dimethyl-2-oxazoline (1c). Following the procedure for **1a**, 50 g of 2,4-dimethoxybenzoic acid gave 35.2 g (56%) of **1c** as a viscous oil, which was purified by chromatography (silica gel) using ethyl acetate as the eluent; IR (film) 1630 cm^{-1}; NMR (CCl_4) δ 7.57 (d, J = 9 Hz, 1), 6.32 (md, 2), 3.85 (s, 2), 3.73 (s, 3), 3.68 (s, 3), 1.27 (s, 6).

Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28. Found: C, 66.12; H, 7.12.

2-(2,6-Dimethoxyphenyl)-4,4-dimethyl-2-oxazoline (1d). Following the procedure for **1a**, 25.0 g of 2,6-dimethoxybenzoic acid gave 24.5 g (76% overall) of **1d**, mp 64–65 °C (hexane); IR (film) 1665 cm^{-1}; NMR (CCl_4) δ 7.22 (t, J = 9 Hz, 1), 6.50 (d, J = 9 Hz, 2), 3.93 (s, 2), 3.77 (s, 6), 1.33 (s, 6).

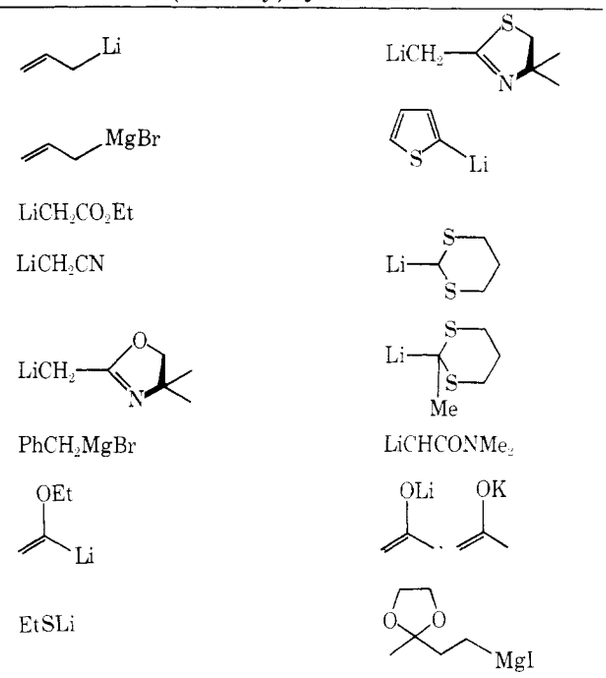
Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28. Found: C, 66.42; H, 7.04.

2-(2,4,5-Trimethoxyphenyl)-4,4-dimethyl-2-oxazoline (1e). This compound was prepared in 60% overall yield from 10 g of 2,4,5-trimethoxybenzoic acid according to the procedure given for **1a**, mp 84–86 °C (hexane); IR (film) 1630 cm^{-1}; NMR (CCl_4) δ 7.27 (s, 1), 6.40 (s, 1), 3.93 (s, 2), 3.82 (s, 6), 3.78 (s, 3), 1.33 (s, 6).

Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22. Found: C, 63.47; H, 7.34.

Reaction of 1 (a–e) with Organolithium Reagents. General Procedure. The formation of compounds **3** in Table I using organolithium reagents was accomplished using the following procedure for all. A solution of **1** (**a–e**), 14.5 mmol, in 60 mL of THF was cooled to −45 °C under a nitrogen atmosphere. To this was added dropwise 15.5–16.0 mmol of organolithium reagent in the appropriate solvent (hexane, ether, or THF). In some cases the addition of organolithium reagent was accompanied by an exotherm (usually alkyllithium), and the reaction was held below −35 °C by adjusting the rate of addition. Stirring of the resulting amber solution at −30 °C was continued until TLC monitoring (ethyl acetate–hexane) indicated the absence of starting material (usually 1–3 h). In most instances the reaction was allowed to slowly warm to 0 °C and quenched in saturated ammonium chloride solution, extracted (3 times) with ether, dried (K_2CO_3), and concentrated. The products were purified by preparative thin-layer or column chromatography on silica gel (ethyl acetate–hexane). In other cases the product was distilled, bulb-to-bulb, under a vacuum.

Table II. Organometallics Failing to React with *o*-(Methoxy)aryloxazolines



Reaction of 1 (a–e) with Grignard Reagents. General Procedure. The formation of **3** in Table I using Grignard reagents was performed as follows. The Grignard reagent (6.00 mmol) in ether or THF was slowly added to 5.8 mmol of **1** (**a–e**) in 10 mL of THF under argon or nitrogen at 25 °C. Stirring of the solution was usually performed for 16–20 h or longer if TLC monitoring (silica gel, ethyl acetate–hexane) indicated the presence of starting material. Workup of the reaction mixture as described above gave the crude product, which was purified by bulb-to-bulb distillation and column or preparative thin-layer chromatography (silica gel, ethyl acetate–hexane).

Hydrolysis of Oxazolines 3 to Benzoic Acids 4. General Procedure. The oxazolines (5 mmol) were dissolved in 100 mL of 4.5 N hydrochloric acid and heated to reflux for 16–24 h. After cooling, the heterogeneous mixture was extracted with ether (3 times). The ethereal extracts were washed with water and saturated brine, dried ($MgSO_4$), and concentrated to give products of acceptable purity. Further purification was achieved by recrystallization from hexane, ethanol–water, or water, depending on the solubility properties.

2-Methoxyvalerophenone from 5 (2-MeO; R = *n*-Bu). In a typical experiment, 2 mL (5.0 mmol) of 2.5 M *n*-BuLi in hexane was added slowly to 1.03 g (5.0 mmol) of **1a** in THF at −35 °C. The solution was stirred for 3 h and then warmed to ambient temperature. The usual aqueous workup afforded 22% of **3** (R = *n*-Bu; *n* = O) and 49% of **5** after preparative TLC (silica gel, 20% ethyl acetate–hexane). Hydrolysis of **5** in 4.5 M hydrochloric acid for 18 h at reflux gave the crude ketone, purified by elution through silica gel with 10% acetone–hexane; IR (film) 1680, 1025 cm^{-1}; NMR (CCl_4) δ 6.75–7.73 (m, 4), 3.87 (s, 3), 2.90 (t, J = 7 Hz, 2), 1.13–1.93 (m, 4), 0.68–1.12 (m, 3).

Anal. Calcd: C, 74.97; H, 8.39. Found: C, 74.87; H, 8.12.

The 2,4-DNP melted at 126.4–126.6 °C (from ethanol).

Reaction of 1b with *tert*-Butyllithium. 2-*tert*-Butyl-3-methoxybenzoic Acid 4 (3-MeO; R = *t*-Bu). In a manner using the

general procedure for organolithium reagents, 0.380 g (1.62 mmol) of **1b** in 40 mL of THF and 1.4 mL (3.22 mmol) of 2.3 M *tert*-butyllithium gave 0.427 g (~99%) of **3** (R = *t*-Bu; 3-MeO) as a clear oil; IR (CCl_4) 1665 cm^{-1}; NMR (CCl_4) δ 7.3–6.6 (m, 3), 3.93 (s, 2), 3.85 (s, 3), 1.48 (s, 9), 1.33 (s, 6).

Without further purification, **3** was stirred with excess methyl iodide at room temperature overnight and the excess methyl iodide removed in vacuo. To the crude methiodide salt was added 12 mL of methanol and 12 mL of 20% aqueous sodium hydroxide, and the mixture was heated to reflux for 12 h. The solution was extracted with ether and the ethereal extracts were discarded. The aqueous solution was neutralized to pH 2 (9 N HCl), extracted with ether, dried ($MgSO_4$), and concentrated to afford **4.** Recrystallization from hexane provided pure 2-*tert*-butyl-3-methoxybenzoic acid (45%), mp 123–124 °C; IR (CCl_4) 1695 cm^{-1}; NMR (CCl_4) δ 11.9 (s, 1), 7.33–6.75 (m, 3), 3.86 (s, 3), 1.53 (s, 9).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.94; H, 8.00.

2-Carboxy-6-methoxy-3′-(*N*-methyl-*N*-*tert*-butoxycarbonyl)biphenyl (9). 3-Bromo(*N*-methyl-*N*-Boc)aniline (0.472 g) was converted to its lithio salt by addition of 0.72 mL of 2.3 M *n*-butyllithium (hexane) to a THF solution at −78 °C. After 15 min, the solution was warmed to −45 °C and 0.353 g of **1b** in 15 mL of THF was added. The solution was stirred for 5 h at −45 °C and then warmed to 25 °C, quenched in ammonium chloride (saturated), extracted with ether, dried, and concentrated. Chromatography, as above, afforded the biaryloxazoline, mp 93–97 °C. Without further purification the latter was hydrolyzed in two fashions.

(A) Acidic Hydrolysis to 10. A solution of the above (0.2 mmol) in 10 mL of 4 N hydrochloric acid was heated to reflux (12 h). Ether extraction gave no ether-soluble material. The pH was adjusted to 6 with saturated sodium bicarbonate. Ether extraction produced crude **10** (40%). Conversion to its hydrochloride (dry HCl passed into an ethereal solution of **10**) gave mp 200 °C dec; IR (KBr) 1695 cm^{-1}; NMR (Me_2SO-d_6) δ 8.7 (brd s, 2), 7.8–7.0 (m, 7), 3.73 (s, 3), 3.13 (s, 3).

Anal. Calcd for $C_{15}H_{16}ClNO_3$: C, 61.33; H, 5.49. Found: C, 61.11; H, 5.78.

(B) Alkaline Hydrolysis to 9. The biaryloxazoline was stirred in the presence of a 5-fold excess of methyl iodide overnight and the excess methyl iodide removed in vacuo. To the crude methiodide (0.097 g) was added 25 mL of a 1:1 solution of methanol and 20% sodium hydroxide, and the mixture was heated to reflux for 15 h. Cooling was followed by ether extraction, and the latter phase was discarded. Acidification of the aqueous phase to pH 2 (9 N HCl) and ether extraction, drying ($MgSO_4$), and concentration gave 0.05 g (65%) of **9** as a colorless solid, mp 52–55 °C (hexane); IR (CCl_4) 1700 cm^{-1}; NMR (CCl_4) δ 7.85 (s, 1), 7.65–6.70 (m, 7), 3.72 (s, 3), 3.22 (s, 3), 1.42 (s, 9).

Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49. Found: C, 67.43; H, 6.26.

2,4′-(Dicarboxy)-6-methoxybiphenyl (16). The preparation of the *p*-(magnesiobromide)phenyloxazoline **12** has been reported.[10] The deep red Grignard reagent was added to 1.18 g (5 mmol) of **1b** in 10 mL of THF at 25 °C. After stirring for 15 h, the solution was worked up in the usual way to give 2.11 g of a yellow solid, **15.** Purification via preparative TLC (50% ethyl acetate–hexane) gave 1.71 g, mp 151–153 °C (90%). Spectral characteristics for **15** were the following: IR (film) 1645, 1045 cm^{-1}; NMR (CCl_4) δ 6.67–8.07 (m, 7), 4.03 (s, 2), 3.67 (s, 3), 3.60 (s, 2), 1.35 (s, 6), 1.15 (s, 6).

The biaryloxazoline **15** was hydrolyzed by heating to reflux 0.75 g in 4.5 N HCl for 18 h. The resulting solid was filtered and recrystallized from ethanol–water to give 0.462 g (85%) of **16** as a colorless solid, mp 224–227 °C; IR (KBr) 2300–2400, 1675, 1050 cm^{-1}; NMR (Me_2SO-d_6) δ 11.7–12.7 (brd s, 2), 7.10–8.23 (m, 7), 3.72 (s, 3).

Anal. Calcd: C, 66.17; H, 4.45. Found: C, 66.01; H, 4.31.

2,2′-(Dicarboxy)-6-methoxybiphenyl (14). In a fashion similar to **16** above, 1.79 g of *o*-bromophenyloxazoline was converted to its Grignard reagent[10] and added to 1.18 g of **1b** in 10 mL of THF. The solution was stirred at 25 °C for 60 h and then poured into saturated ammonium chloride, extracted with ether, dried (K_2CO_3), and concentrated to give 2.25 g of crude **13.** Purification on silica gel using preparative TLC (50% ethyl acetate–hexane) gave 1.66 g (88%) of pure **13,** mp 99–101 °C; IR (film) 1650, 1040 cm^{-1}; NMR (CCl_4) δ 6.70–8.00 (m, 7), 3.57–3.67 (s, 7), 0.88–1.27 (s, 12).

Hydrolysis was performed by heating 0.756 g of **13** in 4.5 N HCl for 24 h. The solid was collected by filtration and recrystallized from water to give 0.467 g (93%) of pure **14,** mp 222–224 °C; IR (film) 2300–3500 broad, 1680, 1060, cm^{-1}; NMR (Me_2SO-d_6) δ 11.67–12.77 (brd, 2), 6.67–8.43 (m, 5), 3.67 (s, 3).

Anal. Calcd: C, 66.17; H, 4.45. Found: C, 66.27; H, 4.35.

2-(3-Methoxy-2-trimethylsilylphenyl)-4,4-dimethyl-2-oxazoline (17). Methyllithium (3.8 mL, 1.45 M) was added to 1.2 mL (6.0 mmol) of hexamethyldisilane in 4 mL of dry HMPA at 0 °C. After stirring for 20 min, 10 mL of dry THF was added and the solution was cooled to −78 °C. A solution of 1.18 g (5 mmol) of **1b** in 5 mL of THF was introduced, and the deep red mixture was stirred for 2 h at −78 °C and then warmed to 0 °C over 1 h. The usual workup gave crude **17,** which was purified by preparative thin-layer chromatography (50% ethyl acetate–hexane), furnishing 58 mg of **1b** and 0.907 g of **17** as an oil. Distillation, bulb-to-bulb, at 70 °C (0.05 mm) gave pure material (66%); NMR (CCl_4) δ 6.67–7.38 (m, 3), 3.95 (s, 2), 3.73 (s, 3), 1.32 (s, 6), 0.30 (s, 9).

Anal. Calcd: C, 64.94; H, 8.36. Found: C, 65.15; H, 7.89.

1,4-Bis(2-oxazinyl-6-methoxyphenyl)butane (23). 1,4-Dibromobutane (0.54 g, 2.5 mmol) was added to 0.243 g of magnesium turnings in 10 mL of dry THF. The resulting Grignard reagent was then added to 1.18 g (5.0 mmol) of **1b** in 5 mL of THF at 25 °C. The solution was stirred at room temperature for 21 h and then heated at reflux for 24 h. The usual workup gave the crude product, which was purified by preparative TLC (silica gel, 50% ethyl acetate–hexane) to give 0.320 g of **25** (3-MeO) and 0.333 g (29%) of **23** as a colorless solid, mp 150–151 °C (hexane); NMR ($CDCl_3$) δ 6.73–7.43 (m, 6), 4.05 (m, 4), 3.82 (m, 6), 2.77 (m, 4), 1.17–1.80 (m, 4), 1.40 (s, 12).

Anal. Calcd: C, 72.39; H, 7.81. Found: C, 72.43; H, 7.95.

1,4-Bis(2-oxazinyl-6-methoxyphenyl)benzene (24). A mixture of 1.18 g of **1b,** 0.170 g of magnesium turnings, and 0.590 g of *p*-dibromobenzene in 15 mL of dry THF was heated under reflux for 24 h. The standard workup gave the crude product, which was purified by preparative TLC (silica gel, 50% ethyl acetate–hexane, eluted twice). There was cut (ether) from the plate 0.116 g of **25** (11%), 0.284 g of **3** (Table I, entry 15; 20% yield), and 0.365 g (30%) of **24.** Recrystallization from ethyl acetate–hexane gave pure **24,** mp 220–221 °C; NMR (CCl_4) δ 6.90–7.47 (m, 10), 3.77 (s, 3), 3.75 (s, 4), 1.27 (s, 12).

Anal. Calcd: C, 74.36; H, 6.66. Found: C, 74.17; H, 6.59.

2-(2,6-Diphenylphenyl)-4,4-dimethyl-2-oxazoline (27). A solution of 1.18 g (5.0 mmol) of **1b** in 5 mL of THF was treated with 12.5 mmol of phenylmagnesium bromide (from 1.96 g of bromobenzene and 0.30 g of magnesium turnings in 17 ml of THF), and the mixture was stirred for 76 h at room temperature. After quenching (saturated NH_4Cl), ether extraction, drying (K_2CO_3), and concentration, the crude mixture was purified by preparative TLC (silica gel, 50% ethyl acetate–hexane). The faster moving band was cut away and extracted with ether to give, after evaporation, 0.70 g (50%) of **27,** mp 96.5–97.5 °C; IR (film) 1660, 1456, 1038, 760, 700 cm^{-1}; NMR (CCl_4) δ 6.27–7.60 (m, 13), 3.47 (s, 2), 0.87 (s, 6).

Anal. Calcd: C, 84.37; H, 6.46. Found: C, 84.65; H, 6.59.

The slower moving band, after similar isolation, gave 0.699 g (49.8%) of **26** (Table I, entry 25). Treatment of **26** with 2.0 equiv of phenylmagnesium bromide in THF for 170 h gave complete recovery of the starting material.

Reaction of 1b with 5-Hexenylmagnesium Bromide. Preparation of 28 and 29. Freshly distilled 6-bromo-1-hexene (1.06 g, 6.50 mmol) was added to 0.160 g of magnesium turnings in 10 mL of dry THF. After the Grignard reagent was completely formed, 0.25 mL was withdrawn and quenched in water. Analysis by VPC indicated 87–90% of 1-hexene and 10–13% of methylcyclopentane. The remainder of the Grignard reagent was added to 1.18 g of **1b** in 7 mL of THF at 25 °C and stirred for 6 h. Standard workup gave 1.46 g of an oil, which was purified to remove starting material (**1b,** 8%) by preparative TLC (50% ethyl acetate–hexane). The overlapping bands were removed together from the silica gel with ether and evaporated to leave 1.08 g of a mixture of **28** and **29.** NMR analysis indicated that the mixture consisted of 87% of **28** and 13% of **29.** Analysis of the mixture gave the following results: NMR (CCl_4) δ 6.67–7.43 (m, 3), 4.77–6.00 [m, vinyl region, 2.5 (87%)], 3.92 (s, 2), 3.75 (s, 3), 2.80–3.23 (m, 2), 1.87–2.33 (m, 2), 1.40–1.77 (m, 4), 1.32 (s, 6).

Anal. Calcd: C, 75.22; H, 8.77. Found: C, 74.91; H, 8.79.

Acknowledgment. Financial support of this work was provided by the National Institutes of Health and the Army Research Office (Durham). An Eastman Kodak Fellowship (E.D.M.) is also gratefully acknowledged.

Registry No.—1a, 57598-33-1; **1a** (HCl), 64957-82-0; **1b,** 57598-32-0; **1b** (HCl), 64957-83-1; **1c,** 64957-84-2; **1c** (HCl), 64957-85-3; **1d,** 64957-86-4; **1d** (HCl), 64957-87-5; **1e,** 64957-88-6; **1e** (HCl), 64957-89-7; **2a,** 579-75-9; **2a** (acid chloride), 21615-34-9; **2b,** 1521-38-6; **2b** (acid chloride), 7169-06-4; **2c,** 91-52-1; **2c** (acid chloride), 39828-35-8; **2d,** 1466-76-8; **2d** (acid chloride), 1989-53-3; **2e,** 490-64-2; **2e** (acid

chloride), 42833-66-9; **3** (R = Bu; n = 0), 57629-47-7; **3** (R = t-Bu; 3-MeO), 57598-43-3; **3** (R = t-Bu; 3-MeO) methiodide, 65000-02-4; **4** (R = t-Bu; 3-MeO), 57598-52-4; **5** (R = Bu; 2-MeO), 64957-90-0; **6** (R = Bu; 2-MeO), 20359-54-0; **9**, 57598-48-8; **10** (HCl), 64957-91-1; **13**, 64957-92-2; **13** (meta analogue), 64957-93-3; **14**, 38197-35-2; **15**, 64957-94-4; **16**, 64957-71-7; **17**, 64957-72-8; **23**, 64957-73-9; **24**, 65000-03-5; **27**, 64957-74-0; **28**, 64957-75-1; **29**, 64957-76-2; thionyl chloride, 7719-09-7; 2-amino-2-methyl-1-propanol, 124-68-5; 3-bromo(N-methyl-N-Boc)aniline, 57598-34-2; 2-p-bromophenyl-4,4-dimethyloxazol-2-ine, 32664-14-5; 2-o-bromophenyl-4,4-dimethyloxazol-2-ine, 32664-13-4; hexamethyldisilane, 1450-14-2; 1,4-dibromobutane, 110-52-1; p-dibromobenzene, 106-37-6; bromobenzene, 108-86-1; 6-bromo-1-hexene, 2695-47-8; 2-methoxyvalerophenone 2,4-DNP, 64957-70-6.

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(23) Professor D. J. Cram (UCLA) informed us that the addition of a large excess of phenylmagnesium bromide to **1d** gave the *m*-terphenyl derivative **27** in quantitative yield.

Sulfenylation and Sulfinylation of Lactams and Imino Ethers

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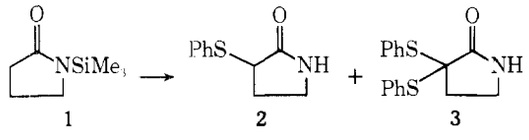
The sulfenylation of 1-trimethylsilyl-2-pyrrolidinone (**1**) with phenyl disulfide under a variety of reaction conditions afforded the bissulfide **3** as the major product along with the monosulfide **2**. The direct sulfinylation of **1** with methyl benzenesulfinate, however, could be achieved to afford the sulfoxide **4**. An analogous sulfinylation of 1-methyl-2-pyrrolidinone gave the sulfoxide **13** in excellent yield. The imino ether **5** could be monosulfenylated effectively by employing a 1:2:1 ratio of lactam/base/electrophile. It was also observed that in the sulfenylation of the N-alkyllactams **7** and **8** that HMPA had no effect on promoting bissulfenylation and that the ratio of substrate/base/electrophile is very important.

Recently, we reported[2] that mono- or bissulfenylation or selenenylation of N-methyllactams can be cleanly controlled by varying the equivalents of base utilized in the reaction. It has also been demonstrated[3] that an α-phenylselenenyl or an α-phenylsulfenyl moiety can be used to introduce a $\Delta^{3,4}$ double bond in an intact 2-pyrrolidinone nucleus.

In order to develop a synthetic sequence that would be compatible with the formation of a 3-pyrrolin-2-one system and also allow modification on the nitrogen, we were interested in utilizing the trimethylsilyllactam **1**[4] and the imino ether **5**. The results of the sulfenylation of **1** and **5** and related lactam chemistry are reported herein.

Reaction of the trimethylsilyllactam **1** with 2 equiv of LDA in THF at −78°C followed by sulfenylation with 1 equiv of phenyl disulfide and subsequent cleavage of the N–Si bond on workup afforded the monosulfide **2** in 29% yield and the

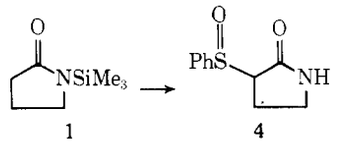


1 2 3

bissulfide **3** in 50% yield. When a 1:2:2 ratio of lactam/base/electrophile was employed, it was found that sulfenylation of **1** gave the bissulfide **3** in 84% yield along with 3% of the monosulfide **2**.

The best yield of the monosulfide was realized when a 1:1:2 ratio of lactam/base/electrophile was used with inverse quenching at 0 °C. In this case, **2** was obtained in a 35% yield and **3** in 33% yield. The results observed by varying the ratio of lactam/base/electrophile with or without the presence of HMPA and with or without inverse quenching are summarized in Table I.

Although the above results with respect to controlling mono- vs. bissulfenylation in the case of silylated lactams were discouraging, the problem could be circumvented, since it was found that sulfinylation of **1** with methyl benzenesulfinate[5]



1 4

could be achieved to afford the desired sulfoxide directly. Thus, reaction of **1** with 2 equiv of LDA in THF at −78 °C and subsequent sulfinylation with methyl benzenesulfinate (45 min at −78 °C and room temperature for 2 h) afforded a 67% yield of the crystalline sulfoxide **4**.

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