The Oxazoline-Benzyne Route to 1,2,3-Trisubstituted Benzenes. Tandem Addition of Organolithiums, Organocuprates, and α-Lithionitriles to Benzynes

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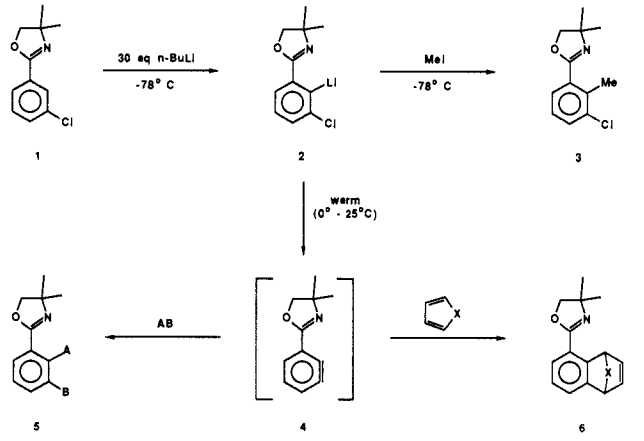
Abstract: The generation of a benzyne intermediate **4** via ortho lithiation of readily available (*m*-chlorophenyl)oxazoline **1** gives rise to a variety of polysubstituted benzene derivatives. The key property of **4** is its ability to form benzyne at temperatures between −10 and 0 °C, which allows a variety of nucleophiles to be placed in solution. As the ortho lithio intermediate loses lithium chloride to form the benzyne, mostly clean regiospecific additions occur in situ. Removal of the oxazoline produces a variety of benzoic acids with substituents derived from nucleophilic and electrophilic entry onto the benzyne intermediate. Kinetic and thermodynamic control has been successfully achieved depending upon the nature of the nucleophile present during benzyne formation. In this fashion, isomeric benzenes with little or no isomeric mixtures were formed. Cycloadditions (4 + 2) using furans, pyrroles, and thiophenes were also performed on the benzynyloxazoline.

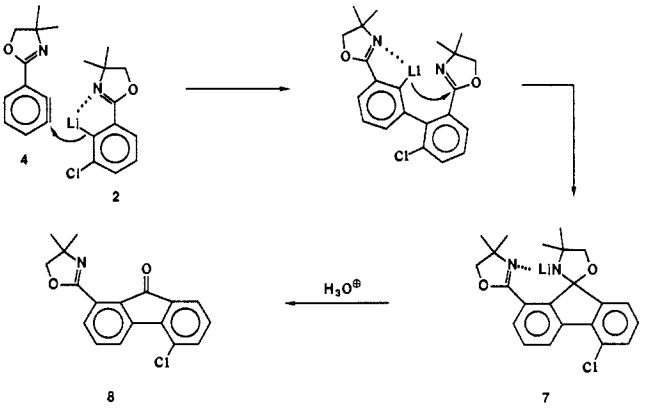
Aromatic substitution has occupied a central role in organic chemistry for over 100 years and still continues to be an area of considerable activity.[1] From the earliest studies on electrophilic substitution,[2] the Friedel–Crafts,[3] nucleophilic aromatic substitution,[4] and free-radical substitution,[5] the stream of publications on every aspect of these important processes continues to appear in periodicals. Among the most notable achievements in aromatic chemistry was the advent of a benzyne[6] intermediate in certain nucleophilic substitutions. The chemistry of benzyne has since been well incorporated into the arsenal of synthetic chemistry and today is accepted as a valuable addition to synthetic design.[7] We now describe in detail our own efforts in adding further to the synthetic utility of benzynes by demonstrating a series of regioselective reactions derived from phenyloxazoline **1**.[8-10] The (*m*-chlorophenyl)oxazoline **1**, shown in Scheme I, is readily prepared in good yields from *m*-chlorobenzoic acid. Upon metalation with *n*-butyllithium at −78 °C in THF, the ortho-lithiated derivative is formed[11] and can be alkylated smoothly with methyl iodide. However, it was our intention to coerce **2** into eliminating LiCl generating the benzyne **4**. This plan was based upon literature precedent[12] for generating benzyne from *o*-lithiochlorobenzene, which eliminates LiCl at ~−100 °C. Thus, the formation of the (2-methyl-3-chlorophenyl)oxazoline **3** was surprising.

Scheme I



However, it was soon discovered that allowing the lithio derivative to warm in THF solution in the presence of excess *n*-BuLi, other nucleophiles, or other reactive species (e.g., a diene), gave the expected benzyne adducts **5** and **6**, respectively. Thus, the sequence shown in Scheme I will form the subject of this report.

Reaction of Benzyne 4 with Organolithiums. When the lithiated phenyloxazoline **2** was allowed to warm in its THF solution, and no nucleophile or electrophile was added, the reaction produced the fluorenone **8** in 68% isolated yield. This interesting process



was presumed to involve addition of the ortho-lithiated oxazoline **2** to the benzyne as the temperature rose. The regioselective addition gave only **8**, which was presumed to be thermodynamically controlled and in agreement with other additions to benzynes containing an electron-withdrawing group.[7c] Furthermore, it was felt that the ortho lithio derivative would be stabilized by chelation in **2**. Addition into the C=N link of the oxazoline would be

(1) For delightful and informative reading on aromatic compounds, their structure and reactions in the early 20th century, see: *Essays on the History of Organic Chemistry in the United States, 1875–1955*; Tarbell, D. S., Tarbell, A. T., Eds.; Folio: Nashville, TN, 1986; pp 139–151.
(2) von Euler, H. J. *Justus Liebigs Ann. Chem.* **1903**, *330*, 280.
(3) Friedel, C.; Crafts, J. M. *C. R. Hebd. Seances Acad. Sci.* **1877**, *84*, 1392.
(4) Miller, J. *Aromatic Nucleophilic Substitution*; Elsevier: New York, 1968.
(5) Bachmann, W. E.; Hoffman, R. A. *Org. React. (N.Y.)* **1944**, *2*, 224.
(6) Roberts, J. D.; Simons, H. E.; Carlsmith, L. A.; Vaughn, C. W. *J. Am. Chem. Soc.* **1953**, *75*, 3290.
(7) For reviews, see: (a) Fields, E. K. *Org. Chem. (N.Y.)* **1973**, *26*, 449. (b) Barton, D. H. R.; Ollis, W. D. In *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon: Oxford, 1979; Vol. 1, p 477. (c) Hoffmann, R. W. *Dehydrobenzene and Cycloalkenes*; Academic: New York, 1967. (d) For a recent innovative method to generate benzynes via fluoride-induced elimination of *o*-silyl triflates, see: Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211. Shankaran, K.; Snieckus, V. *Tetrahedron Lett.* **1984**, *27*, 2827.
(8) Some of the studies reported here have appeared in preliminary form: (a) Meyers, A. I.; Rieker, W. F. *Tetrahedron Lett.* **1982**, *23*, 2091. (b) Meyers, A. I.; Pansegrau, P. D. *Ibid.* **1983**, *24*, 4935. (c) Meyers, A. I.; Pansegrau, P. D. *Ibid.* **1984**, *25*, 2941. (d) Meyers, A. I.; Pansegrau, P. D. *J. Chem. Soc., Chem. Commun.* **1985**, 690.
(9) For a review on aromatic oxazolines in electrophilic and nucleophilic substitution, see: Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *44*, 105.
(10) For a review on asymmetric synthesis involving oxazolines, see: Lutomski, K. A.; Meyers, A. I. In *Asymmetric Syntheses* Morrison. J. D., Ed.; Academic: New York, 1983; Vol. 3, p 213.
(11) Meyers, A. I.; Mihelich, E. D. *J. Org. Chem.* **1975**, *40*, 3158. Geschwend, H. W.; Hamden, A. *J. Org. Chem.* **1975**, *40*, 2008.
(12) Gilman, H.; Gorsich, R. D. *J. Am. Chem. Soc.* **1956**, *78*, 2217.

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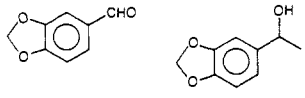
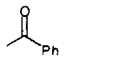
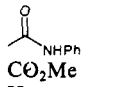
Table I. Addition of BuLi-Electrophile to **1** and Formation of 2,3-Disubstituted Benzoic Esters[a]

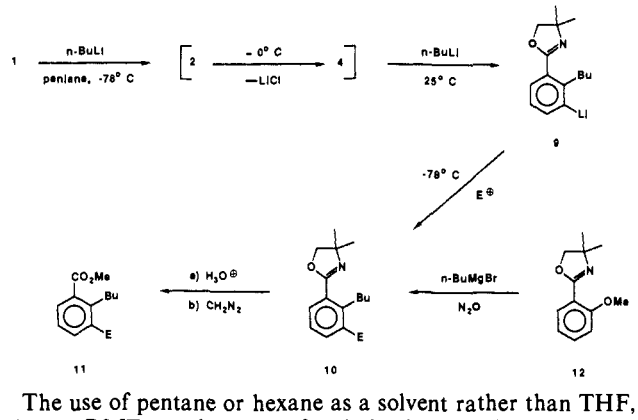
entry	electrophile	E	**10**,[b] %	**11**,[b] %
a	MeI[c]	Me	68	77
b	CH_2O	CH_2OH	58	59
c	$HCONMe_2$	CHO	55	92
d	PhCHO	CH(OH)Ph	58	
e			63	
f	PhCOCl		63	62
g	PhNCO		67	76
h	CO_2	CO_2Me	45	
i	EtOH	H	65	88

[a] Reactions performed in pentane. [b] Represent pure, homogeneous isolated products. [c] HMPA (3.0 equiv) added prior to methyl iodide.

expected to furnish **7**, and aqueous workup provided **8**. In order to confirm the regiochemistry, an X-ray structure of **8** was obtained. This result prompted a study of other organolithium reagents in the hope of preparing a variety of regioselectively 1,2,3-trisubstituted benzenes.

Since it was now established that the benzyne **4** does not form until temperatures of the solution of **2** reached ~0 °C, it would be possible to introduce a variety of nucleophiles and allow benzyne formation to take place in situ and be trapped by the nucleophile present in the solution.

Addition of *n*-butyllithium (3.0 equiv) in pentane to **1** at −78 °C, followed by warming the solution to room temperature to allow butyllithium addition to the benzyne and recooling to −78 °C prior to electrophilic quench, gave the adducts **10**. The results with a variety of electrophiles are summarized in Table I. Hydrolysis (4.5 N HCl) of the oxazoline and esterification with diazomethane gave the benzoic esters **11**, also described in Table I.

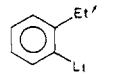
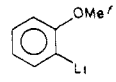


The use of pentane or hexane as a solvent rather than THF, ether, or DME was the result of optimization experiments. It was found that nonpolar solvents, with 3.0 equiv of alkyllithiums as the base and nucleophile, gave the highest yields.

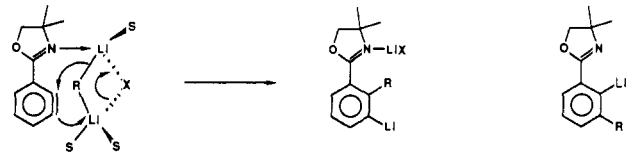
The formation of the regioisomer **10** was confirmed by an alternate unambiguous synthesis. From previous work in this laboratory,[13] we were able to form **10** (E = H) by merely treating known (2-methoxyphenyl)oxazoline **12** with *n*-butylmagnesium bromide. The products were identical in all respects. Furthermore, **11** (E = H) was degraded to phthalic acid for additional confirmation.

The formation of **9** rather than the meta addition product **13** was indeed surprising in light of the meta addition observed earlier to give the adduct **3**. However, on the basis of the solvent polarity study, wherein hexane or pentane proved to be superior to THF, we conclude that the regiochemistry observed is due to a kinetic complex-induced proximity effect (CIPE).[14] Thus, the organolithium approaches the benzyne, by chelation with the highly electron-rich π-system present in the oxazoline **14**, and this

Table II. Addition of Organolithiums (3.0 equiv) to **1** and Ratio of Meta to Ortho Addition

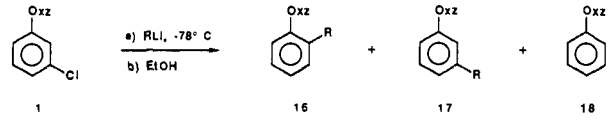
RLi	**16**,[a,d] %	**17**,[a,d] %	RLi	**16**,[a,d] %	**17**,[a,d] %
n-BuLi	70	11[e]		38[b]	31[b]
s-BuLi	46	12[e]			
PhLi	48	24		46	33
			2	0	68[c]

[a] Ratios determined by gas chromatography unless otherwise stated. [b] Ratio determined by HPLC. [c] Isolated yield. [d] Remainder of material was **1** and/or **18**. [e] Contains 12–15% **18**. [f] Ether–pentane (1:1) used to solubilize the lithium reagents at −78 °C.



complex forces the alkyl group into the ortho position of the benzyne bond leading to **15** (or **9**) and ultimately the products described in Table I. That this chelation phenomenon (CIPE) should be totally exclusive caused us some concern, and indeed, upon examination of the crude adduct **10** (E = H) by gas chromatography we could, in fact, observe 10–12% of the *m*-butyl isomer derived from proton quench of **13**. It was now of interest to assess the steric or electronic effects that were responsible for this regiochemistry and to try to explain the difference between major ortho addition with *n*-BuLi and major meta addition with (*o*-lithiophenyl)oxazoline **2**.

A series of organolithium reagents (Table II) were added to **1** in pentane or in 1:1 pentane–ether at −78 °C and allowed to metalate the ortho position of **1**. After being warmed to room

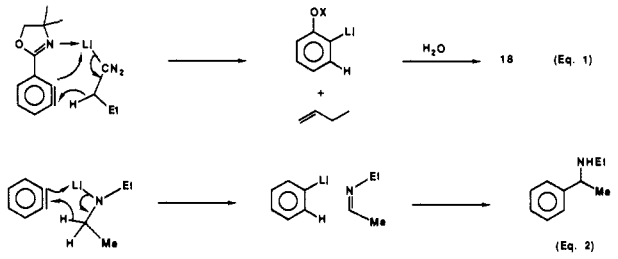


temperature, the organolithium was allowed to add to the benzyne, followed by quenching with ethanol to furnish **16**, **17**, and unexpectedly, **18**. It is seen from the ratio in Table II that there is a definite preference for ortho addition in the benzyne for *n*-butyl, *sec*-butyl, and phenyllithium. On the other hand, *o*-ethyl and *o*-methoxyphenyl lithiums are seemingly more competitive for both ortho and meta positions. This could be due to a steric crowding due to the ortho substituent or, more probably, the presence of ether in the reaction, which increases the polarity of the solvent thereby weakening the coordinating ability of the oxazoline to the organolithium reagent. In support of this, internally coordinated organolithium reagents, such as **2**, ignore the kinetic effect of coordination and simply add to the benzyne in a thermodynamically controlled process, i.e., the meta-substituted product **17** is formed exclusively. The phenyloxazoline **18** in the product mixture is presumed not to come from direct halogen–metal exchange but rather through the intermediacy of the benzyne. Since it was observed only with *n*-butyl- and *sec*-butyllithium (Table II), it can be explained by a β-hydride elimination (eq 1) analogous to the elimination reported[15] with lithium amides and benzynes (eq 2). In an attempt to further elaborate aromatic rings via the benzyne–oxazoline methodology, the *o*-methoxy derivative **19** (prepared from the benzoic acid in 79% overall yield) was subjected to *o*-methoxy displacement by Grignard reagents[9] af-

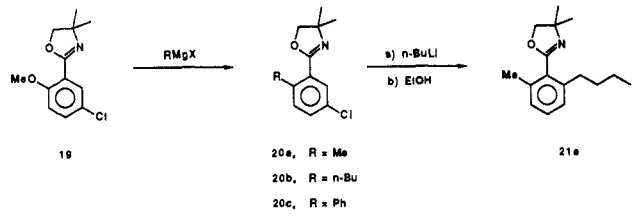
(13) Meyers. A. I.; Mihelich. E. D. *J. Am. Chem. Soc.* **1975**, *97*, 7383.

(14) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356.

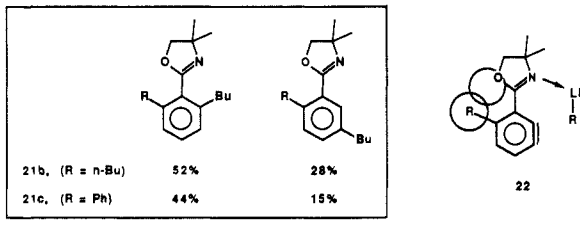
(15) Wittig, G.; Stoeber, I. *Justus Liebigs Ann. Chem.* **1972**, *758*, 84.



fording **20a–c**. It was now desirable to acertain whether treatment

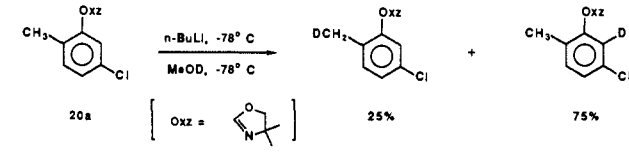


with excess *n*-butyllithium (3–3.5 equiv) in pentane would proceed with ortho metalation and subsequent loss of LiCl to furnish the benzyne or whether benzylic metalation in **20a** would compete with the desired process. Benzylic metalation in (*o*-methylphenyl)oxazolines is well-known.[9,16] As it turned out, benzyne formation, via ortho metalation, was the course followed, providing the bis-ortho-substituted system **21**, exclusively. However, for **20b** and **20c**, the addition to the benzyne intermediate was not as regioselective, giving **21b** and **21c** as mixtures of ortho and meta



addition products. This lack of selectivity of butyllithium addition to the benzynes containing ortho substituents could be due to out-of-plane twisting of the oxazoline moiety by bulky ortho substituents **22**, resulting in loss of proximity between the organolithium reagents and the ortho position of the benzyne. However, these derivatives **21a–c** were all obtained as pure homogeneous isomers after flash chromatography.

The surprising fact that ortho metalation in **20a,b**, rather than benzylic metalation, was the major deprotonation pathway prompted an experiment in competitive metalation using ether rather than pentane as the solvent. Thus, **20a** was metalated in



ether at −78 °C with 1 equiv of *n*-butyllithium and quenched immediately thereafter with methanol-*d*. The ratio of benzylic deuterium to ortho deuterium was 1:3, thus indicating even in a polar solvent such as ether, ring metalation predominates. Before leaving this section on organolithium addition to benzynes, it should be stated that the method utilized to prepare **21b**, namely, the (2,6-di-*n*-butylphenyl)oxazoline and ultimately the 2,6-disubstituted benzoic acid, is inferior to our earlier report wherein symmetrical 2,6-dialkyl derivatives are prepared.[9]

α-Lithionitrile Addition to Benzynes. The addition to the oxazoline benzyne was extended to α-lithionitriles providing an interesting, novel, and useful route to 1,2,3-trisubstituted benzenes **27**. Although nitrile anions have been previously reported[16] to add to benzynes, the process described herein (Scheme II) is

(16) Xin, H. Y.; Biehl, E. R. *J. Org. Chem.* **1983**, *48*, 4397.

Scheme II

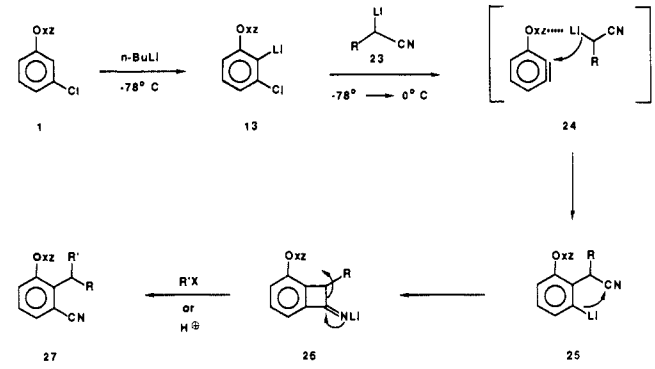


Table III. Addition of Lithionitriles to **1**[a,b] and Formation of Benzenes **27**

entry	lithionitrile **23**, R	electrophile	benzene **27** R	benzene **27** R′	yield,[c] %
a	H	EtOH	H	H	57
b	Et	EtOH	Et	H	68
cx	H	MeI	H	Me	46
d	Me	MeI	Me	Me	73
e	Et	MeI	Et	Me	73
f	H	*n*-BuBr[e]	H	*n*-Bu	45
gf	*i*-Pr	EtOH	*i*-Pr	H	42
h	*n*-hept	EtOH	*n*-hept	H	62
i	$PhCH_2$	EtOH	$PhCH_2$	H	56
j	Ph	EtOH	Ph	H	21[d]

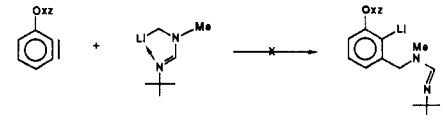
[a] All reactions performed in 1:1 ether–pentane. [b] Lithionitriles were prepared in ether with 0.5 equiv excess LDA. [c] All yields are for isolated, homogeneous material. [d] In addition, 19% of the isomeric 2-cyano-3-phenyl product was isolated. [e] HMPA added prior to addition of the halide.

considerably more interesting in that the net result is a fission of the alkyl cyanide bond which formally adds across the benzyne bonds. Specifically, treatment of **1** with 1.1 equiv of butyllithium in pentane at −78 °C gives the ortho-lithiated species **2**. At this juncture, a solution of lithiated alkyl nitriles **23** in ether was introduced such that the solvent was now 1:1 pentane–ether. Since both species **2** and **23** are nucleophiles, no interaction occurs between them other than possible chelation. As the temperature rises, LiCl is ejected forming the benzyne which, now as an electrophile, is readily attacked (**24**) by the lithiated nitrile furnishing **25**. The latter regiochemical result is again due to the complex-induced proximity effect (CIPE)[14] which influences alkyl attack on the benzyne bond at the ortho position. The 3-lithio-2-alkylnitrile **25** then undergoes intramolecular arylation to the benzocyclobutanimine **26**, which fragments to the more stable 3-cyano-2-alkylbenzene **27** (R′ = Li). Quenching lithiated **27** with a proton or an alkyl halide furnishes the final product as the nitrile **27**. A variety of lithiated nitriles were examined along with a variety of electrophilic quenches. These are tabulated in Table III.

This interesting fragmentation (**25–27**) has some precedent in the addition of enolates to benzynes as reported by Caubere.[17]

(17) Caubere, P. *Acc. Chem. Res.* **1974**, *7*, 301. Caubere, P.; Carre, M. C.; Gregoire, B. *J. Org. Chem.* **1984**, *49*, 2050; Carre, M.; Jamart-Gregoire, B.; Geoffroy, P.; Caubere, P. *Tetrahedron* **1988**, *44*, 127.

(18) Since internally coordinated nucleophiles would be expected to be poorly complexed prior to addition to the benzene, we examined lithioformamidines[19] as potential nucleophilic agents. However, no addition to the

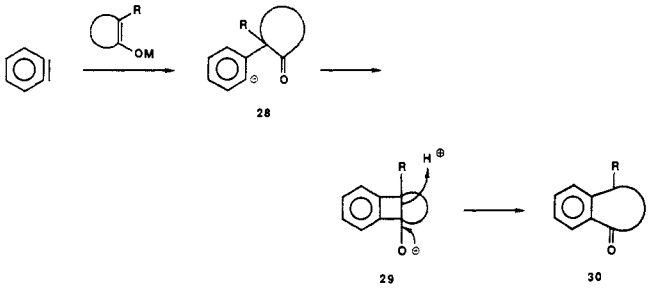


benzyne could be detected.

(19) Meyers, A. I.; ten Hoeve, W. *J. Am. Chem. Soc.* **1980**, *102*, 7125.

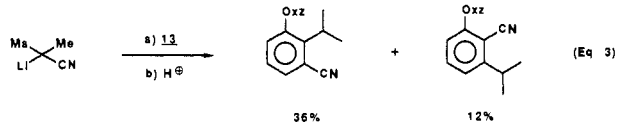
(20) Ellefson, C. R. *J. Org. Chem.* **1979**, *44*, 1533.

The attack of an enolate on benzyne furnishes **28**, which rearranges



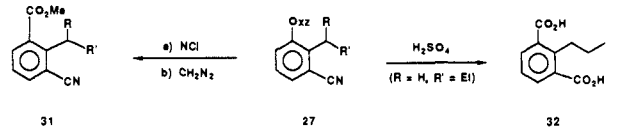
to the benzocyclobutane **29**. Because the enolates are derived from cyclic ketones, the fragmentation of **29** to **30** produces a macrocyclic benzoketone. Thus, this present process may be considered analogous to that described by Caubere.

There were some notable limitations to this tandem alkylation process. For example, tertiary lithionitriles added both poorly and nonselectively to the benzyne as shown in eq 3. Thus, steric



factors begin to play a role in the complexation step **24** allowing addition to occur under thermodynamic control. However, this is not a serious problem since highly branched ortho substitution can be introduced by alkylation of the intermediate **26**. For example, the 2-isopropyl derivative in eq 3, obtained in only 36% yield, was prepared by sequential alkylation in 73% yield (Table III, entry d). Another limitation noted was the poor addition efficiency of (lithiophenyl)acetonitrile (Table III, entry j). The "soft" nature of this anion gave poor yields of **27** and a comparable yield of the 3-phenyl isomer, analogous to the results shown in eq 3.

The cyano derivatives **27** were readily hydrolyzed in 4.5 N HCl furnishing the cyanocarboxylic acids, which were immediately esterified with diazomethane giving the methyl esters in good to

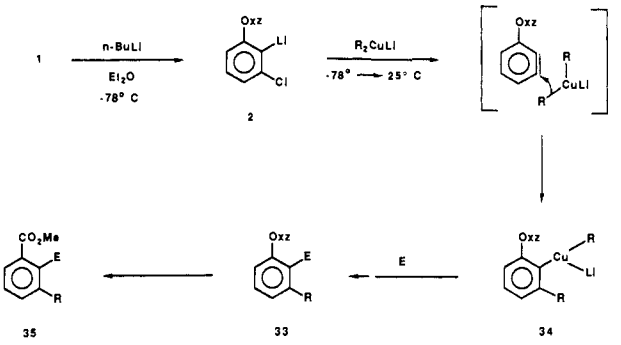


moderate yields (Table IV). If the hydrolysis was performed in refluxing 6 N sulfuric acid, both the cyano and oxazoline groups were hydrolyzed to give the isophthalic acid **32**. Furthermore, this provided additional confirmation that the regiochemical addition of the lithionitriles proceeded as mentioned above (Scheme II).

The data given in Table IV indicate that the overall process **1** → **31** was accomplished in ~50% yield, and this is considered rather satisfactory for the transformation which took place in three steps from commercially available and inexpensive *m*-chlorobenzoic acid.

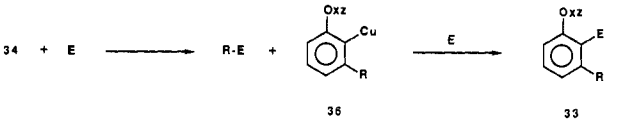
Alkyl Cuprate Additions to Benzynes. In the previous discussion on this methodology, it was shown that alkyllithiums add to the benzyne, furnishing as the major product (2-alkyl-3-E-phenyl)-oxazoline **10**. It was, for reasons outside the scope of this report, further desirable to reach the isomeric series (2-E-3-alkylphenyl)oxazolines **33** (Scheme III). Therefore, nucleophiles that may add to benzyne at the meta position were examined, and the dialkyl cuprates surfaced as the reagent of choice.

Treatment of **1** with 1.0 equiv of *n*-butylithium in ether to generate the ortho lithio derivative **2** was followed by addition of 3.0 equiv of the appropriate cuprate in ether. The two nucleophilic reactants were, once again, inert toward each other until



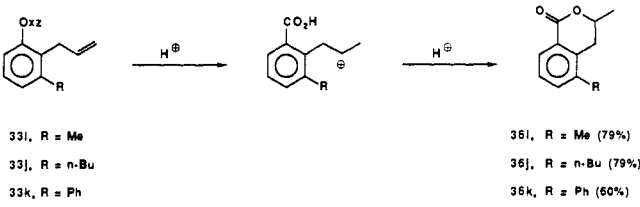
the solution was allowed to warm to room temperature. The transformation of **2** into the benzyne in the presence of the cuprate gave rise to addition product **34**. The resulting mixed cuprate **34** was then recooled and quenched with methanol, acid chloride (acetyl or benzoyl), or allyl bromide. In this fashion, a series of tri-substituted benzenes **33** was obtained (Table V) wherein the *electrophile entered exclusively at the ortho position.* No trace of the isomeric system **10** was found upon gas or high-pressure liquid chromatography. In fact, the gas chromatographic analysis of known mixtures of both isomeric series, compared to the crude reaction product derived from the cuprate addition, showed less than 0.01% (limits of detection) of **10** present in **33**. A study of various cuprates (Table V, entries b–d) showed that the extent of benzyne trapping was not affected by the nature of the cuprate (pentynyl[23] or cyano[24]), so all subsequent reactions were performed with lithium dialkylcuprates.

It was found that only the electrophiles listed in Table V were satisfactorily incorporated into the cuprate **34**, while other typical electrophiles (alkyl halides, carbonyls, epoxides) gave only starting materials or products of decomposition. This was interpreted to mean that the R group on copper in **34** is transferred instead of the aryl group, reacting with the introduced electrophile and producing the organocopper species **36**. In order to effect the



transformation to **33**, 10 equiv of electrophile were introduced into the solution of **34**. Organocopper reagents such as **36** are known to couple with allylic groups[20] and acyl groups.[21] More recently, Alexakis has shown[22] that organocopper reagents will couple with acetals in the presence of certain Lewis acids, however this failed to bring about alkylation of **34**.

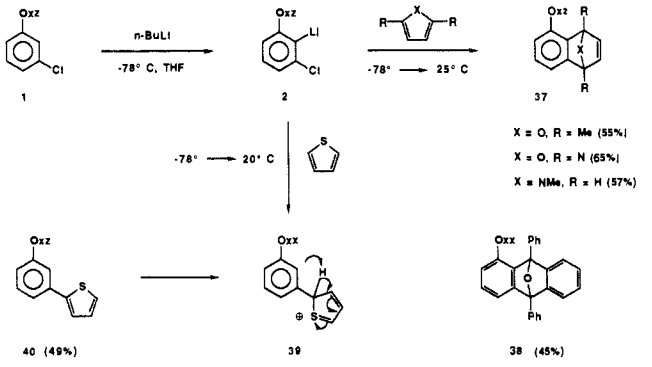
Hydrolysis of the oxazoline **33** using 4.5 N hydrochloric acid at reflux formed the carboxylic acid, which was immediately treated with diazomethane affording the methyl esters of the



benzoic acids **35**. In the case of the allyl-substituted benzenes (**33**, E = allyl), hydrolysis did not give the benzoic acids, but produced the lactones (dihydroisocoumarins) **36** in good yields. Presumably, the acidic medium generates the carbocation which is rapidly cyclized to the lactones.

Cycloaddition to Benzyne 4. The cycloaddition[7c] of several dienes to **4** was briefly examined and gave satisfactory yields of cycloadducts. Thus, a THF solution of **1** was treated with 1.1 equiv of *n*-BuLi at −78 °C, the diene (furan, pyrrole, or thiophene)

(21) Normant, J. F. *Synthesis*, **1972**, 63.
(22) Alexakis, A.; Ghiribi, A.; Normant, J. F. *Tetrahedron Lett.* **1984**, *25*, 3075, 3079.
(23) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210.
(24) Levisalles, J.; Gorlier, J. P.; Hamon, S.; Wagon, J. *J. Chem. Soc., Chem. Commun.* **1973**, 88.



was added, and the solution was allowed to warm to −10 to −15 °C, followed by stirring at room temperature overnight. Cycloadducts from the furan, pyrrole, and 2,5-diphenylisobenzofuran **37** and **38**, respectively, were obtained in moderate yields. Once again, very little cycloadduct was detected (HPLC) below −15 °C, indicating the stability of the lithiated species **2** below −15 °C. In fact, a study of time vs percent yield of cycloadduct at −12 °C showed that after 4 h only 56% cycloadduct and 40% (*m*-chlorophenyl)oxazoline **1** were present. However, at 20 °C the time–yield study showed 85% cycloadduct (~10% **1**) present after 1.75 h. This behavior of **2** going on to benzyne is consistent with all the previous results mentioned earlier in this discussion.

It is interesting to note that previous base-induced benzyne formation gave, on addition of furans, rearranged cycloadducts.[25] However, under the mild conditions employed herein, no rearranged cycloaddition products were observed, only those shown as **37–39**. The reaction of **2** with thiophene, however, did not lead to a simple, expected cycloadduct. Instead, the thiophene addition product **40** was formed. This may be explained as passing through the ylide **39** which is formed by nucleophilic thiophene addition to the benzyne.[26] Proton transfer (1,3) then leads to the product **40**. However, trans-metalation between **2** and thiophene, followed by addition of 2-lithiothiophene to the benzyne cannot be rigorously excluded.

Experimental Section[27]

2-(3-Chlorophenyl)-4,4-dimethyl-2-oxazoline (1). In a 250-mL flask were placed 100 g of 3-chlorobenzoic acid (0.639 mol; Aldrich) and 140 mL of thionyl chloride (228 g, 1.92 mol). The flask was heated in a 100 °C oil bath for 1 h and then removed from the bath. Excess thionyl chloride was then removed from the mixture via distillation. The crude acid chloride was allowed to cool to room temperature, then dissolved in 290 mL of methylene chloride, and placed in a dropping funnel over a 1-L flask containing 114 g of 2-methyl-2-aminopropanol (1.28 mol, 2 equiv) in 290 mL of methylene chloride. The flask was cooled in a 0 °C bath, and the acid chloride was added dropwise to the stirred solution of amino alcohol. After addition of the acid chloride was complete, the reaction mixture was removed from the ice bath and stirred at room temperature for 14 h. The mixture was filtered, the cake washed with methylene chloride (150 mL), and the filtrate concentrated in vacuo to leave a white solid, the crude amide alcohol (148 g, 0.649 mol, 102%). The amide alcohol was immediately carried on by dissolving in 170 mL of benzene and 500 mL of methylene chloride. The mixture was transferred to a 1-L flask fitted with a dropping funnel, condenser, and a mechanical stirrer. A total of 140 mL of thionyl chloride (228 g, 1.92 mol) was slowly added to the stirred solution. The reaction mixture was warmed to reflux and then cooled. The mixture was stirred at room temperature for 2.5 h. The excess thionyl chloride was destroyed via dropwise addition of H_2O and 40% NaOH. Addition of 40% NaOH was continued until the water layer was at pH 11. The water layer (750 mL) was extracted with diethyl ether (2 × 1.75 L). The combined ether layers were dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo to leave crude **1** as a yellow oil (132.2 g, 0.631 mol, 99%). Distillation in vacuo [bp 80–83 °C (0.05 mmHg)] provided **1** (93.7 g, 70%) as a colorless oil: IR (film) 2960 (C—H), 1645 (C=N), 1600 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.36 (s, 6 H), 4.08 (s, 2 H), 7.29 (t, 1 H, *J* = 7.85 Hz), 7.40 (ddd, 1 H, *J* = 1.48, 2.28, 7.58 Hz), 7.80 (dt, 1 H, *J* = 1.36, 7.58 Hz), 7.94 (t, 1 H, *J* = 1.47 Hz); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 28.19, 67.48, 78.99, 125.93, 127.91, 129.14, 129.55, 130.71, 133.93, 160.37. Anal. Calcd for $C_{11}H_{12}NOCl$: C, 63.01; H, 5.77. Found: C, 62.96; H, 5.78.

4-Chloro-8-(2-oxazolinyl)fluorenone (8). To a stirred solution of 566 mg (2.70 mol of **1** in 15 mL of THF cooled to −78 °C under nitrogen was added 1.04 mL of 2.75 M *n*-butyllithium (hexane) and the mixture stirred for 30 min. The solution was then allowed to warm to −10 °C and kept at this temperature for 2–3 h and then allowed to reach room temperature overnight. The reaction mixture was poured into saturated ammonium chloride solution and the organic layer removed by ether extraction. The ether extracts were washed successively with water, brine, and water, dried ($MgSO_4$), and concentrated to a green oil. The oil was subjected to flash chromatography (silica gel, ethyl acetate–hexane 3:7). The first fraction contained a small amount of **1**, the second fraction contained 286 mg (68%) of the fluorenone **8**: mp 136–137 °C (hexane–ethyl acetate); ^1H NMR ($CDCl_3$, 60 MHz) δ 1.52 (s, 6 H), 4.22 (s, 2 H), 7.00–7.60 (m, 5 H), 8.20 (dd, 1 H, *J* = 6.0, 3.7 Hz); IR (KBr) 2995, 2800, 1715, 1660, 1590, 1110, 930, 730 cm^{-1}; MS, *m/e* 313 (M + 2), 311 (M^+), 298, 296 (base, 281, 240, 227, 185, 150, 78). Anal. Calcd for $C_{18}H_{14}NO_2Cl$: C, 69.35; H, 4.53. Found: C, 69.23; H, 4.57.

This analytical sample was subjected to single-crystal X-ray determination (see supplementary material).

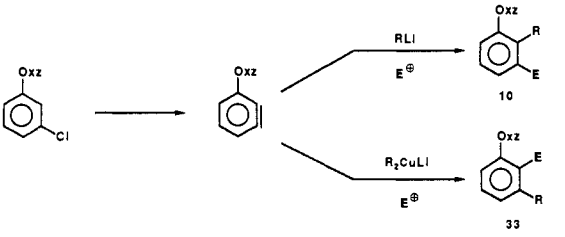
Butyllithium–Electrophile Tandem Additions to 10. Typical Procedure. 2-(2-*n*-Butyl-3-methylphenyl)-4,4-dimethyl-2-oxazoline (10a). A total of 0.398 g of **1** (1.90 mol, 1 equiv) was placed in a 50-mL flask containing an argon atmosphere, 20 mL of pentane was added, and the mixture was stirred until a homogeneous solution was obtained. The solution was then cooled in an acetone–dry ice bath, and 2.60 mL of 2.20 M *n*-butyllithium (5.72 mol, 3 equiv) was added via syringe. The reaction mixture was stirred at low temperature for 0.5 h and then at room temperature for 0.5 h. The flask was then recooled in the acetone–dry ice bath, and 1.0 mL of hexamethylphosphoramide (HMPA) (1.03 g, 5.75 mol, 3 equiv) was added via syringe. No HMPA was used in any of the subsequent procedures that follow. The reaction was stirred 3 min and then methyl iodide (0.60 mL, 1.37 g, 9.64 mol, 5 equiv) was added via syringe. The reaction mixture was allowed to slowly warm to room temperature with stirring. The mixture was stirred a total of 5–6 h following addition of methyl iodide and then concentrated in vacuo. The resulting red oil was taken up in hexane (80 mL) or ether and washed with saturated sodium chloride (2 × 40 mL). The organic layer was dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo to leave a red oil. Medium-pressure chromatography (5% ethyl acetate–hexanes) provided 0.315 g of **10a** (1.29 mol, 68%) as a colorless oil: IR (film) cm^{-1} 2960 (C—H), 1645 (C=N), 1590 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ .94 (t, 3 H, *J* = 6.34 Hz), 1.15–1.46 (m, 4 H), 1.38 (s, 6 H), 2.34 (s, 3 H), 2.89 (t, 2 H, *J* = 7.81 Hz), 4.06 (s, 2 H), 7.00–7.26 (m,

Table IV. Hydrolysis of (Cyanophenyl)oxazolines **27** to Methyl Cyanobenzoates **31**

entry	R	R′	**31**,[a,b] %	% overall from **1**[d]
a	H	H	98	56
b	Et	H	80	54
c	H	Me	87	40
d	Me	Me	86	63
e	Me	Et	77	56
f	H	Bu	70[c]	42
g	H	*i*-Pr	79	48
h	H	*n*-hept	83[c]	50
i	H	$PhCH_2$	86	48

[a] All yields are for pure, homogeneous materials. [b] All hydrolyses were carried out in 4.5 N HCl, reflux, 12–15 h. [c] Hydrolyzed in 1:2 THF–H_2O solution. [d] Physical data are presented as supplmentary material.

Scheme III



(25) Shepard, K. L. *Tetrahedron Lett.* **1975**, 3371. Kobrich, G. *Chem. Ber.* **1959**, *92*, 2985.

(26) A related reaction between benzyne and *N*-methylpyrrole has been reported: Keuhne, M. E.; Kitagawa, T. *J. Org. Chem.* **1964**, *29*, 1270.

(27) Microanalyses were performed by Desert Analytics, Tucson, AZ.

Table V. Addition of Cuprates to Benzyne **1** and Formation of 2,3-Disubstituted Methyl Benzoates **35**

entry	cuprate[a]	electrophile	trisubstituted benzene **33** R	E	% [c]	ester **35**,[e] % [c]	entry	cuprate[a]	electrophile	trisubstituted benzene **33** R	E	% [c]	ester **35**,[e] % [c]
a	Me_2CuLi	MeOH[b]	Me	H	66	92	i	Me_2CuLi		Me		69	*d*
b	$(n\text{-Bu})_2CuLi$	MeOH[b]	*n*-Bu	H	56	95							
c	*n*-BuCuCNLi	MeOH[b]	*n*-Bu	H	47		j	$(n\text{-Bu})_2CuLi$		*n*-Bu		88	*d*
d	*n*-Bu(pentynyl)CuLi	MeOH[b]	*n*-Bu	H	53								
e	Ph_2CuLi	MeOH[b]	Ph	H	67	99	k	Ph_2CuLi		Ph		68	*d*
f	Me_2CuLi	CH_3COCl	Me	MeCO	47	99	l	Me_2CuLi	PhCOCl	Me	PhCO	37	98
g	$(n\text{-Bu})_2CuLi$	CH_3COCl	*n*-Bu	MeCO	67	87	m	$(n\text{-Bu})_2CuLi$	PhCOCl	*n*-Bu	PhCO	70	84
h	Ph_2CuLi	CH_3COCl	Ph	MeCO	28	73	n	Ph_2CuLi	PhCOCl	Ph	PhCO	66	90

[a] Three equivalents of cuprate added to lithiated **1**. [b] Degassed methanol used. [c] Yields are those of pure, homogeneous, material. [d] These products were dihydroisocoumarins **36**. [e] Physical data and experimental details are presented as supplementary material.

2 H), 7.45 (dd, 1 H, J = 1.95, 6.83 Hz); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 14.00, 19.84, 23.29, 28.42, 29.94, 32.51, 67.78, 78.75, 125.11, 127.56, 128.20, 132.12, 136.55, 140.99, 163.18. Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45. Found: C, 78.08; H, 9.09.

Hydrolysis of Oxazolines 10 to Methyl Esters (11). Typical Procedure. Methyl 2-*n*-Butylbenzoate (11i). In a 25-mL flask were placed 0.126 g of oxazoline **10i** (0.545 mol) and 13 mL of 4.5 N HCl. The solution was heated to reflux for 14 h and then allowed to cool to room temperature. The mixture was partitioned between diethyl ether (2 × 80 mL) and saturated sodium chloride. The combined ether layers were treated with 6 equiv of diazomethane, generated from 0.70 g of Diazald (3.27 mol, 6 equiv), stirred for 2 h, then dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo to leave a yellow oil. Column chromatography (16 g of silica, 5% ethyl acetate–hexanes) provided 0.092 g of **11i** (88%) as a colorless oil. A portion was purified via bulb-to-bulb distillation: bp 70 °C (0.05 mmHg); IR (film) 2960 (C—H), 1720 (C=O), 1600 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.93 (t, 3 H, J = 7.33 Hz), 1.34–1.45 (m, 2 H), 1.52–1.63 (m, 2 H), 2.94 (t, 2 H, J = 7.57 Hz), 3.87 (s, 3 H), 7.22 (d, 2 H, J = 7.64 Hz), 7.37 (d, 1 H, J = 7.47 Hz), 7.84 (d, 1 H, J = 7.80 Hz); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 13.94, 22.76, 33.97, 34.14, 51.72, 125.40, 129.31, 130.31, 130.66, 131.53, 144.44, 167.91.

2-(5-Chloro-2-methoxyphenyl)-4,4-dimethyl-2-oxazoline (19). In a 12-L flask equipped with a mechanical stirrer were placed 2.9 L of H_2O and 38 g of NaOH (0.95 mol). The mixture was stirred until a homogeneous solution was obtained. A total of 2.9 L of methylene chloride was added followed by 100 g of 5-chlorosalicylic acid (Aldrich; 0.580 mol) and 19 g of tetra-*n*-butylammonium bromide (0.590 mol). The mixture was stirred vigorously, and 165 mL of dimethyl sulfate (220 g, 1.75 mol) was slowly added to the mixture. The reaction mixture was stirred at room temperature for 4 h, during which the organic layer was separated and the water layer washed with methylene chloride (2 L). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to leave a yellow oil. A portion was purified via bulb-to-bulb distillation: bp 57 °C (0.02 mmHg); IR (film) 2950 (C—H), 1735 (C=O), 1600 (C=C), 1235 (C—O) cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 3.88 (s, 6 H), 6.90 (d, 1 H, J = 9.03 Hz), 7.41 (dd, 1 H, J = 2.69, 9.03 Hz), 7.75 (d, 1 H, J = 2.69 Hz). The material was carried on to 2-methoxy-5-chlorobenzoic acid below.

The ester was placed in a 3-L flask with 1 L of 10% sodium hydroxide. The mixture was stirred at room temperature for 16 h, during which the mixture turned to a white solid. The mass was dissolved in water, by portions, and each portion acidified with concentrated hydrochloric acid to precipitate the acid. Each portion was extracted with diethyl ether, combined with the previous ether extracts, and finally dried over anhydrous magnesium sulfate. Filtration, followed by concentration in vacuo provided the crude acid (104.6 g, 97%), which was immediately carried on to the oxazoline **19**.

The crude acid (104.6 g, 0.558 mol) was placed in a 1-L flask with 121 mL of thionyl chloride (197 g, 1.66 mol). The mixture was stirred at room temperature for 0.5 h and then heated at reflux for 0.5 h. Excess thionyl chloride was removed via distillation. The resulting acid chloride was allowed to cool to room temperature, whereupon it solidified. The solid was dissolved in 300 mL of methylene chloride and placed in a dropping funnel over a 1-L flask containing 100 g of 2-amino-2-methyl-1-propanol (1.12 mol) in 255 mL of methylene chloride. The flask was cooled in an ice bath, and the acid chloride was added dropwise to the stirred solution. After addition of the acid chloride was complete, the mixture was stirred at room temperature for 20 h. The mixture was then filtered and the cake washed with 0.5 L of methylene chloride and concentrated in vacuo to leave 145 g of amide alcohol as a brown solid. The amide alcohol was dissolved in 1 L of methylene chloride and placed in a 2-L flask. To the stirred solution was slowly added 121 mL of thionyl chloride (197 g, 1.66 mol). After addition of the thionyl chloride was complete, the reaction was stirred at room temperature for 1.5 h. Excess thionyl chloride was destroyed by dropwise addition of H_2O and 40% NaOH. Addition of 40% NaOH was maintained until the water layer was pH 11. The mixture was diluted with 1 L of saturated NaCl, and the layers were separated. The water layer was washed with 1.5 L of diethyl ether, and the organic layers were combined and dried over anhydrous potassium carbonate. Filtration and concentration in vacuo gave crude **19** which was purified via bulb-to-bulb distillation to provide 110.0 g (79%) as a white solid: mp 48–50 °C; IR (film) 2970 (C—H), 1650 (C=N), 1600 (C=C), 1280 (C—O) cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.39 (s, 6 H), 3.87 (s, 3 H), 4.09 (s, 2 H), 6.88 (d, 1 H, J = 8.88 Hz), 7.31 (dd, 1 H, J = 2.55, 8.82 Hz), 7.73 (d, 1 H, J = 2.65 Hz); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 36.40, 59.84, 69.15, 78.66, 107.07, 112.09, 117.21, 121.98, 122.47, 143.57, 146.16. The material (**19**) was carried on to the compounds described below.

2-(2-Methyl-5-chlorophenyl)-4,4-dimethyl-2-oxazoline (20a). In a 250-mL flask containing an argon atmosphere were placed 2.56 g (10.7b mol) of **19**, 100 mL of diethyl ether, and 50 mL of THF. To the resulting solution was added 11 mL of 2.9 M methylmagnesium bromide (31.9 mol, 3 equiv) at room temperature with stirring. The reaction was stirred at room temperature for 48 h, then poured into saturated sodium chloride (200 mL), and shaken with diethyl ether (2 × 250 mL). The combined organic layers were dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo to leave a yellow oil. Flash chromatography (70 g of silica gel, 7.5% ethyl acetate–hexanes) provided **20a**, which was further purified via bulb-to-bulb distillation [mp 60 °C (0.02 mmHg)] to provide 1.71 g (7.64 mol, 71%) as a colorless oil: IR (film) 2970 (C—H), 1650 (C=N), 1600 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.37 (s, 6 H), 2.52 (s, 3 h), 4.05 (s, 2 H), 7.12 (d, 1 H, J = 8.17 Hz), 7.25 (dd, 1 H, J = 2.31, 8.21 Hz), 7.76 (d, 1 H, J = 2.29 Hz); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 20.95, 28.42, 67.95, 78.52, 128.90, 129.37, 129.96, 130.95, 132.12, 136.73, 161.13. Anal. Calcd for $C_{12}H_{14}NOCl$: C, 64.43; H, 6.31. Found: C, 64.30; H, 6.32.

2-(2-*n*-Butyl-6-methylphenyl)-4,4-dimethyl-2-oxazoline (21a). In a 50-mL flask containing an argon atmosphere were placed 0.224 g of **20a** (1.00 mol, 1 equiv) and 30 mL of pentane. The resulting solution was cooled in an acetone–dry ice bath, and a total of 1.25 mL of 2.34 M *n*-butyllithium (3.04 mol, 3 equiv) was added via syringe. The reaction was stirred at low temperature for 0.5 h, then removed from the low-temperature bath, and stirred at room temperature for 40 min. The reaction was then quenched with absolute ethyl alcohol and partitioned between diethyl ether (120 mL) and saturated sodium chloride (30 mL). The ether layer was dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo to leave a yellow oil. Flash chromatography (12 g of silica gel, 5% ethyl acetate–hexanes) provided a total of 0.102 g of **21a** (0.415 mol, 42%) as a colorless oil. A portion was further purified via bulb-to-bulb distillation [mp 63 °C (0.05 mmHg)] to provide a sample for combustion analysis: IR (film) 2960 (C—H), 1665 (C=N), 1600 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.91 (t, 3 H, J = 7.17 Hz), 1.31–1.52 (m, 2 H), 1.41 (s, 6 H), 1.52–1.64 (m, 2 H), 2.32 (s, 3 H), 2.63 (t, 2 H, J = 7.77 Hz), 4.08 (s, 2 H), 7.00–7.04 (m, 2 H), 7.18 (t, 1 H, J = 7.65 Hz); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 13.94, 19.49, 22.76, 28.42, 33.44, 33.74, 67.83, 78.69, 126.28, 127.04, 128.50, 128.96, 136.55, 141.51, 161.89. Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45. Found: C, 78.06; H, 9.53.

2-(2,6-Di-*n*-butylphenyl)-4,4-dimethyl-2-oxazoline (21b). In a manner similar to **21a**, the butyl oxazoline **20b** was treated with 3.3 equiv of *n*-butyllithium in pentane. Workup and flash chromatography gave 0.154 g (52%) of **21b** as a colorless oil. A portion was further purified via bulb-to-bulb distillation [mp 70 °C 0.05 mmHz)] to provide a sample for combustion analysis: IR (film) 2960 (C—H), 1670 (C=N), 1030

(C—O) cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.91 (t, 3 H, J = 7.28 Hz), 1.28–1.41 (m, 2 H), 1.41 (s, 6 H), 1.53–1.64 (m, 2 H), 2.62 (t, 2 H, J = 7.77 Hz), 4.07 (s, 2 H), 7.03 (d, 2 H, J = 7.58 Hz), 7.19 (d, 1 H, J = 7.66 Hz); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 13.89, 22.76, 28.31, 33.44, 33.68, 67.78, 78.63, 126.22, 128.09, 128.90, 141.40, 161.83. Anal. Calcd for $C_{19}H_{29}NO$: C, 79.39; H, 10.17. Found: C, 78.74; H, 10.16.

2-(2-Ethyl-3-cyanophenyl)-4,4-dimethyl-2-oxazoline (27c). Typical Procedure. To a stirred solution of **1** (0.285 g, 136 mol) in 20 mL of pentane under an argon atmosphere cooled in an acetone–dry ice bath was added 0.76 mL of 2.39 M *n*-butyllithium (1.33 equiv, 1.82 mol). The reaction was stirred at low temperature (acetone–dry ice) for 0.5 h and then the anion of acetonitrile was added via cannula in 20 mL of diethyl ether. The anion was generated from 4.5 equiv of LDA and 0.30 mL of acetonitrile (4 equiv) in 20 mL of diethyl ether cooled in an acetone–dry ice bath for 0.5 h under an argon atmosphere.

The flask containing both ortho-lithiated **1** and the nitrile anion was then removed from the low-temperature bath and stirred at room temperature for 45 min. During this period the reaction changed from light yellow to dark blue. The reaction was then recooled in an acetone–dry ice bath and 1.0 mL of methyl iodide (or alkyl halide, or ethanol) (16.4 mol, 12 equiv) was added to the flask. The reaction was allowed to slowly warm to room temperature with stirring for 2 h. The reaction was partitioned between anhydrous ether (60 mL) and aqueous NaCl solution. The combined ether layers were dried with anhydrous potassium carbonate. The ether solution was then filtered, and the volatile organics were removed in vacuo to leave a dark red oil. Purification was achieved via flash chromatography on 12 g of silica gel using 7.5% ethylk acetate–hexanes as eluent. In this manner 0.144 g (0.63 mol, 46%) was obtained as a colorless oil following removal of solvents in vacuo. A portion was further purified via bulb-to-bulb distillation [mp 65 °C (0.05 mmHg)] to provide **27c** as a white crystalline solid: mp 50–51 °C; IR (film) 2960 (C—H), 2220 (CN), 1645 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.28 (t, 3 H, J = 7.50 Hz), 1.41 (s, 6 H), 3.24 (q, 2 H, J = 7.50 Hz), 4.12 (s, 2 H), 7.33 (t, 1 H, J = 7.80 Hz), 7.70 (dd, 1 H, J = 1.40, 7.80 Hz), 7.94 (dd, 1 H, J = 1.40, 7.80 Hz); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 15.40, 26.09, 28.36, 68.24, 79.04, 113.84, 117.64, 126.10, 128.90, 134.28, 134.74, 148.41, 160.78. Anal. Calcd for $C_{14}H_{16}N_2$: C, 73.66; H, 7.06. Found: C, 73.44; H, 7.20.

Addition of Cuprates of Benzyne 4. Typical Procedure. 2-(2-Acetyl-3-methylphenyl)-4,4-dimethyl-2-oxazoline (33f). A total of 0.157 g (0.750 mol) of **1** was placed in a 25-mL flask with 10 mL of diethyl ether. The solution was then cooled in a acetone–dry ice bath, and 0.35 mL (0.781 mol) of 2.23 M *n*-butyllithium was added via syringe. The mixture was stirred at low temperature for 0.5 h and then 3 equiv of lithium dimethylcuprate was added via cannula in diethyl ether. The cuprate was generated from 0.420 g (2.20 mol) of CuI and 4.2 mL (4.83 mol) of 1.15 M methyllithium in 10 mL of diethyl ether at −10 °C for 0.5 h.

The main reaction flask was then removed from the low-temperature bath and stirred at room temperature for 40 min. Following this period of time, the flask was recooled in the acetone–dry ice bath and 0.53 mL (7.75 mol) of acetyl chloride was added via syringe. The reaction was allowed to slowly warm to room temperature with stirring. The reaction was stirred for a total of 16 h following addition of the acetyl chloride. If methanol is used as the quench, the reaction may be worked up immediately. The mixture was then poured into a separatory funnel (250 mL) and shaken with diethyl ether (100 mL) and 5.66% ammonium hydroxide (2 × 150 mL). The ether layer was dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo to leave a yellow oil. Flash chromatography of the yellow oil on 12 g of silica gel using 7.5% ethyl acetate–hexanes as eluent provided 0.079 g (0.341 mol, 45%) of **47e** as a colorless oil following combination of appropriate fractions and removal of solvent in vacuo. A portion was subjected to bulb-to-bulb distillation [mp 93 °C (0.10 mmHg)] to provide a sample for combustion analysis: IR (film) 2960 (C—H), 1705 (C=O), 1650 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.34 (s, 6 H), 2.27 (s, 3 H), 2.48 (s, 3 H), 4.05 (s, 2 H), 7.28–7.32 (m, 2 H), 7.70–7.75 (m, 1 H); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 19.02, 28.13, 32.04, 68.01, 79.16, 123.77, 126.45, 128.09, 132.99, 142.28, 160.32, 205.22. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41. Found: C, 72.60; H, 7.49.

Hydrolysis of Allylbenzenes (33i–k) to 5-Substituted 3-Methyl-3,4-dihydroisocoumarins (36). Typical Procedure. 3,5-Dimethyl-3,4-dihydroisocoumarin (36i). In a 25-mL flask were placed 0.123 g (0.537 mol) of **33i**, 12.5 mL of 4.5 N HCl, and a magnetic stir bar. A condenser was added, and the mixture was heated at reflux for 12–13 h. The mixture was then allowed to cool to room temperature and was partitioned between diethyl ether (2 × 100 mL) and aqueous sodium chloride solution (40 mL). The ether layers were combined and dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo to leave a yellow-white solid. Column chromatography on 16 g of column grade silica gel using 5% ethyl acetate–hexanes as eluent provided 0.075 g (0.424 mol, 79%) of **36i** as a white crystalline material following combination of appropriate fractions and removal on solvents in vacuo. A portion was recrystallized from ethyl acetate–hexanes to provide white needles: mp 98–100 °C; IR (film) 2960 (C—H), 1715 (C=O), 1580 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.55 (d, 3 H, J = 6.29 Hz), 2.32 (s, 3 H), 2.77 (dd, 1 H, J = 11.27, 16.27 Hz), 2.95 (dd, 1 H, J = 3.33, 16.64 Hz), 4.65 (m, 1 H), 7.28 (t, 1 H, J = 7.73 Hz), 7.40 (d, 1 H, J = 7.80 Hz), 7.98 (d, 1 H, J = 7.64 Hz); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 18.79, 21.01, 31.93, 74.20, 124.70, 126.74, 127.80, 134.80, 137.49, 165.63. Anal. Calcd for $C_{12}H_{14}O_2$: C, 74.98; H, 6.86. Found: C, 74.99; H, 6.88.

Cycloadditions to Benzyne 4. General Procedure. Benzyne–2,5-Dimethylfuran Adduct 37 (X = O, R = Me). To a stirred solution of 586 mg (2.80 mol) of **1** in 15 mL of THF, cooled to −78 °C, was added 1.08 mL of 2.75 M *n*-butyllithium solution (hexane), and the mixture was allowed to stir for 30 min. Freshly distilled 2,5-dimethylfuran (2.70 g) was added and the solution warmed to −15 °C and stirred at this temperature for 5 h. The mixture was allowed to warm to room temperature and stirred overnight. The mixture was poured into saturated ammonium chloride and the organic material taken up in ether, washed with water, dried ($MgSO_4$), and concentrated. The resulting oil was flash chromatographed (silica gel, 20% EtOAc–hexanes) to give 38 mg of **1** and 442 mg (55%) of the desired adduct: mp 110–111 °C (hexane–ethyl acetate); ^1H NMR ($CDCl_3$) δ 1.37 (s, 6 H), 1.82 (s, 3 H), 1.98 (s, 3 H), 4.02 (s, 2 H), 6.68 (d, J = 5.0 Hz, 1 H), 6.87 (d, J = 5.0 Hz, 1 H), 7.00–7.39 (m, 3 H). Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11. Found: C, 75.46, H, 7.09.

Benzyne–2,5-Diphenylisobenzofuran Adduct 38 (X = O, R = Ph). Following the procedure above, 206 mg of **1** and 203 mg of 1,3-diphenylisobenzofuran gave, after chromatography, 145.4 mg (44%) of the desired product: mp 173.5–174.0 °C (hexane); ^1H NMR ($CDCl_3$) δ 107 (s, 3 H), 1.18 (s, 3 H), 2.71 (s, 1 H), 3.68 (s, 1 H), 6.88–7.96 (m, 17 H). Anal. Calcd for $C_{31}H_{25}NO_2$: C, 83.95; H, 5.68. Found: C, 83.79; H, 5.68.

Benzyne–Furan Adduct 37 (X = O, R = H). Following the procedure above, 503 mg of **1** and 2.5 mL of freshly distilled furan gave, after flash chromatography, 363 mg (6%) of the desired product as an oil: ^1H NMR ($CDCl_3$ δ 1.36 (s, 6 H), 4.03 (s, 2 H), 5.67 (br s, 1 H), 6.28 (br s, 1 H), 6.78–7.68 (m, 5 H). Anal. Calcd $C_{15}H_{15}NO_2$: C, 74.68; H, 6.22. Found: C, 74.39; H, 6.18.

Benzyne–*N*-Methylpyrrole Adduct 37 (X = NMe, R = H). Following the procedure above, 506 mg of **1** and 1.96 g of freshly distilled *N*-methylpyrrole gave, after chromatography (silica gel, 1% Et_3N, 5% MeOH, 94% $CHCl_3$), 350 mg (57%) of the desired adduct, as an unstable oil: MS, m/e 254 (M^+); ^1H NMR ($CDCl_3$) δ 1.33 (s, 6 H), 2.10 (br s, 3 H), 4.00 (s, 2 H), 4.45 (br s, 1 H), 5.18 (br s, 1 H). The compound, due to instability toward air and light, did not give a satisfactory combustion analysis.

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Supplementary Material Available: Physical data for **10**, **11**, **20**, **21**, **27**, **31**, **33**, **35**, and **36**, except for those presented herein, and tables of atomic coordinates, bond lengths, bond angles, and anisotropic thermal parameters for the fluorenone **8** (25 pages). Ordering information is given on any current masthead page.