NMR—the mechanisms could be distinguished. It was concluded that amides with electron-donating substituents exchange by N-protonation, whereas amides with electron-withdrawing substituents exchange via the imidic acid. This latter class includes peptides and proteins, and the implications for solvent accessibility to buried NH protons and for carboxylation of biotin have been discussed. The N-protonation mechanism, in both amides and amidinium ions, shows the novel feature that the intermediate is so strong an acid that it does not live long enough to achieve rotational equilibration about its C–N single bond. Rotation of solvated NH_3^+ is hardly restricted by hydrogen bonding to solvent, as judged from the rotational correlation time of aqueous NH_4^+, which is only 1.1×10^{-12} s. Rotation is considered to be so fast because of multiple coordination of solvent molecules to the hydrogen-bonded protons.

I am grateful to my co-workers, cited in the references, for their excellent skills. This research has been supported by continuing grants from NSF, following an initial grant from Research Corporation.

Synthesis of Polycyclics via Aryne Arylation Reactions

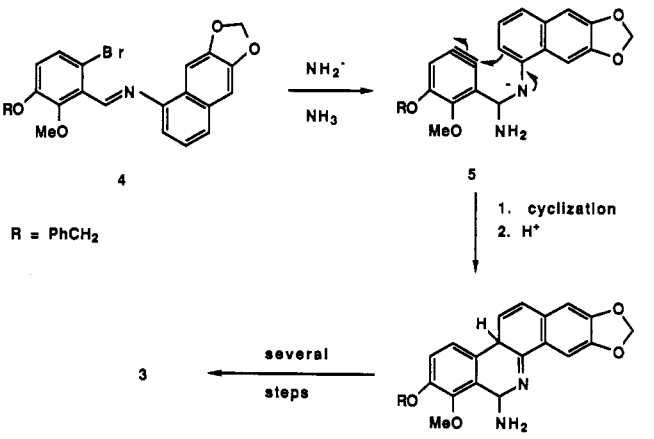
EDWARD R. BIEHL* and SUBHASH P. KHANAPURE

Department of Chemistry, Southern Methodist University, Dallas, Texas 75275

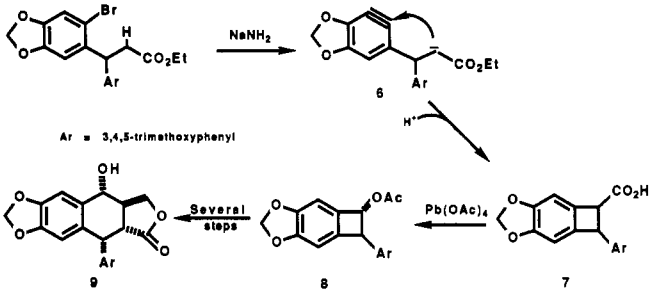
Received February 6, 1989 (Revised Manuscript Received May 5, 1989)

The benzyne molecule was proposed and supported by Wittig[1] as early as 1942 to explain the remarkable ease with which nonactivated haloarenes undero nucleophilic substitution in the presence of a strong base. The intermediacy of benzynes in such reactions was shown conclusively by J. D. Roberts in 1953.[2] Since then, this substance and its derivatives have proven to be potent tools in synthetic design.[3] Fueling the dramatic rise of the use of these reactive intermediates have been the high electrophilicity and dienophilicity of their bent acetylenic bond enforced by the geometry of the benzene ring.[4] These two chemical properties have been exploited in many synthetic strategies, the most notable being the construction of rings (i.e., annulation[5]) onto the highly reactive triple bond of the benzyne. The annulations have been carried out in two general ways. One capitalizes on the superb dienophilic properties of benzyne by treating arynes with dienes to yield polycyclic compounds such as iptycenes,[6] condensed polynuclears,[7] novel rings,[8] and certain natural products.[7,9] The other utilizes the electrophilicity of benzyne by adding appropriately substituted nucleophiles to arynes in an initial step followed by cyclization. These arylations may proceed either intramolecularly or intermolecularly. In the former case, termed "benzyne cyclization", both the ring fusion and the addition of an appropriate side chain occur simultaneously, whereas in the latter case, the initially formed adduct is subsequently cyclized in situ or after suitable structural modification.

Scheme I



Scheme II



This Account will focus on the application of these aryne arylations to the synthesis of polycyclic com-

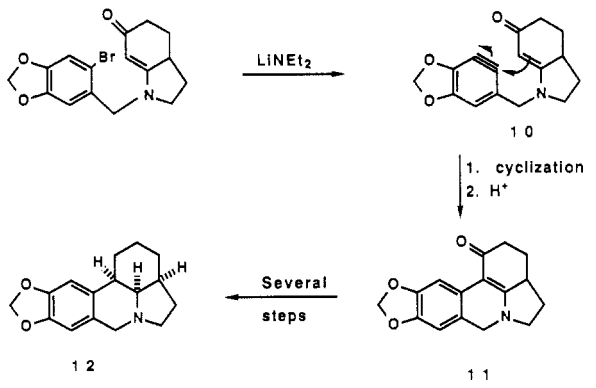
Edward R. Biehl was born in Pittsburgh, PA, on July 14, 1932. He attended the University of Pittsburgh, where he received the B.S. and Ph.D. degrees in chemistry. After being employed by Monsanto Research Corporation for one year, he joined the chemistry faculty at Southern Methodist University in 1962. In 1980, he was appointed to the position of departmental chair, a position he currently holds. In addition to benzyne chemistry, he is interested in the synthesis, structure, and spectral properties of phenothiazines.

Subhash P. Khanapure received his Ph.D. degree from Poona University under the supervision of Dr. K. G. Das at the National Chemical Laboratory, Pune, and Regional Research Laboratory, Hyderabad. After spending one and one-half years working as a postdoctoral fellow in Prof. K. Fuji's laboratory in the Institute for Chemical Research at Kyoto University, he joined Ed Biehl's research group at Southern Methodist University in 1985. His research interests are in the area of synthetic organic chemistry.

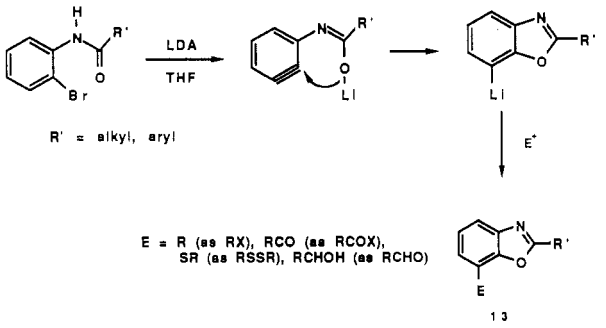
(1) Wittig, G. *Naturwissenschaften* **1942**, *30*, 696–703.
(2) Roberts, J. D.; Simmons, H. E.; Carlsmith, L. A.; Vaughan, C. W. *J. Am. Chem. Soc.* **1953**, *75*, 3290–3291.
(3) For aryne reviews, see: Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes*; Academic: New York, 1967. Reinecke, M. G. *Tetrahedron* **1982**, *38*, 427–498. Levin, R. H. In *Reactive Intermediates*; Jones, M., Moss, R. A., Eds.; J. Wiley: New York, 1978; Vol. 1, pp 1–26; 1981; Vol. 2, pp 1–14; 1985; Vol. 3, pp 1–18. Gilchrist, T. L. *Carbenes, Nitrenes, and Arynes*; Appelton-Century-Croft: New York, 1969.
(4) Strozier, R. W.; Carmella, P.; Houk, K. N. *J. Am. Chem. Soc.* **1979**, *101*, 1340–1342. Rondan, N. G.; Domelsmith, L. N.; Houk, K. N.; Bowne, A. T.; Levin, R. H. *Tetrahedron Lett.* **1979**, 3237–3240. Maier, W. F.; Lau, G. C.; McEwen, A. B. *J. Am. Chem. Soc.* **1985**, *107*, 4724–4731.

0001-4842/89/0122-0275$01.50/0

Scheme III



Scheme IV

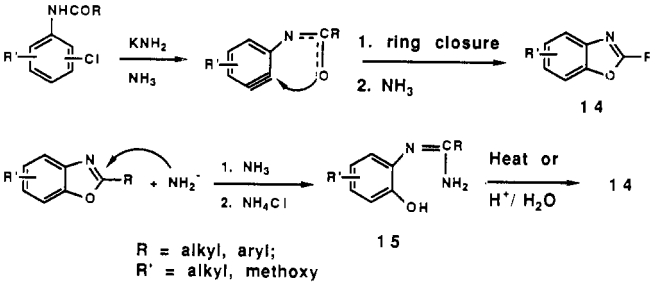


pounds,[10] an area in which we have a continuing interest. Major emphasis will be placed on synthetic applications that have not been previously reviewed. Even with these restrictions, examples of the two methodologies are so numerous that, within the space constraints of this Account, we could not include many interesting examples and offer our apologies to those investigators whose work we cannot include herein.

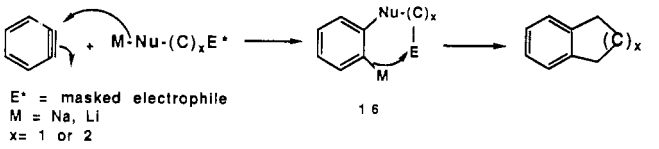
Annulations Involving Aryne Side-Chain Cyclizations

Benzyne side-chain cyclization, introduced independently by Huisgen[11] and Bunnett,[12] involves trapping a benzyne with a side-chain nucleophile, generating

Scheme V

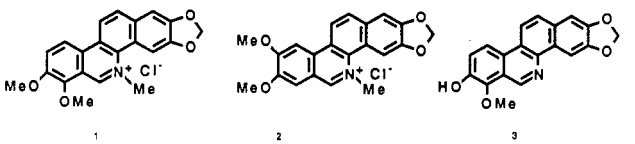


Scheme VI



a bicyclic system. In practice, the aryne is linked to the nucleophile through a chain of suitable length (usually three or four atoms), and the two fused rings can be constructed simultaneously with complete regiochemical control. Schemes I–VI display examples of such syntheses.

Benzyne cyclization methodology is extensively used in natural product synthesis. For example, Kessar[13] recently reported the synthesis of several naturally occurring benzo[*c*]phenanthridine alkaloids,[14] such as chelerythrine (1), nitidine (2), and decarine (3), in 80%, 37%, and 10% yields, respectively, through a benzyne-mediated cyclization of *N*-(2-halobenzyl)-naphthylamines. The steps leading to the preparation



of decarine (3) are typical of these types of annulation reactions and are given in Scheme I. They consist of joining together the two aryl carbons by the intramolecular addition of the ortho naphthalene carbon (rendered reactive by prior amination of the C=N group) to the aryne fragment in 5. The aryne was generated from bromoarene 4 and potassium amide in liquid ammonia. The yields of the 8,9-oxygenated alkaloids, such as 2, were significantly increased when the bulky base LDA in THF was used rather than KNH_2 in ammonia to generate the aryne (70% vs 10%).[13]

Additionally, the total synthesis of podophyllotoxin (9), a valuable precursor to the anticancer drug Etoposide,[15] has been carried out using benzyne cyclization methodology in the key step.[16] As shown in Scheme II, the intramolecular cyclization of aryne 6 gives a mixture of *cis*- and *trans*-1,2-dihydrobenzocyclobutenes

(5) Derived from the Latin word annulatus meaning the making of rings.

(6) Key references include: Hart, H.; Lai, C.; Nwokogu, G. C.; Shamouilian, S. *Tetrahedron* **1987**, *43*, 5203–5224. Hart, H.; Bashir-Abdollah, A.; Luo, J.; Meador, M. A. *Ibid.* **1986**, *42*, 1641–1654.

(7) Luo, J.; Hart, H. *J. Org. Chem.* **1987**, *52*, 4833–4836. Pollart, D. J.; Rickborn, B. *J. Org. Chem.* **1987**, *52*, 792–798. Mirsadeghi, S.; Rickborn, B. *Ibid.* **1987**, *52*, 787–792. Gribble, G. W.; LeHoullier, C. S.; Sibi, M. P.; Allen, R. W. *J. Org. Chem.* **1985**, *50*, 1611–1616. Gribble, G. W.; Saulnier, M. G.; Sibi, M. P.; Obaza-Nutaitis, J. A. *Ibid.* **1984**, *49*, 4518–4523. Gribble, G. W.; Sibi, M. P.; Kumar, S.; Kelley, W. J. *Synthesis* **1983**, 502–504. Pindur, V.; Erfanian-Abdoust, H.; *Liebigs Ann. Chem.* **1988**, 803–806. Pfeuffer, L. P.; Pindar, V. *Chimia* **1986**, *40*, 124–126. Pascal, R. A., Jr.; McMillan, W. D.; Engen, D. V. *J. Am. Chem. Soc.* **1986**, *108*, 5652–5653.

(8) Anthony, I. A.; Byrne, L. T.; McCulloch, R. K.; Wege, D. *J. Org. Chem.* **1988**, *53*, 4123–4124. Cresp, T. M.; Wege, D. *Tetrahedron* **1986**, *42*, 6713–6718.

(9) Martin, G.; Guitân, E.; Castedo, L.; Saá, J. M. *Tetrahedron Lett.* **1987**, *28*, 2407–2408 and references therein. Fishwick, C. W. G.; Gupta, R. C.; Starr, R. C. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2827–2829. May, C.; Moody, C. J. *J. Chem. Soc., Chem. Commun.* **1984**, 926–927. Best, W. M.; Wege, D. *Aust. J. Chem.* **1986**, *39*, 635–645 and 647–666.

(10) For those interested in aryne cycloaddition annulations, see reviews listed in ref 2 and 12 and see: Thummel, R. P. *Acc. Chem. Res.* **1980**, *13*, 70–76.

(11) Huisgen, R.; Sauer, J. *Angew. Chem.* **1960**, *72*, 91–108.

(12) Bunnett, J. F.; Kato, T.; Flynn, R. R.; Skorcz, J. A. *J. Org. Chem.* **1963**, *28*, 1–6 and references therein.

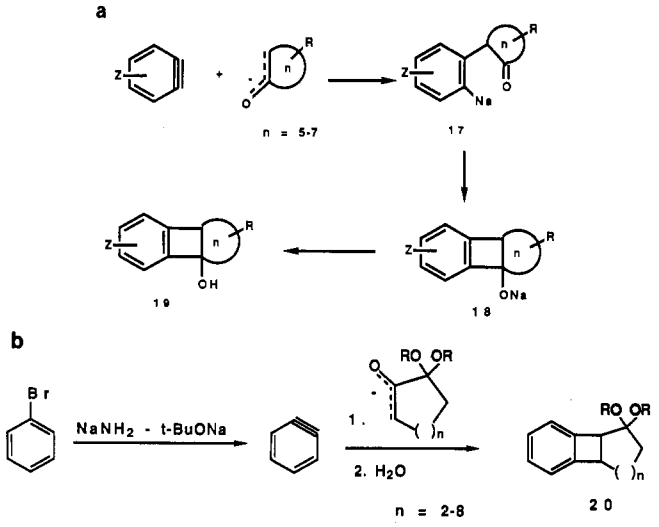
(13) Kessar, S. V.; Gupta, Y. P.; Balakrishnan, P.; Sawal, K. K.; Mohammad, T.; Dutt, M. *J. Org. Chem.* **1988**, *53*, 1708–1713.

(14) The search for alkaloids of this type continues because of the cytotoxic activity associated with various members of this class of compounds. See: Stermitz, F. R.; Larson, K. A. *J. Med. Chem.* **1973**, *16*, 939–945. Suffness, M.; Dours, J. *Methods in Cancer Research*; Devita, V. J., Jr., Busch, H., Eds.; Academic: New York, 1979; Vol. 16, Chapter 3.

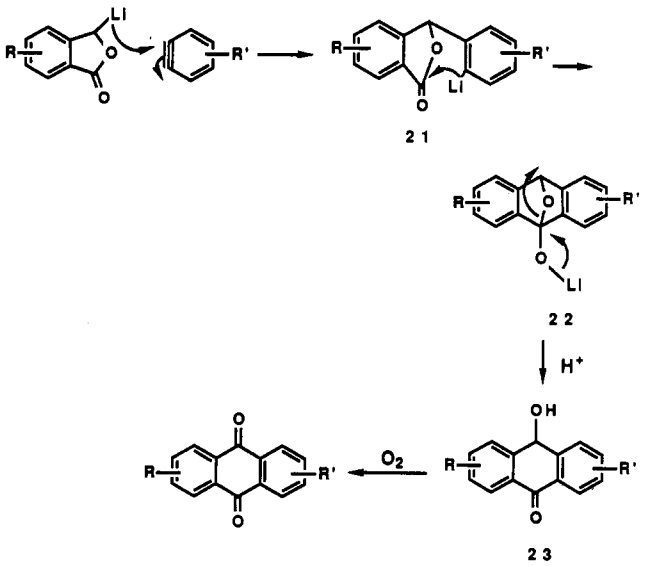
(15) Jardine, I. *Anticancer Agents Based on Natural Product Models*; Cassady, J. M., Doures, J. D., Eds.; Academic: New York, 1980; pp 319–351.

(16) Macdonald, D. I.; Durst, T. *J. Org. Chem.* **1988**, *53*, 3663–3669.

Scheme VII



Scheme VIII



7. This mixture is diastereoselectively oxidized to the trans acetate 8,[17,18] which is then converted to the target compound **9** by a series of well-established reactions.

The reported formal synthesis of γ-lycorane (**12**)[19] shown in Scheme III is particularly interesting since the cyclization step occurs via an unprecedented intramolecular arylation of an enaminone. The addition of the α-carbon of the enamine onto aryne **10** was proposed to account for the formation of (±)-α-dihydrocaranone **11**, after proton quench. The conversion of **11** to the target compound **12** can be accomplished by previously reported methods.[20]

Clark and Caroon[21] showed that anions generated by the intramolecular side-chain additions to arynes in benzoxazole synthesis can be trapped by electrophiles, affording 6-substituted 2-benzoxazoles (**13**) (see Scheme IV). Since these heterocycles can be converted to aminophenols, this method affords access to 6-substituted 2-aminophenols. Numerous other applications of this methodology, such as the preparation of 2-benzothiazolinones, can be envisioned.

Our attempts to prepare a series of benzoxazole derivatives **14** by the benzyne cyclization reaction of *o*- and *m*-halobenzamides with potassium amide in liquid ammonia yielded the corresponding *o*-hydroxyphenyl amidines **15** rather than the expected compounds **14**[22] (see Scheme V). Apparently, the benzoxazoles form initially, but react further with amide ion to yield amidines. The desired benzoxazoles can be obtained by the sublimation or acid hydrolysis of the amidines.

Annulations Involving Intermolecular α-Arylation of Functionalized Nucleophiles by Arynes

Two general aryne arylation methods of this type have been developed. The first takes advantage of the bifunctional nature of benzyne as shown in Scheme VI. It consists of the initial introduction of a functionalized carbanion possessing an electrophilic center (or a masked electrophilic center which can be unmasked during the addition process) to an aryne. The resulting aryl anion **16** can then undergo an intramolecular addition to the electrophilic site to complete the annulation process.

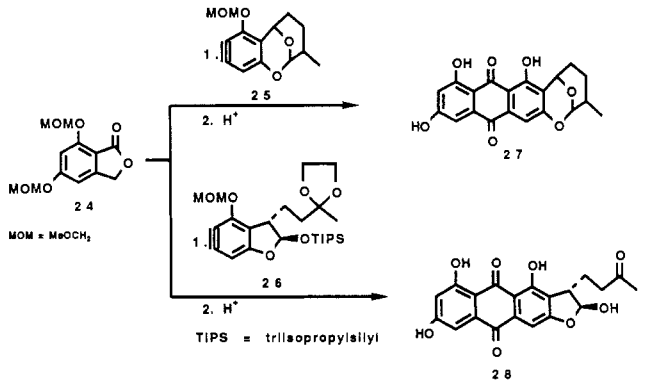
The first to demonstrate the synthetic usefulness of this method was Caubere, who prepared benzocyclobutenols **19** by trapping arynes (generated from the appropriate haloaromatic in the presence of $NaNH_2$ alone or in the presence of a complex base such as $NaNH_2$–*t*-BuONa in an aprotic solvent, e.g., THF, DME) with five- to seven-membered cyclic sodium enolates.[23a] A plausible mechanism is depicted in Scheme VII, part a. As shown in compound **17**, the addition of the sodium enolate to benzyne generates both an aryl anion and a carbonyl electrophilic group, which combine to form the oxyanion **18**. The oxyanion is then neutralized to **19**. The failure of cycloalkanones with ring sizes larger than seven to yield benzocyclobutenols was attributed to the lack of stability of the oxyanion **18** under the basic conditions used in the aryne reaction. The origin of this instability is not yet understood.

Recently, Caubere[23b] has reported a general method for the preparation of benzocyclobutenol derivatives **20** from the arynic condensation of enolates derived from both linear aliphatic and alicyclic diketone monoketals (the use of the latter is depicted in Scheme VII, part b). The ketal oxygen atoms are believed to aid in the stabilization of the oxyanion by complexation with the sodium cation.

These alcohols have been shown to be excellent starting materials for the obtention of benzocyclenediones and indanone derivatives.[23c] Interestingly, benzyne prepared from sodamide in ammonia also reacts smoothly with enolates, but yields simple α-phenylated ketones[24] or esters[25] rather than ring products such as **19** or **20**. Apparently in these cases,

(17) This portion of the synthesis was reported in a preliminary communication. See: Macdonald, D. I.; Durst, T. *Tetrahedron Lett.* **1986**, *27*, 2235–2238.
(18) A similar synthesis of **9** using a nitrile rather than an ester was subsequently reported by Jung and Lowen: Jung, M. E.; Lowen, G. T. *Tetrahedron Lett.* **1986**, *27*, 5319–5322.
(19) Iida, H.; Yuasa, Y.; Kibayashi, C. *J. Org. Chem.* **1979**, *44*, 1074–1080.
(20) Kotera, K. *Tetrahedron* **1961**, *12*, 248–261.
(21) Clark, R. D.; Caroon, J. M. *J. Org. Chem.* **1982**, *47*, 2804–2806.
(22) El-Sheikh, M. I.; Marks, A.; Biehl, E. R. *J. Org. Chem.* **1981**, *46*, 3256–3259.
(23) (a) Caubere, P. *Acc. Chem. Res.* **1974**, *7*, 301–308. (b) Gregoire, B.; Carre, M. C.; Caubere, P. *J. Org. Chem.* **1986**, *51*, 1419–1427. (c) Geoffroy, P.; Caubere, P. *Tetrahedron* **1988**, *44*, 127–137.
(24) Leake, W. W.; Levine, R. *J. Am. Chem. Soc.* **1959**, *81*, 1169–1172.
(25) Leake, W. W.; Levine, R. *J. Am. Chem. Soc.* **1959**, *81*, 1627–1630.

Scheme IX

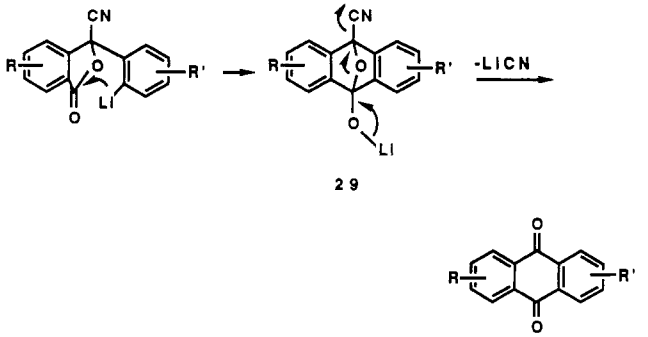


the initially formed aryne adduct **17** is quenched by the protic ammonia solvent before it is able to cyclize to **18**.

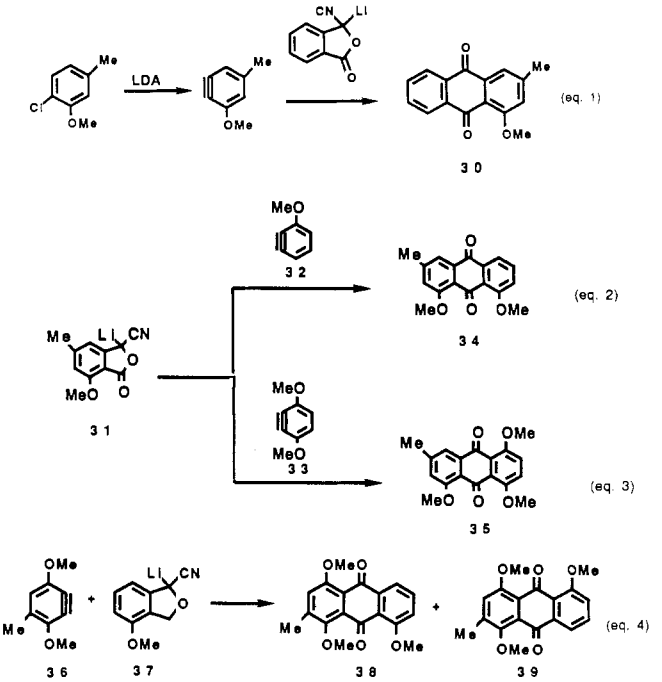
Similarly, Sammes[26] prepared a variety of anthraquinones by treating bromoarenes with lithiated phthalides under aryne-forming conditions (LDA in THF). A plausible mechanism, presented in Scheme VIII, involves the nucleophilic addition of the phthalide anion to aryne, providing **21**, which is converted to the hemiacetal **22** by the attack of the newly formed aryl anion onto the carbonyl group of the ester function. Ring opening of **22** produces the anthranol **23**, which is then air-oxidized (4 h) to the anthraquinone before reaction workup. Almost all authors in this area assume the reactions of 3-lithiophthalide with arynes to occur in a stepwise manner; however, it is possible that the formation of hemiacetal **22** outlined in Scheme VIII may occur via a [4 + 2] concerted pathway. Clearly more work is needed to clear up this difficult mechanistic point.

The extension of this methodology to natural product synthesis was demonstrated by Townsend, who prepared (±)-averufin (**27**)[27] and hydroxyversicolorone (**28**),[28] important intermediates in aflatoxin B_1 biosynthesis. These compounds were obtained by the regioselective addition of the MOM-protected 5,7-dihydroxyphthalide **24** to the highly functionalized arynes **25** and **26**, respectively, to give adducts, which were converted into products **27** and **28** by successive air oxidation and deprotection (Scheme IX).

A more direct route to anthraquinones can be accomplished by treating arynes with lithiated 3-cyanophthalides.[29] The substitution of hydrogen by a cyano group enables the cyano hemiacetal (**29**) to be converted directly to the corresponding anthraquinone, thus obviating the air-oxidation step required in the Sammes synthesis. Russell and Warrener have also shown that anthraquinones can be obtained directly by using 3-(phenylsulfonyl)phthalides.[30] Since they are known to be better annulating agents than the 3-phenylsulfonyl derivatives,[31] we chose to study the preparation of anthraquinones using 3-cyanophthalides. This enhanced reactivity, combined with the facile synthesis of functionalized 3-cyanophthalides[32a] from readily available 3-hydroxyphthalides,[32b] permitted an easy access to anthraquinones with varied substitution patterns.



We have also prepared methyl ethers of several anthraquinones found in plant pigments from 3-cyanophthalides and arynes. Representative examples include pachybasin methyl ether[33] (**30**) (40%) (eq 1), chrysophanol dimethyl ether (**34**) (34%) (eq 2), helminthosporin trimethyl ether (**35**) (53%) (eq 2), digitopurpone trimethyl ether (**38**) (34%) (eq 3), and islandicin trimethyl ether (**39**) (34%) (eq 4).

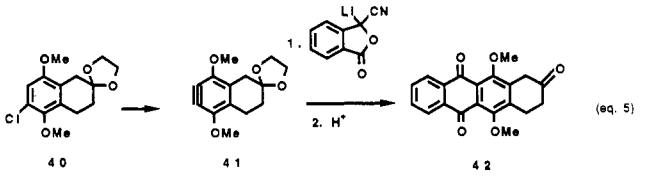


The examples also show the degree of regioselectivity that is exhibited in these reactions. Thus, addition of **31** to the unsymmetric aryne 3-methoxybenzyne (**32**) occurs regioselectively and in accordance with strong meta-directing ability of the methoxy group.[34] However, the addition of 3-lithio-3-cyano-7-methoxyphthalide (**37**) to aryne **36** occurs nonregioselectively to give equal mixtures of ethers of two natural products, digitopurpone trimethyl ether (**38**) (34%) and islandicin trimethyl ether (**39**) (34%), which can be readily separated by flash chromatography. In aryne **36**, the di-

(26) Dodson, D. J.; Calcagno, M.; Ehrmann, E.; Devades, B.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2120–2123.
(27) Townsend, C. A.; Davis, S. G.; Christensen, S. B.; Link, J. C.; Lewis, C. P. *J. Am. Chem. Soc.* **1981**, *103*, 6885–6888.
(28) Townsend, C. A.; Whittamore, P. R. O.; Brobst, S. W. *J. Chem. Soc., Chem. Commun.* **1988**, 726–728.
(29) Khanapure, S. P.; Reddy, R. T.; Biehl, E. R. *J. Org. Chem.* **1987**, *52*, 5685–5690.
(30) Russell, R.; Warrener, R. N. *J. Chem. Soc., Chem. Commun.* **1981**, 108–110.
(31) Li, T.; Walsgrove, T. C. *Tetrahedron Lett.* **1981**, *22*, 3741–3744.
(32) (a) Morrow, G. W.; Swenton, J. S.; Filppi, J. A.; Wolgemuth, R. L. *J. Org. Chem.* **1987**, *52*, 713–719 and references therein. (b) Snieckus, V. *Bull. Soc. Chim. Fr.* **1988**, 67–78.
(33) Pachybasin has been used as a model compound in developing methods for the synthesis of 11-deoxyanthracyclines; see: Jung, M. E. *J. Chem. Soc., Chem. Commun.* **1978**, 95–96. Pavanaram, S. K.; Hofer, P.; Linde, H.; Meyer, K. *Helv. Chim. Acta* **1963**, *46*, 1377–1385.
(34) Roberts, J. D.; Semenov, D. A.; Simmons, H. E., Jr.; Carlsmith, L. A. *J. Am. Chem. Soc.* **1956**, *78*, 611–614.

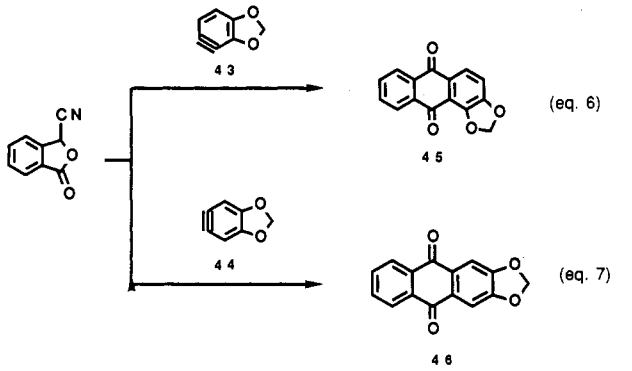
recting effect is determined not by the methoxy groups (since the inductive effect of each methoxy group is canceled by the other), but rather by the weakly directing methyl group.

Additionally, the tetracyclic intermediate **42**, a valuable precursor in the synthesis of the anthracycline antibiotic 4-demethoxydaunomycin,[35] was prepared by the reaction of lithiated 3-cyanophthalide with chloroarene **40** via aryne **41** (eq 5). The aryne precursor **40** was prepared in a straightforward, five-step synthesis from 2,6-dichlorobenzoquinone.



(eq. 5)

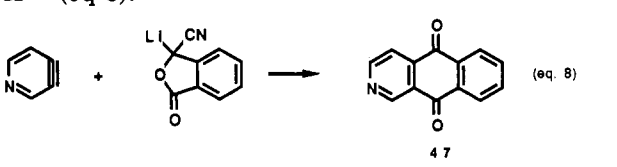
Recently, we[36] carried out the preparation of the natural product morindaparvin-A (**45**) (eq 6) and isomorindaparvin (**46**) (eq 7), which is not naturally occurring, by the reaction of lithiated 3-cyanophthalide with 3,4-(methylenedioxy)benzyne (**43**) and 4,5-(methylenedioxy)benzyne (**44**), respectively. The unsymmetric aryne **43** was generated from 3-bromo-1,2-(methylenedioxy)benzene and LDA in THF, whereas the symmetric isomer **44** was prepared by treating 4-bromo-5-iodo-1,2-(methylenedioxy)benzene with *n*-BuLi in THF.



(eq. 6)

(eq. 7)

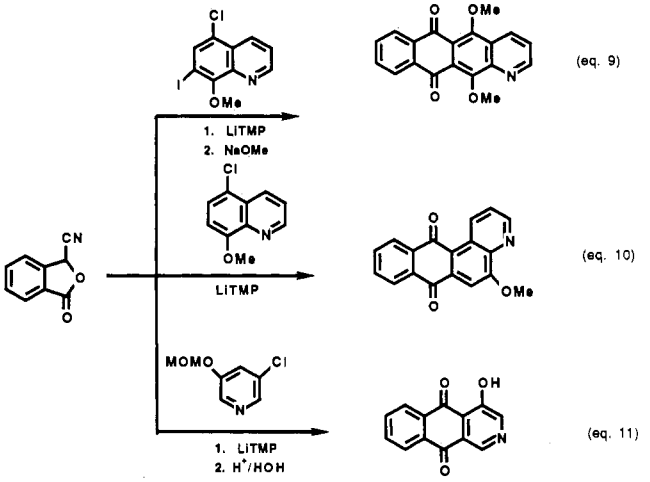
Finally, by treating various 3-lithio-3-cyanophthalides with 3,4-didehydropyridines, we[37] extended this one-pot aryne annulation method to the synthesis of 2-azaanthraquinones. This constitutes the most convenient synthetic route to this interesting class of heterocycles. For example, the parent 2-azaanthraquinone (**47**), a predicted DNA intercalant,[38] can be prepared in 70% yield from the reaction of the readily accessible 3-cyanophthalide and 3-bromopyridine with LDA in THF[39] (eq 8).



(eq. 8)

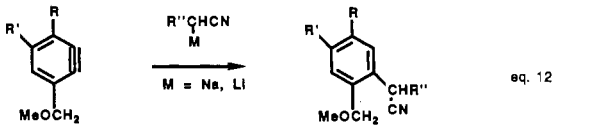
(35) Arcamone, A. *Doxorubicin Anticancer Antibiotics*; Academic: New York, 1981.
(36) Khanapure, S. P.; Biehl, E. R. *J. Nat. Prod.*, submitted.
(37) Khanapure, S. P.; Biehl, E. R. *Heterocycles* **1988**, *27*, 2643–2650.
(38) For a discussion of this general topic, see: Gale, E. F.; Cundliffe, E.; Reynolds, P. E.; Richmond, M. H.; Waring, M. J. *The Molecular Basis of Antibiotic Action*, 2nd ed.; Wiley-Interscience: New York, 1981; pp 280–298.
(39) 2-Azaanthraquinone is currently being sold for ca. $175,000 per pound!

The broad scope of this synthesis is illustrated in eq 9–11, which show a few short azaanthraquinone syntheses from readily available starting materials.[40]



The second annulation method using intermolecular aryne arylation[41] has been used in the syntheses of 4-alkyl and 4-aryl derivatives of isochroman-3-one, which are valuable precursors in the synthesis of condensed polynuclear aromatic compounds. For example, gas-phase pyrolysis of these lactones provides a convenient method[42] for the generation of the synthetically useful *o*-quinodimethanes.[43] These synthetically useful intermediates can be cyclized to benzocyclobutenes or serve as dienes that can be trapped either intramolecularly[44] or intermolecularly[45] by dienophiles to form Diels–Alder adducts. Additionally, isochroman-3-ones have been converted by nonpyrolytic methods to derivatives of isoquinolines[46] and thioisoquinolines.[47]

The key step in this aryne arylation annulation strategy is the introduction of a cyano side chain ortho to a methoxymethyl group by the addition of aliphatic or aromatic nitrile anions. Subsequent hydrolysis and cyclization of the products yields the corresponding isochroman-3-ones. We have prepared three isochroman-3-one precursors (**51–53**) with the required ortho functionality by the addition of anions of alkyl- and arylacetonitriles to the respective arynes (**48–50**) (see eq 12). When aryne **48** was generated in liquid

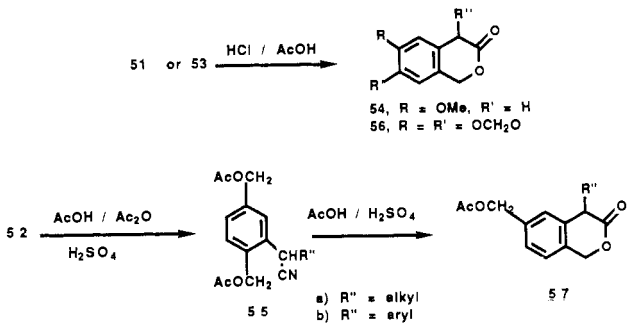


eq. 12

48, R = OMe, R' = H, 51 a, R'' = alkyl
49, R = CH_2OMe, R' = H, 52 b, R'' = aryl
50, R = R' = OCH_2O, 53

(40) Khanapure, S. P.; Biehl, E. R. *Heterocycles*, submitted.
(41) Khanapure, S. P.; Biehl, E. R. *J. Org. Chem.* **1987**, *52*, 1333–1337.
(42) Spangler, R. J.; Beckmann, B. G.; Kim, J. H. *J. Org. Chem.* **1977**, *42*, 2989–2996.
(43) For reviews, see: Kametani, T.; Fukumoto, K. *Heterocycles* **1975**, *3*, 29–56. Kunalt, I. L. *Chem. Rev.* **1970**, *70*, 471–487. Oppolzer, W. *Synthesis* **1978**, 793–802. Funk, R. L.; Vollhardt, K. P. C. *Chem. Soc. Rev.* **1980**, *9*, 41–61. Charlton, J. L.; Alauddin, M. M. *Tetrahedron* **1986**, *43*, 2873–2876.
(44) Oppolzer, W.; Keller, K. *J. Am. Chem. Soc.* **1971**, *93*, 3836–3837.
(45) Kametani, T. *Pure Appl. Chem.* **1979**, *51*, 747–768. Das, K. G.; Afzal, J.; Hazra, B. G.; Bhawal, B. M. *Synth. Commun.* **1983**, *13*, 787–796. Jung, M. E.; Lam, P. Y. S.; Mansuri, M. M.; Speltz, L. M. *J. Org. Chem.* **1985**, *50*, 1087–1105.
(46) Black, G. G.; Sainsbury, M.; Majeed, A. J. *Tetrahedron* **1984**, *40*, 4383.
(47) Pandey, G. D.; Ganesh, O.; Tiwari, K. P. *Can. Sci.* **1980**, *49*, 498–503.

Scheme X



ammonia by the base sodamide, yields of product **51** varied depending on the nature of the nitrile. In general, yields of **51a** from alkyl nitriles were higher than those from aromatic nitriles **51b**. The lower yields of **51b** were due to increased competition by the ammonia solvent for aryne **48**, resulting in amination products. The reaction of the symmetric aryne **49**, generated by sodamide in ammonia, with both types of nitriles gave high yields of both products, **52a** and **52b**. Best yields of nitrile products **53a** and **53b** were obtained by generating aryne **50** with either LiTMP or LDA in THF.

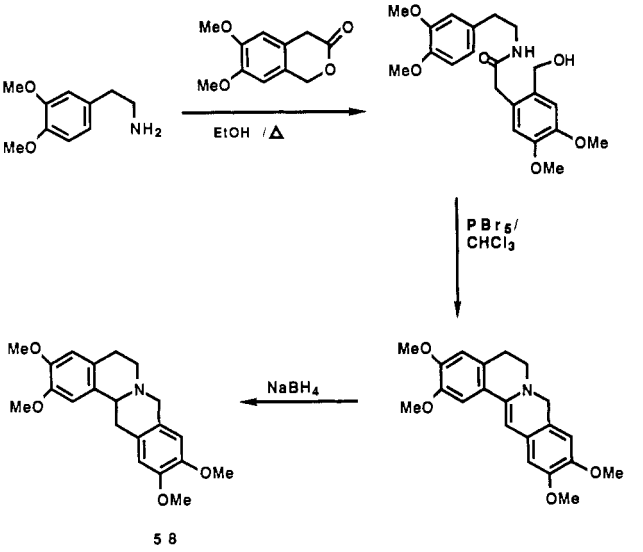
Isochroman-3-ones **54** and **56** were readily obtained by the hydrolysis and cyclization of **51** and **53**, respectively (see Scheme X). Since the methoxymethyl group not involved in the lactonization can undergo a competing conversion to a mixture of products under the usual acid-catalyzed hydrolysis, lactone **57** was prepared as the 6-acetoxymethyl derivative via **55**.

Some noteworthy aspects of this annulation method are (a) 4-alkylisochroman-3-ones are obtained uncontaminated with the 4,4-dialkyl isomers, which form as side products when S_N2 alkylation methods are used,[48] and (b) it constitutes the only known method for the synthesis of 4-arylisochroman-3-ones.

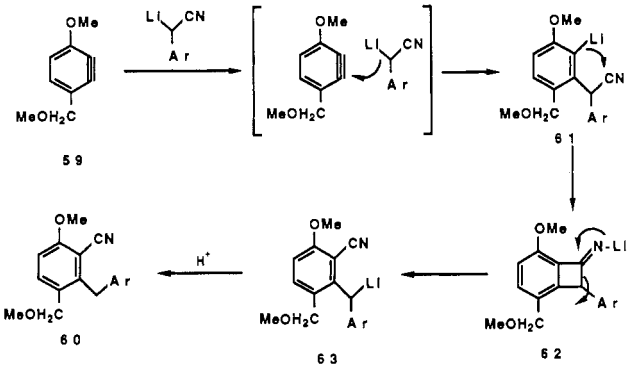
With 4-substituted isochromanones now available, we have been able to convert them to protoberberins by established routes.[49] The synthesis of the parent xylopinine (**58**) is given as a typical example in Scheme XI.

In order to increase the yields of 4-substituted isochroman-3-ones, alkyl- or arylacetonitriles and 2-bromo-4-(methoxymethyl)anisole were treated with LDA in THF. The expectation was that by replacing the ammonia with the aprotic solvent THF the pesky amination side reaction would be drastically reduced. Although the reactions with alkylacetonitriles proceeded as usual, the reactions with arylacetonitriles gave none of the expected α-aryl-2-(methoxymethyl)-5-methoxyphenylacetonitriles, but rather 2-cyano-3-(arylmethyl)-4-(methoxymethyl)anisoles **60**.[50] In this reaction, the rearranged nitriles are possibly formed by the tandem addition rearrangement aryne pathway shown in Scheme XII. As can be seen, compound **61**, formed from the addition of the lithioarylacetonitrile to aryne **59**, cyclizes to the benzocyclobutanimine **62** in a process analogous to that described by Caubere in

Scheme XI



Scheme XII

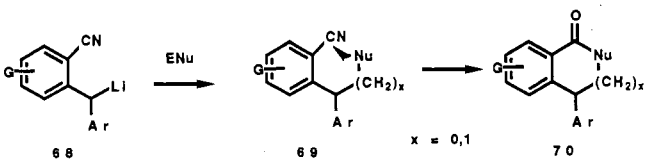


macrocyclic benzo ketone synthesis.[23] Ring opening of **62** affords the synthetically versatile lithioaryl(2-cyanoaryl)methane **63**, which on neutralization gives the rearranged products **60**. A similar mechanism was proposed by Meyers[51] to account for the rearranged products from the addition of lithioalkyl nitriles to 3-oxazolinyl benzyne.

The extent to which bromoarenes are transformed into either rearranged products or typical aryne substitution products is highly dependent on substituent effects. For example, rearranged products are favored for aryne precursors possessing at least two electron-releasing substituents which enhance the nucleophilicity of the 2-lithio site; i.e., the site involved in benzocyclobutenium formation. These include 2-bromo-4-methylanisole,[50] 4-bromo-1,3-dimethoxybenzene,[50] 2-chloro-5-methyl-1,4-dimethoxybenzene,[52] 2-chloro-10-methylphenothiazine,[53] and 3-bromo-5-(methoxymethyl)-1,2-dimethoxybenzene.[52] Those precursors possessing fewer than two electron-releasing groups (e.g., 3,6-dimethoxybenzyne, 3-methoxybenzyne, and 3-bromopyridine[52]) predominantly give typical aryne substitution products. Additionally, mono- and polysubstituted methoxy- and fluorophenylacetonitriles react via a rearrangement pathway, whereas 3-(trifluoromethyl)phenylacetonitrile, α-pyridylacetonitrile,

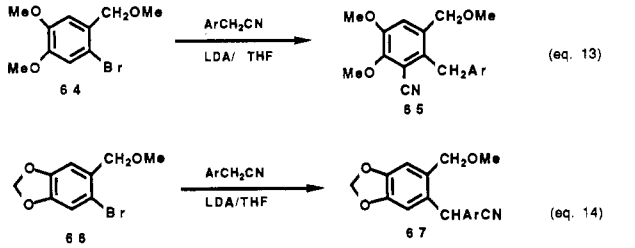
(48) Khanapure, S. P. Ph.D. Thesis, Poona University, 1983.
(49) A preliminary report of this research was presented: Khanapure, S. P.; Biehl, E. R. *Abstracts of Papers*, 191st National Meeting of the American Chemical Society, Dallas, TX, April 13, 1989; American Chemical Society: Washington, DC, 1989; ORGN 469.
(50) Khanapure, S. P.; Crenshaw, L.; Reddy, R. T.; Biehl, E. R. *J. Org. Chem.* **1988**, *53*, 4915–4919.
(51) Pansegrau, P. D.; Rieker, W. F.; Meyers, A. I. *J. Am. Chem. Soc.* **1988**, *110*, 7178–7184.
(52) Unpublished results.
(53) Biehl, E. R.; Khanapure, S. P.; Siriwardane, U.; Tschantz, M. *Heterocycles* **1989**, *29*, 485–496.

Scheme XIII



and α-furylacetonitrile yield typical aryne substitution products.[53]

The course of the tandem addition–rearrangement reaction with arylacetonitriles and LDA is very sensitive to substituent effects. This can be seen in that the aryne reaction of the structurally similar 3,4-dimethoxybromoarenes (**64**) and 3,4-(methylenedioxy)bromoarenes (**66**) with lithio aryl nitriles give entirely different products (eq 13), the former yielding rearranged **65**, the latter giving the usual substitution products **66**[54] (eq 14).

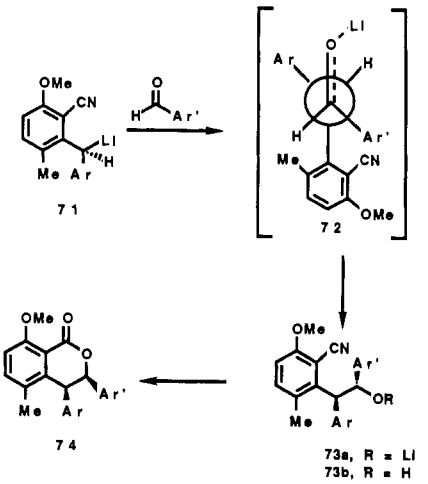


We have recently initiated studies on another aryne annulation method (Scheme XIII), which takes advantage of the ortho bifunctionality introduced in a tandem addition–rearrangement reaction. The first step involves trapping lithioaryl(2-cyanoaryl)methanes **68** with electrophiles of the general type E–Nu*. The Nu* component is a masked nucleophile which is revealed during or after the trapping of **68**. The trapped adducts **69** then are cyclized to five- or six-membered rings **70** by usual chemical means.

To date, the stereocontrolled synthesis of *cis*-3,4-diarylisochroman-1-ones **74** (dihydroisocoumarins) has been accomplished in this way[55] (Scheme XIV). Trapping lithioaryl(2-cyanoaryl)methanes **71** (obtained from the reaction of 2-bromo-4-methylanisole and arylacetonitriles with LDA in THF) with various benzaldehydes gives the lithiated *anti*-1,2,2-triarylethanols **73**. The alcoholates are smoothly converted diastereospecifically to the *cis*-dihydroisocoumarins **74** in situ or by redissolving the isolated alcohols in neat LDA/THF solution. The preferred approach of the two

(54) Khanapure, S. P.; Biehl, E. R. *J. Org. Chem.*, submitted.
(55) Crenshaw, L. C.; Khanapure, S. P.; Siriwardane, U.; Biehl, E. R. *Tetrahedron Lett.* **1988**, *29*, 3777–3780.

Scheme XIV



components, shown by **72**, leads to the anti disposition of the diaryl substituents about the newly formed C–C bond, in accord with Cram's rule.[56]

A wide variety of *cis*-3,4-diarylisocoumarins, with a large selection of substitution patterns, can be prepared from inexpensive, readily available bromoarenes, arylacetonitriles, and benzaldehydes as starting materials. In the future, we hope to extend this method to the synthesis of highly functionalized derivatives of 3,4-dihydroisocoumarins, isoquinolin-1-ones, isocarbostyrils, and 1-tetralones by the use of suitable trapping agents.

Conclusions

This Account has presented several methods by which arynes can be annulated to polycyclics. A large number of publications on every aspect of aryne arylations continues to appear in periodicals with no letup in sight. Clearly, aryne annulations have been incorporated into the arsenal of synthetic design and are accepted as an important addition to synthetic organic chemistry.

I thank the many collaborators who contributed so significantly to the aryne efforts of my research group. Additionally, I thank Prof. Al Meyers for providing me with office space and intellectual stimulation during my research leave at Colorado State University, at which time the bulk of this Account was written. Finally, I acknowledge the Welch Foundation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and Southern Methodist University, who provided generous financial support of our aryne research efforts.

(56) Cram, D. J.; Wilson, D. R. *J. Am. Chem. Soc.* **1963**, *85*, 1245–1249.