Benzyne-Oxazole Cycloadducts: Isolation and Retro-Diels-Alder Reactions[1]

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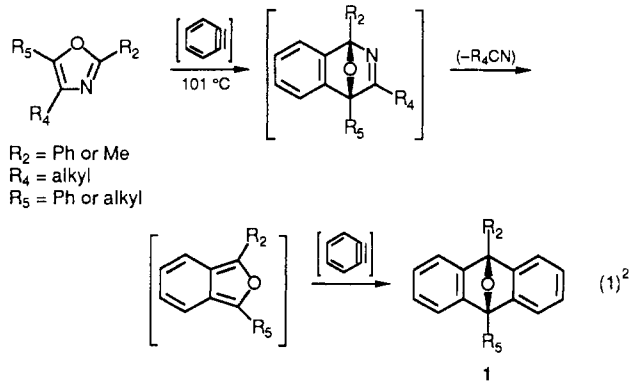
A literature procedure for generating benzyne from 1-aminobenzotriazole and lead tetraacetate was modified by the use of two syringe pumps to effect simultaneous addition through opposing ports of a three-neck flask. Applied to the reaction of benzyne with 4-phenyloxazole at 0 °C, this modification resulted in essentially quantitative formation of cycloadduct. Retro-Diels-Alder expulsion of benzonitrile with concurrent formation of isobenzofuran occurred when the adduct was heated. The sequence constitutes a useful method of preparation of isobenzofuran, which may be utilized in situ or isolated as a solution for subsequent application. Benzyne cycloadducts were also prepared from 4-(4-nitrophenyl)- and 4-(4-methoxyphenyl)oxazoles, in order to assess the effect of remote substituents on the retro-Diels-Alder reaction. First-order rate constants were determined at three temperatures in the range of 40-70 °C. The order of reactivity was p-NO_2 > p-H > p-OMe; the substituent effects were small, with a factor <4 separating the p-NO_2 from p-OMe rate. All three substrates exhibited small $\Delta S^{\ddagger}$ values. Expulsion of the nitrile is believed to occur as a concerted reaction with little charge development. The modified benzyne procedure was also applied to 2,5-diphenyloxazole, at 0 and -78 °C. Oxazole was recovered (59% and 43% at the higher and lower temperature, respectively). No bis(benzyne) adduct was formed, showing that 1,3-diphenylisobenzofuran is not generated during the course of the reaction. The 1:1 benzyne-diphenyloxazole cycloadduct is not observed in the crude product of the 0 °C reaction, but an absorption at 6.09 ppm in the NMR spectrum of crude product from the -78 °C reaction is attributed to this material. The latter crude product on standing at room temperature forms the isobenzofuran. Both reaction mixtures form 1,3-diphenylisobenzofuran by another mechanism involving a second intermediate. This more polar intermediate, which appears to be the major product at 0 °C, slowly gives 1,3-diphenylisobenzofuran. The overall more efficient cycloaddition at -78 °C is attributed to entropy effects, which tend to favor Diels-Alder over other second-order reactions as the temperature is lowered.

The Reddy and Bhatt[2] sequence (eq 1) is intriguing from a mechanistic standpoint. These workers found that simultaneous addition[3] of anthranilic acid and isoamyl nitrite to refluxing dioxane (101 °C) solutions of trisubstituted oxazoles gave good yields of bis(benzyne) adducts (1). This outcome requires that each of the steps: (a) formation of benzyne; (b) Diels-Alder reaction with the oxazole; (c) retro-Diels-Alder expulsion of nitrile; and (d) Diels-Alder reaction of benzyne with the isobenzofuran, must be rapid. In particular, step c must give the isobenzofuran sufficiently rapidly to trap the benzyne as it is formed, or the benzyne would be lost to alternative reactions.



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Benzyne is certainly among the most reactive dienophiles known, and very fast (probably diffusion controlled) cycloaddition with the isobenzofuran is expected. The rate of the unprecedented reaction of benzyne with oxazoles is less easily predicted, since these heterocycles have a mixed reputation as dienes in other Diels-Alder applications. Especially pertinent to this study is cycloaddition with acetylenic dienophiles, which constitutes a useful method for the preparation of furans. The temperatures needed for these reactions depend upon substituents on both the oxazole and alkyne, but in general the retro-Diels-Alder loss of nitrile is sufficiently rapid to preclude observation of the initially formed cycloadduct.[4]

The ability to intercept the Reddy-Bhatt sequence at the initial cycloadduct stage could have useful consequences for isobenzofuran preparations and applications.[5] The obvious way to prevent the retro-Diels-Alder loss of nitrile is to carry out the benzyne cycloaddition at lower temperature, but when this work was initiated it was not clear how low this temperature must be, or whether it would be possible to effect the formation and cycloaddition of benzyne below this limit. A further constraint was found in considering possible oxazoles to be examined. Although hundreds of oxazoles are known, few are commercially available, and some require moderately complex syntheses.[6] The less-substituted oxazoles tend to be among the more difficult to prepare, but there are some exceptions. These include 4-phenyloxazole (2), which along with some analogues were chosen as model oxazoles for this study. Results with commercially available 2,5-diphenyloxazole (4) are also described.

The oxazoles examined by Reddy and Bhatt[2] are all trisubstituted. It was important to determine if other substitution patterns would also enter into this sequence.

(1) A preliminary account has appeared: Whitney, S. E.; Rickborn, B. *J. Org. Chem.* **1988**, *53*, 5595.

(2) Reddy, G. S.; Bhatt, M. V. *Tetrahedron Lett.* **1980**, 3627.

(3) Friedman, L.; Logullo, F. M. *J. Am. Chem. Soc.* **1963**, *85*, 1549. Simultaneous addition of anthranilic acid and alkyl nitrite was recommended as a way to minimize the thermal decomposition of the nitrite in reactions carried out at higher temperatures. This useful method has been adopted in many later studies.

(4) Pertinent references, and discussion of an apparent exception to this generalization, are given in ref 1.

(5) Rickborn, B. Isobenzofurans, Chapter I, Vol. I of *Advances in Theoretically Interesting Molecules*; Thummel, Ed.; R. P., JAI Press: Greenwich, CT, 1989.

(6) Turchi, I. in the Weissberger-Taylor series *Heterocyclic Compounds*; Turchi, I., Ed.; J. Wiley & Sons: New York, 1985; Vol. 45, Chapter I (Oxazoles).

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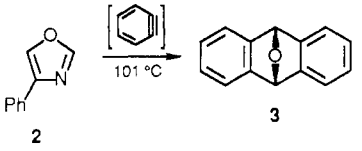
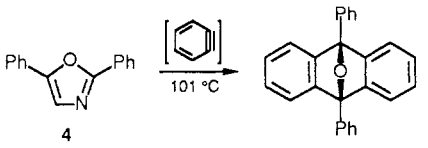
When **2** was subjected to the Reddy–Bhatt conditions (101 °C), the bis(benzyne) adduct **3**[7] was formed in good yield. Thus bridgehead alkyl and/or phenyl substituents (R_2 and R_5 in eq 1) are not required for facile cycloaddition and retro-Diels–Alder loss of nitrile at this temperature.



2 3 (2)

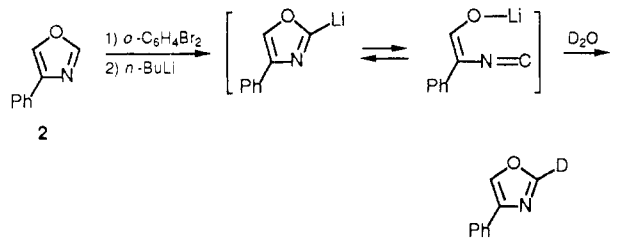
Similarly, the readily available scintillation material **4** gave the diphenyl analogue **5**,[8] demonstrating that the sequence does not require a substituent at the 4-position of the oxazole. These results point up the generality of the Reddy–Bhatt method, which when coupled with Zn/HOAc deoxygenation constitutes a useful synthetic procedure for 9,10-disubstituted anthracenes.[2]



4 5 (3)

Alternative Benzyne-Forming Methods. The anthranilic acid–alkyl nitrite method of generating benzyne is not useful at temperatures below about 40 °C, because of slow decomposition of the diazonium carboxylate in solution. We considered this procedure unlikely to be suitable for isolation of 1:1 benzyne–oxazole cycloadducts, and the results reported below reinforce this view.

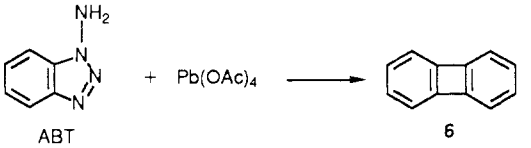
Strong base induced methods of generating benzyne can be used at lower temperatures. However, the acidity of various oxazole sites was a potential problem, especially for the lithium tetramethylpiperidide induced dehydrohalogenation of chlorobenzene, which fails to give cycloadduct even with such weakly acidic materials as furan[9] ($pK_a = 36$)[10] and isobenzofuran ($pK_a \leq 33$).[11] In contrast, the RLi-induced debromination method of forming benzyne works well with isobenzofuran[11] and thus had promise for the desired cycloaddition with oxazoles. However, an attempt to form cycloadduct at 0 °C by addition of *n*-BuLi to a mixture of **2** and *o*-dibromobenzene gave largely recovered oxazole. Repetition of this experiment with quenching by D_2O in place of water gave **2**, which was extensively deuterated in the 2-position (eq 4).



2 (4)

Although the 2-H is generally recognized to be the most acidic site of oxazole, no pK_a value has appeared in the literature. We estimate $pK_a = 20 \pm 2$, based on the Schoellkopf et al.[12] demonstration that 2-lithiooxazoles are in equilibrium with their ring-opened *enolate* tautomers (as illustrated in eq 4), and from H/D exchange observations made by Brown and Ghosh.[13] Although Li–arylBr exchanges and the loss of LiBr from *o*-lithiobromobenzene are both known to be quite rapid in ethereal solvents,[14] in competition with a sufficiently acidic substrate acid–base reaction with RLi can be even faster.[15] Apparently 2-H oxazoles are acidic enough to fall into this latter category. In principle, the 2-lithiooxazole could still function as a diene and give cycloadduct, but previous work shows that lithiation at the 1-position of a 1,3-diene deactivates the system for Diels–Alder reactions.[16]

In 1964 Campbell and Rees[17a] developed a novel method for formation of benzyne, the $Pb(OAc)_4$ oxidation of 1-aminobenzotriazole (ABT). Remarkably, this reaction gives high yields of biphenylene (**6**) over a useful temperature range which extends down at least to −78 °C.[17b] This feature is unprecedented in other solution-phase benzyne-forming reactions.



ABT 6 (5)

The ability to generate benzyne over a range of temperature was clearly of interest for the study of oxazole reactions. However, preliminary attempts to use the procedure as described by Campbell and Rees with **2** and **4** gave discouraging results, complex reaction mixtures which contained (by NMR and TLC) appreciable amounts of biphenylene and recovered starting oxazole. For example, dropwise addition of 3 equiv of ABT to a refluxing (80 °C) benzene solution of diphenyloxazole **4** and $Pb(OAc)_4$ gave at most traces of **5**, along with considerable recovered starting material and biphenylene (**6**). Similarly, dropwise addition of ABT (1 equiv) to a solution of **2** and $Pb(OAc)_4$ in CH_2Cl_2 at 0 °C gave a mixture which contained (by NMR) unknown material[18] in addition to unreacted **2**, and the products **6** and phenyl acetate (**7**); the latter substance, which has the odor of phenol presumably because of facile hydrolysis in the nose, was identified by chromatographic isolation and comparison with a literature NMR spectrum.

These disappointing results forced a reexamination of the ABT–$Pb(OAc)_4$ reaction. Campbell and Rees recognized that dimer formation was an unexpected outcome for a very reactive intermediate such as benzyne and suggested[17b] that a stabilized form (e.g. a Pb complex) might be the actual species generated, allowing the concentration to rise to the level required for efficient dimerization.

A simple calculation ($d[6]/dt = k[\text{benzyne}]^2$) using typical reagent concentrations and experiment times can be used to demonstrate that high dimer yield would require a "steady state" monomer concentration $\geq 10^{-7}$ M, even if

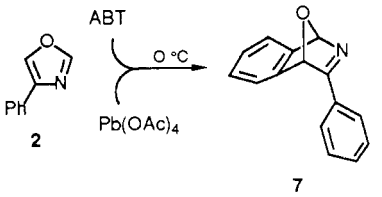
(7) Crump, S. L.; Netka, J.; Rickborn, B. *J. Org. Chem.* **1985**, *50*, 2746.
(8) Wittig, G.; Knauss, E.; Niethammer, K. *Liebigs Ann. Chem.* **1960**, *630*, 10.
(9) Shepard, K. L. *Tetrahedron Lett.* **1975**, 3371.
(10) Fraser, R. R.; Bresse, M.; Mansour, T. S. *J. Chem. Soc., Chem. Commun.* **1983**, 620.
(11) Crump, S. L.; Rickborn, B. *J. Org. Chem.* **1984**, *49*, 304.
(12) Schroeder, R.; Schoellkopf, U.; Blume, E.; Hoppe, I. *Justus Liebigs Ann. Chem.* **1975**, 533.
(13) Brown, D. J.; Ghosh, P. B. *J. Chem. Soc. B* **1969**, 270.
(14) *Dehydrobenzene and Cycloalkynes*; Hoffmann, R. W., Ed.; Academic Press: New York, 1967.
(15) Beak, P.; Musick, T. J.; Chen, C. W. *J. Am. Chem. Soc.* **1988**, *110*, 3538.
(16) Tobia, D.; Rickborn, B. *J. Org. Chem.* **1987**, *52*, 2611.
(17) (a) Campbell, C. D.; Rees, C. W. *Proc. Chem. Soc.* **1964**, 296. (b) *J. Chem. Soc. C* **1969**, 742.
(18) It was subsequently found by examination of NMR spectra that 1:1 benzyne–oxazole adducts had been formed in these reactions, but the mixtures could not be separated.

dimerization is diffusion controlled[19] ($k = 10^{10}$ M^{-1} s^{-1}). A species thus cannot normally be both extremely reactive toward a range of reagents and build up in concentration sufficiently to form a dimer by a second-order process. This explains why **6** is not a major product in any other solution benzyne-forming process, i.e. some other species intercepts the benzyne as it is formed and prevents it from reaching the concentration needed to form dimer. While it is conceivable that the ABT reaction is free of the side reactions which prevent dimer formation in other benzyne methods, it is not clear why this should be. For example, the amino group of ABT appears to be a normal nucleophile and would be expected to react readily with benzyne in the manner of other amines.[14] It is noteworthy that Campbell and Rees found that the order of addition was not critical to the formation of **6** in good yield, i.e. dropwise addition of $Pb(OAc)_4$ to a solution of ABT gave **6** in 60% yield.[17b]

Earlier study of another "abnormal" reaction[20] in this laboratory led us to consider an alternative explanation for the formation of **6** in the Campbell–Rees procedure. Specifically, if the ABT–$Pb(OAc)_4$ reaction itself is so rapid that even with stirring one cannot attain an equilibrium distribution of reagents prior to reaction, then a local non-steady-state concentration of benzyne would be generated in the vicinity of each drop of added reagent. According to this mechanism, the ABT–$Pb(OAc)_4$ reaction will form dimer efficiently regardless of the order of addition because alternative reactions such as (ABT + benzyne → amine products) or (HOAc + benzyne → phenyl acetate) are significantly slower than benzyne formation *and* dimerization. Similarly, desired reactions such as (benzyne + oxazole → cycloadduct) which might otherwise compete effectively with prospective side reactions may fail because of the combined rate constant and (local) concentration advantage enjoyed by the dimerization process. A number of analogous "mixing controlled" reactions are known, and the general phenomenon is discussed in a recent study by Bourne et al.[21]

The Modified ABT–$Pb(OAc)_4$ Procedure. If relatively slow (compared with reaction rates) bulk diffusion (mixing) rates are the effective cause of benzyne dimerization, it should also be possible to use this feature to circumvent dimerization, by simultaneous addition of the reagents. Dropwise addition at opposing ports of a stirred three-neck flask will prevent the development of an appreciable concentration of either reagent, since reaction of the (diluted) materials must still occur rapidly as dictated by the rate constant. If both ABT and $Pb(OAc)_4$ are present in low concentration, the concentration of benzyne will be minimized and will not attain the level needed for dimerization. This very reactive species must then select among alternative reaction pathways.

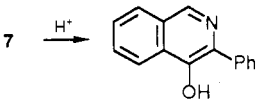
When the modified procedure was applied to **2**, the cycloadduct **7** was formed in essentially quantitative yield. Simultaneous addition was effected by the use of two syringe pumps in order to prevent the development of an excess of either reagent in the reaction flask. A forked arrow is used as a descriptive symbol for this method (eq 6).



(6)

Since the cycloaddition rate should be directly proportional to the concentration of oxazole, a high initial concentration of ca. 0.5 M was used. Excellent yields are obtained from near-stoichiometric amounts of **2**, ABT, and $Pb(OAc)_4$, showing that the process is intrinsically efficient. Methylene chloride is a good solvent choice for all three reagents. Fairly concentrated (ca. 0.3 M) solutions of ABT and $Pb(OAc)_4$ were used to minimize dilution of the oxazole during addition/reaction. The first attempt at 0 °C was succesful, and most subsequent reactions were also carried out at this temperature. Reactions at lower temperatures are also feasible.

The aminal linkage of **7** renders it sensitive to acids. Acetic acid is formed in the oxidation of ABT by $Pb(OAc)_4$ and causes slow rearrangement (eq 7), which can be



(7)

avoided by limiting the reaction time (typically 0.3–0.5 h for the addition), and by immediately washing the reaction mixture with bicarbonate solution. Also, a small amount of Et_3N added to $CDCl_3$ solutions prevented rearrangement catalyzed by the trace of acid usually present in this solvent; this technique was used to follow kinetics in this solvent as described below. The acid-catalyzed rearrangement may prove useful for the preparation of certain isoquinolines. Thus **8**[22] was formed cleanly and rapidly when a solution of **7** was treated with a drop of trifluoroacetic acid.

The Retro-Diels–Alder Reaction. The generality of the Reddy–Bhatt reaction implies that all oxazole–benzyne adducts will prove unstable at 100 °C but provides no guidance on the potential for isolation at lower temperatures. The fact that **7** could be prepared in excellent yield at 0 °C and handled even at room temperature without obvious decomposition was therefore welcome information. It was subsequently established that solid **7** is stable for at least several months when stored in a freezer at −20 °C. It is possible to purify **7** by recrystallization with limited warming, but thermal instability is evident. The solid decomposes when heated, and above 110 °C rapidly gives a discolored mass and benzonitrile.

Controlled retro-Diels–Alder reaction of **7** constitutes a mild and useful method to prepare isobenzofuran (IBF, **9**), either as a reactive intermediate or by isolation as a solution for subsequent application. These features were demonstrated by the reactions shown in Scheme I. Thus when warmed in the presence of a small excess of *N*-methylmaleimide (NMM), cycloadduct **10** is formed (endo/exo = 88/12) in essentially quantitative yield. Based on an extrapolated $t_{1/2} = 0.5$ h at 80 °C, a benzene solution of **7** was refluxed for 3 h, cooled to room tem-

(19) Shafer, M. E.; Berry, R. S. *J. Am. Chem. Soc.* **1965**, *87*, 4497; the gas-phase reaction of benzyne to form **6** was shown to occur at or near the diffusion controlled limit.

(20) Mir-Mohamad-Sadeghy, B.; Rickborn, B. *J. Org. Chem.* **1984**, *49*, 1477. The mechanism of the Meerwein orthoester reaction was examined, when it was noted that addition of *O*-ethylphthalidium tetrafluoroborate to excess NaOMe in MeOH led to dimethoxyphthalan as the major product. This example is striking because it depends upon a localized acidic region in a overall strongly basic medium. For other examples of bulk diffusion-limited reactions, see Beak et al.[15] and Bourne et al.[21]

(21) Bourne, J. R.; Ravindranath, K.; Thoma, S. *J. Org. Chem.* **1988**, *53*, 5166.

(22) Gilchrist, T. L.; Gymer, G. E.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1*, **1975**, 1.

Scheme I

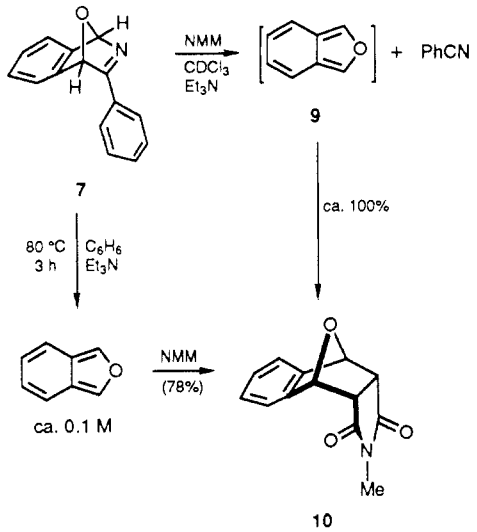


Table I. Rate Constants and Activation Parameters[a] for Retro-Diels–Alder Reactions

	10^6k, s^{-1}				
compound	40.6 °C	61.3 °C	69.4 °C	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
14 (*p*-NO_2)	4.27	73.3	168	26.6	2
7 (unsub)	1.92	36.3	92.9	28.1	5
12 (*p*-OMe)	1.10	22.9	55.9	28.9	6

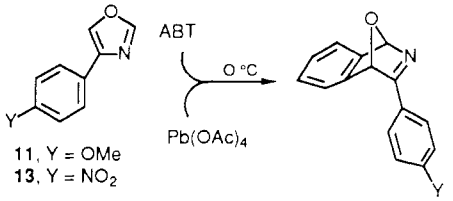
[a] Activation parameter units are $\Delta H^{\ddagger}$ = kcal mol^{-1} and $\Delta S^{\ddagger}$ = cal mol^{-1} deg^{-1}.

perature, and treated with NMM. The 78% isolated yield of **10** represents a minimum yield of "isolated" IBF. Solutions of IBF are especially useful for carrying out cycloadditions with recalcitrant dienophiles, where diene concentration effects can be critical to success.[5] This experiment shows not only that IBF solutions can be formed in this manner, but at the concentration level employed, these solutions are at least moderately stable even at 80 °C.

Solutions of **7** in $CDCl_3$ containing an equivalent of NMM and a small amount of Et_3N were used to determine rate constants for the retro-Diels–Alder step. Sealed NMR tubes were immersed in baths of refluxing solvents and removed for examination periodically. The reactions were shown to proceed to completion at the higher temperatures, and complete cycloreversion is (reasonably) assumed for the slower reactions. NMR spectra at all points were consistent with mixtures of starting materials and/or expected products. Endo **10** comprised 85 ± 3% of the cycloadduct mixture, the remainder being the exo isomer. Rate constants were determined at three temperatures, to give the activation parameters displayed in Table I. The small $\Delta S^{\ddagger}$ value (5 cal mol^{-1} deg^{-1}) is consistent with this step being a normal concerted cycloreversion process.

Substituent effects on the rates of heterodienophile expulsion in retro-Diels–Alder reactions have apparently not been previously studied. The question of charge development in the transition state is especially pertinent in such systems. We therefore prepared the *p*-methoxyphenyl and *p*-nitrophenyl analogues **11** and **13**, which were converted to the cycloadducts **12** and **14**, respectively, by the modified benzyne procedure as outlined in eq 8.

The rates of retro-Diels–Alder reactions of **12** and **14** were determined as with **7**, and the results are also displayed in Table I. Low $\Delta S^{\ddagger}$ values are again found for these systems. The effects of the substituents on rate are small,[23] with less than a factor of 4 separating the fastest



(8)

from the slowest reaction at a given temperature. Interestingly, the *p*-nitro derivative is the most and the *p*-methoxy derivative the least reactive, suggesting a (small) net decrease of the C → N dipole as the imine functionality is converted to nitrile. Overall the results support a concerted process which lacks the significant substituent effects which might be expected for a stepwise mechanism involving a polar intermediate. We conclude that the expulsion of the nitrile heterodienophile is similar to other concerted retro-Diels–alder reactions.

Reactions of 4. Although both **2** and **4** enter into the Reddy–Bhatt sequence at 101 °C (eq 2 and 3), a marked difference between the two oxazoles appeared when **4** was subjected to the modified benzyne procedure at 0 °C. Under the near-stoichiometric conditions which gave an essentially quantitative yield of cycloadduct from **2**, **4** was recovered mostly unchanged (59%). Even when a 3-fold excess of ABT–$Pb(OAc)_4$ was employed, considerable **4** remained unreacted. Thus substituent effects appear to result in **2** being much more reactive than **4**. Supporting this view, parallels can be drawn with the effects of phenyl substitution on butadiene (k_{rel} for 1,4-diphenylbutadiene = 0.04, 2-phenylbutadiene = 8.8, unsubstituted = 1, for reaction with maleic anhydride at 30 °C),[24] and on isobenzofuran, where the 1,3-diphenyl derivative is 0.09 times as reactive as the unsubstituted parent with NMM at room temperature.[16] Although no quantitative assessments have been made, phenyl substituents at the 2,5-positions of oxazoles are known to diminish reactivity with traditional dienophiles.[25] Possible rate enhancement by 4-phenyl substitution has not been previously discussed. It is noteworthy that these substituent effects appear to be retained in reactions with benzyne, which is many orders of magnitude more reactive as a dienophile than e.g. NMM.

Diminished cycloaddition reactivity of **4** relative to **2** may be ascribed simply to the effects of phenyl substitution, but alternative explanations must be considered in light of the further observations described below. Recovery of **4** could, for example, be associated with further reaction of cycloadduct (or other product) with the limited supply of benzyne.

Some **4** is consumed in these reactions. Part or all of the oxazole that reacts appears to be converted to the 1:1 cycloadduct **15**, as shown by the formation of 1,3-diphenylisobenzofuran (**16**). The intense blue-green fluorescent color of **16** was evident in reaction mixtures held at room temperature, although the time required to observe **16** depended on the history of the sample in interesting ways. This product was identified by its NMR fingerprint and by formation and isolation of NMM cy-

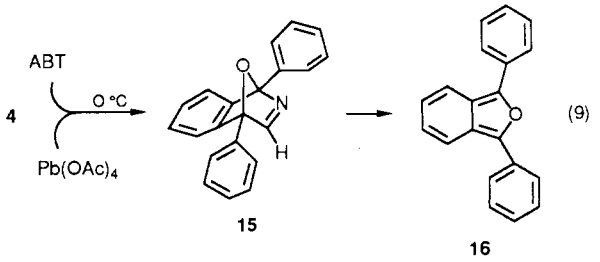
(23) A (3-point) Hammett plot of log *k* vs ϕ_p gave a ρ value of +0.5 (corr coeff 0.97).

(24) Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779.

(25) Lakhan, R.; Ternai, B. *Adv. Heterocycl. Chem.* **1974**, *17*, 99 (see p 183). Also, phenyl substitution may have played a role in deterring some intramolecular Diels–Alder reactions of oxazoles.[26]

(26) Padwa, A.; Cohen, L. A. *J. Org. Chem.* **1984**, *49*, 399.

cloadduct. Importantly, no 2:1 adduct (5) is formed in reactions of 4 carried out at 0 °C or colder. Since this Reddy–Bhatt sequence product is not observed, the retro-Diels–Alder loss of HCN from 15 does not occur at these temperatures *in the time frame of benzyne formation.*



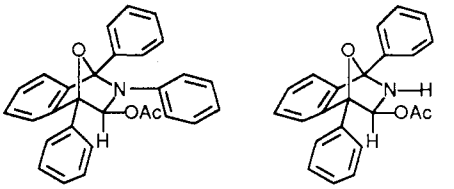
15 16

A reaction may fail either because its activation energy is too high or because its activation energy is higher than those of competing processes. In the first condition, heating is the usual approach to force the reaction; in the second, lowering the temperature may work to advantage if the entropic component is favorable. Since Diels–Alder reactions typically have more negative $\Delta S^{\ddagger}$ parameters than many other second-order processes, this can lead to a competitive advantage at reduced temperature. This reasoning led to treatment of 4 with benzyne at −78 °C. The amount of unreacted 4 recovered by chromatography was reduced to 43% (compared with 59% at 0 °C). An aliquot of the crude reaction mixture was examined by NMR immediately after workup and exhibited a singlet at 6.09 ppm, which we attribute to the *HC*=N proton in cycloadduct 15, along with absorptions characteristic of 16. The color of 16 developed during the workup, indicating that the conversion of 15 to 16 occurs readily at 25 °C. Brief warming of this solution in the presence of NMM caused formation of the Diels–Alder adduct of 16 with NMM and loss of the 6.09 ppm singlet. The NMM cycloadduct[16] of 16 was isolated in 32% yield by column chromatography. This is taken as the *minimum* yield of cycloadduct 15 formed at −78 °C. Similar treatment of a 0 °C crude product gave only 6% of NMM cycloadduct, and this is believed to arise from a different intermediate as discussed below.

The material (25%) not accounted for as 4 or 15/16 has not been completely identified, but some interesting features have emerged. The crude product NMR exhibits another singlet at 6.85 ppm, which is not lost when the mixture is heated with NMM. Silica gel chromatography of crude reaction mixtures gave rapidly eluted 16, with a more polar material remaining on the column packing. On standing, the color of 16 developed at the top of the column, and subsequent elution gave additional 16, along with its known oxidation product *o*-dibenzoylbenzene (interestingly, the protons of the central ring of this material have identical chemical shifts, leading to a singlet even at 500 MHz). Thus this unknown product decomposes on silica gel (but not readily on mild heating) to form 16. Air oxidation may play a role, perhaps via singlet oxygen.

Careful isolation and chromatography under N_2 of a 0 °C reaction product followed by solvent removal without warming gave two new more polar fractions. The minor material which eluted first was thermally unstable even at room temperature, decomposing to give diphenylisobenzofuran (color, NMR), acetic acid (NMR, odor), and unidentified substance(s). The largest m/z fragment in its MS corresponds to diphenylisobenzofuran, indicating that this substructure is intact. Based on its NMR spectrum, structure 17 is tentatively suggested for this product, which could be formed by benzyne attack at the nitrogen of 15 coupled with the addition of acetic acid. Based on this assumed structure, 17 was isolated in 6% yield.

The second more polar product was reasonably stable thermally but decomposed on prolonged contact with silica gel to give diphenylisobenzofuran inter alia. It was obtained as a colorless crystalline solid which melted with decomposition above 200 °C. Structure 18 is tentatively proposed for this substance, with the exo acetoxy stereochemistry assumed by analogy with additions of other reagents to [2.2.1]bicylic olefins. This structure is supported by ^{1}H NMR spectral features, including an exchangeable (D_2O) singlet (N–H) at 2.96 ppm, and two other singlets at 1.97 (3 H) and 6.85 ppm (1 H). Although the usual MS techniques gave no parent ion peak, a FAB spectrum showed a modest peak at 358 (P + H), in agreement with this structure. The isolated yield of 18 is 12%.



17 18

The improved utilization of 4 at −78 °C demonstrates that the cycloaddition of 4 does not suffer from an *intrinsic* or *absolute* activation energy barrier problem and supports the view that Diels–Alder reactions can be favored by lower temperature when in competition with other second-order processes. This improvement at −78 °C occurs in spite of the limited solubility (visual observation) of 4 at this temperature.

The formation of products 17 and 18 also explains why no 15 is observed in the 0 °C reaction (no singlet at 6.09 ppm). Consumption of 15 by subsequent second-order process should be favored (relatively as well as absolutely) by the higher temperature.

These results are in keeping with the view that 2,5-diphenyloxazole (4) is less reactive than 4-phenyloxazole (2) toward benzyne cycloaddition and illustrate the complexity that can occur when subsequent reactions alter the effective stoichiometry of the step of interest. Thus 4 appears to be less reactive that is actually the case, perhaps because the product reacts more rapidly than the oxazole itself with benzyne.

The novel benzyne/oxazole cycloadducts allow the study of substituent effects on retro-Diels–Alder reactions, a relatively neglected topic until recently.[27] Further work along these lines is in progress.

Experimental Section

NMR spectra ($CDCl_3$) were recorded on Varian EM-360A, Nicolet NT-300, or GE 500 instruments. MS and MS/CI (chemically induced, methane flow gas) data were obtained by Dr. Hugh Webb on a VG 70-250 instrument. Melting points were obtained in open capillary tubes on a Mel-Temp apparatus and are uncorrected. The 1-aminobenzotriazole (ABT) was prepared (42%) from *o*-nitroaniline by the method of Campbell and Rees,[17b] with the hydrogenation step carried out in a Parr shaker. Lead tetraacetate and 2,5-diphenyloxazole were used as received from Aldrich Chemical Co., and reagent grade CH_2Cl_2 was used without further purification.

4-Phenyloxazole (2). (a) Two-Step Method. The general procedure described by Davidson et al.[28] was modified as follows.

(27) Chung, Y.; Duerr, B. F.; McKelvey, T. A.; Nanjappan, P.; Czarnik, A. W. *J. Org. Chem.* **1989**, *54*, 1018.

A mixture of 20.0 g (0.100 mol) of phenacyl bromide and 8.84 g (0.13 mol) of sodium formate in 200 mL of DMF was stirred for 12 h. It was then poured into 800 mL of water and extracted with CH_2Cl_2 until the aqueous layer was colorless. The organic phase was washed with saturated brine, dried over Na_2SO_4, and evaporated. Residual DMF was removed by vacuum distillation, leaving 13.6 g (83%) of α-(formyloxy)acetophenone as a yellow oil: ^1H NMR (500 MHz) δ 5.44 (s, 2 H), 7.50 (t, 2 H, J = 7.5 Hz), 7.62 (t, 1 H, J = 7.5 Hz), 7.92 (d, 2 H, J = 7.5 Hz), and 8.25 ppm (s, 1 H).

A mixture of 10.4 g (63.4 mmol) of this crude α-(formyloxy)-acetophenone and 24.3 g (315 mmol) of ammonium acetate in 125 mL of acetic acid was refluxed for 1.5 h. After cooling, it was added to 500 mL of water and extracted with CH_2Cl_2. The organic phase was neutralized by careful addition (foaming) of saturated $NaHCO_3$ solution, washed with brine, dried over Na_2SO_4, evaporated, and distilled to yield 4.52 g (49.5%) of **2**: bp 60–61 °C (0.1 Torr), a liquid which solidified when stored at −20 °C; ^1H NMR (300 MHz) δ 7.31 (t, 1 H, J = 7 Hz), 7.41 (t, 2 H, J = 7 Hz), 7.76 (d, 2 H, J = 7 Hz), and 7.94 ppm (br s, 2 H); ^{13}C NMR δ 150.87, 139.77, 133.28, 130.27, 128.22, 127.59, 125.05 ppm.

(b) One-Step Method. The procedure of Hutton et al.[29] was used, with minor modifications. A solution of phenacyl bromide (20.0 g, 0.101 mol) and ammonium formate (22 g, 0.35 mol) in 117 mL of 97% formic acid was refluxed for 2 h. After cooling, the deep red mixture was taken up in ca. 0.5 L of water and made basic by addition of 50% NaOH. The pH was adjusted to 8 by addition of 1 M HCl, and it was then extracted several times with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and rotary evaporated. Vacuum distillation failed to remove some impurities, and so the distillate was chromatographed (silica gel, 15% ether/85% hexanes, R_f 0.5) to give **2** as a yellow liquid (5.6 g, 39%), essentially pure by NMR. Liquid oxazoles were stored under N_2 in a freezer to prevent discoloration.

9,10-Epoxy-9,10-dihydroanthracene (3). The procedure outlined by Reddy and Bhatt[2] was followed. A three-necked flask fitted with a reflux condenser was charged with 4-phenyloxazole (0.726 g, 5.00 mmol) and 10 mL of dioxane. The solution was brought to reflux, and solutions of anthranilic acid (2.06 g, 15.0 mmol) in 10 mL of dioxane and isoamyl nitrite (2.15 mL, 16.0 mmol) in 9.0 mL of dioxane were added simultaneously via syringe over a period of 1 h. Heating was continued for 0.5 h after addition was complete. The mixture was cooled, and 50 mL of ether was added, followed by ca. 50 mL of 3 M NaOH solution. The layers were separated, and the aqueous phase was washed twice with small volumes of ether. The combined organic phase was dried over Na_2SO_4 and evaporated to give a dark oily residue which by NMR consisted mainly of **3** and benzonitrile. Column chromatography (silica gel, 10% ether/90% hexanes) gave 53% of essentially pure but still discolored **3**. This material was washed with 0.5 mL of ice-cold methanol to remove most of the color, and the remaining solid was recrystallized from 4 mL of methanol (cooled to −20 °C before filtration) to afford 476 mg (49%) of pure **3**, mp 158–160 °C, identical by melting point and NMR data with material reported previously.[7]

9,10-Epoxy-9,10-dihydro-9,10-diphenylanthracene (5). Identical treatment of a refluxing solution of 1.106 g (5.00 mmol) of 2,5-diphenyloxazole (**4**) in 10 mL of dioxane gave a crude product which by NMR contained about 70% of **5** and 25% of the starting oxazole **4**. Silica gel chromatography (20% CH_2Cl_2, 80% hexanes) gave 0.96 g (55%) of essentially pure **5**. Recrystallization from isopropyl alcohol gave, with negligible loss of material, pure **5**: mp 193.5–194 °C (lit.[8] mp 188–188.5 °C); NMR (500 MHz) δ 7.00–7.04 (AA′BB′, 4 H), 7.34–7.38 (AA′BB′, 4 H), 7.48 (t, 2 H, J = 7.5 Hz), 7.59 (t, 4 H, J = 7.5 Hz), 7.94 (d, 4 H, J = 7.5 Hz).

4-(4-Methoxyphenyl)oxazole (11). The procedure outlined by Sherchuk and Dombrowski[30] was used to brominate the ketone. A 1-L Erlenmeyer flask containing a stir bar, *p*-methoxyacetophenone (20.1 g, 0.133 mol), 250 mL of ether, and 150 mL of dioxane was treated with bromine (dropwise addition of 7.1 mL, 0.137 mol) at room temperature. The mixture was heated to reflux, which caused the red coloration to fade to yellow. After cooling, water was added, the phases were separated, and the aqueous layer was extracted with ether. The combined organic material was dried over Na_2SO_4 and rotary evaporated to give a light brown oil which crystallized on standing. This material is light sensitive; exposure to laboratory conditions over a 2-day period caused considerable darkening. The solid was taken up again in ether and decolorized by charcoal/Celite filtration. On standing in a freezer 11.1 g (36%) of colorless crystals of α-bromo-*p*-methoxyacetophenone were deposited; mp 70–72 °C (lit.[30] mp 73–74 °C); ^1H NMR (60 MHz) δ 3.9 (s, 3 H), 4.4 (s, 2 H), 7.0 (d, 2 H, J = 9 Hz), and 8.0 ppm (d, 2 H, J = 9 Hz).

The α-bromo-*p*-methoxyacetophenone (11.1 g, 48.5 mmol) was added with stirring to a solution of ammonium formate (10.7 g, 169 mmol) in 77 mL of 97% formic acid. The mixture was refluxed under N_2 for 2.75 h, which caused a change from colorless to yellow to red. When cool, it was taken up in water, neutralized by addition of 50% NaOH solution (120 mL), and extracted several times with CH_2Cl_2. After drying (Na_2SO_4), concentration of the organic phase led to the deposition of a red-orange solid which was removed by filtration through silica gel. The remaining oil was subjected to column chromatography (silica gel, 40% ether/60% hexanes), which afforded 0.83 g (10%) of yellow crystalline 4-(4-methoxyphenyl)oxazole (**11**): R_f 0.3; mp 89–91 °C (lit.[31] mp 88–89 °C), ^1H NMR (500 MHz) δ 3.84 (s, 3 H), 6.95 (d, 2 H, J = 9 Hz), 7.68 (d, 2 H, J = 9 Hz), 7.86 (s, 1 H), and 7.92 (s, 1 H); ^{13}C NMR δ 159.56, 151.13, 140.12, 132.60, 126.84, 123.36, 114.17, 55.28 ppm; MS m/z (rel intensity) 176 (11.1), 175 (P^+, 100), 160 (9.5), 147 (16.4), 133 (3.2), 132 (5.3), 120 (2.6); MS(CI, methane) calcd for P + H, 176.0711, found 176.0699.

4-(4-Nitrophenyl)oxazole (13). The preparation of this compound is noted in a Dutch patent. Since the abstract[33] lacks experimental detail, the procedure we have used is described.

A 125-mL Erlenmeyer flask containing a magnetic stir bar was cooled in an ice bath; with stirring, 8 mL of concentrated H_2SO_4 was added, followed by 3 mL of 90% fuming HNO_3. Approximately 1 g (1 mL) of 4-phenyloxazole (**2**) was added over a period of a few minutes. A precipitate was observed. After an additional 5 min of stirring, the mixture was poured onto ice, extracted with CH_2Cl_2, dried over Na_2SO_4, and rotary evaporated to give a solid residue. Recrystallization from methanol yielded 0.847 g of **13** as thin yellow needles: mp 186–188 °C (lit.[31] mp 177–180 °C); ^1H NMR (500 Mz) δ 7.93 (d, 2 H, J = 8.5 Hz), 8.01 (s, 1 H), 8.12 (s, 1 H), and 8.29 ppm (d, 2 H, J = 8.5 Hz); ^{13}C NMR δ 151.79, 147.35, 138.70, 136.96, 135.73, 126.11, 124.22 ppm; MS/CI calcd for P + H 191.0457, found 191.0431.

1,4-Dihydro-1,4-epoxy-3-phenylisoquinoline (7). A 50-mL round-bottom three-neck flask was fitted with a magnetic stirrer and three rubber septa, the center one being used for a nitrogen purge needle. The 4-phenyloxazole (**2**, 0.285 g, 1.96 mmol) and 4.0 mL of CH_2Cl_2 were added and the flask was immersed in an ice/water bath.

Two 10-mL syringes were filled, respectively, with: (a) a solution of 1-aminobenzotriazole (0.276 g, 2.06 mmol) in 5.0 mL of CH_2Cl_2, and (b) a solution of $Pb(OAc)_4$ (0.958 g, 2.16 mmol) in 5.0 mL of CH_2Cl_2. These syringes were attached to two syringe pumps, and the needles were inserted into the two side-arm septa. The pumps were activated, effecting the simultaneous delivery of the two solutions over a period of 0.5 h. The needle dead-space volumes were then added by drawing up nitrogen into the syringes and expelling the remaining liquid into the vessel by hand.

As soon as addition was complete, the mixture was poured into a separatory funnel and washed with 10% aqueous $NaHCO_3$ solution to remove the acetic acid which is formed in the reaction. (NOTE: The desired product is acid sensitive as described in

(28) Davidson, D.; Weiss, M.; Jelling, M. *J. Org. Chem.* **1937**, *2*, 328.
(29) Hutton, J.; Potts, B.; Southern, P. F. *Synth. Commun.* **1974**, *9*, 789.
(30) Sherchuk, M.; Dombrowski, A. *Zh. Obschei Khim.* **1963**, *33*(4), 1135.
(31) Terent'ev, P. B.; Lomakina, N. P. *Khim. Geterotsikl. Soedin.* **1974**, (11), 1472. This paper deals with MS fragmentation, and does not describe the preparation of **11**. A more recent paper[32] describes the preparation of **11** by a procedure similar to that used in the present study, but which gave in low yield material of mp 72–76 °C.
(32) Jones, H.; Fordice, M. W.; Greenwald, R. B.; Hannah, J.; Jacobs, A.; Ruyle, W. V.; Walford, G. L.; Shen, T. Y. *J. Med. Chem.* **1978**, *21*(11), 1100. Compound **11** is misnamed in this reference.
(33) *Chem. Abstr.* **1966**, *65*, 13721*g*.

the text, and this wash should not be delayed). The solution was then washed with brine and dried over K_2CO_3. Rotary evaporation without heating, followed by vacuum pump treatment, gave a tan solid (459 mg, 106%) which melted with decomposition at 105–110 °C (open capillary, heating rate ca. 2 °C/min). A sample obtained by −78 °C precipitation from ether/hexane had mp 110–112 °C (decomposition by retro-Diels–Alder reaction was apparent from the odor of benzonitrile detected when the melting point tube was crushed). Compound **7** has ^{1}H NMR (500 MHz) δ 6.26 (s, 1 H), 6.93 (s, 1 H), 7.05 (t, 1 H, J = 7.5 Hz), 7.08 (t, 1 H, J = 7.5 Hz), 7.42–7.52 (m, 5 H), and 7.84 ppm (d, 2 H, J = 7.5 Hz); ^{13}C NMR δ 182.59, 146.68, 142.53, 132.03, 130.91, 128.91, 127.39, 126.29, 126.00, 121.12, 120.94, 99.05, 82.67 ppm; IR (KBr) 3090 (w), 3040 (w), 1592 (m), 1575 (s), 1500 (w), 1450 (s), 1332 (m), 1290 (m), 1190 (m), 1100 (m), 1030 (s), 990 (s) cm^{-1}; MS/CI 222 (P + H, 7.5), 221 (5.8), 120 (5.9), 119 (50.5), 118 (isobenzofuran$^+$, 100), 105 (7.4), 104 (77.6), 103 (benzonitrile$^+$, 36.4); calcd for $C_{15}H_{11}NO$ 221.0841, found 221.0842.

1,4-Dihydro-1,4-epoxy-3-(4-methoxyphenyl)isoquinoline (12). The dual syringe pump procedure described above was used, with the following modifications. The oxazole **11** (0.174 g, 0.995 mmol) in 2.0 mL of solvent was simultaneously treated with solutions of 1-aminobenzotriazole (0.140 g, 1.05 mmol, in 4.0 mL) and $Pb(OAc)_4$ (0.485 g, 1.10 mmol, in 4.0 mL), over ca. 25 min. Workup as before gave a brown solid, which was purified by washing with ether and filtration to give 178 mg (71%) of **12** as a colorless solid: mp 129–130 °C dec; ^{1}H NMR (300 MHz) δ 3.85 (s, 3 H), 6.22 (s, 1 H), 6.88 (s, 1 H), 6.96 (d, 2 H, J = 9 Hz), 7.05 (m, 2 H), 7.41 (d, 2 H, J = 8 Hz), and 7.79 ppm (d, 2 H, J = 9 Hz); ^{13}C NMR δ 181.67, 162.77, 146.89, 142.56, 129.30, 126.29, 125.91, 123.61, 121.03, 120.74, 114.38, 98.85, 82.52, and 55.42 ppm; IR (KBr) 3020 (w), 3000 (w), 2955 (w), 2830 (w), 1600 (s), 1558 (s), 1500 (s), 1448 (m), 1418 (s), 1310 (s), 1250 (s), 1172 (s), 1106 (m), 1081 (m), 1028 (s), 978 (s) cm^{-1}; MS/CI calcd for P + H 252.1024, found 252.1005.

In a separate experiment, an attempt to purify the product resulted in the isolation of a yellow solid, mp 201–205 °C, which was identified as the rearrangement product 3-(4-methoxyphenyl)isoquinolin-4-ol on the basis of its NMR spectrum: ^{1}H NMR (300 MHz) δ 3.89 (s, 3 H), 5.8 (br s, OH), 7.09 (d, 2 H, J = 9 Hz), 7.61 (dt, 1 H, J = 8 and 1 Hz), 7.71 (d, 2 H, J = 9 Hz), 7.72 (dt, 1 H, J = 8 and 1 Hz), 7.96 (d, 1 H, J = 8 Hz), 8.24 (d, 1 H, J = 8 Hz), and 8.93 ppm (s, 1 H).

1,4-Dihydro-1,4-epoxy-3-(4-nitrophenyl)isoquinoline (14). The dual-syringe pump method and solvent volumes given in the preceding example were used, with 183 mg (0.96 mmol) of **13**, 142 mg (1.06 mmol) of 1-aminobenzotriazole, and 510 mg (1.15 mmol) of $Pb(OAc)_4$. The crude product was washed with ether to give 183 mg (72%) of **14** as a discolored solid, essentially pure as judged by NMR: ^{1}H NMR (300 MHz) δ 6.28 (s, 1 H), 6.99 (s, 1 H), 7.10 (m, 2 H), 7.46 (m, 2 H), 8.00 (d, 2 H, J = 9 Hz), and 8.31 ppm (d, 2 H, J = 9 Hz); ^{13}C NMR δ 181.39, 149.72, 146.06, 141.91, 136.44, 128.27, 126.68, 126.41, 124.14, 121.50, 121.29, 99.49, and 82.77 ppm; IR (KBr) 3125 (m), 1605 (m), 1500 (s), 1353 (s), 1339 (s), 1312 (m), 1287 (m), 1108 (s), 1080 (m), 1060 (m) cm^{-1}. The lower activation energy for retro-Diels–Alder reaction of this material is reflected in the absence of parent ions and large fragment peaks in MS/CI: 150 (8.8), 149 (100), 148 (*p*-nitrobenzonitrile$^+$, 10.9), 120 (8.3), 119 (53), 118 (isobenzofuran$^+$, 81).

Kinetics of Retro-Diels–Alder Reactions. Solutions were prepared in $CDCl_3$ solvent of the three cycloadducts **7**, **12**, and **14**, and a small amount to triethylamine (ca. 2 equiv) was added to prevent trace acid catalyzed rearrangement. *N*-Methylmaleimide (1+ equiv) was added, and the solutions were placed in NMR tubes fitted with screw-cap seals. The tubes were directly immersed in refluxing solvents (CH_2Cl_2, $CHCl_3$, and hexane) via a rubber septum pierced for this purpose, and a common thermometer was used to measure the temperature of each bath (40.6, 61.3, and 69.4 °C, respectively). The tubes were removed at timed intervals and maintained in an ice bath until analyzed by NMR and were then returned to the refluxing bath. The NMR analyses were done on either a 300- or 500-MHz instrument, by comparing the integrals for the upfield singlet (1 H at ca. 6.3 ppm) for the benzyne–oxazole adduct starting material with the (2 H) signal of the *N*-methylmaleimide–isobenzofuran cycloadduct product at 5.7 ppm (mainly endo multiplet, plus exo singlet). Examination of the complete spectra at the conclusion of the reactions showed that very little if any starting material was lost to competing processes. The first-order rate constants displayed in Table I were obtained from plots of −ln (cycloadduct) vs time. These exhibited good straight line behavior through at least 2 half-lives.

Reactions of 4. Two simultaneous addition reactions were carried out with identical concentrations of reagents, at 0 °C and at −78 °C (ice and dry ice/acetone baths, respectively). A solution of **4** (1.00 mmol in 4.0 mL of CH_2Cl_2) was treated with ABT (1.05 mmol in 3.0 mL) and $Pb(OAc)_4$ (1.10 mmol in 3.0 mL) over a period of 15-min, and the reaction mixture was then poured into aqueous sodium carbonate. The organic phase was separated, dried, and vacuum evaporated without heating. It was then taken up in 20 mL of benzene, 1.10 mmol of NMM was added, and the solution was refluxed for 30 min. Chromatography on silica gel gave recovered **4** followed by the NMM cycloadduct[16] of 1,3-diphenylisobenzofuran.

Small amounts of *o*-biphenylene were formed in both reactions. Based upon integration of the crude product NMR spectra, it is estimated that ≤14% and 9% of the available benzyne had been consumed by this pathway at 0 °C and −78 °C, respectively.

The 0 °C reaction gave 131 mg (59%) of recovered **4**. The NMM–1,3-diphenylisobenzofuran cycloadduct yield (6%) was estimated from the NMR spectrum.

The −78 °C reaction gave 95.3 mg (43%) of **4**, and 158 mg of a mixture of the NMM cycloadduct of **16** (32%) of *o*-dibenzoylbenzene (12%). The 500-MHz ^{1}H NMR spectrum of an authentic sample of *o*-dibenzoylbenzene used for comparison had the following characteristics: δ 7.38 (t, 4 H, J = 7.5 Hz), 7.52 (t, 2 H, J = 7.5 Hz), 7.62 (s, 4 H), and 7.70 ppm (d, 4 H, J = 7.5 Hz).

In other experiments at −78 °C followed by room temperature workup, NMR spectra prior to treatment with NMM showed a singlet at 6.09 ppm, attributed to the cycloadduct **15**, as well as the characteristic absorptions of 1,3-diphenylisobenzofuran **16**. Both of these features were absent in 0 °C reaction crude products.

Compound 17. Repetition of the reaction of **4** at 0 °C followed by vacuum evaporation (no heating) of the solvent gave a residue that was chromatographed with avoidance of contact with air. Compound **17** (R_f = 0.2, silica gel TLC with 1:1 ether/Skelly solv) was obtained as a semisolid (25 mg, 6%) which discolored on standing. The cleanest sample obtained had the following spectral characteristics: ^{1}H NMR δ 2.26 (s, 3 H), 6.69 (s, 1 H), 7.20–7.25 (m, 4 H), 7.33–7.48 (m, 11 H), 7.57–7.60 (m, 3 H), 7.87 (d, 1 H, J = 7.5 Hz); MS (the MW of structure **17** is 433) 297 (27), 286 (28), 270 (100), 241 (14), 209 (16), 165 (25), 150 (34), 105 (29), 92 (16), 77 (48), 60 (16), 51 (18), 45 (28), 43 (47); MS (CI): 326 (6.5), 314 (23), 298 (100), 287 (14), 286 (11), 282 (21), 270 (72), 209 (8), 120 (14), 105 (31), 61 (10), 43 (23). When heat was used to remove solvent from this compound, the NMR spectrum broadened and a new singlet at 2.03 ppm appeared, and the odor of acetic acid was evident in samples that had been held for several days at ambient temperature.

Compound 18. This material had R_f = 0.1 and was isolated as needles by chromatography: mp 205.5–207 °C dec; ^{1}H NMR δ 1.97 (s, 3 H), 2.96 (s, 1 H, exchanges with D_2O), 6.85 (s, 1 H), 6.92–6.94 (m, 1 H), 7.35–7.52 (m, 9 H), 7.55 (d, 2 H, J = 7.5 Hz), and 7.68 ppm (d, 2 H, J = 7.5 Hz); MS 297 (18), 280 (29), 270 (23), 165 (10), 105 (6), 91 (11), 84 (14), 77 (11), 69 (12), 62 (37), 55 (20), 45 (100), 44 (98), 43 (26); MS (FAB) 358 (P + H).

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra for compounds **7**, **12**, and **14**, and the ^{1}H NMR spectrum of **18** (9 pages). Ordering information is given on any current masthead page.