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Synthesis of diazo compounds with azidotris(diethylamino)phosphonium bromide

McGuiness, Mark Joseph, Ph.D.

The Ohio State University, 1991

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SYNTHESIS OF DIAZO COMPOUNDS WITH
AZIDOTRIS(DIETHYLAMINO)PHOSPHONIUM BROMIDE

DISSERTATION

Presented in partial fulfillment of the requirements for
the degree of Doctor of Philosophy in the Graduate
School of the Ohio State University

by

Mark J. McGuiness, B.S., B.A.

The Ohio State University
1991

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Department of Chemistry
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To Kathy
ACKNOWLEDGMENTS

I am of course grateful to Professor Harold Shechter for providing a stimulating research environment in which I could pursue my own ideas and develop independently as a scientist. His dedication to teaching was outstanding, and I learned more from helping him teach sophomore organic chemistry than from all my graduate course work.

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STATEMENT OF PROBLEM

Diazoalkanes are versatile organic compounds which are of enormous interest because of their high reactivity with a variety of reaction partners, the ease with which they decompose under acidic conditions to give diazonium ions or carbocations, and their unparalleled utility as carbene precursors. These properties have made diazoalkanes one of the most widely used and highly studied organic functional classes.

Diazo compounds bearing two electron-withdrawing groups on the diazo carbon are prepared from the parent alkanes via diazo transfer reactions. Diazo compounds bearing one electron-withdrawing group are not usually accessible via diazo transfer reactions; a related method, deformylating diazo transfer, is useful for the synthesis of these diazoalkanes. Diazoalkanes having no electron-withdrawing substituents are inaccessible via diazo transfer, but may be prepared by oxidation of hydrazones with various reagents.

The goal of this research was to develop safe, effective reagents which could be used for diazo transfer to systems bearing either one or two electron-withdrawing groups, and for the oxidation of hydrazones to diazoalkanes. To this end, azidotris(diethylamino)phosphonium bromide (1), azidotris(dimethylamino)-phosphonium bromide (2), and azidotripiperidinophosphonium bromide (3), were prepared for study as potential reagents for the preparation of varied diazoalkanes.

![Chemical Structures](image)
CHAPTER I
HISTORICAL BACKGROUND

Introduction

The long history of diazoalkane chemistry dates back to the synthesis of ethyl diazoacetate by Theodor Curtius in 1883.¹ Alkyl diazo compounds exhibit incredibly diverse reactivities depending on their substituents. Because of their wide use in carbene, cycloaddition, and carbocation chemistry, numerous methods for the preparation of diazoalkanes have been developed over the years. These methods can be categorized as follows: (1) methods in which the future diazo carbon bears one nitrogen atom, which then reacts with a source of positive nitrogen, e.g. amine diazotization (Equation 1) or the Forster reaction (Equation 2); (2) methods in which the future diazo carbon bears two nitrogen atoms, the diazo functionality being formed via 1,1-elimination or oxidation reactions (Equations 3-5); or (3) the diazo group transfer method, wherein the two nitrogen atoms of the diazo group are simultaneously introduced in the proper oxidation state onto the carbon (Equation 6).

In this last method the \(-N_2\) moiety is transferred from a diazo transfer reagent \(\text{(N=N=A)}\) to a substrate in exchange for covalently bonded groups, typically two hydrogen atoms. Since it is conceptually the most elegant method for the synthesis of diazo compounds, prodigious efforts have been devoted to development of the diazo transfer reaction. There are still very few effective diazo transfer reagents, however.
Aryl azides were the first functional group to be utilized as diazo transfer reagents. Dimroth found in 1910 that reaction of phenyl azide with 2-(carbomethoxy)acetamide gave 2-diazo-2-(carbomethoxy)acetamide 4 (Figure 1). At the time, the structure of the diazo group was represented as a diazirine. Curtius and Klavehn were the first to use arylsulfonyl azides as diazo transfer reagents, preparing 5 from dimethyl malonate and p-toluenesulfonyl azide. This foreshadowed the popular use of tosyl azide for synthesis of α-diazo-β-dicarbonyl compounds as well as the frequent complication of displacement of ester alkoxy groups.

Figure 1: The First Recorded Examples of Diazo Transfer

---


In 1953 Doering and DePuy prepared diazocyclopentadiene, 6, via the diazo transfer reaction of cyclopentadienyllithium with tosyl azide.

Figure 2: Synthesis of Diazocyclopentadiene

Doering was apparently unaware of the early work of Dimroth² and Curtius³ because he expounds at some length on his rationale for the choice of tosyl azide as the diazo transfer reagent:

......a new reaction was designed for the synthesis of [diazocyclopentadiene]. In order to utilize the readily accessible cyclopentadienyllithium, a reagent N=N=A is required in which A must
perform three functions: the negative charge introduced by the addition of the carbanion to the terminal nitrogen must be stabilized; the proton remaining at C₁ of the cyclopentadiene ring in this intermediate must be transferred to some atom A so that, in the final stage AH⁻ may break away (as a relatively stable anion) from its bond to the second nitrogen atom, thereby removing the negative charge from the five-membered ring and forming [diazocyclopentadiene]. Among the many groups considered, RSO₂N⁻ represented an available reagent which satisfied the conditions.......

This is the first statement in the literature of the currently accepted three-step mechanism of diazo transfer, that is (1) attack of the nucleophile or carbanion on the terminal nitrogen of the diazo transfer reagent, (2) proton transfer, and (3) fragmentation of the adduct to give the diazo compound and the by-product.

In late 1963 and early 1964 diazo transfer was rediscovered yet again in a flurry of publications from several independent research groups. Within a period of only a few months the applications of tosyl azide for diazo transfer were greatly expanded to encompass a wide variety of acidic methylene compounds.

First, the Italian group of Fusco, Bianchetti, Pocar, and Ugo reported that some γ-keto enamines 7 react with tosyl azide to give triazoles 8 which cleave to α-keto diazo compounds 9 and arylsulfonylamidine 10, among other products.⁵

---


Figure 3: Diazo Transfer to γ-Keto Enamines

Although the reaction shown in Figure 3 may not superficially resemble diazo transfer, all of the mechanistic elements of diazo transfer are present. First, a nucleophilic carbon (the enamine β-carbon) attacks the terminal nitrogen of tosyl azide; second, a group (the enamine α-carbon) is transferred to the sulfonamide nitrogen (in simple diazo transfer this group is a hydrogen); and finally the adduct cleaves giving the diazo compound and a sulfonamide by-product containing the transferred group. Conceptually, the methylene substituent on the β-carbon has been exchanged for the \(-\dfrac{\text{N}_2}{2}\) group. Although the Italian workers were not specifically looking for a route to diazo compounds, a variant of this reaction, known as “deformylating diazo transfer,” is now one of the primary methods for preparing α-keto diazo compounds (vide infra).
Within a year after this work appeared, Klages and Bott reported the synthesis of bis(arylsulfonyl)diazomethanes from the parent bis(arylsulfonyl)methanes using tosyl azide.\textsuperscript{6} Regitz followed within the same year with a paper describing a "new synthesis for \(\alpha\)-diazo-\(\beta\)-dicarbonyl compounds" using tosyl azide.\textsuperscript{7} This was the first in a long series of papers on diazo transfer to active methylene compounds—the same reaction which had been discovered fifty years previously by Dimroth. The group of Rosenberger, Yates, Henderson, and Wolf, working independently, prepared \(\alpha\)-diazo-\(\beta\)-dicarbonyl compounds similar to those reported just months before by Regitz, using milder and simpler procedures.\textsuperscript{8}

Rosenberger, et al also described deformylating diazo transfer (Figure 4) for the preparation of \(\alpha\)-keto diazo compounds from ketones. This reaction is mechanistically identical to the reaction of enamines with tosyl azide reported by the Italian group less than a year prior. Deformylating diazo transfer as currently practiced circumvents the formation of the enamine derivative: the hydroxymethylene (formyl) derivative gives the diazo compound directly upon reaction with tosyl azide.\textsuperscript{9} Other moieties may also be used to activate ketones for diazo transfer. Recently, Danheiser, et al have advocated the trifluoroacetyl group as a more reactive alternative to the formyl group traditionally employed in deformylating diazo transfer.\textsuperscript{10}

\textsuperscript{6} Klages, F.; Bott, K. \textit{Chem. Ber.} 1964, 97, 735.
\textsuperscript{7} Regitz, M. \textit{Ann. Chem.} 1964, 676, 101.
One of the primary remaining challenges in the field of diazo transfer is development of good methods for the direct conversion of ketones to α-diazo ketones without the need for prior functionalization.

\[ RCH_2CHO \xrightarrow{\text{ArSO_2N_3}} RCH(NH_2)\text{SO_2Ar} \xrightarrow{\text{Reduction}} RCH(NH_2)\text{SO_2Ar} \]

**Figure 4: Preparation of α-Diazo Ketones by Deformylating Diazotransfer**

After the flurry of publications in 1963-64, most of the important studies in the field of diazo group transfer were carried out by Manfred Regitz and co-workers.\(^\text{11}\) Diazotransfer to active methylene compounds using tosyl azide has become a commonplace synthetic procedure which has been used for the preparation of hundreds of different diazo compounds.

Overview of Diazo Transfer Reagents

The most easily prepared and commonly used diazo transfer reagents have the azide moiety (11a-b). The group "A" is typically a strong electron-withdrawing group such as ArSO₂⁻ (as in tosyl azide) or (RO)₂PO⁻. This group stabilizes the resonance form 11a in which the negative charge is on the internal nitrogen, and also imparts considerable triple-bond character to the terminal nitrogen-nitrogen bond. The accepted mechanism for diazo transfer with azide reagents is shown below.

In diazo transfer with azide reagents, the intermediate triazenes 12 and 13 as well as the by-product 14 are all salts. Polar solvents are usually used for diazo transfer reactions with azide reagents due to the ionic nature of the intermediates 12 and 13.
The other important commonly used diazo transfer reagents are the N-diazonium imines (16 a-b). Unlike the azide reagents, N-diazonium imines are cationic, and thus more electrophilic. The groups "W" are typically electron-donating moieties which stabilize the partial positive charge on the imine carbon.

![Diagram of diazo transfer mechanism with N-diazonium imine reagents.

Figure 6: Mechanism of Diazot Transfer with N-Diazonium Imine Reagents]

The intermediate triazenes 17 and 18 as well as the by-product 19 resulting from diazo transfer with N-diazonium imines are neutral. The mechanisms depicted in Figures 5 and 6 differ substantively from the archetypal diazo transfer reaction shown in Equation 6 in that the reactive species is not a hydrocarbon, but rather its anion. In practice, the generality of diazo transfer is restricted by the fact that for weakly acidic hydrocarbons the equilibria 12 $\rightleftharpoons$ 13 and 17 $\rightleftharpoons$ 18 lie far to the left, and
competing side reactions arising from the triazenes 12 and 17 reduce the yields of the desired product 15. With few exceptions, the only substrates amenable to diazo transfer are those activated by two electron withdrawing groups.

Some frequently used diazo transfer reagents are shown in Figure 7. Tosyl azide (20), the most commonly used diazo transfer reagent, and diphenyl phosphoroazidate (21) are typical azide reagents. Balli's reagent, 2-azido-3-ethylbenzthiazolium tetrafluoroborate (22), is the most commonly used reagent in the N-diazonium imine family, however the more recently discovered N,N-dimethylazidochloromethyleniminium chloride (23) is easier to prepare.

Figure 7: Some Commonly Used Diazo Transfer Reagents
Diphenyl phosphoroazidate (21) has enjoyed a modicum of success as a diazo transfer reagent, primarily because it is the reagent of choice for the preparation of trimethylsilyldiazomethane, which is becoming increasingly important as a synthetic building block.\(^{12}\)

By far the most successful competitors with tosyl azide are reagents belonging to the N-diazonium imine family. The bicyclic reagent 2-azido-3-ethylbenzthiazolium tetrafluoroborate (22), is a highly electrophilic diazo transfer reagent which is reactive even in neutral or slightly acidic solutions. Reagent 22 has been widely used to prepare a number of base-sensitive diazo compounds which are inaccessible using the traditional conditions of tosyl azide with auxiliary bases.\(^{13}\)

The other popular N-diazonium imine reagent, N,N-dimethylazidochloromethyleniminium chloride (23), has been touted as an economical alternative to the costly reagent 22. Initial studies indicate that 23 is reactive in neutral or mildly acidic media and that it reacts with enolic species, such as phenols.\(^{14}\)

Diazo transfer reagents 22 and 23 are structurally quite different from tosyl azide. The advantages which these reagents have over tosyl azide will be discussed in the section concerning the mechanism of the diazo transfer process (p. 21).

Although tosyl azide continues to be the most important and commonly used diazo transfer reagent, principally because it can be prepared easily and inexpensively from sodium azide and tosyl chloride, several other sulfonyl azides have been examined


as diazo transfer reagents over the last 30 years. These reagents are 4-carboxybenzenesulfonyl azide (24), “polymer-bound tosyl azide” (25), N,N-dimethylsulfamoyl azide (26), methanesulfonfonyl azide (27), p-nitrobenzenesulfonyl azide (28), p-acetamidobenzenesulfonyl azide (29), p-dodecylbenzenesulfonyl azide (30), and 2,4,6-triisopropylbenzenesulfonyl azide (31).

![Chemical structures of alternative sulfonyl azide diazo transfer reagents](image)

**Figure 8**: Alternative Sulfonyl Azide Diazo Transfer Reagents
As with tosyl azide, these alternative sulfonyl azide reagents are prepared from the corresponding sulfonyl chlorides by reaction with sodium azide in a polar solvent or under phase transfer conditions. These reagents offer advantages over tosyl azide in terms of lower cost, toxicity, or explosion sensitivity, or they may provide easier product workup or wider substrate applicability, as discussed below. Some of these materials are commercially available on a small scale for laboratory preparations. Although a few of these alternative reagents have met with modest success, none has yet supplanted tosyl azide as the dominant diazo transfer reagent.

A problem sometimes encountered with the use of tosyl azide is separation of the p-toluenesulfonamide by-product or excess tosyl azide from the desired diazo compound.\(^{15}\) This problem is overcome by 4-carboxybenzenesulfonyl azide (24), the by-product of which, 4-carboxybenzenesulfonamide (32), is readily removed by an alkaline wash.\(^{16}\) Several carbapenem syntheses have employed 24 to form α-diazo ester intermediates.\(^{17}\) Although commercially available, 24 is expensive.\(^{18}\)

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\(^{18}\) 4-Carboxybenzenesulfonyl azide is available from Aldrich Chemical Co. at $15.00 for 2.5 g.
Another reagent which avoids the separation problems associated with the sulfonamide by-products of diazo transfer with tosyl azide is “polymer-bound tosyl azide” (25). This material is prepared by treatment of Amberlite XE 305 (a crosslinked polystyrene/divinylbenzene resin) with chlorosulfonic acid and then sodium azide. Despite the fact that this polymeric sulfonyl azide gives very impressive yields with several 1,3-dicarbonyl compounds, it has yet to enjoy widespread use in preparative applications.

Henderson and Wolf found that N,N-dimethylsulfamoyl azide (26) gave good yields of α-diazo-β-dicarbonyl compounds in typical diazo transfer reactions. The water-soluble by-product, (CH$_3$)$_2$NSO$_2$NH$_2$, of diazo transfer reactions with 26 was easily separable from α-diazo-β-dicarbonyl compounds, however, if the reagent itself was present in excess it was difficult to remove. Reagent 26 has not been reexamined since this first report. The same paper also described the use of 4-nitrobenzenesulfonyl azide (28) as a diazo transfer reagent. In a comparison with

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tosyl azide, 28 gave a lower yield of 2-diazo-1,2-diphenylethanone upon reaction with benzyl phenyl ketone in the presence of base.

The early paper of Henderson and Wolf also claimed that methanesulfonyl azide (27) was inferior to tosyl azide.16 This assertion appears to be based on a single experiment, however. There have been isolated instances over the years of the use of 27 as a diazo transfer reagent,20a and recently Taber et al have shown that 27 is comparable if not superior to tosyl azide in many diazo transfer applications, including deformylating diazo transfer.20b

Huw Davies and several co-workers have recently demonstrated that \( p \)-acetamidobenzenesulfonyl azide (29) is a very promising diazo transfer reagent.21 Not only does 29 perform admirably in diazo transfer reactions with 1,3-dicarbonyl compounds, but it also gives good yields of \( \alpha \)-diazo-\( \beta \)-carbonyl-\( \beta \)-vinyl compounds from \( \gamma,\delta \)-unsaturated carbonyls (Figure 10).22 Toxicity tests on 29 also indicate that it is relatively safe; 29 is structurally related to the antibacterial compound sulfanilamide.21

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Figure 10: Diazo Transfer to γ,δ-Unsaturated Carbonyls Using p-Acetamidobenzenesulfonyl Azide (29)

One of the major limitations of tosyl azide is that (with few exceptions\(^\text{23}^\)) it does not permit direct diazo transfer to simple ketones or other systems where the incipient diazo carbon bears a single electron-withdrawing group. Although this problem can frequently be circumvented by deformylating diazo transfer, the direct introduction of a diazo group \(\alpha\) to a single electron-withdrawing functionality has been a longstanding challenge in the field. Mander and Lombardo discovered that 2,4,6-triisopropylbenzenesulfonyl azide (31) is often effective for introducing a diazo group adjacent to a ketone without the need for an additional activating group (Figure 11, next page).\(^\text{24}\)

The methodology illustrated in Figure 11 appears to work best when the ketone is sterically encumbered, strongly suggesting that steric strain in the triazene intermediates is helping to drive the reaction towards the desired product. The lower yields obtained when the ketone is less sterically hindered suggest that this method will not supplant deformylating diazo transfer in most cases. Reagent 31 may confer real

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\(^{24}\) Lombardo, L.; Mander, L. N. Synthesis 1980, 368.
advantages, however, for the preparation of sterically hindered α-diazo ketones in natural product synthesis.25

![Reaction Scheme](image)

**Figure 11:** Direct Diazo Transfer to a Ketone with 2,4,6-Triisopropylbenzenesulfonyl Azide (31)

The often-ignored explosive potential of tosyl azide is one of the primary motivations for the development of new diazo transfer reagents. Under German law, tosyl azide is classified as an explosive, and some researchers have had serious accidents while attempting to distill diazo compounds away from excess tosyl azide.26 A mixture of p-dodecylbenzenesulfonyl azides, 30, (prepared from a commercial alkylsulfonic acid mixture) was found to have a lower impact sensitivity, rate of thermal decomposition, and specific heat of decomposition than tosyl azide.27 Decomposition data for several benzenesulfonyl azides are given in Table 1.21,27

Table 1: Decomposition Data For Several Benzene Sulfonyl Azides

<p>| Benzene-        | m.p. | ΔH_decomp | Initiation | Impact sens. |</p>
<table>
<thead>
<tr>
<th>Sulfonyl Azide</th>
<th>°C</th>
<th>kcal/mol</th>
<th>temp °C</th>
<th>kg cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-CH₃ (tosyl azide)</td>
<td>19-20</td>
<td>-79.9</td>
<td>120</td>
<td>50</td>
</tr>
<tr>
<td>p-Carboxy- (24)</td>
<td>184-6</td>
<td>-53.6</td>
<td>163</td>
<td>300</td>
</tr>
<tr>
<td>2,4,6-Triisopropyl- (31)</td>
<td>39-40</td>
<td>-62.4</td>
<td>136</td>
<td>300</td>
</tr>
<tr>
<td>p-Dodecyl- (30)</td>
<td>liq.</td>
<td>-58.9</td>
<td>151</td>
<td>&gt;150</td>
</tr>
<tr>
<td>p-Acetamido- (29)</td>
<td>108</td>
<td>-56.0</td>
<td>120</td>
<td>&gt;140</td>
</tr>
</tbody>
</table>

As can be seen from the table, 30 has the lowest heat of decomposition on a per gram basis. Tosyl azide is the most sensitive to impact, has the lowest intiation temperature for thermal decomposition, and has the most exothermic heat of decomposition on a weight basis by far. Tosyl azide is clearly the most hazardous of the benzenesulfonyl azide reagents. The safer reagent 30 has been used infrequently\(^{28}\) despite the fact that it gives good yields of \(α\)-diazo-\(β\)-dicarbonyl compounds. The by-product of diazo transfer with this material is a high-molecular weight \(p\)-dodecylbenzenesulfonamide mixture which can be difficult to separate from the product diazo compound.

Mechanism of Diazo Transfer

Any discussion of the relative merits of new diazo transfer reagents must begin with a thorough understanding of the mechanism of the diazo transfer process, which is illustrated for arylsulfonyl azides below.

Figure 12: Mechanism of Diazo Transfer for Arylsulfonyl Azides
The overall diazo transfer reaction is a four-step process. First, the anion 34 must be formed. Typically this is accomplished by the action of an auxiliary base, "B", on the substrate hydrocarbon 33. In most cases, the groups Z and Z' are electron-withdrawing, thus making 33 a moderately strong acid; relatively weak bases such as triethylamine, or even fluoride ion\textsuperscript{29} suffice for these preparations. Stronger bases such as alkoxides are often used when the groups Z and Z' are not strongly acidifying. \textit{In principle}, 34 may be a strongly basic anion such as a Grignard or alkyl lithium reagent, which can be prepared prior to the following steps. Since there are numerous established methods for the generation of all types of carbanions, this step of the diazo transfer process is never problematic.

The second step of the overall reaction is nucleophilic attack of 34 on the terminal nitrogen of diazo transfer reagent giving the triazene intermediate 35. The only requirement at this stage is that the diazo transfer reagent must compete effectively with the other electrophiles in the reaction mixture for the nucleophile 34. This is often not a trivial concern. The groups Z and Z', which are electron-withdrawing in most cases, usually contain electrophilic moieties such as carbonyl groups which can react with 34. Moreover, the terminal nitrogen of the product diazo compound 37 can also be a potent electrophile if Z and Z' are very strong electron-withdrawing moieties such as -SO\textsubscript{2}R, -CN, or -NO\textsubscript{2}. Attack of 34 on the product diazo compound 37 is a frequently encountered complication known as azo transfer.

The third step of the diazo transfer reaction is tautomerization of triazene 35 to the zwitterionic form 36. Since proton transfers are usually fast, there is no \textit{a priori} reason to expect that this would be the rate limiting step of the overall mechanism, except perhaps if the equilibrium 35\rightleftharpoons 36 lies very far to the left. Another factor to

be considered is whether the proton transfer is inter- or intramolecular. Intermolecular proton transfers will naturally require the intervention of an auxiliary species which can act as both a Brønsted base and a Brønsted acid.

The final step of the diazo transfer process is cleavage of the zwitterionic triazene 36 to give the diazo compound 37 and the co-product 38. This step is formally a 1,1-elimination from the middle nitrogen of 36 (the alternative resonance structure of 36 has a negative charge as well as the leaving group on the middle nitrogen). Since many of the undesirable side reactions which compete with the diazo transfer process arise from the triazene intermediates 35 and 36, the facility of this cleavage step often determines whether the major product is the diazo compound or an unwanted by-product. The primary criterion at this step is, of course, the leaving-group ability of 38.

Each step of the diazo transfer process will now be discussed separately, comparing the merits of various diazo transfer reagents to tosyl azide. The criteria which favor one step of the reaction mechanism often disfavor another, and the limiting step of the overall diazo transfer mechanism can vary depending on the substrate of the reaction. Unwanted side reactions often result in the failure of the diazo transfer process, however, an intelligent choice of the diazo transfer reagent will often minimize or eliminate these processes. Side reactions which compete with diazo transfer will also be discussed.

Electrophilic Attack on the Terminal Nitrogen

The electron donating or withdrawing ability of the sulfur substituents in sulfonyl azide diazo transfer reagents should affect the electrophilicity of the azide groups. Electron-withdrawing groups G on sulfur should favor resonance structure 39a (Figure 13) and thus increase the electrophilicity of the terminal nitrogen. No quantitative rate studies have been carried out, however, to compare the effects of
various substituents on the rates of diazo transfer with sulfonyl azides. Qualitatively, though, neither electron-withdrawing groups, as in p-nitrobenezesulfonyl azide (28) or electron-donating groups, as in methanesulfonyl azide (27) and p-acetamidobenezesulfonyl azide (29) confer any obvious rate or yield enhancement over tosyl azide.

![Figure 13: Resonance Contributors of Sulfonyl Azides](image)

The SO\textsubscript{2} group may effectively insulate the azide moiety from the substituent G to such an extent that the electronic effects of G on the electrophilicity of the azide are negligible, especially when compared to the large intrinsic electron-withdrawing effect of the SO\textsubscript{2} moiety itself.

In their early paper, Henderson and Wolf described the synthesis and use of the interesting reagent 40 (Figure 14, next page).\textsuperscript{16} The authors argued that if the first step of diazo transfer (attack of the anion 34 on the terminal nitrogen) were reversible, then reagent 40 would excel because the initial triazene adduct could intramolecularly displace the chloride ion and thus drive the equilibrium of the first step to the right.
Furthermore, if reagent 40 performed as expected, the resultant intermediate 41 could then fragment with elimination of the excellent leaving group 42, thus accelerating the last step of the diazo transfer reaction as well. Surprisingly, 40 proved to be less effective than tosyl azide in typical applications. The experimental observations indicate that the internal nitrogen of the triazene did not displace the chlorine.

Despite the fact that nucleophilic addition of the anion 34 to the terminal nitrogen is not a distinguishing step for sulfonyl azide reagents, it has been argued that the N-diazonium imine reagents 2-azido-3-ethylbenzthiazolium tetrafluoroborate (22) and N,N-dimethylazidochloromethyleniminium chloride (23, Figure 7, p. 12) are more electrophilic, and that this fact alone accounts for their enhanced reactivity over the
sulfonyl azides. As stated previously, the primary criterion for the first step of the overall diazo transfer mechanism is that the diazo transfer reagent must react faster than other electrophiles in the reaction mixture with the substrate carbanion 34. A problem frequently encountered with sulfonyl azide reagents is azo coupling (Figure 15).

![Chemical structure](image)

**Figure 15: The Azo Coupling Reaction**

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Azo coupling occurs when Z and Z' are strong electron-withdrawing groups such as -NO₂, -CN, or in some cases -SO₂R. These groups stabilize resonance contributor 37b of the target diazo compound thus making 37 susceptible to attack by 34. Reagent 22 prevents azo coupling in many cases because unlike tosyl azide, it is more electrophilic than the diazo products 37.

As seen from the two examples in Figure 16 above, 22 is reactive in acidic solutions, a characteristic which is shared by the other popular N-diazonium imine reagent, 23. It seems probable that reagents 22 and 23 are reacting with weakly...
nucleophilic enol tautomers of the substrates rather than with substrate anions 34. Negligible concentrations of 34 would account for the absence of azo coupling products. This hypothesis that N-diazonium imine reagents react with enols is supported by the observation that 23 converts phenols to o- and p-hydroxy aryl diazonium salts (Figure 17)\textsuperscript{14}.

\[ \text{HO} \quad \text{Me}_2\text{N} \subset \text{N} \rightarrow \text{N}_2^+ \text{Cl}^- \]

\[ \text{CH}_2\text{Cl}_2, \text{r.t., } 8\text{h} \]

\[ \text{HO} \]

\[ \text{CH}_3 \quad \text{OH} \]

\[ \text{CH}_3 \]

\[ \text{Figure 17: Reaction of N,N-Dimethylazidochloromethyleniminium Chloride (23) with Phenols} \]

The N-diazonium imine reagent 22 is thus far the only diazo transfer reagent which permits the synthesis of α-nitro\textsuperscript{31} and α-cyanodiazooalkanes\textsuperscript{32}. The pronounced

\[ \text{31 Balli, H.; Löw, R. Tetrahedron Lett. 1966, 5821.} \]

electron-withdrawing effect of nitro and cyano substituents makes these diazo compounds prone to azo coupling.

In conclusion, the sulfonyl azide diazo transfer reagents all appear to be equally efficacious with respect to the first step of the diazo transfer mechanism—nucleophilic attack of the substrate anion 34 on the diazo transfer reagent. In cases where the diazo product has very powerful electron-withdrawing groups on the diazo carbon, the diazo moiety itself becomes a very potent electrophile which in may react preferentially with anion 34 to give the products of azo coupling. In these cases, the highly electrophilic N-diazonium imine reagents, 2-azido-3-ethylbenzthiazolium tetrafluoroborate (22), and N,N-dimethylazidochloromethyleniminium chloride (23) must be used. It is likely that in acidic solutions the reactive nucleophilic partners for 22 and 23 are enols rather than enolate anions.

**Proton transfer**

The addition of the carbanion 34 to the terminal nitrogen of the diazo transfer reagent (Figure 12, p. 21) gives the triazene intermediate 35. The literature on diazo transfer typically depicts the Z isomer around the N=N bond for this intermediate. Implied by this representation (sometimes explicitly) is an intramolecular proton transfer giving triazene tautomer 36. The literature on 1,3,3-trialkyltriazenes would seem to suggest that the E isomer of 35 probably predominates33, therefore geometrically prohibiting an intramolecular proton transfer (Figure 18).

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Figure 18: Comparison of the E and Z Isomers of Triazene Intermediates with Respect to Intramolecular Proton Transfer

It is not known whether the E and Z isomers of triazenes 35 and 36 can interconvert. If the E isomer indeed predominates (as seems likely) and the isomers do not rapidly interconvert, then the reaction medium must supply some species which can act as both a Brönsted acid and a Brönsted base to facilitate an intermolecular proton transfer. This consideration is not problematic since the triazenes themselves can serve as proton donors and acceptors, and the by-products of the diazo transfer reaction as well as the auxiliary bases typically employed are capable of facilitating an intermolecular proton transfer.

Proton transfers are usually fast compared to addition or elimination reactions, therefore the natural assumption is that in the overall diazo transfer mechanism either the
first step (addition of 34 to the diazo transfer reagent) or the last step (fragmentation of the triazene tautomer 36) should be the rate limiting step of the overall reaction.

This assumption is not supported by experimental observations, however. The success of diazo transfer to methylene compounds decreases as the acidity of the methylene hydrogens decreases, as illustrated in Table 2 below. The pKa data for the methylene compounds was excerpted from Bordwell’s extensive compilation of equilibrium acidities in DMSO. The data indicate that when the pKa of the methylene substrate is above 23, the diazo transfer reaction with tosyl azide is always unsuccessful. At pKa’s below 23, however, diazo transfer with tosyl azide is extremely reliable. This strong correlation of the success of diazo transfer reactions with the pKa of the substrate strongly suggests that proton transfer is the critical step.

This assertion becomes more intuitive when one considers the probable effects of the substrate substituents and the substrate acidity on the rates of the various steps in the mechanism. Consider the rate constants for Equation 7 (following Table 2). Equation 7 represents a typical diazo transfer reaction to the anion of an active methylene compound with an arylsulfonyl azide reagent. The first step and last step are assumed to be essentially irreversible (k_1 and k_3 negligible). Also shown is a typical first-order side reaction such as azido transfer or Wolff rearrangement (vide infra) arising from triazene 35. The rate constant of the side reaction is k_s.
Table 2: pKa's of Methylene Compounds and Success of Diazo Transfer with Tosyl Azide

<table>
<thead>
<tr>
<th>Substrate</th>
<th>pKa&lt;sup&gt;a&lt;/sup&gt; Success&lt;sup&gt;b&lt;/sup&gt;</th>
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<td><img src="image" alt="Substrate" /></td>
<td>26.4 no</td>
<td></td>
</tr>
</tbody>
</table>


<sup>b</sup> Success of diazo transfer to the methylene with tosyl azide and auxiliary bases.
As the substituents $Z$ and $Z'$ become less able to stabilize the negative charge on the methylene carbon (i.e. as the substrate becomes less acidic), the rate constant $k_1$ should increase. This follows from the fact that the methylene anion will become more unstable relative to the triazene 35 as $Z$ and $Z'$ become less electron-withdrawing. Similarly, as $Z$ and $Z'$ become less electron-withdrawing, the rate constant for the last step, $k_3$, should also increase because the energy of triazene tautomer 36 having the negative charge on carbon will increase relative to the stable arylsulfonamide anion 38. The reverse proton transfer ($k_2$) would also increase as $Z$ and $Z'$ become less able to stabilize the negative charge. The effect of $Z$ and $Z'$ on $k_5$ will be negligible in most cases because the negative charge on the sulfonamide nitrogen of 35 is the reactive center and it is insulated from any electronic effects of $Z$ and $Z'$. The only rate constant which would be adversely impacted by decreasing the electron-withdrawing power of $Z$ and $Z'$ is the forward proton transfer, $k_2$. The failure of diazo transfer to give diazo compounds when the substituents $Z$ and $Z'$ are only weakly electron-withdrawing can thus be attributed to the failure of the rate of the forward proton transfer ($k_2$) to compete with the rate $k_5$ of the side reaction(s).

This deduction has major implications for the design of new diazo transfer reagents. If the applicability of the diazo transfer reaction is to be extended to systems
where the groups Z and Z' are only weakly electron-withdrawing, then the diazo transfer reagent will have to incorporate structural features which accelerate the rate of the forward proton transfer relative to the side reactions. Specifically, the basicity of the internal nitrogen of triazene intermediate 35 must be increased. Replacement of the electron-withdrawing -SO₂Ar group of the arylsulfonyl azide reagent with an electron-donating moiety should in principle lead to reagents which are more effective for diazo transfer to substrates having only weak electron-withdrawing substituents Z and Z'.

Cleavage of the Triazene Adducts

The last step of the overall diazo transfer reaction involves cleavage of the triazene tautomer 36 to give the product diazo compound, 37, and the co-product arylsulfonamide anion, 38 (Figure 19). Arylsulfonamide anions are weak bases and thus are good leaving groups for this step of the reaction. As discussed previously, removal of 38 from the diazo compound can be problematic in some cases, and considerable effort has been devoted to the development of reagents which give water-soluble, polymer-bound, or otherwise readily separable by-products.

![Figure 19: Cleavage Step of the Diazotransfer Reaction](image)

In principle, the co-product of diazo transfer (e.g. 38) does not have to be "dead." The co-product is required to be a basic compound by the nature of the diazo
transfer mechanism. Although the co-products arising from arylsulfonyl azide reagents are weakly basic sulfonamides, in principle the co-product of diazo transfer could be a strongly basic entity which could form the anion 34 from the substrate active methylene compound. In such a case the diazo transfer reaction could be base catalyzed; each cycle of the reaction would produce the a basic co-product which would form anion 34 for the next cycle.

Reagents 22 and 23 give co-products which are amidine bases (which are stronger bases than triethylamine). In most applications the isolated co-products from diazo transfer with these reagents are not the free amidine bases but rather their salts, suggesting that diazo transfer reactions with 22 and 23 can succeed with only catalytic amounts of base present. This observation is supported by the fact that 22 and 23 are also reactive in mildly acidic solutions.
Side Reactions to Diazo Transfer

One of the side reactions which competes with diazo transfer to very acidic methylene substrates, azo coupling, has been discussed previously in the section dealing with the electrophilic addition step of the diazo transfer reaction (p. 23). Formally, azo coupling represents a successful diazo transfer, since the azo products arise from reaction of the target diazo compound with the substrate carbanion. The side reactions discussed below, azido transfer, Wolff rearrangement, and ester amidation all arise from the triazene intermediate 35 prior to the proton transfer step of diazo transfer.

Azido Transfer

Tosyl azide reacts with tertiary carbanions to give triazenes 42, which decompose with loss of p-toluenesulfinate ion, 44, giving tertiary azides 43.34

![Diagram of azido transfer reaction]

Figure 20: Azido Transfer to 3° Carbanions with Arylsulfonyl Azides

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The same process has also been observed in some cases with the secondary carbanion substrates employed for diazo transfer, particularly when the substrate is activated by only a single electron-withdrawing group. An illustrative example is shown in Figure 21. When triazene salt 45 was warmed from -70° C, azidoacetidine 46 was formed; none of the diazo transfer product 47 was detected.35

![Chemical Diagram](image)

Figure 21: Azido Transfer from Attempted Diazo Transfer to an Amide Enolate

**Wolff Rearrangement**

The Wolff rearrangement process, depicted in Figure 22, was one of the first identified side reactions to diazo transfer.\(^ {36} \) This process is initiated by nucleophilic attack of the sulfonamide nitrogen of triazene 48 on a carbonyl group. The resulting triazoline 49 decomposes with migration of the substituent R and elimination of nitrogen giving 50.

![Chemical structure of Wolff Rearrangement](image)

**Figure 22:** Wolff Rearrangement from Attempted Diazo Transfer to a Ketone Enolate

---

Hendrickson and Wolf found that this rearrangement/decomposition process was often the major process for systems where $R'$ was an aryl group and triethylamine was used as the base catalyst. The migrating group, $R$, can be alkyl, aryl, or hydrogen.

**Ester Amidation**

Whereas azido transfer and the Wolff rearrangement are only troublesome when the incipient diazo carbon is activated by just a single electron-withdrawing group, ester amidation is a side reaction which can plague diazo transfer to $\beta$-keto esters, where the future diazo carbon is doubly activated (Figure 23). The ester amidation process results in the displacement of the ester alkoxy group by the arylsulfonamidyl moiety. Like the Wolff rearrangement, this side reaction is initiated by attack of the sulfonamide nitrogen of the triazene, 51, on a carbonyl group, specifically an ester carbonyl. The resulting triazoline, 52, eliminates the alkoxy group giving 53, which then undergoes base-catalyzed cleavage to the diazo compound 54. Formally this process is a successful diazo transfer, since the $=\text{N}_2$ moiety is incorporated onto the methylene carbon. The concomitant transformation of the ester group is rarely the desired result.

The choice of solvent and base for the diazo transfer reaction can often mitigate the ester amidation side reaction. Thus using tosyl azide in ethanol with sodium ethoxide as the auxiliary base, ethyl acetylacetate ($R = \text{Et}$, $Z = \text{COCH}_3$) and diethyl malonate ($R = \text{Et}$, $Z = \text{CO}_2\text{Et}$) both gave tosylamide products 54. The same substrates with tosyl azide in acetonitrile with triethylamine as the base, however, gave clean diazo transfer without any displacement of the ester ethoxy groups.37

Figure 23: Origin of Sulfonamide Products from Diazotransfer Reactions of Arylsulfonyl Azides with β-Keto Esters
Synthesis of Diazo Compounds by Oxidation of Hydrazones

Diazoalkanes having no stabilizing electron-withdrawing groups on the diazo carbon cannot be synthesized via the convenient diazo transfer methodology. A popular and convenient method for the synthesis of diazoalkanes having no electron-withdrawing substituents is hydrazone oxidation.

Hydrazones, 56 (R,R' = alkyl, aryl, H), can usually be prepared from the corresponding aldehyde or ketone, 55, by direct reaction with excess hydrazine. This process can lead to the formation of appreciable amounts of azines, 57, and/or 3,3,6,6-tetraalkylhexahydro-s-tetrazines, 58. Reaction of the aldehyde or ketone with 1,1-dimethylhydrazine to give the dimethylhydrazone, 59, followed by reaction of 59 with hydrazine can avoid the formation of 57.\textsuperscript{38}

\textbf{Figure 24: Synthesis of Hydrazones}

Most of the reagents used for the oxidation of hydrazones are metal oxides. A general mechanism for such reagents is depicted in Figure 25.

Formally, the oxidation is a 1,1 elimination from the hydrazone nitrogen. The oxidizing agent introduces a good leaving group, the metal hydroxide of 61 and 62, onto the nitrogen prior to the elimination step. The mechanism implies (and experiments confirm) that hydrazone oxidations with metal oxides are accelerated by hydroxide ion and desiccants (to absorb the reaction water).

The traditional reagent for hydrazone oxidation is mercuric oxide, which is most effective when freshly prepared in “active” form by reaction of mercury (II) chloride.
with potassium hydroxide.\textsuperscript{39} Mercuric oxide can be used for the preparation of a wide variety of diazo compounds from hydrazones, especially in cases where the diazo carbon bears a stabilizing aryl group.\textsuperscript{40} Other metallic reagents which have wide applicability are silver oxide,\textsuperscript{41} lead tetraacetate,\textsuperscript{42} manganese dioxide,\textsuperscript{43} nickel peroxide,\textsuperscript{44} and barium manganate.\textsuperscript{45}


Non-metallic oxidizing agents have also been used to convert hydrazones to diazo compounds. Iodine,\textsuperscript{46} and alkaline hypochlorite\textsuperscript{47} are the two most frequently employed non-metallic reagents. These reagents must be heavily buffered to prevent decomposition of the diazo compounds by the acidic co-products.

A novel method for converting hydrazones to diazo compounds using tosyl azide was discovered by Fischer and Anselme. These workers had developed a methodology for the conversion of primary amines to azides with tosyl azide in the presence of strong bases.\textsuperscript{48} Fischer and Anselme categorized this process as a diazo transfer reaction, because the hydrogens of the -NH\textsubscript{2} group were replaced by an =N\textsubscript{2} moiety in the product azide. They expected that N-azidimines (R\textsubscript{2}C=N-N\textsubscript{3}) could be prepared by an analogous diazo transfer reaction to the -NH\textsubscript{2} group of hydrazones.

Fischer and Anselme found, however, that treatment of benzophenone hydrazone with methyl magnesium chloride followed by tosyl azide gave none of the desired N-azidimine, but rather diazodiphenylmethane (50\% yield), p-toluenesulfonamide anion, and N\textsubscript{2}.\textsuperscript{49} The same reaction with acetophenone hydrazone gave 1-diazo-1-phenylethane, fluorenone hydrazone gave 9-diazofluorene, and benzil monohydrazone produced azibenzil. These reactions left appreciable amounts


of unreacted hydrazone.\textsuperscript{50} No further examples of this methodology have been reported, presumably because of the modest yields obtained.

Fischer and Anselme proposed two possible mechanisms to account for these results. First, they postulated that the desired N-azidimines (R$_2$C=N-N$_3$) had formed, but that they rapidly decomposed with loss of nitrogen to the diazo compounds. Their second proposed mechanism is shown in Figure 26 below. This mechanism postulates that the hydrazone anions add to the terminal nitrogen of tosyl azide giving intermediate pentazenes 64, which undergo proton transfer to 65. Concerted elimination of nitrogen and p-toluenesulfonamide anion, 38, from 65 gives the diazo compounds 63.

This interesting use of tosyl azide as an oxidizing agent for hydrazone salts raises the possibility that a more potent diazo transfer reagent could be used for the preparation of all types of diazoalkanes: diazo compounds with either one or two electron-withdrawing groups on the diazo carbon could be prepared by direct diazo transfer, and diazo compounds with no electron-withdrawing groups on the diazo carbon could be prepared by oxidation of the corresponding hydrazone salt with the diazo transfer reagent.

Figure 26: Conversion of Hydrazine Anions to Diazooalkanes with Tosyl Azide
Phosphazides and Phosphorimines: Intermediates and Products of the Staudinger Reaction

The discussion of diazo transfer emphasized that the success of the diazo transfer process depends on the fate of intermediates 35. When the groups Z and Z' are electron-withdrawing, compounds 35 decompose smoothly via proton transfer and cleavage to the diazo compound. When only one or neither of the groups Z and Z' are electron-withdrawing, intermediates 35 typically fail to give good yields of diazo compounds. Conceptually, compounds 35 are N3-monosubstituted triazene anions.

Another family of triazenes which one would expect to be closely related to 35 are 1-alkyl-3-phosphoranyldenetriazenes, 66. Since the P=N bond is ylide-like, with substantial negative charge on the nitrogen atom, 66 are isoelectronic with 35. This isoelectronic similarity immediately begs the question of whether compounds 66 decompose to diazo compounds as do 35.
1-Alkyl-3-phosphoranylidenetriazenes, 66, commonly called "phosphazides," are intermediates in the Staudinger reaction (see figure below).\textsuperscript{51} The Staudinger reaction is a venerable and versatile method for the preparation of phosphorimines 67: virtually any organic azide 68 will react with any phosphine 69 to give an intermediate phosphazide 66 which typically decomposes cleanly with loss of nitrogen to phosphorimine 67. Many inorganic azides such as trimethylsilyl azide, tosyl azide, and phosphorus azides can be used in place of the organic azides 68. The accepted mechanism of the Staudinger reaction is illustrated in the figure.

![Diagram of the Staudinger Reaction](image)

**Figure 28: The Staudinger Reaction**

Decomposition of phosphazides 66 labeled with $^{15}\text{N}$ demonstrated that N1 of 66 is eventually incorporated into the phosphorimine product 67. This result suggests the mechanism where 70 is a transition state or intermediate. Most phosphazides 66 are not isolable; they decompose under the conditions of their formation to give 67. As the mechanism above implies, electron-withdrawing substituents R which decrease the nucleophilicity of N1, and electron-donating or sterically bulky substituents W, X, and Y which retard nucleophilic attack on the phosphorus retard the decomposition of 66.

Indeed, there are several examples of isolable phosphazides 66 which incorporate these stabilizing features. Examples are 1-methyl-3-tris(dimethylamino)-phosphoranylidenetriazene,53 71 (bulky, electron donating groups on phosphorus), 1-(p-nitrophenyl)-3-diethylphenylphosphoranylidinetriazene,54 72 (electron withdrawing group on N1), and 1-tosyl-3-triphenylphosphoranylidenetriazene,54 73 (electron-withdrawing group on N1).

\[
\begin{align*}
\text{CH}_3 & \quad \text{O}_2\text{N} \\
\text{N} & \quad \text{N} \\
\text{Me}_2 & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{O}_2\text{N} & \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{N} & \quad \text{N} \\
\text{Me}_2 & \quad \text{Me}_2 \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{Me}_2 & \quad \text{Me}_2 \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{O}_2\text{N} & \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{N} & \quad \text{N} \\
\text{Me}_2 & \quad \text{Me}_2 \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{Me}_2 & \quad \text{Me}_2 \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{O}_2\text{N} & \\
\text{CH}_3 & \quad \text{CH}_3 \\
\end{align*}
\]

Despite the fact that the Staudinger reaction has been known for more than 70 years, and that numerous phosphazides have been isolated, there are no known examples of such materials decomposing to give diazo compounds (Figure 29). This is surprising given the isoelectronic relationship of the phosphazides to the triazene intermediates of the diazo transfer reaction.

![Figure 29: Decomposition of Phosphazides 74 to Diazo Compounds is a Heretofore Unknown Process](image)

The lack of any references in the literature to phosphazides decomposing to diazo compounds via the mechanism put forth in Figure 29 is probably due to the fact that appropriate systems have not been examined: there are no examples in the literature of phosphazides 74 having electron-withdrawing groups Z and/or Z' to facilitate the proton transfer to 75. Indeed, the vast majority of phosphazides reported in the literature do not have the requisite proton in the position $\alpha$ to N1. This observation raises the interesting possibility that phosphazides having a proton $\alpha$ to N1 along with electron-
withdrawing groups $Z$ and $Z'$ might very well decompose to diazo compounds, thus providing a new route to these materials. The competing Staudinger reaction could be minimized by the presence of bulky, electron-donating substituents $W$, $X$, and $Y$ on phosphorus.

Electron-donating substituents, such as dialkylamino groups, on phosphorus would also substantially increase the basicity of $N_3$ (the phosphorimine nitrogen). This is due to extensive delocalization of the positive charge in the cation (Figure 30). In such systems the proposed decomposition to diazo compounds would be accelerated at the stage of the proton transfer.

![Figure 30: Delocalization of the Positive Charge in Tris(dialkylamino)-phosphoriminium Cations](image)

The high basicity of systems having four nitrogens around a central phosphorus is well documented. Numerous derivatives of the parent system, phosphorimidic triamide (77) have been prepared. Studies of $N''''$-unsubstituted hexaalkylphosphorimidic triamides, 78, by the research group of Professor Pinchuk in
The Soviet Union have shown that such compounds are much more basic than tertiary amines. Lately, Professor Schwesinger has demonstrated that sterically hindered peralkylphosphorimidic triamides, 79, are powerful non-ionic bases which excel in a variety of synthetic applications.

![Phosphorimidic Triamides](image)

**Figure 31: Phosphorimidic Triamides**

The peralkylphosphorimidic triamides synthesized by Schwesinger, e.g. 80-83, are more basic than the frequently used amidine bases DBU and DBN, and they are even more basic than tetramethyl- and pentamethylguanidine (see Figure 32 below). The bases 80-83 are excellent for E2 eliminations on sterically unhindered systems which typically alkylate the base rather than eliminate. Compounds 80-83 are much more inert than DBU and DBN to hydrolysis and reaction with alkylating agents.

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56 Schwesinger, R. Chimia 1985, 39, 269.
1,5-Diazabicyclo[4.3.0]non-5-ene "DBN", pKa = 23.8

1,8-Diazabicyclo[5.4.0]undec-7-ene "DBU", pKa = 24.3

R = H, Tetramethylguanidine, pKa = 23.8
R = Me, Pentamethylguanidine, pKa = 25.0

$\text{CH}_3$

a 2,4 Diaminovinimidine pKa = 26.95

$\text{CH}_3$

80, pKa = 27.53

81, pKa = 27.58

82, pKa = 26.89

83, pKa = 28.27

**Figure 32**: Some Neutral Nitrogen Bases with the pKas of their Conjugate Acids in Acetonitrile\textsuperscript{56, 57}

CHAPTER II
RESULTS AND DISCUSSION

Introduction

The foregoing historical background emphasized that the development of improved methods for the preparation of diazo compounds has been an ongoing effort by numerous researchers for several decades and continues to be an area of active research. Significant advances in this field have been diazo transfer reagents having the diazonium-imine structure, such as 2-azido-3-ethylbenzthiazolium tetrafluoroborate (22), which has recently become purchasable in small quantities,\(^{58}\) and N,N-dimethylazidochloromethyleniminium chloride (23) (See Figure 7, p. 12). These reagents are highly reactive, electrophilic diazo transfer reagents which have distinct advantages over tosyl azide.

The historical section also highlighted the peralkylphosphorimidic triamides, which are an easily accessible family of extremely strong neutral bases. The enormous potential of these materials as non-ionic, sterically encumbered bases for organic synthesis has recently prompted their commercialization.\(^{59}\)

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58 Reagent 22 is available from Aldrich Chemical Co., Milwaukee, Wis. for $19.00/g.

59 For example, 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (83, previous page) is now available from Aldrich Chemical Co.
Azidotris(dialkylamino)phosphonium halides (Figure 33) merge the peralkylphosphorimidic triamide functionality with the diazonium-imine moiety to give a promising new class of diazo transfer reagents incorporating both the electrophilicity of the diazonium-imines as well as the high basicity of the peralkylphosphorimidic triamides. Azidotris(dialkylamino)phosphonium halides were predicted to excel as reagents for diazo transfer, and it was anticipated that they would overcome some of the limitations which are encountered with tosyl azide and be more economical than the N-diazonium imine reagents 22 and 23.

**Figure 33:** Merger of the Diazonium-Imine & Peralkylphosphorimidic Triamide Functionalities.

Diazot transfer is not suitable for the preparation of diazoalkanes which do not have stabilizing electron-withdrawing substituents. Other methods such as hydrazone oxidation must be employed for the synthesis of these diazoalkanes. If the low-yield
transformation of hydrazone anions to diazo compounds with tosyl azide (Figure 26, p. 46) could be improved with a better diazo transfer reagent, it could easily become a "workhorse" reagent applicable to the synthesis of many different diazo compounds.

It was also anticipated that reactions of azidotris(dialkylamino)phosphonium halides with alkyl carbanions would give 1-alkyl-3-tris(dialkylamino)phosphoranylidenedi triazenes (phosphazides). Little is known about this moiety due to the rapidity with which most phosphazides decompose with loss of nitrogen (Staudinger reaction). This research presented an opportunity to form phosphazides with sterically hindering, electron-donating substituents on phosphorus, which would be more stable than previous examples of this functional group. Reactions of phosphazides with various reagents could then be studied.

\[
\begin{align*}
\Theta & \quad + \\
R: & \quad \rightarrow \\
\begin{array}{c}
\text{N} \quad \text{N} \\
\text{P} \\
\text{R}_2 \text{N} \quad \text{NR}_2
\end{array} & \quad X \\
\rightarrow & \\
\begin{array}{c}
\text{N} \quad \text{N} \\
\text{P} \\
\text{NR}_2 \quad \text{NR}_2
\end{array} & \quad \Theta
\end{align*}
\]

**Figure 34:** Reaction of Carbanions with Azidotris(dialkylamino)phosphonium Halides Giving 1-Alkyl-3-tris(dialkylamino)phosphorany lidenedi triazenes

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Synthesis and Properties of Azidotris(dialkylamino)phosphonium Bromides

The general strategy for the preparation of azidotris(dialkylamino)phosphonium bromides is shown in Figure 35. In principle, any secondary amine and any halogen can be used in the synthesis, however there are several practical considerations which limit the choices. The cost and availability of the amine are important considerations when designing a reagent for use in the chemical community. In this regard, dimethyl-, diethyl-, and diisopropylamine are the obvious choices, along with simple cyclic amines such as piperidine, morpholine, and pyrrolidine.

Since the halogen ultimately provides only the counter ion for the reagent 86, the choice of the halogenating agent for the second step is based solely on cost and convenience. Bromine was chosen because it is easier to handle than chlorine, however the latter is a more economical choice for large-scale preparations.

Figure 35: Synthesis of Azidotris(dialkylamino)phosphonium Bromides
A third consideration, which could only be evaluated after several reagents were synthesized, was the effect of the dialkylamino groups on the properties of the target reagent 86 as well as the precursors 84 and 85.

Synthesis of the intermediate triaminophosphines 84 proceeds in high yield with diethylamine,\textsuperscript{61} and piperidine,\textsuperscript{62} and the dimethylamine derivative (hexamethylphosphorustriamide, HMPT) is commercially available. It seemed desirable to maximize the steric bulk of the dialkylamino groups in 86 in order to minimize undesirable side reactions involving nucleophilic attack on phosphorus. Molecular models indicate, however, that three diisopropylamino groups result in extreme steric crowding around the phosphorus center. No references to tris(diisopropylamino)phosphine could be found in the literature, and attempts to synthesize this compound by prolonged heating of PCl\textsubscript{3} with diisopropylamine failed. From a practical standpoint, compounds 86 are limited to dialkylamino groups which have no branching at the α-position.

Although α-branched alkyl groups are not practical in structures 84, 85, and 86, secondary amines without α-branching are sterically accommodated quite readily around phosphorus. Despite this fact, morpholine and pyrrolidine fail to give 84 in good yield. Morpholine upon reaction with PCl\textsubscript{3} under the same conditions which yield 81\% of tripiperidinophosphine, gives only 38\% of trimorpholinophosphine. The reaction of pyrrolidine with PBr\textsubscript{3} gives little tripyrrolidinophosphine; the protonated pyrrolidine ring presumably opens under attack by bromide ion. The reaction of pyrrolidine with PCl\textsubscript{3} was not attempted.


Hexamethylphosphorustriamide, hexaethylphosphorustriamide, and tripiperidinophosphine are converted to the corresponding reagents in good yields by the process illustrated in Figure 35. Thus azidotris(dimethylamino)phosphonium bromide (2), azidotris(diethylamino)phosphonium bromide (1), and azidotripiperidinophosphonium bromide (3) (Figure 36) were available for study as diazo transfer reagents, and a systematic comparison of their physical properties was then undertaken.

![Figure 36: Readily Accessible Azidotris(dialkylamino)phosphonium Bromides](image)

The physical properties of compounds 2, 1, and 3 are greatly dependent on the dialkylamino substituents. Compound 3 crystallizes much more readily than 1, despite having roughly the same steric bulk at the phosphorus center. Presumably this is due to the lower number of conformations available to the cyclic alkyl groups of 3. Whereas 3 reliably precipitates as a white crystalline solid from THF upon cooling at 0° C, 1 often fails to crystallize under the same conditions if impurities are present. The only difficulty encountered in the synthesis of 1 is its tendency to separate as an oil rather
than a solid. Seeding of the oils rarely induces crystallization, however the oils are substantially free of non-solvent impurities. It was thought that longer straight-chain alkyl groups would exacerbate the problems which are encountered in crystallizing 1, and therefore the dipropylamine and dibutylamine analogs were not prepared.

Phosphonium salts 1, 2, and 3 are all hygroscopic, however the aliphatic groups have pronounced effects on the rate of water uptake in a humid atmosphere. Compound 2 is a highly deliquescent material which has to be handled rapidly in order to prevent its complete liquification. Even when stored over desiccants in vacuo, 2 tends to remain tacky. Lengthening the alkyl chains by one carbon significantly reduces the rate of water uptake. Thus 1, although still deliquescent, can be handled in the atmosphere much more easily than 2, and 1 remains a crystalline solid when stored in a vacuum desiccator. Even the small structural difference between reagents 3 and 1 makes the former much less hygroscopic. No difficulties were ever encountered in handling 3 in a humid atmosphere or in its storage.

All three of the compounds 1, 2, and 3 decompose with N\textsubscript{2} evolution when heated. Gas evolution occurs concurrently with melting at 174° C for compound 2, and at 152° C for 3. Reagent 1 decomposes with gas evolution above 130° C, but melts beforehand at 90-92° C.\textsuperscript{63} The gas evolution is slow in all three cases. Several attempts were made to detonate 1: rapid heating (hot plate), friction (mortar and pestle), shock (hammer), and flame all fail to initiate detonation or deflagration of 1. Large quantities of 1 have been stored for periods greater than one year in a vacuum desiccator without detectable decomposition.

\textsuperscript{63} Due to the deliquescent nature of 1, 2, and 3, accurate melting points could not be obtained in open capillary tubes. The samples for melting point determinations had to be loaded into melting-point capillary tubes in a dry box under argon. The capillary tubes were then rapidly sealed using a gas/oxygen torch.
Of the three reagents, 1 is the most soluble in typical solvents: it dissolves in DMF, DMSO, alcohols, CH$_3$CN, CH$_2$Cl$_2$, CHCl$_3$, benzene, warm THF, and partially in diethyl ether. The polar nature of 1 makes it insoluble in alkanes. Compound 2 has the undesirable quality of absorbing water from wet solvents giving insoluble gums. The solubility of 3 parallels that of 1, however 3 often takes longer to dissolve.

The spectral data for 1, 2, and 3 support the proposed structures. The $^{31}$P NMR spectra show single peaks (1 in CDCl$_3$ δ 36.15, 2 in d$_6$-DMSO δ 36.61, 3 in d$_6$-DMSO δ 29.15) thus ruling out equilibrating ionization isomers such as 86i (Figure 37) in which the bromide counter-ion has displaced the azide group on phosphorus. The chemical shifts are in the range expected for tetrahedral phosphorus with four nitrogen ligands.$^{64}$

\[
\begin{align*}
\text{R}_2\text{N} &- \text{P} - \text{NR}_2 \\
\text{NR}_2 & \quad 86 \\
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{Br}
\end{array} & \quad \begin{array}{c}
\text{N} \\
\text{N} \\
\text{Br}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{R}_2\text{N} &- \text{P} - \text{NR}_2 \\
\text{NR}_2 & \quad 86a \\
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{Br}
\end{array} & \quad \begin{array}{c}
\text{N} \\
\text{N} \\
\text{Br}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{R}_2\text{N} &- \text{P} - \text{NR}_2 \\
\text{NR}_2 & \quad 86i \\
\begin{array}{c}
\text{N} \equiv \text{N} \equiv \text{N}
\end{array}
\end{align*}
\]

Figure 37: Non-equilibration of Possible Ionization Isomers

The infrared spectra also support structure 86/86a rather than 86i. Compounds 1, 2, and 3 all exhibit single sharp bands in the region where covalent azides typically...

---

appear: 1 at 2160 cm\(^{-1}\), 2 at 2167 cm\(^{-1}\), and 3 at 2164 cm\(^{-1}\). These strong IR bands are due to an asymmetric N=N=N- stretch from resonance structure 86a, which is equivalent to an N≡N- stretch from resonance structure 86. Larger wave numbers for the N=N=N- asymmetric stretch/N≡N- stretch are indicative of higher N≡N- bond order and lower electron density on the terminal nitrogen of the azide. This in turn correlates with increased electrophilicity for the terminal nitrogen. Regitz and Maas state that the high reactivity of 2-azido-3-ethylbenzthiazolium tetrafluoroborate (22, Figure 7, p. 12) at neutral or even acidic pH is due to the electrophilicity of its N-diazonium group, which correlates with the high N≡N- IR stretch of 2175 cm\(^{-1}\).\(^{65}\) Another diazo transfer reagent which is active under acidic conditions, N,N-dimethylazidochloromethyleniminium chloride (23, Figure 7) exhibits a similar band at 2140-2160 cm\(^{-1}\).\(^{66}\)

Thus the strong bands at 2160-2167 cm\(^{-1}\) in the IR spectra of compounds 1, 2, and 3 indicate that the electrophilicities of these reagents lie between that of 22 (2175 cm\(^{-1}\)) and 23 (2140-2160 cm\(^{-1}\)). By comparison, tosyl azide exhibits at band at 2130 cm\(^{-1}\),\(^{67}\) indicating that it is substantially less electrophilic than the reagents having the N-diazonium imine structure.

Both 3 and 1 appeared from their physical properties to be attractive candidates for diazo transfer reagents. Although 3 is somewhat easier to handle than 1, the latter is a more economical diazo transfer reagent because of the lower cost of diethylamine.

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\(^{66}\) Viehe, H. G.; George, P. *Chimia*, 1975, 29, 209.

($1.02/lb) relative to piperidine ($3.15/lb)\textsuperscript{68}. Reagent 2 was discounted because it is extremely deliquescent, and because bulk preparation of hexamethylphosphorustriamide requires working with large quantities of highly volatile dimethylamine.

Reactions of 1 with Acidic Methylene Compounds

Preliminary experiments immediately indicated the success of azidotris(dialkylamino)phosphonium bromides as diazo transfer reagents. Reagents 1 and 3 transformed acidic methylene compounds into α-diazo-β-dicarbonyl compounds in the presence of catalytic amounts of base (Equation 8).

\[
\begin{align*}
\text{O} & \quad \text{O} \\
Y & \quad Y' = R, OR
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
Y & \quad N_2
\end{align*}
\]

Equation 8

The first reaction attempted with 3 gave spectacular results: stirring 3 with diethyl malonate \((Y, Y' = \text{OEt})\) for 3h in THF with 0.1 equivalent of potassium \(\text{t}-\text{butoxide}\) gave an 83% isolated yield of diethyl 2-diazo malonate. The co-product salt, aminotripyrindinophosphonium bromide, was easily precipitated by evaporating the THF and adding pentane. The co-product was recovered in 84% yield in this experiment. Similar results were obtained with ethyl acetoacetate \((Y = \text{CH}_3, Y' = \text{OEt})\) and 2,4-pentanedione \((Y, Y' = \text{CH}_3)\).

Since 1 is more economical to prepare than 3, the greatest effort was devoted to the optimization of a simple procedure for diazo transfer using 1. The thermal stability of α-diazo-β-dicarbonyl compounds permitted gas chromatographic analysis of typical diazo transfer reactions of 1 in several solvents. Table 3 shows the percentage of
conversion of 2,4-pentanedione, ethyl acetoacetate, and diethyl malonate to the diazo compounds with 1 using base catalysis in several solvents. The gas chromatograms indicate that the reactions proceed in very high yields in all of the indicated solvents.

Table 3: Conversions of $YCOCH_2COY'$ to $\alpha$-Diazobeta-dicarbonyl Compounds with 1 as Measured by Gas Chromatography

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Y</th>
<th>Y'</th>
<th>Percent Diazo Compound&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Percent Unreacted Dicarbonyl&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentane</td>
<td>CH₃</td>
<td>CH₃</td>
<td>91</td>
<td>--&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>CH₃</td>
<td>OEt</td>
<td>94</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>OEt</td>
<td>OEt</td>
<td>73</td>
<td>27</td>
</tr>
<tr>
<td>Benzene</td>
<td>CH₃</td>
<td>CH₃</td>
<td>94</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>CH₃</td>
<td>OEt</td>
<td>95</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>OEt</td>
<td>OEt</td>
<td>92</td>
<td>8</td>
</tr>
<tr>
<td>Ether</td>
<td>CH₃</td>
<td>CH₃</td>
<td>80</td>
<td>--&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>CH₃</td>
<td>OEt</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>OEt</td>
<td>OEt</td>
<td>96</td>
<td>4</td>
</tr>
<tr>
<td>THF</td>
<td>CH₃</td>
<td>CH₃</td>
<td>94</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>CH₃</td>
<td>OEt</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>OEt</td>
<td>OEt</td>
<td>93</td>
<td>7</td>
</tr>
<tr>
<td>CH₂Cl₂</td>
<td>CH₃</td>
<td>CH₃</td>
<td>92</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>CH₃</td>
<td>OEt</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>OEt</td>
<td>OEt</td>
<td>96</td>
<td>4</td>
</tr>
<tr>
<td>CHCl₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>CH₃</td>
<td>OEt</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>OEt</td>
<td>OEt</td>
<td>99</td>
<td>1</td>
</tr>
<tr>
<td>CH₃CN</td>
<td>CH₃</td>
<td>CH₃</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>CH₃</td>
<td>OEt</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>OEt</td>
<td>OEt</td>
<td>99</td>
<td>1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Percentage of the total volatile components (other than solvent) in the gas chromatogram.

<sup>b</sup> The remaining percentage was an unidentified volatile compound with a high retention time.

The proposed mechanism of the base-catalyzed diazo transfer reactions of 1 with acidic methylene compounds is illustrated in Figure 38 below.
Figure 38: Proposed Mechanism of Diazo Transfer Reactions of 1
The mechanism in Figure 38 is essentially identical to that proposed for all previously studied diazo transfer reagents, with the exception that there is no need for an equivalent amount of an auxiliary base because of the high basicity of hexaethyphosphorimidic triamide, 87, which is reformed during each cycle of the reaction. The structural features of reagent 1, as discussed below, are conducive to all the steps of the proposed mechanism.

The first step of the diazo transfer reaction involves deprotonation of active methylene compounds, 33, by a base to give anions 34. In this case compound 87, which is produced as a co-product of the diazo transfer process, functions as the base. The analogous co-products formed during diazo transfer with most other reagents are typically weak bases which will not deprotonate 33. For instance, the co-product of diazo transfer reactions using tosyl azide is the weakly basic toluenesulfonamide anion. Various hexaalkylphosphorimidic triamides, such as 87, have been synthesized by Russian researchers, and were found to completely deprotonate triethylamine hydrochloride.69 Thus 87 is a stronger base than triethylamine, which is typically used as the auxiliary base for diazo transfer reactions with tosyl azide.

The studies of Schwesinger indicate that peralkylphosphorimidic triamides such as 80-83 (Figure 32, p. 53) are stronger bases than DBN, DBU, and pentamethylguanidine.70 It can be safely assumed that the pKa of 87 is comparable to that of the closely allied compounds 80-83.

The second step of the diazo transfer reaction of 1 involves attack of the anion 34 on the terminal nitrogen of 1 to form triazene (or phosphazide) intermediate 88.

70 Schwesinger, R. Chimia, 1985, 39, 269.
This step also results in the formation of phosphonium bromide salt 89, which is the co-product of the reaction. This step of the diazo transfer reaction is facile because of the electrostatic attraction of 34 for 1. The electrophilicity of reagent 1, as indicated by the high IR stretching frequency of the terminal N≡N- bond, has been discussed previously (see p. 62.). This N≡N- stretch of 2160 cm⁻¹ in the IR indicates that 1 is more electrophilic than reagents such as tosyl azide, and that the electrophilicity of 1 lies somewhere between that of Balli's reagent (22) and N,N-dimethylazidochloromethyleniminium chloride (23).

The third step of the diazo transfer reaction shown in Figure 38 is the equilibration of the triazene (or phosphazide) 88 with its tautomer 90. In this step of the overall mechanism, the goal is to force the equilibrium towards 90 by making N3 of triazene 88 as basic as possible. Since this nitrogen (N3) is the highly basic phosphorimine nitrogen, it is assumed qualitatively that this step of the diazo transfer reaction is quite facile.

In order to quantitatively compare different diazo transfer reagents with respect to this proton transfer step of the mechanism, model compounds were chosen to assess the relative basicities of the various triazene intermediates. The triazene intermediates of the diazo transfer reactions of 1, tosyl azide, and 2-azido-3-ethylbenzthiazolium tetrafluoroborate (Balli's reagent, 22) are shown in Figure 39 below, along with the model compounds chosen to estimate the basicities of the triazenes.
Triazenes

Model Compounds

Figure 39: Triazene Intermediates of Some Diazo Transfer Reagents and Model Compounds for pKₐ Comparisons

1-Alkyl-3-tris(diethylamino)phosphoranylidetriazenes (91), prepared by addition of alkyllithium reagents to 1, are stable enough to use as model compounds for intermediate 88 (vide infra). Benzenesulfonamide anion (92) was chosen as the model for the tosyl azide triazene anion (51) and tetramethylguanidine (94) was selected to
model the triazene intermediate of Balli's reagent (93). Compounds 91 deprotonate phenol, suggesting that 88 is a stronger base than phenoxide ion. Bordwell found that in DMSO phenol is a weaker acid (pKₐ 18.0) than benzenesulfonamide (pKₐ 16.1).⁷¹ Thus benzenesulfonamide anion 92 and the triazene anion of tosyl azide, 51, are weaker bases than phenoxide ion. Therefore, the triazene intermediate 88 formed in the diazo transfer reactions of 1 is more basic than the triazene anion intermediate 51 formed from tosyl azide. The equilibrium 88 ⇌ 90 must then lie further to the right than the corresponding equilibrium in the diazo transfer reactions of tosyl azide.

Triazene 88 is certainly more basic than 93. This assertion is well supported by the pKa data listed in Figure 32, p.53 together with the structural similarities of 93 with tetramethylguanidine (94), DBU, and DBN.

As is the case with all other diazo transfer reagents, there is no evidence that the proton transfer 88 ⇌ 90 is intramolecular. Indeed, there is no evidence that the intermediate 88 exists as the Z-isomer around the N=N bond (as shown in Figure 38), which is a geometric necessity for an intramolecular proton transfer. Thus it is possible that the mechanism shown in Figure 38 also requires some species acting as both a Brönsted acid and a Brönsted base to accomplish an intermolecular proton transfer leading from 88 to 90.

The last step of the proposed mechanism shown in Figure 38 is unimolecular elimination of 90 to give the product diazo compound 37 as well as phosphorimidic triamide 87, which is consumed in the next cycle of the reaction. As with the analogous mechanisms for reagents 22 and 23, the leaving group for this elimination step is a neutral moiety. Tosyl azide, on the other hand, requires a negatively charged species, toluenesulfonamido anion, to act as the leaving group at this stage of the diazo

transfer process. Based on the general principal that neutral species are better leaving
groups than negative species, it is quite possible that the final step of the mechanism for
1 is faster than the corresponding step in the diazo transfer reactions of tosyl azide.

The choice of solvent and reaction conditions for the diazo transfer reactions of 1
were evaluated in light of the proposed mechanism. Diazo transfer reactions of tosyl
azide are typically run in polar solvents such as ethanol, acetonitrile, or neat
triethylamine\(^{72}\)--good choices considering that the intermediates in the process are
charged and equivalent amounts of strong auxiliary bases are needed (see Figure 12, p.
21). The intermediates 88 and 90 in the diazo transfer reactions of 1 are electrically
neutral, however, and in the first step of the proposed reaction mechanism, two charged
species collapse to form neutral 88. Reactions of this type where charge is diminished
in the transition state are accelerated by non-polar solvents. Furthermore, the co-product
of the reaction, \((\text{Et}_2\text{N})_3\text{P=NH}_2^+ \text{Br}^-\) (89), precipitates from solvents of low polarity,
thus simplifying the workup. These considerations suggested that a non-polar solvent
would be best for the diazo transfer reactions of 1. Reagent 1 is not soluble in
hydrocarbon solvents, however, and this fact may have accounted for the lower yield
observed by gas chromatography for the reaction of 1 with diethyl malonate (Table 3).
Diethyl ether, in which 1 is partially soluble seemed like a good compromise between
low polarity and the solubility constraints of 1. Most polar solvents were eliminated
from consideration on other grounds as well: it was feared that 1 might solvolyze in
alcohols, and solutions of 1 in acetonitrile turn very dark in the presence of base,
indicating that some reaction is occurring.\(^{73}\) Thus those two polar solvents were

1986; see Table 13.3, pp.345-352.

\(^{73}\) No volatile products from this reaction were evident in the GC traces. The products of this reaction
with acetonitrile were not identified.
eliminated from consideration because of chemical incompatibility. Other polar solvents, such as DMF and DMSO were not considered because of the anticipated difficulties in removing these high-boiling solvents from the diazo products.

Several preparative-scale reactions of 1 with acidic methylene compounds in diethyl ether were then examined. The majority of the co-product 89 precipitated from the reaction mixture, however the precipitation was not clean: when the supernant was directly evaporated the residue contained appreciable amounts of 89 in addition to the product diazo compound.

Several procedures for removal the remaining 89 from the diazo product were then examined. Evaporation of the ether and dilution with pentane precipitates the remaining 89, however a small amount of 87 remains in the pentane (this should in theory be equivalent to the amount of base catalyst used in the reaction). Aqueous washes remove both 89 and the catalytic amount of 87, however the simplest procedure involves passing the entire reaction solution rapidly through a short column of silica gel. Both 89 and 87, being highly polar, are immobile on silica gel. Acidic methylene compounds which are converted to diazo compounds with 1 by a base-catalyzed diazo transfer reaction are shown in Table 4 below. All but one of these reactions were run under identical conditions: the substrate was stirred with a suspension of 1 (small excess) in dry ether overnight at 20-25° C with a catalytic amount (5-10%) of potassium t-butoxide. The crude reaction mixture was worked up by filtering any precipitated 89, and rapidly passing the filtrate through silica gel.74

Table 4: α-Diazo-β-Dicarbonyl Compounds Synthesized with 1 by Base-Catalyzed Diazo Transfer Reactions

95 (76%)  
96 (67-85%)  
97 (71%)

98 (75-89%)  
99 (71%)  
100 (75-81%)

101 (76-81%)  
102 (77%)  
103 (76%)

104 (84%)

* Reaction run in CH₂Cl₂.
Base-catalyzed diazo transfer reactions with 1 do not work with methylene compounds which are less acidic than the 1,3-dicarbonyls discussed above. Diazo transfer to less-acidic substrates with 1 works well however when equivalent amounts of tetramethylguanidine are added. Methylene chloride is the best solvent when full equivalents of base are employed. The workup for this procedure entails aqueous extraction of the tetramethylguanidine with dilute NH$_4$Cl, followed by flash chromatography of the crude product.

This procedure employing a full equivalent of base also dramatically shortens the reaction times for the 1,3-dicarbonyl compounds discussed above. For instance, 97 is formed in 71% yield after 12 h using the base-catalyzed procedure, but a 76% yield is obtained after only 10 min when a full equivalent of tetramethylguanidine is added as an auxiliary base. Examples of diazo transfer with 1 and equivalent amounts of tetramethylguanidine in CH$_2$Cl$_2$ are shown below.

**Table 5: Diazo Compounds Synthesized with 1 and Tetramethylguanidine**

<table>
<thead>
<tr>
<th></th>
<th>105 (51%)</th>
<th>99 (80%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Structure105" /></td>
<td><img src="image2" alt="Structure99" /></td>
<td><img src="image2" alt="Structure99" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>1061 (87%)</th>
<th>97 (76%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image3" alt="Structure1061" /></td>
<td><img src="image4" alt="Structure97" /></td>
<td><img src="image4" alt="Structure97" /></td>
</tr>
</tbody>
</table>
The reaction which forms 2-diazo-1,3-diphenyl-1,3-propanedione, 97, is very interesting to observe; when the substrate (dibenzoylmethane) is added to a CH$_2$Cl$_2$ solution of 1 and tetramethylguanidine, the initially colorless mixture turns orange within seconds, indicating formation of the triazene intermediate. Within 2-3 min, the orange color of the triazene intermediate fades to the yellow color of 97.

Optimized yields for some of the compounds in Tables 4 and 5 as synthesized with tosyl azide are slightly higher, but 1 gives consistently high yields of α-diazo-β-dicarbonyl compounds and α-aryl-α-acyl diazo compounds using uniform procedures. Reagent 1 also gives α-diazo-β-dicarbonyl compounds with only catalytic amounts of base, suggesting that 1 can confer real advantages over tosyl azide for routine preparations or where the substrates are base sensitive.

The remarkable consistency of the yields observed for the various compounds in Table 4 immediately begged the question of whether these base-catalyzed diazo transfer reactions of 1 were actually proceeding quantitatively (as suggested by the GC yields in Table 3) and that a relatively constant amount of product was being lost during the standard workup. Alternative aqueous workups failed to significantly increase the yields, as did increasing the amount of 1 used in the reaction. Changing the reaction solvent to CH$_2$Cl$_2$ raises the yield in the cases of 2-diazo-1,3-diphenyl-1,3-propanedione, 97, and 2-diazo-1,3-indanedione, 104, but for the other 1,3-dicarbonyl compounds studied, ether is the solvent of choice.

The co-product (Et$_2$N)$_3$P=NH$_2^+$ Br$^-$ (89) precipitates from all of the crude reaction mixtures run in ether. Although the literature indicates that 89 is a colorless solid, the material which separates is always colored yellow, orange, or brown, and it is often an oil rather than a solid. These colored materials are virtually immobile on silica.

---

gel. This observation raises the possibility that there are competing side-reactions which produce colored, polar by-products and uniformly reduce the yields for all base-catalyzed diazo transfer reactions to active methylene compounds.

Diazo transfer reactions of tosyl azide with β-keto esters are sometimes complicated by attack of the toluenesulfonamidyl moiety on the ester carbonyl at the stage of the triazene (Figure 23, p. 40). The initial suspicion therefore was that the colored by-products observed in the diazo transfer reactions of 1 arise from a similar process at the stage of the phosphazide or triazene intermediate, 88.

![Proposed Side Reactions Competing with Diazo Transfer](image)

**Figure 40: Proposed Side Reactions Competing with Diazo Transfer**
The studies of Pinchuk and co-workers on phosphorimidic triamides cast doubts on the proposed by-products 107 and 108, however. They found that N"'-unsubstituted hexaalkylphosphorimidic triamides react with carbonyls only under severe conditions. For instance, (Et₂N)₃P=N=NH (87) reacts with neat benzaldehyde only at temperatures over 200° C. Thus it seems unlikely that the phosphorimine nitrogen of 88 would add to a carbonyl to give 106 at room temperature.

Another possibility which could account for the polar by-products is decomposition of phosphazides 88 via a Staudinger reaction process, shown below.

\[
\begin{align*}
\text{88 (Z,Z' = COY, Y = R, Ar, OR, NR₂)} & \rightarrow \\
\text{88b} & \\
109 & \rightarrow \\
110 & \\
\end{align*}
\]

Figure 41: Proposed Staudinger Reaction By-Product Pathway
This mode of decomposition had to be seriously considered because the conventional wisdom holds that all phosphazides are thermally susceptible to the Staudinger reaction decomposition pathway.76

The initial decomposition products of this Staudinger reaction process, 110, could tautomerize to the enolic forms 111 (Figure 42) which would be highly stabilized by intramolecular hydrogen bonding. When the carbonyl substituents in compounds 110 are different, this enolization could occur in two directions, thus giving rise to two different regioisomers of 111. The alternative isomers around the C=C bond of the enolic forms, 112, are also stabilized by hydrogen bonding and would be in equilibrium with 110 and 111. Compounds 111 could also cyclize to give pentacoordinate phosphorus compounds, 113. Thus if the Staudinger decomposition pathway shown in Figure 41 were to occur, a host of equilibrating polar by-products would arise from the diazo transfer reactions of 1, thus matching the bulk properties of the observed precipitates nicely.

Figure 42: Proposed Polar By-Products from the Staudinger Decomposition Pathway

It was not at all certain, however, whether the steric crowding of intermediate (or transition state) 109 would permit this Staudinger decomposition pathway to operate. Phosphazides having three dimethylamino groups on phosphorus are isolable species which decompose via the Staudinger reaction much slower than phosphazides having carbon or alkoxy substituents on phosphorus. Goldwhite and co-workers found that decomposition of 1-methyl-3-tris(dimethylamino)phosphoranylidenetriazene (71, Figure 43) occurs at room temperature with a half life of less than 1h, but that 1-phenyl-3-tris(dimethylamino)phosphoranylidenetriazene (114) is stable at room temperature.
Kinetic studies of the Staudinger decomposition of 114 show a "substantial negative entropy of activation" of \(-39.9 \pm 8 \text{ J mol}^{-1} \text{ K}^{-1}\), implying a high degree of order in the cyclic transition state (i.e. 109).\(^7\) These unfavorable entropic factors which stabilize 114 are further enhanced in compounds such as 88 because of the additional steric bulk of the diethylamino groups and the substituents, Z and Z'. Thus it seemed quite possible that the Staudinger reaction decomposition shown in Figure 41 might be retarded by steric factors to such an extent as to be insignificant.

![Chemical Structures](image)

**Figure 43:** Isolable Phosphazides with Dimethylamino Groups on Phosphorus

In order to assess the stability of phosphazides 88 with diethylamino substituents towards the Staudinger reaction decomposition pathway, it was necessary to prepare model compounds which would not also be prone to the diazo transfer decomposition pathway. For this purpose, methyl- and n-butyllithium were added to 1 to give 1-methyl-3-tris(diethylamino)phosphoranyldenetriazene (115) and 1-butyl-3-tris(diethylamino)phosphoranyldenetriazene (116).

Compounds 115 and 116 are yellow oils which decompose very slowly at room temperature via the Staudinger reaction pathway (vide infra). Neat samples of 115 and 116 take several weeks at 0°C to decompose completely, and the majority of 115 remains unchanged after heating in boiling THF for 20 min. The behavior of these model compounds suggests that phosphazides, formed in the diazo transfer reactions of 1, do not decompose to Staudinger reaction products 110-113 at rates which can compete with the diazo transfer process. Since 115 and 116 do exhibit slow decomposition at room temperature, however, the Staudinger process could not be conclusively ruled out without further evidence.

The polar precipitate which forms during the diazo transfer reactions carried out in diethyl ether was isolated in an attempt to identify the colored impurity(s). A typical diazo transfer reaction was run with 2,4-pentanediene, a slight excess of 1, and a catalytic amount of potassium t-butoxide. This sample reaction was carried out in dry diethyl ether in a flask connected to a gas measuring cylinder. After 16 h, a dark-brown, polar liquid phase had formed in the reaction mixture, which is typical of the by-products observed in most diazo transfer reactions of 1. No gas was evolved from during the reaction, thus suggesting that the proposed Staudinger reaction by-products, 110-113, are minimal, because their formation necessitates the evolution of N₂. The
polar phase was removed from the reaction mixture and examined by NMR after evaporation of the entrapped solvent. The only compounds visible in the NMR spectra of the residue are \((\text{Et}_2\text{N})_3\text{P}=\text{NH}_2^+ \cdot \text{Br}^-\) (\(^3\text{P NMR } \delta 40.5\)), along with unreacted 1 (\(^3\text{P NMR } \delta 36.1\)) and 2,4-pentanedione. There are no discernable peaks in the spectra which can be attributed to any of the proposed by-products (i.e. 107, 108, or 110-113). The \(^1\text{H}, \) and \(^3\text{P NMR} \) spectra of the polar phase of this sample reaction are recorded in Appendix B, Figures 136, and 137. The source of the intense dark color observed in the polar phase remains unclear. The absence of noticeable impurity peaks in the NMR spectra indicate that the colored material is present in trace amounts.

Other than the highly-colored trace impurity(s) in the polar precipitate, the product spectrum of the diazo transfer reactions of 1 is very clean, consisting almost entirely of the diazo compound and the co-product \((\text{Et}_2\text{N})_3\text{P}=\text{NH}_2^+ \cdot \text{Br}^-\) along with minor amounts of unreacted starting materials. The discrepancy between the 70 - 80% yields obtained in the preparative scale reactions and the 90 - 100% yields observed by GC in small-scale reactions remains undetermined.

Several preparative-scale base-catalyzed diazo transfer reactions were also carried out in CH\(_2\)Cl\(_2\), in which 1 is completely soluble. The co-product \((\text{Et}_2\text{N})_3\text{P}=\text{NH}_2^+ \cdot \text{Br}^-\) (89) did not precipitate from CH\(_2\)Cl\(_2\), however, as it did from ether. Washing the crude CH\(_2\)Cl\(_2\) solutions with 25% aqueous ethylene glycol removes most of 89. The yields of the base-catalyzed diazo transfer reactions run in CH\(_2\)Cl\(_2\) are no higher than those run ether except in the cases of 2-diazo-1,3-indanedione and 2-diazo-1,3-diphenyl-1,3-propanedione.
Reactions of 1 with Alkylithiums

As mentioned previously, addition of methyl- or butyllithium to suspensions of 1 at low temperature gives 1-alkyl-3-tris(diethylamino)phosphoranylidenetriazenes, 115 or 116, (Figure 44, p. 81). These reactions are best carried out in THF from -78° C up to 0° C. The 31P NMR chemical shifts of 115 (δ 40.1) and 116 (δ 40.2) correspond closely with the reported 31P shift of δ 40.7 for 1-methyl-3-tris(dimethylamino)phosphoranylidenetriazene (71, Figure 45 below).78

Phosphazides 115 and 116 are yellow oils which are soluble in a variety of organic solvents; 115 and 116 are not hydrolyzed by neutral or alkaline aqueous washes. The thermal stability of compound 115 differs substantially with that of its less sterically encumbered homolog, 71. Goldwhite and co-workers report that 71 decomposes rapidly at room temperature (t1/2 < 1h) to heptamethylphosphorimidic triamide, 117, with no detectable by-products (Figure 45). In contrast, 115 remains mostly unchanged after hours at room temperature or 30 min in boiling THF. Further, when a THF solution of 115 is distilled, there are small amounts of diazomethane in the distillate. The diazomethane was detected by IR and by reaction with benzoic acid giving methyl benzoate and N₂. Butyl phosphazide 116 behaves similarly.

Formation of diazomethane from 115 can be rationalized by the mechanism shown in Figure 45, although a concerted proton transfer and elimination cannot be ruled out. This mechanism formally represents diazo transfer to a carbanion (methyl anion) having no electron-withdrawing groups. The slow rate of decomposition of the phosphazides 115 and 116 via the Staudinger route is certainly due to the high steric encumbrance around the phosphorus atom. This retards nucleophilic attack of N1 on phosphorus, which is the first step of the Staudinger decomposition pathway.

78 ibid., p. 17.
Presumably, even greater steric encumbrance around phosphorus could completely shut down the Staudinger reaction and thus direct the thermal decomposition of phosphazides entirely along the diazo transfer pathway.

![Chemical structures](image)

**Figure 45: Comparison of Thermal Decompositions of 71 and 115**

The stability of phosphazides 115 and 116 provided an opportunity to study some elementary reactions of this functional group. Other than the Staudinger reaction decomposition pathway, little is known about the chemistry of phosphazides. When 115 or 116 are treated with protic acids an exothermic reaction occurs and nitrogen is
rapidly evolved. This reaction results in transfer of the methyl or butyl group from the phosphazide to the conjugate base of the protic acid. For instance, treatment of 116 with benzoic acid gives butyl benzoate. These results are interpreted by the mechanism shown in Figure 46.

Other mechanisms proceeding from 120 were also considered. Intermediate 120 could fragment unimolecularly to give an alkylidiazonium ion and 87. This mechanism is unlikely, however, since the products of carbocation rearrangement were not observed in the case where R = C₃H₇. Another possibility is that 120 eliminates to
give diazomethane or diazobutane which then reacts with the acid. This mechanism should also proceed through a diazonium ion and give rearranged products, though. The absence of rearranged products in the reactions of 116 implies that protonated phosphazides 120 act as excellent alkylating agents for $S_{N2}$ processes. It remains to be seen whether secondary or tertiary alkyl groups on N1 of such phosphazides would give carbocations upon treatment with acid.

Reaction of $p$-bromophenol with 116 at -78° C gives a mixture of O-alkylated and C-alkylated products (Figure 47) in low yield. Presumably the mechanism of this reaction is the same as that shown in Figure 46 except that the nucleophile ($p$-bromophenoxide) is ambident. Compounds which are less acidic than phenol fail to react with 115 and 116. Thus it appears that the basicities of phosphazides 115 and 116 are comparable to phenoxide ion, and that the acid/base reaction to give intermediate 120 becomes the rate limiting step of the mechanism shown in Figure 46 for weaker acids.

Figure 47: Reaction of $p$-Bromophenol with 1-Butyl-3-tris(diethyl-amino)phosphoranylideneriatriazene (116)
The rates of reaction of protic acids with 115 or 116 can be easily observed visually by the rate of gas evolution. All acids which are as acidic or more acidic than phenol react rapidly, whereas the rates of reaction for compounds less acidic than phenol are very slow. The observation that 115 and 116 deprotonate phenol is instrumental in assigning the relative base strengths of the triazene intermediates of the diazo transfer reactions of 1 and tosyl azide (vide ante, p. 69).

In principle, any alkyl carbanion should react with 1 to form stable phosphazides in the same family as 115 and 116. The thermal stability of these sterically hindered phosphazides should permit the further elaboration of the chemistry of this functional group. The tantalizing results obtained in the reactions of 116 with protic acids implies that the chemistry of the phosphazides may indeed prove to be quite rich. The exact mechanism and limitations of the alkylation reaction shown in Figure 46 could be investigated with primary, secondary, and tertiary alkyl groups. One can easily envision the use of such isolable phosphazides as sources of diazonium ions or carbocations.
Reactions of 1 with Enolates

One of the primary goals of this research program was to extend the applicability of the diazo transfer reaction to systems other than active methylene compounds. With few exceptions, the only substrates amenable to diazo transfer are those activated by two electron-withdrawing groups on the methylene carbon. Thus simple ketone and aldehyde enolates, 122, cannot usually be directly transformed into α-diazo ketones or aldehydes, 123, via diazo transfer (Figure 48). This limitation has been circumvented in many cases by first converting the ketone or aldehyde to the α-formyl derivative, 124, which then is amenable to deformylating diazo transfer (vide ante).

![Diagram](image)

**Figure 48:** Failure of Direct Diazo Transfer to Aldehyde and Ketone Enolates Necessitates Deformylating Diazo Transfer
As discussed in the historical section, the failure of traditional diazo transfer reagents with most aldehyde and ketone enolates may well be due to an unfavorable equilibrium (125 $\rightleftharpoons$ 126) at the proton transfer step of the overall mechanism (Figure 49). The side products often observed from reactions of aldehyde and ketone enolates with arylsulfonyl azides arise from triazenes 125. It was hoped that reagent 1 would permit direct conversion of 122 to 123 via diazo transfer because the equilibrium at the proton transfer step (127 $\rightleftharpoons$ 128) would lie further to the right.

Figure 49: Comparison of Proton Transfer Equilibria in the Diazo Transfer Reactions of Tosyl Azide and 1 with Aldehyde and Ketone Enolates
Unfortunately, this expectation was false. Reaction of several ketone enolates with 1 under a variety of conditions gave intractable mixtures of polar products (tentatively identified as 127; see below). Only small amounts of α-diazo ketones were ever detected, and this was only with the hindered enolates of pinacolone and camphor.

The enolates of cyclohexanone, 1-indanone, pinacolone, and camphor were examined. The enolates were generated by slow addition of the ketone to solutions of n-butyllithium in THF or ether at -78° C. Dropwise addition of the enolates to 1 (or vice versa) at low temperature give bright yellow solutions which turn dark red or brown upon warming. In all cases, thin layer chromatography shows that the crude reaction mixtures contain several colored compounds which are highly polar (most are immobile, even with polar eluents).

The presence of several compounds in the crude enolate reaction mixtures was confirmed by NMR: a typical reaction was carried out by adding a solution of cyclohexanone enolate (generated in dry THF at -78° C) dropwise to a small excess of 1 in THF (also at -78° C). After warming slowly to ambient temperature and stirring overnight, most of the THF was evaporated and the oily red residue was examined by NMR. The 1H and 31P NMR spectra (Appendix B, Figures 138, and 139) show the presence of unreacted 1 (31P 836.3) in addition to two major and five minor phosphorus-containing compounds. Although the structures of these compounds cannot be unequivocally assigned from the NMR spectra, it is likely that some or all of the compounds 129 - 132 are present.

The peak at δ 39.8 in the 31P NMR spectrum could indicate either 129, which is the initial product of nucleophilic addition of the enolate carbon to 1, or a tautomer, 130 or 131. Compounds 129 and 130 are 1-alkyl-3-tris(diethylamino)phosphoranylidene-triazenes, and are structurally similar to 115 and 116 (p. 83), which give peaks in the 31P spectra at δ 40.1 and 40.2 respectively. E and Z isomers of 129 - 131 are possible.
Since triazene 129 (or a tautomer) is one of the products suspected to be present in the crude reaction mixture, and since this is the intermediate which is expected to form during a successful diazo transfer reaction, attempts were made to drive triazene 129 to the desired 2-diazocyclohexanone. Treatment with catalytic or equivalent amounts of NH₄Cl or with excess 1M HCl fail to give the desired 2-diazocyclohexanone from the initial adduct(s). Prolonging the reaction time or heating the crude reaction mixtures (refluxing THF) also fail to yield any of the α-diazo ketone. Very similar results were obtained with the enolate of 1-indanone.

Compound 132 is postulated to be the other major product in the crude reaction mixture of cyclohexanone enolate with 1. In a related experiment the oxygen of lithium phenoxide attacked phosphorus displacing the azide group of 1 giving
tris(diethylamino)phenoxyphosphonium azide, 135 (Figure 52, p. 93). Compound 132 would result from a similar displacement of the azide group by the oxygen of cyclohexanone enolate. The $^{31}$P NMR spectrum of the crude reaction mixture of cyclohexanone enolate and 1 shows a prominent peak at $\delta31.1$, which is very close to the chemical shift of $\delta33.8$ observed for 135. The presence of 132 in the crude reaction mixture is therefore proposed by analogy with 135.

N,N-Dimethylazidochloromethyleniminium chloride, 23, reacts with phenols at room temperature to give $o$- and $p$-hydroxyphenyldiazonium chlorides (Figure 17, p. 28). It was hoped that 1 would give similar results. Prolonged stirring of 1 with resorcinol failed to give any reaction, however.

In a similar vein, it was anticipated that phenoxide ion might react with 1 to give 6-diazo-2,4-cyclohexadienone (133) and/or 4-diazo-2,5-cyclohexadieneone (134). These compounds would result from nucleophilic attack of C2 or C4 of the phenoxide ion the terminal nitrogen of 1, followed by the proton-transfer and cleavage steps of diazo transfer.

![Figure 51: Anticipated Reactions of 1 with Phenoxide Ion](attachment:image.png)
Neither of these compounds was observed, however. Rather, the oxygen atom of the phenoxide ion attacked nucleophilically on phosphorus, displacing the azide group from 1 to give tris(diethylamino)phenoxyphosphonium azide (135).

Figure 52: Reaction of 1 with Lithium Phenoxide

Phosphonium salt 135 is a hygroscopic material which could not be separated from excess 1 or lithium phenoxide. The spectra of 135 (Appendix A) show minor amounts of 1 and lithium phenoxide.
Oxidation of Hydrazones with 1

Dropwise addition of THF or CH₂Cl₂ solutions of 1 to the lithium salts of aldehyde or ketone hydrazones, 136, (in THF or pentane) at 0° C results in the rapid, high yield conversion of the hydrazone anion to the corresponding diazo compound, 137 (Equation 9). The reaction liberates an equivalent of nitrogen gas and gives hexaethylphosphorimidic triamide, 87, as a co-product.

Despite the fact that Anselme obtained only modest yields of stabilized aryl diazo compounds from the reaction of tosyl azide with hydrazone anions (Figure 26, p. 46), the present reactions with 1 give excellent yields for varied primary and secondary arylalkyl- and dialkyldiazo compounds (Table 5). The crude yields of the diazo compounds were determined by measurements of the nitrogen evolved during addition of 1 to the hydrazone salts (See Appendix C). The yields of the diazo compounds after
isolation were determined by gas measurements during acid-catalyzed decompositions of the compounds following a standard workup.

Table 5: Diazocompounds Prepared from Hydrazone Anions and 1

<table>
<thead>
<tr>
<th>Diazo Compound</th>
<th>% Formed</th>
<th>% Isolated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenyl</td>
<td>85 ± 2 (4)</td>
<td>67 ± 11 (3)</td>
</tr>
<tr>
<td>Cyclonaphtyl</td>
<td>86 ± 5 (10)</td>
<td>90 ± 4 (5)</td>
</tr>
<tr>
<td>Naphthyl</td>
<td>78 ± 2 (4)</td>
<td>78 ± 2 (4)</td>
</tr>
<tr>
<td>Cyclohexyl</td>
<td>60 ± 2 (2)</td>
<td>53 (1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diazo Compound</th>
<th>% Formed</th>
<th>% Isolated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n-C₈H₁₇</td>
<td>57 ± 3 (3)</td>
<td>46 ± 7 (2)</td>
</tr>
<tr>
<td>Cyclohexyl</td>
<td>77 (1)</td>
<td>77 (1)</td>
</tr>
<tr>
<td>n-C₈H₁₇</td>
<td>74 ± 3 (4)</td>
<td>73 ± 4 (4)</td>
</tr>
<tr>
<td>Phenyl</td>
<td>81 (1)</td>
<td>58 (1)</td>
</tr>
</tbody>
</table>

* Yield of the crude reaction as determined by gas evolution during addition of 1. Number of trials in parenthesis.

† Yield after the standard workup as determined by gas evolution during acid-catalyzed decomposition.

The hydrazones were prepared by the procedure advocated by Holton, wherein the aldehyde or ketone is directly converted to the hydrazone by reaction with a large excess of hydrazine, either neat or in ethanol. The hydrazone anions were prepared

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by addition of the hydrazones to solutions of n-butyllithium in pentane or THF at -78° C.

When THF or CH₂Cl₂ solutions of 1 are added to the hydrazone anions at 0° C, evolution of N₂ begins immediately, and within 15 min the reactions are complete. To remove the co-product 87 the crude reaction mixture is diluted with pentane which has been cooled to -78° C and then washed with several portions of aqueous alkaline ethylene glycol. The last traces of 87 are then precipitated from the hydrocarbon solution of the diazo compound by adding solid CO₂, which reacts with 87 forming the insoluble carbamate, 138 (Figure 53). This low-temperature workup procedure effectively removes the co-product 87 and protects the sensitive diazo compounds from thermal and acid decomposition.

![Figure 53: Conversion of 87 to Its Insoluble Carbamate](image)

liberation of N\textsubscript{2} from the reaction provides a built-in gauge of the crude yield of the diazo compound. With proper prior calibration of the gas measurement apparatus (See Appendix C) the gasimetric determination of the yield is accurate and reproducible. In most instances, the isolated yield of the diazo compound does not differ markedly from the crude yield indicated by the gas evolution during the hydrazone oxidation reaction.

A second advantage is the extremely fast reaction rate. Within fifteen minutes at 0\textdegree\text{C} the reactions have gone to completion. The commonly used metallic oxidants do not give such short reaction times. This aspect is especially important because dialkyl diazo compounds often degrade in only a few hours at 0\textdegree\text{C}.\textsuperscript{81}

Third, there are no metallic by-products such as mercury, lead (II) salts, or manganese (II) oxide, which necessitate special waste separation, disposal or recovery. This can be especially important for large-scale or repetitive preparations. The highly basic co-product \textsuperscript{87} also protects the sensitive diazo compounds from acidic impurities. Metallic oxidants often give co-products which are mild Lewis acids.

Finally, this procedure gives good yields of both primary and secondary aryl and alkyl diazo compounds under uniform reaction conditions. The reaction rates for all of the examples listed in the table above appeared to be roughly the same (as monitored by the rate of N\textsubscript{2} evolution).

A tentative mechanism for this reaction of hydrazone anions with 1 is shown in Figure 54 below. This mechanism is operationally the same as that proposed by Anselme for the reaction of hydrazone anions with tosyl azide (Figure 26, p. 46).

Another possibility (also proposed by Anselme for the tosyl azide reaction) is that pentazene intermediate 140 fragments with loss of 87 to give a short-lived N-azido imine, which quickly loses nitrogen to give diazo compound 137. Substantively, these two mechanistic pathways are identical. A more intriguing possibility is that the hydrazone anions 136 add to 1 on carbon (Figure 55) giving compounds 141, which then cleave via the indicated route.
If the first step were rate-determining, this second mechanism should be sensitive to the steric bulk of the substituents R and R' on the hydrazone carbon. Increasing the steric bulk of these groups should retard the formation of 141. The conversions of hydrazones to diazo compounds 137 proceed at approximately the same rates regardless of the steric bulk of R and R'. Therefore either the mechanism shown in Figure 54 is operative, or if the mechanism shown in Figure 55 is operative then the formation of 141 must not be the rate-limiting step.

In principle, the hydrazone oxidation reactions of 1 could be base catalyzed (Equation 10). This would require either that 87 deprotonate the hydrazone or that the neutral hydrazone attack nucleophilically on 1. In practice, the base catalyzed hydrazone oxidation is very slow. A full equivalent of the hydrazone anion 136 has to be formed in order to obtain good yields.
Equation 10

\[
\text{[Diagram showing chemical reactions and structures]}\]

Equation 10
Summary

The reagent azidotris(diethylamino)phosphonium bromide, 1, is an easily synthesized, safe, storable diazo transfer reagent. Numerous 1,3-dicarbonyl compounds are converted to α-diazo-β-dicarbonyl compounds in good yields using 1. A uniform reaction procedure requiring only catalytic amounts of base was developed. The co-product (Et₂N)₃P=NH₂⁺ Br⁻, 89, is easily removed by passing the reaction solution through silica gel.

Less acidic active methylene compounds, such as α-aryl ketones, are converted to diazo compounds via diazo transfer reactions with 1 promoted with equivalent amounts of tetramethylguanidine.

Reaction of alkyllithiums with 1 afford 1-alkyl-3-tris(diethylamino)-phosphoranylidenetriazenes, which are isolable examples of phosphazides. An interesting reaction of these phosphazides with protic acids results in transfer of the phosphazide alkyl group to the conjugate base of the acid. Further development of this reaction might result in a useful alkylation methodology. Thermal decomposition of these phosphazides results in the formation of small amounts of diazoalkanes.

The addition of 1 to hydrazone anions results in the fast, high-yield conversion to the corresponding diazo compounds. A low-temperature workup procedure gives clean solutions of diazo compounds. This methodology offers distinct advantages over other hydrazone oxidation methods in that (1) the nitrogen liberated during the process provides a built-in gauge of the yield, (2) the reactions are very rapid at low temperatures, (3) the strongly basic by-product protects the diazo compounds from acidic impurities, (4) the workup procedure is mild and fast, and (5) there are no toxic metallic by-products.
CHAPTER III
EXPERIMENTAL SECTION

General Information

$^1$H NMR: All spectra were obtained on Bruker AC-300 or AM-250 Fourier Transform Nuclear Magnetic Resonance Spectrometers at 300.133 or 250.132 MHz respectively. Signals are reported as parts per million downfield from tetramethylsilane at δ 0.00. Residual protic solvents used for internal references on most spectra were CHCl$_3$ (in CDCl$_3$) δ 7.26, d$_5$-acetone (in d$_6$-acetone) δ 2.04, d$_5$-DMSO (in d$_6$-DMSO) δ 2.50.

$^{13}$C NMR: Carbon nuclear magnetic resonance spectra were obtained on the same instruments as the proton spectra at operating frequencies of 75.469 MHz on the AC-300 instrument, or 62.896 MHz on the AM-250 spectrometer. Chemical shifts are reported as parts per million downfield from tetramethylsilane at δ 0.00. The solvent carbon signals used for internal references were as follows: CDCl$_3$ δ 77.0, d$_6$-acetone δ 205.7 and 29.8, d$_6$-DMSO δ 39.7.

$^{31}$P NMR: Phosphorus nuclear magnetic resonance spectra were obtained on a Bruker AM-250 instrument at an operating frequency of 101.256 MHz. Signals are reported in parts per million downfield from 80% H$_3$PO$_4$ at δ 0.00. No internal reference was used for the phosphorus spectra, and therefore the reported chemical shifts are only approximate.
Infrared spectra: Fourier transform infrared spectra were obtained on a Perkin Elmer Model 1600 Fourier Transform single-beam infrared spectrophotometer. Continuous-wave infrared spectra were obtained on a Perkin Elmer Model 457 Grating Infrared Spectrophotometer. Samples were examined either as neat thin films between KBr plates or as solid dispersions in pressed KBr pellets.

Melting points: Open-ended capillary melting tubes were used for all melting point determinations. Stem corrections were not made for the thermometer used for the melting point determinations.

Boiling points: Boiling points of bulk liquids were determined during distillation.

Rotary evaporation: Solvents were typically removed on a rotary evaporator connected to a laboratory house vacuum system unless the experimental text specifically states that higher vacuum was used. The house vacuum varied between 40 and 80 torr.

Solvents: Commercially available "reagent grade" or "technical grade" solvents were routinely used without prior purification. When the experimental text states that a solvent was "dry" or "anhydrous," the commercial solvent was distilled from an appropriate desiccant prior to use. Ether was typically dried by distillation from sodium, THF from lithium aluminum hydride, acetonitrile and benzene from calcium hydride, and amines from barium oxide.
Synthesis of Azidotris(dialkylamino)phosphonium Bromides

Azidotris(dimethylamino)phosphonium bromide (2)

Chemical Abstracts Nomenclature: Azidotris(N-methylmethanaminato)phosphorus (+1) Bromide

A solution of bromine (1.00 mL, 19.5 mmol) in dry acetonitrile (25 mL) was added dropwise to a solution of hexamethylphosphorustriamide (3.60 mL, 19.81 mmol) in dry acetonitrile (50 mL) over a period of about 10 min. A faint bromine color persisted at the end of the addition. As soon as the bromine addition was complete, sodium azide (1.234 g, 18.99 mmol) was added along with a few milligrams of 18-Crown-6, and the reaction mixture was stirred at ambient temperature overnight under argon. The sodium bromide and unreacted sodium azide were removed by filtration. Rotary evaporation of the filtrate left a sticky yellow residue which was rinsed with dry THF (3 x 20 mL). Drying the solid product in vacuo gave 4.77 g (88%) of off-white azidotris(dimethylamino)phosphonium bromide, mp 174° C, which decomposes with gas evolution.

$^1$H NMR (d$_6$-DMSO) δ 2.83 (d, J = 11.02 Hz, -N(CH$_3$)$_2$).

$^{13}$C NMR (d$_6$-DMSO) δ 36.23 (d, J=17.17 Hz, -N(CH$_3$)$_2$).

$^{31}$P NMR δ 36.61.

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IR (KBr pellet) 3000, 2930, 2830, 2167, 1625, 1490, 1460, 1403, 1319, 1295, 1272, 1170, 1070, 1012, 785, 770, 752, 735, 562 cm\(^{-1}\).

The 250 MHz \(^1\)H, 63 MHz \(^{13}\)C, and 101 MHz \(^{31}\)P FTNMR spectra of 2 are recorded in Appendix A, Figures 56-58.

**Hexaethylphosphorustriamide (142)**

Diethylamine (1500 mL, 14.5 mol), which had been freshly distilled from BaO, was placed in a 3-neck flask equipped with an addition funnel, condenser, and mechanical stirrer.

Phosphorus trichloride (100 mL, 1.15 mol) was added dropwise over 12 h to the diethylamine at 0° C. After the addition was complete, the reaction mixture was stirred overnight at ambient temperature under argon, refluxed for 4 h, cooled, and filtered. The filter cake was thoroughly washed with several portions of petroleum ether. The filtrate was evaporated on a rotary evaporator, giving 267 g (94%) of crude hexaethylphosphorustriamide as a pale yellow liquid. (The crude product was satisfactory for the preparation of 1 without further purification).

Vacuum distillation of the crude product through a 30 cm x 2 cm Vigreux column gave 142 as a colorless liquid, bp 66-69° C/0.15 torr (lit. 80-90° C/ 1.0 torr). The yield of distilled material was 250 g (88%).

\(^1\)H NMR: (\(d_6\)-acetone) \(\delta\) 1.02 (unresolved m, 18H, \(-N(CH_2CH_3)_2\)), 2.91 (unresolved m, 12H, \(-N(CH_2CH_3)_2\)).

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13C NMR: (d$_6$-acetone) $\delta$ 14.18 (s, -N(CH$_2$CH$_3$)$_2$), 39.79 (d, J$_{C/P}$ = 19.7 Hz, N(CH$_2$CH$_3$)$_2$).

$^{31}$P NMR: (d$_6$-acetone) $\delta$ 117.45

The 101 MHz $^{31}$P, and 63 MHz $^{13}$C FTNMR spectra of 142 are recorded in Appendix A, Figures 59,60.

**Azidotris(diethylamino)phosphonium bromide (1)**

Chem. Abst. Nomenclature: Azidotris(N-ethylethanaminato)phosphorus (+1) Bromide

Crude hexaethylphosphorus-triamide (189 g, 0.76 mol) was dispersed in dry acetonitrile (2000 mL) by rapid mechanical stirring. Bromine (38 mL, 0.74 mol) was added dropwise while the reaction mixture was cooled in an ice bath. One hour after the bromine addition was complete, sodium azide (52 g, 0.80 mol) was added to the solution along with 18-Crown-6 (0.4 g, 1.5 mmol). The reaction mixture was stirred mechanically for 3 d at ambient temperature.

After removing the unreacted sodium azide and the co-product sodium bromide by suction filtration, the solvent was removed from the filtrate on a rotary evaporator at at < 3 torr. The crude product was recrystallized twice at low temperature from dry THF and dried in vacuo to give 212.1 g (77.6%) of 1 as white, hygroscopic crystals, mp 90-92° C, decomposition point >130° C.

$^1$H NMR (CDCl$_3$) $\delta$ 1.31 (t, J = 7.1 Hz, 18H, -N(CH$_2$CH$_3$)$_2$), 3.32 (d of q, J$_{H/P}$ = 12.5 Hz, 12H, -N(CH$_2$CH$_3$)$_2$).

$^{13}$C NMR (CDCl$_3$) $\delta$ 13.52 (d, J$_{C/P}$ = 4.5 Hz, -N(CH$_2$CH$_3$)$_2$), 40.63 (d, J$_{C/P}$ = 17.6 Hz, -N(CH$_2$CH$_3$)$_2$); $^{31}$P NMR (CDCl$_3$) $\delta$ 36.15.
FTIR (KBr pellet) 2976, 2935, 2160 (N=N=N), 1734, 1624, 1460, 1386, 1286, 1214, 1161, 1098, 1061, 1028, 979, 954, 925, 807, 752, 712, 637 cm⁻¹.

The 250 MHz ¹H, 63 MHz ¹³C, and 101 MHz ³¹P FTNMR and FTIR spectra of 1 are recorded in Appendix A, Figures 61-64.

**Tripiperidinophosphine (143)⁸⁵,⁸⁴**

Freshly distilled piperidine (200 mL, 2.02 mol) was dissolved in anhydrous ether (1500 mL) in a 3-neck flask which was equipped with a mechanical stirrer, addition funnel, and condenser. A solution of PCl₃ (20.0 mL, 0.23 mol) in dry ether (200 mL) was added dropwise under argon at 0° C. After the addition, the reaction mixture was stirred for 1 h at 0° C, 1 h at reflux, and then overnight at ambient temperature.

The piperidine hydrochloride was removed by suction filtration and rinsed with ether (500 mL). The filtrate was set aside, and the filter cake was dissolved in 1 N NaOH (1000 mL) and extracted with ether (6 x 100 mL). The extracts were washed with water, dried (MgSO₄) and combined with the original reaction filtrate. Rotary evaporation at ~40° C gave crude 143 as a cloudy oil which solidified upon standing at 0° C. Reprecipitation from pentane (200 mL) at -78° C and drying in vacuo over CaSO₄ gave 53.2 g (82%) of 143 as a white powder, mp 37.2-38.3° C (lit. 37-38° C).

¹H NMR (d₆-acetone) δ 1.43 (m, 2H, -CH₂-), 1.49 (m, 4H, -NCH₂CH₂-), 2.80 (m, 4H, -NCH₂-).

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13C NMR (d6-acetone) δ 25.63 (s, -NCH2CH2CH2-), 27.02 (d, J_C/P = 4.9 Hz, 
-NCH2CH2-), 46.88 (d, J_C/P = 16.6 Hz, -NCH2-); 31P NMR δ 114.76.

The 250 MHz 1H, 63 MHz 13C, and 101 MHz 31P FTNMR spectra of 143 are
recorded in Appendix A, Figures 65-67.

Azidotripiperidinophosphonium bromide (3)

Tripiperidinophosphine (16.8 g, 59.3 mmol) was suspended in dry
acetonitrile (100 mL) to which was
added a solution of bromine (3.00 mL, 58.6 mmol) in dry acetonitrile (50 mL)
over a period of ~30 min. Sodium azide
(4.22 g, 64.9 mmol) and 18-Crown-6
(0.02 g, 0.08 mmol) were then added, and the mixture was stirred overnight at room
temperature under an argon atmosphere. The reaction mixture was filtered, and the
solvent was removed by rotary evaporation at ~60°C. The residue was rinsed with dry
THF (3 x 15 mL), leaving white crystals which were dried briefly in vacuo. The yield
of 3 was 19.3 g (81%); mp 152°C, decomposing with gas evolution.

1H NMR (d6-DMSO) δ 1.57 (multiplet appearing as a very broad singlet, 6H,
-NCH2CH2CH2-), 3.20 (unresolved multiplet, 4H, -NCH2CH2).

13C NMR (d6-DMSO) δ 22.93 (s, -NCH2CH2CH2), 25.20 (d, J_C/P = 15.9 Hz, 
-NCH2CH2), 45.31 (s, -NCH2). 31P NMR (d6-DMSO) δ 29.15.

IR (KBr pellet) 2940, 2860, 2164 (N=N=N), 1470, 1454, 1447, 1388, 1350, 1296,
1290, 1202, 1171, 1100, 1089, 1062, 1028 (P=N), 971, 861, 754, 720 cm⁻¹.
The 250 MHz 1H, 63 MHz 13C, and 101 MHz 31P FTNMR spectra of 3 are recorded in
Appendix A, Figures 67-69.
Diazo Transfer Reactions of 1

**Standard Procedure A: Base-Catalyzed Diazo Transfer to 1,3-Dicarbonyl Compounds**

The 1,3-dicarbonyl compound is combined with 1 (~1.1 equiv) in anhydrous diethyl ether (20 mL per gram of 1) at room temperature. Most of 1 will not dissolve under these conditions. Catalytic (<0.1 equiv.) amounts of potassium t-butoxide powder are added to the suspension until a color change is apparent. The mixture is stirred in the dark for 12 to 16 h while being protected from atmospheric moisture.

At the end of the reaction period, the co-product 89 along with trace amounts of colored, polar by-products will have separated as a solid or an oil. If an oil forms, Na$_2$SO$_4$ is added and stirring is continued until the oil solidifies or becomes viscous. The ether solution is then filtered or decanted from the polar phase and forced rapidly through a 10-cm-deep plug of silica gel, eluting with an additional volume of ether. The total eluent is evaporated, leaving the product diazo compound. Yields for this procedure are typically 70 - 80%. The diazo compounds so obtained are usually >95% pure.

In some cases using CH$_2$Cl$_2$ as the solvent or using an aqueous workup gave better results. These deviations from the standard procedure are noted in the experimental details for the individual diazo compounds.

**Standard Procedure B: Tetramethylguanidine-Promoted Diazo Transfer to Active Methylene Compounds**

A solution of the active methylene compound in CH$_2$Cl$_2$ (5 mL per mmol of solute) is added to a mixture of 1 (~1.1 equiv) and tetramethylguanidine (~1.2 equiv) also in CH$_2$Cl$_2$ (10 mL per gram of 1) at room temperature. The reaction is monitored by TLC. Reactions with 1,3-dicarbonyl compounds are typically complete in 10 min using this procedure. Less acidic methylene compounds take longer.
After all of the active methylene compound has been consumed (5 min to 12 h depending upon the substrate) the reaction mixture is washed with 0.25 M NH₄Cl (3 volumes), 1 M NaOH (1 volume), H₂O (1 volume), and saturated aqueous NaCl (1 volume). The CH₂Cl₂ solution of the diazo compound is then dried briefly over MgSO₄, filtered, and the solvent is removed on a rotary evaporator. The crude product contains 5-10 mol% of (Et₂N)₃P=NH₂⁺ Br⁻ (89) and (Et₂N)₃P=NH (87) as impurities.

Pure material may be obtained by rapidly passing the crude product through a short column of silica gel, eluting with CH₂Cl₂. The impurities are usually highly polar and do not elute. The yield of pure diazo compound obtained by this procedure is typically ~80%. If the column chromatography is performed, the NaOH, H₂O, and aqueous NaCl washes may be omitted.

**Synthesis of 3-Diazo-2,4-pentanedione (95) with 1**

2,4-Pentanedione (1.00 mL, 9.74 mmol) and 1 (3.6 g, 9.7 mmol) gave 95 as a yellow-orange liquid using the standard procedure “A” for 1,3-dicarbonyl compounds. Two trials gave 0.86 g (70%) and 0.99 g (81%). The spectra match those in the literature.86a

1H NMR (CDCl₃) δ 2.44 (s, 6H, -CH₃).

13C NMR (CDCl₃) δ 28.04 (-CH₃), 84.28 (C=N₂), 187.95 (C=O).

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IR (thin film): 3000, 2125 (diazo band), 1660, 1416, 1372, 1311, 1244, 1137, 1053, 1028, 969, 937, 662 cm⁻¹.

The 250 MHz ¹H and 63 MHz ¹³C FTNMR spectra of 95 are recorded in Appendix A, Figures 70 and 71.

**Synthesis of 4-Diazo-3,5-heptanedione (96) with I**

Reaction of 3,5-heptanedione (2.00 mL, 14.8 mmol) with I (5.5 g, 14.8 mmol) using the standard procedure “A” for 1,3-dicarbonyl compounds produced 96 as a yellow-orange liquid. Yields were 1.53 g (67%), and 0.75 g (66%, at half scale).

Compound 96 was obtained in higher yield by substituting an aqueous workup for the flash chromatography of the standard procedure: the crude reaction mixture was filtered to remove the (Et₂N)₃P=NH₂⁺ Br⁻ and the filtrate was concentrated on a rotary evaporator to give a dark red oil. The oil was dissolved in a mixture of petroleum ether (25 mL) and ether (25 mL) and then extracted with water (25 mL). The organic phase was removed and dried over MgSO₄. Filtration and rotary evaporation gave 1.94 g (85%) of 96 as an orange liquid. The product obtained by this workup contained traces of (Et₂N)₃P=NH₂⁺ Br⁻.

¹H NMR (CDCl₃) δ 1.15 (t, J = 7.3 Hz, 6H, -CH₃), 2.78 (q, J = 7.3 Hz, 4H, -CH₂-).

¹³C NMR (CDCl₃) δ 7.69 (-CH₃), 33.77 (-CH₂CH₃), 82.64 (C=N₂), 191.45 (C=O).
IR (thin film): 2986, 2932, 2899, 2868, 2115 (diazo band), 1667, 1450, 1375, 1254, 1207, 1081, 1033, 1012, 898, 808 cm⁻¹.

The 250 MHz ¹H and 63 MHz ¹³C FTNMR spectra of 96 are recorded in Appendix A, Figures 72 and 73.

Synthesis of 2-Diazo-1,3-diphenyl-1,3-propanedione (97) with 1

Dibenzoylmethane (2.00 g, 8.91 mmol) upon reaction with 1 (3.62 g, 9.81 mmol) under the conditions of procedure “A” gave 1.58 g (71%) of 97 as a yellow solid.

Procedure “B” gave 0.90 g (76%) of 97 using the following amounts of reagents: dibenzoylmethane (1.06 g, 4.72 mmol), tetramethylguanidine (0.70 g, 6.0 mmol), and 1 (2.0 g, 5.42 mmol).

A deviation from the standard procedures gave a higher yield. Dibenzoylmethane (1.17 g, 5.10 mmol) and 1 (2.00 g, 5.42 mmol) were dissolved in CH₂Cl₂ (50 mL) at 0° C. Potassium tert-butoxide (0.05 g, 0.4 mmol) was added and the solution was stirred overnight as the solution slowly warmed to ambient temperature. Dilution with pentane (50 mL) and cooling to 0° C caused partial precipitation of the (Et₂N)₃P=NH₂⁺ Br⁻. The mixture was filtered, washed with 33% aqueous ethylene glycol (5 x 25 mL) and saturated NaCl (25 mL), and dried (MgSO₄). Rotary evaporation at 0° C gave 1.25 g (98%) of 97. The spectra showed 8 mol% (Et₂N)₃P=NH₂⁺ Br⁻, thus the true yield was 90%.

¹H NMR (CDCl₃) δ 7.29 - 7.35 (m, 4H, m-ArH), 7.42 - 7.48 (m, 2H, p-ArH), 7.56 - 7.60 (m, 4H, o-ArH).
The 250 MHz $^1$H and 63 MHz $^{13}$C FTNMR spectra of 97 are recorded in Appendix A, Figures 74 and 75.

**Synthesis of 2-Diazoo-1,3-indanedione (104)**

1,3-Indanedione (0.745 g, 5.10 mmol) and 1 (2.00 g, 5.42 mmol) were dissolved in CH$_2$Cl$_2$ (50 mL) at 0°C. Potassium $t$-butoxide (0.01 g, 0.1 mmol) was added and the solution turned dark purple instantly.

After stirring overnight, the mixture was diluted with pentane (50 mL), cooled to 0°C, and washed with 33% aqueous ethylene glycol (5 x 25 mL) and saturated NaCl (25 mL). The organic phase was dried (MgSO$_4$) and evaporated onto silica gel on a rotary evaporator. Chromatography through a 1.5 x 25 cm column of Silica Gel 60 (70-240 mesh), eluting with CH$_2$Cl$_2$ and ethyl acetate gave yellow 104 as the first compound off of the column. Rotary evaporation of the eluents and drying in vacuo gave 0.738 g (84%) of 104 as a bright yellow solid. Several colorful products followed 104 during the chromatography; these compounds were not characterized.

$^1$H NMR (CDCl$_3$) $\delta$ 7.72 - 7.77 (m, 2H, m-ArH), 7.79 - 7.7.85 (m, 2H, o-ArH).

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13C NMR (CDCl₃) δ 122.68 (m- Ar), 134.75 (o-Ar), 137.12 (ipso-Ar), 182.07 (C=O). The 250 MHz 1H and 63 MHz 13C FTNMR spectra of 104 are recorded in Appendix A, Figures 76 and 77.

**Synthesis of Ethyl 2-Diazo-3-oxobutanoate (98) with 1**

Reaction of ethyl acetoacetate (2.00 mL, 15.69 mmol) and 1 (6.37 g, 17.3 mmol) under the conditions for procedure “A” for 1,3-dicarbonyl compounds gave ethyl 2-diazoacetoacetate, 98, as a yellow liquid. Yields for the standard procedure were 1.86 g (75%), and 2.18 g (89%).

As an alternative to the flash chromatography of procedure “A”, the following aqueous workup also gave good results: the crude reaction mixture was first filtered to remove the (Et₂N)₃P=NH₂⁺ Br⁻ precipitate. The filtrate was then concentrated to a volume of about 10 mL on a rotary evaporator, diluted with ether (25 mL), and extracted with water (25 mL). Drying of the organic phase (MgSO₄) and rotary evaporation gave 1.99 g (81%) of 98 containing traces of (Et₂N)₃P=NH₂⁺ Br⁻.

1H NMR (CDCl₃) δ 1.28 (t, J = 7.1 Hz, 3H, -CH₂CH₃), 2.42 (s, 3H, CH₃CO-), 4.25 (q, J = 7.1 Hz, 2H, -CH₂CH₃).

13C NMR (CDCl₃) δ 14.06 (-OCH₂CH₃), 27.90 (CH₃CO-), 61.16 (-OCH₂CH₃), 76.02 (C=N₂), 161.13 (O=C=O), 189.81 (CH₃C=O).

IR (thin film): 2975, 2927, 2135 (diazo band), 1717, 1659, 1375, 1324, 1253, 1176, 1154, 1077, 1025, 968, 746, 632 cm⁻¹.

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The 250 MHz $^1$H and 63 MHz $^{13}$C FTNMR spectra of 98 are recorded in Appendix A, Figures 78 and 79.

Synthesis of Ethyl 2-Diazo-3-oxo-3-phenylpropanoate (99) with 1

Ethyl benzoylacetate (2.00 mL, 11.5 mmol) and 1 (4.69 g, 12.7 mmol) gave diazo compound 99 as a yellow liquid using the standard procedure "A". The yield was 1.79 g (71%). The NMR spectra showed traces of unreacted ethyl benzoylacetate.

Procedure "B" also gave very good results with this substrate. Ethyl benzoylacetate (0.96 g, 5.00 mmol), 1 (2.0 g, 5.4 mmol), and tetramethylguanidine (0.7 g, 6.0 mmol) in CH$_2$Cl$_2$ (40 mL) gave 0.87 g (80%) of 99 as a yellow oil after flash chromatography.

$^1$H NMR (CDCl$_3$) $\delta$ 1.23 (t, $J = 7.1$ Hz, 3H, -CH$_2$CH$_3$), 4.22 (q, $J = 7.1$ Hz, 2H, -CH$_2$CH$_3$), 7.36-7.43 (m, 2H, m-ArH), 7.46-7.53 (m, 1H, p-ArH), 7.60-7.64 (m, 2H, o-ArH).

$^{13}$C NMR (CDCl$_3$) $\delta$ 13.98 (-OCH$_2$CH$_3$), 61.39 (-OCH$_2$CH$_3$), 76.02 (C=N$_2$), 127.64, 128.14 (o,m-Ar), 132.03 (p-Ar), 136.93 (ipso-Ar), 160.78 (O-C=O), 186.64 (C$_6$H$_5$-C=O).

IR (thin film): 3055, 2975, 2925, 2905, 2140, 1725, 1690, 1630, 1600, 1580, 1450, 1373, 1310, 1270, 1180, 1120, 1020, 943, 925, 789, 748, 709, 795 cm$^{-1}$.

The 250 MHz $^1$H and 63 MHz $^{13}$C FTNMR spectra of 99 are recorded in Appendix A, Figures 80 and 81.
Synthesis of Ethyl 2-Diazo-3-oxohexanoate (100) with 1

Procedure “A” with ethyl butyroacetate (2.00 mL, 12.70 mmol) and 1 (4.7 g, 12.7 mmol) gave 100 as a yellow liquid in yields of 1.52 g (65%), 1.84 g (79%), and 1.88 g (81%). The spectra showed traces of unreacted ethyl butyroacetate.

\[ \begin{align*}
\text{H NMR (CDCl}_3 \text{)} & \delta 0.97 (t, J = 7.4 \text{ Hz, } 3 \text{H, } -CH_2CH_2CH_3), 1.34 (t, J = 7.1 \text{ Hz, } 3 \text{H, } -OCH_2CH_3), 1.67 (t \text{ of q, } J = 7.4, 7.4 \text{ Hz, } 2 \text{H, } -CH_2CH_2CH_3), 2.83 (t, J = 7.4 \text{ Hz, } 2 \text{H, } -CH_2CH_2CH_3), 4.30 (q, J = 7.1 \text{ Hz, } 2 \text{H, } -OCH_2CH_3). \\
\text{C NMR (CDCl}_3 \text{)} & \delta 13.62 (-CH_2CH_2CH_3), 14.22 (-OCH_2CH_3), 17.74 (-CH_2CH_2CH_3), 41.98 (-CH_2CH_2CH_3), 61.21 (-OCH_2CH_3), 75.85 (C=N_2), 161.29 (O-C=O), 192.75 (CH_2-C=O).
\end{align*} \\
\text{IR (thin film): } 2962, 2929, 2870, 2126 (diazo band), 1718, 1656, 1373, 1305, 1214, 1141, 1098, 1026, 747 \text{ cm}^{-1}.

The 250 MHz \( ^1 \text{H} \) and 63 MHz \( ^{13} \text{C} \) FTNMR spectra of 100 are recorded in Appendix A, Figures 82 and 83.
Synthesis of Diethyl 2-Diazomalonate (101) with 1

Diethyl malonate (2.00 mL, 13.2 mmol) gave 101 as a pale yellow liquid upon reaction with 1 (4.9 g, 13.3 mmol) using standard procedure "A" for 1,3-dicarbonyls. Diazo ester 101 was obtained in yields of 1.91 g (78%), 1.94 g (79%), and 1.60 g (63%).

An aqueous workup, previously described for 98, gave 101 in 81% yield. The product obtained from the aqueous workup contained a small amount of (Et₂N)₃P=NH₂⁺ Br⁻.

1H NMR (CDCl₃) δ 1.32 (t, J = 7.1 Hz, 3H, -CH₃), 4.31 (q, J = 7.1 Hz, 2H, -CH₂).

13C NMR (CDCl₃) δ 13.98 (-OCH₂CH₃), 61.23 (-OCH₂CH₃), 65.02 (C=N₂), 160.66 (O-C=O).

IR (thin film): 2985, 2935, 2905, 2130 (diazo band), 1762, 1738, 1691, 1467, 1448, 1397, 1376, 1323, 1272, 1193, 1171, 1098, 1021, 762 cm⁻¹.

The 250 MHz ¹H and 63 MHz ¹³C FTNMR spectra of 101 are recorded in Appendix A, Figures 84 and 85.

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Synthesis of Triethyl Diazophosphonoacetate\textsuperscript{90} (102) with 1

The reaction of 1 (3.72 g, 10.1 mmol) with triethyl phosphonoacetate (2.00 mL, 10.1 mmol) by procedure “A” gave 102 as a pale yellow liquid. Yields were 1.60 g (63\%) and 1.94 g (77\%).

\textsuperscript{1}H NMR (CDCl\textsubscript{3}) \(\delta\) 1.27 (t, J = 7.1 Hz, 3H, \(-\text{CO}_2\text{CH}_2\text{CH}_3\)), 1.33 (d of t, \(J_{H/H} = 7.0\), \(J_{P/H} = 0.8\) Hz, 6H, POCH\(_2\)CH\(_3\)), 4.12-4.28 (m, 6H, -CO\(_2\)CH\(_2\) & -POCH\(_2\)).

\textsuperscript{13}C NMR (CDCl\textsubscript{3}) \(\delta\) 14.19 (-CO\(_2\)CH\(_2\)CH\(_3\)), 16.01 (d, \(J_{C/P} = 8.6\) Hz, -POCH\(_2\)CH\(_3\)), 61.56 (-CO\(_2\)CH\(_2\)CH\(_3\)), 63.52 (d, \(J_{C/P} = 5.9\) Hz, -POCH\(_2\)CH\(_3\)), 65.70 (C=N\(_2\)), 163.27 (d, \(J_{C/P} = 12.5\) Hz, O-C=O); \textsuperscript{31}P NMR (CDCl\textsubscript{3}) \(\delta\) 9.17.

IR (thin film): 2980, 2935, 2905, 2125 (diazo band), 1705, 1393, 1372, 1288, 1220, 1168, 1100, 1027, 982, 800, 749, 735 cm\(^{-1}\).

The 250 MHz \textsuperscript{1}H, 63 MHz \textsuperscript{13}C, and 101 MHz \textsuperscript{31}P FTNMR spectra of 102 are recorded in Appendix A, Figures 86-88.

Synthesis of 5-Diazo-1,3-dimethyl-6-oxo-2,4-pyrimidinedione (103) with 1

To a suspension of 1,3-dimethyl-6-oxo-2,4-pyrimidinedione (2.00 g, 12.8 mmol) and 1 (5.20 g, 14.1 mmol) in dry ether (100 mL) was added potassium tert-butoxide (0.02 g). The mixture was stirred for 48 h at \(-25^\circ\) C.

\textsuperscript{90} Maas, G.; Regitz, M. Chem. Ber. 1976, 109, 2039.
Sodium sulfate (1.0 g) and ammonium sulfate (0.2 g) were added and stirring of the suspension was continued for 24 h. The reaction mixture was filtered and the precipitate was washed with several portions of water. The bright orange powder was dried *in vacuo* over P$_2$O$_5$ overnight, giving 1.78 g (76%) of 103. The spectra match those reported in the literature.\textsuperscript{91}

$^1$H NMR (d$_6$-DMSO) δ 3.16 (s, 6H, -CH$_3$).

$^{13}$C NMR (d$_6$-DMSO) δ 28.08 (-NCH$_3$), 150.40 (NC=ON), 158.36 (CC=ON).

IR (KBr pellet): 2915, 2155, 1712, 1476, 1425, 1387, 1297, 1251, 1078, 761, 752, 700 cm$^{-1}$.

The 250 MHz $^1$H and 63 MHz $^{13}$C FTNMR spectra of 103 are recorded in Appendix A, Figures 89 and 90.

**Synthesis of Diazoanthrone (106)\textsuperscript{92} with 1**

Anthrone (0.97 g, 5.00 mmol) was added to 1 (2.0 g, 5.4 mmol), and tetramethylguanidine (0.7 g, 6.09 mmol) in CH$_2$Cl$_2$ (30 mL). An exothermic reaction gave a dark solution from which 0.966 g (88%) of 106 was isolated by the workup of procedure “B”.

$^1$H NMR (CDCl$_3$) δ 7.26 - 7.45 (m, 4H, H$_{d,f}$), 7.68 - 7.73 (m, 2H, H$_e$), 8.54 - 8.57 (d, J = 7 Hz).


\textsuperscript{92} Regitz, M. *Chem. Ber.* 1964, 97, 2742.
13C NMR (CDCl₃) δ 120.63 (Cf), 125.27 (Cd), 128.40 (Cg), 129.00 (Ce), 129.77 (Cb), 132.92 (Cc), 180.02 (Ca); C₇ (C=N₂) did not give an observable signal.

FTIR: (KBr pellet) 2066 (diazo band), 1734, 1641, 1605, 1594, 1486, 1303, 1271, 1168, 932, 752, 670, 624 cm⁻¹.

The 250 MHz ¹H and 63 MHz ¹³C FTNMR and FTIR spectra of 106 are recorded in Appendix A, Figures 91-93.

Synthesis of (4-Methoxybenzoyl)phenyldiazomethane (105) with 1

Application of procedure “B” to p-methoxy-2-phenylacetophenone (1.13 g, 5.0 mmol), 1 (2.0 g, 5.4 mmol), and tetramethylguanidine (0.70 g, 6.1 mmol) gave 0.637 g (51%) of 105 as an orange powder.

Compound 105 was the third compound to elute during the column chromatography of the workup (a 1.5 x 10 cm column of silica gel 60, 70-230 mesh was used with CH₂Cl₂ as the eluent). Two minor impurities eluted in the first 25 mL and were discarded.

¹H NMR (CDCl₃) δ 3.85 (s, 3H, -OCH₃), 6.87 - 6.91 (m, 2H, H₇), 7.22 - 7.27 (m, 1H, H₄), 7.37 - 7.46 (m, 4H, Hₖ, i), 7.59 - 7.62 (m, 2H, H₉).

¹³C NMR (CDCl₃) δ 55.39 (-OCH₃), 72.36 (Ca), 113.69 (Ch), 126.20 (C₉), 126.85 (Cₖ), 129.00 (Cₗ), 130.06 (Cd), 162.47 (Cf), 187.26 (Cb). Cₖ and Cₗ could not be discriminated from impurity peaks.
FTIR: (KBr pellet) 3057, 3016, 2971, 2931, 2842, 2085 (diazo band), 1624, 1613, 1597, 1573, 1510, 1497, 1454, 1444, 1415, 1353, 1330, 1306, 1285, 1261, 1241, 1190, 1174, 1122, 1072, 1022, 860, 844, 788, 760, 693, 642, 622 cm⁻¹.

The 250 MHz $^1$H and 63 MHz $^{13}$C FTNMR and FTIR spectra of 105 are recorded in Figures 94-96.
Reaction of 1 with Alkylithiums

1-Methyl-3-tris(diethylamino)phosphoranyldenetriazene (115)

Reagent 1 (2.00 g, 5.4 mmol) was suspended in dry THF (50 mL) at -78° C. A suspension of methyllithium (5.04 mmol) in pentane (20 mL) was added dropwise. The mixture was stirred at -78° C for 15 min and at 0° C for 1 h.

The reaction mixture was washed with cold water (5 x 25 mL), and dried over Na₂CO₃ at 0° C. Removal of the solvent on a rotary evaporator below 0° C followed by high vacuum (0.5 torr) for 30 min gave 0.80 g (52%) of 115 as a yellow oil.

1H NMR (CDCl₃) δ 0.98 (t, J = 7.1 Hz, 18H, -NCH₂CH₃), 2.99 (d of q, Jₗ/ₘ = 9.9 Hz, Jₘ/ₚ = 7.1 Hz, 12H, -NCH₂CH₃), 3.11 (s, 3H, =NCH₃).

13C NMR (CDCl₃) δ 13.44 (d, Jₗ/C = 2.1 Hz, -NCH₂CH₃), 39.39 (d, Jₗ/P = 2.9 Hz, -NCH₂CH₃), 39.77 (d, Jₗ/P = <1 Hz, =NCH₃).

31P NMR (CDCl₃) δ 40.1.

FTIR: (thin film) 2971, 2931, 2873, 1459, 1380, 1352, 1297, 1207, 1179, 1141, 1059, 1020, 949, 792, 709, 696.

The 250 MHz 1H, 101 MHz 31P, and 63 MHz 13C FTNMR spectra of 115 are recorded in Appendix A, Figures 97-99.
**1-Butyl-3-tris(diethylamino)phosphoranylidenedetriazene (116)**

A solution of 1 (2.0 g, 5.4 mmol) in dry THF (40 mL) was cooled to -78° C; n-butyllithium (5.0 mmol) in pentane (20 mL) was added dropwise. The mixture was then warmed to 0° C for 30 min.

Cold pentane (75 mL, -78° C) was then added, and the resulting solution was extracted with 33% aqueous ethylene glycol (5 x 25 mL). The organic phase was dried at 0° C (MgSO₄), and the solvent was removed on a rotary evaporator below 0° C. High vacuum (0.3 torr) was applied for 30 min, leaving 1.67g (96%) of pale yellow oil.

The NMR spectra showed that some THF (19 mol%) and ethylene glycol (17 mol%) remained entrapped in the oil. By NMR integration the product was 64 mol% (89 wt%) 116, thus the true yield was 86% (96% by weight x 89 wt% purity).

**¹H NMR (CDCl₃) δ 0.85 (t, J = 7.3 Hz, 3H, -CH₂CH₂CH₂CH₃), 1.01 (t, J = 7.1 Hz, 18H, -NCH₂CH₃), 1.39 (m, 2H, -CH₂CH₂CH₂CH₃), 1.73 (m, 2H, -CH₂CH₂CH₂CH₃), 3.01 (d of q, JₗH/P = 10.0 Hz, JₗH/H = 7.1 Hz, 12H, -NCH₂CH₃), 3.36 (t, J = 7.1 Hz, 2H, -CH₂CH₂CH₂CH₃).

**¹³C NMR (CDCl₃) δ 13.54 (d, JₗC/P = 2.4 Hz, -NCH₂CH₃), 13.93 (-CH₂CH₂CH₃), 21.27 (-CH₂CH₂CH₂CH₂-), 30.42 (-CH₂CH₂CH₂CH₂-), 39.49 (d, JₗC/P = 3.0, -NCH₂CH₃), 51.39 (d, JₗC/P = 1.4, -NCH₂CH₃). **³¹P NMR (CDCl₃) δ 40.2.

IR: (thin film) 2970, 2931, 2871, 1464, 1413, 1380, 1297, 1207, 1179, 1060, 1021, 947, 838, 792, 711.

The 250 MHz ¹H, 101 MHz ³¹P, and 63 MHz ¹³C FTNMR spectra of 116 are recorded in Appendix A, Figures 100-102.
Reaction of 116 with \( p \)-Bromophenol

1-Butyl-3-tris(diethylamino)phosphoranylidenetriazene (116) was formed \textit{in situ} by the dropwise addition of \( n \)-butyllithium (4.95 mmol) in dry diethyl ether (50 mL) to a -78° C solution of 1 (1.85 g, 5.0 mmol) in dry ether (100 mL). After the addition, the mixture was warmed slowly for 20 min, and then recooled to -78° C.

A solution of \( p \)-bromophenol (2.08 g, 12.0 mmol) in dry ether (50 mL) was rapidly added dropwise. This addition resulted in the vigorous evolution of \( N_2 \) and the formation of a white precipitate. The reaction mixture was washed with 1M HCl (3 x 40 mL), 1 N NaOH (2 x 40 mL), H\( _2 \)O (2 x 40 mL), and saturated aqueous NaCl (40 mL). The ether phase was dried over MgSO\( _4 \), and the solvent was removed on a rotary evaporator, giving 0.53 g (47%) of an oil which was primarily a mixture of \( p \)-bromophenyl butyl ether and 4-bromo-2-butylphenol.

The 250 MHz \( ^1H \) and 63 MHz \( ^13C \) NMR spectra of the product mixture are shown in Appendix B, Figures 140 and 141.
Synthesis of Hydrazones

All of the hydrazones synthesized for this work were prepared by the method advocated by Holton: the ketone or aldehyde is added directly to a large excess of hydrazine in ethanol or THF. Most ketones require reflux overnight to complete the reaction, however aldehydes are generally converted to the hydrazones at room temperature. The hydrazone product is extracted into pentane or methylene chloride and the excess hydrazine is washed out aqueous NaCl. The solvents are generally removed from the hydrazones at low temperature.

**Acetophenone Hydrazone (144)**

Acetophenone (20 g, 0.166 mol) was carefully added to a solution of hydrazine (32 mL, 1.0 mol) in absolute ethanol (25 mL) and the solution was refluxed for 15 h under argon.

The reaction mixture was cooled in ice and poured into a mixture of ether (50 mL) and saturated aqueous NaCl (50 mL). The aqueous phase was removed and extracted with additional portions of ether (3 x 50 mL). The combined organic phases were washed with saturated aqueous NaCl (2 x 50 mL) and dried over MgSO4 at 0° C. The solvent was removed at low temperature on a rotary evaporator at 0.5 torr, leaving 20.05 g (90%) of acetophenone hydrazone as a pale yellow liquid. The product solidified upon standing at -15° C.

\[ ^1H \text{NMR (CDCl}_3) \delta 2.08 \text{ (s, 3H, -CH}_3) , 5.35 \text{ (br. s, 2H, -NH}_2) , 7.26-7.36 \text{ (m, 3H, o,p-ArH), 7.59-7.64 \text{ (m, 2H, m-ArH).} \]

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$^{13}$C NMR (CDCl$_3$) δ 11.55 (-CH$_3$), 125.43 (o-Ar), 127.96 (p-Ar), 128.21 (m-Ar), 139.35 (ipso-Ar), 147.22 (C=N-NH$_2$).

The 250 MHz $^1$H and 75 MHz $^{13}$C FTNMR spectra of 144 are recorded in Appendix A, Figures 103 and 104.

**Synthesis of Isobutyrophenone Hydrazone (145)**

Isobutyrophenone (25 mL, 0.17 mol) and hydrazine (32 mL, 1.0 mol) were mixed in absolute ethanol (50 mL) and refluxed for 4 d under a CaSO$_4$ drying tube. The reaction mixture was cooled in ice, diluted with saturated NaCl solution (50 mL), and extracted with petroleum ether (4 x 50 mL). The combined organic extracts were washed with saturated aqueous NaCl (2 x 50 mL) and dried over MgSO$_4$. The solution was filtered and the solvent was removed on a rotary evaporator at <1 torr below 20° C, leaving 23.82 g (88%) of isobutyrophenone hydrazone as a viscous liquid which solidified upon standing at -15° C. The spectra showed the product to be a mixture of E and Z isomers around the C=N bond, with the E isomer predominating.

E isomer:

$^1$H NMR (CDCl$_3$) δ 1.04 (d, J = 6.9 Hz, 6H, -CH$_3$), 2.68 (heptet, J = 6.9 Hz, 1H, -CH(CH$_3$)$_2$), 4.92 (br. s, 2H, -NH$_2$), 7.09 -7.15 (m, 2H, o-ArH), 7.24-7.44 (m, 3H, m,p-ArH).

$^{13}$C NMR (CDCl$_3$) δ 20.10 (-CH(CH$_3$)$_2$), 35.77 (-CH(CH$_3$)$_2$), 127.54 (o-Ar), 128.16 (p-Ar), 128.79 (m-Ar), 134.10 (ipso-Ar), 156.93 (C=N-NH$_2$).

The 200 MHz $^1$H and 63 MHz $^{13}$C FTNMR spectra of 145 are recorded in Appendix A, Figures 105 and 106.
Synthesis of $\alpha$-Tetralone Hydrazone (146)

Distilled $\alpha$-tetralone (22 mL, 0.17 mol) and anhydrous hydrazine (32 mL, 1.0 mol) were dissolved in absolute ethanol (150 mL) and heated at reflux for 18 h under calcium oxide in a Soxhlet extractor.

Most of the solvent and unreacted hydrazine were removed at low temperature on a rotary evaporator at $<1$ torr. The oily residue was diluted with petroleum ether (50 mL) and CH$_2$Cl$_2$ (20 mL) and extracted with saturated NaCl (50 mL). The organic phase was dried over MgSO$_4$ and filtered. Removal of the solvent on a rotary evaporator gave a crude yellow solid which was recrystallized from petroleum ether/CH$_2$Cl$_2$ at -78° C. Suction filtration and drying in vacuo gave 14.56 g (55%) of $\alpha$-tetralone hydrazone as a white solid.

$^1$H NMR (CDCl$_3$) $\delta$ 1.90 (m, 2H, H$_c$), 2.45 (t, $J = 6.6$ Hz, 2H, H$_b$), 2.71 (t, $J = 6.0$ Hz, 2H, H$_d$), 5.30 (br. s, 2H, -NH$_2$), 7.06-7.10 (m, 1H, H$_g$), 7.12-7.21 (m, 2H, H$_h$), 7.92-7.96 (m, 1H, H$_f$).

$^{13}$C NMR (CDCl$_3$) $\delta$ 21.41 (C$_c$), 23.73 (C$_b$), 29.55 (C$_d$), 123.74 (C$_i$), 126.29 (C$_h$), 127.71, 128.07 (C$_{f,g}$), 133.33 (C$_e$), 138.35 (C$_j$), 147.14 (C$_a$).

The 250 MHz $^1$H and 63 MHz $^{13}$C FTNMR spectra of 146 are recorded in Appendix A, Figures 107 and 108.
Synthesis of 1-Indanone Hydrazone (147)

A solution of 1-indanone (8.0 g, 60 mmol) in ethanol (20 mL) was carefully added to a solution of hydrazine (19 mL, 0.6 mol) in ethanol (20 mL). The mixture was heated 18 h at reflux under a CaSO₄ drying tube.

The reaction mixture was cooled, diluted with CH₂Cl₂, and extracted with saturated aqueous NaCl (50 mL, 4 x 25 mL), then diluted with pentane (50 mL) and extracted with H₂O (50 mL). The organic phase was dried over MgSO₄, and the solvent was removed at <20° C on a rotary evaporator. The residue was recrystallized at -78° C from CH₂Cl₂/pentane (1:5), and dried in vacuo giving 4.95 g (56%) of 1-indanone hydrazone as fine white needles, m.p. 84.5-86° C. An additional 1.90 g (22%) of amorphous white material was obtained from the mother liquor, mp 80-84° C. This material was identical by both ¹H and ¹³C NMR to the sharper-melting product.

¹H NMR (CDCl₃) δ 2.65 (m, 2H, Hₘ), 3.09 (m, 2H, Hₙ), 5.15 (br. s, 2H, -NH₂), 7.18-7.28 (m, 3H, Hₖ, Hₗ, Hₗ'), 7.61-7.66 (m, 1H, Hₙ).

¹³C NMR (CDCl₃) δ 24.88 (Cₙ), 28.29 (Cₙ), 120.74 (Cₖ), 125.28 (Cₗ), 126.91 (Cₗ'), 129.18 (Cₖ), 138.49 (Cₙ), 146.78 (Cₙ), 157.12 (Cₖ).

The 250 MHz ¹H and 63 MHz ¹³C FTNMR spectra of 147 are recorded in Appendix A, Figures 109 and 110.
Synthesis of Pinacolone Hydrazone (148)

Pinacolone (16.65 g, 0.166 mol) was slowly added to a solution of hydrazine (32 mL, 1.0 mol) in absolute ethanol (40 mL). The mixture was refluxed for 15 h under argon.

The reaction mixture was cooled in ice and extracted with petroleum ether (4 x 50 mL) and ether (50 mL). The combined ether and petroleum ether extracts were then dried over MgSO₄. The solvents were removed below 20°C on a rotary evaporator at 0.6 torr, leaving 16.43 g (87%) of pinacolone hydrazone as a very pale yellow liquid.

\[ ^1H \text{NMR (CDCl}_3) \delta 1.07 (s, 9, -C(CH}_3)_3), 1.70 (s, 3, -CH}_3), 4.83 (b.s, 2, -NH}_2). \]

\[ ^13C \text{NMR (CDCl}_3) \delta 9.85 (-CH}_3), 27.54 (-C(CH}_3)), 37.88 (-C(CH}_3)). \]

The 250 MHz \(^1H\) and 75 MHz \(^13C\) FTNMR spectra of 148 are recorded in Appendix A, Figures 111 and 112.

Synthesis of R-(+)-Camphor Hydrazone (149)

R-(+)-Camphor (25.0 g, 0.167 mol) and anhydrous hydrazine (32 mL, 1.02 mol) were refluxed in methanol (50 mL) overnight under a CaSO₄ drying tube. After cooling, the methanol solution was extracted with pentane (2 x 50 mL), then diluted with saturated aqueous NaCl (50 mL) and extracted with additional pentane (2 x 50 mL). The combined pentane extracts were dried over MgSO₄ and evaporated on a rotary evaporator below 20°C. Dilution with CH₂Cl₂ and evaporation of the solvent at 1.0 torr on a rotary evaporator gave 25.4 g (91%) of R-(+)-camphor hydrazone as a white wax.
\( ^1H \) NMR (CDCl\(_3\)) \( \delta \) 0.61 (s, 3H), 0.78 (s, 3H), 0.84 (s, 3H), 1.06 (t of d, J = 10, 4 Hz, 1H), 1.26 (t of d, J = 9, 4 Hz, 1H), 1.53 (t of d, J = 12, 4 Hz, 1H), 1.64 (d, J = 16 Hz, 1H), 1.71 (m, 1H), 1.83 (t, J = 4 Hz, 1H), 2.17 (d of t, J = 16, 4 Hz, 1H), 4.58 (br. s, 2H, -NH\(_2\)).

\( ^13C \) NMR (CDCl\(_3\)) \( \delta \) 10.96, 18.44, 19.16, 27.16, 31.95, 32.35, 43.75, 47.53, 51.50, 164.07 (C=N-NH\(_2\)).

The 250 MHz \( ^1H \) and 75 MHz \( ^13C \) FTNMR spectra of 149 are recorded in Appendix A, Figures 113 and 114.

**Synthesis of 2-Ethylbutanal Hydrazine (150)**

Anhydrous hydrazine (32 mL, 1.0 mol) was dispersed in dry THF (50 mL) by rapid stirring and cooled to 0\(^\circ\) C. Neat 2-ethylbutanal (20.0 mL, 0.162 mol) was added dropwise, and stirring was continued at 0\(^\circ\) C for 3 h, then overnight at room temperature.

The reaction mixture was diluted with pentane (75 mL), and the lower phase was removed. The pentane phase was washed with saturated aqueous NaCl (4 x 50 mL), dried (MgSO\(_4\)), and reduced in volume on a rotary evaporator to about 25 mL. The concentrated solution was diluted with CHCl\(_3\) and then all solvents were removed on a rotary evaporator at high vacuum (1.0 torr), leaving 16.95 g (92%) of clear, colorless liquid. The NMR spectra of the product showed it to be 88 mol% (81 weight %) 150, contaminated with 7 mol% of azine, 151, and 4 mol% of hexahydro-s-tetrazine, 152.
The 250 MHz $^1$H and 63 MHz $^{13}$C FTNMR spectra of impure 150 are recorded in Appendix A, Figures 115 and 116.

**Synthesis of Nonanal Hydrazone (153)**

Freshly distilled nonanal (3.00 mL, 17.4 mmol) in absolute ethanol (40 mL) was added dropwise to a solution of hydrazine (5.0 mL, 0.159 mol) in absolute ethanol (40 mL) at 0° C.

After stirring at 0° C for 3h, the reaction mixture was shaken with a cold (0° C) mixture of saturated aqueous NaCl (20 mL) and pentane (50 mL), and the organic phase was removed. The aqueous phase was extracted further with pentane (2 x 20 mL), and
the combined organic phases were dried over MgSO₄. Evaporation of the solvent on a rotary evaporator below 0° C at 0.3 torr gave 0.77 g (28%) of crude nonanal hydrazone as a white powder. The crude material was immediately used without purification for the preparation of 1-diazononane. NMR spectra taken one day after the preparation showed that the majority of the product had dimerized to either the tetrazine or the azine.
Hydrazone Oxidation Reactions of 1

**General Procedure for Conversion of Hydrazones to Diazo Compounds**

A hexane solution of n-butyllithium (1 equiv) is dissolved in dry THF (10 mL per mmol of n-butyllithium) which has been cooled to -78° C in an argon-flushed flask. The flask is equipped with a pressure equalizing addition funnel, and should have a stopcock outlet if gas measurements are to be performed (see Appendix C for a description of the gas measurement apparatus and its calibration). A solution of the hydrazone (1 equiv) dissolved in dry THF or pentane (5 mL per mmol of hydrazone) is then added dropwise to the solution of n-butyllithium. After stirring for several minutes at -78° C, the solution of the lithium hydrazonate is warmed to 0° C by immersing the reaction flask in an ice bath.

The stopcock outlet is connected to a gas-measuring cylinder at this time. After expansion of the gas due to the temperature increase in the reaction vessel ceases, a zero reading is taken on the measuring cylinder. A solution of 1 (1.1 equiv) in dry THF or CH$_2$Cl$_2$ (10 mL per mmol of solute) is rapidly added dropwise to the solution of hydrazone anion. The addition of 1 results in steady evolution of N$_2$ which is monitored in the gas-measuring cylinder.

After N$_2$ evolution ceases, the reaction mixture is poured into a cold separatory funnel and diluted with an equal volume of pentane which has been cooled to -78° C. The resulting solution is extracted with cold 25-35% aqueous ethylene glycol (five portions). The pentane phase is then poured carefully over solid CO$_2$ in order to precipitate any remaining (Et$_2$N)$_3$P=NH as the insoluble carbamate (Et$_2$N)$_3$P-NH-COO. The precipitate is removed by suction filtration and the filtrate is stirred under intermittent low vacuum for 15 min in order to remove most of the
dissolved CO₂. The remaining solution consists of the diazo compound in a mixture of pentane and THF in approximately a 4:1 ratio.

The more stable aryl diazo compounds can be analyzed by NMR and thin-film IR. Samples are prepared for NMR spectroscopy by concentrating ~40 mL of the cold pentane/THF solution of the diazo compound below 0° C on a rotary evaporator under high vacuum (1 torr). When the volume has been reduced to ~1 mL, cold CDCl₃ (5 mL) is added. The volume is again reduced on a rotary evaporator to ~1 mL. Another dilution with CDCl₃ (5 mL) followed by concentration leaves a solution which is free of pentane, but still contains some THF. Such samples give adequate NMR spectra in most cases.

Infrared spectra of the more stable diazo compounds are obtained by evaporating a few drops of a concentrated pentane/THF solution of the diazo compound directly on a NaCl window, leaving a thin film of the solute.

1-Diazo-1-phenylethane (154) from 1 and Acetophenone Hydrazone (144)

A solution of hydrazone 144 (0.40 g, 3.0 mmol) in dry THF (20 mL) was added dropwise to a solution of n-butyllithium (2.74 mmol) in dry THF (25 mL) at -78° C. The mixture was then warmed to 0° C.

A solution of 1 in CH₂Cl₂ (20 mL) was then added dropwise, resulting in the loss of N₂ from the reaction mixture, which concurrently turned bright red. After the effervescence ceased, the reaction mixture was diluted with pentane (75 mL) which had been cooled to -78° C, and then washed with cold 33% aqueous ethylene glycol (5 x 25
The organic phase was then cooled to -78°C, causing the precipitation of (Et₂N)₃P=NH. Filtration gave a clean solution of 154.

The average yield of 154 formed in the crude reaction mixture, as determined by the measurement of the N₂ evolved, was 85 ± 2% (4 trials). The average yield of 154 after the workup as determined by gas measurements taken during acid-catalyzed decomposition (see below) was 67 ± 11% (3 trials).

Diazo compound 154 could be isolated and crudely characterized by NMR and IR. Partial dimerization to a mixture of (E,E), (E,Z), and (Z,Z) acetophenone azines was observed when solutions of 154 were concentrated to obtain the samples for spectroscopy.

**¹H NMR (CDCl₃)**  δ 2.12 (s, 3H, -CH₃), 6.86 - 6.91 (d, J = 8 Hz, 2H, o-ArH), 6.97 - 7.04 (t, J = 8 Hz, 1H, p-ArH), 7.27 - 7.31 (t, J = 8 Hz, 2H, m-ArH).

**¹³C NMR (CDCl₃)**  δ 10.08 (-CH₃), 51.32 (C=N₂), 121.08 (o-Ar), 123.15 (p-Ar), 128.78 (m-Ar), 132.24 (ipso-Ar).

FTIR (thin film) 3060, 2974, 2035 (diazo band), 1597, 1574, 1499, 1463, 1446, 1382, 1332, 1210, 1171, 1076, 1025, 749, 714, 690, 633 cm⁻¹.

The 250 MHz ¹H and 63 MHz ¹³C FTNMR and FTIR spectra of 154 are recorded in Appendix A, Figures 117-119.

**(+)-1-Phenylethyl Acetate (155) from Decomposition of 154 with Acetic Acid**

A pentane/CH₂Cl₂ solution of 154 (~2.3 mmol), as prepared above, was cooled to 0°C in a flask equipped for gas measurement. Acetic acid (10 mL) was added in a single portion,
resulting in the conversion of 154 to 155. After the nitrogen evolution ceased, the reaction mixture was washed with water (5 x 25 mL), dried (MgSO₄) and evaporated on a rotary evaporator leaving 155 as a pale yellow oil. The NMR spectrum also showed small amounts of styrene and azines in the product.

1H NMR (CDCl₃) δ 1.53 (d, J = 6.6 Hz, 3H, -CHCH₃), 2.05 (s, 3H, -COCH₃), 5.88 (d, J = 6.6 Hz, 1H, -CH(CH₃)O-), 7.22 - 7.43 (m, 5H, ArH).

The 250 MHz ¹H FTNMR spectrum of 155 is recorded in Appendix A, Figure 120.

1-Diazo-2-methyl-1-phenylpropane (156) from 1 and Isobutyrophenone Hydrazo

A 2.7 M solution of n-butyllithium in hexanes (1.0 mL, 2.7 mmol) was added to dry THF (25 mL) which had been cooled to -78°C in an argon-flushed flask. Hydrazone 145 (0.40 g, 2.5 mmol) was dissolved in dry THF (20 mL) and added dropwise to the n-butyllithium solution. The resulting mixture was stirred at -78°C for several minutes and then warmed to 0°C. A solution of 1 (1.0 g, 2.71 mmol) in dry THF (25 mL) was rapidly added dropwise and the reaction mixture was stirred for 10 min, until the N₂ evolution ceased.

The solution was diluted with pentane (75 mL), which had been cooled to -78°C, washed with cold 25% aqueous ethylene glycol (5 x 25 mL), and then poured over solid CO₂. After standing for 15 min in the dark, the mixture was filtered to remove the precipitated (Et₂N)₃P·NH·COO, giving a clean solution of 156 in pentane/THF.

The average yield for the crude reaction prior to workup, as determined by gas measurement during the addition of 1, was 78 ± 2% (four trials). The average yield of
156 after the workup as determined by gas measurement during acid-catalyzed decompositions (see below) was 78 ± 2 % (three trials).

Diazo compound 156 proved stable enough to characterize by NMR and infrared spectroscopy. The NMR spectra of 156 showed no appreciable impurities (except residual THF).

$^1$H NMR (CDCl$_3$) δ 1.18 (d, J = 6.8 Hz, 6H, -CH$_3$), 2.79 (heptet, J = 6.8 Hz, 1H, -CH(CH$_3$)$_2$), 6.86 - 6.96 (m, 3H, o,p-ArH), 7.25 (m, 2H, m-ArH).

$^{13}$C NMR (CDCl$_3$) δ 20.09 (-CH(CH$_3$)$_2$), 22.56 (-CH(CH$_3$)$_2$), 63.52 (C=N$_2$), 121.44 (o-Ar), 122.98 (p-Ar), 128.82 (m-Ar), 131.26 (ipso-Ar).

FTIR (thin film) 2966, 2031 (diazo band), 1595, 1496, 1278, 690 cm$^{-1}$.

The 250 MHz $^1$H and 63 MHz $^{13}$C FTNMR and FTIR spectra of 156 are recorded in Appendix A, Figures 121-123.

(±)-(2-Methyl-1-phenyl-1-propyl) Acetate (157) from 156 and Acetic Acid

A pentane/THF solution of 156 (ca. 2.5 mmol) was cooled to 0°C in a septum-sealed flask which was connected to a gas measuring cylinder. Acetic acid (15 mL) was added via syringe in one portion. After the N$_2$ evolution ceased, the reaction mixture was extracted with cold water (5 x 25 mL). The organic phase was dried over MgSO$_4$ and filtered. Rotary evaporation gave a yellow oil which was predominantly (2-methyl-1-phenyl-1-propyl) acetate. The crude product was purified by chromatography through a 1.5 x 20 cm column of silica gel 60 (70-200 mesh) using CH$_2$Cl$_2$ and ethyl acetate as eluents.
$^1$H NMR (CDCl$_3$) $\delta$ 0.82 (d, $J = 6.8$ Hz, 3H, H$_c$), 0.99 (d, $J = 6.8$ Hz, 3H, H$_d$), 2.08 (s, 3H, -COCH$_3$), 2.09 (heptet, $J = 6.8$ Hz, 1H, H$_b$), 5.49 (d, $J = 7.5$ Hz, H$_a$), 7.24 - 7.36 (m, 5H, ArH).

$^{13}$C NMR (CDCl$_3$) $\delta$ 18.40 (C$_c$), 18.61 (C$_d$), 33.44 (-COCH$_3$), 80.86 (C$_a$), 126.96 (o-Ar), 127.59 (p-Ar), 128.07 (m-Ar), 139.71 (ipso-Ar), 170.17 (C=O).

IR (thin film) 3033, 2964, 2933, 2874, 1736, 1686, 1495, 1455, 1371, 1238, 1178, 1121, 1074, 1022, 950, 913, 758, 701, 634 cm$^{-1}$.

The 300 MHz $^1$H and 75 MHz $^{13}$C FTNMR spectra of 157 are recorded in Appendix A, Figures 124 and 125.

**Synthesis of 1-Diazotetralin (158) from 1 and α-Tetralone Hydrazone (146)**

A 2.74 M hexane solution of $n$-butyllithium (3.0 mL, 8.22 mmol) was dissolved in dry THF (50 mL) which had been cooled to -78°C. A solution of 146 (1.2 g, 7.5 mmol) in dry THF (25 mL) was added dropwise to the $n$-butyllithium mixture, and the resulting solution of hydrazone anion was warmed to 0°C. Upon the dropwise addition of 1 (2.95 g, 8.0 mmol) in dry THF (30 mL), the solution rapidly gave off nitrogen.

As soon as the nitrogen evolution ceased, the crude reaction mixture was diluted with pentane (100 mL) which had been cooled to -78°C and then extracted with 25% aqueous ethylene glycol (4 x 50 mL). The pentane/THF phase was poured over solid CO$_2$ to precipitate any remaining (Et$_2$N)$_3$P=NH as the carbamate, which was removed by suction filtration after 15 min. Finally, the pentane/THF solution of 158 was stirred under intermittent vacuum at 0°C for 15 min to remove the dissolved CO$_2$.
The average yield of 158 formed in the crude reaction mixture, determined by gas evolution during the addition of 1, was $86 \pm 5\%$ (ten trials). The average yield of 158 after the workup, determined by gas evolution during acid-catalyzed decompositions (see below), was $90 \pm 4\%$ (five trials).

Compound 158 was stable enough to permit characterization by NMR and IR.

$^{13}$C NMR (CDCl$_3$) $\delta$ 21.11 (C$_c$), 22.01 (C$_b$), 29.39 (C$_d$), 63.37 (C$_a$), 120.49 (C$_i$), 122.64 (C$_g$), 126.44 (C$_f$), 126.89 (C$_e$), 128.49 (C$_h$), 132.58 (C$_j$).

IR: (thin film, with some THF) 3016, 2935, 2033 (diazo band), 1598, 1569, 1488, 1454, 1361, 1324, 1088, 1040, 884, 747 cm$^{-1}$.

The crude 63 MHz $^{13}$C FTNMR and FTIR spectra of 158 are recorded in Appendix A, Figures 126 and 127.

(±)-1-Acetoxytetralin (159) From Decomposition of 158 with Acetic Acid

A cold solution of 158 (ca. 7.5 mmol) in pentane/THF as prepared by the above procedure was warmed to 0° C. Addition of acetic acid (15 mL, 0.262 mol) in a single portion resulted in the rapid decomposition of 158 and the concomitant loss of nitrogen. When N$_2$ evolution stopped, the reaction mixture was washed with cold water (5 x 30 mL), dried (MgSO$_4$), and evaporated on a rotary evaporator, leaving 1.23 g (86%) of 159. The product is >95% pure (by NMR) without further purification.

$^1$H NMR (CDCl$_3$) $\delta$ 1.80 (m, 1H, H$_c$ syn), 1.90 - 2.00 (m, 3H, H$_b$ syn,anti, H$_c$ anti), 2.06 (s, 3H, -COCH$_3$), 2.65 - 2.90 (m, 2H, H$_d$ syn,anti), 5.99 (t, J = 4 Hz, 1H, H$_a$), 7.08 - 7.28 (m, 4H, ArH).
\(^{13}\text{C} \text{NMR (CDCl}_3\) \(\delta 18.73 \text{ (C}_b\), 21.35 \text{ (C}_c\), 28.88 \text{ (C}_d \text{ or -COCH}_3\), 29.00 \text{ (C}_d \text{ or OCH}_3\), 69.90 \text{ (C}_a\), 125.98 \text{ (C}_h\), 127.98 \text{ (C}_f\), 128.97 \text{ (C}_g\), 129.33 \text{ (C}_i\), 134.49 \text{ (C}_e\), 137.81 \text{ (C}_j\), 170.65 (-CO_2).}

IR: (thin film) 3024, 2939, 2868, 1731, 1606, 1492, 1454, 1371, 1239, 1210, 1154, 1117, 1062, 1016, 965, 925, 899, 835, 808, 765, 742, 608 cm\(^{-1}\).

The 250 MHz \(^1\text{H}\) and 63 MHz \(^{13}\text{C}\) FTNMR spectra of 159 are recorded in Appendix A, Figures 128 and 129.

**Synthesis of 1-Diazoindane (160) from 1 and 1-Indanone Hydrazine (147)**

To dry THF (25 mL) which had been cooled to -78° C under argon was added a 2.74 M solution of \(n\)-butyllithium in hexanes (1.0 mL, 2.74 mmol). A solution of 147 (0.365 g, 2.5 mmol) in dry THF (20 mL) was added dropwise to the \(n\)-butyllithium, and the resulting mixture was warmed to 0° C. Upon adding 1 (1.0 g, 2.7 mmol) in dry THF (25 mL), the reaction mixture gave off \(N_2\).

After the gas evolution ceased, the reaction mixture was diluted with cold pentane (-78° C, 75 mL) and then washed with cold 25% aqueous ethylene glycol (5 x 25 mL). The pentane/THF phase was poured over solid CO\(_2\), and after 15 min the precipitated \((\text{Et}_2\text{N})_3\text{P-NH-COO}\) was removed by suction filtration. Stirring the solution under intermittent vacuum at 0° C for 15 min removed the dissolved CO\(_2\).

The yield of 1-diazoindane formed in the crude reaction mixture was 59% (two trials). The yield of 160 after the workup was 53% (one trial), as determined by gas measurement during the acid-catalyzed decomposition (see below).
(+)-1-Acetoxyindane (161) from Decomposition of 160 with Acetic Acid

A pentane/THF solution of 1-diazoyindane, 160, (ca. 1.5 mmol) was cooled to 0° C and acetic acid (15 mL, 0.262 mol) was added, resulting in rapid decomposition of the diazo compound.

As soon as the N₂ evolution stopped, the reaction mixture was washed with water (4 x 25 mL), dried (MgSO₄), and evaporated onto silica gel (ca. 2 g) using a rotary evaporator. Chromatography through a 1.5 x 15 cm column of Silica Gel 60 (70-230 mesh) using CH₂Cl₂ and ethyl acetate as eluents gave 161 as a clear, slightly yellow liquid.

1H NMR (CDCl₃) δ 2.08 (s, 3H, -COCH₃), 2.05 - 2.17 (m, 1H, Hₜₜ), 2.44 - 2.59 (m, 1H, Hₛₛ), 2.85 - 2.95 (m, 1H, Hₜₜ), 3.07 - 3.13 (m, 1H, Hₜₜ), 6.22 (d of d, J = 7.0, 3.7 Hz, 1H, Hₗₗₗ), 7.23 - 7.32 (m, 3H, Hₗₗₗ), 7.44 (d, J = 6.9 Hz, 1H, Hₗₗₗ).

13C NMR (CDCl₃) δ 21.18 (Cₜₜ), 30.09 (-COCH₃), 32.20 (Cₜₜ), 78.24 (Cₗₗₗ), 124.70, 125.46, 126.61, 128.84 (Cₗₗₗ), 141.01, 144.30 (Cₗₗₗ), 170.92 (CO₂).

IR: (thin film) 3681, 3072, 3029, 2975, 2944, 2852, 1734 (C=O), 1479, 1462, 1371, 1311, 1239 (C=O), 1182, 1153, 1020, 958, 893, 755, 612 cm⁻¹.

The 250 MHz ¹H and 63 MHz ¹³C FTNMR spectra of 161 are recorded in Appendix A, Figures 130 and 131.
R-(+)-1,7,7-Trimethyl-2-diazobicyclo[2.2.1]heptane (162) from 1 and 149

A 2.74 M solution of n-butyl-lithium in hexanes (1.0 mL, 2.74 mmol) was added to dry THF (25 mL) which had been cooled to -78° C. R-(+)-camphor hydrazone, 149, (0.50 g, 3.0 mmol) in THF (20 mL) was then added dropwise. After stirring at -78° C for ~15 min, the mixture of the hydrazone anion was warmed to 0° C. Dropwise addition of 1 (1.1 g, 3.0 mmol) in dry THF (25 mL) resulted in the steady evolution of N₂.

As soon as the effervescence abated, pentane (75 mL) which had been pre-cooled to -78° C was added, and the mixture was washed with cold 33% aqueous ethylene glycol (5 × 25 mL). The pentane/THF phase was then cooled to -78° C and the remaining (Et₂N)₃P=N precipitated.

After warming the pentane/THF solution of 162 to 0° C, acid-catalyzed decomposition with one drop of acetic acid resulted in the rapid loss of nitrogen. The average yield of 162 formed in the crude reaction mixture, as measured by gas evolution, was 74 ± 3% (four trials). The average yield of 162 after the workup, as measured by gas evolution during the acid-catalyzed decomposition, was 73 ± 4% (four trials).
1-Diazo-2-ethylbutane (163) from 1 and 2-Ethylbutenal Hydrazone (150)

To a -78°C solution of n-butyllithium (2.74 mmol) in dry THF (25 mL) was added dropwise hydrazone 150 (81 wt% pure, 0.42 g, 3.0 mmol) in pentane (30 mL). After stirring at -78°C for ~10 min, the solution was warmed to 0°C, and then 1 (1.1 g, 3.0 mmol) in dry THF (30 mL) was added. Immediately after the gas evolution had ceased, the reaction mixture was diluted with pentane (75 mL), which had been cooled to -78°C. The mixture was then washed with cold 33% aqueous ethylene glycol (5 x 25 mL). Cooling to -78°C caused precipitation of the remaining (Et₂N)₃P=NH, which was removed by decantation.

The yield of 163 was 77% (determined by gas measurement during the addition of the lithium salt of 150 to 1). After the workup, 163 was decomposed with one drop of acetic acid; the gas evolved during this decomposition also corresponded to a 77% yield.

1-Diazononane (164) from 1 and Nonanal Hydrazone (163)

Crude nonanal hydrazone (0.56 g, 3.58 mmol assuming 100% purity) was dissolved in pentane (20 mL) and added dropwise to a solution of n-butyllithium (2.74 mmol) in dry THF (20 mL) at -78°C in an argon-flushed flask.
After the addition was complete, the mixture was warmed to 0° C and a solution of 1 (1.1 g, 2.98 mmol) in dry THF (20 mL) was added dropwise, resulting in N₂ evolution. The formation of orange 163 occurred in 81% yield, as measured gasimetrically. The reaction mixture was diluted with pentane (75 mL) which had been cooled to -78° C, and then washed with 33% aqueous ethylene glycol (5 x 25 mL). Cooling the organic layer to -78° C resulted in precipitation of the remaining traces of (Et₂N)₃P=NH, which was removed by decantation of the supernant. An aliquot of the solution was evaporated onto salt plates and an FTIR spectrum of crude 163 was obtained.

Warming the pentane/THF solution of 163 to 0° C and adding acetic acid (10 mL) resulted decomposition of the diazo compound. The N₂ evolved during the decomposition corresponded to a 58% yield.

FTIR: (thin film) 2923, 2853, 2054 (C=N=N), 1716, 1652, 1464, 1378, 1208, 1091.
Reactions of 1 with Miscellaneous Anions

**Tris(diethylamino)phenoxyposphonium Azide (135) from Reaction of 1 with Lithium Phenoxide**

To phenol (0.52 g, 5.5 mmol) in dry THF (20 mL) was added a 2.74 M solution of n-butyllithium in hexanes (2.0 mL, 5.5 mmol). After 15 min, the lithium phenoxide mixture was warmed to -20° C, and a solution of 1 (2.03 g, 5.5 mmol) in dry THF (20 mL) was added. The resulting solution was then immediately recooled to -78° C. The mixture was allowed to stir overnight under argon and warm slowly to ambient temperature.

Removal of the solvent on a rotary evaporator gave a quantitative mass balance. The crude product was mostly 135 with small amounts of unreacted 1, solvent, and trace impurities. Attempts to purify 135 by crystallization failed.

**1H NMR (d$_6$-DMSO)** $\delta$ 1.05 (t, $J = 7.1$ Hz, 18H, -CH$_3$), 3.15 (d of q, $J_{H/P} = 11.3$ Hz, $J_{H/H} = 7.1$ Hz, 12H, -CH$_2$CH$_3$), 7.30 (d, $J = 7.7$ Hz, 2H, o-Ar-H), 7.36 (d, $J = 6.6$ Hz, 1H, p-Ar-H), 7.50 (t, $J = 7.7$ Hz, 2H, m-Ar-H).

**13C NMR (d$_6$-DMSO)** $\delta$ 12.78 (d, $J_{C/P} = 2.6$ Hz, -CH$_3$), 39.87 (d, $J_{C/P} = 16.4$ Hz, -CH$_2$CH$_3$), 120.77 (d, $J_{C/P} = 3.8$ Hz, o-Ar), 126.69 (p-Ar), 130.71 (m-Ar), 149.02 (d, $J_{C/P} = 8.63$ Hz, ipso-Ar).

**31P NMR (d$_6$-DMSO)** $\delta$ 33.83.

**FTIR:** (thin film) 2975, 2937, 2874, 2053 (N=N=N), 1589, 1488, 1467, 1386, 1297, 1213, 1194, 1160, 1102, 1064, 1028, 978, 961, 935, 800, 773, 714, 694.

The 250 MHz $^1$H, 101 MHz $^{31}$P, and 63 MHz $^{13}$C FTNMR and FTIR spectra of 135 are recorded in Figures 132-135.
A solution of cyclohexanone (1.0 mL, 9.64 mmol) in dry THF (30 mL) was added dropwise to a solution of n-butyllithium (10.61 mmol) in dry THF (30 mL) at -78°C. After stirring for ~15 min, the mixture containing cyclohexanone enolate was transferred dropwise via cannula into a solution of 1 (4.27 g, 11.57 mmol) and 15-crown-5 (0.2 g, 0.9 mmol) in dry THF (50 mL) which was also at -78°C. After the cannulation was complete, the bright yellow mixture was allowed to warm slowly to ambient temperature.

After stirring overnight, the color of the reaction mixture had changed to red. TLC (ethyl acetate eluent) showed only highly polar compounds which were immobile. The THF was removed on a rotary evaporator, leaving a red oil which was examined by NMR. The proton NMR was very complex, but showed the presence of three different major -P(NEt\textsubscript{2})\textsubscript{3} moieties, one being unreacted 1. The 31P spectrum showed the presence of some unreacted 1 along with two major and five minor phosphorus-containing products.

The 1H and 31P NMR spectra of this reaction mixture are recorded in Appendix B, Figures 138 and 139.
LIST OF REFERENCES


56 Schwesinger, R. Chimia 1985, 39, 269.


70 Schwesinger, R. *Chimia*, 1985, 39, 269.


78 ibid., p. 17.


APPENDIX A

$^1$H, $^{13}$C, $^{31}$P NUCLEAR MAGNETIC RESONANCE SPECTRA
AND FOURIER TRANSFORM INFRARED SPECTRA OF ISOLABLE
COMPONUDS
Figure 56: 250 MHz $^1$H NMR spectrum of Azidotris(dimethylamino)phosphonium bromide (2)
Figure 57: 63 MHz $^{13}$C NMR spectrum of Azidotris(dimethylamino)phosphonium bromide (2)
Figure 58: 101 MHz $^{31}$P NMR spectrum of Azidotris(dimethylamino)phosphonium bromide (2)
Figure 59: 250 MHz$^3$P NMR spectrum of Hexaethylphosphorustriamde (142)
Figure 60: 63 MHz $^{13}$C NMR spectrum of Hexaethylphosphorustriamide (142)
Figure 61: 250 MHz $^1$H NMR spectrum of Azidotris(diethylamino)phosphonium bromide (1)
Figure 62: 63 MHz $^{13}$C NMR spectrum of Azidotris(diethylamino)phosphonium bromide (1)
Figure 63: 101 MHz $^{31}$P NMR spectrum of Azidotris(diethylamino)phosphonium bromide (1)
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Figure 64: FTIR spectrum of Azidotris(diethylamino)phosphonium bromide (1)
Figure 65: 250 MHz $^1$H NMR spectrum of Trippiperidinophosphate (143)
Figure 66: 63 MHz $^{13}$C NMR spectrum of Tripiperidinophosphine (143)
Figure 67: 101 MHz $^{31}$P NMR spectrum of Tripiperidinophosphine (143)
Figure 67: 250 MHz $^1$H NMR spectrum of Azidotriperidinophosphonium bromide (3)
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Figure 70: 250 MHz $^1$H NMR spectrum of 3-Diazo-2,4-pentanedione (95)
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Figure 72: 250 MHz $^1$H NMR spectrum of 4-Diazo-3,5-heptanedione (96)
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Figure 74: 250 MHz $^1$H NMR spectrum of 2-Diazo-1,3-diphenyl-1,3-propanedione (97)
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Figure 76: 250 MHz $^1$H NMR spectrum of 2-Diazo-1,3-indanodione (104)
Figure 77: 63 MHz $^{13}$C NMR spectrum of 2-Diazo-1,3-indanedione (104)
Figure 78: 250 MHz $^1$H NMR spectrum of Ethyl 2-Diazo-3-oxobutanoate (98)
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Figure 82: 250 MHz $^1$H NMR spectrum of Ethyl 2-Diazo-3-oxo-hexanoate (100)
Figure 83: 63 MHz $^{13}$C NMR spectrum of Ethyl 2-Diazo-3-oxo-hexanoate (100)
Figure 84: 250 MHz $^1$H NMR spectrum of Diethyl 2-Diazo malonate (101)
Figure 85: 63 MHz $^{13}$C NMR spectrum of Diethyl 2-Diazomalonate (101)
Figure 86: 250 MHz $^1$H NMR spectrum of Triethyl Diazophosphonoacetate (102)
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Figure 105: 200 MHz $^1$H NMR spectrum of Isobutyrophenone Hydrazone (145)
Figure 106: 63 MHz $^{13}$C NMR spectrum of Isobutyrophenone Hydrazone (145)
Figure 107: 250 MHz $^1$H NMR spectrum of α-Tetralone Hydrazone (146)
Figure 108: 63 MHz $^{13}$C NMR spectrum of α-Tetralone Hydrazone (146)
Figure 109: 250 MHz $^1$H NMR spectrum of 1-Indanone Hydrazone (147)
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Figure 112: 63 MHz $^{13}$C NMR spectrum of Pinacolone Hydrazone (148)
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Figure 114: 63 MHz $^{13}$C NMR spectrum of R-(+)-Camphor Hydrazone (149)
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Figure 132: 250 MHz $^1$H NMR spectrum of impure Tris(diethylamino)phenoxyphosphonium Azide (135)
Figure 133: 63 MHz $^{13}$C NMR spectrum of impure Tris(diethylamino)phenoxyphosphonium Azide (135)
Figure 134: 101 MHz $^{31}$P NMR spectrum of impure Tris(diethylamino)phenoxyphosphonium Azide (135)
Figure 135: FTIR spectrum of impure Tris(diethylamino)phenoxyphosphonium Azide (135)
APPENDIX B

$^1$H, $^{13}$C, $^{31}$P NUCLEAR MAGNETIC RESONANCE SPECTRA
OF REPRESENTATIVE REACTION MIXTURES
Figure 136: 250 MHz $^1$H NMR spectrum of the polar by-products of the reaction of 1,3-pentanedione with 1
Figure 137: 101 MHz $^{31}$P NMR spectrum of the polar by-products of the reaction of 1,3-pentanedione with 1
Figure 138: 250 MHz $^1$H NMR spectrum of the crude reaction mixture of cyclohexanone enolate (Li salt) with 1
Figure 139: 101 MHz $^{31}$P NMR spectrum of the crude reaction mixture of cyclohexanone enolate (Li salt) with 1
Figure 140: 250 MHz $^1$H NMR spectrum of the non-polar products from reaction of $p$-bromophenol with 1-Butyl-3-tris(diethylamino)phosphoranylidene-triazene (116)
Figure 141: 63 MHz $^{13}$C NMR spectrum of the non-polar products from reaction of p-bromophenol with 1-Butyl-3-tris(diethylamino)phosphoranylidene triazene (116)
APPENDIX C

DETERMINATION OF YIELDS BY GAS MEASUREMENTS

Diazoalkanes without electron-withdrawing groups on the diazo carbon are thermally and photochemically labile and are prone to explode in the absence of solvent, so it is usually impractical to determine the yields of such compounds by direct isolation and weighing of the products. Since these unstabilized diazoalkanes decompose almost quantitatively with loss of nitrogen upon treatment with acid, a more practicable procedure is to measure the nitrogen which is liberated during an acid-catalyzed decomposition of the diazoalkane product. *A priori* one would assume that since N\(_2\) behaves as a nearly ideal gas that the simple equation \(PV = nRT\) could be used to quantify the moles of N\(_2\) evolved, given that the pressure, temperature, and volume of the evolved gas could be accurately measured.

Given the apparatus in Figure 142 one would assume that nitrogen evolved from the reaction solution “A” would warm to the temperature indicated by thermometer “E” as it passed over the ballast “F” (Ascarite pellets). The volume of the evolved gas could then be read in the gas buret “H.” The pressure in the system is equalized with atmospheric pressure by means of the leveling bulb “I.”
Gas Measurement Apparatus

A = Pentane/THF solution of diazo compound
B = Headspace over solution
C = 3-Way stopcock
D = Inlet for purging system with argon
E = Thermometer for measuring temperature of ballast
F = Ballast (Ascarite pellets) for warming gas to ambient temperature
G = 2-Way stopcock; open port allows prior zeroing of buret without disturbing system.
H = Gas buret. Calibrated in 0.5 mL increments
I = Leveling bulb filled with water.

Figure 142: Apparatus for Measuring N₂ Evolved During Acid-Catalyzed Decompositions of Diazo Compounds
When 1-diazotetralin and 1-diazo-1-phenylethane were decomposed at 0° C with acetic acid in pentane/THF, however, the temperature on thermometer “E,” the volume read from buret “H,” and the pressure from a laboratory barometer consistently indicated yields over 100% when those values were inserted into the ideal gas law equation. Changing the limiting reagent for the preparation of the diazo compound failed to alleviate this discrepancy. The excess volume measured in buret “H” was not due to the volume of mixing when the acetic acid was added, nor was it due to a highly exothermic reaction causing a temperature expansion of the gas in the headspace “B” over the reaction mixture. (This condition was mimicked by adding acetic acid to a solution of tetramethylguanidine in the same pentane/THF solvent mixture used for the diazo compound decompositions.)

The root cause of the high yields was the faulty assumption that the gas that is measured is the nitrogen evolved from the diazo compound. In fact the gas which is measured in buret “H” is not the nitrogen from the diazo compound decomposition, but rather the gas in the headspace “B” and in the ballast tube “F” which is displaced by the evolved nitrogen. This gas is saturated with the vapor of the solvent in the reaction vessel as well as with water vapor from the water in the buret “H.” Apparently this solvent- and water-saturated gas does not behave ideally when it warms from 0° C (the temperature in the headspace “B”) to the temperature of the ballast. This was confirmed by the following experiment:

A syringe with a long needle was filled with dry nitrogen and the whole syringe was immersed in an ice bath until the gas had cooled to 0° C. A septum-sealed flask was filled with the pentane/THF solvent mixture used for the diazo compound decompositions and cooled to 0° C. The syringe needle was inserted through septum until it was below the liquid level. Exactly 40 mL of 0° C N₂ was injected into the flask. The temperature of the ballast was 22° C. The ideal gas law would indicate that the
40 mL of N2 injected at 0° C should expand to 42.9 mL at 22° C (V2 = T2V1/T1, T1 and T2 in degrees Kelvin). The actual reading in the buret was 48 mL, however. Numerous repetitions indicated that this result was quite consistent.

Since all of the decompositions of diazo compounds were carried out at 0° C in the same solvent mixture, a calibration curve was developed which correlated the reading on buret “H” with the amount of dry, 0° C nitrogen injected via syringe into the reaction flask. The data obtained fit the linear relationship

\[ V_{\text{injected}} = 0.7644 V_{\text{measured}} + 1.46 \text{ mL} \]

with a correlation of 0.9974. This linear relationship between the amount of ideal gas introduced into the reaction vessel at 0° C and the reading on the buret permitted the ideal gas law to be used for the calculation of yields. For example if the buret reading for an experiment was 55 mL:

\[ V_{\text{evolved}} = 0.7644 (55 \text{ mL}) + 1.46 \text{ mL} \]

\[ V_{\text{evolved}} = 43.5 \text{ mL} \]

This volume of 43 mL corresponds to the amount of N2 evolved in the reaction vessel at 0° C at atmospheric pressure. Therefore the relationship PV = nRT is used to calculate the number of moles of nitrogen “n” with V = 43.5 mL and T = 0° C (273 degrees Kelvin).