PROAZAPHOSPHATRANES: SUPERIOR BASES AND CATALYSTS

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Recent Applications of Proazaphosphatranes in Organic Synthesis

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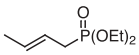

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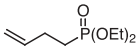
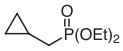


Diethyl cyclopropylmethylphosphonate, 97%

63,582-0 1g, 5g

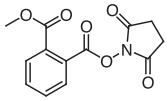


Phosphonates have been utilized extensively in the Horner–Wadsworth–Emmons reaction for the construction of carbon–carbon double bonds. These phosphonates have been employed in the preparation of 3-acetoxy-1-alkenyl phosphonates.[1] They were also exploited in an efficient and regiospecific synthesis of 4-oxo-2-alkenylphosphonates.[2]

(1) Principato, B. et al. *Tetrahedron* **1996**, *52*, 2087. (2) Lee, B.S. et al. *J. Org. Chem.* **2000**, *65*, 4175.

Methyl 2-((succinimidooxy)carbonyl)benzoate, 97%

63,392-5 5g

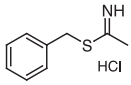


This reagent efficiently undergoes N-phthaloylation with α-amino acids, α-amino alcohols, α-amino carboxamides, α-amino esters, and dipeptides in high yields without racemization.

Casimir, J. et al. *J. Org. Chem.* **2002**, *67*, 3764.

Benzyl thioacetimidate hydrochloride, 96%

63,711-4 1g, 5g

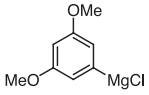


This functionalized thioimidate is a useful reagent for the conversion of anilines to N-substituted acetamidines.[1,2]

(1) Doise, M. et al. *Tetrahedron Lett.* **1990**, *31*, 1155. (2) Collins, J. L. et al. *J. Med. Chem.* **1998**, *41*, 2858.

3,5-Dimethoxyphenylmagnesium chloride 1*M* in tetrahydrofuran

63,762-9 50mL



This Grignard reagent was used recently to make materials for studies in crystal engineering.

Tanaka, T. et al. *J. Am. Chem. Soc.* **2002**, *124*, 12453.

2-Bromo-3-thiophenecarboxylic acid, 97%

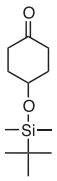
63,812-9 1g, 5g

This bifunctional building block was recently utilized in the preparation of oligothiophenes for materials science applications.[1,2]

(1) Zhang, O. T.; Tour, J. M. *J. Am. Chem. Soc.* **1997**, *119*, 9624. (2) Pomerantz, M. et al. *J. Org. Chem.* **2002**, *67*, 6931.

4-(*tert*-Butyldimethylsilyloxy)cyclohexanone

63,815-3 1g, 5g

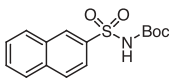


As a protected 4-hydroxycylclohexanone, this compound has been exploited in the synthesis of butenolides,[1] (±)-cocculolidine,[2] and the enyne A-ring synthon of 1α-hydroxy vitamin D_3.[3]

(1) Majewski, M. et al. *Tetrahedron: Asymmetry* **1995**, *6*, 1837. (2) Kawasaki, T. et al. *Tetrahedron Lett.* **2001**, *42*, 8003. (3) Parker, K. A.; Dermatakis, A. *J. Org. Chem.* **1997**, *62*, 6692.

***N*-Boc-2-naphthalenesulfonamide**, 97%

63,921-4 1g, 5g

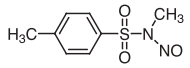


This novel reagent allows the stepwise synthesis of secondary aliphatic amines, such as selectively protected derivatives of spermidine. Cleavage of the sulfonylcarbamate group can be achieved with catalytic amounts of $Mg(ClO_4)_2$ without affecting other Boc-protected amines.

Grehn, L.; Ragnarsson, U. *J. Org. Chem.* **2002**, *67*, 6557.

Diazald®, 20 wt. % mixture with sodium sulfate

64,053-0 25g

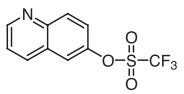


20 wt. % mixture with sodium sulfate

This well-known reagent has been used for the safe production of diazomethane. Aldrich now proudly presents this mixture to address shipping and handling concerns.

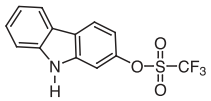
6-Quinolyl trifluoromethanesulfonate, 97%

63,344-5 1g, 5g



9*H*-Carbazol-2-yl trifluoromethanesulfonate, 97%

63,920-6 1g, 5g



These heterocyclic triflates are convenient building blocks for the synthesis of the corresponding halides,[1] thiols,[2] and alkenes.[1] They have also been exploited in cross-coupling reactions with Grignard reagents.[3]

(1) Ritter, K. *Synthesis* **1993**, 735. (2) Arnould, J. C. et al. *Tetrahedron Lett.* **1996**, *37*, 4523. (3) Fürstner, A. *J. Am. Chem. Soc.* **2002**, *124*, 13856.

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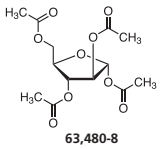
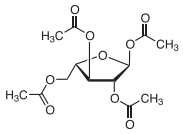
Professor Masaru Kobayashi of Hokkaido University, Japan, kindly suggested we offer 1,2,3,5-tetra-*O*-acetyl-α-D-arabinofuranose and 1,2,3,5-tetra-*O*-acetyl-α-L-arabinofuranose. These fully protected carbohydrates are convenient reagents for determining the absolute configuration of secondary alcohols by ^{13}C NMR spectroscopy.

Kobayashi, M. *Tetrahedron* **2002**, *58*, 9365.



63,480-8



63,744-0

63,480-8 1,2,3,5-Tetra-*O*-acetyl-α-D-arabinofuranose
63,744-0 1,2,3,5-Tetra-*O*-acetyl-α-L-arabinofuranose

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Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page or on the inside back cover.

TABLE OF CONTENTS

ABOUT OUR COVER

Photograph © Board of Trustees, National Gallery of Art, Washington.

Flower Beds in Holland (oil on canvas, 48.9 x 66.0 cm) was painted by Vincent van Gogh, probably in 1883. Born in 1853, he left school at the age of sixteen to work for the Goupil art firm in The Hague. This was followed by a period of wandering and spiritual anguish that took him to London (1873), Paris (1875), and Belgium (1878), after which he returned to Holland determined to become an artist.

Van Gogh studied at the Antwerp Academy, but was impatient with formal training and, in 1886, left for Paris. His earliest works portray sympathetically the lives of peasants and workmen, but after he met Pissarro, Degas, Gauguin, Seurat, and Toulouse-Lautrec, he developed an obsessive interest in the symbolic and expressive possibilities of colors. In a frenzy of creation during the last years of his life, he produced over 800 paintings and 850 drawings.

Although its date makes it one of Van Gogh's earliest known works, one can already see in *Flower Beds in Holland* the interest in surface texture and expressive color so prominent in his later works. The bright stripes of color of the flower beds in the foreground contrast strongly with the relatively flat outlines of the tree branches against the gray sky. The low horizon follows the tradition of Dutch landscape painting, which reflects the natural geography of the country. Van Gogh's handling of paint and use of color, however, show the influence of his contacts with contemporary French artists, and point the way to the ever more impassioned and brilliantly colored works of his later career.

This painting is in the Collection of Mr. and Mrs. Paul Mellon at the National Gallery of Art, Washington, DC.

Lab Notes

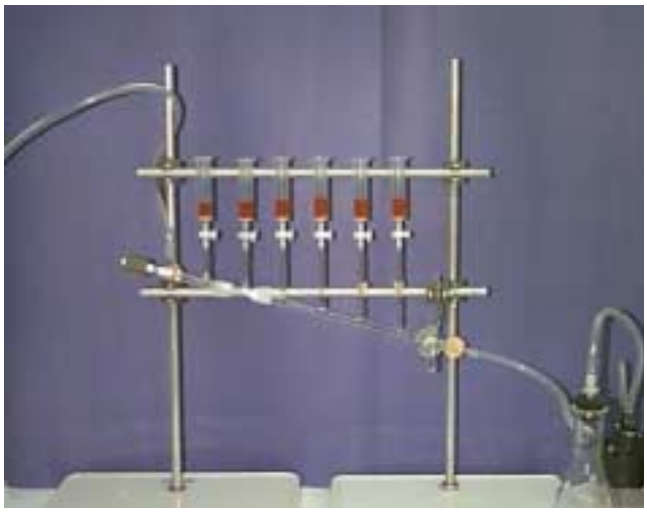
An Inexpensive, Manually Operated, Solid-Phase, Parallel Synthesizer

Solid-phase synthesis is routinely used for the preparation of peptides and small molecules.[1–6] Because solid-phase synthesis involves sequential mixing and draining steps, it is frequently performed in automated solid-phase synthesizers. Although solid-phase synthesis offers many advantages over its solution-phase counterpart, the cost of instrumentation is a limiting factor that prevents many laboratories from venturing into this methodology.[7] Reaction vessels for manual synthesis are commercially available, but each usually requires its own setup for mixing and draining. This makes it more complicated to run multiple reactions at a time. To address this shortcoming, we have designed an inexpensive, manually operated, solid-phase, multiple synthesizer ("CHOIR")[8] that is easy to use and maintain, and that should be affordable (~$250 for glassware) to a wide variety of researchers and educators, especially in cost-conscious academic laboratories.

CHOIR, in its current design, permits up to six syntheses to be performed simultaneously and independently. It consists of a modified vacuum manifold (Chemglass custom Cat. No. UM-2008-301D) with 8 outlets (see figure). The left end of the manifold serves as an inlet for the inert gas, which is bubbled through the reaction vessels in order to mix the reactants and resins. A regulator controls the gas flow and maintains enough gas pressure through the reaction vessels to prevent premature drainage of the solvents. The right end has a three-way stopcock that is opened only when the solvents are being drained. Solvents are drained into a solvent trap with the aid of a vacuum pump or aspirator. The remaining six outlets have LUER® connectors, which are used to attach the reaction vessels via two-way stopcocks. Solid-phase extraction tubes with polyethylene frits, available in a variety of sizes (e.g., Supelco Cat. No. 57176), are used as reaction vessels. These tubes are inexpensive and can be discarded after each synthesis. The inert gas, the solvent trap, and the vacuum pump are connected to CHOIR by means of chemically resistant tubing (e.g., Aldrich Cat. No. Z27,986-2). CHOIR is very easy to operate, since each reaction vessel can be controlled separately by closing and opening the individual stopcock attached to it. Once the parallel syntheses are completed, the reaction vessels are removed from CHOIR, and the peptides individually cleaved from the resins in the same reaction vessels.

We have used CHOIR for the synthesis, partial or complete, of a large number (100–150) of linear and cyclic peptides of various sizes (5–11 residues) in high yields and purities, or for the optimization of the reaction conditions leading to these peptides. Examples of peptides synthesized include cyclic and linear analogs of the opioid peptide dynorphin A:[5,6,9–11]

- *cyclo*[D-Asp^2,Xxx^3,Dap^5]Dyn A-(1–11)NH_2 and linear [D-Asp^2,Xxx^3,Dap^5]Dyn A-(1–11)NH_2, where Xxx = Gly, Ala, D-Ala, Trp, D-Trp, or Pro.
- *cyclo*[D-Asp^2,Xxx^4,Dap^5]Dyn A-(1–11)NH_2 and linear [D-Asp^2,Xxx^4,Dap^5]Dyn A-(1–11)NH_2, where Xxx = Phe, D-Phe, HomoPhe, or D-HomoPhe.
- *cyclo*^{N,5}[Trp^3,Trp^4,Glu^5]Dyn A-(1–11)NH_2 and its cyclic and linear analogs.
- *cyclo*^{N,5}[$COCH_2$Tyr^1,Lys^5]Dyn A-(1–11)NH_2 and analogs.
- *cyclo*^{N,5}[$COCH_2$Tyr^1,Lys^3]Dyn A-(1–11)NH_2 and analogs.



References and Notes: (1) For a review, see *Solid-Phase Synthesis, A Practical Guide*; Kates, S. A., Albericio, F., Eds.; Marcel Dekker, Inc.: New York, 2000. (2) Gorman, J. J. *Anal. Biochem.* **1984**, *136*, 397. (3) Stewart, J. M.; Young, J. D. *Solid Phase Peptide Synthesis*, 2nd ed.; Pierce Chemical Co.: Rockford, IL, 1984. (4) Knapp, D. R.; Oatis, J. E., Jr.; Papac, D. I. *Int. J. Pept. Protein Res.* **1993**, *42*, 259. This report describes a similar albeit less practical synthesizer, and gives a brief history of systems devised to carry out parallel syntheses of peptides. (5) Bennett, M. A.; Murray, T. F.; Aldrich, J. V. *J. Med. Chem.* **2002**, *45*, 5617. (6) Vig, B. S.; Murray, T. F.; Aldrich, J. V. *J. Med. Chem.* **2003**, *46*, 1279. (7) For example, the Bohdan MiniBlock® system, which is convenient to use, is roughly 14 times more expensive than the system described here ($3,500 vs $250). (8) CHOIR = Cheap Homemade Organic Inline Reactor. (9) Vig, B. S.; Aldrich, J. V. Strategies for the Synthesis of Novel Head-to-Side Chain Cyclic Peptides: Application to Dynorphin A Analogs. In *Peptides: The Wave of the Future*; Lebl, M., Houghten, R. A., Eds.; American Peptide Society: San Diego, CA, 2001; pp 144–145. (10) Vig, B. S.; Murray, T. F.; Aldrich, J. V. *J. Med. Chem.* **2004**, *47*, 446. (11) Vig, B. S.; Murray, T. F.; Aldrich, J. V. *Biopolymers* **2004**, in press.

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Recent Applications of Proazaphosphatranes in Organic Synthesis†

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Outline

1. Introduction

Proazaphosphatranes (**Figure 1**) are bicyclic, nonionic bases in which the phosphorus atom functions as the site of electron-pair donation.[1] Among the most commonly used nonionic bases are the nitrogen compounds triethylamine (TEA), pyridine, tetramethylguanidine (TMG), 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo-[4.3.0]non-5-ene (DBN), 4-dimethylaminopyridine (DMAP), 1,4-diazabicyclo[2.2.2]octane (Dabco®), diisopropylethylamine (DIPEA), and 1,8-bis(dimethylamino)naphthalene (Proton-Sponge®).[1a] Phosphazene bases,[2] such as those shown in **Figure 2**, also have useful synthetic applications.[1a]

In contrast to all the phosphazene bases, which are protonated on a nitrogen atom, proazaphosphatranes are protonated on the bridgehead phosphorus atom with a resultant transannulation[1] to form the corresponding azaphosphatranes (**2**). Although phosphazenes[2] and proazaphosphatranes both contain phosphorus, this review will deal only with bases that become protonated on the phosphorus atom, namely, proazaphosphatranes. Several recent reviews address more general aspects of the chemistry and properties of proazaphosphatranes in considerably greater depth than the present article.[1] Here, we survey reactions mediated by these bases by classifications that reflect their mechanistic pathways. We also attempt for the first time to offer rationales for the selectivities observed to date in some of the reactions.

Strong nonionic bases are very useful in a number of important organic transformations such as dehydrohalogenations, the nitroaldol (Henry) reaction, and the silylation and acylation of alcohols.[1a,d] Among this class of bases, proazaphosphatranes are securing a growing niche. The high pK_a values of the conjugate acids of proazaphosphatranes and phosphazenes (17–42[2,3]) allow

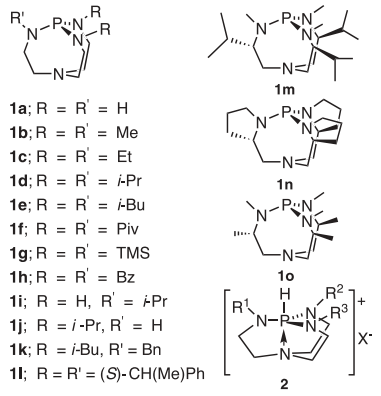


Figure 1. Proazaphosphatranes: Bicyclic, Nonionic Bases.

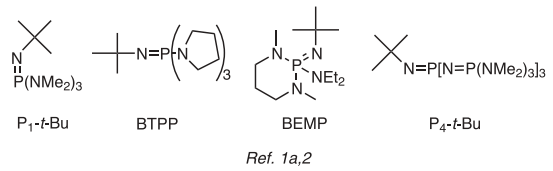
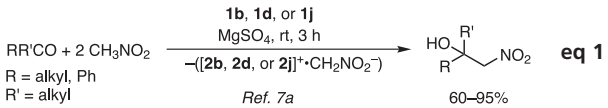
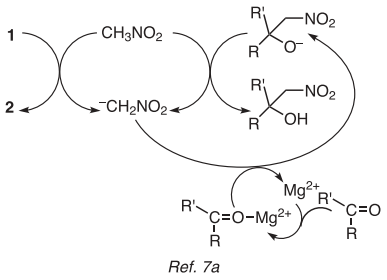
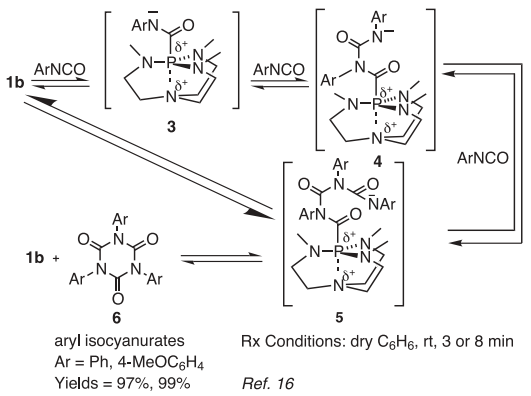


Figure 2. Phosphazene Bases.





Scheme 1. Proposed Mechanistic Pathway for the Nitroaldol Reaction.



Scheme 2. Proposed Pathway for the Trimerization of Arylisocyanates Catalyzed by **1b**.

these bases to effectively facilitate reactions previously restricted to ionic bases such as NaH, KO*t*-Bu, LDA, and NaHMDS.[1,2,4] During the course of many reactions involving proazaphosphatranes, the phosphorus is protonated to form the putative bulky cationic phosphatrane **2** (δ ^{31}P –33 to 0 ppm), which renders the carbanions produced essentially "naked"[1]—a scenario that improves their reactivity and selectivity, and that facilitates the recovery of the proazaphosphatrane for recycling. It is common for the crude products obtained in such reactions to have a better than 95% purity, since the reactions are generally devoid of side reactions that chronically plague transformations mediated by ionic bases.

Base **1b** was the first, broadly useful proazaphosphatrane to be synthesized and characterized.[5] The impetus for its synthesis was its potential as a linear difunctional P,N ligand for making linear metal coordination polymers, but this goal was elusive owing to the poor donor ability of the bridgehead nitrogen. Following our discovery of the unusual basicity of **1b** and its usefulness in stoichiometrically and catalytically facilitating organic transformations,[1] the number of proazaphosphatranes prepared in our laboratories and by others has continued to grow (see Figure 1),[6] as has the number of reactions they promote.[1]

2. Catalytic Reactions

Most of the transformations mediated by proazaphosphatranes are catalytic in nature. Of such reactions, some proceed by nucleophilic attack of the phosphorus on a substrate atom such as carbon or silicon, but most involve deprotonation of a reactant. Although the free base can be detected spectroscopically throughout some of these reactions, others are characterized by a pre-equilibrium in which the proazaphosphatrane is essentially completely protonated by a substrate bearing an acidic proton to give cation **2**, thus generating an anion that acts as the catalyst. The nitroaldol (Henry) reaction is a typical example of the latter reaction.[7] When proazaphosphatrane **1** is used in this reaction (**eq 1**),[7a] no free proazaphosphatrane is detectable by ^{31}P NMR spectroscopy after adding the base to a nitroalkane such as nitromethane. The catalytic cycle for such a nitroaldol reaction is shown in **Scheme 1**.[7a] Because nitriles are less acidic than nitroalkanes, reactions involving the former proceed in the presence of catalytic amounts of proazaphosphatranes.[8–12] It is possible to observe both the free base and its protonated form in the ^{31}P NMR spectrum throughout the course of these reactions.[8–10]

As will be discussed below, proazaphosphatranes also function very effectively as ligands in palladium-catalyzed reactions, providing high product yields. However, only **1e** has so far behaved consistently in this capacity.[13–15]

2.1. Nucleophilic Catalysis

2.1.1. Trimerization of Isocyanates

Several reactions promoted by proazaphosphatranes proceed without detection of the intermediate conjugate acid cation **2**. Based on spectroscopic evidence, it has been concluded that these reactions occur via nucleophilic attack of the proazaphosphatrane phosphorus on an electron-deficient center in the substrate. This process can lead to a partially transannulated intermediate[1] that acts as the active catalytic species. Among the first such catalytic reactions discovered for **1b** was the trimerization of isocyanates in which high product yields (e.g., 97%) were obtained with very low (e.g., 0.33 mol %) catalyst loadings (**Scheme 2**).[16] Triaryl isocyanurates are commonly used as activators for continuous anionic polymerization and post-polymerization reactions of ε-caprolactam in the commercial synthesis of nylon-6 that has a

low unreacted monomer content and a highly stable melt viscosity.[16] Isocyanurates **6** were devoid of any detectable monomer impurities, whose presence usually leads to low-quality nylon. ^{31}P NMR spectroscopic observations suggest that the reaction proceeds via coordination of the phosphorus atom to the carbonyl group of the aryl isocyanate to form the activated species, **3**.[16] This presumably partially transannulated species nucleophilically attacks a second molecule of aryl isocyanate producing **4**. The sequence is repeated to form **5**, which then cyclizes to liberate trimer **6**.

2.1.2. Acylation–Deacylation of Alcohols

Nucleophilic attack of proazaphosphatranes on carbonyl groups has also been implicated in the acylation[17,18] and deacylation of alcohols,[17] and in the transesterification of esters (vide infra).[17] Similarly, and as discussed in Section 2.1.4 below, the silylation and desilylation of alcohols apparently proceed via silicon activation by the proazaphosphatrane.[19–21]

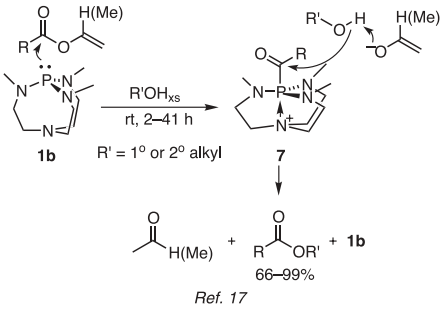
Although many catalysts have been reported for the acylation of alcohols,[22] routes to the selective acylation of hindered alcohols (see Section 3.1.2) and to the efficient acylation of labile alcohols remain in high demand. In the presence of 10 mol % of **1b** or **1d**, allylic, primary, secondary, and benzylic alcohols are readily acylated with vinyl carboxylates such as vinyl acetate, vinyl benzoate, or 2-propenyl acetate.[17] These reactions have been proposed to proceed through activation of the vinyl carboxylate by **1b** or **1d** (**Scheme 3**) to form the P-acylated intermediate, **7**, which then delivers the acyl group to the alcohol with liberation of the carbonyl byproduct (typically acetaldehyde or acetone).[17] The acylation of primary alcohols using this methodology proceeds in 2–6 hours at room temperature, while secondary and other hindered alcohols require up to 41 hours for complete conversion (with the exception of 1-methylcyclohexanol which resisted acylation).[17] Yields are generally high regardless of the enol ester employed.

Iminophosphoranes[23] (e.g., **8** and **9** in **Figure 3**), which are produced by the reaction of proazaphosphatranes (or HMPT) with azides, also serve as catalysts for the acylation of alcohols.[24] Because of their lower reactivity and sterically hindered nature, these bases are efficient catalysts for the selective acylation of primary alcohols in the presence of sterically hindered alcohols (**eq 2**). The acylated product can be easily deprotected with a proazaphosphatrane by simply changing the solvent to a low-molecular-weight alcohol such as methanol.[17] In this deprotection process, the ester carbonyl is activated by the free base (see **7** in Scheme 3) with subsequent acyl group transfer to the solvent and release of the desired alcohol (**eq 3**). These alcohol deprotection reactions are completed in less than 20 minutes for less sterically hindered alcohols. Sterically hindered alcohols, however, require up to 41 hours probably because the rather bulky proazaphosphatrane nucleophile is inhibited from attacking the carbonyl group of the sterically hindered ester.[17] Thus, the process in equation 3 is very selective and the acetylene functionality survives intact, unlike transformations in which DIBAL-H is employed to reduce the alkynyl moiety as well as deprotect the alcohol.[25]

2.1.3. Transesterifications

The above mechanistic ideas were extended to the facile transesterification of labile alcohols such as those containing epoxide and tetrahydrofuran moieties. In the presence of a proazaphosphatrane and an alcohol, such as allyl alcohol or cinammyl alcohol, undesirable ester functional groups can be converted to desirable esters that are either easier to deprotect or are better suited to survive a given set of reaction conditions (**eq 4**).[17] These transesterification reactions proceed in excellent yields and without attack on epoxide or acetonide moieties as has been observed with Ti(O*i*-Pr)$_4$.[26] NaOMe, on the other hand, induces racemization of amino acids.[27] Moreover, the mild conditions employed with the proazaphosphatranes increase their attractiveness over conventional catalysts.

The use of **1b** in equation 4 led to epimerization of the phenylalanine moiety to give a 96% yield of product.[17] Although replacing the catalyst in equation 4 with **1d** preserved the stereochemistry, this strategy did not work with the acetonide of dimethyl tartarate (**10**, **Figure 4**), which epimerized regardless of the base employed.[17] On the other hand, the corresponding methyl valine ester **11** underwent quantitative transesterification to produce the desired allyl ester **12** in the presence of **1b** after 13



Scheme 3. Proposed Pathway for the Acylation of Alcohols with Vinyl Carboxylates Catalyzed by **1b**.

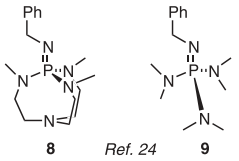
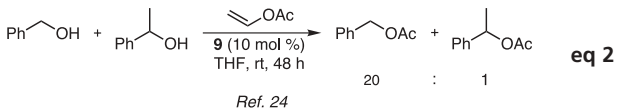
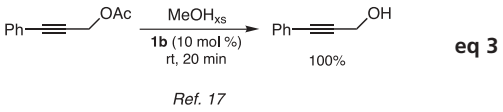
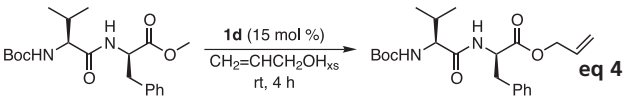


Figure 3. Iminophosphoranes.







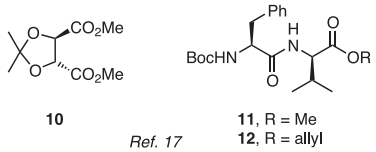
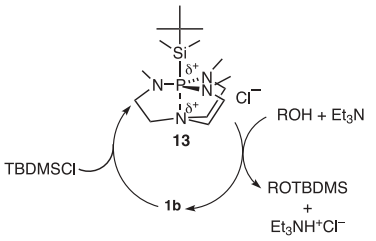
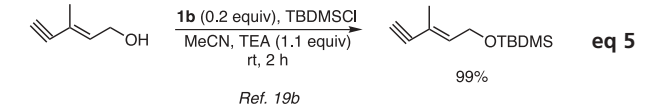


Figure 4. Contrasting Epimerization Behavior of **10** and **11** in the Presence of **1b**.



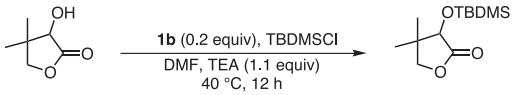
Ref. 19a,b

Scheme 4. Proposed Catalytic Cycle for Alcohol Silylation with **1b**.



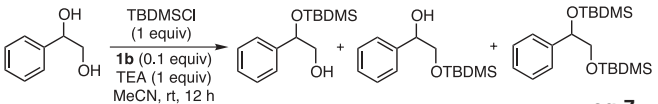
Ref. 19b

eq 5



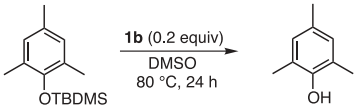
Ref. 19b

eq 6



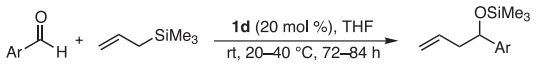
Ref. 19b

eq 7



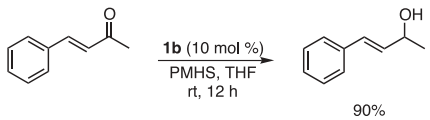
Ref. 21

eq 8



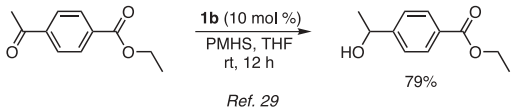
Ref. 28

eq 9



Ref. 29

eq 10



Ref. 29

eq 11

hours with no observable epimerization.[17] Transesterification of methyl benzoate proceeded with allyl alcohol, 2-propanol, ethanol, and cinnamyl alcohol in 82–91% yields. However, transesterification with *tert*-butyl alcohol was not observed even after 24 hours.[17]

2.1.4. Alcohol Silylation–Desilylation

Activation of a silicon center via nucleophilic attack by a proazaphosphatrane has been postulated for the silylation[19,20] and desilylation of alcohols.[21] Both aromatic and aliphatic alcohols are readily silylated in high yields in the presence of catalytic amounts (10–30 mol %) of proazaphosphatranes. ^{1}H and ^{31}P NMR spectroscopic observations of a five-coordinate intermediate analogous to **13** (**Scheme 4**) has led to the belief that these reactions proceed through the formation of an activating P→Si bond between the catalyst and the silyl chloride.[19a] The silyl group is then delivered from **13** to the alcohol, and the freed catalyst re-enters the catalytic cycle.[19,20] Although the yields of silylated products are high with both sterically encumbered and less sterically encumbered alcohols, a number of the latter types of alcohols (e.g., **eq 5**) are silylated in less than 2 hours. In contrast, more sterically hindered alcohols (e.g., **eq 6**) require 3–24 hours.[19b] It is worth mentioning that base **1b** (0.1–0.3 equiv) has also been used successfully in the silylation of alcohols using the bulkier silylating reagent TBDPSCl in 3–24 hours, affording product yields of 67–98%.[19b] The regioselectivity of the silylation depicted in **eq 7**, although in accord with literature results, is much higher than those reported with other bases.[19b] We do not currently have sufficient evidence to support initial silylation of the primary hydroxyl group followed by migration of the silyl group to the secondary hydroxyl group. We do, however, have evidence that the primary silylated hydroxyl group easily undergoes desilylation. The proazaphosphatrane oxide $OP(MeNCH_2CH_2)_3N$ (prepared by oxidation of **1b** with a peroxide) also promotes the silylation of alcohols;[20] in this case, the observed reaction times and yields are comparable to those obtained with **1b**.[20]

The reverse reaction (i.e., the desilylation of alcohols) necessitated the use of more forcing conditions, namely, temperatures of up to 80 °C (**eq 8**), 20–40 mol % of the catalyst, and 24–36 hours.[21] Although both the TBDMS and the TBDPS groups could be removed under these conditions, generally lower yields (22–45%) were observed with TBDPS as compared with the TBDMS group (68–94%). The resistance of silylated alcohols to deprotection at room temperature can be associated with the higher yields observed in the silylation of alcohols as compared to their acylation reactions.[17,18] Both reaction types are assumed to be reversible, with the difference being that the equilibria for the latter reactions lie more toward the deprotected state.[17]

Noteworthy about the desilylation of TBDMS ethers is the observation that DMSO or MeCN was required as solvent, and that the byproducts were TBDMSA (A = CH_2CN, CH_2SOMe) in which the Si–C bond was formed presumably after activation of the silicon by **1b**.[21] As we now describe, activation of a silicon center can also be exploited for the preparation of homoallylic alcohols,[28] in the reduction of carbonyl compounds using poly(methylhydrosiloxane) (PMHS),[29] and in the preparation of alcohols and TMS ethers.[30]

The preparation of homoallylic alcohols in 44–80% yields was achieved by reacting aromatic aldehydes with allyltrimethylsilane in the presence of 20 mol % of **1d** at 20–40 °C for up to 84 hours (**eq 9**).[28] Lower yields were recorded for aldehydes bearing electron-donating groups (e.g., 4-methylbenzaldehyde and 4-methoxybenzaldehyde), while 2-thiophenecarboxaldehyde gave an 80% product yield. For reasons not presently clear, the less sterically hindered base **1b** proved to be ineffective for this transformation. The reaction is assumed to proceed via activation of the allylsilane by attack of the phosphorus atom of **1d** at the allylic silicon atom to form a phosphonium ion, with concomitant formation of an allylic anion that then adds to the aldehyde. This mechanism is supported by the observation that the reaction of crotyltrimethylsilane leads to the formation of both α- and γ-addition products, although the reaction is rather sluggish.[28]

In the presence of catalytic amounts of **1b**, poly(methylhydrosiloxane) (PMHS) reduces aldehydes and

ketones selectively in the presence of other reducible functional groups such as double bonds (**eq 10**) and esters (**eq 11**).[29] These reactions occur by activation of the methylhydrosiloxane moiety to form an activated species (**Scheme 5**) that attacks the carbonyl oxygen via its silicon atom, followed by delivery of a formal hydride to the carbonyl carbon. The intermediate siloxane so produced liberates the alcohol during acidic or basic workup.[29]

In accord with this mechanism, it was found that the activated species—presumably formed from TMSCN and **1b**—adds to aldehydes (**eq 12**) and ketones (**eq 13**) to form the corresponding TMS ethers.[30] However, the reaction with aldehydes led to the formation of a mixture of the alcohol and the corresponding silyl ether even at 0 °C, presumably owing to the presence of adventitious water. This mixture of products was easily converted completely to the alcohol upon treatment with 1.0 M HCl.[30]

The foregoing mechanistic rationales can also be applied to the desulfurization of organic compounds with proazaphosphatranes. This stoichiometric reaction is assumed to proceed through activation of the sulfur by the phosphorus of the proazaphosphatrane followed by liberation of the desulfurized product.[31]

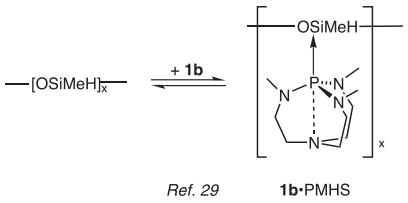
2.2. Base Catalysis

2.2.1. Deprotonation of Simple Nitriles

A substantial fraction of reactions promoted by proazaphosphatranes proceeds via direct protonation of the latter by acidic substrate protons. An example of the usefulness of this process is the deprotonation of simple nitriles to generate anions that are very efficiently utilized for the preparation of β-hydroxy nitriles,[12] α,β-unsaturated nitriles,[8] glutaronitriles,[9] β,γ-unsaturated nitriles,[10] and ω-unsaturated ketones.[11] It should be noted that nitriles can provide α,β-unsaturated or β-hydroxy nitriles by a small change in the reaction conditions. Thus, the preparation of *E* cinnamyl nitriles was achieved in 50–99% yields by heating a benzyl nitrile with an aromatic aldehyde at 40–50 °C for 3–6 hours in the presence of **1b** or **1j** (**eq 14**).[8] Similar reactions were also accomplished with benzyl cyanide in THF, methanol, or benzene—producing the corresponding trisubstituted nitriles exclusively and in generally excellent yields.[8] The formation of these products is assumed to proceed by deprotonation of benzyl nitrile to generate an anion that adds to the aldehyde and produces an intermediate β-hydroxy nitrile. This intermediate is then dehydrated via deprotonation by the proazaphosphatrane, or is thermally dehydrated at the moderate temperatures employed.[8] Dehydration mediated by proazaphosphatranes was also reported from our laboratories in the synthesis of nitriles from aldoximes (**eq 15**)[32] and, as we shall see in Section 2.2.2, this process also occurs in the preparation of coumarins,[33] benzofurans,[34] oxazolines,[35] and α,β-unsaturated esters.[36]

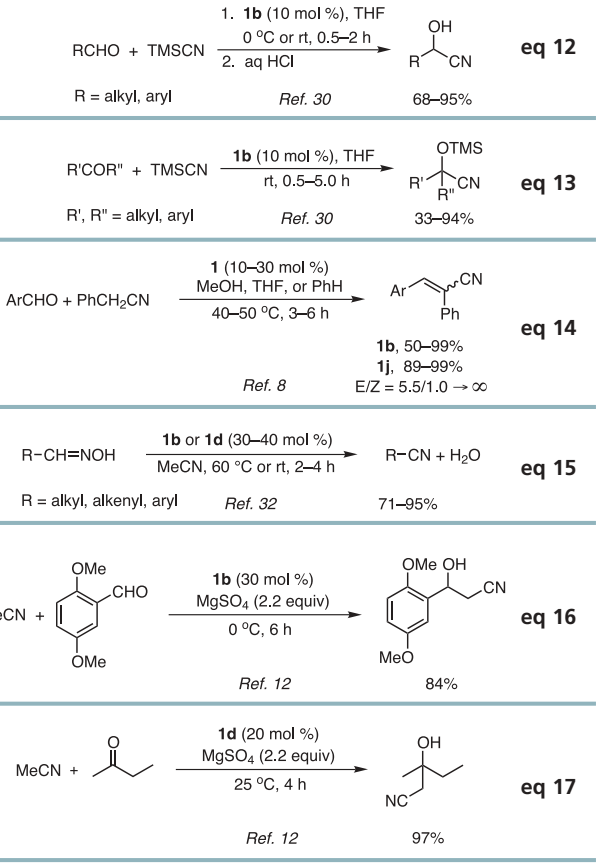
The synthesis of α,β-unsaturated nitriles just described affords a direct route to this class of compounds, which have traditionally been prepared by indirect routes. Among the latter processes are the thermal dehydration of an intermediate β-hydroxy nitrile[37] and the Wittig–Horner reaction.[38] Also reported is the utilization of various metals such as Zn,[39a] Pd,[39b] and $RuH_2(PPh_3)_4$[39c]—and, more recently, the use of cetyltrimethylammonium chloride as a surfactant[40]—for the preparation of α,β-unsaturated nitriles. However, all of these indirect methodologies are less versatile than our direct approach, owing to the occurrence of a number of side reactions that reduce yields and render purifications tedious.[8]

The β-hydroxy nitrile anion intermediate described above can be stabilized by magnesium ions. Advantage of this observation was taken in an efficient synthesis of β-hydroxy nitriles.[12] Thus,



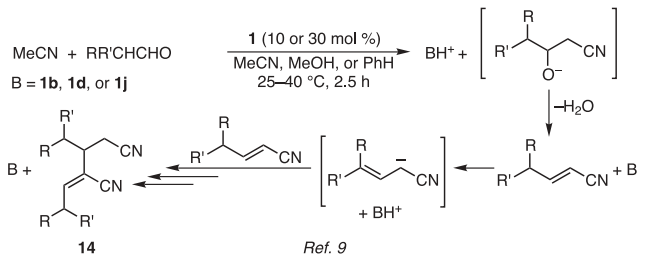
Ref. 29 **1b**·PMHS

Scheme 5. Proposed Activation Mode of PMHS by **1b**.

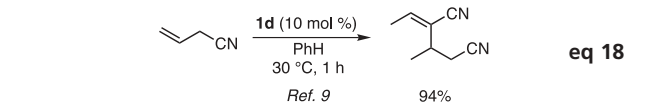


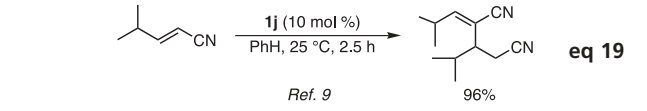
when the reaction of acetonitrile with carbonyl compounds, including ketones and aromatic as well as aliphatic aldehydes (except primary ones), is carried out in the presence of 2 equivalents of magnesium sulfate, the predominant product is the β-hydroxy nitrile (**eq 16** and **17**). Primary aliphatic aldehydes, such as *n*-heptaldehyde, produce the aldol product; while enones, such as 2-cyclohexenone, produce dimers in 99% yields.[12]

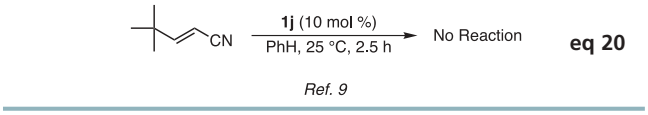
The reaction in equation 16 often produces significant amounts of the undesired corresponding α,β-unsaturated nitrile. However, this side product was efficiently suppressed to 2–6% by carrying out the reaction at 0 °C, followed by quenching with methanol at this temperature before workup.[12] Our methodology for preparing β-hydroxy nitriles is more convenient than classical methods, which include the opening of epoxides with an inorganic nitrile such as KCN[41a] or acetone cyanohydrin,[41b] the three-component coupling of acrylonitrile with an alkyl iodide and a ketone in the presence of a manganese–lead system in THF–DMF,[41c] and the use of mercuric fulminate (among other environmentally undesirable reagents).[41d] Strong ionic bases have also been used to prepare β-hydroxy nitriles. However, the yields are poor to moderate and the reactions require cryogenic temperatures.[12] In this regard, it should be mentioned that the preparation of a β-hydroxy nitrile

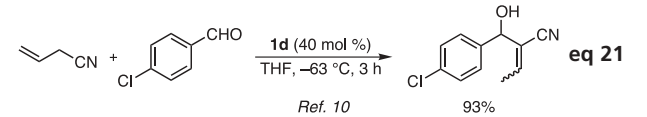


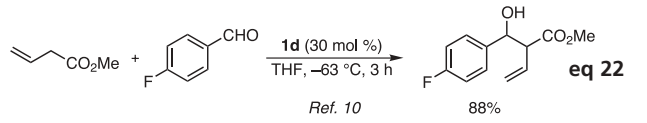
Scheme 6. Proposed Pathway for Glutaronitrile Formation Facilitated by **1b**, **1d**, or **1j**.

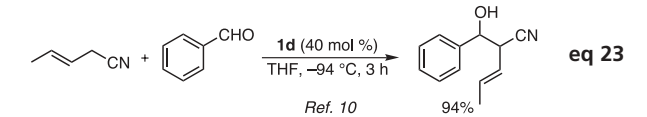


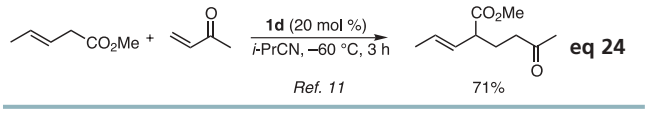


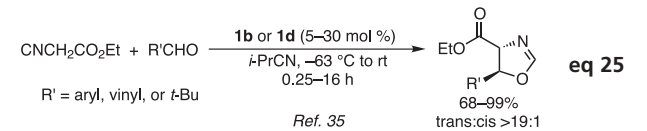


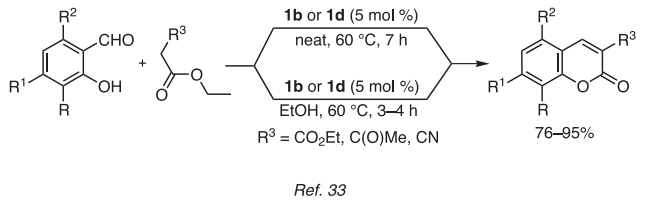












Scheme 7. Coumarin Synthesis Using **1b** or **1d** and a Diactivated Methylene Substrate.

from benzyl cyanide in THF in the presence of $P(MeNCH_2CH_2)_3N$ (**1b**) also required a temperature of –78 °C.[12]

In the absence of magnesium ions, secondary aldehydes such as isobutyraldehyde, 2-methylbutyraldehyde, and 2-ethylbutyraldehyde react with acetonitrile in the presence of 10–30 mol % of proazaphosphatranes to generate glutaronitriles, **14**, which are useful in copolymerization reactions, in 81–98% yields (**Scheme 6**).[9]

This reaction is assumed to proceed through a Michael-type addition of an allylic anion to an already formed molecule of an α,β-unsaturated nitrile. The presumed presence of an allylic anion during the reaction was made plausible by the observation that β,γ-unsaturated nitriles (**eq 18**) and an α,β-unsaturated nitrile bearing a γ proton (**eq 19**) readily dimerized in the presence of proazaphosphatranes such as **1b**, **1d**, or **1j**.[9] On the other hand, 3-*tert*-butylacrylonitrile, which lacks a γ proton, failed to dimerize (**eq 20**). Further support for this pathway was provided in two subsequent reports, the first of which showed that allylic nitriles and esters could be employed in a Baylis–Hillman-type reaction and in the preparation of β,γ-unsaturated nitriles and esters (**eq 21–23**).[10] In the second report, it was demonstrated that the preparation of δ,ε-unsaturated ketones can be carried out via a Michael-type addition of an allylic nitrile or an allylic ester (**eq 24**) to α,β-unsaturated ketones.[11]

2.2.2. Preparation of Oxygen Heterocycles

We now examine the use of proazaphosphatranes in the preparation of heterocyclic compounds such as oxazolines,[35] coumarins,[33] and benzofurans.[34] The preparation of isocyanurates[16] has already been discussed (Section 2.1.1), while the synthesis of pyrroles (Section 3.2.3),[42] oxazoles (Section 3.2.3),[42] and epoxides (Section 3.1.3)[43] will be discussed in some detail later.

In catalytic amounts, **1b** and **1d** deprotonate ethyl isocyanoacetate to generate an anion that adds to aldehydes (including 2-furaldehyde, cinnamaldehyde, and trimethylacetaldehyde) (**eq 25**).[35] This reaction produces oxazolines in moderate-to-excellent yields and with high trans diastereoselectivities (>19:1) for reasons that are not clear at this time.[35] It also provides a direct route to trans oxazolines that overcomes the lack of selectivity that has been experienced with other reagents such as NaCN/EtOH, $ZnCl_2$, $ZnCl_2$/CuCl, or Cu_2O.[35] The proazaphosphatrane-promoted synthesis of oxazolines typically requires 5–30 mol % of the catalyst at –63 °C to room temperature in isobutyronitrile as the solvent. Aldehydes bearing electron-withdrawing groups (such as 4-chloro-, 4-cyano-, 4-nitro-, and 4-fluorobenzaldehyde) as well as 2,5-dimethylbenzaldehyde and pivalaldehyde react at lower temperatures (typically –63 to 0 °C). Unfortunately, the reaction of primary alkyl aldehydes forms mixtures of products.[35]

Although several high-yield reactions exist for the synthesis of coumarins, the use of proazaphosphatranes offers a mild alternative.[33] Thus, 5 mol % of **1b** or **1d** readily promotes the reaction of salicylaldehydes with a variety of diactivated methylene compounds, affording the corresponding coumarins in high yields (**Scheme 7**). Coumarins prepared from carbonyl compounds bearing only one activating group require prior preparation of the intermediate phenol ester (**Scheme 8**), and ring closure typically requires a higher catalyst loading (0.4 equiv) for optimum yields.[33]

Benzofurans can be prepared in 80–90% yields by heating 2-(2-formylphenyloxy)acetates (generated from salicylaldehydes and ethyl bromoacetate) with 40 mol % of **1b** in ethanol at 70 °C for 3 hours (**Scheme 9**).[34] The ease of this reaction makes it a

practical route for the synthesis of this class of compounds. Other bases employed have routinely afforded lower yields or have required indirect approaches.[34]

2.2.3. Michael Additions of Nitroalkanes, Alcohols, and Esters

As discussed earlier, proazaphosphatranes **1b**, **1d**, **1e**, **1f**, and **1j** easily deprotonate nitroalkanes, and the nitronate ions thus produced add to aldehydes and ketones in the presence of magnesium sulfate to produce nitroalkanols (Scheme 1**)**.[6b,7] This proazaphosphatrane-mediated reaction affords the advantages of high yields and short reaction times as compared with other bases. In addition, the proazaphosphatrane is completely protonated during the reaction, forming the corresponding azaphosphatrane nitronate (**2**), which is insoluble. At the end of the reaction, removal of the salt by filtration through silica gel or by aqueous workup affords the product in high purity. This route eliminates the need for acid neutralization of the reaction mixture, a process that usually leads to the Nef reaction[44] if not performed carefully.

The nitronate generated by proazaphosphatranes can also undergo facile Michael addition to α,β-unsaturated compounds (**eq 26**).[45] This transformation is especially useful for hindered nitroalkanes for which the Michael addition has thus far remained problematic.[45] Yields are often nearly quantitative and purities of the crude products are in excess of 95%.

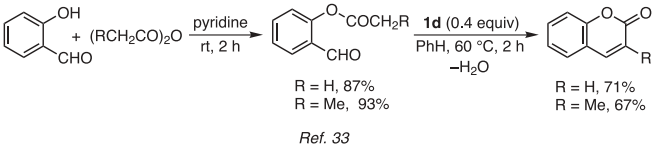
Proazaphosphatranes can also be used in the Michael addition reactions of alcohols or a Schiff base.[45] Hence, the deprotonation of methanol or allyl alcohol using 10–20 mol % of a proazaphosphatrane at 50 or 70 °C leads to the formation of β-alkoxy ketones (**Scheme 10**), which are important intermediates in organic synthesis. Michael addition of the Schiff base $Me_3CCH{=}NCH_2CO_2Me$ to α,β-unsaturated ketones or esters occurs at room temperature in the presence of 10 mol % of the proazaphosphatrane (**eq 27**).[45] This reaction proceeds with selective formation of the anti diastereomer (7:1 to absolute) without production of the corresponding cycloaddition product as is observed with DBU.[46] Interestingly, the use of DBU requires the presence of LiBr to stop the reaction at the Michael adduct stage.

2.3. Catalysis by Metal Complexes

Proazaphosphatranes function as electron-rich ligands for palladium(0) by virtue of the amino substituents adjacent to the phosphorus and because of the potential for transannulation by the bridgehead nitrogen. Another advantage of these ligands is that their steric bulk can be fine-tuned by varying the substituent R in P–N–R. Proazaphosphatranes have recently been found to promote palladium-catalyzed cross-coupling reactions such as the extensively investigated Suzuki reaction,[47] the Hartwig–Buchwald amination reaction,[48] and the direct α arylation of nitriles.[49] We will also touch on the titanium(IV)-catalyzed Baylis–Hillman reaction,[50] which is greatly improved by the thiono derivative of **1b**, namely, **15** (**Figure 5**).

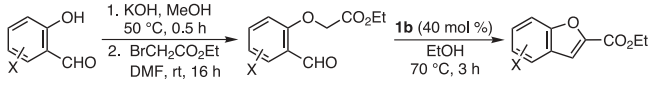
2.3.1. Suzuki Cross-Coupling Reaction

We have recently demonstrated that 4 mol % of **1e** in the presence of 2 mol % of palladium acetate serves as an effective catalyst system for the cross-coupling of boronic acids with aryl bromides in 4–12 hours (**eq 28**).[13] The reaction requires 1.5 equivalents of cesium carbonate to proceed to completion, and yields are generally in the 90–99% range. The acyclic analogue $P(NMe_2)_3$ affords lower yields under similar reaction conditions. The coupling of aryl chlorides, on the other hand, requires higher loadings of **1e** and longer reaction times (**eq 29**).[13]



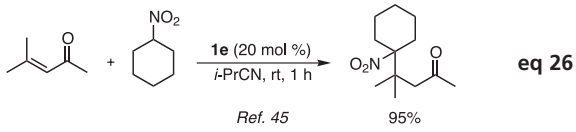
Ref. 33

Scheme 8. Coumarin Synthesis Through the Intermediacy of Acylated Salicylaldehydes.



Ref. 34

Scheme 9. Benzofuran Synthesis Using **1b**.



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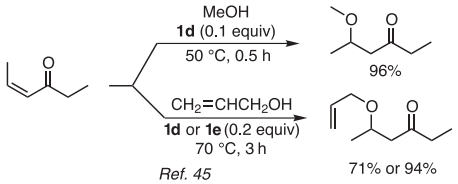
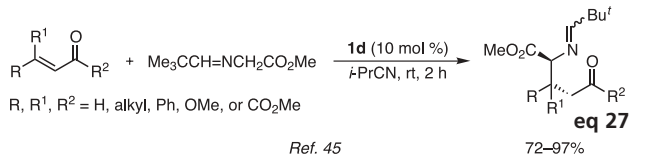


Ref. 45

Scheme 10. Oxa-Michael Addition Facilitated by **1d**, **1e**, or **1f**.



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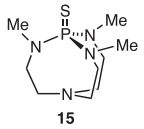
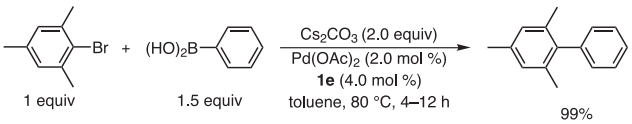
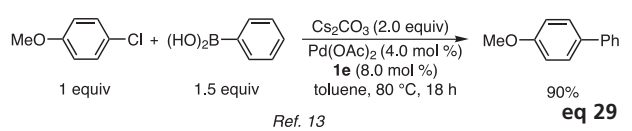


15

Figure 5. Thiono Derivative of **1b** Used in the Ti(IV)-Catalyzed Baylis–Hillman Reaction.



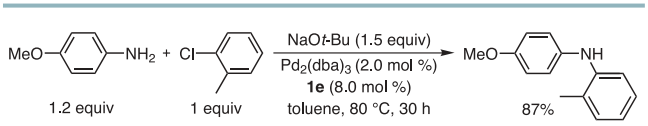
Ref. 13



Ref. 13

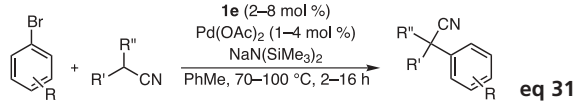
2.3.2. Coupling of Aryl Halides with Amines

These results motivated us to investigate other palladium-mediated cross-coupling reactions. Thus aryl bromides and iodides effectively couple with both aliphatic and aromatic amines in the presence of catalytic amounts of palladium acetate and **1e**.[14a] Other proazaphosphatranes investigated for this reaction



Ref. 14b

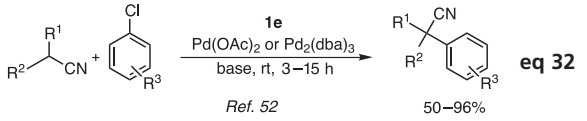
eq 30



R = H, *t*-Bu, OMe, CN
R' = H, Me, Et
R'' = H, Me, Ph, $PhSO_2$

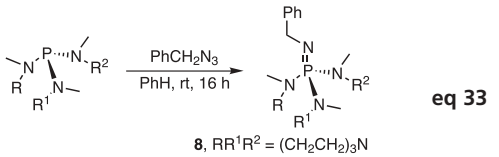
Ref. 51

eq 31



Ref. 52

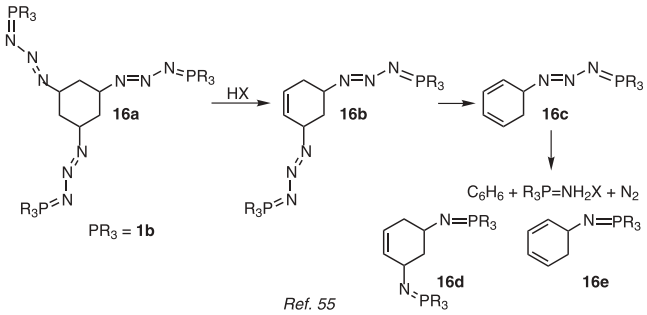
eq 32



8, $RR^1R^2 = (CH_2CH_2)_3N$
9, $R = R^1 = R^2 = Me$

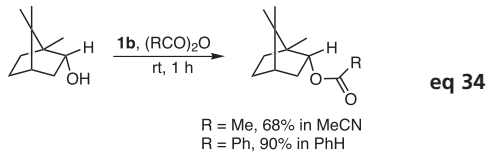
Ref. 24

eq 33



Ref. 55

Scheme 11. Benzene Formation by Sequential Protonation of Azido Groups.



R = Me, 68% in MeCN
R = Ph, 90% in PhH

Ref. 18

eq 34

performed poorly, probably because of their unfavorable balance of electron-donor and steric properties. Aromatic amines and aliphatic secondary amines afforded good-to-excellent yields, while aliphatic primary amines provided modest yields.[14a] The coupling of aryl chlorides with amines was also successful under similar reaction conditions, or in the presence of $Pd_2(dba)_3$ (**eq 30**).[14b] Products were obtained in high yields with both aromatic and aliphatic amines, although some acyclic secondary amines gave lower yields.

2.3.3. Coupling of Aryl Halides with Aliphatic Nitriles

α-Aryl-substituted nitriles are not only very important building blocks for synthesizing pyridines, carboxylic acids, primary amines, bicyclic amidines, lactones, aldehydes, and esters; but such nitriles are also valuable for constructing biologically active compounds containing a tertiary benzylic nitrile.[51] Usually, such compounds are synthesized by displacement of an activated benzylic alcohol or halide with cyanide, followed by α alkylation. Using ligand **1e**, ethyl cyanoacetate and primary as well as secondary nitriles are directly and efficiently coupled with a wide variety of aryl bromides possessing electron-rich, electron-poor, electron-neutral, and sterically hindered groups (**eq 31**).[51]

Although aryl chlorides are both more abundant and less expensive than their corresponding iodides, bromides, and fluorides, they are much less reactive and, to date, the addition of a nitrile anion to an aryl chloride has been realized only with relatively acidic cyanoacetates in the presence of a Pd–P(*t*-Bu)$_3$ or $Ph_5C_5FeC_5H_4P(t\text{-Bu})_2$ catalyst system.[49d,e] A general solution to this long-standing challenge has been achieved by employing bicyclic **1e** as a ligand for palladium, which leads to efficient coupling of an array of nitriles with a broad range of aryl chlorides (**eq 32**).[52]

2.3.4. Coupling of Activated Alkenes with Carbonyl Compounds

The Baylis–Hillman (BH) reaction, i.e., the coupling of an activated alkene or alkyne with an aldehyde or ketone, has recently been a very attractive tool.[50] The reaction usually requires Lewis bases as catalysts, among which Dabco® is the most popular. However, this transformation requires very long reaction times (up to 7 days), which limits the scope of substrates that could take part. Among Lewis acids that are commonly used for activating the carbonyl group[53] is $TiCl_4$, but yields are generally only moderate and limitations are encountered on the structures of the alkene/alkyne and the carbonyl compounds that undergo addition. We were surprised to discover that at room temperature the proazaphosphatrane sulfide, **15**, greatly accelerates BH reactions of activated alkenes catalyzed by $TiCl_4$.[54] To our knowledge, **15**/$TiCl_4$ is the most effective and selective catalytic system reported thus far for BH reactions, tolerating a wide scope of acceptors and carbonyl compounds. Our protocol is applicable to activated alkenes such as enones (including the less reactive β-substituted derivatives), acrylonitrile, and acrylates.

3. Stoichiometric Reactions

3.1. Nucleophile-Mediated Reactions

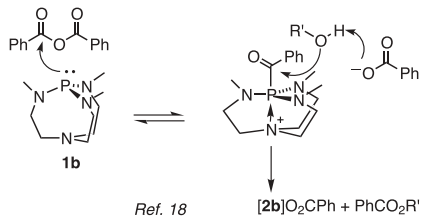
3.1.1. Reaction with Azides

A number of transformations are known in which proazaphosphatranes attack electron-deficient centers with concomitant formation of a covalent bond, either as part of the product or the byproduct. For example, bases **1b** and P(NMe$_2$)$_3$ have been used to prepare iminophosphoranes **8** and **9** by allowing them to react with azides such as benzyl azide (**eq 33**).[24] Compounds **8** and **9** have been used as mild catalysts for the acylation of alcohols (see Section 2.1.2) with enol esters.[24] Chiral proazaphosphatrane **1l** reacts with chiral azides to give diastereomeric products, whose ee values can be determined by ^{31}P and ^{1}H NMR analyses.[6d] Good peak separations in both types of NMR spectra permit consistent ee values to be obtained.

Interestingly, the novel triazide **16a**, which incorporates **1b**, gives benzene in the presence of a stoichiometric amount of a weak acid at room temperature (**Scheme 11**).[55] This process proceeds through sequential protonation of the azido moieties of **16a** followed by their decomposition, via **16b** and **16c**, to nitrogen gas and the $^{+}H_2N{=}PR_3$ cation, which has been isolated as its chloride salt. Evidence for this mechanism was adduced from the observed side products, **16d** and **16e**, which formed competitively.

3.1.2. Activation of Anhydrides

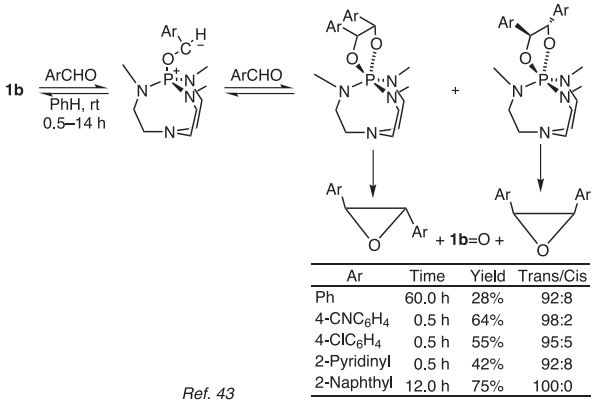
In the presence of stoichiometric amounts of proazaphosphatranes such as **1b** or **1c**, acetic anhydride (or benzoic anhydride) reacts with acid-labile or sterically hindered alcohols to give acylated alcohols in 48–99% yields (**eq 34**).[18] The reaction is believed to proceed by activation of the anhydride with the proazaphosphatrane as illustrated in **Scheme 12**. This methodology is very effective for sterically hindered alcohols and phenols, and it complements the aforementioned use of iminoproazaphosphatranes **8** and **9**, which are catalysts for the more efficient acylation of less sterically hindered alcohols.[24]



Scheme 12. Proposed Intermediate in the Benzoylation of Alcohols Mediated by **1b**.

3.1.3. Symmetrical Epoxides from Aromatic Aldehydes

Reaction of proazaphosphatrane **1b** with aldehydes over 0.5–60 h leads to the formation of symmetrical trans epoxides in high yields and selectivities.[43] The epoxides are generated in yields ranging from 28% for benzaldehyde up to 75% for 2-naphthaldehyde—with 4-cyanobenzaldehyde, 4-chlorobenzaldehyde, and 2-pyridinecarboxaldehyde, among others, producing yields toward the high end of this range.[43] Here, the proazaphosphatrane presumably nucleophilically attacks the carbonyl oxygen to form a zwitterionic species (**Scheme 13**). This intermediate reacts with a second molecule of aldehyde to form a tricylic 1,3,2-dioxaphospholane intermediate in which the aryl groups have either a cis or a trans relationship. Steric interaction between the aryl rings and the proazaphosphatrane methyl groups favors the cis intermediate, which subsequently epimerizes to the trans epoxide.[43] Reactions carried out under similar conditions with the acyclic analogue $P(NMe_2)_3$ afford mediocre yields; selectivities are also poor, probably because $P(NMe_2)_3$ lacks the required rigidity inherent in the cage structure of **1b**.

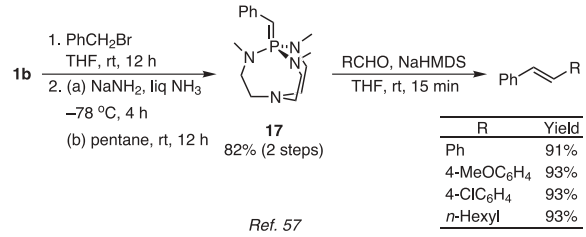


Ar	Time	Yield	Trans/Cis
Ph	60.0 h	28%	92:8
4-CNC_6H_4	0.5 h	64%	98:2
4-ClC_6H_4	0.5 h	55%	95:5
2-Pyridinyl	0.5 h	42%	92:8
2-Naphthyl	12.0 h	75%	100:0

Scheme 13. Proposed Pathway to Trans Epoxides Facilitated by **1b**.

3.1.4. Conversion of Benzyl Halides to *E* Alkenes

Proazaphosphatrane **1b** reacts with primary alkyl halides (via nucleophilic displacement of the halide) to form rather insoluble halide salts.[56] These salts react with strong bases such as $NaNH_2$, LDA, KHMDS, *t*-BuOK, or LiHMDS to form a novel class of semistabilized and nonstabilized phosphorus ylides, such as **17**, which react with aldehydes to form *E* olefins highly selectively (**Scheme 14**).[57] It is worth mentioning that traditional semistabilized phosphorus ylides afford a mixture of *E* and *Z* olefins in such reactions, while their nonstabilized counterparts yield exclusively *Z* olefins.[57] The reversal in selectivity observed with proazaphosphatrane ylides has been attributed to steric interactions in the transition state of the reaction with the aldehyde. It has also been shown that the selectivity is not influenced by the metal ion employed, as is observed with ylides derived from the acyclic analogue $P(NMe_2)_3$.[57]



R	Yield
Ph	91%
4-$MeOC_6H_4$	93%
4-ClC_6H_4	93%
n-Hexyl	93%

Scheme 14. Conversion of Benzyl Halides to *E* Alkenes.

3.2. Base-Mediated Reactions

3.2.1. Dehydrohalogenation of Organic Halides

Among these transformations are the formation of olefins[56,58-60] and phosphorus ylides[61] via dehydrohalogenation of organic halides. Dehydrohalogenation using **1b** stoichiometrically was recently used in the preparation of derivatives of vitamin A.[60]

Although the unsubstituted proazaphosphatrane **1a** has not been isolated,[1] its salt **2a**X and the Merrifield resin mounted **[polymer]•2a** (**Figure 6**) have recently been treated with NaH to generate their respective bases in situ, which act as promoters in dehydrohalogenation reactions.[59] It is worth mentioning that, by itself, NaH was not able to promote the reaction appreciably. Yields observed in the dehydrohalogenation reaction are comparable to those using free **1b** stoichiometrically.[58] Although the dehydrohalogenation can proceed via the pathway shown in **Scheme 15**, NMR evidence indicates that acetonitrile used as solvent in these reactions can also act as the catalytically active species (**Scheme 16**).[56,58] Debromination to alkenes is also feasible, and this process is proposed to occur via a nucleophilic abstraction of a bromonium ion, followed by bromide ion elimination and subsequent phosphonium ion reduction with NaH to regenerate the catalyst (**Scheme 17**).[59]

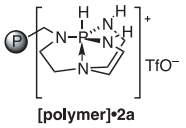
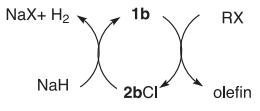


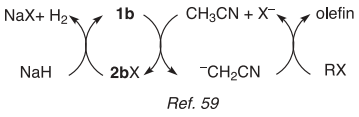
Figure 6. Merrifield Resin Mounted Proazaphosphatrane Salt **2a**.

Alkylphosphonium halides and diethyl alkylphosphonates can be converted by **1b** to the corresponding ylides, which can be used in situ for Wittig and Wittig–Horner olefinations with yields and selectivities comparable to those observed with other bases such as NaH or KO*t*-Bu.[61]



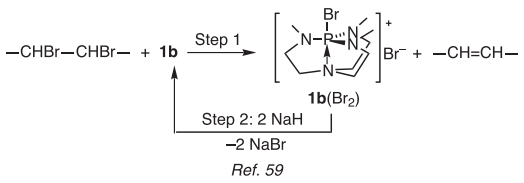
Ref. 59

Scheme 15. Dehydrohalogenation of Organic Halides by Direct Deprotonation with **1b**.



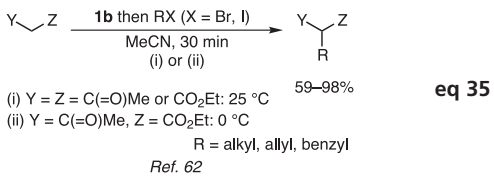
Ref. 59

Scheme 16. Dehydrohalogenation of Organic Halides by Indirect Deprotonation with $^{-}CH_2CN$.



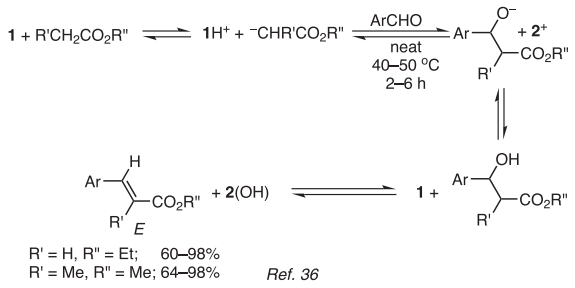
Ref. 59

Scheme 17. Proposed Pathway for Debromination Facilitated by **1b**.



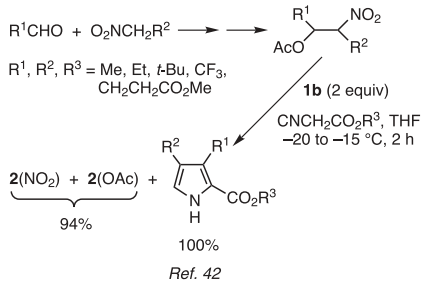
eq 35

Ref. 62



Ref. 36

Scheme 18. Synthesis of *E* α,β-Unsaturated Esters Promoted by **1**.



Ref. 42

Scheme 19. One-Pot Synthesis of Alkyl Pyrrole-2-carboxylates.

3.2.2. Monoalkylation of Activated Methylene Compounds

Proazaphosphatranes such as **1b** and **1d** stoichiometrically mediate the monoalkylation of activated methylene compounds (**eq 35**).[62] This process has traditionally been plagued by side-product formation such as O-alkylation and condensation reactions. Base **1b** mediates a facile monoalkylation of malonates and 2,4-pentanedione at room temperature with yields of 59–98%. Methylation of the unsymmetrical substrate ethyl acetoacetate using **1b** provides a 98:2 selectivity for monoalkylation over dialkylation. Switching from **1b** to the more sterically hindered **1d** decreased the selectivity to 92.5:7.5.[62]

3.2.3. Miscellaneous Base-Mediated Reactions

Proazaphosphatranes **1b**,[36] **1d**,[36] and **1e**[6b] are efficient bases for the direct synthesis of *E* α,β-unsaturated esters from aromatic aldehydes and simple esters such as ethyl acetate and methyl propionate (**Scheme 18**). The selectivity for the formation of the *E* esters is high even with the trisubstituted olefinic moiety obtained with methyl propionate.[6b,36] Although the reactions can be carried out in isobutyronitrile as solvent, the use of the starting esters as solvents leads to higher *E* selectivities.[36] The mechanistic pathway shown in Scheme 18 gives, in addition to the desired unsaturated ester, **2**(OH) which has been isolated in one case (from the reaction of **1b** with water) and characterized.[63] Moreover, proazaphosphatranes **1d** and **1e** are more effective than **1b** for the synthesis of *E* α,β-unsaturated esters.[36]

Proazaphosphatrane **1b** facilitates the efficient synthesis of pyrroles and oxazoles.[42] Pyrroles are important intermediates in the synthesis of biologically active molecules such as porphyrins, bile pigments, drugs, and agrochemicals.[42] An efficient, one-pot synthesis of α-(alkoxycarbonyl)pyrroles and an improved route to octaethylporphyrin (giving an impressive overall yield of 62%) were developed using **1b** as a stoichiometric base.[42] It is believed that the strong basicity of **1b** promotes a facile and complete elimination of HOAc in the first step, followed by a rapid conversion of the isocyanoacetate to the enolate (**Scheme 19**). This process is followed by Michael addition of the enolate to the α-nitro olefin, even at low temperature. This pathway is supported by the reaction shown in **eq 36**.[42]

Oxazoles have been widely employed as synthetic intermediates in the preparation of a number of biologically active α-*C*-acyl amino acids, which are used in the preparation of sympathomimetic agents such as ephedrine and epinephrine.[42] Proazaphosphatrane **1b** permits the preparation of oxazoles in nearly quantitative yields in 1.5 hours from acid chlorides or anhydrides and isocyanoacetates (**Scheme 20**).[42] Hydrolysis of the oxazoles affords α-*C*-acyl amino acids in high yields. This procedure is more advantageous than those employing DBU or TEA, because of the lower base loading required, shortened reaction times, and the formation of salts of **2b**. These salts, which precipitate out of the reaction medium, are readily separated, and the free base is subsequently easily regenerated.[42]

Proazaphosphatrane **1b** has been used to create an oxazole moiety in the synthesis of highly fluorescent (fluorescence quantum yield of 0.99) compounds from the corresponding chiral isocyanides.[64] Optically active fluorescent materials with high quantum yields and/or strong circular dichroism signals are rare, but they are important standards in fluorescence-detected circular dichroism for on-column capillary electrophoresis.

Base **1b** was successfully employed in the synthesis of nonstable and somewhat stable sulfur ylides from sulfonium salts. These ylides were then trapped with aldehydes to form oxiranes

(**Scheme 21**).[65] Although other bases such as *n*-BuLi and LDA can be used in such reactions, the ambient temperature utilized for **1b** is advantageous over the cryogenic conditions required by the ionic bases. Furthermore, ylides generated from allylsulfonium salts using **1b** do not undergo [2,3]-sigmatropic rearrangements as is observed when *n*-BuLi is employed.[66]

4. Conclusions and Outlook

Proazaphosphatranes have proven their usefulness in organic synthesis as catalysts and as stoichiometric bases, with new applications being discovered on an ongoing basis. In catalytic applications, proazaphosphatranes can vary in their activities, thus allowing for fine tuning of their activities by changing substituents, especially on the nitrogens adjacent to phosphorus. We are currently examining recyclable polymer- and mesoporous-silica-bound proazaphosphatranes as well as new polycyclic aminophosphine bases in catalytic applications. We are also exploring the use of pentavalent derivatives of proazaphosphatranes (such as the imino, oxo, and thio derivatives) as catalysts, as well as the use of chiral proazaphosphatranes that may yet prove to be efficacious in catalytic asymmetric synthesis.

5. References and Notes

(†) This article is based on a more comprehensive review published by the authors in *Tetrahedron* **2003**, *59*, 7819–7858.

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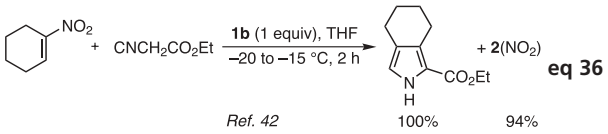
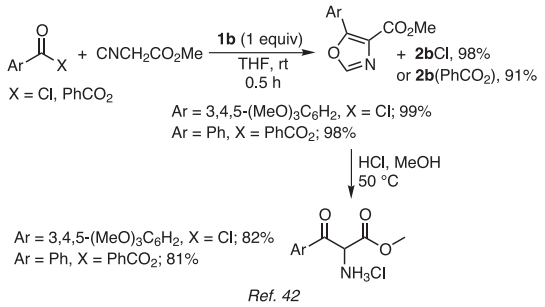
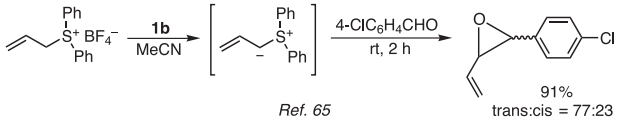




Scheme 20. High-Yield Synthesis of Oxazoles, Precursors of α-*C*-Acyl Amino Acids.



Scheme 21. Formation of Sulfur Ylides Facilitated by **1b**.

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John Verkade was born in Chicago to Dutch immigrant parents. He earned his B.S. degree in chemistry in 1956 from the University of Illinois at Urbana-Champaign, and his M.A. degree in chemistry in 1958 from Harvard University. After graduation from Harvard, he returned to the University of Illinois, where he obtained his Ph.D. degree in inorganic chemistry in 1960, with a sole minor in organic chemistry, under the guidance of the late Professor Stan Piper. He then joined the Chemistry Department at Iowa State University, where he has been Full Professor of Chemistry since 1971 and University Professor since 1997. His current research emphases include the improvement of organic transformation methodologies through the synthesis of new "green" homogeneous and heterogeneous organo*non*metallic and organometallic catalyst systems, and the conversion of biomass and biomass components to value-added nonfood products. He is the author or co-editor of 3 books and 15 patents, and over 350 publications.

Philip B. Kisanga was born in Yambio in South Sudan. He received his B.S. (Honors) in chemistry from the University of Cairo in Cairo, Egypt, followed by an M.A. in organic chemistry from the University of Northern Iowa under the supervision of Professor Kirk P. Manfredi. After leaving UNI, Philip pursued graduate studies with Professor John G. Verkade at Iowa State University, working on the synthesis and applications of proazaphosphatranes. After graduating in 1999, he moved to Duke University for postdoctoral training with Professor Ross A. Widenhoefer. In 2000, he accepted a research scientist position at Aldrich Chemical Company. He then joined Albany Molecular Research (Syracuse Research Center) in 2001, where he is now a senior research scientist in the Chemical Development group.

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$C_{10}H_{14}ClIN_2$
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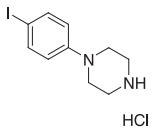
250mg



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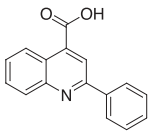

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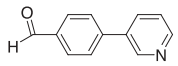

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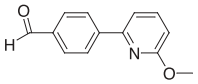

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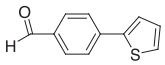

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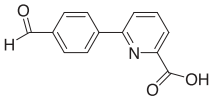

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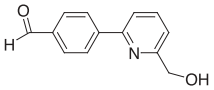

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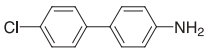

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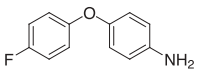

L30,084-5
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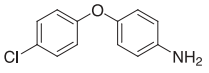
MW 219.67
250mg



L30,085-3
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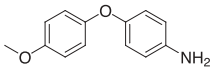
MW 215.25
250mg



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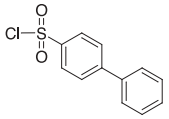
MW 252.72
5g



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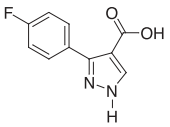

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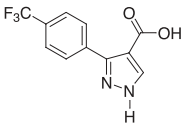

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$C_{11}H_{10}N_2O_3$
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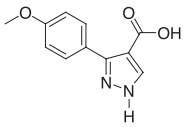

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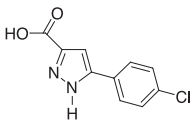

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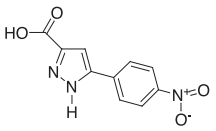

L32,460-4
$C_{11}H_9NO_4$
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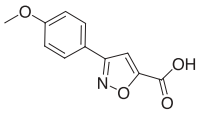

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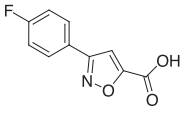

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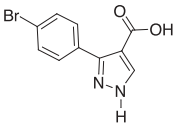

L32,463-9
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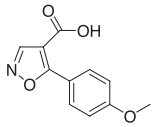

L32,464-7
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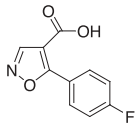

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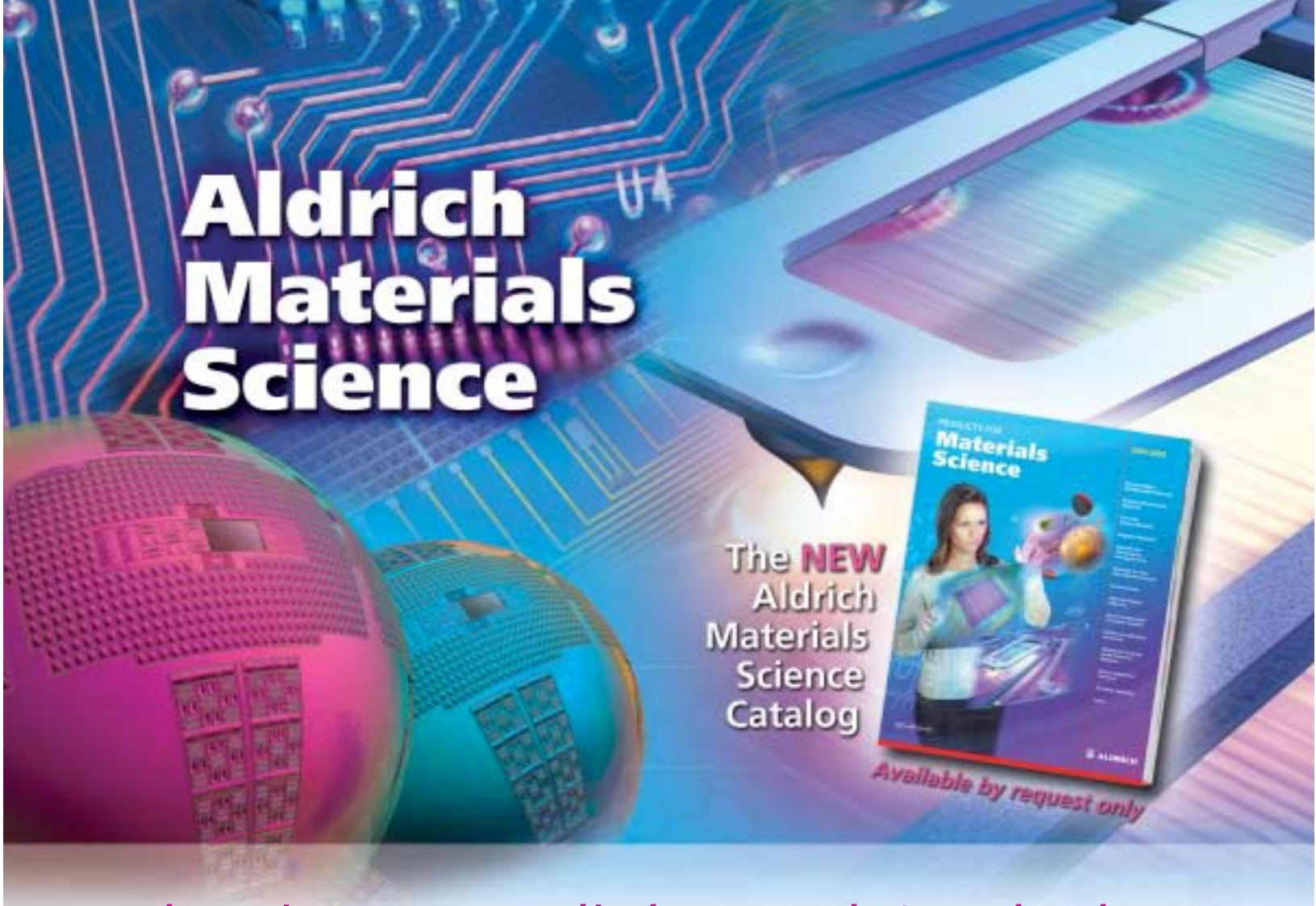

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Chemistry Without Reagents: Synthetic Applications of Flash Vacuum Pyrolysis

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Outline

1. Introduction

"gas-phase pyrolysis is a synthetic method of general utility. It is usually clean, convenient, and efficient, and frequently has advantages over other synthetic methods for accomplishing the same goals."[1]

Synthetic transformations in organic chemistry are rightly dominated by solution-phase, reagent-based reactions. Yet, it is clear from the above quotation that, in appropriate cases, pyrolysis reactions in the gas phase can make a major contribution to the armory of the synthetic chemist. Important syntheses in which one or more key steps have been carried out in the gas phase include those of superphane (**1**),[1] corannulene (**2**)[2] (and related geodesic polyarenes[2]) and, most spectacularly, C_{60} (**3**) itself (**Figure 1**).[3]

The purpose of this article is to demonstrate how, with very simple apparatus, gas-phase reactions can provide new disconnections that give rapid access to unusual systems. It is a very personal account, and most of the examples have been chosen from work carried out in our laboratories over the past 20 years. Interested readers are referred to other reviews[4] for a more representative overview of the field.

2. Flash Vacuum Pyrolysis (FVP)

Organic chemists have enjoyed distilling compounds through hot tubes since the early days of the subject in the 19th century.[5] However, a renaissance of pyrolytic methods began about 40 years ago, when a number of workers independently explored the idea that breakdown mechanisms in electron-impact mass spectrometry might be reproduced under purely thermal conditions.[6] The terms "flash vacuum pyrolysis" (FVP) and "flash vacuum thermolysis" (FVT) are used interchangeably for the method which evolved from these investigations.[4]

The FVP experiment is easy to carry out and simply involves vacuum distillation of a substrate through a hot tube. The design of our apparatus is shown in **Figure 2**, and differs only in detail from that suggested by Wiersum in an earlier *Aldrichimica Acta* article.[4d] We use a commercially available tube furnace to heat an empty, silica pyrolysis tube (35 × 2.5 cm, B24 sockets at both ends). The substrate is contained in a borosilicate glass test tube (the "inlet"), heated with a small Kugelrohr oven and connected via a B24 cone to the furnace tube. Our products are usually trapped in a borosilicate glass U-tube, cooled with liquid nitrogen (though we also use other designs of trap for specialized purposes). The whole apparatus is evacuated to ca. 0.01 Torr by a high-capacity, rotary oil pump. The apparatus is robust and simple to use, and it is easy to carry out 4–5 small-scale (ca. 50 mg) or one large-scale (5 g or more) pyrolysis over a period of 2–3 hours. For preparative purposes, a typical throughput rate is 1–2 grams of substrate per hour. Under these conditions, individual substrate molecules spend only a fraction of a second in the hot zone.[4a]

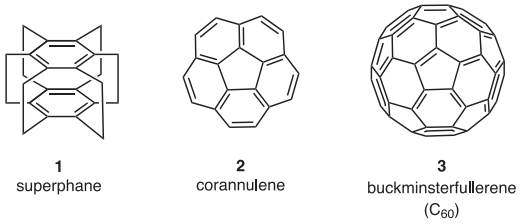


Figure 1. Important Non-Natural Products Obtained by FVP Reactions.

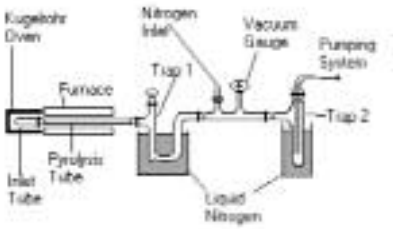
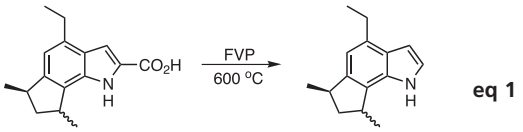
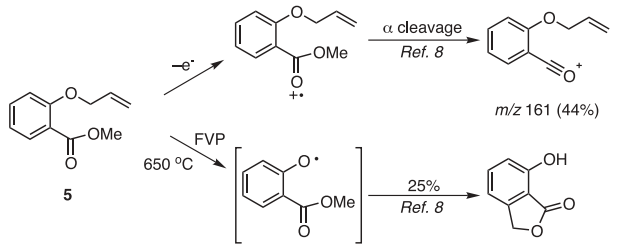


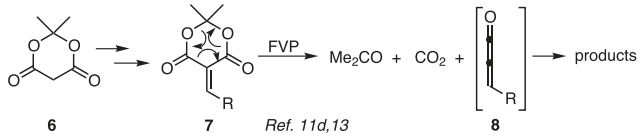
Figure 2. Apparatus for Flash Vacuum Pyrolysis (FVP).



eq 1



Scheme 1. Contrasting Cleavage Pathways in EI-MS and FVP.



Scheme 2. The Thermal Chemistry of Meldrum's Acid Derivatives under FVP Conditions.

The major advantage of the FVP experiment is that the individual molecules are isolated from solvent, precursor, and products, when the actual pyrolysis event takes place. Consequently, FVP is an excellent technique for intramolecular reactions such as eliminations and cyclizations. In addition, workup is simple since the product(s) are condensed at low temperatures in the absence of oxygen, solvent, and reagents. The use of FVP, therefore, has an added benefit for the efficient isolation of thermally stable, yet reactive, species, which can then be used directly for further reactions.

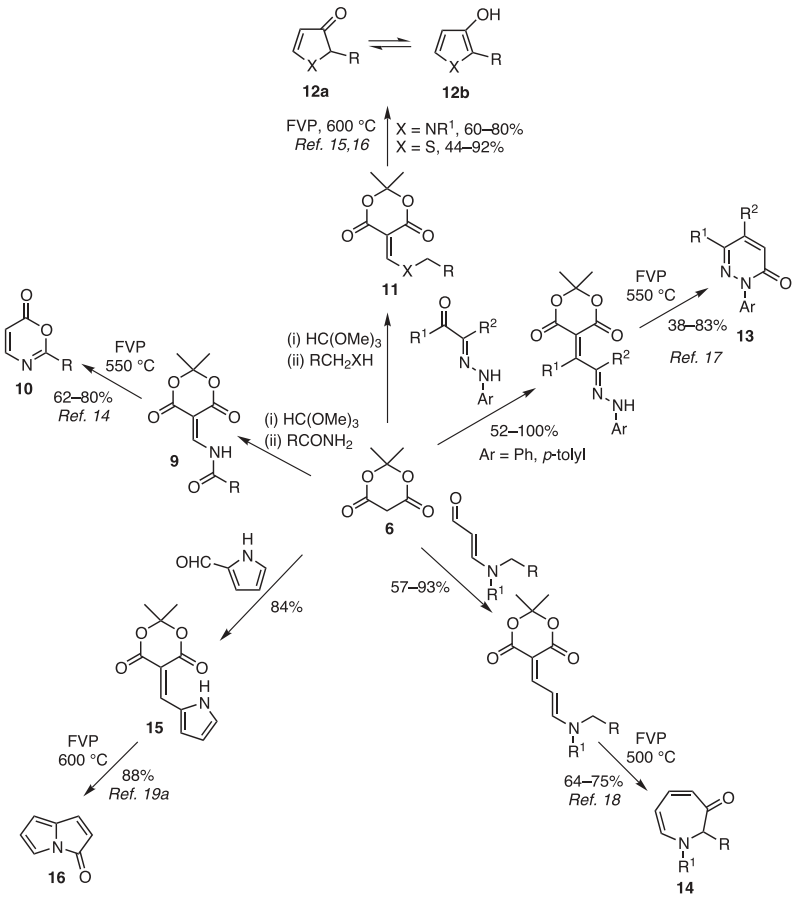
On the other hand, a serious limitation of the classic FVP procedure is the requirement that the substrate must be volatile at low pressures; poorly volatile precursors simply decompose (in the condensed phase) on heating in the inlet tube. It may also be difficult to scale up a procedure, if the precursor is of marginal volatility. In practice, efficient FVP reactions can be carried out with a large variety of aromatic or heteroaromatic substrates with nonpolar functional groups, but they are generally less successful for saturated substrates with multiple functional groups. As a guide, a compound which gives a molecular ion in its electron-impact mass spectrum is likely to "fly" under FVP conditions.

Because of the short contact times involved in the FVP experiment, the required furnace temperatures (300–1000 °C) are much higher than the range intuitively familiar to organic chemists used to working in the solution phase. In practice, a reaction which occurs in solution at 180–200 °C may require temperatures in excess of 750 °C under FVP conditions. Conditions can be regarded as "mild" at temperatures where most common functional groups are stable; this is true up to 650 °C or so in our apparatus. At higher temperatures, degradation of some functional groups can take place. In itself, this may be useful: at about 850–900 °C and above, aromatic carboxylic acids cleanly decarboxylate, aromatic aldehydes decarbonylate, and aromatic bromo or nitro compounds lose the substituent to provide useful sources of aryl radicals. FVP decarboxylation of an indole-2-carboxylic acid derivative has been used as a key step in the first synthesis of the trikentrin natural product system **4** (**eq 1**), when traditional decarboxylation methods were inadequate.[7] On the other hand, we have found that aromatic and heteroaromatic nitriles are stable even at 1000 °C in our apparatus, and so, in principle, the cyano group can be used as a thermal protecting group for a variety of other functionalities.

It is useful to place FVP in the context of other pyrolytic methods. As we have seen, FVP is particularly good for intramolecular processes (some of which do not take place under other conditions) and for the isolation and characterization of "reactive" products. FVP is generally not useful if the substrate is not volatile or if intermolecular reactions are required. Both solution-phase and sealed-tube pyrolytic methods suffer from the disadvantage that reactive intermediates are generated in the presence of precursors, products, and solvent so that intermolecular secondary products are often formed. However, these methods are much better than FVP for nonvolatile substrates or for intermolecular reactions of reactive intermediates. Finally, there is considerable current interest in the application of microwave heating, particularly with the availability of commercial apparatus. Microwave chemistry is excellent for intermolecular reactions that happen to require high temperatures; but the possibility of secondary reactions remains, if intramolecular reactions or reactive products are required. If the compound is sufficiently volatile, FVP remains the method of choice for such applications.

2.1. FVP and Mass Spectrometry

Although FVP reactions may have parallels in electron-impact mass spectrometry (EI-MS), the relationship, when it occurs, is only coincidental. Fragmentation pathways in EI-MS are driven by the properties of a radical cation species (and hence the location of the HOMO), whereas in FVP they are driven by cleavage of the weakest bond in the precursor molecule. For example, the initial cleavage in the mass spectrum of ester **5** (**Scheme 1**) is due to a classic α cleavage after ionization at the carbonyl group, whereas under FVP conditions products are formed after a radical cleavage of the *O*-allyl group (cf. Section 4).[8]



Scheme 3. Unusual Heterocyclic Systems Obtained by FVP of Meldrum's Acid Derivatives.

2.2. Typical FVP Reactions

Most FVP reactions fall into one of three categories:

- Pericyclic reactions: electrocyclizations, sigmatropic shifts, and retro-Diels–Alder-type processes.
- Radical reactions: initiated by cleavage of the weakest single bond in the substrate.
- Cleavage of small molecules (e.g., N_2, CO, CO_2) leading to diradical, carbene, or nitrene intermediates.

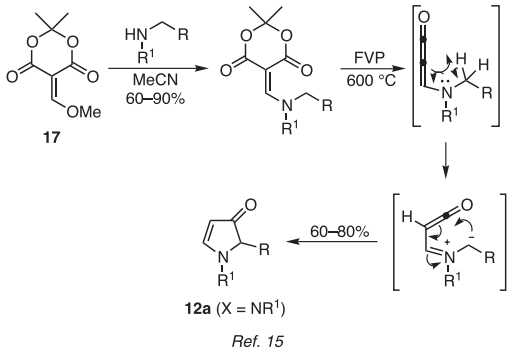
In the absence of solvation, ionization energies are very high and, therefore, ionic intermediates are never encountered under the vibrational activation conditions of the FVP experiment.

The design of a novel FVP process often involves the generation of a reactive intermediate by one of the above methods in the presence of a suitable trapping group for intramolecular reaction. The application of these principles is exemplified by the case studies in Sections 3 and 4 below.

3. Meldrum's Acid

Meldrum's acid was discovered in the early years of the 20th century by the Scottish chemist A. N. Meldrum,[9] who was working at the time at the University of Aberdeen. In assigning a structure to the condensation product of acetone and malonic acid, he was unfortunately misled by its high acidity, and the correct structure was not confirmed as 2,2-dimethyl-1,3-dioxane-4,6-dione (**6**) until 1948.[10,11] The thermal chemistry of Meldrum's acid derivatives was worked out by Brown and Eastwood during the 1970s in a classic series of papers entitled "Methyleneketenes and Methylenecarbenes",[6,12] and the details of the process were later refined by the matrix isolation work of Wentrup and co-workers.[13] This work has been reviewed,[11d] and so only the very basics will be repeated here. Thus, under FVP conditions, methylene Meldrum's acid derivatives, **7**, generally lose acetone and CO_2 to generate methyleneketene intermediates, **8**. These intermediates often rearrange by a hydrogen shift from a remote position in the group R to provide more stable unsaturated ketenes, which collapse to the final products (**Scheme 2**).

Most of our work has involved the application of these processes to the synthesis of unusual heterocyclic systems (e.g., **Scheme 3**). For example, a [1,3]-prototropic shift in the methyleneketene derived from amide derivative **9** provides a good route to oxazinones **10**.[14] A [1,4]-prototropic shift in the corresponding intermediates derived from secondary amines **11** gives the best synthetic route to pyrrol-3(2*H*)-ones **12a** (X = NR[1]), which exist in equilibrium with their 3-hydroxypyrrole tautomers **12b** (see Section 3.1).[15] The corresponding thiophenes **12** (X = S) are obtained in analogous fashion.[16] Formation of pyridazinones **13**[17] requires a [1,5]-prototropic shift; and azepinones **14**,[18] vinylogues of pyrrolones **12**, are obtained by a [1,6]-prototropic shift (see Section 3.2). Finally, cyclization of the condensation product **15** to pyrrolizin-3-ones **16** requires a [1,7]-prototropic shift in the intermediate methyleneketene (Section 3.3).[19] New chemistry, which has been developed as a result of the discovery of these synthetic routes, is described in the remainder of this section.



Scheme 4. Mechanism of the FVP of Aminomethylene Derivatives of Meldrum's Acid.

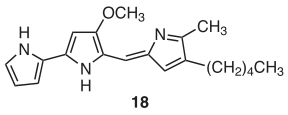
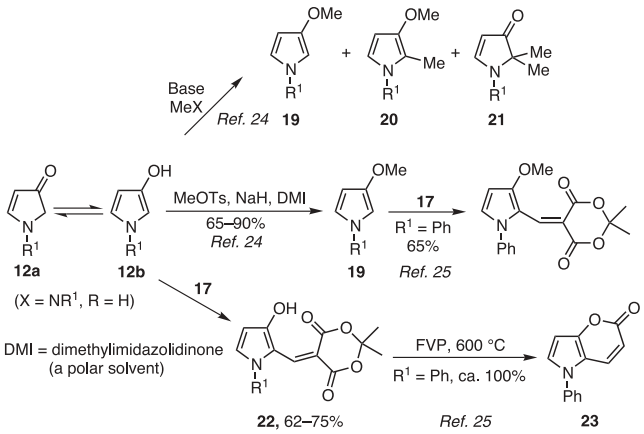
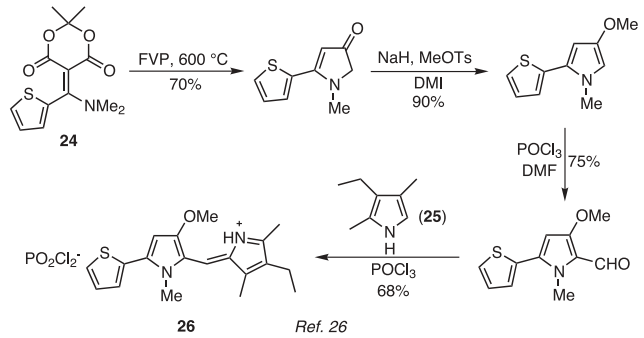


Figure 3. Prodigiosin, a 3-Oxygenated Pyrrole and an Antibiotic and Immunosuppressive Agent.



Scheme 5. Model Alkylation and FVP Studies of 3-Hydroxypyrroles and Derivatives.



Scheme 6. FVP as a Key Early Step in a Multistep Synthesis of a Prodigiosin Analogue.

3.1. Pyrrol-3(2H)-ones and Thiophen-3(2H)-ones

As shown in Scheme 3, FVP of *N*,*N*-disubstituted aminomethylene derivatives of Meldrum's acid provides pyrrol-3(2*H*)-ones **12a** (X = NR[1]), which are tautomeric with 3-hydroxypyrroles **12b**. The detailed mechanism is still a matter of some debate,[20] but can be rationalized by the process shown in **Scheme 4**. The starting materials are readily prepared by reaction of methoxymethylene Meldrum's acid (**17**) with an appropriate secondary amine. The pyrolyses are efficient (yields, 60–80%) making this a simple and effective two-step route to sensitive, electron-rich pyrrole derivatives.[15] 1-Substituted, 1,2-disubstituted, 1,5-disubstituted, 1,2,2-trisubstituted, and 1,2,5-trisubstituted 3-hydroxypyrrole derivatives have been synthesized; and the 1-substitutent may be alkyl or aryl. When R = Ph, and R[1] also contains an appropriately situated hydrogen atom, highly selective hydrogen transfer from the benzyl group occurs to give 2-phenyl-3-hydroxypyrroles **12b** (X = NR[1], R = Ph) exclusively.[15]

3-Hydroxypyrroles are unstable compounds, partly because they are highly electron-rich, and partly because, as monocyclic analogues of indoxyl, they are prone to oxidative dimerization to indigo analogues.[21] For this reason, their synthesis is ideally suited to FVP methodology (absence of reagents, absence of oxygen, rapid quenching at the exit point of the furnace, simple workup). As an example, the 1-phenyl compound, **12b** (X = NPh, R = H), was previously isolated by classical solution chemistry as "an unstable oil";[22] by FVP methods, we have routinely carried out the pyrolysis on a 5–10-g scale to provide the product as a crystalline yellow solid, mp 80–81 °C, in 63% yield.

One of the most important 3-oxygenated pyrrole derivatives is the natural antibiotic and immunosuppressive agent prodigiosin (**18**) (**Figure 3**).[23] Analogues of this material are attractive synthetic targets, which provide the opportunity to explore the chemistry of simple 3-hydroxypyrroles. The first problem in their solution-phase synthesis is regioselective *O*-alkylation; under most conditions, alkylation of the enolate derived by proton abstraction from hydroxypyrrole **12** (X = NR[1]) gives mixtures of *O*- and *C*-alkylation products, **19–21** (**Scheme 5**). However, use of a polar solvent (dimethylimidazolidinone, DMI), sodium hydride as base, and methyl tosylate as the alkylating agent gives essentially quantitative *O*-alkylation and hence a general route to 3-alkoxypyrroles **19**.[24] Electrophilic substitution reactions of both 3-alkoxy- and 3-hydroxypyrroles have been investigated, using methoxymethylene Meldrum's acid (**17**) as a model electrophile. In both series, the 2 position was found to be the most reactive; when this position is blocked, substitution will usually take place at the 5 position, though it can be diverted to the 4 position if the *N*-substitutent is sterically crowded.[25] FVP of "Meldrumsated" products **22** provides an efficient route to pyranopyrroles **23**.[25]

With these results in hand, the prodigiosin analogue **26** was synthesized as shown in **Scheme 6**.[26] The starting material, **24**, was made by application of the method of Huang and Chen.[27] Pyrolysis gave the expected pyrrolone (70%), and the *O*-alkylation and Vilsmeier formylation took place with the anticipated regioselectivities. The final coupling with kryptopyrrole (**25**) occurred under standard conditions to give **26** in 68% yield. The X-ray structure of **26** shows hydrogen bonding between the NH and the alkoxy groups. This synthesis demonstrates that multistep procedures can be successfully carried out using FVP as a key (early) step in the sequence.

Alkylsulfanylmethylene derivatives of Meldrum's acid, **11** (X = S), have been made by reaction of a thiol with methoxymethylene Meldrum's acid (**17**). FVP of **11** takes place in

a fashion similar to that of the corresponding aminomethylene derivatives, to provide an excellent route to a range of thiophen-3(2*H*)-ones (3-hydroxythiophenes) **12** (X = S). The parent compound (**12**; X = S, R = H; 80%), 2-substituted, 2,5-disubstituted, and 2,2-disubstituted derivatives have been synthesized in 44–92% yields.[16]

3.2. Azepin-3(2H)-ones

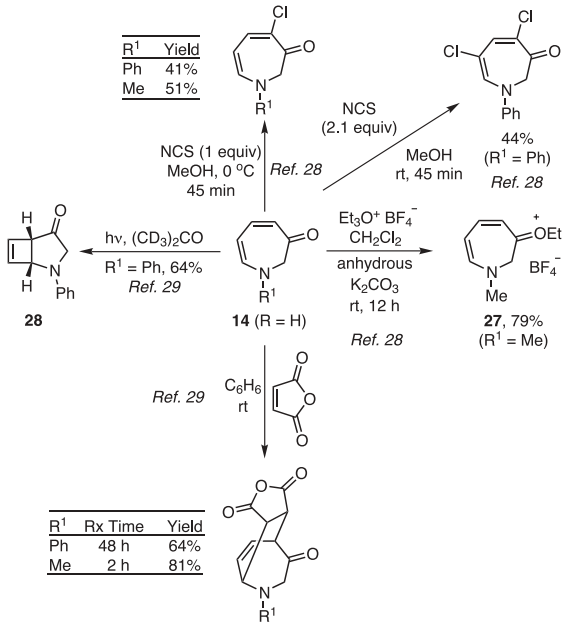
Knoevenagel condensation of enaminones with Meldrum's acid provides the precursors to a novel series of seven-membered heterocycles, azepin-3(2*H*)-ones **14** (see Scheme 3). Here, the pyrolysis mechanism is similar to that of pyrrolone formation (see Scheme 4), except that a [1,6]-prototropic shift takes place to provide the dipolar intermediate. Prior to the FVP route, only one highly substituted example of this system was known, and no study of its chemistry had been carried out. A summary of our work is shown in **Scheme 7**.[28,29] Unlike pyrrolones, the azepinones are nonplanar[18] and show no tendency to tautomerize to the (antiaromatic) hydroxyazepine structure. They readily protonate and alkylate on oxygen to provide a stabilized cation (e.g., **27**), and react with other electrophiles (e.g., *N*-chlorosuccinimide), first at the 4 position and then at the 6 position.[28] The diene unit of the azepinone structure takes part in cycloaddition reactions and undergoes a photolytic electrocyclic ring closure to the fused cyclobutene **28**.[29]

3.3. Pyrrolizin-3-ones

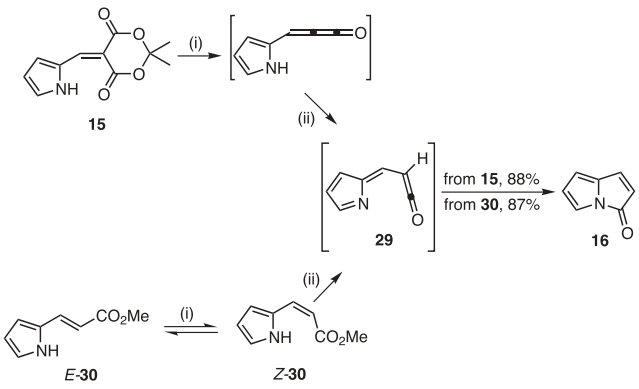
Knoevenagel condensation of Meldrum's acid (**6**) with pyrrole-2-carbaldehyde provides the methylene derivative **15**, which, upon FVP at 600 °C gives pyrrolizin-3-one (**16**) as a deep-red liquid in very high yield (**Scheme 8**).[19a] This pyrolysis can be carried out on a multigram (> 10 g) scale, and the product is readily purified by distillation. The mechanism involves a [1,7]-hydrogen shift, presumably at the methyleneketene stage to generate ketene **29**, which collapses to heterocycle **16** by electrocyclization. To overcome volatility problems in more complex precursors, an alternative route to the key ketene intermediates (e.g., **29**) was devised using acrylate esters **30** as precursors.[19b] The ketene is formed by *E/Z* isomerization of the alkene—known to take place under FVP conditions[30]—and elimination of methanol. This variant has greatly extended the versatility of the synthetic approach. We have made over twenty pyrrolizinone (and azapyrrolizinone[31]) derivatives by these methods and, with one exception, all are stable.[19] The exception is 1-carbomethoxypyrrolizin-3-one (**31**), a "captodative olefin", which spontaneously dimerizes at room temperature to give a 2:1 mixture of the trans and cis dimers, **32** (**eq 2**).[32]

In a further variant of the synthetic route, we have been able to access the key ketene intermediates from readily available *N*-substituted pyrroles (e.g., **33**), or indoles, by a [1,5]-sigmatropic shift of the *N*-aryl group followed by elimination of methanol (**eq 3**).[33] Although this requires high temperatures (925 °C) and is consequently not compatible with every substitution pattern, the strategy provides easy access to benzopyrrolizinones such as **34** (79%).[33]

Relatively little was known about pyrrolizin-3-ones[34] until the FVP route was developed. As a consequence, the properties of pyrrolizin-3-one (**16**) and its analogues have been studied. They are planar, strained-ring systems;[35] the lactam functionality is atypical both structurally (long C–N bond and short C=O bond[35]) and chemically. For example, ring opening takes place readily by reaction with hard nucleophiles, whereas electrophiles (e.g., HCl) add cleanly to the 1–2 double bond.[36] These reactions were both

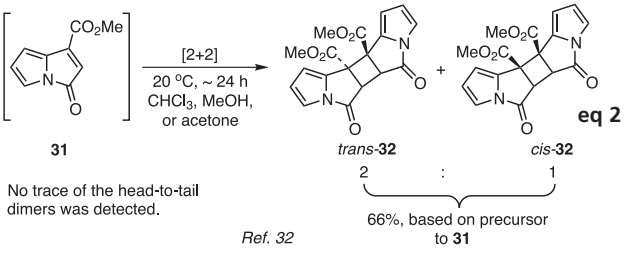


Scheme 7. Highlights of the Chemistry of Azepin-3(2*H*)-ones.

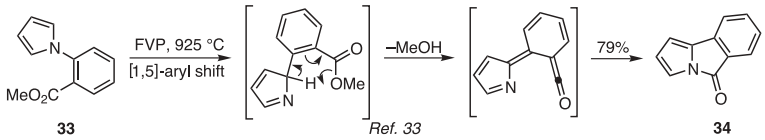


Top pathway (*Ref. 19a*): (i) FVP, 600 °C, – $(CH_3)_2CO$, – CO_2; (ii) [1,7]-hydrogen shift.
Bottom pathway (*Ref. 19b*): (i) FVP, 850 °C; (ii) – MeOH

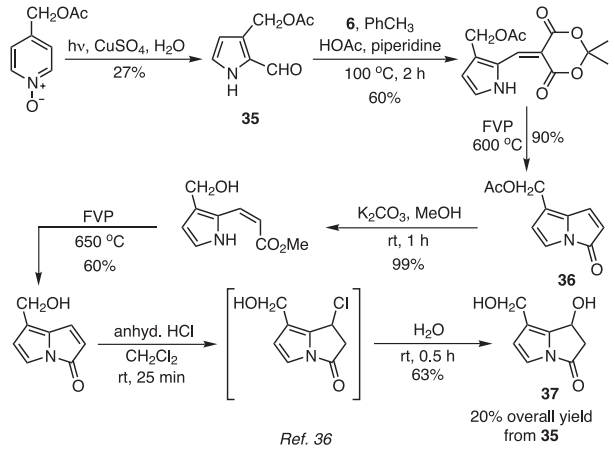
Scheme 8. Pyrrolizin-3-ones via FVP.



encountered in the synthesis of the pyrrolizidine alkaloid 3,8-didehydroheliotridin-5-one (**37**) (**Scheme 9**).[36] The 3-substituted pyrrole-2-aldehyde precursor, **35**, was prepared by a novel photochemical ring contraction,[37] and the 7-substituted pyrrolizinone, **36**, was obtained by our standard route. The unwanted ring opening, which occurred upon



eq 3



Scheme 9. Synthesis of the Pyrrolizidine Alkaloid 3,8-Didehydroheliotridin-5-one (**37**).

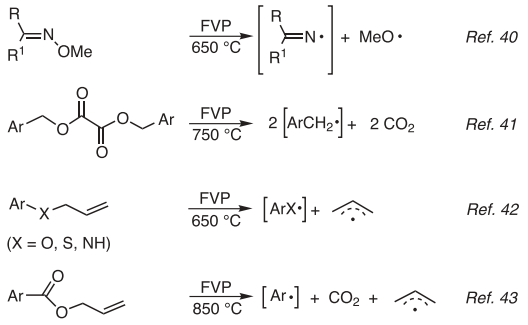
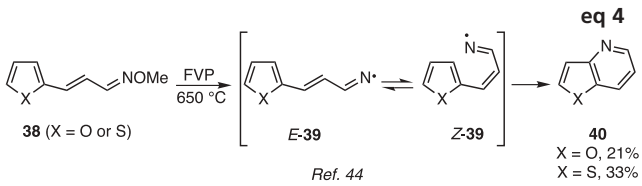


Figure 4. Generation of Iminyl, Benzyl, Phenoxyl (and Related) Radicals, and Phenyl Radicals under FVP Conditions. (The Temperatures Shown Are Representative of These Transformations, When Carried Out in the Edinburgh Apparatus.)

eq 4



deprotection of **36**, was reversed by a second FVP step, and the synthesis of **37** was completed by a one-pot hydrochlorination and nucleophilic substitution to introduce the 1-hydroxyl group. Other pyrrolizidine natural products have been synthesized from the pyrrolizin-3-one (and pyrrolizidin-3-one[38]) templates.[39]

4. Radicals

Solution radical chemistry is dominated by chain-reaction sequences that cannot be maintained under the dilute conditions of the FVP experiment. Under such conditions, formation of the radical takes place by cleavage of a weak single bond in the substrate and, consequently, each molecule of precursor carries its own radical generator. Typical methods for the generation of iminyl radicals from oxime ethers;[40] benzyl radicals from oxalate esters;[41] phenoxyls, thiophenoxyls, and aminyls from the appropriate allyl derivative;[42] and phenyl radicals from allyl esters[43] are all shown in **Figure 4**. Most FVP radical reactions are oxidative, and many cyclizations involve loss of a hydrogen atom as the final step. We summarized the status of this field in a review in 1986,[42] but it was clear that very few systematic investigations had been carried out until then. Our primary aim was to achieve an understanding of the mechanisms of radical chemistry under FVP conditions, and then to identify useful transformations which could be applied in synthesis. In the remainder of this section, we present short case studies that reflect how this has been achieved in three areas of radical chemistry.

4.1. Iminyl Radicals

Cyclization of conjugated iminyl radicals (e.g., **39**) derived from oxime ethers, **38**, is a useful route to fused pyridine systems (e.g., **40**) (**eq 4**).[44] Although the yields of the FVP steps are low in these particular cases, the synthetic potential of the sequence is increased, because *E*–Z isomerism of the alkene takes place under the pyrolysis conditions and the product can be isolated without chromatography. On the other hand, it is known that in some related cases the cyclization proceeds via an intermediate spirodienyl radical, which can lead to scrambling of the substitution pattern.[45]

Recently, in collaboration with Professors R. Leardini and D. Nanni (University of Bologna), we have investigated the product distributions obtained when the same ortho-substituted phenylalkaniminyls are generated in the solution phase and in the gas phase.[46] These processes can be considerably complex, especially if phenoxyl radicals are generated by radical–radical rearrangement (cf. Section 4.2).

4.2. Benzyl and Related Radicals

Although their structures are superficially related, it still came as a surprise to discover that the intramolecular reactions of benzyl and thiophenoxyl radicals on the one hand, and phenoxyl and aminyl radicals on the other hand, are dramatically different. If a thiophenoxyl or benzyl radical is generated ortho to a benzyl or thiophenoxyl group (as in **41** and **41′**; X,Y = CH_2, S), respectively, efficient cyclization reactions take place to provide the 6-membered-ring product **43** via spirodienyl radical intermediates **42** (**Scheme 10**).[47] In contrast, phenoxyl (and to a lesser extent phenylaminyl) radicals have a high affinity for hydrogen atoms and, consequently, undergo intra- or even intermolecular hydrogen abstraction rather than cyclization.[48] In a classic example of this behavior, 2-benzylphenoxyl (**41**; X = O, Y = CH_2) and 2-phenoxybenzyl radicals (**41′**; X = O, Y = CH_2) both give 1-hydroxyfluorene (**45**) as a major product via the phenyl radical **44**.[48c] The chemistry of phenoxyl, benzyl, and related radicals appears to be controlled by their "hardness" or "softness".

If the substrate does not contain a hydrogen atom in an appropriate position for abstraction, phenoxyl radicals can be used in heterocyclic ring synthesis. In one series, we have exploited a phenoxyl radical cyclization, coupled with the use of a carboxylic ester as a radical leaving group, to provide a general route to benzofurans (e.g., **46**) (**eq 5**).[49] This approach was applied to a 4-step synthesis of the natural product angelicin (**47**) (**Scheme 11**).[49]

4.3. Phenyl and Related Radicals

Phenyl radicals do not couple well under FVP conditions; rather, they abstract hydrogen atoms from contact with the walls of the tube to provide benzene. On the other hand, they are very reactive in intramolecular processes as shown in a spectacular fashion by Scott and co-workers.[3] We have prepared dibenzofurans and dibenzothiophenes (e.g., **51**; X = O and S, respectively) via phenyl radical intermediates, using aryl esters **48** or allyl esters **49** as precursors (**Scheme 12**).[50,51] Either of these routes provides moderate-to-good yields of the target heterocycles, though in some substituted cases the synthetic utility is restricted by equilibration of isomeric phenyl radicals **50** and **50′**. In more recent work, we have used this equilibration as a mechanistic probe for the involvement of phenyl radicals in other cyclization processes.[52]

5. Conclusions

It is hoped that the above examples have demonstrated, in the words of Boekelheide, that "gas-phase pyrolysis is a synthetic method of general utility".[1] By creating new disconnections, we have been able to synthesize and study reactive systems like 3-hydroxypyrroles and azepin-3(2*H*)-ones. By discovering new syntheses of pyrrolizine systems, we have revealed new routes to simple pyrrolizidine alkaloids. Finally, by investigating the fundamentals of gas-phase, free-radical chemistry, we have discovered new cyclization reactions and demonstrated their synthetic potential. Gas-phase chemistry will not solve every problem in synthesis, but it remains a simple and underused technique with considerable potential in eliminations, cyclizations, and heterocycle synthesis.

6. Acknowledgements

It is a pleasure to have this opportunity to acknowledge the wisdom and encouragement of my mentors, Douglas Lloyd, Bill Crow, and Sir John Cadogan, whose influences in our work will be apparent to those who are familiar with theirs. Of course, I am also most grateful to the skill and determination of my co-workers (and co-thinkers) many of whose names appear in the references. Our work could not have been carried out without the generous support of the Engineering and Physical Sciences Research Council (EPSRC); The University of Edinburgh; and the specialty chemical industry, particularly British Petroleum, Kodak Ltd., Avecia, and Lonza Ltd.

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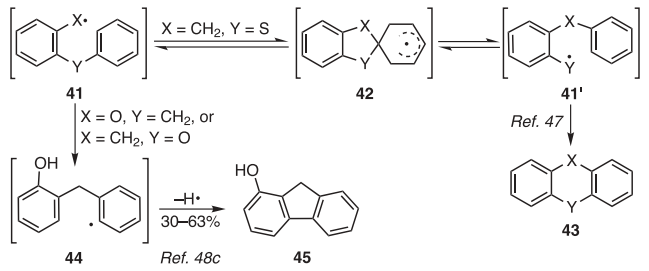
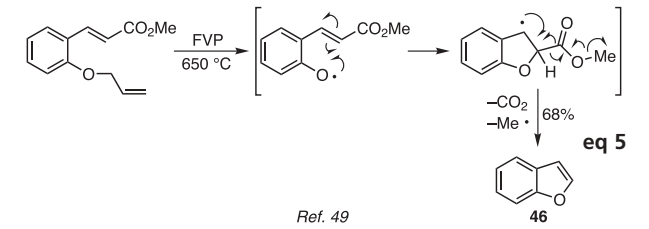
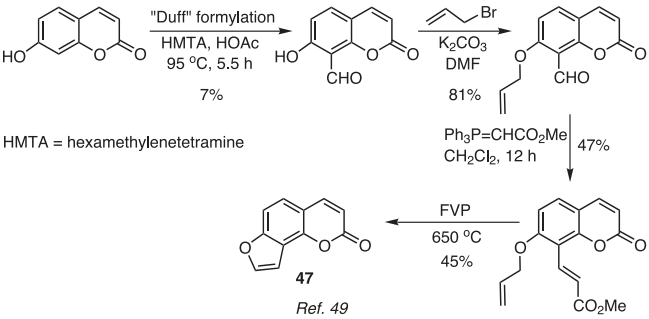
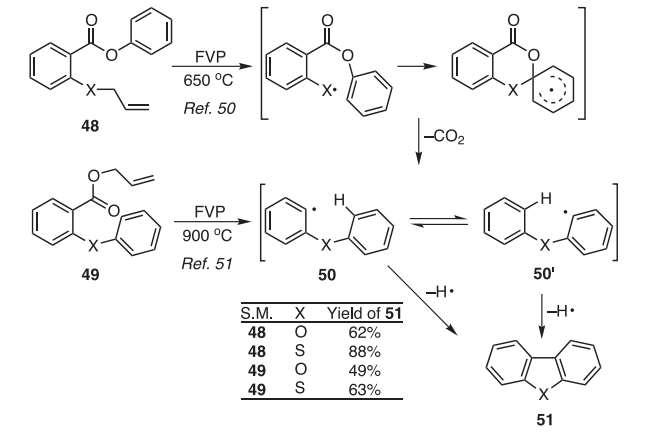


Scheme 10. Contrasting FVP Reactivities of Benzyl and Thiophenoxyl Radicals vis-à-vis Phenoxyl Radicals.





Scheme 11. Synthesis of the Natural Product Angelicin via a Phenoxyl Radical Cyclization.



Scheme 12. Dibenzofurans and Dibenzothiophenes via Phenyl Radical Cyclizations.

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About the Author

Hamish McNab was born in Kirkcaldy, Scotland. He was raised in St. Andrews and entered the University of St. Andrews in 1967, graduating in 1971. He remained at St. Andrews to carry out research on the chemistry of "push–pull" conjugated systems under the direction of Dr. D. Lloyd, and graduated Ph.D. in 1974. He spent the academic years 1975 and 1976 at The Australian National University as Research Assistant to Professor W. D. Crow, where he worked in the field of carbene–carbene rearrangements. In 1976, he returned to Scotland to join the research group of Professor J. I. G. (now Sir John) Cadogan as Senior Demonstrator at The University of Edinburgh. He was appointed Lecturer in 1978, and subsequently promoted to Senior Lecturer (1990) and Reader (1992).

Hamish McNab's research has centered on the applications of flash vacuum pyrolysis (FVP) in synthetic and mechanistic organic chemistry. His group has discovered "best synthetic routes" to many sensitive heterocyclic systems such as 3-hydroxythiophenes, azepin-3(2*H*)-ones, and pyrrolizin-3-ones, thus allowing their properties to be studied. He has also explored the gas-phase generation and rearrangement reactions of radical species such as iminyls and phenoxyls. At an early stage, he recognized the potential of Meldrum's acid as a reagent, and his 1978 review on this topic is one of the most cited of his 200 papers.

He has served the Royal Society of Chemistry as a committee member (1985–1988) and Secretary (1989–1992) of the Heterocyclic Group. In 2003, he was awarded the RSC Bader Prize "for many distinguished contributions to flash vacuum pyrolysis, to the chemistry of Meldrum's acid and to heterocyclic chemistry".

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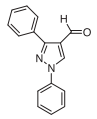
L32,022-6

$C_{16}H_{12}N_2O$
MW 248.29
250mg



L32,084-6

$C_{15}H_{11}N_3O$
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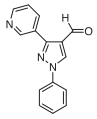
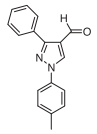


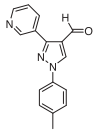
L32,028-5

$C_{17}H_{14}N_2O$
MW 262.31
250mg



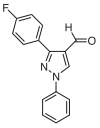
L32,092-7

$C_{16}H_{13}N_3O$
MW 263.30
250mg



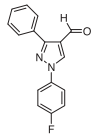
L32,026-9

$C_{16}H_{11}FN_2O$
MW 266.28
250mg



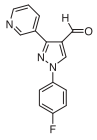
L32,045-5

$C_{16}H_{11}FN_2O$
MW 266.28
250mg



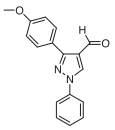
L32,112-5

$C_{15}H_{10}FN_3O$
MW 267.26
250mg



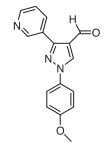
L32,027-7

$C_{17}H_{14}N_2O_2$
MW 278.31
250mg



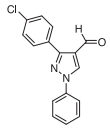
L32,119-2

$C_{16}H_{13}N_2O_2$
MW 279.30
250mg



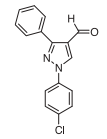
L32,024-2

$C_{16}H_{11}ClN_2O$
MW 282.73
250mg



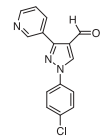
L32,033-1

$C_{16}H_{11}ClN_2O$
MW 282.73
250mg



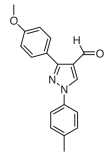
L32,100-1

$C_{15}H_{10}ClN_3O$
MW 283.72
250mg



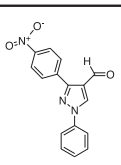
L32,032-3

$C_{18}H_{16}N_2O_2$
MW 292.34
250mg



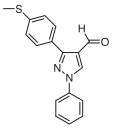
L32,083-8

$C_{16}H_{11}N_3O_3$
MW 293.28
250mg



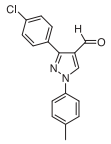
L32,080-3

$C_{17}H_{14}N_2OS$
MW 294.38
250mg



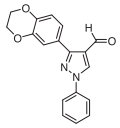
L32,029-3

$C_{17}H_{13}ClN_2O$
MW 296.76
250mg



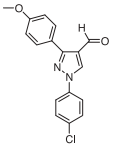
L32,085-4

$C_{18}H_{14}N_2O_3$
MW 306.32
250mg



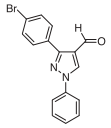
L32,039-0

$C_{17}H_{13}ClN_2O_2$
MW 312.76
250mg



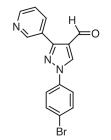
L32,025-0

$C_{16}H_{11}BrN_2O$
MW 327.18
250mg



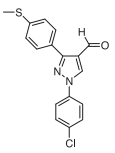
L32,106-0

$C_{15}H_{10}BrN_3O$
MW 328.17
250mg



L32,097-8

$C_{17}H_{13}ClN_2OS$
MW 328.82
250mg



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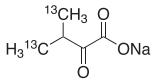
Labeled Keto Acids from Isotec

Cutting-edge technology involving stable-isotope-labeled α-keto acids has sparked great interest among the protein research community. The stable-isotope-labeled α-keto acids can be used as biosynthetic precursors to selectively incorporate protonated methyl groups into a largely deuterated protein. The intense signals of the methyl groups in NMR then allow 3-D protein structure determination. Pioneering research laboratories are now using this unique tool in their protein expression work. Isotec manufactures the widest variety of selectively labeled α-keto acids, available globally through the extensive Sigma-Aldrich/Isotec distribution network. For more information, please contact Isotec by phone at 937-859-1808 or 800-448-9760 (USA), by email at isosales@sial.com, or download it from the web at www.sigma-aldrich.com/keto.

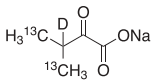
2-Keto-3-(methyl-^{13}C)-butyric acid-4-^{13}C, sodium salt
99 atom % ^{13}C

57,133-4 100mg



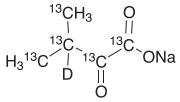
2-Keto-3-(methyl-^{13}C)-butyric acid-4-^{13}C,3-d$_1$, sodium salt
99 atom % ^{13}C, 98 atom % D

58,906-3 100mg



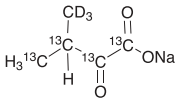
2-Keto-3-methylbutyric acid-^{13}C$_5$,3-d$_1$, sodium salt
99 atom % ^{13}C, 98 atom % D

60,756-8 250mg



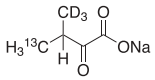
2-Keto-3-(methyl-d$_3$)-butyric acid-1,2,3,4-^{13}C$_4$, sodium salt
99 atom % ^{13}C, 98 atom % D

59,641-8 100mg



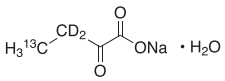
2-Keto-3-(methyl-d$_3$)-butyric acid-4-^{13}C, sodium salt
99 atom % ^{13}C, 98 atom % D

59,490-3 100mg



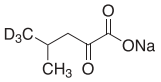
2-Ketobutyric acid-4-^{13}C,3,3-d$_2$, sodium salt, hydrate
99 atom % ^{13}C, 98 atom % D

58,927-6 100mg



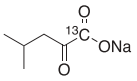
2-Keto-4-(methyl-d$_3$)-pentanoic acid, sodium salt, 98 atom % D

61,662-1 500mg



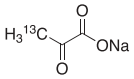
2-Keto-4-methylpentanoic acid-1-^{13}C, sodium salt, 99 atom % ^{13}C

48,771-6 250mg



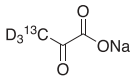
Sodium pyruvate-3-^{13}C, 99 atom % ^{13}C

49,073-3 250mg



Sodium pyruvate-3-^{13}C,d$_3$, 99 atom % ^{13}C, 50–60 atom % D

60,848-3 1g



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New Phosphonium-Based Ionic Liquids

Ionic liquids have received a lot of attention in the past few years for use in reactions and extraction applications.[1–3] Of the different possible ionic liquids, this attention has been focused mostly on imidazolium-based compounds.

Fluka, in collaboration with Cytec Industries, now offers a new promising class of ionic liquids that are based on phosphonium cations ($[PR_3R']^+$).

These ionic liquids possess several interesting properties:

- Liquid at rt or melting at T <100 °C
- High thermal stability
- Immiscible with water
- Soluble in organic solvents (however, when an excess of water is added to the system, three liquid phases are formed)
- Stable under basic conditions
- Mostly lighter than water
- Lower costs compared with other ionic liquids

Catalog No.	Product Name	Trade Name	Unit
89744	Trihexyltetradecylphosphonium chloride	CYPHOS® IL 101	5g 50g
96662	Trihexyltetradecylphosphonium bromide	CYPHOS® IL 102	5g 50g
50826	Trihexyltetradecylphosphonium decanoate	CYPHOS® IL 103	5g 50g
28612	Trihexyltetradecylphosphonium bis(2,4,4-trimethylpentyl)phosphinate	CYPHOS® IL 104	5g 50g
56776	Trihexyltetradecylphosphonium dicyanamide	CYPHOS® IL 105	5g 50g
90145	Triisobutyl(methyl)phosphonium tosylate	CYPHOS® IL 106	5g 50g
50971	Trihexyltetradecylphosphonium bis(trifluoromethanesulfonyl)amide	CYPHOS® IL 109	5g 50g
40573	Trihexyltetradecylphosphonium hexafluorophosphate	CYPHOS® IL 110	5g 50g
15909	Trihexyltetradecylphosphonium tetrafluoroborate	CYPHOS® IL 111	5g 50g

References: (1) Zao, H.; Malhotra, S. V. *Aldrichimica Acta* **2002**, *35*, 75. (2) Bradaric, C. J.; Downard, A.; Kennedy, C.; Robertson, A. J.; Zhou, Y. *Green Chem.* **2003**, *5*, 143. (3) McNulty, J.; Capretta, A.; Wilson, J.; Dyck, J.; Adjabeng, G.; Robertson, A. *J. Chem. Soc., Chem. Commun.* **2002**, 1986.

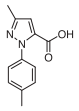
New Building Blocks V

For Medicinal Chemistry and Organic Synthesis

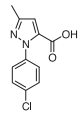
Aldrich is proud to offer a series of building blocks called SmartBlocs™, which constitute a unique collection of products having a wide range of applications in organic synthesis and in medicinal chemistry. Each of these SmartBlocs™ contains two reactive sites, and could serve as the core for library synthesis. Below are examples of some of the newest additions of heterocyclic monomers and polyfunctional template molecules.

L32,295-4
$C_{11}H_{10}N_2O_2$
MW 202.21
250mg

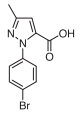
L32,296-2
$C_{12}H_{12}N_2O_2$
MW 216.24
250mg



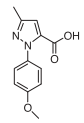
L32,297-0
$C_{11}H_9ClN_2O_2$
MW 236.66
250mg



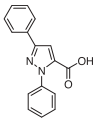
L32,298-9
$C_{11}H_9BrN_2O_2$
MW 281.11
250mg



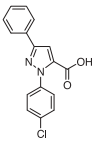
L32,299-7
$C_{12}H_{12}N_2O_3$
MW 232.24
250mg



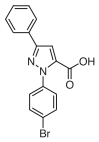
L32,300-4
$C_{16}H_{12}N_2O_2$
MW 264.29
250mg



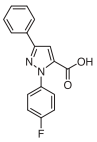
L32,302-0
$C_{16}H_{11}ClN_2O_2$
MW 298.73
250mg



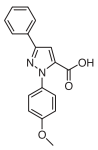
L32,303-9
$C_{16}H_{11}BrN_2O_2$
MW 343.18
250mg



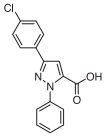
L32,304-7
$C_{16}H_{11}FN_2O_2$
MW 282.28
250mg



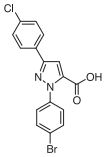
L32,305-5
$C_{17}H_{14}N_2O_3$
MW 294.31
250mg



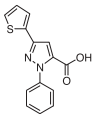
L32,329-2
$C_{16}H_{11}ClN_2O_2$
MW 298.73
250mg



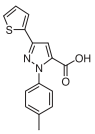
L32,334-9
$C_{16}H_{10}BrClN_2O_2$
MW 377.63
250mg



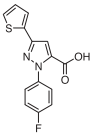
L32,380-2
$C_{14}H_{10}N_2O_2S$
MW 270.31
250mg



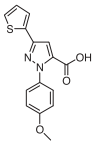
L32,381-0
$C_{15}H_{12}N_2O_2S$
MW 284.34
250mg



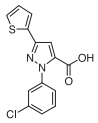
L32,383-7
$C_{14}H_9FN_2O_2S$
MW 288.30
250mg



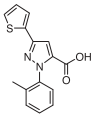
L32,384-5
$C_{15}H_{12}N_2O_3S$
MW 300.34
250mg



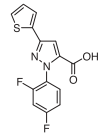
L32,386-1
$C_{14}H_9ClN_2O_2S$
MW 304.76
250mg



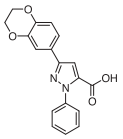
L32,389-6
$C_{15}H_{12}N_2O_2S$
MW 284.34
250mg



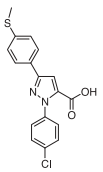
L32,391-8
$C_{14}H_8F_2N_2O_2S$
MW 306.29
250mg



L32,407-8
$C_{18}H_{14}N_2O_4$
MW 322.32
250mg



L32,415-9
$C_{17}H_{13}ClN_2O_2S$
MW 344.82
250mg



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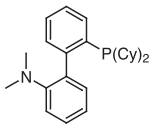
More New Products from Aldrich R&D

Novel Phosphines

63,802-1

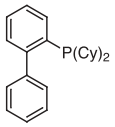
$C_{26}H_{36}NP$



1g
5g
25g

63,809-9

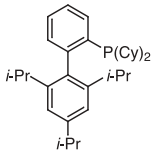
$C_{24}H_{31}P$



1g
5g
25g

63,806-4

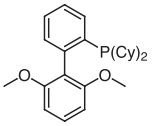
$C_{33}H_{49}P$



1g
5g
25g

63,807-2

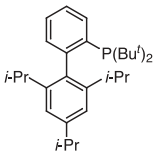
$C_{26}H_{35}O_2P$



1g
5g
25g

63,808-0

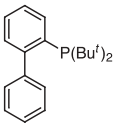
$C_{29}H_{45}P$



1g
5g
25g

63,843-9

$C_{20}H_{27}P$



1g
5g
25g

64,262-9

$C_9H_{21}P$

5g

63,934-6

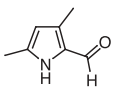
$C_{10}H_{23}P$

1g
5g

Heterocyclic Building Blocks

64,051-4

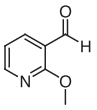
C_7H_9NO



1g

63,213-9

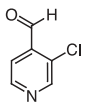
$C_7H_7NO_2$



1g
5g

63,674-6

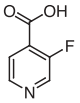
C_6H_4ClNO



1g
5g

63,875-7

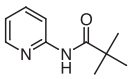
$C_6H_4FNO_2$



1g
10g

63,248-1

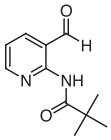
$C_{10}H_{14}N_2O$



1g
5g

63,822-6

$C_{11}H_{14}N_2O_2$



1g
5g

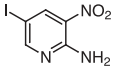
63,910-9

$C_6H_6N_2O$

1g
5g

64,016-6

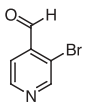
$C_5H_4IN_3O_2$



1g
5g

63,828-5

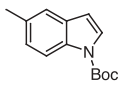
C_6H_4BrNO



1g
5g

63,647-9

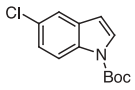
$C_{14}H_{17}NO_2$



1g
5g

63,675-4

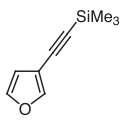
$C_{13}H_{14}ClNO_2$



1g

63,447-6

$C_9H_{12}OSi$

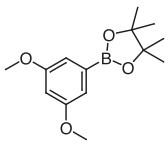


1g
10g

Boronic Acids and Esters

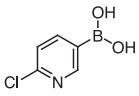
63,390-9

$C_{14}H_{21}BO_4$ — 1g, 5g



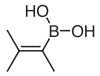
63,738-6

$C_5H_5BClNO_2$ — 1g, 5g



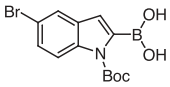
63,907-9

$C_5H_{11}BO_2$ — 1g, 5g



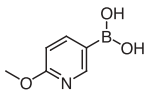
63,739-4

$C_{13}H_{15}BBrNO_4$ — 1g



63,761-0

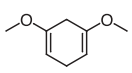
$C_6H_8BNO_3$ — 1g, 5g



Organic Building Blocks

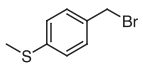
64,111-1

$C_8H_{12}O_2$ — 1g, 5g



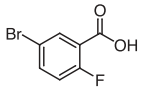
63,481-6

C_8H_9BrS — 1g, 5g



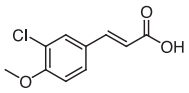
63,645-2

$C_7H_4BrFO_2$ — 1g, 5g



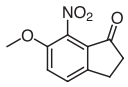
63,876-5

$C_{10}H_9ClO_3$ — 1g, 5g



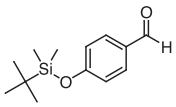
64,067-0

$C_{10}H_9NO_4$ — 1g, 5g



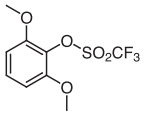
59,615-9

$C_{13}H_{20}O_2Si$ — 1g



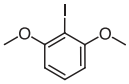
63,787-4

$C_9H_9F_3O_5S$ — 5g, 25g



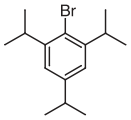
63,813-7

$C_8H_9IO_2$ — 1g, 5g



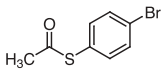
63,793-9

$C_{15}H_{23}Br$ — 1g, 5g



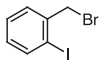
63,465-4

C_8H_7BrOS — 1g, 5g



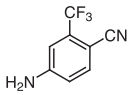
63,460-3

C_7H_6BrI — 1g, 5g



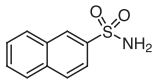
63,175-2

$C_8H_5F_3N_2$ — 1g, 5g



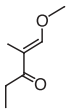
63,407-7

$C_{10}H_9NO_2S$ — 1g, 10g



64,071-9

$C_7H_{12}O_2$ — 1g, 5g



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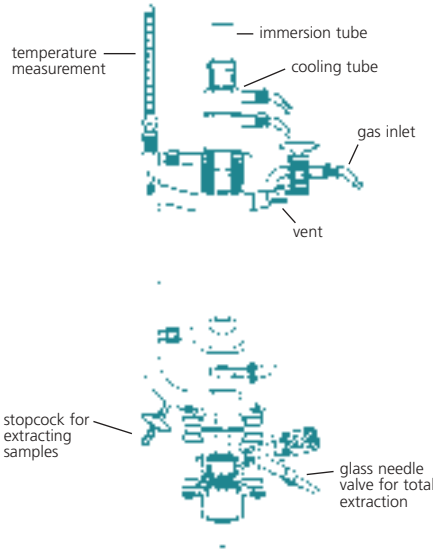
NEW NORMAG® Photoreactors

Exclusively from Aldrich

"Provide intensive mixing of the reaction solution and a thin film in the immediate vicinity of the light source to maximize reaction efficiency."

PRINCIPLE OF OPERATION:

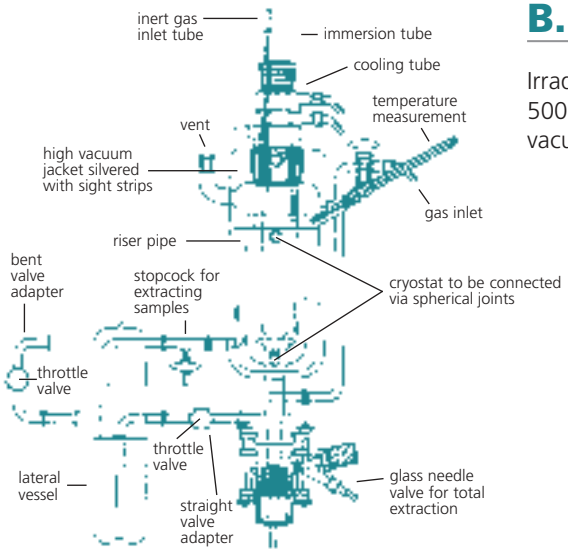
- **Forced liquid circulation:** a glass pump, with polymer-coated pump rotor, is fixed below actual reaction vessel and effectively circulates liquid to be irradiated. Liquid above pump is sucked down, thrown outwards by the pump rotor, forced up the riser pipe, and fed back to the reaction chamber through the upper end of the pipe. A separate drive motor is required to drive circulating pump.
- **Falling film design:** minimizes volume of liquid required. The UV light of specific wavelength is fully utilized due to the falling thin film of solution and its efficient circulation.
- **Gas formation or consumption:** reactions can be monitored very precisely in the completely closed apparatus.
- **Temperature control:** jacketed reaction vessel permits exterior heating or cooling.



A. NORMAG® Photoreactor with Forced Liquid Circulation

Cooling tube and immersion tube are made of quartz. Approximate volume 350 to 400 mL. Reactor is suitable for the mercury low-pressure lamp TNN 15/32 and mercury high-pressure lamps TQ 150, TQ 150Z, TQ 150 Z1, TQ 150 Z2, and TQ 150 Z3. Purchase UV lamps and power supply separately (see facing page).

Z60,280-9



B. NORMAG® Falling-Film Photoreactor

Irradiation vessel working volume is 200 mL. Volume may be increased with 250-, 500-, 1,000-, or 2,000-mL lateral vessel. May be cooled to –70 °C. Silvered vacuum jacket. Purchase UV lamps and power supply separately (see facing page).

Z60,281-7

For technical assistance or applications questions, please contact us at aldglass@sial.com or call 800-231-8327 (USA) or 414-273-3850 (international).

ALDRICH®

NORMAG® UV Lamps

Model	Cat. No.	Spectral Characterizations
Mercury high-pressure immersion lamps		
TQ 150	Z60,336-8	Several wavelengths, most intense at 366 nm
TQ 150 Z1	Z60,337-6	Enhanced radiation in 400–450 nm range
TQ 150 Z2	Z60,338-4	Intense green line, 500–550 nm
TQ 150 Z3	Z60,339-2	Various spectral lines: 280–360, 460–510, and visible red
TQ 718	Z60,340-6	Several wavelengths, most intense at 366 nm
TQ 718 Z1	Z60,341-4	Enhanced radiation in 400–450 nm range
TQ 718 Z2	Z60,342-2	Intense green line, 500–550 nm
TQ 718 Z3	Z60,343-0	Various spectral lines: 280–360, 460–510, and visible red
Mercury low-pressure immersion lamps		
TNN 15/32	Z60,344-9	254 nm, practically monochromatic

NORMAG® Power Supplies

Choose a power supply that matches the UV lamp series above.

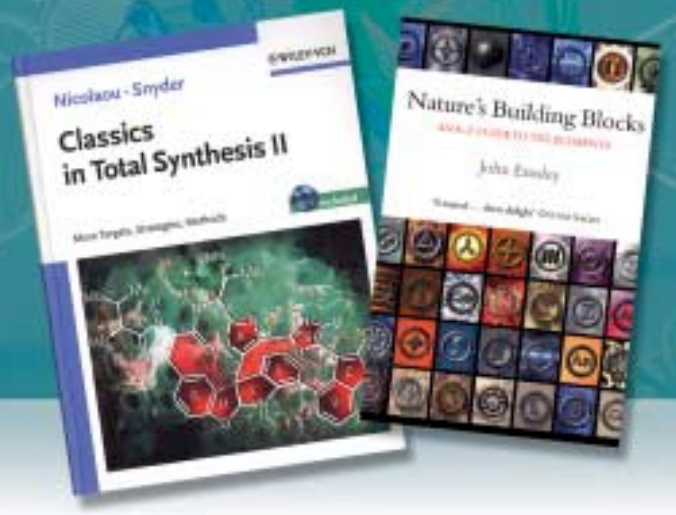
Model	*115V* Cat. No.	*230V* Cat. No.
TNN 15/32	Z55,313-1	Z60,282-5
TQ 150 Series	Z55,315-8	Z60,283-3
TQ 718 Series	Z55,316-6	Z60,284-1

Micro Photochemical Reaction Assemblies

New reactor design[1] handles volumes from 5 to 15 mL. Borosilicate glass body with #25 Ace-Thred at top, and 14/10 outer side standard joint externally threaded to allow an O-ring cap-seal connection with mating male joints. Porosity E (4 to 8 µm) filter disc for use as a gas inlet to remove oxygen from the solution or for agitation. Includes an 11-mm (i.d.), jacketed, immersion well in quartz or borosilicate glass, and a quartz Pen-Ray 5.5 W, low-pressure, cold cathode, mercury lamp with matching 115 V, 60 Hz power supply.

(1) Designed by John H. Penn and Richard D. Orr, West Virginia University, Department of Chemistry, Morgantown, WV 26506.

Description	Cat. No.
Reactor assembly with quartz well	Z21,455-8
Reactor assembly with borosilicate well	Z21,456-6



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Handbook of Organic–Inorganic Hybrid Materials and Nanocomposites

H. S. Nalwa, Ed., American Scientific Publishers, 2003, 900pp. Hardcover. Covers molecular building blocks for preparing hybrid materials and nanocomposites, different synthetic routes tolerating multiple functionalities and a wide range of compositions, sol-gel chemistry, processing and fabrication into ultrathin films, fibers, xerogels, spectroscopic characterization, mechanical, thermal, electronic, optical, catalytic, and biological properties, polymer–metal interfaces, and their potential commercial applications.

Z55,013-2

Handbook of Polyelectrolytes and Their Applications (3-Volume Set)

S. Tripathy, J. Kumar, and H. S. Nalwa, Eds., American Scientific Publishers, 2002, 1200pp. Hardcover. This book covers all aspects of polyelectrolytes: their chemical synthesis, spectroscopic characterization, fabrication, processing into multilayers, self-assemblies, thin films and nanostructures, physical properties, solution behavior, theoretical models, and industrial applications of polyelectrolytes currently studied in academic and industrial research. Contains more than 6,000 bibliographic citations and thousands of illustrations, figures, tables, and equations.

Z54,718-2

Molecular Nanoelectronics

M. A. Reed and T. Lee, Eds., American Scientific Publishers, 2003, 400pp. Hardcover. This book covers topics on transport theory through nanostructures, processing, self-assembly, device fabrication and architecture for nanoelectronic device applications. Contains about 2,000 bibliographic citations and hundreds of illustrations, figures, tables, chemical structures, and equations.

Z55,011-6

Principles of Chemical Vapor Deposition: What's Going on Inside the Reactor?

D. M. Dobkin and M. K. Zuraw, Kluwer Academic Publishers, 2003, 288pp. Hardcover. Provides a simple introduction to heat and mass transfer, surface and gas-phase chemistry, and plasma discharge characteristics. The book includes discussions of practical films and reactors to help in the development of better processes and equipment.

Z55,220-8

Handbook of Luminescence, Display Materials, and Devices (3-Volume Set)

H. S. Nalwa and L. S. Rohwer, Eds., American Scientific Publishers, 2003, 1200pp. Hardcover. Provides coverage on organic light-emitting diodes (OLEDs) and inorganic display devices. Includes synthetic strategies, processing and fabrication methods, screening methods, spectroscopic characterization, energy transfer processes, luminescence in conjugated oligomers, polymers, nanostructured materials, carbon nanotubes, flexible display technologies, up-conversion phosphor materials and aging process, emissive displays, display device reliability, and electrode material degradation.

Z54,768-9

SPECIAL INTEREST TITLES

Hazardous Laboratory Chemicals Disposal Guide, 3rd edition

M.-A. Armour, CRC Press, 2003, 592pp. Hardcover. The extensive list of references has been updated and includes entries for 15 pesticides commonly used in greenhouses. Emphasis is placed on disposal methods that turn hazardous waste materials into nontoxic products. These methods fall into several categories, including acid or base neutralization, oxidation or reduction, and precipitation of toxic ions as insoluble solids. The text also provides data on hazardous reactions of chemicals, in order to assist laboratory managers in developing a plan of action for emergencies such as the spill of any of the chemicals listed.

Z55,214-3

Nature's Building Blocks: An A–Z Guide to the Elements

J. Emsley, Oxford University Press, 2001, 538pp. Softcover. A complete guide to all 115 of those elements that are currently known, with more extensive coverage of those elements we encounter in our everyday life. The entry on each element reveals where it came from, what role it may have in the human body, and the foods that contain it. There are also sections on its discovery, its part in human health or illness, the uses and misuses to which it is put, and its environmental role. A list of the main scientific data and an outline of properties are given for every element. Each section ends with an "Element of Surprise", which highlights some unexpected way in which each element influences our everyday life.

Z55,128-7

ORGANIC BUILDING BLOCKS TITLES

Classics in Total Synthesis II

K. C. Nicolaou, S. A. Snyder, John Wiley & Sons, 2003, 658pp. Hardcover. Discusses in detail the most impressive accomplishments in natural product total synthesis during the 1990s and the first years of the 21st century. All of the features that made the first volume a valuable teaching tool have been maintained in this new edition. The latest techniques and advances in organic synthesis are presented, as the works of some of the most renowned synthetic organic chemists of our time are described.

Z70,161-0

Handbook of Metathesis (3-Volume Set)

R. H. Grubbs, Ed., Wiley-VCH, 2003, 1180pp. Hardcover. There is probably no name more closely linked to metathesis than that of Robert H. Grubbs of the California Institute of Technology. His pioneering work has led to the success of this important and fascinating reaction. In this comprehensive three-volume work, he presents all of its important aspects. The handbook is clearly divided into catalyst developments, organic synthesis applications, and polymer synthesis.

Z55,157-0

Supported Catalysts and Their Applications

D. C. Sherrington and A. P. Kybett, Eds., Royal Society of Chemistry, 2001, 270+pp. Hardcover. Discusses aspects of the design, synthesis, and application of solid-supported reagents and catalysts, including supported reagents for multistep organic synthesis; selectivity in oxidation catalysis; mesoporous molecular sieve catalysts; and the use of Zeolite Beta in organic reactions. Useful to industrialists and researchers, particularly in the agrochemicals and pharmaceuticals industries.

Z55,551-7

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56,193-2	**Deblock** (Contains 3% trichloroacetic acid in dichloromethane)	1L 2L
55,404-9	**Activator** (1*H*-Tetrazole, 3 wt. % solution in acetonitrile)	1L 2L
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