PROAZAPHOSPHATRANES: SUPERIOR BASES AND CATALYSTS

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Recent Applications of Proazaphosphatranes in Organic Synthesis

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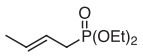
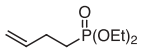
Diethyl 2-butenylphosphonate, 95%, predominantly trans

59,759-7 — 1g, 5g



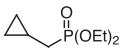
Diethyl 3-butenylphosphonate

64,052-2 — 1g, 10g



Diethyl cyclopropylmethylphosphonate, 97%

63,582-0 — 1g, 5g

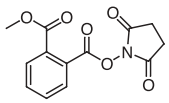


Phosphonates have been utilized extensively in the Horner–Wadsworth–Emmons reaction for the construction of carbon–carbon double bonds. These phosphonates have been employed in the preparation of 3-acetoxy-1-alkenyl phosphonates.[1] They were also exploited in an efficient and regiospecific synthesis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

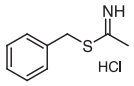


This reagent efficiently undergoes N-phthaloylation with α-amino acids, α-amino alcohols, α-amino carboxamides, α-amino esters, and dipeptides in high yields without racemization.

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

Benzyl thioacetimidate hydrochloride, 96%

63,711-4 — 1g, 5g

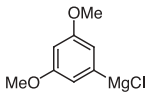


This functionalized thioimidate is a useful reagent for the conversion of anilines to N-substituted acetamidines.[1,2]

(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

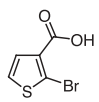


This Grignard reagent was used recently to make materials for studies in crystal engineering.

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

2-Bromo-3-thiophenecarboxylic acid, 97%

63,812-9 — 1g, 5g

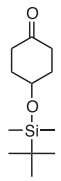


This bifunctional building block was recently utilized in the preparation of oligothiophenes for materials science applications.[1,2]

(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

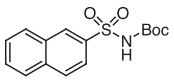


As a protected 4-hydroxycylclohexanone, this compound has been exploited in the synthesis of butenolides,[1] (±)-cocculolidine,[2] and the enyne A-ring synthon of 1α-hydroxy vitamin D_3.[3]

(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

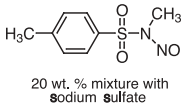


This novel reagent allows the stepwise synthesis of secondary aliphatic amines, such as selectively protected derivatives of spermidine. Cleavage of the sulfonylcarbamate group can be achieved with catalytic amounts of $Mg(ClO_4)_2$ without affecting other Boc-protected amines.

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

Diazald®, 20 wt. % mixture with sodium sulfate

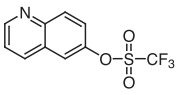
64,053-0 — 25g



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.

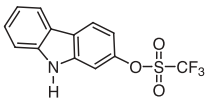
6-Quinolyl trifluoromethanesulfonate, 97%

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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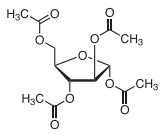
"PLEASE BOTHER US."

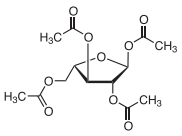
Joe Porwoll, President

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

Naturally, we made these valuable reagents. It was no bother at all, just a pleasure to be able to help.

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.

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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

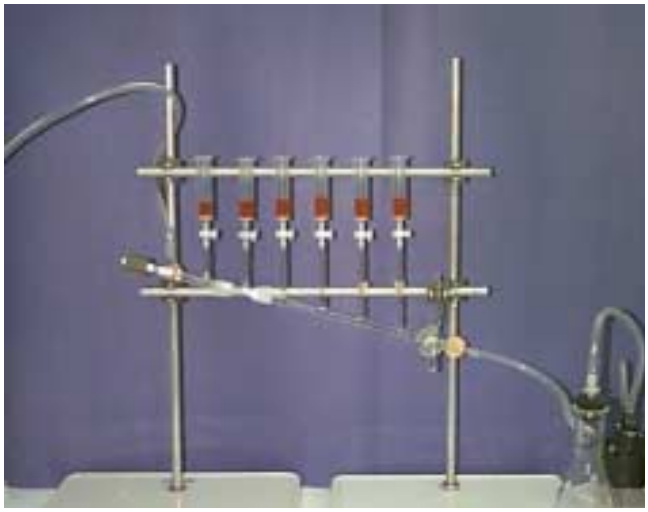
An Inexpensive, Manually Operated, Solid-Phase, Parallel Synthesizer

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

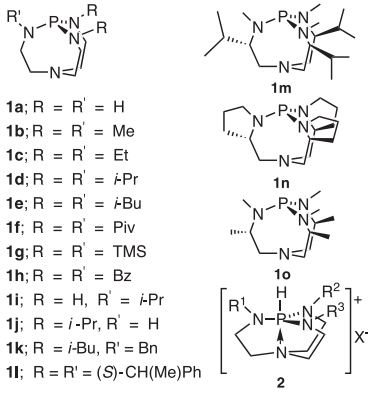
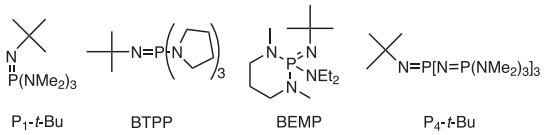
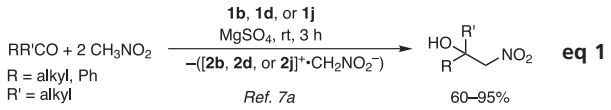


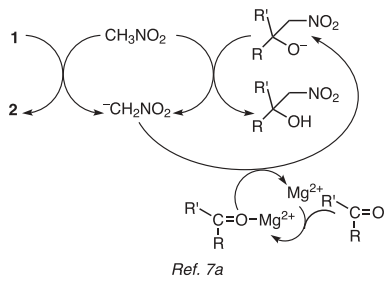
Figure 1. Proazaphosphatranes: Bicyclic, Nonionic Bases.



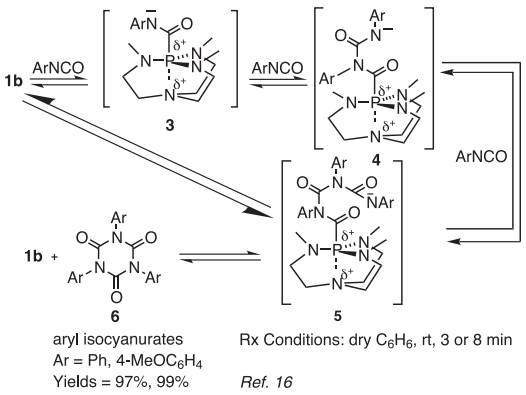
Ref. 1a,2

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]

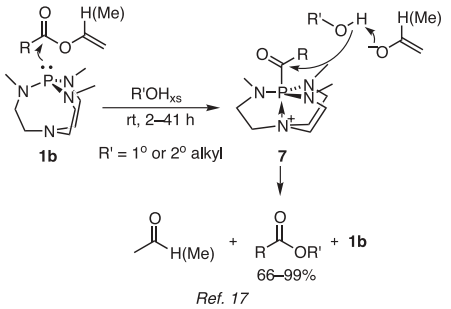
Although many catalysts have been reported for the acylation of alcohols,[22] routes to the selective acylation of hindered alcohols (see Section 3.1.2) and to the efficient acylation of labile alcohols remain in high demand. In the presence of 10 mol % of **1b** or **1d**, allylic, primary, secondary, 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**.

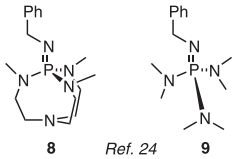
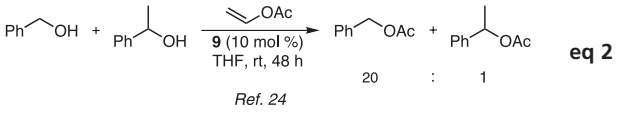
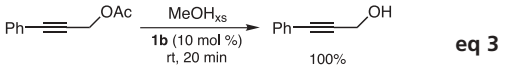
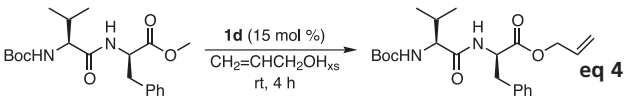


Figure 3. Iminophosphoranes.







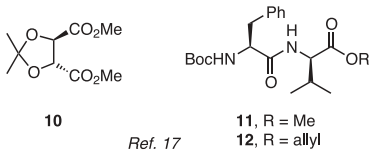
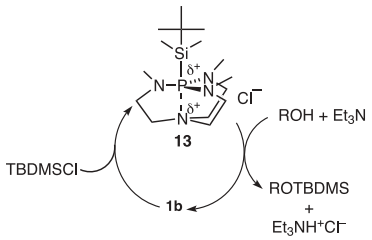
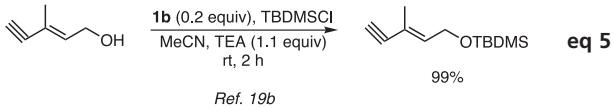


Figure 4. Contrasting Epimerization Behavior of **10** and **11** in the Presence of **1b**.



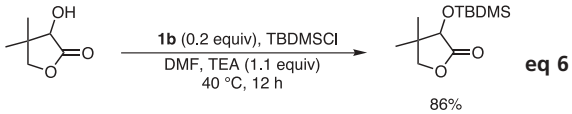
Ref. 19a,b

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



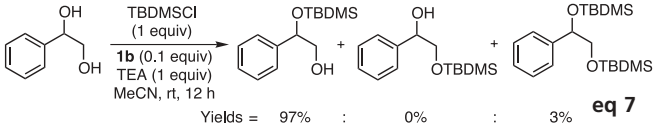
Ref. 19b

eq 5



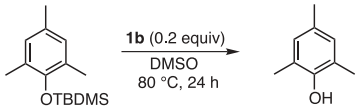
Ref. 19b

eq 6



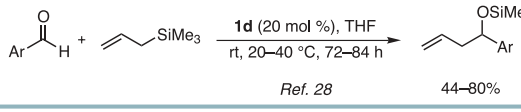
Ref. 19b

eq 7



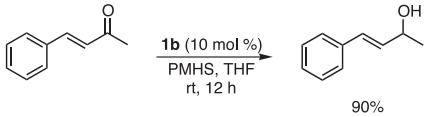
Ref. 21

eq 8



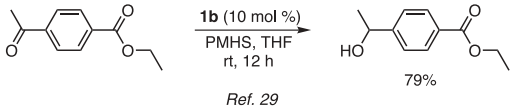
Ref. 28

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]

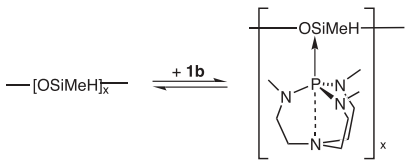
2.2. Base Catalysis

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]

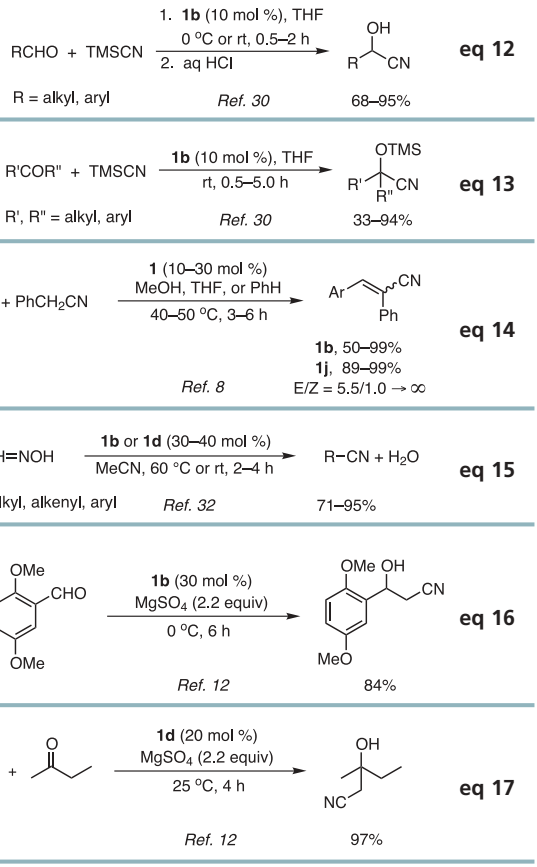
The synthesis of α,β-unsaturated nitriles just described affords a direct route to this class of compounds, which have traditionally been prepared by indirect routes. Among the latter processes are the thermal dehydration of an intermediate β-hydroxy nitrile[37] and the Wittig–Horner reaction.[38] Also 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,



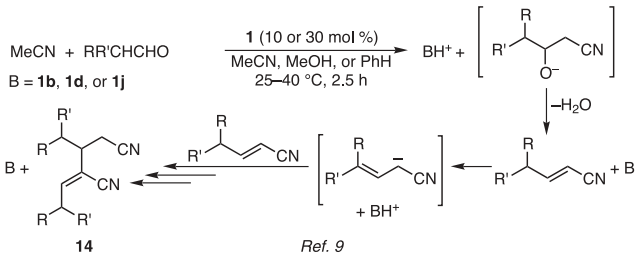
Ref. 29 **1b**•PMHS

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

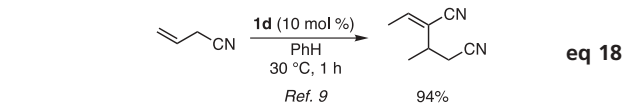


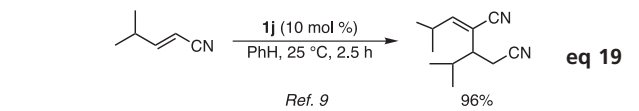
when the reaction of acetonitrile with carbonyl compounds, including ketones and aromatic as well as aliphatic aldehydes (except primary ones), is carried out in the presence of 2 equivalents of magnesium sulfate, the predominant product is the β-hydroxy nitrile (**eq 16** and **17**). Primary aliphatic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

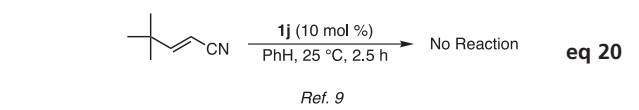
The reaction in equation 16 often produces significant amounts of the undesired corresponding α,β-unsaturated nitrile. However, this side product was efficiently suppressed to 2–6% by carrying out the reaction at 0 °C, followed by quenching with methanol at this temperature before workup.[12] Our methodology 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

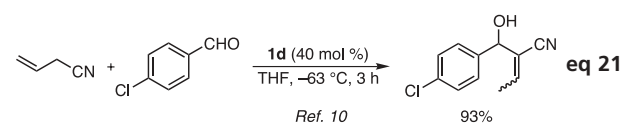


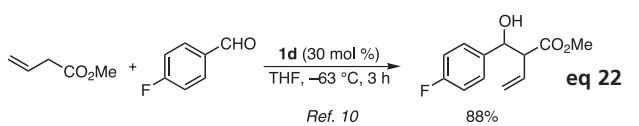
Scheme 6. Proposed Pathway for Glutaronitrile Formation Facilitated by **1b**, **1d**, or **1j**.

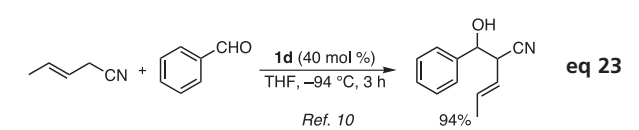


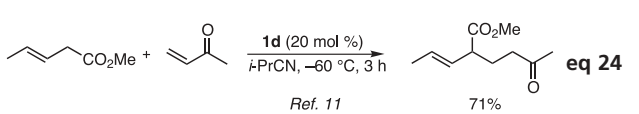


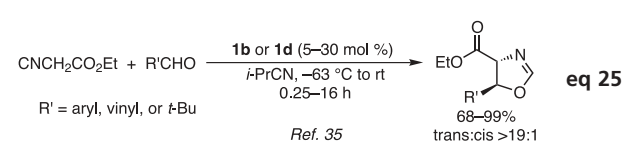


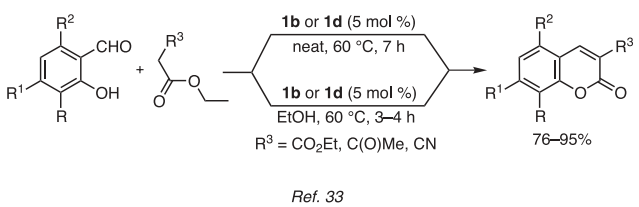












Scheme 7. Coumarin Synthesis Using **1b** or **1d** and a Diactivated Methylene Substrate.

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%.

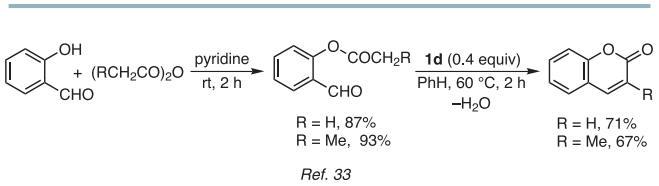
Proazaphosphatranes can also be used in the Michael addition reactions of alcohols or a Schiff base.[45] Hence, the deprotonation of methanol or allyl alcohol using 10–20 mol % of a proazaphosphatrane at 50 or 70 °C leads to the formation of β-alkoxy ketones (**Scheme 10**), which are important intermediates 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**).

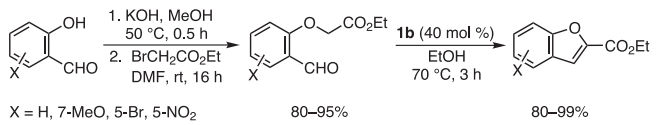
2.3.1. Suzuki Cross-Coupling Reaction

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]



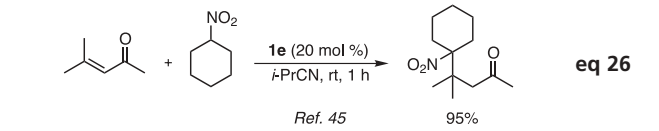
Ref. 33

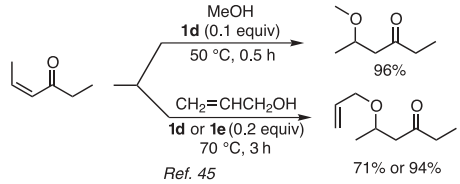
Scheme 8. Coumarin Synthesis Through the Intermediacy of Acylated Salicylaldehydes.



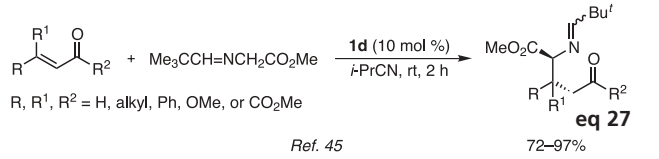
Ref. 34

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





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



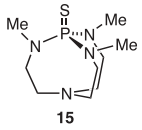
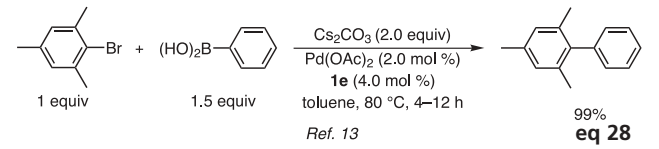
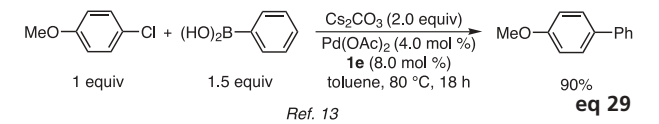


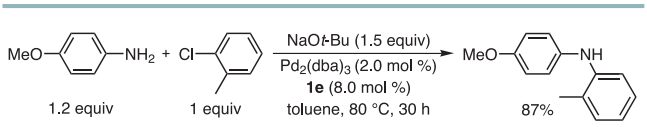
Figure 5. Thiono Derivative of **1b** Used in the Ti(IV)-Catalyzed Baylis–Hillman Reaction.





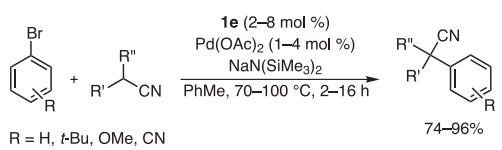
2.3.2. Coupling of Aryl Halides with Amines

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

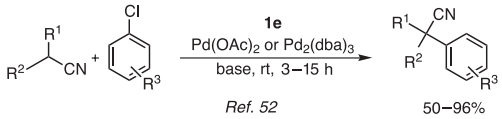
eq 30



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

Ref. 51

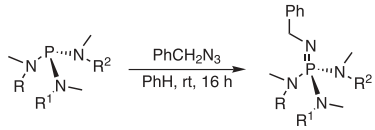
eq 31



Ref. 52

50–96%

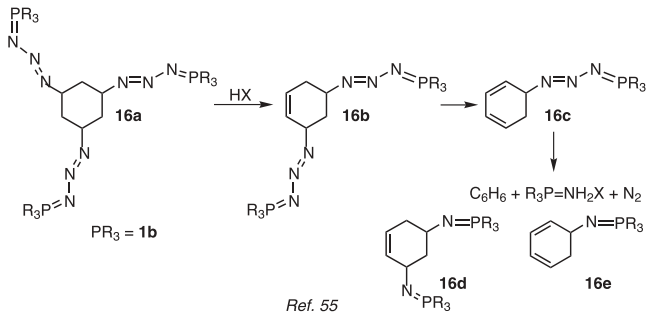
eq 32



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

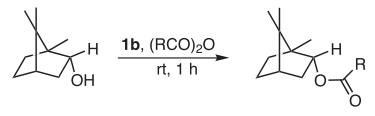
Ref. 24

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

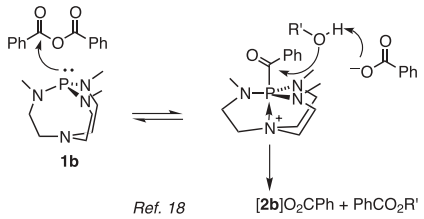
3.1.1. Reaction with Azides

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

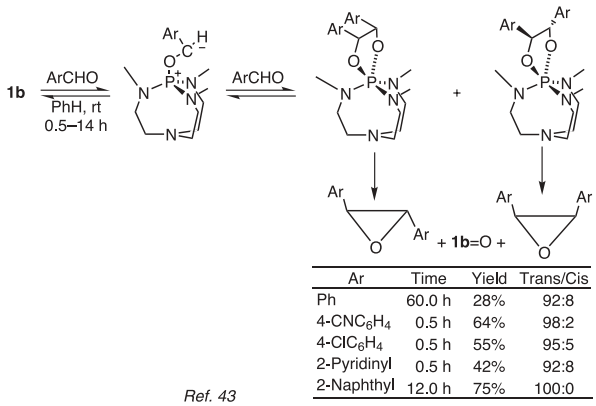
In the presence of stoichiometric amounts of proazaphosphatranes such as **1b** or **1c**, acetic anhydride (or benzoic anhydride) reacts with acid-labile or sterically hindered alcohols to give acylated alcohols in 48–99% yields (**eq 34**).[18] The reaction is believed to proceed by activation of the 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**.

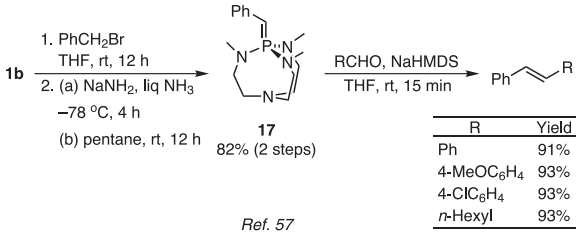


Ar	Time	Yield	Trans/Cis
Ph	60.0 h	28%	92:8
4-CNC_6H_4	0.5 h	64%	98:2
4-ClC_6H_4	0.5 h	55%	95:5
2-Pyridinyl	0.5 h	42%	92:8
2-Naphthyl	12.0 h	75%	100:0

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]

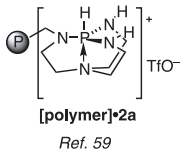
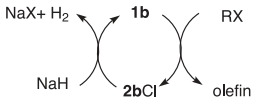


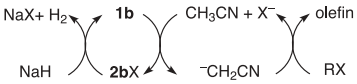
Figure 6. Merrifield Resin Mounted Proazaphosphatrane Salt **2a**.

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]



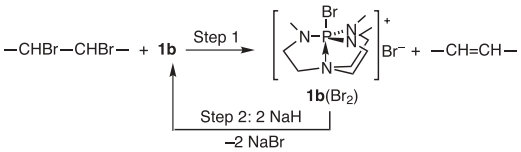
Ref. 59

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



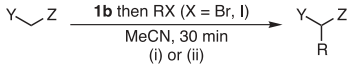
Ref. 59

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



Ref. 59

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

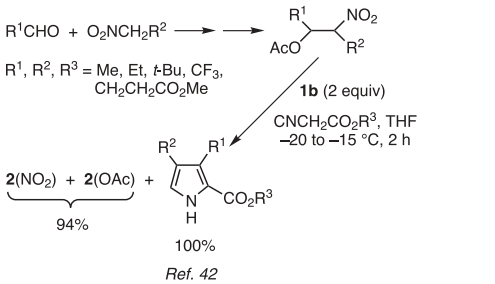


(i) Y = Z = C(=O)Me or CO_2Et: 25 °C
(ii) Y = C(=O)Me, Z = CO_2Et: 0 °C
R = alkyl, allyl, benzyl

eq 35

Ref. 62

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.

(1) For reviews, see: (a) Verkade, J. G. *Top. Curr. Chem.* **2003**, *223*, 1. (b) Verkade, J. G. *Coord. Chem. Rev.* **1994**, *137*, 233. (c) Verkade, J. G. *Acc. Chem. Res.* **1993**, *26*, 483. (d) Verkade, J. G.; Kisanga, P. B. *Tetrahedron* **2003**, *59*, 7819.

(2) Schwesinger, R.; Schlemper, H.; Hasenfratz, C.; Willaredt, J.; Dambacher, T.; Breuer, T.; Ottaway, C.; Fletschinger, M.; Boele, J.; Fritz, H.; Putzas, D.; Rotter, H. W.; Bordwell, F. G.; Satish, A. V.; Ji, G.-Z.; Peters, E.-M.; Peters, K.; von Schnering, H. G.; Walz, L. *Liebigs Ann.* **1996**, 1055.

(3) Kisanga, P. B.; Verkade, J. G.; Schwesinger, R. *J. Org. Chem.* **2000**, *65*, 5431.

(4) Kraus, G. A.; Zhang, N.; Verkade, J. G.; Nagarajan, M.; Kisanga, P. B. *Org. Lett.* **2000**, *2*, 2409.

(5) (a) Lensink, C.; Xi, S. K.; Daniels, L. M.; Verkade, J. G. *J. Am. Chem. Soc.* **1989**, *111*, 3478. (b) Laramay, M. A. H.; Verkade, J. G. *J. Am. Chem. Soc.* **1990**, *112*, 9421. (c) Tang, J.-s.; Verkade, J. G. *Tetrahedron Lett.* **1993**, *34*, 2903. (d) Tang, J.-s.; Verkade, J. G. *J. Am. Chem. Soc.* **1993**, *115*, 1660.

(6) (a) Wróblewski, A. E.; Pinkas, J.; Verkade, J. G. *Main Group Chem.* **1995**, *1*, 69. (b) Kisanga, P. B.; Verkade, J. G. *Tetrahedron* **2001**, *57*, 467. (c) D'Sa, B. A.; Verkade, J. G. *Phosphorus, Sulfur, Silicon* **1997**, *123*, 301. (d) Liu, X.; Ilankumaran, P.; Guzei, I. A.; Verkade, J. G. *J. Org. Chem.* **2000**, *65*, 701. (e) Cernerud, M.; Adolfsson, H.; Moberg, C. *Tetrahedron: Asymmetry* **1997**, *8*, 2655. (f) Lake, F.; Hagberg, L.; Svensson, M.; Moberg, C. *Collect. Czech. Chem. Commun.* **2000**, *65*, 570. (g) Ishihara, K.; Karumi, Y.; Kondo, S.; Yamamoto, H. *J. Org. Chem.* **1998**, *63*, 5692.

(7) (a) Kisanga, P. B.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 4298. (b) For a recent review, see: Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915.

(8) D'Sa, B. A.; Kisanga, P.; Verkade, J. G. *J. Org. Chem.* **1998**, *63*, 3961.

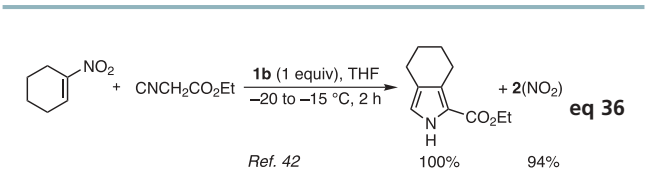
(9) Kisanga, P.; D'Sa, B.; Verkade, J. G. *J. Org. Chem.* **1998**, *63*, 10057.

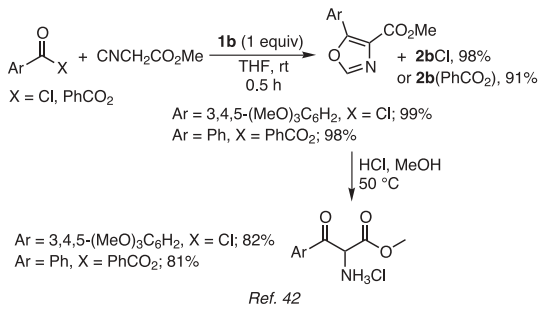
(10) Kisanga, P. B.; Verkade, J. G. *J. Org. Chem.* **2002**, *67*, 426.

(11) Wroblewski, A. E.; Bansal, V.; Kisanga, P.; Verkade, J. G. *Tetrahedron* **2003**, *59*, 561.

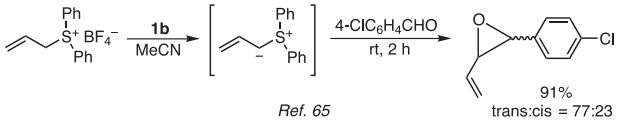
(12) Kisanga, P.; McLeod, D.; D'Sa, B.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 3090.

(13) Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Tetrahedron Lett.* **2002**, *43*, 8921.





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



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

(14) (a) Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 452. (b) Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Org. Lett.* **2003**, *5*, 815.

(15) Su, W.; Urgaonkar, S.; You, J.; McLaughlin, P.; Verkade, J. G. Iowa State University, Ames, IA. Unpublished work, 2000.

(16) Tang, J.-S.; Verkade, J. G. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 896 and references therein.

(17) Ilankumaran, P.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 3086.

(18) D'Sa, B. A.; Verkade, J. G. *J. Org. Chem.* **1996**, *61*, 2963.

(19) (a) D'Sa, B. A.; Verkade, J. G. *J. Am. Chem. Soc.* **1996**, *118*, 12832. (b) D'Sa, B. A.; McLeod, D.; Verkade, J. G. *J. Org. Chem.* **1997**, *62*, 5057.

(20) Liu, X.; Verkade, J. G. *Heteroat. Chem.* **2001**, *12*, 21.

(21) Yu, Z.; Verkade, J. G. *J. Org. Chem.* **2000**, *65*, 2065.

(22) For recent examples, see: (a) Nahmany, M.; Melman, A. *Org. Lett.* **2001**, *3*, 3733. (b) Orita, A.; Tanahashi, C.; Kakuda, A.; Otera, J. *J. Org. Chem.* **2001**, *66*, 8926. (c) Yamada, S.; Katsumata, H. *J. Org. Chem.* **1999**, *64*, 9365.

(23) Ilankumaran, P.; Zhang, G.; Verkade, J. G. *Heteroat. Chem.* **2000**, *11*, 251.

(24) Ilankumaran, P.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 9063.

(25) Corey, E. J.; Kirst, H. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 6314.

(26) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557.

(27) Brenner, M.; Huber, W. *Helv. Chim. Acta* **1953**, *36*, 1109.

(28) Wang, Z.; Kisanga, P.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 6459.

(29) Wang, Z.; Wroblewski, A. E.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 8021.

(30) Wang, Z.; Fetterly, B.; Verkade, J. G. *J. Organomet. Chem.* **2002**, *646*, 161.

(31) Yu, Z.; Verkade, J. G. *Heteroat. Chem.* **1999**, *10*, 544.

(32) Fei, X.-S.; Verkade, J. G. *Heteroat. Chem.* **1999**, *10*, 541.

(33) Kisanga, P.; Fei, X.; Verkade, J. *Synth. Commun.* **2002**, *32*, 1135.

(34) D'Sa, B. A.; Kisanga, P.; Verkade, J. G. *Synlett* **2001**, 670.

(35) Kisanga, P.; Ilankumaran, P.; Verkade, J. G. *Tetrahedron Lett.* **2001**, *42*, 6263 and references therein.
(36) Kisanga, P.; D'Sa, B.; Verkade, J. G. *Tetrahedron* **2001**, *57*, 8047.
(37) (a) Kaiser, E. M.; Hauser, C. R. *J. Org. Chem.* **1968**, *33*, 3402. (b) Fleming, F. F.; Shook, B. C. *J. Org. Chem.* **2002**, *67*, 3668.
(38) Tanaka, K.; Ono, N.; Kubo, Y.; Kaji, A. *Synthesis* **1979**, 890.
(39) (a) Palomo, C.; Azipurua, J. S.; Aurrekoetxea, N. *Tetrahedron Lett.* **1990**, *31*, 2209. (b) Minami, I.; Yuhara, M.; Shimizu, I.; Tsuji, J. *J. Chem. Soc., Chem. Commun.* **1986**, 118. (c) Naota, T.; Taki, H.; Mizuno, M.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1989**, *111*, 5954.
(40) Fringuelli, F.; Pani, G.; Piermatti, O.; Pizzo, F. *Tetrahedron* **1994**, *50*, 11499.
(41) (a) Chini, M.; Crotti, P.; Favero, L.; Macchia, F. *Tetrahedron Lett.* **1991**, *32*, 4775. (b) Mitchell, D.; Koenig, T. M. *Tetrahedron Lett.* **1992**, *33*, 3281. (c) Takai, K.; Ueda, T.; Ikeda, N.; Moriwake, T. *J. Org. Chem.* **1996**, *61*, 7990. (d) You, Z.; Lee, H. J. *Tetrahedron Lett.* **1996**, *37*, 1165.
(42) Tang, J.; Verkade, J. G. *J. Org. Chem.* **1994**, *59*, 7793.
(43) Liu, X.; Verkade, J. G. *J. Org. Chem.* **2000**, *65*, 4560.
(44) (a) Hwu, J. R.; Gilbert, B. A. *J. Am. Chem. Soc.* **1991**, *113*, 5917. (b) Ballini, R.; Bosica, G.; Fiorini, D.; Petrini, M. *Tetrahedron Lett.* **2002**, *43*, 5233. (c) Gil, M. V.; Román, E.; Serrano, J. A. *Tetrahedron Lett.* **2000**, *41*, 10201. (d) Shahi, S. P.; Vankar, Y. D. *Synth. Commun.* **1999**, *29*, 4321.
(45) Kisanga, P. B.; Ilankumaran, P.; Fetterly, B. M.; Verkade, J. G. *J. Org. Chem.* **2002**, *67*, 3555.
(46) (a) Kanemasa, S.; Uchida, O.; Wada, E. *J. Org. Chem.* **1990**, *55*, 4411. (b) Yamamoto, H.; Kanemasa, S.; Wada, E. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2739.
(47) For recent reviews, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Maes, B. U. W.; Košmrlj, J.; Lemière, G. L. F. *J. Heterocycl. Chem.* **2002**, *39*, 535. (c) Zapf, A.; Beller, M. *Top. Catal.* **2002**, *19*, 101. (d) Yasuda, N. *J. Organomet. Chem.* **2002**, *653*, 279.
(48) For a recent review of the Hartwig–Buchwald reaction, see: (a) Kočovský, P.; Malkov, A. V.; Vyskočil, S.; Lloyd-Jones, G. C. *Pure Appl. Chem.* **1999**, *71*, 1425. See also: (b) Mallesham, B.; Rajesh, B. M.; Reddy, P. R.; Srinivas, D.; Trehan, S. *Org. Lett.* **2003**, *5*, 963. (c) Ferreira, I. C. F. R.; Queiroz, M.-J. R. P.; Kirsch, G. *Tetrahedron* **2003**, *59*, 975.
(49) For recent literature on the α arylation of nitriles, see: (a) Caron, S.; Vazquez, E.; Wojcik, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 712. (b) Satoh, T.; Inoh, J.-i.; Kawamura, Y.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2239. (c) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9330. (d) Stauffer, S. R.; Beare, N. A.; Stambuli, J. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4641. (e) Beare, N. A.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 541. (f) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234.
(50) For recent reviews, see: (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811. (b) Langer, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3049.
(51) You, J.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8003.
(52) You, J.; Verkade, J. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 5051.
(53) (a) Shi, M.; Jiang, J.-K; Feng, Y.-S. *Org. Lett.* **2000**, *2*, 2397. (b) Basaviah, D.; Sreenivasulu, B.; Rao, A. J. *J. Org. Chem.* **2003**, *68*, 5983. (c) Shi, M.; Feng, Y.-S. *J. Org. Chem.* **2001**, *66*, 406.
(54) You, J.; Xu, J.; Verkade, J. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 5054.
(55) Liu, X.; Zhang, G.; Verkade, J. G. *Tetrahedron Lett.* **2001**, *42*, 4449.
(56) Mohan, T.; Arumugam, S.; Wang, T.; Jacobson, R. A.; Verkade, J. G. *Heteroat. Chem.* **1996**, *7*, 455.
(57) Wang, Z.; Zhang, G.; Guzei, I.; Verkade, J. G. *J. Org. Chem.* **2001**, *66*, 3521.
(58) Arumugam, S.; Verkade, J. G. *J. Org. Chem.* **1997**, *62*, 4827.
(59) Liu, X.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 4840.
(60) Wróblewski, A. E.; Verkade, J. G. *J. Org. Chem.* **2002**, *67*, 420.
(61) Wang, Z.; Verkade, J. G. *Heteroat. Chem.* **1998**, *9*, 687.
(62) Arumugam, S.; McLeod, D.; Verkade, J. G. *J. Org. Chem.* **1998**, *63*, 3677.
(63) Mohan, T.; Verkade, J. G. Iowa State University, Ames, IA. Unpublished work, 1997.
(64) Tang, J. S.; Verkade, J. G. *J. Org. Chem.* **1996**, *61*, 8750.
(65) Fei, X.-S.; Verkade, J. G. *Heteroat. Chem.* **1999**, *10*, 538.
(66) Trost, B. M.; LaRochelle, R. *Tetrahedron Lett.* **1968**, *9*, 3327.

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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.

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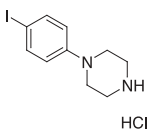
L16,323-6
$C_{10}H_{14}ClIN_2$
MW 324.59
250mg



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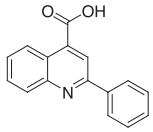

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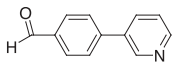

L30,013-6
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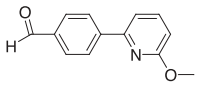
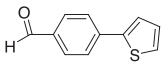
MW 213.24
1g



L30,014-4
$C_{11}H_8OS$
MW 188.25
1g



L30,015-2
$C_{13}H_9NO_3$
MW 227.22
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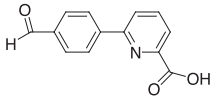

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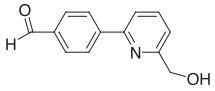

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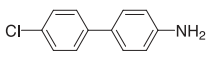

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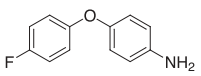

L30,084-5
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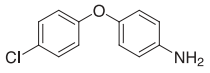

L30,085-3
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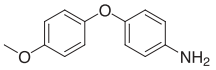
250mg



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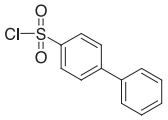
5g



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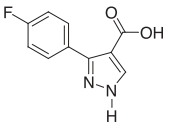
250mg



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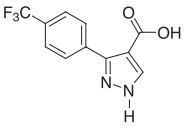

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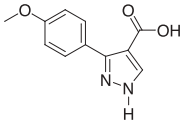

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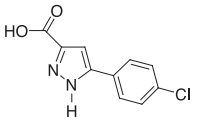

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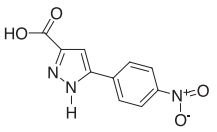

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$C_{11}H_9NO_4$
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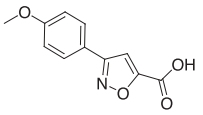

L32,461-2
$C_{10}H_6FNO_3$
MW 207.16
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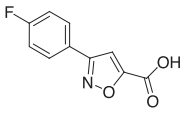

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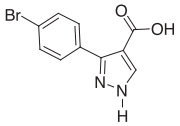

L32,463-9
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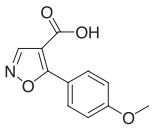

L32,464-7
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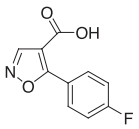

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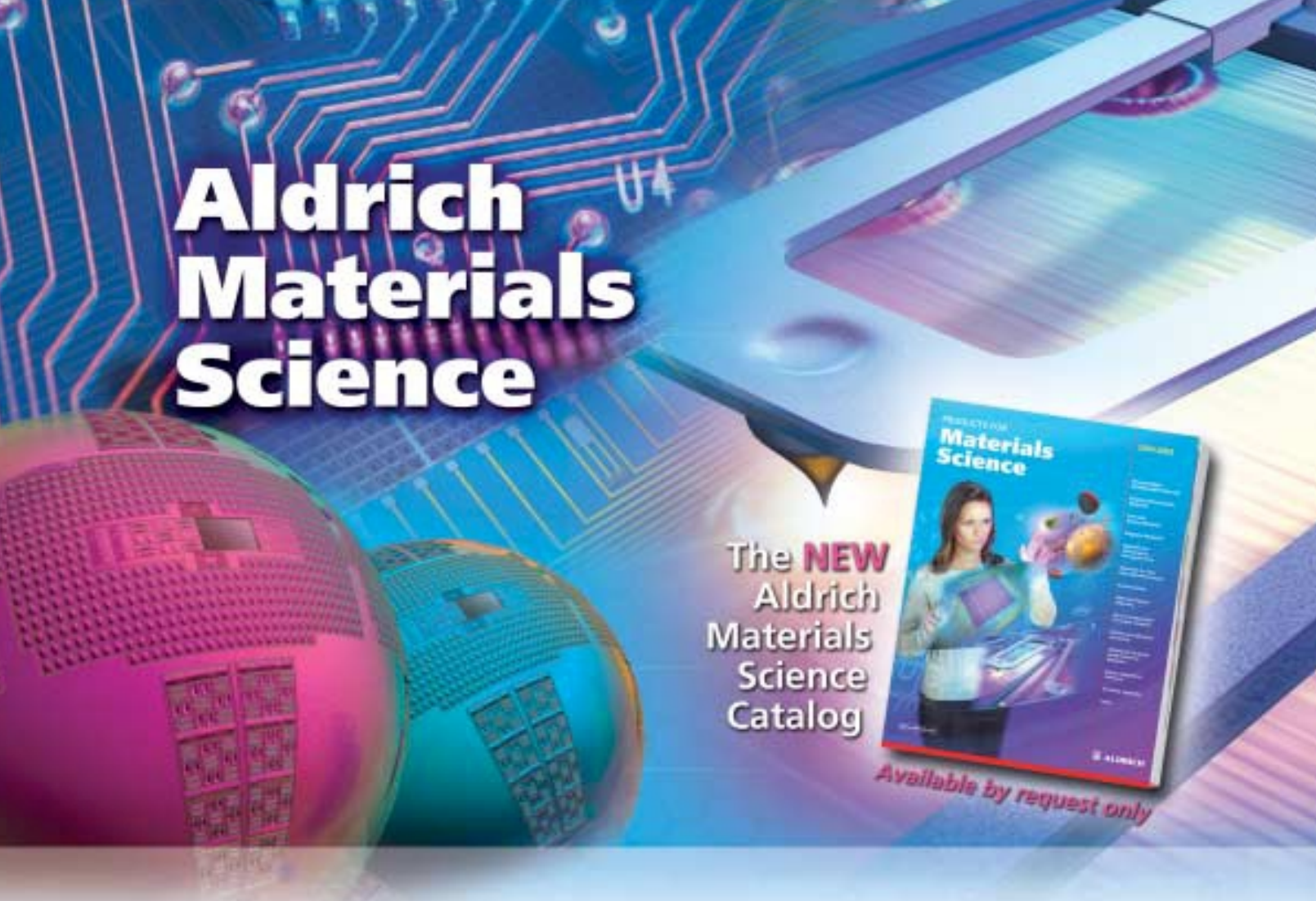

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Chemistry Without Reagents: Synthetic Applications of Flash Vacuum Pyrolysis

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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]

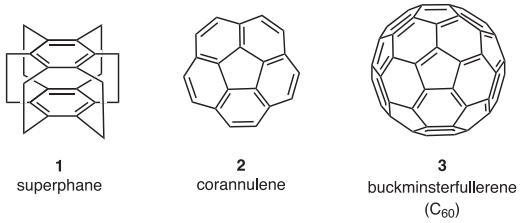


Figure 1. Important Non-Natural Products Obtained by FVP Reactions.

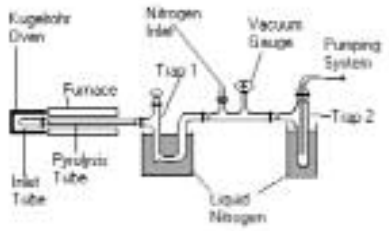
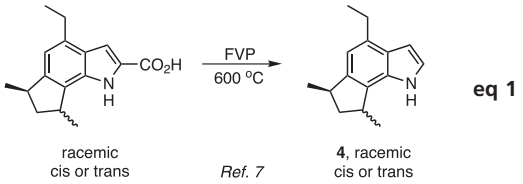
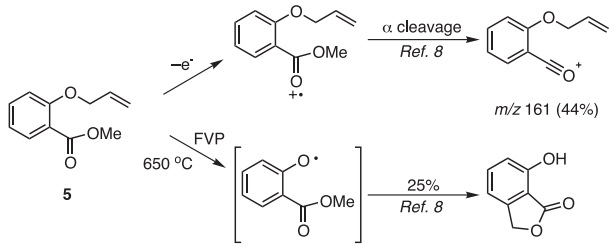


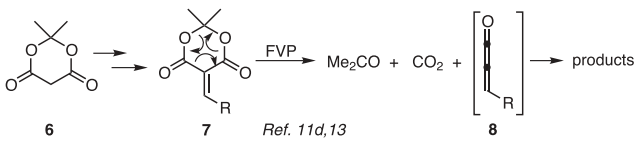
Figure 2. Apparatus for Flash Vacuum Pyrolysis (FVP).



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.

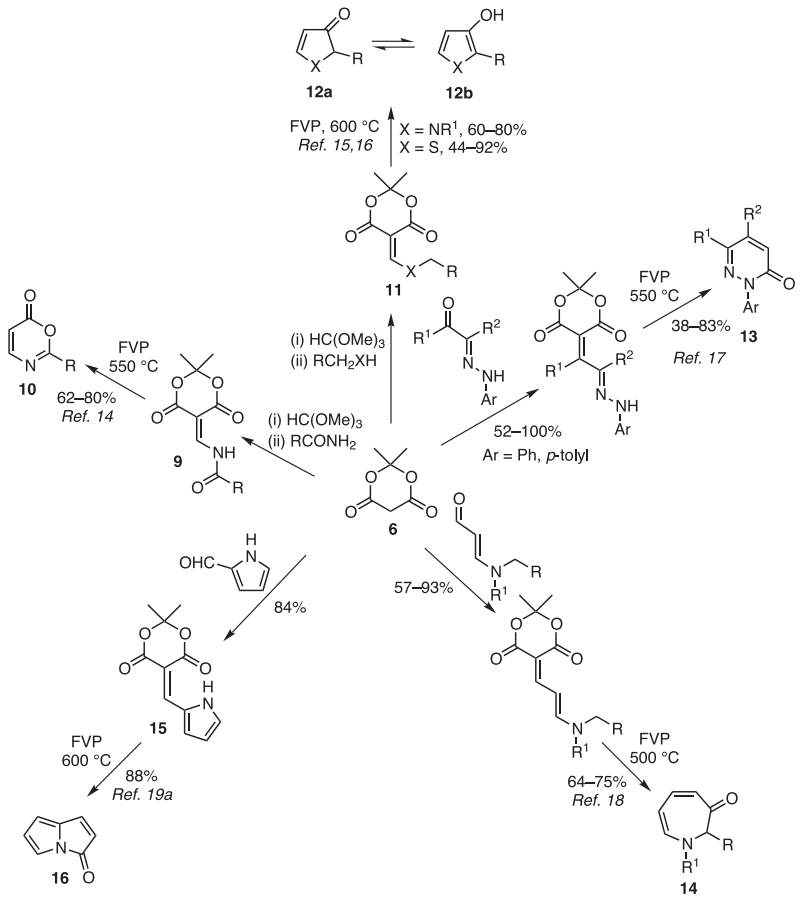
On the other hand, a serious limitation of the classic FVP procedure is the requirement that the substrate must be volatile at low pressures; poorly volatile precursors simply decompose (in the condensed phase) on heating in the inlet tube. It may also be difficult to scale up a procedure, if the precursor 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.

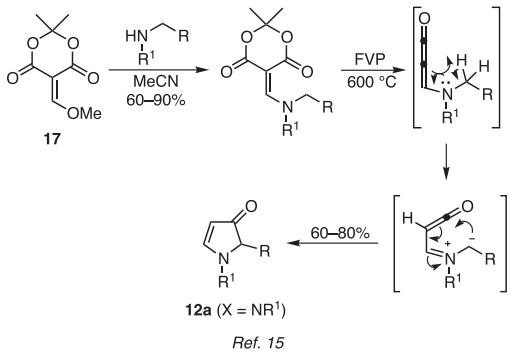
In the absence of solvation, ionization energies are very high and, therefore, ionic intermediates are never encountered under the vibrational activation conditions of the FVP experiment.

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.

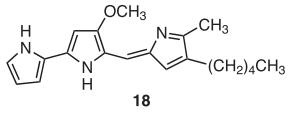
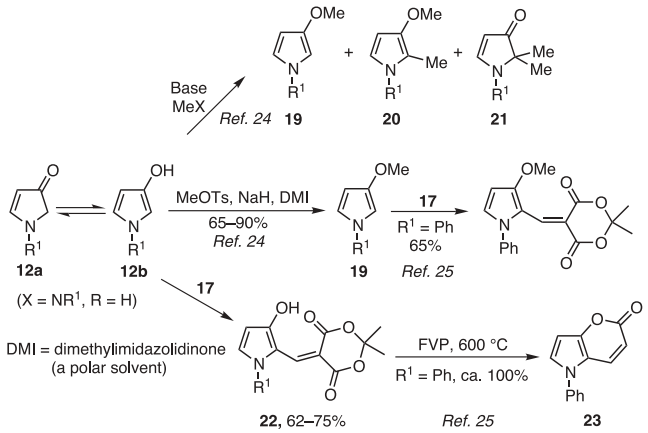
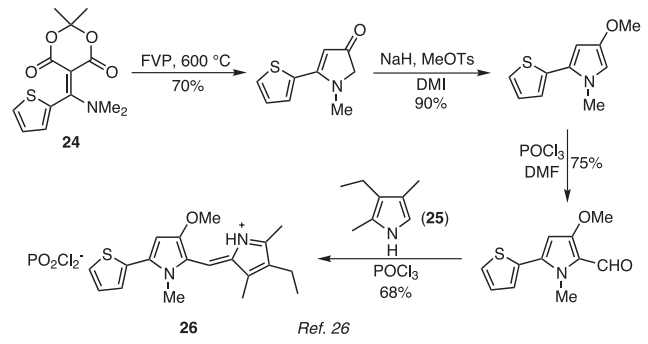


Figure 3. Prodigiosin, a 3-Oxygenated Pyrrole and an Antibiotic and Immunosuppressive Agent.



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

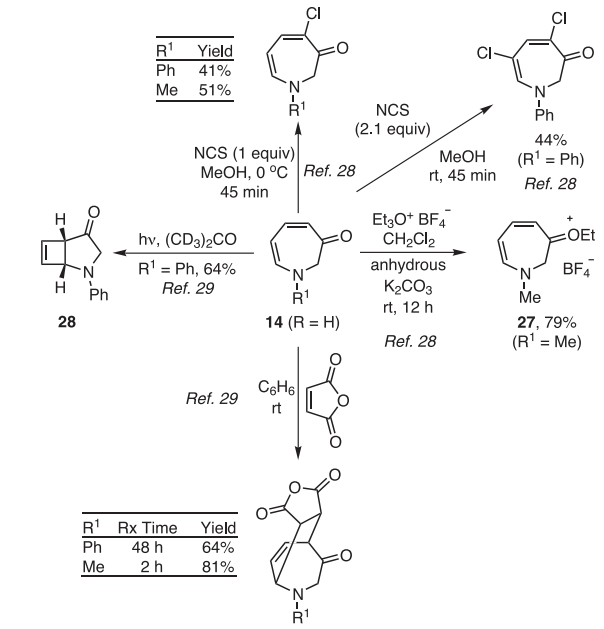
Knoevenagel condensation of enaminones with Meldrum's acid provides the precursors to a novel series of seven-membered heterocycles, azepin-3(2*H*)-ones **14** (see Scheme 3). Here, the pyrolysis mechanism is similar to that of pyrrolone formation (see Scheme 4), except that a [1,6]-prototropic shift 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

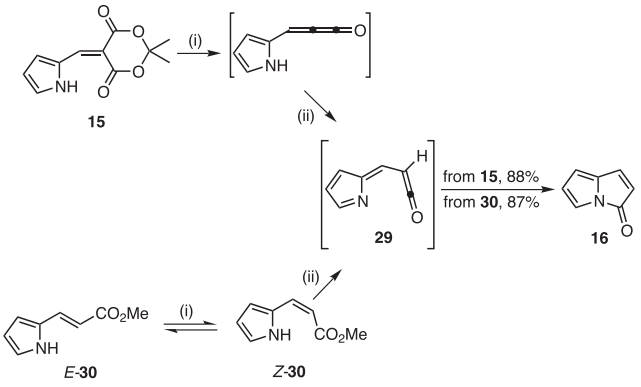
Knoevenagel condensation of Meldrum's acid (**6**) with pyrrole-2-carbaldehyde provides the methylene derivative **15**, which, upon FVP at 600 °C gives pyrrolizin-3-one (**16**) as a deep-red liquid in very high yield (**Scheme 8**).[19a] This pyrolysis can be carried out on a multigram (> 10 g) scale, 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

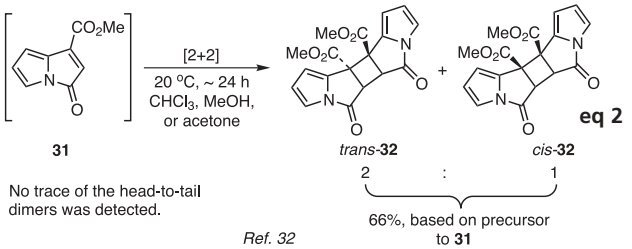


Scheme 7. Highlights of the Chemistry of Azepin-3(2*H*)-ones.

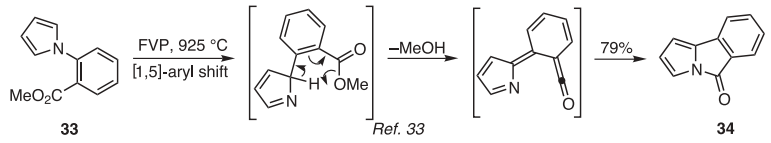


Top pathway (*Ref. 19a*): (i) FVP, 600 °C, – $(CH_3)_2CO$, – CO_2; (ii) [1,7]-hydrogen shift.
Bottom pathway (*Ref. 19b*): (i) FVP, 850 °C; (ii) – MeOH

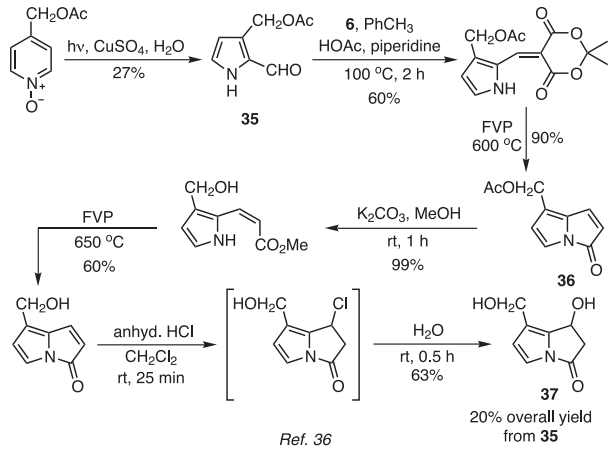
Scheme 8. Pyrrolizin-3-ones via FVP.



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**).

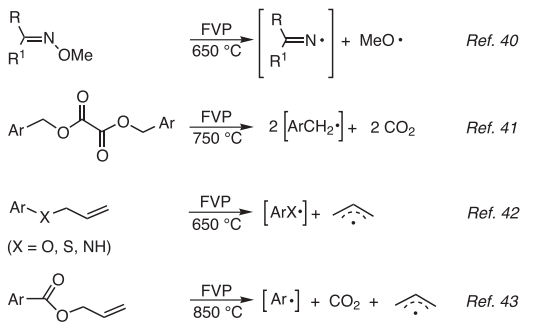
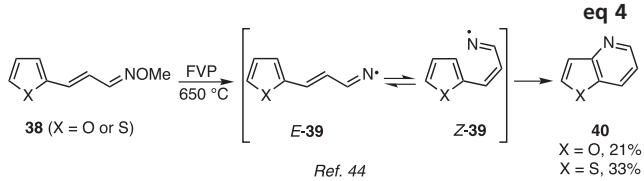


Figure 4. Generation of Iminyl, Benzyl, Phenoxyl (and Related) Radicals, and Phenyl Radicals under FVP Conditions. (The Temperatures Shown Are Representative of These Transformations, When Carried Out in the Edinburgh Apparatus.)

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.

7. References and Notes

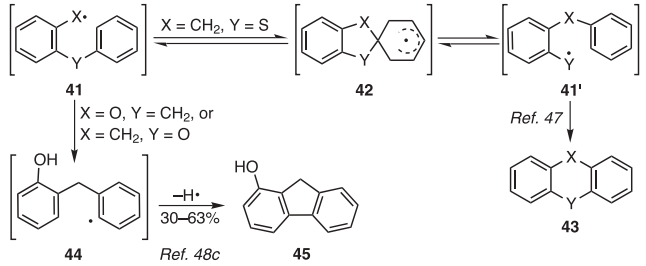
(1) Boekelheide, V. *Acc. Chem. Res.* **1980**, *13*, 65.

(2) For example, (a) Rabideau, P. W.; Sygula, A. *Acc. Chem. Res.* **1996**, *29*, 235. (b) Scott, L. T.; Cheng, P.-C.; Hashemi, M. M.; Bratcher, M. S.; Meyer, D. T.; Warren, H. B. *J. Am. Chem. Soc.* **1997**, *119*, 10963.

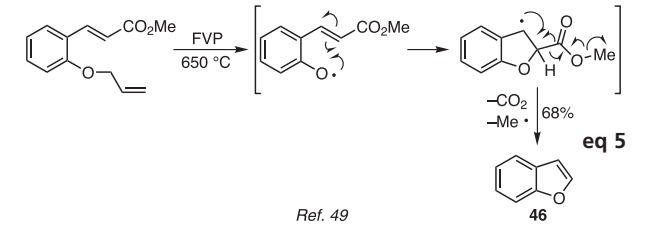
(3) Scott, L. T.; Boorum, M. M.; McMahon, B. J.; Hagen, S.; Mack, J.; Blank, J.; Wegner, H.; de Meijere, A. *Science* **2002**, *295*, 1500.

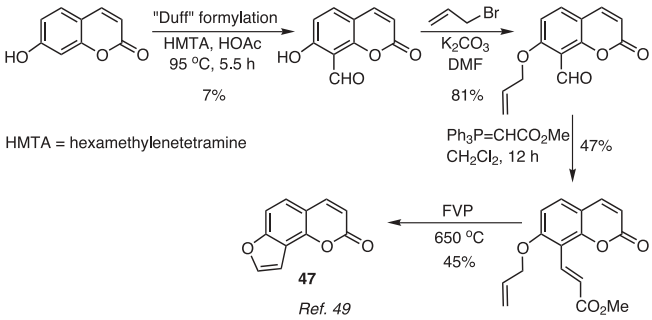
(4) For example, (a) Brown, R. F. C. *Pyrolytic Methods in Organic Chemistry*; Academic Press: New York, 1980. (b) Wiersum, U. E. *Recl. Trav. Chim. Pays-Bas* **1982**, *101*, 317. (c) Wiersum, U. E. *Recl. Trav. Chim. Pays-Bas* **1982**, *101*, 365. (d) Wiersum, U. E. *Aldrichimica Acta* **1984**, *17*, 31. (e) Brown, R. F. C. *Pure Appl. Chem.* **1990**, *62*, 1981. (f) McNab, H. *Contemp. Org. Synth.* **1996**, 373 and references therein. (g) Vallée, Y. *Gas Phase Reactions in Organic Synthesis*; Gordon and Breach: Amsterdam, 1997.

(5) Hurd, C. D. *The Pyrolysis of Carbon Compounds*; American

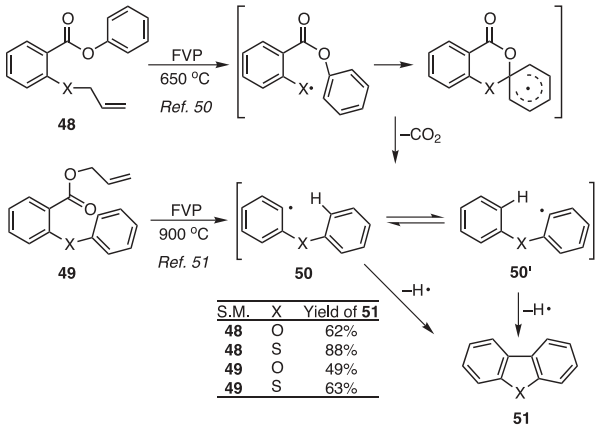


Scheme 10. Contrasting FVP Reactivities of Benzyl and Thiophenoxyl Radicals vis-à-vis Phenoxyl Radicals.





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



Scheme 12. Dibenzofurans and Dibenzothiophenes via Phenyl Radical Cyclizations.

Chemical Society: New York, 1929.
(6) Brown, R. F. C. *Chemobiography*; Royal Australian Chemical Institute: Melbourne, 2001.
(7) MacLeod, J. K.; Monahan, L. C. *Aust. J. Chem.* **1990**, *43*, 329.
(8) Black, M.; Cadogan, J. I. G.; McNab, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 155.
(9) For a description of the scientific career of A. N. Meldrum, see Forster, M. O. *J. Chem. Soc.* **1934**, 1476.
(10) Davidson, D.; Bernhard, S. A. *J. Am. Chem. Soc.* **1948**, *70*, 3426.
(11) Reviews: (a) McNab, H. *Chem. Soc. Rev.* **1978**, *7*, 345. (b) Chen, B.-C. *Heterocycles* **1991**, *32*, 529. (c) Strozhev, M. F.; Lielbriedis, I. É.; Neiland, O. Y. *Khim. Geterotsikl. Soedin.* **1991**, 579 (*Chem. Heterocycl. Compnd.* **1991**, 457). (d) Gaber, A. M.; McNab, H. *Synthesis* **2001**, 2059.
(12) Brown, R. F. C.; Eastwood, F. W.; Harrington, K. J. *Aust. J. Chem.* **1974**, *27*, 2373 and later papers in the series.
(13) For example, Wentrup, C.; Gross, G.; Berstermann, H.-M.; Lorencˆak, P. *J. Org. Chem.* **1985**, *50*, 2877.
(14) McNab, H.; Withell, K. *Tetrahedron* **1996**, *52*, 3163.
(15) McNab, H.; Monahan, L. C. *J. Chem. Soc., Perkin Trans. 1* **1988**, 863.
(16) Hunter, G. A.; McNab, H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1209.
(17) McNab, H.; Stobie, I. *J. Chem. Soc., Perkin Trans 1* **1982**, 1845.
(18) Blake, A. J.; McNab, H.; Monahan, L. C. *J. Chem. Soc., Perkin Trans. 1* **1989**, 425.
(19) (a) McNab, H. *J. Org. Chem.* **1981**, *46*, 2809. (b) Campbell, S. E.; Comer, M. C.; Derbyshire, P. A.; Despinoy, X. L. M.; McNab, H.; Morrison, R.; Sommerville, C. C.; Thornley, C. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2195.
(20) McNab, H.; Morrow, M. *Arkivoc* [Online] **2002**(viii), 125; http://www.arkat-usa.org/ark/journal/2002/Padwa/AP-509H/509H.htm (accessed Feb 2004).
(21) McNab, H.; Monahan, L. C. In *Pyrroles*; Jones, R. A., Ed.; Wiley: New York, 1992; Volume 2, pp 525–616.
(22) Momose, T.; Tanaka, T.; Yokota, T.; Nagamoto, N.; Yamada, K. *Chem. Pharm. Bull.* **1979**, *27*, 1448.
(23) (a) Gerber, N. N. *Crit. Rev. Microbiol.* **1974**, *3*, 469. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3582.
(24) Hunter, G. A.; McNab, H.; Monahan, L. C.; Blake, A. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3245.
(25) Derbyshire, P. A.; Hunter, G. A.; McNab, H.; Monahan, L. C. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2017.
(26) Blake, A. J.; Hunter, G. A.; McNab, H. *J. Chem. Soc., Chem. Commun.* **1990**, 734.
(27) Huang, X.; Chen, B.-C. *Synthesis* **1987**, 480.
(28) McNab, H.; Monahan, L. C.; Blake, A. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3163.
(29) McNab, H.; Monahan, L. C. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3169.
(30) Hickson, C. L.; McNab, H. *J. Chem. Res. (S)* **1989**, 176.
(31) (a) McNab, H. *J. Chem. Soc., Perkin Trans. 1* **1987**, 653. (b) McNab, H.; Thornley, C. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2203.
(32) Comer, M. C.; Despinoy, X. L. M.; Gould, R. O.; McNab, H.; Parsons, S. *J. Chem. Soc., Chem. Commun.* **1996**, 1083.
(33) (a) McNab, H.; Parsons, S.; Stevenson, E. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2047. (b) McNab, H.; Tyas, R. G. The University of Edinburgh, Edinburgh, U.K. Unpublished work, 2002.
(34) McNab, H.; Thornley, C. *Heterocycles* **1994**, *37*, 1977.
(35) Blockhuys, F.; Hinchley, S. L.; Robertson, H. E.; Blake, A. J.; McNab, H.; Despinoy, X. L. M.; Harris, S. G.; Rankin, D. W. H. *J. Chem. Soc., Perkin Trans. 2* **2001**, 2195.
(36) McNab, H.; Thornley, C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3584.
(37) Bellamy, F.; Streith, J.; Fritz, H. *Nouv. J. Chim.* **1979**, *3*, 115.
(38) Despinoy, X. L. M.; McNab, H. *Tetrahedron* **2000**, *56*, 6359.
(39) Despinoy, X. L. M.; McNab, H. The University of Edinburgh, Edinburgh, U.K. Unpublished work, 1998.
(40) Hickson, C. L.; McNab, H. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1569.
(41) Trahanovsky, W. S.; Ong, C. C.; Lawson, J. A. *J. Am. Chem. Soc.* **1968**, *90*, 2839.
(42) Cadogan, J. I. G.; Hickson, C. L.; McNab, H. *Tetrahedron* **1986**, *42*, 2135.
(43) Marty, R. A.; de Mayo, P. *J. Chem. Soc., Chem. Commun.* **1971**, 127.
(44) Hickson, C. L.; McNab, H. *Synthesis* **1981**, 464.
(45) McNab, H.; Smith, G. S. *J. Chem. Soc., Perkin Trans. 1* **1984**, 381.
(46) (a) Calestani, G.; Leardini, R.; McNab, H.; Nanni, D.; Zanardi, G. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1813. (b) Black, M.; Cadogan, J. I. G.; Leardini, R.; McNab, H.; McDougald, G.; Nanni, D.; Reed, D.; Zompatori, A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1825. (c) Leardini, R.; McNab, H.; Nanni, D.; Parsons, S.; Reed, D.; Tenan, A. G. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1833. (d) Leardini, R.; McNab, H.; Minozzi, M.; Nanni, D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1072. (e) Creed, T.; Leardini, R.; McNab, H.; Nanni, D.; Nicolson, I. S.; Reed, D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1079.
(47) Cadogan, J. I. G.; Hutchison, H. S.; McNab, H. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2875.
(48) (a) Cadogan, J. I. G.; Hutchison, H. S.; McNab, H. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1407. (b) Cadogan, J. I. G.; Hickson, C. L.; Hutchison, H. S.; McNab, H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 377. (c) Cadogan, J. I. G.; Hutchison, H. S.; McNab, H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 385.
(49) Black, M.; Cadogan, J. I. G.; McNab, H.; MacPherson, A. D.; Roddam, V. P.; Smith, C.; Swenson, H. R. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2483.
(50) Black, M.; Cadogan, J. I. G.; McNab, H. *J. Chem. Soc., Chem. Commun.* **1990**, 395.
(51) Cadogan, J. I. G.; Hutchison, H. S.; McNab, H. *Tetrahedron* **1992**, *48*, 7747.
(52) Crawford, L. A.; McNab, H.; Wharton, S. I. The University of Edinburgh, Edinburgh, U.K. Unpublished work, 2002.

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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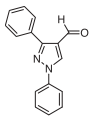
L32,022-6

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



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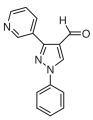

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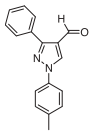

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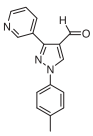

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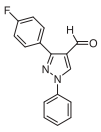

L32,045-5

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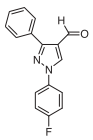

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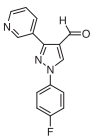

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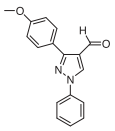

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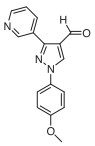

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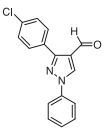

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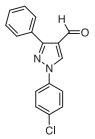

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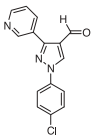

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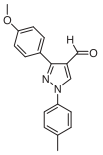

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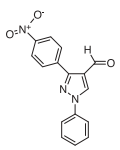

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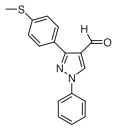

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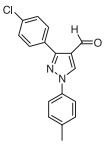

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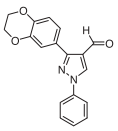

L32,039-0

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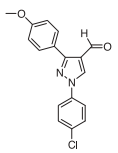

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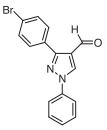

L32,106-0

$C_{15}H_{10}BrN_3O$
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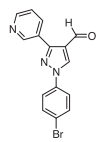

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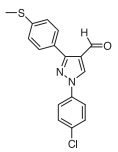

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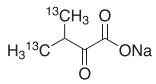
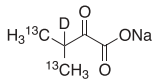
2-Keto-3-(methyl-^{13}C)-butyric acid-4-^{13}C, sodium salt
99 atom % ^{13}C

57,133-4 100mg



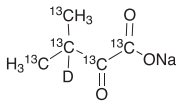
2-Keto-3-(methyl-^{13}C)-butyric acid-4-^{13}C,3-d$_1$, sodium salt
99 atom % ^{13}C, 98 atom % D

58,906-3 100mg



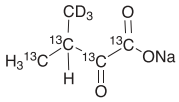
2-Keto-3-methylbutyric acid-^{13}C$_5$,3-d$_1$, sodium salt
99 atom % ^{13}C, 98 atom % D

60,756-8 250mg



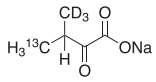
2-Keto-3-(methyl-d$_3$)-butyric acid-1,2,3,4-^{13}C$_4$, sodium salt
99 atom % ^{13}C, 98 atom % D

59,641-8 100mg



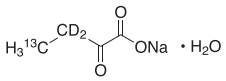
2-Keto-3-(methyl-d$_3$)-butyric acid-4-^{13}C, sodium salt
99 atom % ^{13}C, 98 atom % D

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



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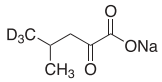
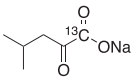
61,662-1 500mg



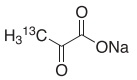
2-Keto-4-methylpentanoic acid-1-^{13}C, sodium salt, 99 atom % ^{13}C

48,771-6 250mg



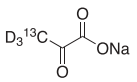
Sodium pyruvate-3-^{13}C, 99 atom % ^{13}C

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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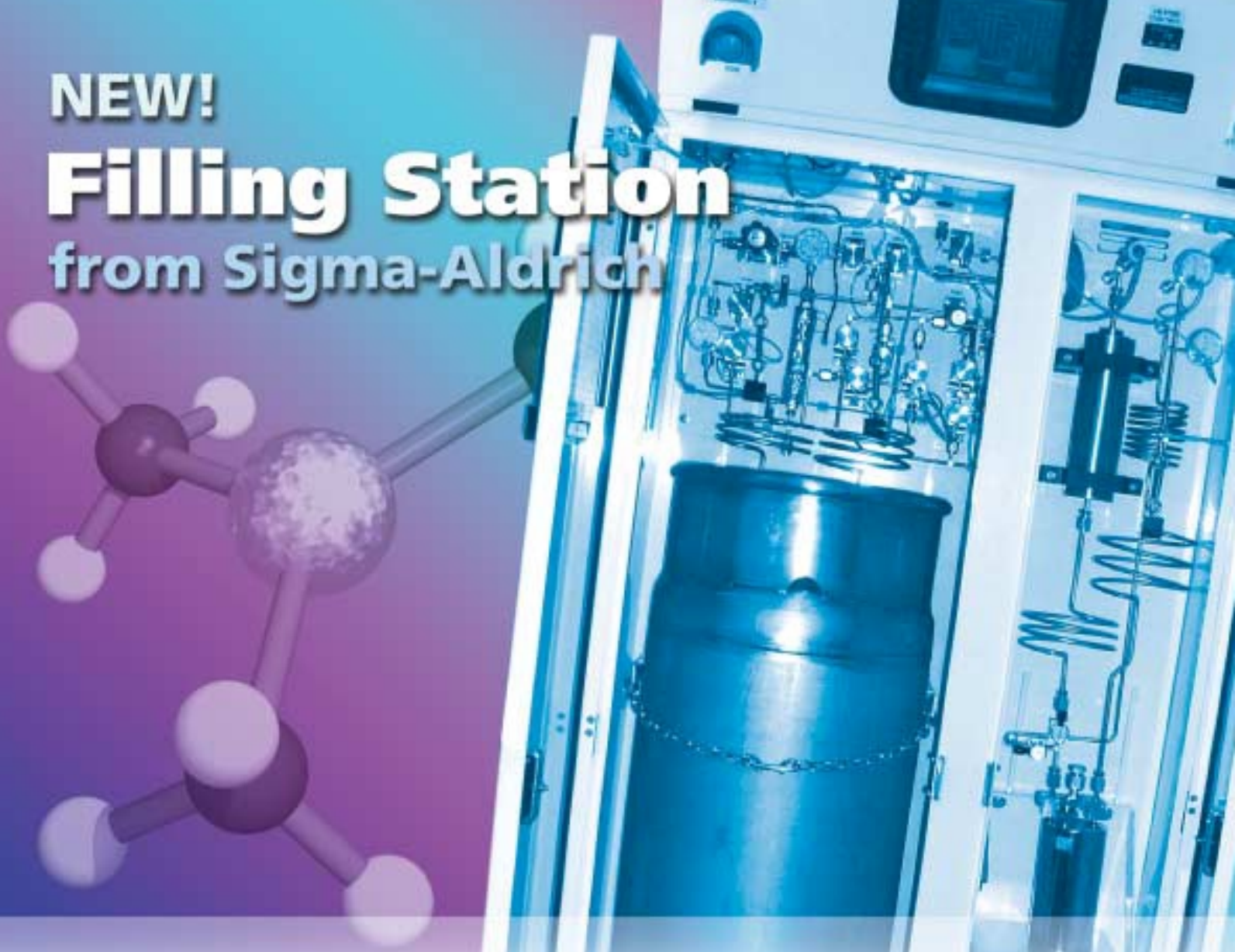

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Fluka, in collaboration with Cytec Industries, now offers a new promising class of ionic liquids that are based on phosphonium cations ($[PR_3R']^+$).

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

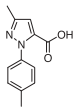
Aldrich is proud to offer a series of building blocks called SmartBlocs™, which constitute a unique collection of products having a wide range of applications in organic synthesis and in medicinal chemistry. Each of these SmartBlocs™ contains two reactive sites, and could serve as the core for library 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

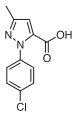
L32,296-2

$C_{12}H_{12}N_2O_2$
MW 216.24
250mg



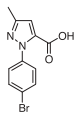
L32,297-0

$C_{11}H_9ClN_2O_2$
MW 236.66
250mg



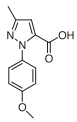
L32,298-9

$C_{11}H_9BrN_2O_2$
MW 281.11
250mg



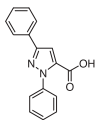
L32,299-7

$C_{12}H_{12}N_2O_3$
MW 232.24
250mg



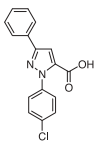
L32,300-4

$C_{16}H_{12}N_2O_2$
MW 264.29
250mg



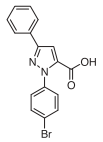
L32,302-0

$C_{16}H_{11}ClN_2O_2$
MW 298.73
250mg



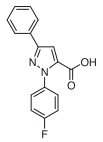
L32,303-9

$C_{16}H_{11}BrN_2O_2$
MW 343.18
250mg



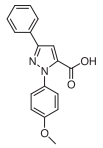
L32,304-7

$C_{16}H_{11}FN_2O_2$
MW 282.28
250mg



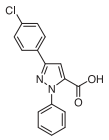
L32,305-5

$C_{17}H_{14}N_2O_3$
MW 294.31
250mg



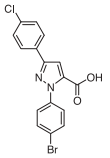
L32,329-2

$C_{16}H_{11}ClN_2O_2$
MW 298.73
250mg



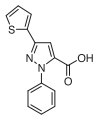
L32,334-9

$C_{16}H_{10}BrClN_2O_2$
MW 377.63
250mg



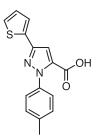
L32,380-2

$C_{14}H_{10}N_2O_2S$
MW 270.31
250mg



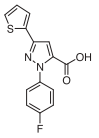
L32,381-0

$C_{15}H_{12}N_2O_2S$
MW 284.34
250mg



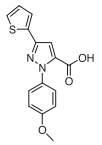
L32,383-7

$C_{14}H_9FN_2O_2S$
MW 288.30
250mg



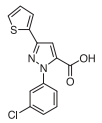
L32,384-5

$C_{15}H_{12}N_2O_3S$
MW 300.34
250mg



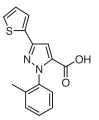
L32,386-1

$C_{14}H_9ClN_2O_2S$
MW 304.76
250mg



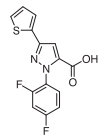
L32,389-6

$C_{15}H_{12}N_2O_2S$
MW 284.34
250mg



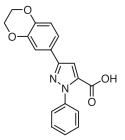
L32,391-8

$C_{14}H_8F_2N_2O_2S$
MW 306.29
250mg



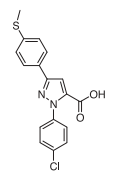
L32,407-8

$C_{18}H_{14}N_2O_4$
MW 322.32
250mg



L32,415-9

$C_{17}H_{13}ClN_2O_2S$
MW 344.82
250mg



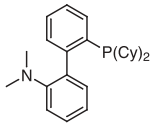
For more information on these products, or to preview other similar products, please call us at 800-333-7306 (USA) or email us at bwandler@sial.com.

More New Products from Aldrich R&D

Novel Phosphines

63,802-1

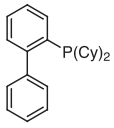
$C_{26}H_{36}NP$



1g
5g
25g

63,809-9

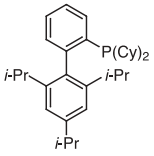
$C_{24}H_{31}P$



1g
5g
25g

63,806-4

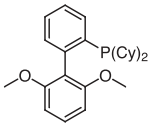
$C_{33}H_{49}P$



1g
5g
25g

63,807-2

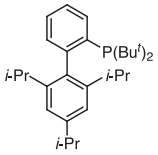
$C_{26}H_{35}O_2P$



1g
5g
25g

63,808-0

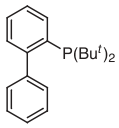
$C_{29}H_{45}P$



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

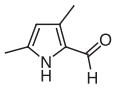
$C_{10}H_{23}P$

1g
5g

Heterocyclic Building Blocks

64,051-4

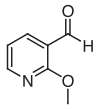
C_7H_9NO



1g

63,213-9

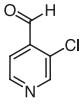
$C_7H_7NO_2$



1g
5g

63,674-6

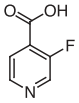
C_6H_4ClNO



1g
5g

63,875-7

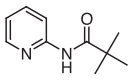
$C_6H_4FNO_2$



1g
10g

63,248-1

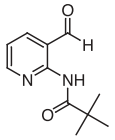
$C_{10}H_{14}N_2O$



1g
5g

63,822-6

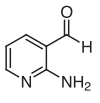
$C_{11}H_{14}N_2O_2$



1g
5g

63,910-9

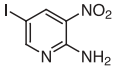
$C_6H_6N_2O$



1g
5g

64,016-6

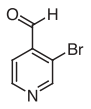
$C_5H_4IN_3O_2$



1g
5g

63,828-5

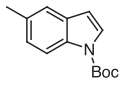
C_6H_4BrNO



1g
5g

63,647-9

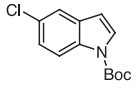
$C_{14}H_{17}NO_2$



1g
5g

63,675-4

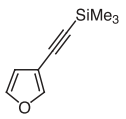
$C_{13}H_{14}ClNO_2$



1g

63,447-6

$C_9H_{12}OSi$

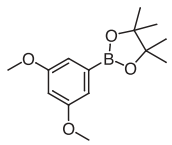


1g
10g

Boronic Acids and Esters

63,390-9

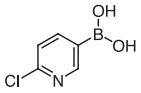
$C_{14}H_{21}BO_4$



1g
5g

63,738-6

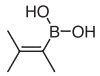
$C_5H_5BClNO_2$



1g
5g

63,907-9

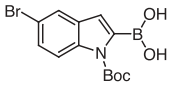
$C_5H_{11}BO_2$



1g
5g

63,739-4

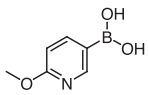
$C_{13}H_{15}BBrNO_4$



1g

63,761-0

$C_6H_8BNO_3$

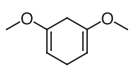


1g
5g

Organic Building Blocks

64,111-1

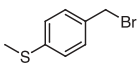
$C_8H_{12}O_2$



1g
5g

63,481-6

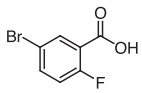
C_8H_9BrS



1g
5g

63,645-2

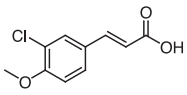
$C_7H_4BrFO_2$



1g
5g

63,876-5

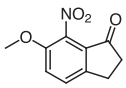
$C_{10}H_9ClO_3$



1g
5g

64,067-0

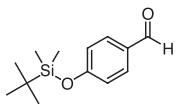
$C_{10}H_9NO_4$



1g
5g

59,615-9

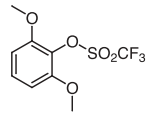
$C_{13}H_{20}O_2Si$



1g

63,787-4

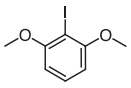
$C_9H_9F_3O_5S$



5g
25g

63,813-7

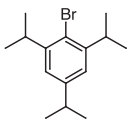
$C_8H_9IO_2$



1g
5g

63,793-9

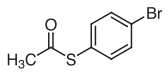
$C_{15}H_{23}Br$



1g
5g

63,465-4

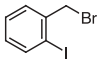
C_8H_7BrOS



1g
5g

63,460-3

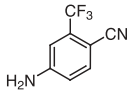
C_7H_6BrI



1g
5g

63,175-2

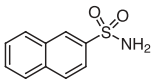
$C_8H_5F_3N_2$



1g
5g

63,407-7

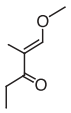
$C_{10}H_9NO_2S$



1g
10g

64,071-9

$C_7H_{12}O_2$



1g
5g

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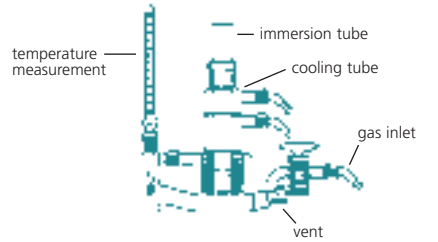
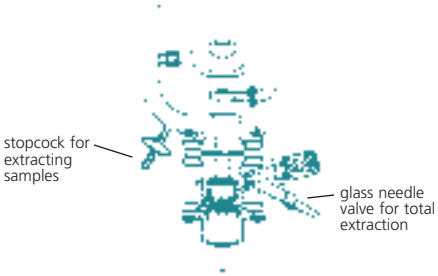
PRINCIPLE OF OPERATION:

- **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.

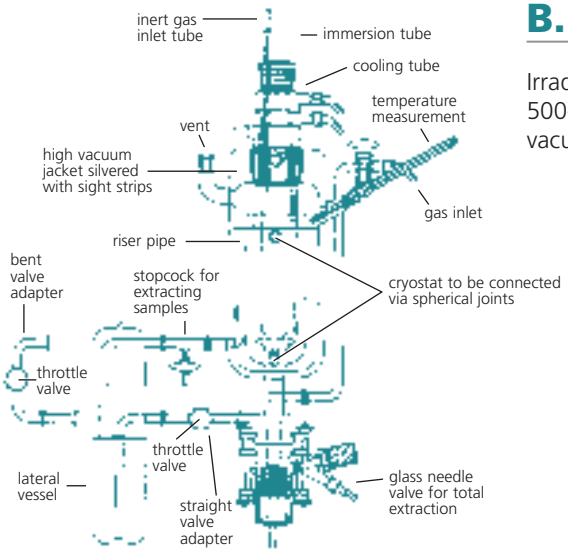




A. NORMAG® Photoreactor with Forced Liquid Circulation

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

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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.

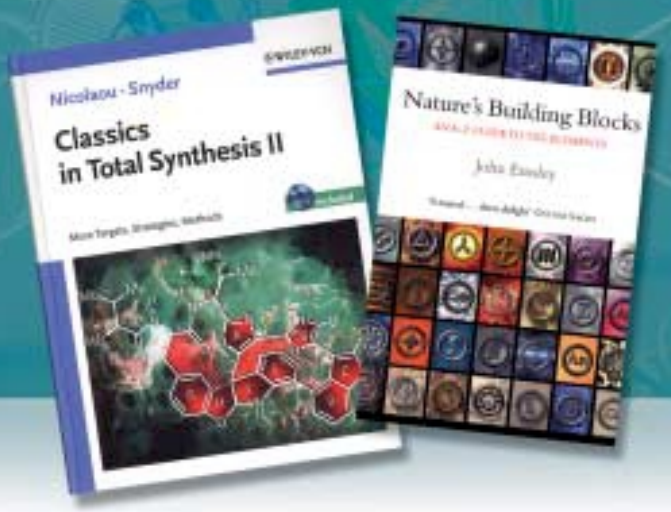
Model	*115V* Cat. No.	*230V* Cat. No.
TNN 15/32	Z55,313-1	Z60,282-5
TQ 150 Series	Z55,315-8	Z60,283-3
TQ 718 Series	Z55,316-6	Z60,284-1

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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MATERIALS SCIENCE TITLES

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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55,531-2	**Cap Mix A, with 2,6-lutidine** (Contains 80% tetrahydrofuran: 10% acetic anhydride: 10% 2,6-lutidine)	1L 2L
55,533-9	**Cap Mix A, with pyridine** (Contains 80% tetrahydrofuran: 10% acetic anhydride: 10% pyridine)	1L 2L
55,532-0	**Cap Mix B** (Contains 84% tetrahydrofuran: 16% 1-methylimidazole)	1L 2L

Catalog No.	Product Name	Unit
55,535-5	**Cap Mix B, with pyridine** (Contains 80% tetrahydrofuran: 10% pyridine: 10% 1-methylimidazole)	1L 2L
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
63,457-3	**Activator** (5-Ethylthio-1*H*-tetrazole, 0.25*M* in acetonitrile)	1L 2L

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DENDRIMERS: BUILDING BLOCKS FOR NANOSCALE SYNTHESIS

Aldrichimica ACTA

VOL. 37, NO. 2 • 2004

Birth of a New Macromolecular Architecture: Dendrimers as Quantized Building Blocks for Nanoscale Synthetic Organic Chemistry

Recent Advances in Microwave-Assisted Synthesis

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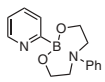
New Products from Aldrich R&D

2-Pyridineboronic acid [2,2′-(phenylimino)diethanol] ester

64,728-4 — 1 g, 5 g, 10 g

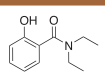


A stable 2-pyridinylboronate that is suitable for Suzuki–Miyaura coupling reactions.[1] This air-stable solid is a practical alternative to unstable 2-pyridinylboronic acids or esters.[2,3]

(1) Hodgson, P. B.; Salingue, F. H. *Tetrahedron Lett.* **2004**, *45*, 685. (2) Fischer, F. C.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 21. (3) Thompson, W. J. et al. *J. Org. Chem.* **1988**, *53*, 2052.

N,*N*-Diethylsalicylamide, 97%

64,423-4 — 5g, 25g



N-(2-Hydroxybenzoyl)pyrrolidine, 97%

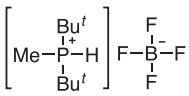
64,293-2 — 5g, 25g

These ligands have recently been utilized in copper-catalyzed aminations of aryl bromides with primary alkylamines under mild, solvent-free conditions and are compatible with a variety of functional groups. High yields have been obtained regardless of the ortho-, meta-, or para- substitution pattern on the aryl bromide.

Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793.

Di-*tert*-butylmethylphosphine tetrafluoroborate

64,377-7 — 1g, 5g

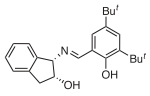


This reagent is a convenient substitute for the air-sensitive di-*tert*-butylmethylphosphine (Aldrich Cat. No. **64,262-9**), and displays a remarkable reactivity in palladium-catalyzed Suzuki cross-coupling reactions.

Kirchhoff, J. H. et al. *J. Am. Chem. Soc.* **2002**, *124*, 13662.

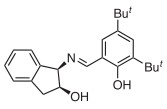
(1*R*,2*S*)-1-[(2-Hydroxy-3,5-di-*tert*-butylbenzylidene)]-aminoindan-2-ol

64,295-9 — 1g, 5g



(1*S*,2*R*)-1-[(2-Hydroxy-3,5-di-*tert*-butylbenzylidene)]-aminoindan-2-ol

64,414-5 — 1g, 5g

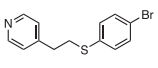


These chiral ligands have recently been used in the vanadium-catalyzed oxidation of sulfides in conjunction with hydrogen peroxide. Optically active sulfoxides are obtained in high yields and selectivities.

Pelotier, B. et al. *Synlett* **2002**, 1055.

4-[2-(4-Bromophenylsulfanyl)ethyl]pyridine, 97%

64,223-1 — 1g, 5g

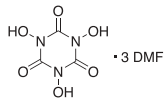


The pyridinylethyl group protects the phenylthio group for subsequent modification. The later-freed thio group in phenylethynyl oligomers was used to anchor self-assembled monolayers (SAMs)[1] and molecular wires.[2]

(1) Collman, J. P. et al. *Synthesis* **2001**, 367. (2) YU, C. J. et al. *J. Org. Chem.* **1999**, *64*, 2070.

N,*N*′,*N*″-Trihydroxyisocyanuric acid dimethylformamide complex, 97%

64,341-6 — 1g, 5g



An efficient catalyst for the aerobic oxidation of alkylbenzenes.

Hirai, N. et al. *J. Org. Chem.* **2003**, *68*, 6587.

Bromobis(triphenylphosphine)(*N*-succinimide)palladium(II)

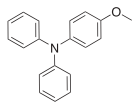
64,374-2 — 250mg, 1g

This bromosuccinimide-based palladium catalyst is used for Stille cross-coupling of allylic and benzylic halides.

Crawforth, C. M. et al. *Chem. Commun.* **2003**, 2194.

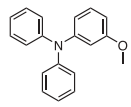
4-Methoxy-*N*,*N*-diphenylaniline

64,612-1 — 1g, 10g



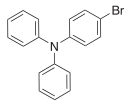
3-Methoxy-*N*,*N*-diphenylaniline, 97%

64,054-9 — 1g, 5g



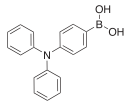
4-Bromo-*N*,*N*-diphenylaniline, 97%

64,383-1 — 5g, 25g



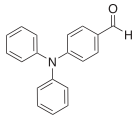
4-(*N*,*N*-Diphenylamino)phenylboronic acid, 95%

64,729-2 — 1g, 5g



4-(*N*,*N*-Diphenylamino)benzaldehyde

64,720-9 — 1g, 5g



A substantial amount of research has been undertaken in the development of organic-based materials exhibiting metallic properties. Triarylamines have been extensively employed in electroluminescent materials as hole-transport materials and hole-transport emitters.[1] Triarylamines have also been used in the development of molecule-based magnets.[2,3] The compounds above are some of the new triarylamines that Aldrich now offers.

(1) Mitschke, U.; Bäuerle, P. *J. Mater. Chem.* **2000**, *10*, 1471. (2) Miller, J. S.; Epstein, A. J. *MRS Bull.* **2000**, November, 21. (3) Veciana, J.; Iwamura, H. *MRS Bull.* **2000**, November, 41.

Please see pages 62–63 for additional new products.

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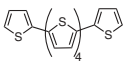
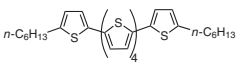
Joe Porwoll, President

Dr. Karl Pichler of Nanosolar, Inc. kindly suggested that we offer α,ω-dihexylsexithiophene (DH-6T). Oligothiophenes have attracted a lot of attention because of their high charge mobilities and on/off ratios as p-type semiconductors.[1–5] Garnier et al. fabricated the first all-organic transistor based on α-sexithiophene (6T).[1] Substituting the terminal α-hydrogen atoms on sexithiophene with alkyl chains increases the charge-carrier mobility further, as well as the solubility and thus the ease of processing.[6]

(1) Garnier, F. et al. *Adv. Mater.* **1990**, *2*, 592. (2) Dodabalapur, A. et al. *Science* **1995**, *268*, 270. (3) Garnier, F. *Acc. Chem. Res.* **1999**, *32*, 209. (4) Sakamoto, Y. et al. *J. Am. Chem. Soc.* **2001**, *123*, 4643. (5) Locklin, J. et al. *Langmuir* **2002**, *18*, 877. (6) Garnier, F. et al. *J. Am. Chem. Soc.* **1993**, *115*, 8716.



59,468-7



63,321-6

59,468-7	**α-Sexithiophene (6T)**	**1g**
63,321-6	**α,ω-Dihexylsexithiophene (DH-6T)**	**500mg**

Naturally, we made both α-sexithiophene and α,ω-dihexylsexithiophene for applications in various fields. It was no bother at all, just a pleasure to be able to help.

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.

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ABOUT OUR COVER

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

The Harbor at Lorient (oil on canvas, 43.5 × 73.0 cm) was painted by the French artist Berthe Morisot in 1869. In the right foreground of the picture, a young woman holding a parasol is shown seated on a low stone wall bordering the waters of the harbor, in which ships and boats of various sizes are anchored. The strong diagonal of the wall leads our eye straight to the figure of the woman, making her the obvious focal point of the painting. In the background can be seen the buildings of Lorient, a busy port on the south coast of Brittany on the estuary of the river Blavet. Morisot came to visit the town in 1869 to stay with her sister Edma, whose husband was a naval officer stationed there, and it is Edma who posed for the painting.

Morisot had studied with the painter Camille Corot, whose influence can be seen in the delicate palette and soft, atmospheric effects of this painting. In 1868, she began to study with the painter Édouard Manet. She came to know the impressionist painters, with whom she shared a preference for subjects from everyday life and for painting directly from nature to capture as much as possible the immediacy of visual experience. Beginning with the first group exhibition of these artists in 1874, she exhibited in all but one of the eight impressionist exhibitions held between that date and the last, in 1886. She married Manet's younger brother Eugène in 1874, but despite this close family tie, Morisot never convinced Manet to exhibit with the impressionist group. She had a uniquely important effect on the art of her brother-in-law, however, as it was under her influence that Manet abandoned the use of black, and adopted a lighter and more colorful impressionist palette.

This painting is in the Ailsa Mellon Bruce Collection at the National Gallery of Art, Washington, DC.

Queen's University Honors

Alfred Bader on His 80th Birthday

Alfred Bader—chemist, art collector, philanthropist, and cofounder of Aldrich Chemical Company—has had a long association with Queen's University (Kingston, Ontario). He was a student there from 1941 to 1947, and has since been one of its most loyal supporters and generous benefactors.

It was no surprise, therefore, that Queen's University invited a group of distinguished guests and longtime friends of Alfred to participate in a celebration of his 80th birthday. The two-day gala, on May 12 and 13 of this year, combined festive social events with scholarly lectures organized by the chemistry and art departments at the university, as well as a public lecture by Dr. Bader (*The Aldrich Chemical Company Story*) and a student awards luncheon. Nobel Laureate Barry Sharpless and Columbia Professor Emeritus Gilbert Stork were speakers at the chemistry symposium. In addition, the university renamed Queen's Crescent, a street running through the center of campus, Bader Lane in gratitude to Alfred and his family's many contributions to the university over the years.

Left to right: Barry Sharpless, Alfred Bader, Gilbert Stork, and Victor Snieckus at the chemistry symposium.

Alfred Bader with mementos of the event.

Left to right: Henry van Oudenaren (Sigma-Aldrich), Gilbert Stork, and Alfred Bader.

Alfred, his wife Isabel, and his two sons, Daniel and David, attended the celebrations. Sigma-Aldrich was represented by Henry van Oudenaren (Country Manager, Canada). Some highlights of these events are captured in the accompanying photographs.

Alfred Bader at the student awards luncheon.

Alfred, Your Sigma-Aldrich Family Wishes You a Happy 80th Birthday.

We Look Forward to Celebrating Your 90th!

All four photographs are courtesy of Linda Raber, Assistant Managing Editor, *Chemical & Engineering News*.

Birth of a New Macromolecular Architecture: Dendrimers as Quantized Building Blocks for Nanoscale Synthetic Organic Chemistry

Donald A. Tomalia
Dendritic NanoTechnologies, Inc.
Central Michigan University
2625 Denison Drive
Mt. Pleasant, MI 48858, USA
Email: tomalia@dnanotech.com

Outline

1. Introduction

During the 20th century, at least six major technological movements emerged and evolved into mature disciplines that have revolutionized scientific thinking, enhanced the prosperity of many countries, and dramatically improved the human condition. They have been referred to as major technological ages and, in approximate chronological order, are recognized as the *chemical, nuclear, plastics, materials, biotechnology, and computer* ages. An apparent driving force behind each technological age has been the quest for "new properties". As proposed by Philip W. Anderson, (Nobel Laureate in Physics, 1977) an attractive list of rewards, consequences, and possibilities accrue for society whenever scientists are successful at "breaking through new boundaries in the hierarchical complexity of matter" and such new properties emerge.[1] Presently, just such an event may be occurring at the interface of two very active scientific frontiers: the nanotechnology revolution[2,3] and the birth of a new class of macromolecular architecture, namely dendritic polymers.[4,5] This review will describe the emergence of the dendritic state relative to the traditional small-organic-molecule and traditional polymer chemistries. An overview of the critical properties and function of dendritic nanostructures, and the synthetic opportunities that are enabling the design and use of these nanostructures as fundamental building blocks in the emerging field of synthetic nanochemistry, will follow.[6]

Historically, the introduction of well-defined, quantized building blocks (e.g., atoms or monomers) into new synthetic strategies has led to major technological revolutions. Such has been the significance of Dalton's atom modules and Staudinger's monomers in the evolution of traditional small-molecule (organic) chemistry, macromolecular chemistry and, now, nanoscale chemistry **(Figure 1)**.[3] In this regard, the role of the synthetic chemist in five of the above technological ages has been incalculable. Implicit in each of these events is the familiar pattern: advancement to a new covalent complexity level yields novel materials with behaviors that cannot be understood by simple extrapolation of the properties of their building blocks. These advancements generally produce entirely new structures (architectures) with properties that follow strange new rules and require unprecedented explanations, concepts, and generalizations. In essence, "new complexity is not only different, but always more than the linear summation of its components".[1] Such is the expectation as the field of synthetic nanochemistry emerges.

2. Covalent Complexity: Traditional Organic and Polymer Syntheses

As a synthetic and physical organic chemist, I reflect on a handful of profound breakthroughs that contributed so dramatically to our present understanding of synthetic, covalent complexity. My list[6,7] includes: the atom hypothesis (Lavoisier, 1789), the molecular hypothesis (Dalton, 1808), organic chemistry (Wöhler, 1828), architectural isomerism (Berzelius, 1832), and the macromolecular hypothesis (Staudinger, 1926).[8,9]

In 1808, Dalton described his "New System of Chemical Philosophy",[7] a provocative hypothesis for its time, that has since led to the synthesis of literally millions of small inorganic and organic structures of incalculable value. Based on his envisioned atom modules (bricks) and their propensity to form bonds (electronic mortar), an unlimited number of mathematically defined small-molecule compositions, architectures, and chemical functionalities have been combinatorially assembled at the picoscale or subnanoscale level.[10-13] These structures bear no similarity to the structures of their building blocks, exhibit profoundly different properties, and adhere to substantially different bonding rules. The well-known importance of architecture in the determination of properties, even within the same covalent complexity level, was amply demonstrated by Berzelius over 170 years ago with the simple rearrangement of identical elemental compositions into new architectural isomers, allotropes, etc.[7,11] Most noteworthy was the simple Wöhler isomerization of ammonium cyanate into urea, that ushered in the traditional era of organic chemistry in 1829.[7] The complexity of organic synthesis since that time has been steadily enhanced by utilizing the known hybridization states of carbon and specific heteroatoms to produce key molecular-level hydrocarbon building blocks (modules) and functional groups (connectors). These two construction parameters have been used to assemble literally millions of more complex structures. Relatively small (i.e., < 1

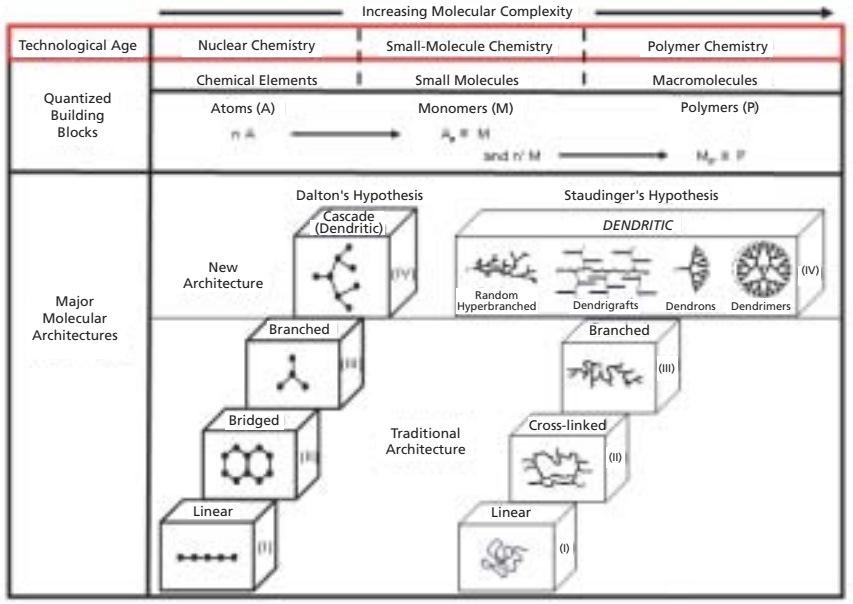


Figure 1. A Comparison of Complexity as a Function of Molecular Architecture, Strategy, Quantized Building Block, and Technological Age. (See Reference 3.)

nm) molecules were produced, the structures of which could be controlled as a function of their shape, mass, flexibility, and functional group placement. Based on the various hybridization states of carbon, at least four major carboskeletal architectures are known.[12,13] They are recognized as the (I) linear, (II) bridged (2D/3D), (III) branched and, more recently, the (IV) dendritic (cascade)[14] type. Consistent with the skeletal isomer principles demonstrated by Berzelius,[11] these major architectural classes exhibit very important differentiated physicochemical properties that are recognized as defining major areas within traditional organic chemistry (e.g., aromatic vs. linear, branched hydrocarbons, etc.). Such analogous macromolecular architectural classes have been recently defined together with their differentiated properties **(Figure 2)**.[13]

In 1926, Herman Staudinger[8] broke a second important complexity barrier—encountered by all synthetic organic chemists at the time—when he demonstrated his macromolecular hypothesis. This profound complexity breakthrough allowed the catenation (polymerization) of small, quantized monomer building blocks into megasized covalent structures (polymers) of nanoscale proportions, albeit with broad, statistical molecular-weight distributions. Three major macromolecular architectures have evolved from Staudinger's hypothesis. The first two architectural classes (i.e., linear and cross-linked)[15] literally defined the origins of traditional polymer science as well as major polymer property differences (i.e., thermoplastics vs. thermosets).[15] The third architectural class (i.e., branched)[16] is presently experiencing dramatic growth related to new polyolefin topologies derived from single-site, metallocene-type catalysts.[17] Historically, it has been widely recognized that macromolecular topologies significantly influence polymer behavior. The advent of each new architecture has invariably produced unique and important properties that have spawned many new products and industries, which have led to essentially all the significant benefits that have emerged from the plastics revolution.[9,18]

3. The Convergence of Nanotechnology and a New Macromolecular Architecture

3.1. The Quest for Quantized Nanoscale Building Blocks

Presently, an international focus is emerging on nanotechnology, which has been described as the "ultimate scientific frontier" that will both define and lead the world into the next industrial revolution.[2,3,19] While this description is surely exaggerated as today's challenges become tomorrow's routine accomplishments, nanotechnology still faces a very significant obstacle. In essence the growth and development of synthetic nanotechnology will be largely dependent upon successfully identifying appropriate quantized building blocks, much as was required for the development of the traditional fields of chemistry and polymer science. The challenge is to develop critical structure-controlled methodologies to produce appropriate nanoscale modules that will allow cost-effective synthesis and controlled assembly of more complex nanostructures in a very routine manner. Such structures will be macromolecular, require the controlled assembly of as many as 10^3–10^9 atoms, and possess molecular weights ranging from 10^4–10^{10} Daltons.

3.2. The Importance of Controlled Organic Nanostructures in Biology

All critical biological structures (e.g., cells) required for life have been based on the evolutionary development of quantized building blocks derived from controlled organic nanostructures. This evolutionary development occurred in two significant phases and involved bottom-up synthesis.[3,10,19,20] Clearly, critical parameters such as mass and dimensions had to increase in size to define the appropriate building modules. The first phase was abiotic and involved molecular evolution from atoms to small molecules. Nature dealt with this problem several billion years ago and shattered this nanoscale synthesis barrier with its evolutionary biological strategy for producing precise nanoscale modules such as DNA, RNA, and proteins. These modules were generally collections of precisely bonded atoms that occupied space with dimensions ranging from 1 to 10^2 nm. These building blocks set the stage for the synthesis of more complex nanostructures, and defined the dimensional (size) scaling that determines essentially all significant molecular-level factors required for initiating and sustaining life. These critical factors include: nanoscale sizes, nanosurfaces and interfaces, nanocontainment, nanoscale transduction and amplification, and information storage.[20] They have important implications, not only in biology, but also in significant abiotic areas such as catalysis, computer miniaturization, nanotribology, sensors, and new materials. Bottom-up synthetic strategies that produce size-monodispersed, well-defined, organic and inorganic nanostructures with dimensions between 1 and 100 nm will be of utmost importance. It will be essential that these strategies allow the systematic construction of nanoscale structures and devices with precise atom-by-atom control as a function of size, shape, and surface chemistry **(Figure 3)**.[19]

3.3. The Wet and Dry Worlds of Nanotechnology

The world of nanotechnology can be divided into two major areas: the wet and dry sides.[19,21] The former, of course, includes the biological domain, wherein the water-based chemistry of living entities is dependent upon hydrophilic nanostructures and devices that may function within biological cells. Dendritic nano-polymers, especially dendrimers, fulfill many applications in the wet world of nanotechnology. In contrast, the dry side includes those applications that derive from hydrophobic architectures. Progress in this second area is expected to enhance the tensile strength of materials, increase their electrical conductivity, or allow the reduction of computer chip size to levels unattainable with traditional bulk materials.

Although substantial progress has been made in the use of fullerenes and carbon nanotubes as nanomodules for dry nanotech

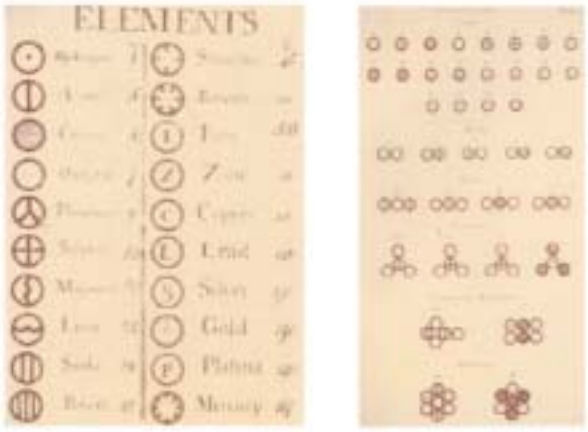


Figure 2. Dalton's Quantized Elemental Building Blocks and Their Combinatorial Possibilities That Led to His *New System of Chemical Philosophy* in 1808. (Reproduced from Reference 13 with Permission from VCH Publishers.)

applications, their use in biological applications has been hindered by the fact that they are highly hydrophobic and available in only specific sizes (i.e., usually approximately 1 nm).[22] However, recent advances have shown that a limited functionalization of fullerenes may be possible, and that these materials have a promising future in selected biological applications.[23]

4. The Dendritic State

4.1. Dendritic Polymers: A Fourth, Major New Class of Macromolecular Architecture

Dendritic architecture is one of the most pervasive topologies observed in nature at the macro- and microdimensional-length scales (i.e., m to μm). At the nanoscale (molecular level), there are relatively few natural examples of this architecture. Most notable are glycogen and amylopectin, macromolecular hyperbranched structures that nature uses for energy storage. In the polymer field, dendritic topology has now been recognized as a fourth major class of macromolecular architecture.[5,24,25] The signature for such a distinction is the unique repertoire of new properties manifested by this class of polymers.[5,24,26–30] Numerous synthetic strategies have been reported for the preparation of these materials, which have led to a broad range of dendritic structures. Presently, this architectural class consists of four dendritic (cascade) subclasses: (IVa) random hyperbranched polymers, (IVb) dendrigraft polymers, (IVc) dendrons, and (IVd) dendrimers **(Figure 4)**. The order of this subset, from (a) to (d), reflects the relative degree of structural control present in each of these dendritic architectures.[4,5]

All dendritic polymers are open, covalent assemblies of branch cells **(Figure 4a)**. They may be organized as very symmetrical, monodispersed arrays, as is the case for dendrimers, or as irregular, polydispersed assemblies that typically define random, hyperbranched polymers. The respective subclasses and the level of structure control are defined by the propagation methodology used to produce these assemblies, as well as by the branch-cell (BC) construction parameters. The BC parameters are determined by the composition of the BC monomers, as well as the nature of the excluded volume defined by the BC. The excluded volume of the BC is determined by the length of the arms, the symmetry, rigidity or flexibility, as well as the branching and rotation angles within each of the branch-cell domains. As shown in Figure 4a, these dendritic arrays of branch cells usually manifest covalent connectivity relative to some molecular reference marker (I) or core. As such, these branch-cell arrays may be very nonideal and polydispersed (e.g., $M_w/M_n \cong$ 2–10), as observed for random hyperbranched polymers (IVa), or very ideally organized into highly controlled core–shell-type structures, as noted for dendrons and dendrimers (IVc) and (IVd): $M_w/M_n \cong 1.0000$–1.05 and less. Dendrigraft polymers (IVb) reside between these two extremes of structure control, frequently manifesting narrow polydispersities of $M_w/M_n \cong$ 1.1–1.5, depending on their mode of preparation **(Figure 4b)**.

4.2. Random Hyperbranched Polymers

Flory first hypothesized dendritic polymer concepts,[15,31] which are now recognized to apply to statistical, or random hyperbranched polymers. However, the first experimental confirmation of dendritic topologies did not produce random hyperbranched polymers but rather the more precise, structure-controlled, dendrimer architecture.[4,5] This work was initiated nearly a decade before the first examples of random hyperbranched polymers were confirmed independently by Gunatillake[32] et al. and by Kim and Webster[33,34] in 1988. At that time, Kim and Webster coined the popular term "hyperbranched polymers" that has been widely used to describe this subclass of dendritic macromolecules.

Hyperbranched polymers are typically prepared by polymerization of ABx monomers. When x is 2 or more, polymerization of such monomers gives highly branched

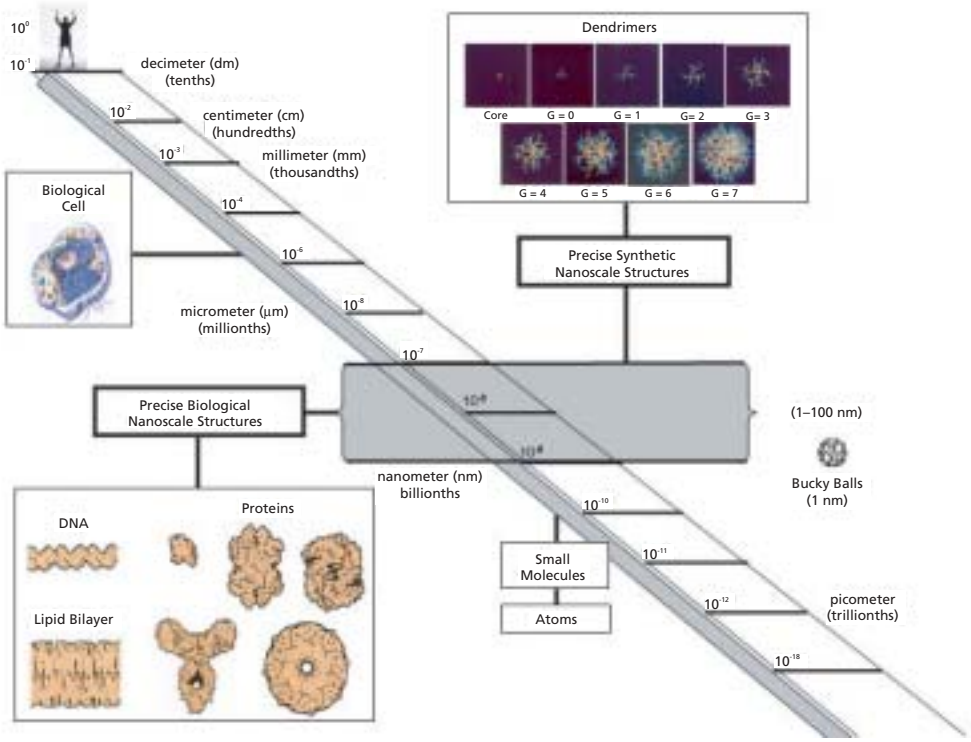


Figure 3. Nanoscale Dimensional Comparison of Poly(amidoamine) Dendrimers [NH_3 Core] (Gen = 0–7) with a Biological Cell, Proteins, DNA, Lipid Bilayer, Bucky Balls, Small Molecules, and Atoms. (Reproduced from Reference 19 with Permission from CRC Press.)

polymers (see Figure 4), as long as A reacts only with B from another molecule. Reactions between A and B from the same molecule result in termination of polymerization by cyclization. This approach produces hyperbranched polymers with a degree of polymerization n, possessing one unreacted A functional group and $[(x - 1)_n + 1]$ unreacted B terminal groups. In a similar fashion, copolymerization of A_2 and B_3 or other such polyvalent monomers can give hyperbranched polymers,[35,36] if the polymerization is maintained below the gel point by manipulating monomer stoichiometry or limiting polymer conversion.

Random hyperbranched polymers are generally produced by the one-pot polymerization of AB_x-type monomers or macromonomers involving polycondensation, ring opening, or polyaddition reactions. Hence, the products usually have broad, statistical molecular-weight distributions, much as is observed for traditional polymers.

Over the past decade, literally dozens of new AB_2-type monomers have been reported leading to an enormously diverse array of hyperbranched structures. Some general types include poly(phenylenes) obtained by the Suzuki coupling;[33,34] poly(phenylacetylenes) prepared by the Heck reaction;[37] polycarbosilanes, polycarbosiloxanes,[38] and poly(siloxysilanes) by hydrosilylation;[39] poly(ether ketones) by nucleophilic aromatic substitution;[40] and polyesters[41] or polyethers[42] by polycondensations or by ring-opening polymerization.[43]

New advances beyond the traditional AB_2 Flory-type, branch-cell monomers have been reported by Fréchet and co-workers.[44,45] They have introduced the concept of latent AB_2 monomers, referred to as self-condensing vinyl polymerizations (SCVP). These monomers, which possess both initiation and propagation properties, may follow two modes of polymerization; namely, polymerization of the double bond (i.e., chain growth) and condensation of the initiating group with the double bond (i.e., step growth). Recent progress involving the derivative process of self-condensing, ring-opening polymerizations (SCROP) has been reviewed by Sunder et al.[46] In addition, the use of enhanced processing techniques, such as pseudo chain growth by slow monomer addition,[47] allow somewhat better control of hyperbranched structures.[46]

4.3. Dendrigraft Polymers

Dendrigraft polymers are the most recently discovered and currently the least understood subset of dendritic polymers. The first examples were reported in 1991 independently by Tomalia et al.[48] and Gauthier and Möller.[49] Whereas traditional monomers are generally employed in constructing dendrimers, reactive oligomers or polymers are used in protect–deprotect or activation schemes to produce dendrigrafts. Consequently, dendrigraft polymers are generally larger structures than dendrimers, grow much faster, and amplify surface groups more dramatically as a function of generational development.

Both hydrophilic (e.g., polyoxazolines and poly(ethyleneimines)) and hydrophobic dendrigrafts (e.g., polystyrenes) were reported in these early works. These first methodologies involved the iterative grafting of oligomeric reagents derived from living polymerization processes in various iterative *graft-on-graft* strategies. By analogy to dendrimers, each iterative grafting step is referred to as a generation. An important feature of this approach is that branch densities, as well as the size of the grafted branches can be varied independently for each generation. Furthermore, by initiating these iterative grafting steps from a point-like core versus a linear core it is possible to produce spheroidal and cylindrical dendrigrafts, respectively. Depending on the graft densities and molecular weights of the grafted branches, ultrahigh-molecular-weight dendrigrafts (e.g., $M_w > 10^4$ kDa) can be obtained at very low generation levels (e.g., G = 3). Dramatic molecular-weight enhancements vis-à-vis other dendrimer propagation methodologies are possible using dendrigraft techniques.[50] Further elaboration of these dendrigraft principles allowed the synthesis of a variety of core–shell-type dendrigrafts, in which elemental composition as well as the hydrophobic or hydrophilic character of the core were controlled independently.[51]

In general, the above methodologies have involved convergent-type grafting principles, wherein preformed, reactive oligomers are grafted onto successive branched precursors to produce semicontrolled structures. Compared to dendrimers, dendrigraft structures are less controlled since grafting may occur along the entire length of each generational branch, and the exact branching densities are somewhat arbitrary and difficult to control.

More recently, both Gnanou[52,53] and Hedrick[54,55] have developed approaches to dendrigrafts that mimic dendrimer topologies by confining the graft sites to the branch termini for each generation. These methods involve so-called *graft from* techniques, and allow better control of branching topologies and densities as a function

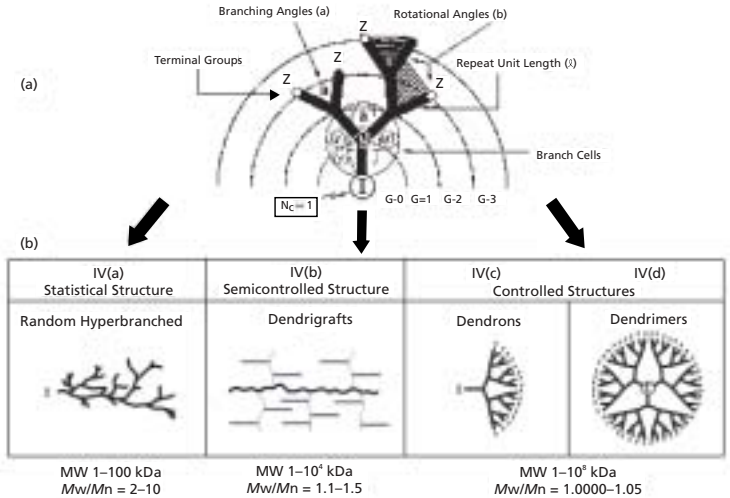


Figure 4. (a) Dendritic Polymers as Open, Covalent Assemblies of Branch Cells. (b) Dendritic Polymers: Subclasses of the Fourth Major New Class of Macromolecular Architecture.

of generation. Topologies produced by these methods are reminiscent of the dendrimer architecture. Since the branch-cell arms are derived from oligomeric segments, they are referred to as polymeric dendrimers.[56] These more flexible and extended structures exhibit unique and different properties as compared to the more compact traditional dendrimers. Fréchet, Hawker, and co-workers[57] have utilized the techniques of living polymerization and a staged polymerization process—in which latent polymerization sites are incorporated within growing chains—to produce dendrigrafts of mixed composition and narrow polydispersity.

Another exciting development has been the emerging role that dendritic architecture is playing in the production of commodity polymers. A recent report by Guan et al.[58] has shown that ethylene polymerizes to *dendrigraft*-polyethylene at low pressures in contrast to high-pressure conditions, which produce only branched topologies. This occurs when using late-transition-metal or Brookhart catalysts. Furthermore, these authors also state that small amounts of *dendrigraft*-polyethylene architecture may be expected from analogous early-transition-metal metallocene catalysts.

4.4. Dendrons and Dendrimers

Dendrons and dendrimers are the most intensely investigated subset of dendritic polymers. In the past decade, over 5000 literature references have appeared dealing with this unique class of structure-controlled polymers. The word dendrimer is derived from the Greek words *dendri-* (tree branch-like) and *meros* (part of), and was coined by Tomalia et al. about 20 years ago in the first full paper on poly(amidoamine) (PAMAM) dendrimers.[59,60] Since this early disclosure, over 100 dendrimer compositions (families) and 1000 dendrimer surface modifications have been reported. The two most widely studied dendrimer families are the Fréchet-type polyether compositions and the Tomalia-type PAMAM dendrimers. PAMAM dendrimers constitute the first dendrimer family to be commercialized, and represent the most extensively characterized and best-understood series at this time.[4]

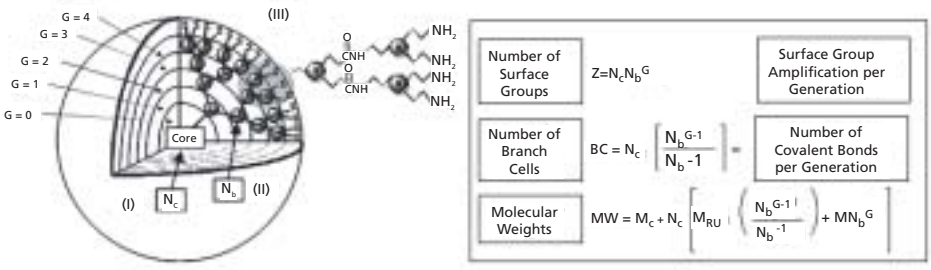
In view of the vast amount of literature in this field, the remaining overview will focus on PAMAM dendrimers. Its scope will be limited to a discussion of their critical properties and unique quantized nanomodule features that make these materials very suitable for nanoscale synthesis.

4.4.1. Dendrimer Synthesis: Divergent and Convergent Methods

In contrast to traditional polymers, dendrimers are unique core–shell structures possessing three basic architectural components **(Figure 5)**: a core (I), an interior of shells (generations) consisting of repeating branch-cell units (II), and terminal functional groups (the outer shell or periphery) (III).

In general, dendrimer synthesis involves divergent or convergent hierarchical assembly strategies that require the construction components shown in **Scheme 1**. Within each of these major approaches there may be variations in methodology for branch-cell construction or dendron construction. Many of these issues, together with experimental laboratory procedures, have been reviewed elsewhere.[61–63]

PAMAM dendrimers are synthesized by the divergent approach. This methodology involves in situ branch-cell construction in stepwise, iterative stages around a desired core to produce mathematically defined core–shell structures. Typically, ethylenediamine [core multiplicity (N_c) = 4], ammonia (N_c = 3), or cystamine (N_c = 4) may be used as cores and allowed to undergo reiterative, two-step reaction sequences. These sequences consist of: (a) an exhaustive alkylation of primary amines (Michael addition) with methyl acrylate, and (b) amidation of amplified ester groups with a large excess of ethylenediamine to produce primary amine terminal groups **(Scheme 2)**. This first reaction sequence on the exposed core creates G = 0 (i.e., the core branch cell), wherein the number of arms (i.e., dendrons) anchored to the core is determined by N_c. Iteration of the alkylation–amidation sequence produces an amplification of terminal groups from 1 to 2 with the in situ creation of a branch cell at the anchoring site of the dendron that constitutes G = 1. Repeating these iterative sequences



Gen	No. of NH_2 Surface Groups	Molecular Formula	MW	Hydrodynamic Diameter (nm)
0	4	$C_{24}H_{52}N_{10}O_4S_2$	609	1.5
1	8	$C_{64}H_{132}N_{26}O_{12}S_2$	1,522	2.2
2	16	$C_{144}H_{292}N_{58}O_{28}S_2$	3,348	2.9
3	32	$C_{304}H_{612}N_{122}O_{60}S_2$	7,001	3.6
4	64	$C_{624}H_{1252}N_{250}O_{124}S_2$	14,307	4.5
5	128	$C_{1264}H_{2532}N_{506}O_{252}S_2$	28,918	5.4
6	256	$C_{2544}H_{5092}N_{1018}O_{508}S_2$	58,140	6.7
7	512	$C_{5104}H_{10212}N_{2042}O_{1020}S_2$	116,585	8.1

Z = monomer-shell-saturation level, N_c = core (cystamine) multiplicity, N_b = branch cell (BC) multiplicity, G = generation.

Figure 5. Mathematical Expressions for Calculating the Theoretical Number of Surface Groups (Z), Branch Cells (BC), and Molecular Weights (MW) for [Cystamine Core]-PAMAM Dendrimers as a Function of Generation. Approximate Hydrodynamic Diameters (Gen = 0–7) Based on Gel Electrophoretic Comparison with the Corresponding [Ethylenediamine Core]-PAMAM Dendrimers.

(see Scheme 2) produces additional shells (generations) of branch cells that amplify mass and terminal groups according to the mathematical expressions described in the box (see Figure 5).

It is apparent that both the core multiplicity (N_c) and branch-cell multiplicity (N_b) determine the precise number of terminal groups (Z) and mass amplification as a function of generation (G). One may view those generation sequences as quantized polymerization events. The assembly of reactive monomers,[27,64] branch cells[4,27,65] or dendrons[4,66,67] around atomic or molecular cores, to produce dendrimers according to divergent or convergent dendritic branching principles, has been well demonstrated. Such systematic filling of molecular space around cores with branch cells as a function of generational growth stages (branch-cell shells)—to give discrete, quantized bundles of nanoscale mass—has been shown to be mathematically predictable.[68–70] Predicted molecular weights have been confirmed by mass spectrometry[71–74] and other analytical methods.[27,66,75,76] Predicted numbers of branch cells, terminal groups (Z), and molecular weights as a function of generation for a cystamine-core (N_c = 4) PAMAM dendrimer are shown in Figure 5. It should be noted that the molecular weights approximately double as one progresses from one generation to the next. The surface groups (Z) and branch cells (BC) amplify mathematically according to a power function, thus producing discrete, monodispersed structures with precise molecular weights and a nanoscale diameter enhancement as described in Figure 5. These predicted values are routinely verified by mass spectrometry for the earlier generations (i.e., G = 4–5); however, with divergent dendrimers, minor mass defects are often observed for higher generations as congestion-induced *De Gennes dense packing* begins to take effect.[27,77]

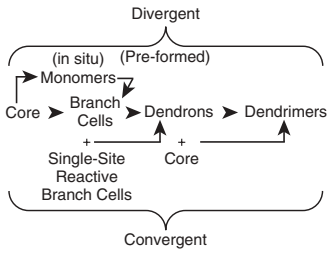
4.4.2. Dendrimer Features of Interest to Nanoscientists

Dendrimers may be viewed as unique, information-processing, nanoscale devices. Each architectural component manifests a specific function, while at the same time defining properties for these nanostructures as they are grown generation by generation. For example, the *core* may be thought of as the molecular information center from which size, shape, directionality, and multiplicity are expressed via the covalent connectivity to the outer shells. Within the *interior*, one finds the branch-cell amplification region, which defines the type and volume of interior void space that may be enclosed by the terminal groups as the dendrimer is grown. Branch-cell multiplicity (N_b) determines the density and degree of amplification as an exponential function of generation (G). The interior composition and volume of solvent-filled void space determines the extent and nature of guest–host (endo-receptor) properties that are possible within a particular dendrimer family and generation. Finally, the *surface* consists of reactive or passive terminal groups that may perform several functions. With appropriate functionalization, they serve as a template polymerization region as each generation is amplified and covalently attached to the precursor generation. The surface groups may also function as passive or reactive gates controlling entry or departure of guest molecules from the dendrimer interior. These three architectural components (core, interior, and periphery) essentially determine the physical and chemical properties, as well as the overall size, shape, and flexibility of a dendrimer. It is important to note that dendrimer diameters increase linearly as a function of shells or generations added, whereas the terminal functional groups increase exponentially as a function of generation. This dilemma enhances the "tethered congestion" of the anchored dendrons as a function of generation, due to the steric crowding of the end groups. As a consequence, lower generations are generally open, floppy structures, whereas higher generations become robust, less deformable spheroids, ellipsoids, or cylinders—depending on the shape and directionality of the core (see Figure 3).

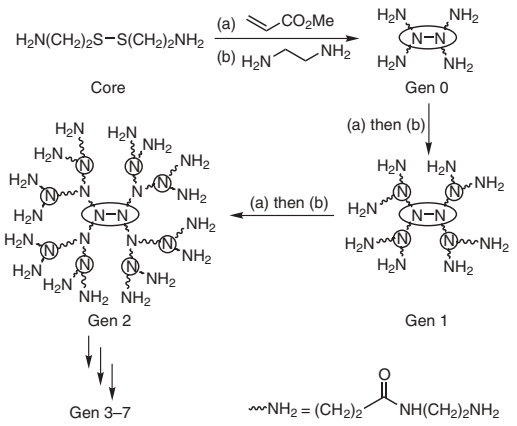
4.4.3. Dendrimers: Molecular-Level, Core–Shell Analogs of Atoms

4.4.3.1. Quantized, Core–Shell Modules as Building Blocks for Small-Molecule (Organic and Inorganic) Synthesis

We have compared the core–shell architecture of dendrimer-based, nanoscale modules to the core–shell architecture of subnanoscale atoms.[69,70] It is well recognized that the sequence of electron orbital filling of the elements occurs according to discrete, well-defined principles of quantum mechanics. Patterns for electron filling of the elements in the periodic table are defined by principal quantum numbers (i.e., n = 1, 2, 3, 4) associated with saturated electron shells leading to stable inert gas configurations (i.e., 2, 8, 8, 18, 32, etc.). Generally, the reactivity of the atom-based, small-molecule chemistry set is associated with the unsaturated electronic state of the atomic modules preceding the inert gas configurations in the respective periods. The inert gas configurations possessing filled shells are generally considered not to be highly reactive. It has been recognized since Wöhler



Scheme 1. Hierarchical Assembly Scheme Illustrating the Options for Constructing Dendrimers by Either Divergent (Tomalia-Type) or Convergent (Fréchet-Type) Synthetic Strategies.



Scheme 2. Divergent Synthesis of [Cystamine]-*dendri*-PAMAM Dendrimers Utilizing the Iterative Sequence: (a) Alkylation with Methyl Acrylate, Followed by (b) Amidation with Excess Ethylenediamine to Produce Generations 3 to 7.

(1828) that elements in the second period (carbon in particular) may combine with first-period elements (hydrogen), second-period elements (oxygen, nitrogen, boron), and third-period elements (sulfur, silicon, etc.) to produce nearly all the compounds we classify today as organic. Essentially all other combinations are referred to as inorganic.

Approximately 50 years after Mendeleev published his traditional periodic table of the elements (1869), Niels Bohr introduced a nontraditional organization of the elements in a unique periodic table presentation in his Nobel lecture of 1922.[78] Coincidentally, in the same year, F. Aston was awarded a Nobel Prize for his invention of the mass spectrometer and his proof that the elements were precise bundles of mass that could be systematically organized and understood relative to both Mendeleev's and Bohr's periodic presentations. Bohr's representation provides the familiar electron configuration accounting system, as well as a facile visualization of several important periodic and quantized features associated with atoms (**Figure 6**).[79] Bohr's unique periodic table displays the quantized electron space-filling features of atoms as a function of their atomic number and electron shell level. This clearly illustrates the systematic electron-filling rank of the respective, reactive elements possessing unfilled electron shells in each period. Moving to the end of each period leads to the saturated shell elements (i.e., noble gas configurations). Bohr's periodic table offers a visual appreciation of atomic module reactivity as a function of electron-shell saturation, and allows a very crude but relative size comparison of the respective elements (atoms) in the subnanoscale region (i.e., 0.01–1 nm).

It was from Bohr's periodic presentation of the elements that we were inspired to produce an analogous two-dimensional molecular display of the quantized, monomer-shell-filling features of dendrimers. It was hoped that such a presentation would allow a crude but, nevertheless, relative comparison of module size and perhaps reactivity in the nanoscale region (i.e., 1–100 nm) (**Figure 7**).

By analogy to electron-saturation levels found in elemental atoms, dendrimers possessing unfilled monomer shells are very reactive at the molecular level via their terminal functional groups. *They may autoreact to form dendrimer multiples (i.e., dimers, trimers, etc.) or, in essence, nanoscale compounds called megamers by interdendrimer surface reactions.* Alternatively, they may simply undergo intramolecular reactions to produce macrocyclic sites. *In sharp contrast, dendrimer species possessing saturated monomer shells, mathematically defined by* $Z = N_c N_b^G$ *(see Figure 5), are not autoreactive,* nor do they react with reagents possessing a compatible surface functionality (i.e., either nucleophilic or electrophilic moieties, respectively)

4.4.3.2. Core–Shell Architectural Features of Core-Cleavable [Cystamine Core]-PAMAM Dendrimers

The core–shell architectural features of dendrimers have been described earlier in great detail.[69,70] Certain features of these dendritic architectures were shown to be quantized as a function of core (N_c) and branch-cell (N_b) multiplicity. The concentric monomer shells (generations) surrounding the nucleus (core) of the dendrimer were shown to have well-defined monomer-shell-saturation levels analogous to those observed for electrons at the atomic level, albeit at a Newtonian dimensional size scale. By analogy to electron shells in atoms, the parameters of certain quantized monomer shells surrounding a dendrimer core can be mathematically predicted. The maximum monomer content per generation is defined by the simple expression $Z = N_c N_b^G$.

More specifically, the divergent strategy involving the in situ branch-cell approach to PAMAM dendrimers may be described as a series of quantized, molecular-level "aufbau" events. Formally, such construction involves the covalent, self-assembly of *N*-(2-aminoethyl)acrylamide (2-AEA) monomer units. These structure-controlled, building events are completed by appropriate iterations of the familiar two-step sequence involving (a) alkylation of amino precursors with methyl acrylate, and (b) amidation of amplified ester-terminated intermediates using excess ethylenediamine. These amine (nucleophilic) and acrylate (electrophilic) reagents are assembled to produce a dendritic covalent connectivity consisting of β-alanine units. The *N*-(2-aminoethyl)acrylamide monomer degree of polymerization (DP_{RU}) for each generation (monomer shell level) of a perfect structure is discrete and quantized according to the expression in **eq 1**.

More recently, new synthetic options have been developed for dendrimers by introducing cleavable cores such as the one found in [cystamine core]-PAMAM dendrimers.[79] As such, the monomer

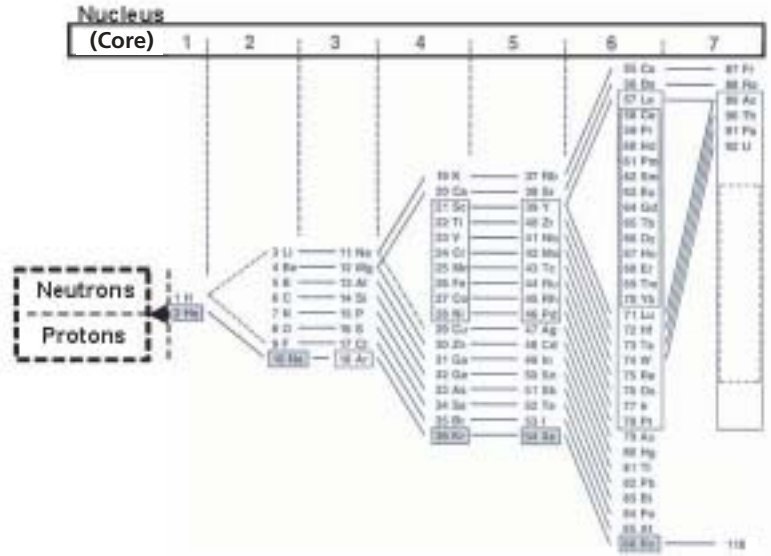


Figure 6. Core–Shell Representation of the Elements as a Function of Principal Quantum Numbers (Electron Shells) According to Niels Bohr (1922). (Reproduced from Reference 79 with Permission from Elsevier Science.)

shell level (G) and degree of polymerization (DP_{RU}) for the cleaved [cystamine core]-PAMAM dendrimer can be described relative to the new core or sulfhydryl focal point. This focal point resides at a terminus opposite to the surface groups and must be nonreactive toward the surface functionality on the hemiellipsoid as shown in **Figure 8**. Such a two-dimensional display illustrates the core, monomer shells, and crude coordinates for specific monomer units or terminal groups relative to the core. An abbreviated notation for these coordinates lists the monomer unit degree of polymerization (DP_{RU}) in bold sequential numbers as they appear in each principal shell or generation. These monomer units are associated with generation (monomer shell) levels and are designated by bold numbers in brackets. The superscript associated with each bracket indicates the number of monomer units in that shell. This serves as a monomer accounting system. In this manner, the monomer content is audited within a particular shell as each sequentially introduced monomer unit advances the shell toward a maximum quantized value. This saturation limit is defined by $Z = N_c N_b^G$. This monomer accounting system demonstrates how the monomer content per shell (generation) is quantized as a maximum value for each generational level. The total accumulation (DP_{RU}) of monomer units around the core can be predicted (see equation 1).

5. Unique Dendrimer Properties

5.1. Nanoscale Monodispersity

The monodispersed nature of dendrimers, as observed for atoms by Aston, has been verified extensively by mass spectrometry, size-exclusion chromatography, gel electrophoresis, and electron microscopy (TEM)[80]—as illustrated by TEMs for a Gen 5–10 series of PAMAM dendrimers **(Figure 9)**.[80] As is often the case, the level of monodispersity is determined by the skill of the synthetic chemist, as well as the isolation and purification methods utilized.

In general, convergent methods produce the most nearly monodisperse dendrimers as determined by mass spectrometry. This is because the convergent growth process allows purification at each step of the synthesis and eliminates cumulative effects due to failed couplings.[62] Appropriately purified, convergently produced dendrimers are probably the most precise synthetic macromolecules that exist today.

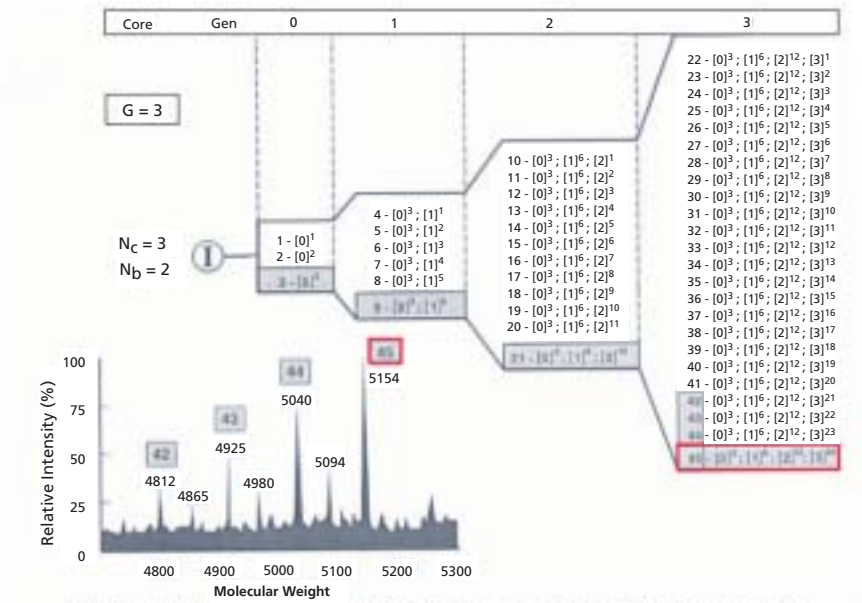
Mass spectrometry has shown that PAMAM dendrimers produced by the divergent method are remarkably monodisperse and have masses consistent with predicted values for the earlier generations (i.e., G = 0–5) (see Figure 7).[69,70,74] Even at higher generations, as one enters the De Gennes densely packed region, the molecular-weight distributions remain very narrow (i.e., 1.05) and consistent, in spite of the fact that experimental masses deviate substantially from predicted theoretical values. Presumably, De Gennes dense packing produces a very regular and dependable effect that is manifested in the narrow molecular-weight distributions.[19,77]

5.2. Nanoscale Container and Scaffolding Properties

Unimolecular container and scaffolding behavior appears to be a periodic property that is specific to each dendrimer family or series. These properties are determined by the size, shape, and multiplicity of the construction components that are used for the core, interior, and surface of the dendrimer **(Figure 10)**.[19] Higher-multiplicity components and those that contribute to "tethered congestion" will hasten the development of container properties and rigid-surface scaffolding as a function of generation. Within the PAMAM dendrimer family, these periodic properties are generally manifested in three phases as shown in Figure 10.

The earlier generations (i.e., G = 0–3) do not exhibit any well-defined interior characteristics, whereas interior development related to geometric closure is observed for the intermediate generations (i.e., G = 4–7). Accessibility and departure from the

$$DP_{RU} = N_c \left[\frac{N_b^{G+1} - 1}{N_b - 1} \right] \qquad \text{eq 1}$$



The shaded boxes refer to saturated-shell, nonautoreactive dendrimers. The rest of the listings refer to unsaturated-shell, autoreactive dendrimers.

Figure 7. Core–Shell (Niels Bohr Type Representation) of [Ammonia Core]-PAMAM Dendrimer (Gen 3) as a Function of Principal Monomer Shell Levels (Generations). Mass Spectrometry Data Illustrating Mass Corresponding to a Nonautoreactive Saturated-Shell Structure (i.e., DP = 45; M_r = 5154) Accompanied by Autoreactive Unsaturated-Shell Structures (DP = 44, 43, and 42; M_r = 5040, 4295, 4812, Respectively).

interior is determined by the size and gating properties of the surface groups. At higher generations (i.e., G > 7), where De Gennes dense packing is severe, rigid-scaffolding properties are observed, allowing relatively little access to the interior except for very small guest molecules. The site-isolation and encapsulation properties of dendrimers have been reviewed recently by Esfand and Tomalia,[81] Hecht and Fréchet,[26] and Weener et al.[82]

5.3. Amplification and Functionalization of Dendrimer Surface Groups

Dendrimers within a generational series can be expected to present their terminal groups in at least three different modes, namely as a *flexible, semiflexible, or rigid functionalized scaffolding* (see Figure 10). Based on mathematically defined dendritic branching rules (i.e., $Z = N_c N_b^G$), the various surface presentations become more congested and rigid as a function of increasing generation level. It is implicit that this surface amplification can be designed to control gating properties associated with unimolecular-container development. Furthermore, dendrimers may be viewed as versatile, nanosized objects that can be surface-functionalized with a vast array of chemical and application features **(Figure 11)**. The ability to control and engineer these parameters provides an endless list of possibilities for utilizing dendrimers as modules for nanodevice design.[69,83,84,85] Recent reviews have begun to focus on this area.[26,27,85–87]

5.4. Nanoscale Dimensions and Shapes That Mimic Proteins

In view of the extraordinary structure control and nanoscale dimensions observed for dendrimers, it is not surprising to find extensive interest in their use as globular protein mimics **(Figure 12)**.[19] Based on their systematic, size-scaling properties and electrophoretic and hydrodynamic[75,76] behavior, they are referred to as artificial proteins.[79,81,83] Substantial effort has been focused recently on the use of dendrimers for site-isolation mimicry of proteins,[27] enzyme-like catalysis,[88] as well as other biomimetic applications,[83,89] drug delivery,[81] surface engineering,[90] and light harvesting.[91,92] These fundamental properties have in fact led to their commercial use as globular protein replacements for gene therapy, immunodiagnostics,[93,94] and a variety of other biological applications.

6. Importance of Dendrons and Dendrimers for Synthetic Nanochemistry

6.1. Nanostructure Control Within a Dendrimer

6.1.1. Size- and Shape-Designing Features of the Single-Site, Mercapto-Core, Functionalized Dendrons

We recently reported the synthesis of [cystamine core]-PAMAM dendrimers and their facile cleavage under reducing conditions to give single-site, mercapto-functionalized didendrons.[79] A general strategy for the facile synthesis of both

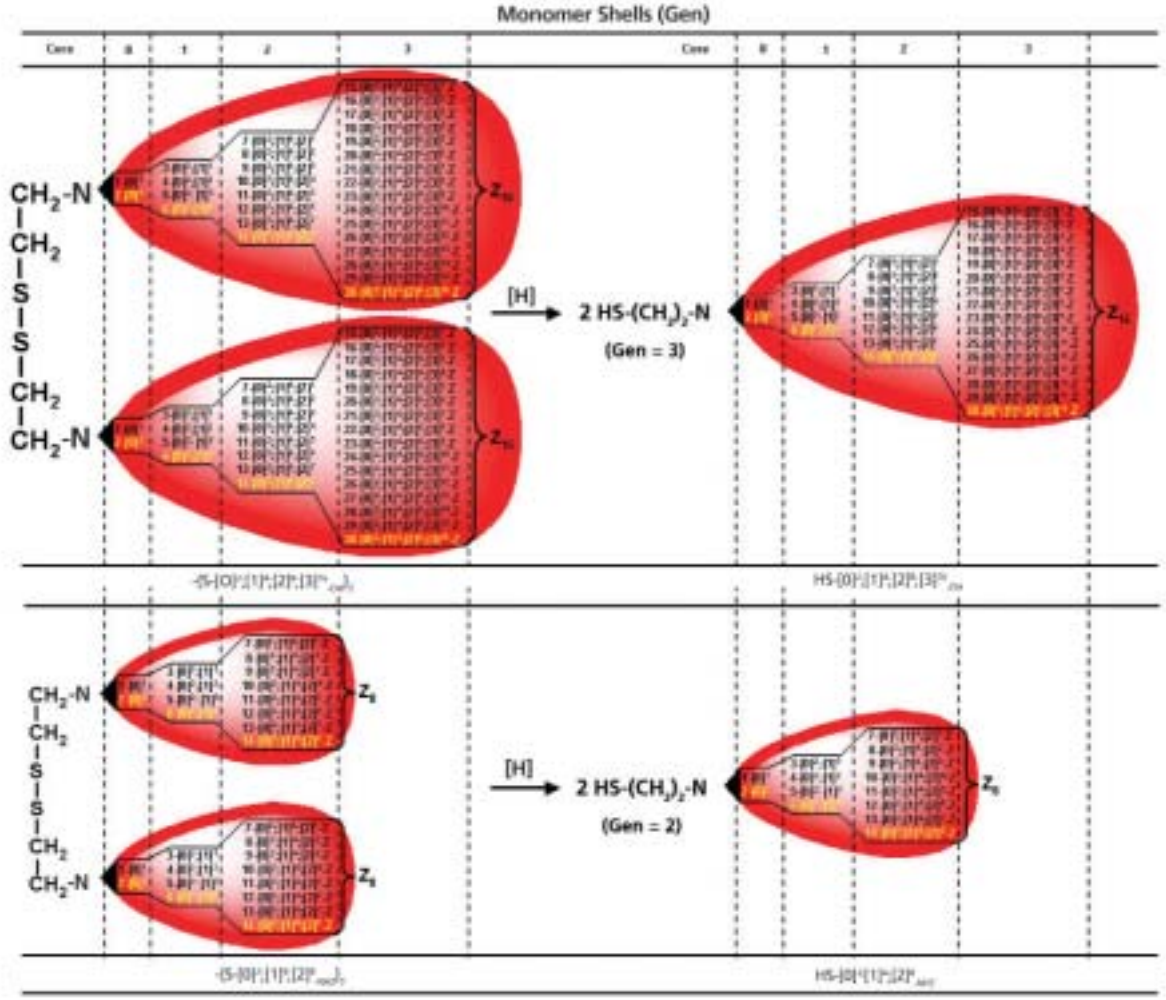


Figure 8. Niels Bohr Type, Core–Shell Representation of Gen 2–3 [Cystamine Core]-PAMAM Dendrimers in Their Oxidized and Reduced Forms.

surface- and generation-differentiated PAMAM dendrimers was demonstrated by hybridizing two different core-functionalized, mercapto-dendron reagents **(Figure 13)**.[79]

[Cystamine core]-PAMAM dendrimers (Gen 0–3) are displayed vertically as coupled spheres above the bucky ball **(Figure 14)**. They are represented with abbreviated notations in brackets to designate the generation level of the respective sulfur-bonded didendrons attached to the core before cleavage (i.e., Gen 3 [CYS]-PAMAM is designated as [3]:[3]). By cleaving these homodimers, performing subsequent oxidative coupling reactions on the mercapto-core, functionalized didendrons (i.e., [G]–SH), and utilizing various generation levels and surfaces, a wide variety of size-, shape-, and chemo-differentiated homo- and heterodimer-type nanoscale modules are possible (see Figure 13). A brief catalogue of size- and shape-differentiated products that are possible by hybridizing various combinations of homo-functionalized (Gen 0–3) cystamine precursors are shown in Figure 14. Two experimentally demonstrated examples of size-, shape-, and regiochemically differentiated hybridization products are illustrated by structures [0]:[1] and [1]:[3]. To the right of these hybridized dendrimers are two well-known globular proteins, namely insulin (diam 3.0 nm) and *Cytochrome c* (diam 4.0 nm). It should be noted that not only do the overall dimensions of these proteins scale closely to those of these two dendrimers, but the ability to synthesize nanoscale clefts and cusps, defined in the hybridized dendrimer architectures, is an important step toward mimicking unique and important differentiated shapes and surfaces found in these biostructures.[20,70,83]

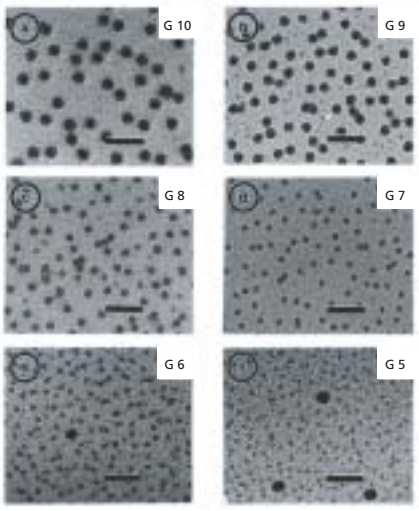


Figure 9. Transmission Electron Micrographs (TEMs) of Gen 5–10 PAMAM Dendrimers. Sample ⓕ Contains Three Molecules of Gen 10 Dendrimer for Comparison. Bar Length = 50 nm. (Reproduced from Reference 80 with Permission from ACS.)

6.1.2. Size Comparison of Dendrimers with Buckminsterfullerene and Small Molecules

The variety of sizes, shapes, and chemically differentiated surfaces that are possible by the combination of atoms to form molecular orbitals is staggering. A sampling and comparison may be visualized, to a crude first approximation, as space-filling objects represented by Corey–Pauling models. Such models are arranged in ascending complexity from right to left, as shown at the bottom of Figure 14. The importance of these parameters in defining the central dogma (size, shape, and functionality) of traditional chemistry cannot be overstated. A scaled comparison of these small-molecule parameters with buckminsterfullerene, a reference structure that defines the entry into the nanoscale region, reveals several interesting features. Glucose has a diameter of approximately 0.5 nm. Although it is about half the size of a bucky ball, it possesses surfaces which are richly decorated with chemically differentiated primary and secondary hydroxyl groups, as well as ether domains whose molecular orbitals define subnanoscale cusps and clefts in space. In contrast, the bucky ball symmetry presents an undifferentiated spheroidal surface with a dimension of approximately 1 nm.

Buckminsterfullerenes (diam ≅ 1 nm) are precise, quantized nanostructures consisting of 60 or 70 carbon atoms, which have been polymerized into the familiar soccer-ball-type structures.[22] In contrast, nanotubes derived from carbon and other elements[95] are available in various lengths, but with only several discrete

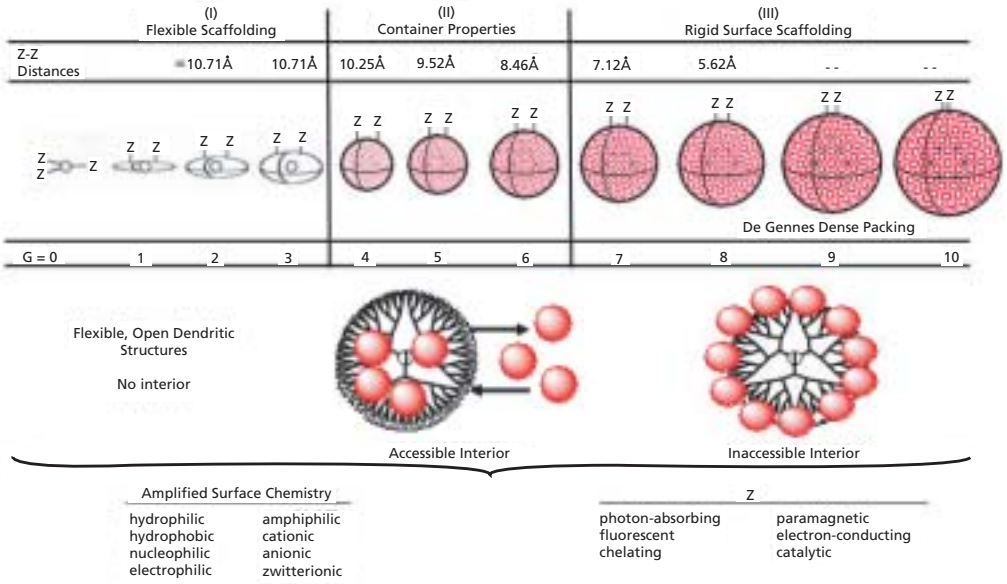


Figure 10. Periodic Properties of PAMAM Dendrimers as a Function of Generation. Various Chemophysical Dendrimer Surfaces Amplified According to $Z = N_c N_b^g$, Where N_c = Core Multiplicity, N_b = Branch-Cell Multiplicity, and G = Generation. (Reproduced from Reference 19 with Permission from CRC Press.)

diameters. Bucky balls and carbon nanotubes are some of the most intensely studied modules for abiotic nanoscale device design.[96,97] As nanoscale building blocks, these modules allow very limited opportunity to control structure relative to size, shape, and compositional or functional group design. It should be apparent that the above dendrimer-based strategies offer promising new alternatives for controlling these parameters.

6.2. Nanostructure Control Beyond the Dendrimer

Dendrimer-synthesis strategies now provide virtual control of macromolecular nanostructures as a function of size,[80,98] shape,[99] and surface or interior functional groups.[27] These strategies involve the covalent assembly of hierarchical components such as reactive monomers (A),[64] branch cells (B),[65,68] and dendrons (C)[67] around atomic or molecular cores according to divergent or convergent dendritic branching principles **(Figure 15)**.[4,68,100] Systematic filling of space around a core with shells (layers) of branch cells (i.e., generations) produces discrete core–shell dendrimer structures. Dendrimers are quantized bundles of mass that possess amplified surface functionality and are mathematically predictable.[68] Predicted molecular weights and surface stoichiometry have been confirmed experimentally by mass spectrometry,[68,69,71] gel electrophoresis,[75,76] and other analytical methods.[80,98] It is now recognized that empirical structures such as B, C, and D may be used to define these hierarchical constructions. Such synthetic strategies have produced traditional dendrimers with dimensions that extend well into the lower nanoscale region (i.e., 1–20 nm).[101] The precise structure control and unique new properties exhibited by these dendrimeric architectures have yielded many interesting advanced-material properties.[26,102,103] Nanoscale dendrimeric containers[102,104,105] and scaffoldings[27] have been used to template zero-valent-metal nanodomains,[86,106] nanoscale magnets,[107–109] electron-conducting matrices,[110,111] as well as provide a variety of novel optoelectronic properties.[112,113]

However, the use of such traditional strategies for the synthesis of precise nanostructures (i.e., dendrons (B) and dendrimers (C)) larger than 15–20 nm has several serious disadvantages. Firstly, it is hampered by the large number of reiterative synthetic steps required to attain these higher dimensions (e.g., Gen 9; PAMAM dendrimer, diam ≅ 10 nm, requires 18 reaction steps). Secondly, these constructions are limited by the De Gennes dense-packing

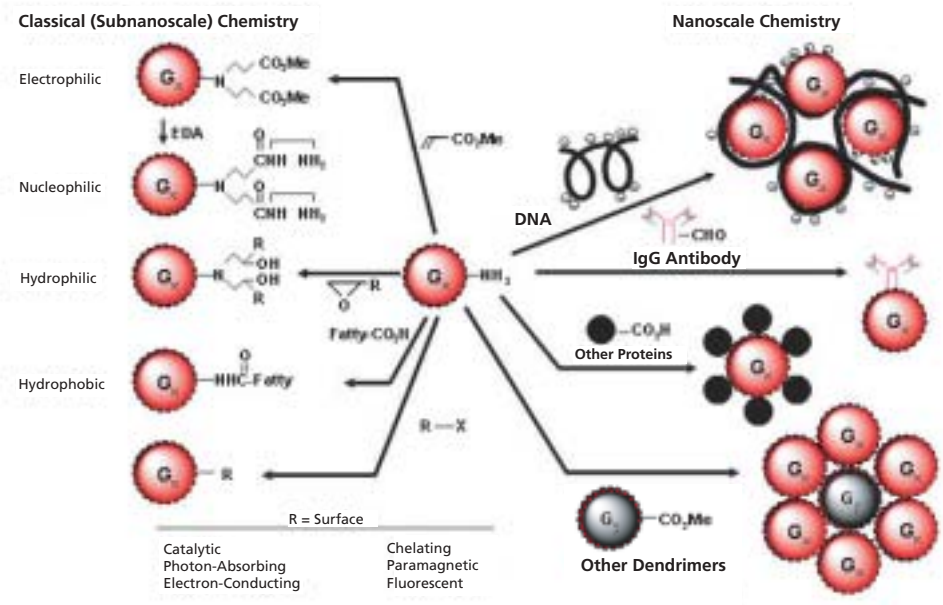


Figure 11. Options for Modifying Amine-Terminated Dendrimers by Utilizing Classical Subnanoscale and Nanoscale Reagents.

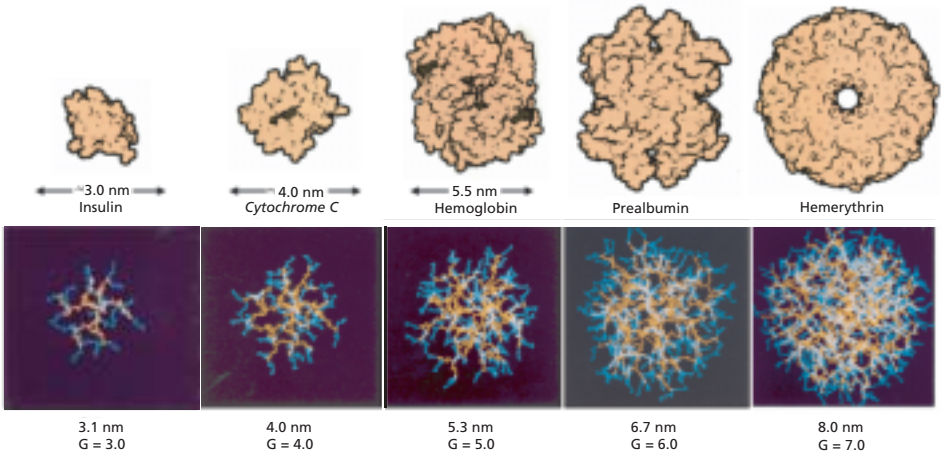


Figure 12. The Close Dimensional Size (nm) of Selected Proteins to Respective Generations of [Ammonia Core]-*dendri*-PAMAM Dendrimer. (Reproduced from Reference 19 with Permission from CRC Press.)

phenomenon, which precludes ideal dendritic construction beyond certain limiting generations.[68,114] For these reasons, our attention has turned to the use of dendrimers as reactive modules for the rapid construction of controlled nanoarchitectures possessing a higher complexity and dimensions beyond the dendrimer. We refer to these generic poly(dendrimers) as *megamers*.[118] Both randomly assembled megamers,[115] as well as structure-controlled megamers,[116–118] have been demonstrated. Recently, new mathematically defined megamers (dendrimer clusters) or core–shell tecto(dendrimers) have been reported.[103,116,119,120] The principles of these structure-controlled-megamer syntheses mimic those used for the traditional core–shell construction of dendrimers. First, a megamer-core reagent (usually a spheroid) is selected. Next, a limited amount of this reactive core reagent is combined with an excess of a megamer-shell reagent. The objective is to completely saturate the spheroid target core surface with covalently bonded spheroidal megamer-shell reagent. Since the diameters of the megamer-core and shell reagents are very well defined, it is possible to mathematically predict the number of megamer-shell molecules required to saturate a targeted core dendrimer.[121]

These core–shell relationships have been analyzed mathematically as a function of the ratio of core (r_1) and shell (r_2) radii.[121] At low r_1/r_2 values (i.e., 0.1–1.2), very important symmetry properties emerge as shown in **Figure 16**. It can be seen that, when the core reagent is small and the shell reagent is larger, only a very limited number of shell-type dendrimers can be attached to the core dendrimer based on available space. However, when $r_1/r_2 \geq 1.2$, the space becomes available to attach many more spheroidal shell reagents up to a discrete saturation level. The saturation number (N_{max}) is well defined and can be predicted from a general expression that is described by the Mansfield–Tomalia–Rakesh equation (see Figure 16).

6.3. Dendrimers as Reactive Modules for the Synthesis of More Complex Nanoscale Architectures (Megamers)

6.3.1. Saturated-Shell-Architecture Approach

The general chemistry used in this approach involves the combination of a limited amount of an amine-terminated, dendrimeric core reagent (e.g., G = 5–7; NH_2-terminated PAMAM dendrimer) with an excess of a carboxylic acid terminated (e.g., PAMAM) dendrimeric shell reagent.[119] These two charge-

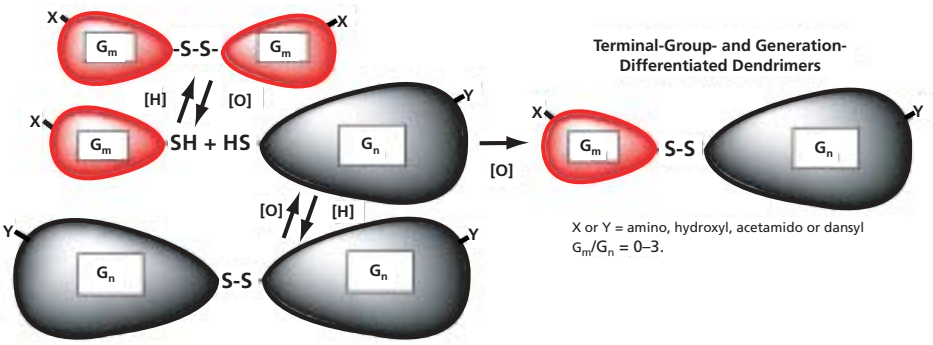


Figure 13. Reduction and Re-Oxidation of Cystamine-Core Dendrimers Possessing Different Surface Groups and Generational Levels to Produce Terminal-Group- and Generation-Differentiated Hybrid Dendrimers. (Reproduced from Reference 79 with Permission from Elsevier Science.)

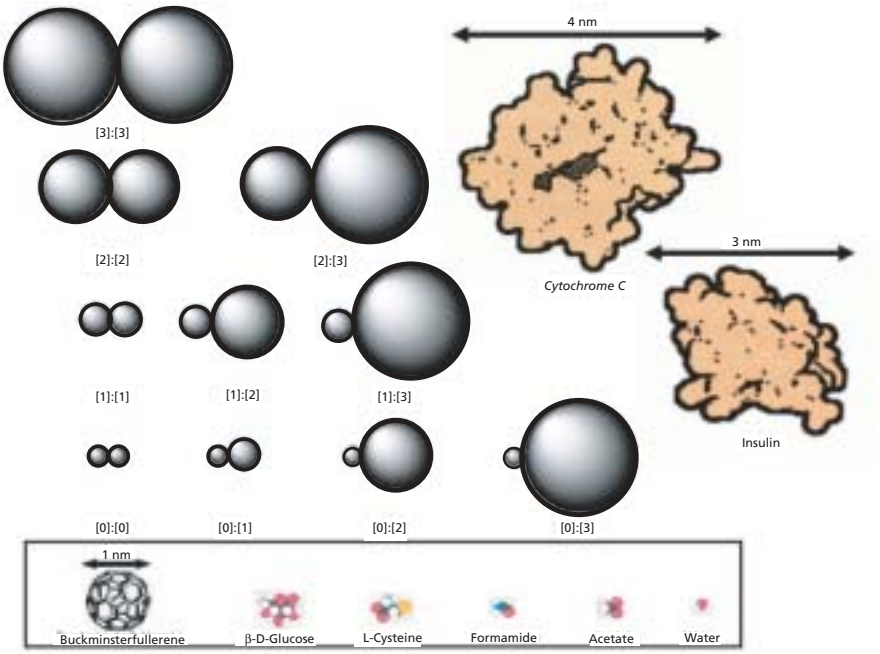


Figure 14. Scaled Space-Filling Models Comparing Small Molecules (Corey–Pauling) to Buckminsterfullerene and Various [Cystamine Core]-PAMAM Dendrimers (Represented as Spheres). Bold Numbers in Brackets Indicate the Generation Level of the Respective Dendrimer Hemiellipsoids. These Size-Scaled Synthetic Structures Are Compared to Two Globular Proteins: Insulin and *Cytochrome C*.

differentiated species are allowed to self-assemble into the electrostatically driven, supramolecular, core–shell tecto-(dendrimer) architecture. After equilibration, covalent-bond formation at these charge-neutralized, dendrimer contact sites is induced with carbodiimide reagents **(Figure 17)**.[119,120]

The carboxylic acid terminated shell-reagent dendrimers (e.g., G = 3 or 5) were synthesized by ring opening of succinic anhydride with the appropriate amine-terminated PAMAM dendrimers.

All reactions leading to core–shell tecto(dendrimers) were performed in the presence of LiCl at room temperature as dilute solutions (~ 0.5 wt %) in water. Equilibration times of 16–20 h were required to complete the charge-neutralized self-assembly of excess shell reagent around the limited core dendrimer reagent. Following this self-assembly and equilibration, a linking reagent, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, was added to covalently bond the assembly of dendrimeric shell reagents to a single dendrimeric core reagent at the amine–carboxylic acid interaction sites. These sites are presumed to reside primarily at the exterior of the core dendrimer reagent.[118,119]

Remarkably monodispersed products were obtained by performing the core–shell self-assembly reactions in the presence of LiCl. In the absence of LiCl, these reactions yielded bimodal or trimodal product-mass distributions (as observed by SEC). Core–shell products formed in the absence of LiCl are multimodal, and are presumed to be due to clustering of the amine-terminated core reagent into various domain sizes. Such clustering of amine-terminated PAMAM dendrimers has been noted in earlier work.[80] Attempts to subsequently charge-neutralize these polydispersed domains with anionic dendrimeric shell reagent produced a broad product distribution. Reversing the terminal functional groups on the core and shell reagents, respectively (i.e., using carboxylic acid terminated PAMAM dendrimer as the core and excess amine-terminated PAMAM dendrimer as the shell reagent) under identical reaction conditions, did not yield the desired product. The reason for this is not evident from our studies so far.

6.3.2. Unsaturated-Shell-Architecture Approach

The second method, the direct covalent-bond-formation method, produces semi-controlled, partially filled shell structures.[83,118] It involves the reaction of a limited amount of a nucleophilic dendrimeric core reagent with an excess of electrophilic dendrimeric shell reagent as illustrated in **Figure 18**.[120] This route involves the random parking of the reactive shell reagent on a core-substrate surface. As a consequence, partially filled shell products are obtained, which possess relatively narrow, but not precise molecular-weight distributions as noted for saturated-shell architectures.[119] These distributions are determined by the core–shell parking efficiency prior to covalent-bond formation.

Various PAMAM dendrimeric core reagents (either amine- or ester-functionalized) were each allowed to react with an excess of an appropriate PAMAM dendrimeric shell reagent. The reactions were performed at 40 °C in methanol and monitored by FT-IR, ^{13}C NMR, size-exclusion chromatography (SEC), and gel electrophoresis. Conversions in Step A (see Figure 18) were monitored by SEC and confirmed by observing the formation of shorter-retention-time products, consistent with higher-molecular-weight structures. Additional evidence was gained by observing the loss of the migratory band associated with the dendrimeric core reagent present in the initial reaction mixture, accompanied by the formation of a higher-molecular-weight product, which displayed a much shorter migratory band position on the electrophoretic gel. In fact, the molecular weights of the resulting core–shell tecto(dendrimers) could be estimated by comparing the migratory time of the core–shell products with the migration distances of the PAMAM dendrimer reagents (e.g., G = 2–10) used for their construction.[75]

It was important to perform capping reactions on the surface of the resulting unsaturated, ester-terminated core–shell products, in order to pacify the highly reactive amine cleft surfaces against further reaction. Preferred capping reagents for pacifying the ester domains of the surface were either 2-aminoethanol or tris(hydroxymethyl)aminomethane (TRIS).[83]

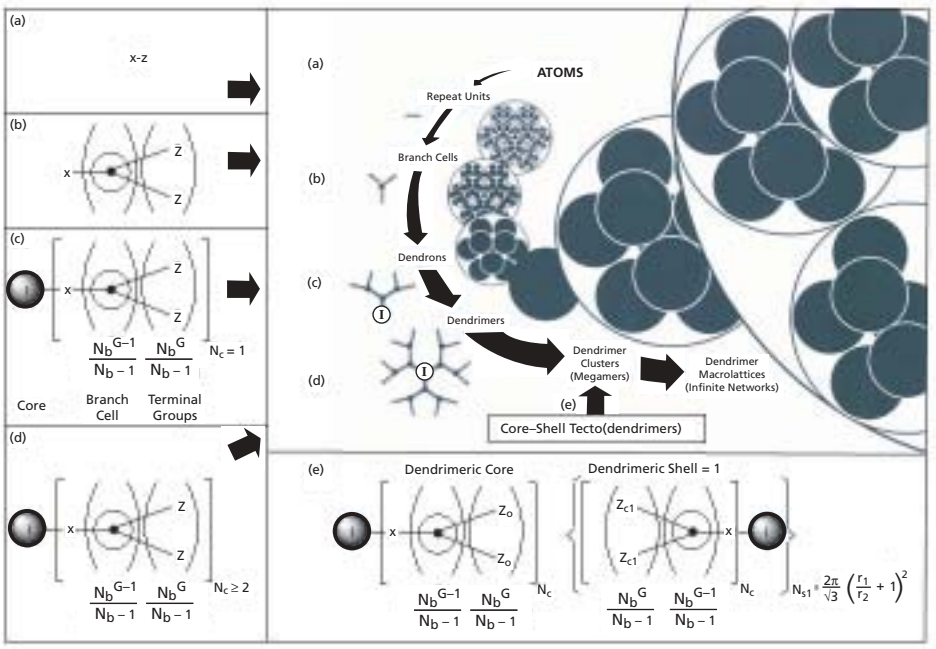


Figure 15. Hierarchy of Empirical Construction Components: Monomers (a), Branch Cells (b), Dendrons (c), and Dendrimers (d) Leading to Core–Shell Tecto(dendrimers) (e).

7. Core–Shell Patterns Influencing the Modular Reactivity of Dendrimers

Dendritic species, possessing an unsaturated outer monomer shell consisting of ester and amine domains, exhibited autoreactive behavior. They were often encountered, if a completely saturated state of either ester or amine groups was not attained. These species, which included missing-branch structures, led to the formation of monodendrimers containing macrocyclic terminal groups as well as moderate amounts of megamers (i.e., dimeric, trimeric, etc. species). Ideal dendrimer structures (i.e., saturated-outer-monomer-shell products) could, however, be separated from these side products by silica gel column chromatography and preparative TLC isolation techniques. Ideal dendrimer structures that exhibited mathematically predictable masses, as well as unsaturated-monomer-shell products exhibiting mass defects, were readily characterized by electrospray (ESI) and MALDI-TOF mass spectrometry.[71–74]

Recently, we have reported work that offers additional evidence that unfilled-outer-monomer-shell species are autoreactive intermediates that do indeed lead to megamer formation. In general, saturated-shell PAMAM dendrimers (i.e., all-amine- or all-ester-group-saturated surfaces) are very robust species (i.e., are analogous to inert gas configurations observed at the atomic level). In this regard, *they do not exhibit autoreactive characteristics*. Such samples may be stored for months or years without change. On the other hand, PAMAM dendrimer samples possessing unfilled monomer shells (i.e., amine and ester group domains on the dendrimer surface) are notorious for exhibiting autoreactive properties leading to terminal looping (i.e., macrocycle formation) and megamer formation.[69,70]

Remarkably, these autoreactivity patterns are also observed for the dimensionally larger core–shell tecto(dendrimer)

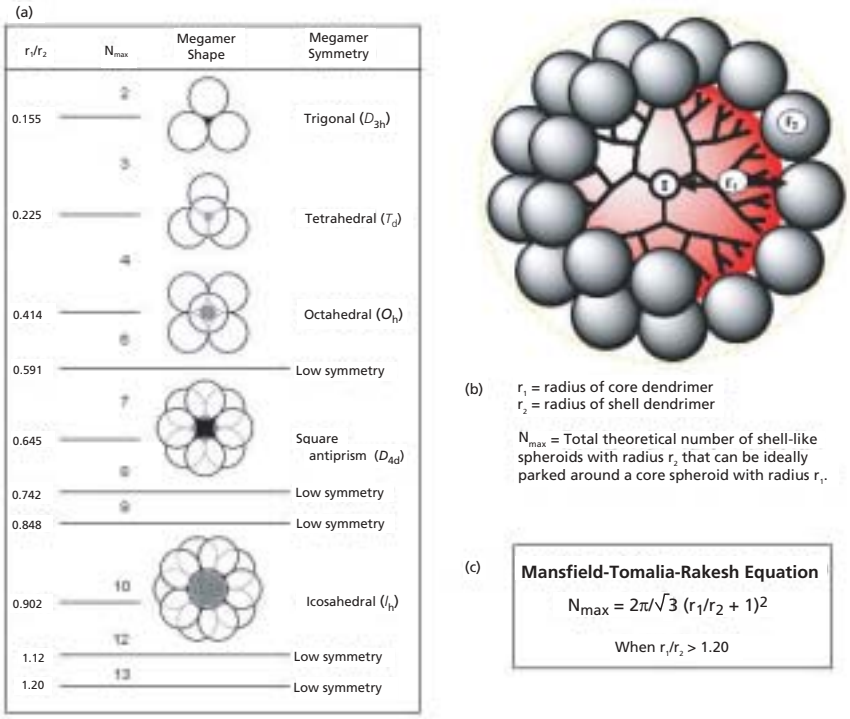


Figure 16. (a) Symmetry Properties of Core–Shell Structures, Where $r_1/r_2 < 1.20$. (b) Sterically Induced Stoichiometry (SIS) Based on the Respective Radii of Core and Shell Dendrimers. (c) Mansfield–Tomalia–Rakesh Equation for Calculating the Maximum Shell Filling When $r_1/r_2 > 1.20$.

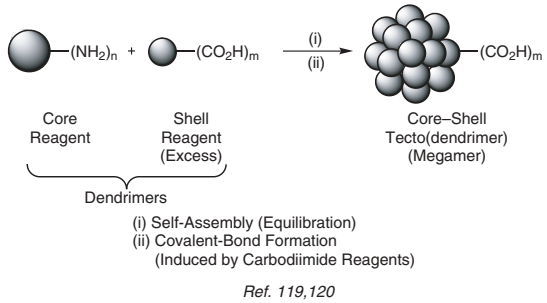


Figure 17. The Saturated-Shell-Architecture Approach to Megamer Synthesis. All Surface Dendrimers Are Carboxylic Acid Terminated.

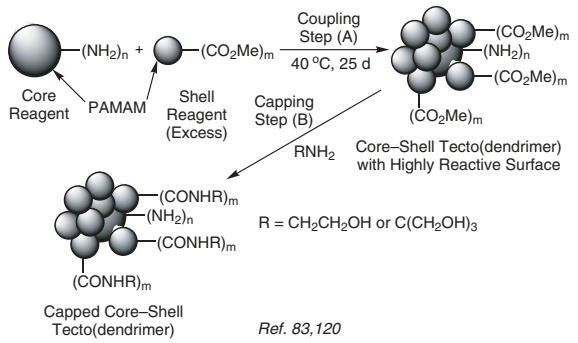


Figure 18. Step A: The Unsaturated-Shell-Architecture Approach to Megamer Synthesis. Step B Describes Surface-Capping Reactions.

architectures. For example, saturated-shell, core–shell tecto(dendrimer) architectures *exhibit no autoreactivity*; whereas partially filled shell, core–shell tecto(dendrimers) *exhibit profound autoreactivity*, unless pacified by reagents possessing orthogonally reactive functionalities. This behavior is comparable to that of atoms and basic dendrimers **(Figure 19)**.[83,120]

8. An Overview of New Nanosynthetic Strategies for the Organic Chemist

An overview of the hierarchical complexity that leads to precise, controlled nanostructures clearly illustrates the importance of quantized building blocks for viable bottom-up synthetic strategies **(Figure 20)**.[19] The importance of atom modules (0.1–0.6 nm) for the small-molecule (traditional chemistry) age and monomers (0.5–1.0 nm) for the macromolecular (polymer) age clearly hints at the significant role that dendrimers (1.0–20 nm) are expected to play as appropriately length-scaled, quantized building blocks for the synthesis of well-defined, more complex nanostructures. Experimental work has already demonstrated the ability to control size, shape, and chemical functionality within a wide variety of dendrimer structures. The first steps have been taken to demonstrate the use of these designed dendrimeric structures as fundamental building blocks for the synthesis of well-defined nanostructures beyond dendrimers (i.e., megamers), specifically the recent new class of core–shell tecto(dendrimers).[83,118,119,120]

9. From Atom-Based (Classical) to Dendrimer-Based (Nanoscale) Chemistry

Historically, it is well recognized that Dalton's proposed use of atom modules for the synthesis of higher chemical complexity in his *New System of Chemical Philosophy* (1808)[7] and Staudinger's catenation of monomers to create macromolecules[8] provided the critical enabling building blocks, and hence the synthetic platforms, for the very important fields they pioneered. These historical events encountered resistance at their inception and, in some cases, these individuals faced severe peer criticism.[8] It is from this perspective and in view of recent concept demonstrations that I am compelled to make the bold proposal that "what atoms have been to traditional chemistry and monomers to polymer chemistry, dendrimers should be to the emerging science of synthetic nanochemistry" **(Figure 21)**.[69,70] The future use of dendrimers as fundamental, reactive building blocks is expected to provide the enabling platform required for the routine synthesis of broad classes of well-defined synthetic organic, inorganic, and hybridized biomolecular nanostructures (see Figure 11). The significant role that synthetic organic and polymer

	Atoms	Dendrimers	Core–Shell Tecto(dendrimers)
Dimensions	0.05–0.6 nm	1–15 nm	5.0 to ≥ 100 nm
Valency (Reactivity)	Unfilled Outer Electron Shell	Unfilled Outer Branch-Cell Shell	Unfilled Outside Dendrimer Shell
(Core–Shell) Architecture-Induced Reactivity (Unfilled Shells)	(e.g., fluorine) Unfilled Shell (x)	Unfilled Shell (x)	Unfilled Shell (x)
Functional Components Directing Valency	Missing One Electron (y) in Outer Shell (x) Penultimate to Saturated Noble Gas Configuration	Missing One Terminal Branch Cell in Outer Shell (x) Exposing Functionality (y)	Missing One Dendrimer Shell Reagent Exposing Functionality (y)

Figure 19. Quantized Module (Building Block) Reactivity Patterns at the Subnanoscale (Atoms), Lower Nanoscale (Dendrimers), and Higher Nanoscale (Core–Shell Tecto(dendrimers)) Levels Involving Unsaturated Electron, Monomer, or Dendrimer Shells.

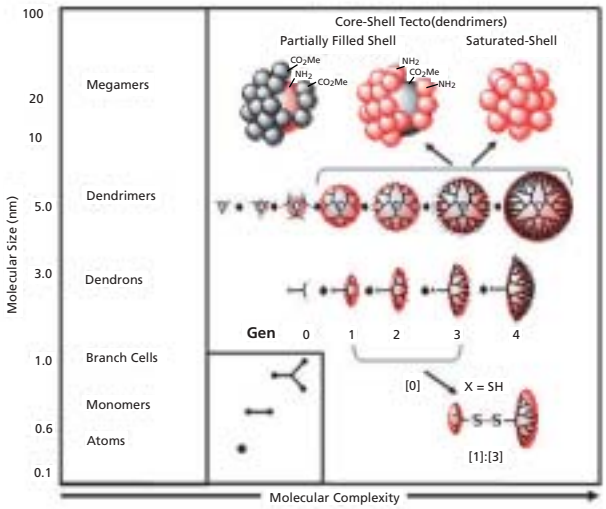


Figure 20. Approximate Nanoscale Dimensions as a Function of Atoms, Monomers, Branch Cells, Dendrons, Dendrimers, and Megamers.

chemists are presently playing in the development of this new field is readily apparent from a recent issue of *Tetrahedron Symposia-in-Print*.[122]

10. Conclusions

Dendritic polymers are expected to play a key role as enabling building blocks for nanotechnology during the 21st century, just as the first three traditional architectural classes of synthetic polymers have so successfully fulfilled critical material and functional needs in the plastics age during the past half century. The controlled shape, size, and differentiated functionality of dendrimers; their ability to provide both isotropic and anisotropic assemblies; their compatibility with many other nanoscale building blocks such as DNA, metal nanocrystals, and nanotubes; their potential for ordered self-assembly; their ability to combine both organic and inorganic components; and their propensity to either encapsulate or be engineered into unimolecular functional devices make dendrimers uniquely versatile amongst existing nanoscale building blocks and materials. Dendritic polymers, especially dendrons and dendrimers, are expected to fulfill an important role as fundamental modules for nanoscale synthesis. It is from this perspective that it is appropriate to be optimistic about the future of this new major polymer class, the *dendritic state*.

11. Acknowledgements

This work was funded by the Army Research Laboratory (ARL), Dendritic Polymer Center of Excellence (Contract DAAL-01-1996-02-044). I would like to express my sincere appreciation to Ms. L. S. Nixon for preparing the manuscript.

12. References

(1) Anderson, P. W. *Science* **1972**, *177*, 393.
(2) Atkinson, W. I. *Nanocosm: Nanotechnology and the Big Changes Coming from the Inconceivably Small*; American Management Association: New York, 2003.
(3) National Nanotechnology Initiative Home Page. http://www.nano.gov/ (accessed Feb 2004).
(4) *Dendrimers and Other Dendritic Polymers*; Fréchet, J. M. J., Tomalia, D. A., Eds.; Wiley: Chichester, 2001.
(5) Tomalia, D. A.; Fréchet, J. M. J. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 2719.
(6) Tomalia, D. A. *Mater. Today* **2003**, *6 (December)*, 72.
(7) Partington, J. R. *A Short History of Chemistry,* 3rd ed.; Dover Publications: New York, 1989. (An unaltered republication of the same work that was published by St. Martin's Press in 1957.)
(8) Staudinger, H. *From Organic Chemistry to Macromolecules*; Wiley-Interscience: New York, 1970.
(9) Morawetz, H. *Polymers. The Origin and Growth of a Science*; Wiley: New York, 1985.
(10) Pullman, B. *The Atom in the History of Human Thought*; Oxford University Press: New York, 1998.
(11) Berzelius, J. *Fortsch. Phys. Wissensch.* **1832**, *11*, 44; cited in reference 7, pp 203–205.
(12) Corey, E. J.; Cheng, X.-m. *The Logic of Chemical Synthesis*; Wiley: New York, 1989.
(13) Heilbronner, E.; Dunitz, J. D. *Reflections on Symmetry*; VCH Publishers: New York, 1993.
(14) Buhleier, E.; Wehner, W.; Vögtle, F. *Synthesis* **1978**, 155.
(15) Flory, P. J. *Principles of Polymer Chemistry*; Cornell University Press: Ithaca, NY, 1953.
(16) Roovers, J., Ed. *Advances in Polymer Science, Branched Polymers II*; Springer-Verlag: Berlin, 2000; Vol. 143.
(17) *Metallocene-Based Polyolefins*; Scheirs, J., Kaminsky, W., Eds.; Wiley: Chichester, 2000; Vol. 1 and 2.
(18) Elias, H.-G. *An Introduction to Polymer Science*; VCH: Weinheim, 1997.
(19) Tomalia, D. A.; Mardel, K.; Henderson, S. A.; Holan, G.; Esfand, R. In *Handbook of Nanoscience, Engineering, and Technology*; Goddard, W. A., III, Brenner, D. W., Lyshevski, S. E., Iafrate, G. J., Eds.; CRC Press: Boca Raton, 2003; pp **20**–1 to **20**–34.
(20) Goodsell, D. S. *Am. Scientist* **2000**, *88*, 230.
(21) Atkinson, W. I. *Nanocosm: Nanotechnology and the Big Changes Coming from the Inconceivably Small*; American Management Association: New York, 2003, pp 167–194.

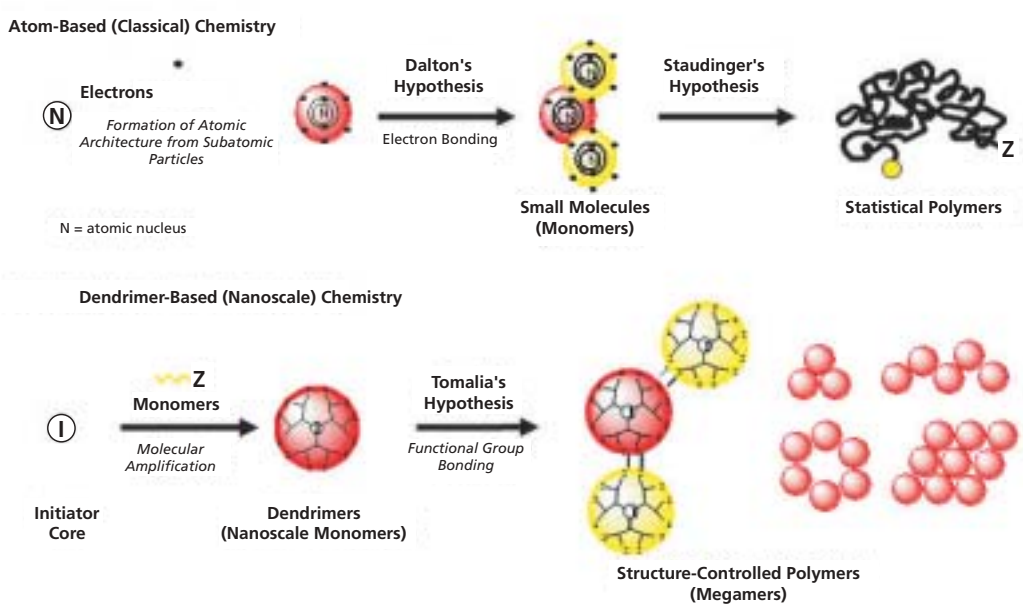


Figure 21. A Comparison of Atom-Based Classical Chemistry (Dalton and Staudinger Hypotheses) with Dendrimer-Based Nanoscale Chemistry (Tomalia Hypothesis) for Synthesizing Higher-Complexity Structures.

(22) *Buckminsterfullerenes*; Billups, W. E., Ciufolini, M. A., Eds.; VCH Publishers: New York, 1993.
(23) Richardson, C. F.; Schuster, D. I.; Wilson, S. R. *Org. Lett.* **2000**, *2*, 1011.
(24) Tomalia, D. A. *Macromol. Symp.* **1996**, *101*, 243.
(25) Naj, A. K. Persistent Inventor Markets a Molecule. *The Wall Street Journal,* Feb 26, 1996, p B1.
(26) Hecht, S.; Fréchet, J. M. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 74.
(27) Tomalia, D. A.; Naylor, A. M.; Goddard, W. A., III *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 138.
(28) Fréchet, J. M. J.; Hawker, C. J.; Gitsov, I.; Leon, J. W. *J. Macromol. Sci., Pure Appl. Chem.* **1999**, *A33*, 1399.
(29) Voit, B. I. *Acta Polymer.* **1995**, *46*, 87.
(30) Fischer, M.; Vögtle, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 884.
(31) Flory, P. J. *J. Am. Chem. Soc.* **1952**, *74*, 2718.
(32) Gunatillake, P. A.; Odian, G.; Tomalia, D. A. *Macromolecules* **1988**, *21*, 1556.
(33) Kim, Y. H.; Webster, O. W. *Polym. Prepr.* **1988**, *29*, 310.
(34) Kim, Y. H.; Webster, O. W. *J. Am. Chem. Soc.* **1990**, *112*, 4592.
(35) Emrick, T.; Chang, H.-T.; Fréchet, J. M. J. *J. Polym. Sci., Part A: Polym. Chem.* **2000**, *38*, 4850.
(36) Emrick, T.; Chang, H.-T.; Fréchet, J. M. J. *Macromolecules* **1999**, *32*, 6380.
(37) Bharathi, P.; Moore, J. S. *J. Am. Chem. Soc.* **1997**, *119*, 3391.
(38) Muzafarov, A. M.; Rebrov, E. A.; Gorbatsevich, O. B.; Golly, M.; Gankema, H.; Moller, M. *Macromol. Symp.* **1996**, *102*, 35.
(39) Miravet, J. F.; Fréchet, J. M. J. *Macromolecules* **1998**, *31*, 3461.
(40) Chu, F.; Hawker, C. J. *Polym. Bull.* **1993**, *30*, 265.
(41) Hawker, C. J.; Lee, R.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1991**, *113*, 4583.
(42) Uhrich, K. E.; Hawker, C. J.; Fréchet, J. M. J.; Turner, S. R. *Macromolecules* **1992**, *25*, 4583.
(43) Liu, M.; Vladimirov, N.; Fréchet, J. M. J. *Macromolecules* **1999**, *32*, 6881.
(44) Fréchet, J. M. J.; Henni, M.; Gitsov, I.; Aoshima, S.; Leduc, M. R.; Grubbs, R. B. *Science* **1995**, *269*, 1080.
(45) Hawker, C. J.; Farrington, P. J.; Mackay, M. E.; Wooley, K. L.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1995**, *117*, 4409.
(46) Sunder, A.; Heinemann, J.; Frey, H. *Chem. Eur. J.* **2000**, *6*, 2499.
(47) Gong, C.; Miravet, J.; Fréchet, J. M. J. *J. Polym. Sci., Part A: Polym. Chem.* **1999**, *37*, 3193.
(48) Tomalia, D. A.; Hedstrand, D. M.; Ferritto, M. S. *Macromolecules* **1991**, *24*, 1435.
(49) Gauthier, M.; Möller, M. *Macromolecules* **1991**, *24*, 4548.
(50) Kee, R. A.; Gauthier, M.; Tomalia, D. A. In *Dendrimers and Other Dendritic Polymers*; Fréchet, J. M. J., Tomalia, D. A., Eds.; Wiley: Chichester, 2001; pp 209–235.
(51) Gauthier, M.; Li, J.; Dockendorff, J. *Macromolecules* **2003**, *36*, 2642.
(52) Six, J.-L.; Gnanou, Y. *Macromol. Symp.* **1995**, *95*, 137.
(53) Taton, D.; Cloutet, E.; Gnanou, Y. *Macromol. Chem. Phys.* **1998**, *199*, 2501.
(54) Trollsas, M.; Hedrick, J. L. *J. Am. Chem. Soc.* **1998**, *120*, 4644.
(55) Trollsas, M.; Hedrick, J. L. *Macromolecules* **1998**, *31*, 4390.
(56) *Advances in Polymer Science, Branched Polymers I*; Roovers, J., Ed.; Springer-Verlag: Berlin, 1999; Vol. 142.
(57) Grubbs, R. B.; Hawker, C. J.; Dao, J.; Fréchet, J. M. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 270.
(58) Guan, Z.; Cotts, P. M.; McCord, E. F.; McLain, S. J. *Science* **1999**, *283*, 2059.
(59) Tomalia, D. A.; Dewald, J. R.; Hall, M. J.; Martin, S. J.; Smith, P. B. In *Preprints of the 1st SPSJ International Polymer Conference,* Society of Polymer Science Japan: Kyoto, Japan, August 1984; p 65.
(60) Tomalia, D. A.; Baker, H.; Dewald, J.; Hall, M.; Kallos, G.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P. *Polym. J. (Tokyo)* **1985**, *17*, 117.
(61) Esfand, R.; Tomalia, D. A. In *Dendrimers and Other Dendritic Polymers*; Fréchet, J. M. J., Tomalia, D. A., Eds.; Wiley: Chichester, 2001; pp 587–604.
(62) Fréchet, J. M. J.; Ihre, H.; Davey, M. In *Dendrimers and Other Dendritic Polymers*; Fréchet, J. M. J., Tomalia, D. A., Eds.; Wiley: Chichester, 2001; pp 569–586.
(63) Van Genderen, M. H. P.; Mak, M. H. A. P.; De Brabander-van den Berg, E. M. M.; Meijer, E. W. In *Dendrimers and Other Dendritic Polymers*; Fréchet, J. M. J., Tomalia, D. A., Eds.; Wiley: Chichester, 2001; pp 605–616.
(64) Tomalia, D. A. *Sci. Am.* **1995**, *272*(5), 42.
(65) Newkome, G. R.; Moorefield, C. N.; Vögtle, F. *Dendritic Molecules*; VCH: Weinheim, 1996.
(66) Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638.
(67) Zeng, F.; Zimmerman, S. C. *Chem. Rev.* **1997**, *97*, 1681.
(68) Lothian-Tomalia, M. K.; Hedstrand, D. M.; Tomalia, D. A.; Padias, A. B.; Hall, H. K., Jr. *Tetrahedron* **1997**, *53*, 15495.
(69) Tomalia, D. A. *Adv. Mater.* **1994**, *6*, 529.
(70) Tomalia, D. A. *Aldrichimica Acta* **1993**, *26*, 91.
(71) Kallos, G. J.; Tomalia, D. A.; Hedstrand, D. M.; Lewis, S.; Zhou, J. *Rapid Commun. Mass Spectrom.* **1991**, *5*, 383.
(72) Dvornic, P. R.; Tomalia, D. A. *Macromol. Symp.* **1995**, *98*, 403.
(73) Hummelen, J. C.; Van Dongen, J. L. J.; Meijer, E. W. *Chem. Eur. J.* **1997**, *3*, 1489.
(74) Peterson, J.; Allikmaa, V.; Subbi, J.; Pehk, T.; Lopp, M. *Eur. Polym. J.* **2003**, *39*, 33.
(75) Brothers, H. M., II; Piehler, L. T.; Tomalia, D. A. *J. Chromatogr. A* **1998**, *814*, 233.
(76) Zhang, C.; Tomalia, D. A. In *Dendrimers and Other Dendritic Polymers*; Fréchet, J. M. J., Tomalia, D. A., Eds.; Wiley: Chichester, 2001; pp 239–252.
(77) Tomalia, D. A.; Fréchet, J. M. J. In *Dendrimers and Other Dendritic Polymers*; Fréchet, J. M. J., Tomalia, D. A., Eds.; Wiley: Chichester, 2001; pp 3–44.
(78) Bohr, N. The Structure of the Atom. In *Nobel Lectures. Physics 1922–1941*; Elsevier: Amsterdam, 1965 (out of print); available at http://www.nobel.se/physics/laureates/1922/bohr-lecture.html (accessed May 2004).
(79) Tomalia, D. A.; Huang, B.; Swanson, D. R.; Brothers, H. M., II; Klimash, J. W. *Tetrahedron* **2003**, *59*, 3799.
(80) Jackson, C. L.; Chanzy, H. D.; Booy, F. P.; Drake, B. J.; Tomalia, D. A.; Bauer, B. J.; Amis, E. J. *Macromolecules* **1998**, *31*, 6259.
(81) Esfand, R.; Tomalia, D. A. *Drug Discovery Today* **2001**, *6(8)*, 427.
(82) Weener, J.-W.; Baars, M. W. P. L.; Meijer, E. W. In *Dendrimers and Other Dendritic Polymers*; Fréchet, J. M. J., Tomalia, D. A., Eds.; Wiley: Chichester, 2001; pp 387–424.
(83) Tomalia, D. A.; Brothers, H. M., II; Piehler, L. T.; Durst, H. D.; Swanson, D. R. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 5081.
(84) De A. A. Soler-Illia, G. J.; Rozes, L.; Boggiano, M. K.; Sanchez, C.; Turrin, C.-O.; Caminade, A.-M.; Majoral, J.-P. *Angew. Chem., Int. Ed.* **2000**, *39*, 4250.
(85) Tomalia, D. A.; Majoros, I. In *Supramolecular Polymers*; Ciferri, A., Ed.; Marcel Dekker: New York, 2000; Chapter 9, pp 359–434.
(86) Crooks, R. M.; Lemon, B., III; Sun, L.; Yeung, L. K.; Zhao, M. In *Topics in Current Chemistry*; Springer-Verlag: Berlin, 2001; Vol. 212, pp 81–135.

(87) Freeman, A. W.; Koene, S. C.; Malenfant, P. R. L.; Thompson, M. E.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2000**, *122*, 12385.
(88) Piotti, M. E.; Rivera, F., Jr.; Bond, R.; Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1999**, *121*, 9471.
(89) Bieniarz, C. In *Encyclopedia of Pharmaceutical Technology*; Marcel Dekker: New York, 1999; Vol. 18, pp 55–89.
(90) Tully, D. C.; Fréchet, J. M. J. *Chem. Commun.* **2001**, 1229.
(91) Andronov, A.; Fréchet, J. M. J. *Chem. Commun.* **2000**, 1701.
(92) Jiang, D.-L.; Aida, T. In *Dendrimers and Other Dendritic Polymers*; Fréchet, J. M. J., Tomalia, D. A., Eds.; Wiley: Chichester, 2001; pp 425–439.
(93) Singh, P.; Moll, F., III; Lin, S. H.; Ferzli, C. *Clin. Chem.* **1996**, *42*, 1567.
(94) Singh, P. In *Dendrimers and Other Dendritic Polymers*; Fréchet, J. M. J., Tomalia, D. A., Eds.; Wiley: Chichester, 2001; pp 463–484.
(95) Nath, M.; Rao, C. N. R. *J. Am. Chem. Soc.* **2001**, *123*, 4841.
(96) O'Connell, M. J.; Bachilo, S. M.; Huffman, C. B.; Moore, V. C.; Strano, M. S.; Haroz, E. H.; Rialon, K. L.; Boul, P. J.; Noon, W. H.; Ma, J.; Hauge, R. H.; Weisman, R. B.; Smalley, R. E. *Science* **2002**, *297*, 593.
(97) Zhao, Y.; Yakobson, B. I.; Smalley, R. E. *Phys. Rev. Lett.* **2002**, *88*, 185501.
(98) Li, J.; Piehler, L. T.; Qin, D.; Baker, J. R., Jr.; Tomalia, D. A.; Meier, D. J. *Langmuir* **2000**, *16*, 5613.
(99) Yin, R.; Zhu, Y.; Tomalia, D. A.; Ibuki, H. *J. Am. Chem. Soc.* **1998**, *120*, 2678.
(100) Matthews, O. A.; Shipway, A. N.; Stoddart, J. F. *Prog. Polym. Sci.* **1998**, *23*, 1.
(101) Majoral, J.-P.; Caminade, A.-M. *Chem. Rev.* **1999**, *99*, 845.
(102) Jansen, J. F. G. A.; De Brabander-van den Berg, E. M. M.; Meijer, E. W. *Science* **1994**, *266*, 1226.
(103) Freemantle, M. *Chem. Eng. News* **1999**, *77(44)*, 27.
(104) Balogh, L.; Tomalia, D. A.; Hagnauer, G. L. *Chem. Innovation* **2000**, *30*(3), 19.
(105) Tomalia, D. A.; Esfand, R. *Chem. Ind.* **1997**, No. 11, 416.
(106) Balogh, L.; Tomalia, D. A. *J. Am. Chem. Soc.* **1998**, *120*, 7355.
(107) Shull, R. D.; Balogh, L.; Swanson, D. R.; Tomalia, D. A. In *Book of Abstracts,* 216th National Meeting of the American Chemical Society, Boston, MA, Aug 23–27, 1998; American Chemical Society: Washington, DC, 1998; MACR-069.
(108) Rajca, A.; Utamapanya, S. *J. Am. Chem. Soc.* **1993**, *115*, 10688.
(109) Rajca, A.; Wongsriratanakul, J.; Rajca, S.; Cerny, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1229.
(110) Tabakovic, I.; Miller, L. L.; Duan, R. G.; Tully, D. C.; Tomalia, D. A. *Chem. Mater.* **1997**, *9*, 736.
(111) Miller, L. L.; Duan, R. G.; Tully, D. C.; Tomalia, D. A. *J. Am. Chem. Soc.* **1997**, *119*, 1005.
(112) Kawa, M.; Fréchet, J. M. J. *Chem. Mater.* **1998**, *10*, 286.
(113) Sato, T.; Jiang, D.-L.; Aida, T. *J. Am. Chem. Soc.* **1999**, *121*, 10658.
(114) De Gennes, P. G.; Hervet, H. *J. Phys., Lett. (Paris)* **1983**, *44*, L-351.
(115) Tomalia, D. A.; Hedstrand, D. M.; Wilson, L. R. In *Encyclopedia of Polymer Science and Engineering*; Kroschwitz, J. I., Ed.; Wiley: New York, 1990; Index Volume, Second Edition, pp 46–92.
(116) Li, J.; Swanson, D. R.; Qin, D.; Brothers, H. M., II; Piehler, L. T.; Tomalia, D. A.; Meier, D. J. *Langmuir* **1999**, *15*, 7347.
(117) Uppuluri, S.; Swanson, D. R.; Brothers, H. M., II; Piehler, L. T.; Li, J.; Meier, D. J.; Hagnauer, G. L.; Tomalia, D. A. *Polym. Mater. Sci. Eng.* **1999**, *80*, 55.
(118) Tomalia, D. A.; Uppuluri, S.; Swanson, D. R.; Li, J. *Pure Appl. Chem.* **2000**, *72*, 2343.
(119) Uppuluri, S.; Swanson, D. R.; Piehler, L. T.; Li, J.; Hagnauer, G. L.; Tomalia, D. A. *Adv. Mater* **2000**, *12*, 796.
(120) Tomalia, D. A.; Swanson, D. R. In *Dendrimers and Other Dendritic Polymers*; Fréchet, J. M. J., Tomalia, D. A., Eds.; Wiley: Chichester, 2001; pp 617–629.
(121) Mansfield, M. L.; Rakesh, L.; Tomalia, D. A. *J. Chem. Phys.* **1996**, *105*, 3245.
(122) *Tetrahedron Symposia-in-Print*; Smith, D. K., Ed.; Elsevier Science: Amsterdam, 2003; Vol. 59: Recent Developments in Dendrimer Chemistry, pp 3787–4024.

Note Added in Proof

Silicon- and gallium-based nanowire components have been used recently to construct unique nanoscale dendrigraft structures (Wang, D.; Qian, F.; Yang, C.; Zhong, Z.; Lieber, C. M. *Nano Lett.* **2004**, *4*, 871).

About the Author

Donald A. Tomalia received his B.A. in chemistry from the University of Michigan and, while at the Dow Chemical Company (1962–1990), completed his Ph.D. in physical organic chemistry at Michigan State University (1968) under Professor Harold Hart. His discovery of the cationic polymerization of 2-oxazolines led to two international industrial research awards (R&D–100) in 1978 and 1986. His discovery of dendrimers (dendritic architecture) in 1979 led to a third R&D–100 award in 1991 and the Leonardo da Vinci Award (Paris, France) in 1996. He has recently received the Society of Polymer Science Japan (SPSJ) Award for Outstanding Achievement in Polymer Science (2003).

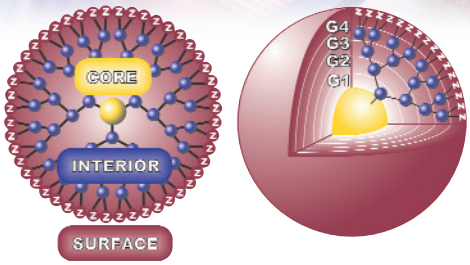
In 1990, he joined the Michigan Molecular Institute (MMI) as Professor and Director of Nanoscale Chemistry & Architecture, and served in that capacity until 1999. He cofounded Dendritech, Inc., the first commercial producer of dendrimers, and served as its founding President and Chief Scientist from 1992 to 2000. He became Vice President of Technology for MMI (1998–2000), while simultaneously serving as Scientific Director of the Biologic Nanotechnology Center, University of Michigan Medical School (1998–2000).

Dr. Tomalia founded Dendritic NanoTechnologies, Inc. (DNT) in 2002 as a joint venture with Starpharma Ltd. (Melbourne, Australia). He currently serves as President and C.T.O. of DNT with production and laboratory facilities located at Central Michigan University, Mt. Pleasant, Michigan. Dr. Tomalia was recently appointed Director of the National Center for Dendrimer Based Nanotechnology located on the Central Michigan University campus (2003). He was recently appointed Principal Investigator for DNT's participation in MIT's Institute for Soldier Nanotechnologies (MIT/ISN) (2003). Other positions currently held by Dr. Tomalia include Distinguished Visiting Professor (Columbia University) and Distinguished Research Scientist/Professor (Central Michigan University).

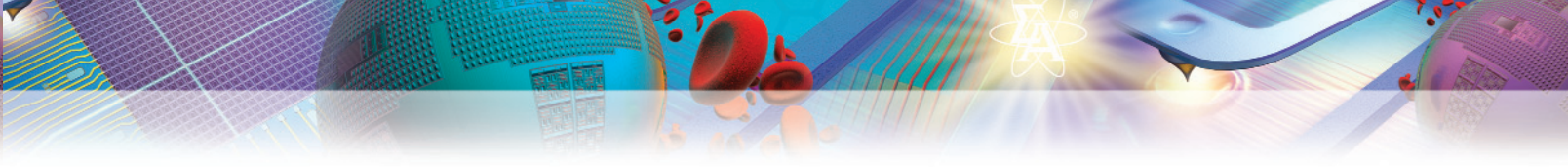
He is listed as the inventor on over 110 U.S. patents, and is author or co-author of more than 185 peer-reviewed publications. Over 155 papers are focused in the dendrimer or dendritic polymer field, including a monograph entitled *Dendrimers and Other Dendritic Polymers* that was co-edited with J. M. J. Fréchet (Wiley, 2001). Dr. Tomalia serves on the editorial advisory boards of *Bioconjugate Chemistry* (1999–present) and *Nano Letters* (2000–present).

Dendrimers from Aldrich

In recent years, a new structural class of macromolecules, the *dendritic polymers*, has attracted the attention of the scientific community. Dendrimers are defined by their three components: a central core, an interior dendritic structure (the branches), and an exterior surface (the end groups).



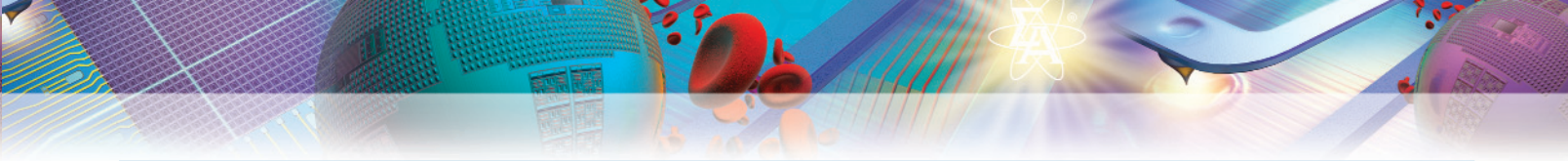
Aldrich Cat. No.	Generation	Form	Formula	Surface Groups
BHA-Lysine-100% Boc Dendrimers				
tert-Butoxycarbonyl-protected amines†				
63,598-7	0	powder	$(C_6H_5)_2CHNHC(O)CH[NHC(O)CH(NHBoc)(CH_2)_4NHBoc](CH_2)_4NHC(O)CH(NHBoc)(CH_2)_4NHBoc$	4
63,597-9	1	powder	$(C_6H_5)_2CHNHC(O)CH(NH_2)(CH_2)_4NH_2$;dendri C(O)$CH(NH_2)(CH_2)_4NH_2$ with Boc-protected terminal amines	8
PAMAM Dendrimers with Cystamine Core				
Amidoethanol Surface Groups†				
64,763-2	0	20 wt. % in methanol	$[NH_2CH_2CH_2SSCH_2CH_2NH_2]$:(G=0);dendri PAMAM$(NH_2)_4$	4
64,771-3	1	20 wt. % in methanol	$[NH_2CH_2CH_2SSCH_2CH_2NH_2]$:(G=1);dendri PAMAM$(NH_2)_8$	8
64,782-9	2	20 wt. % in methanol	$[NH_2CH_2CH_2SSCH_2CH_2NH_2]$:(G=2);dendri PAMAM$(NH_2)_{16}$	16
64,794-2	3	10 wt. % in methanol	$[NH_2CH_2CH_2SSCH_2CH_2NH_2]$:(G=3);dendri PAMAM$(NH_2)_{32}$	32
64,804-3	4	10 wt. % in methanol	$[NH_2CH_2CH_2SSCH_2CH_2NH_2]$:(G=4);dendri PAMAM$(NH_2)_{64}$	64
64,815-9	5	10 wt. % in methanol	$[NH_2CH_2CH_2SSCH_2CH_2NH_2]$:(G=5);dendri PAMAM$(NH_2)_{128}$	128
64,826-4	6	10 wt. % in methanol	$[NH_2CH_2CH_2SSCH_2CH_2NH_2]$:(G=6);dendri PAMAM$(NH_2)_{256}$	256
PAMAM Dendrimers with Ethylenediamine Core (2-Carbon Core)				
Amidoethanol Surface Groups*				
47,783-4	2	20 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=2);dendri PAMAM$(NHCH_2CH_2OH)_{16}$	16
47,784-2	3	20 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=3);dendri PAMAM$(NHCH_2CH_2OH)_{32}$	32
47,785-0	4	10 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=4);dendri PAMAM$(NHCH_2CH_2OH)_{64}$	64
53,681-4	5	5 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=5);dendri PAMAM$(NHCH_2CH_2OH)_{128}$	128
53,682-2	6	5 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=6);dendri PAMAM$(NHCH_2CH_2OH)_{256}$	256
53,683-0	7	5 wt. % in methanol	$[NH_2(CH_2)_4NH_2]$:(G=7);dendri PAMAM$(NHCH_2CH_2OH)_{512}$	512
Amidoethylethanolamine Surface Groups†				
59,790-2	2	10 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=2);dendri PAMAM$[NH(CH_2)_2NH(CH_2)_2OH]_{16}$	16
59,253-6	3	10 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=3);dendri PAMAM$[NH(CH_2)_2NH(CH_2)_2OH]_{32}$	32
59,779-1	4	10 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=4);dendri PAMAM$[NH(CH_2)_2NH(CH_2)_2OH]_{64}$	64
Amino Surface Groups*				
41,236-8	0	20 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=0);dendri PAMAM$(NH_2)_4$	4
41,238-4	1	20 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=1);dendri PAMAM$(NH_2)_8$	8
41,240-6	2	20 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=2);dendri PAMAM$(NH_2)_{16}$	16
41,242-2	3	20 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=3);dendri PAMAM$(NH_2)_{32}$	32
41,244-9	4	10 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=4);dendri PAMAM$(NH_2)_{64}$	64
53,670-9	5	5 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=5);dendri PAMAM$(NH_2)_{128}$	128
53,671-7	6	5 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=6);dendri PAMAM$(NH_2)_{256}$	256
53,672-5	7	5 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=7);dendri PAMAM$(NH_2)_{512}$	512
53,674-1	8	5 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=8);dendri PAMAM$(NH_2)_{1024}$	1024
53,676-8	9	5 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=9);dendri PAMAM$(NH_2)_{2048}$	2048
53,677-6	10	5 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=10);dendri PAMAM$(NH_2)_{4096}$	4096
75% Amino and 25% [*N*-(2-Hydroxydodecyl)] Surface Groups*				
53,684-9	2	20 wt. % in methanol	12 primary amino groups and 4 [*N*-(2-hydroxydodecyl)] groups	16
53,686-5	3	20 wt. % in methanol	24 primary amino groups and 8 [*N*-(2-hydroxydodecyl)] groups	32
53,696-2	4	10 wt. % in methanol	48 primary amino groups and 16 [*N*-(2-hydroxydodecyl)] groups	64
50% Amino and 50% [*N*-(2-Hydroxydodecyl)] Surface Groups*				
53,685-7	2	20 wt. % in methanol	8 primary amino groups and 8 [*N*-(2-hydroxydodecyl)] groups	16
53,687-3	3	20 wt. % in methanol	16 primary amino groups and 16 [*N*-(2-hydroxydodecyl)] groups	32
53,697-0	4	10 wt. % in methanol	32 primary amino groups and 32 [*N*-(2-hydroxydodecyl)] groups	64
3-Carbomethoxypyrrolidinone Surface Groups†				
64,786-1	2	10 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=2);dendri PAMAM(PYR-$COOMe)_{16}$	16
64,788-8	3	10 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=3);dendri PAMAM(PYR-$COOMe)_{32}$	32
64,789-6	4	10 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=4);dendri PAMAM(PYR-$COOMe)_{64}$	64
64,791-8	5	10 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=5);dendri PAMAM(PYR-$COOMe)_{128}$	128
64,792-6	6	10 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=6);dendri PAMAM(PYR-$COOMe)_{256}$	256
Hexylamide Surface Groups†				
59,736-8	3	10 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=3);dendri PAMAM$[NHCO(CH_2)_4CH_3]_{32}$	32



Aldrich Cat. No.	Generation	Form	Formula	Surface Groups
Sodium Carboxylate Surface Groups*				
52,614-2	-0.5	Neat powder	$[-CH_2N(CH_2CH_2COONa)_2]_2$	4
41,237-6	0.5	20 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=0.5);dendri PAMAM$(NHCH_2CH_2COONa)_8$	8
41,239-2	1.5	20 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=1.5);dendri PAMAM$(NHCH_2CH_2COONa)_{16}$	16
41,241-4	2.5	10 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=2.5);dendri PAMAM$(NHCH_2CH_2COONa)_{32}$	32
41,243-0	3.5	10 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=3.5);dendri PAMAM$(NHCH_2CH_2COONa)_{64}$	64
47,045-7	4.5	5 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=4.5);dendri PAMAM$(NHCH_2CH_2COONa)_{128}$	128
53,678-4	5.5	5 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=5.5);dendri PAMAM$(NHCH_2CH_2COONa)_{256}$	256
53,679-2	6.5	5 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=6.5);dendri PAMAM$(NHCH_2CH_2COONa)_{512}$	512
53,680-6	7.5	5 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=7.5);dendri PAMAM$(NHCH_2CH_2COONa)_{1024}$	1024
Succinamic Acid Surface Groups†				
59,230-7	2	10 wt. % in water	$[NH_2(CH_2)_2NH_2]$:(G=2);dendri PAMAM$(NHCOCH_2CH_2COOH)_{16}$	16
59,219-6	3	10 wt. % in water	$[NH_2(CH_2)_2NH_2]$:(G=3);dendri PAMAM$(NHCOCH_2CH_2COOH)_{32}$	32
59,812-7	4	10 wt. % in water	$[NH_2(CH_2)_2NH_2]$:(G=4);dendri PAMAM$(NHCOCH_2CH_2COOH)_{64}$	64
59,801-1	5	10 wt. % in water	$[NH_2(CH_2)_2NH_2]$:(G=5);dendri PAMAM$(NHCOCH_2CH_2COOH)_{128}$	128
Tris(hydroxymethyl)amidomethane Surface Groups†				
59,769-4	2	10 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=2);dendri PAMAM$[NHC(CH_2OH)_3]_{16}$	16
59,758-9	3	10 wt. % in methanol	$[NH_2(CH_2)_2NH_2]$:(G=3);dendri PAMAM$[NHC(CH_2OH)_3]_{32}$	32
PAMAM Dendrimers with 1,4-Diaminobutane Core (4-Carbon Core)				
Amidoethanol Surface Groups†				
63,518-9	2	10 wt. % in methanol	$[NH_2(CH_2)_4NH_2]$:(G=2);dendri PAMAM$(NHCH_2CH_2OH)_{16}$	16
63,519-7	3	10 wt. % in methanol	$[NH_2(CH_2)_4NH_2]$:(G=3);dendri PAMAM$(NHCH_2CH_2OH)_{32}$	32
63,520-0	4	10 wt. % in methanol	$[NH_2(CH_2)_4NH_2]$:(G=4);dendri PAMAM$(NHCH_2CH_2OH)_{64}$	64
63,521-9	5	10 wt. % in methanol	$[NH_2(CH_2)_4NH_2]$:(G=5);dendri PAMAM$(NHCH_2CH_2OH)_{128}$	128
63,522-7	6	10 wt. % in methanol	$[NH_2(CH_2)_4NH_2]$:(G=6);dendri PAMAM$(NHCH_2CH_2OH)_{256}$	256
Amino Surface Groups†				
59,576-4	0	20 wt. % in methanol	$[NH_2(CH_2)_4NH_2]$:(G=0);dendri PAMAM$(NH_2)_4$	4
59,586-1	1	20 wt. % in methanol	$[NH_2(CH_2)_4NH_2]$:(G=1);dendri PAMAM$(NH_2)_8$	8
59,598-5	2	20 wt. % in methanol	$[NH_2(CH_2)_4NH_2]$:(G=2);dendri PAMAM$(NH_2)_{16}$	16
59,609-4	3	20 wt. % in methanol	$[NH_2(CH_2)_4NH_2]$:(G=3);dendri PAMAM$(NH_2)_{32}$	32
59,619-1	4	10 wt. % in methanol	$[NH_2(CH_2)_4NH_2]$:(G=4);dendri PAMAM$(NH_2)_{64}$	64
59,630-2	5	10 wt. % in methanol	$[NH_2(CH_2)_4NH_2]$:(G=5);dendri PAMAM$(NH_2)_{128}$	128
59,642-6	6	10 wt. % in methanol	$[NH_2(CH_2)_4NH_2]$:(G=6);dendri PAMAM$(NH_2)_{256}$	256
3-Carbomethoxypyrrolidinone Surface Groups†				
64,786-1	2	10 wt. % in methanol	$[NH_2(CH_2)_4NH_2]$:(G=2);dendri PAMAM$(PYR\text{-}COOMe)_{16}$	16
64,788-8	3	10 wt. % in methanol	$[NH_2(CH_2)_4NH_2]$:(G=3);dendri PAMAM$(PYR\text{-}COOMe)_{32}$	32
64,789-6	4	10 wt. % in methanol	$[NH_2(CH_2)_4NH_2]$:(G=4);dendri PAMAM$(PYR\text{-}COOMe)_{64}$	64
64,791-8	5	10 wt. % in methanol	$[NH_2(CH_2)_4NH_2]$:(G=5);dendri PAMAM$(PYR\text{-}COOMe)_{128}$	128
64,792-6	6	10 wt. % in methanol	$[NH_2(CH_2)_4NH_2]$:(G=6);dendri PAMAM$(PYR\text{-}COOMe)_{256}$	256
Hexylamide Surface Groups†				
64,092-1	4	10 wt. % in methanol	$[NH_2(CH_2)_4NH_2]$:(G=4);dendri PAMAM$(NHCO(CH_2)_4CH_3)_{64}$	64
64,091-3	5	10 wt. % in methanol	$[NH_2(CH_2)_4NH_2]$:(G=5);dendri PAMAM$(NHCO(CH_2)_4CH_3)_{128}$	128
64,094-8	6	10 wt. % in methanol	$[NH_2(CH_2)_4NH_2]$:(G=6);dendri PAMAM$(NHCO(CH_2)_4CH_3)_{256}$	256
Propylenimine Amine Surface Groups†				
59,576-4	0	20 wt. % in methanol	$[NH_2(CH_2)_4NH_2]$:(G=0);dendri PAMAM$(NHCH_2CH_2CH_2NH_2)_4$	4
59,586-1	1	20 wt. % in methanol	$[NH_2(CH_2)_4NH_2]$:(G=1);dendri PAMAM$(NHCH_2CH_2CH_2NH_2)_8$	8
59,598-5	2	20 wt. % in methanol	$[NH_2(CH_2)_4NH_2]$:(G=2);dendri PAMAM$(NHCH_2CH_2CH_2NH_2)_{16}$	16
59,609-4	3	20 wt. % in methanol	$[NH_2(CH_2)_4NH_2]$:(G=3);dendri PAMAM$(NHCH_2CH_2CH_2NH_2)_{32}$	32
59,619-1	4	10 wt. % in methanol	$[NH_2(CH_2)_4NH_2]$:(G=4);dendri PAMAM$(NHCH_2CH_2CH_2NH_2)_{64}$	64
Sodium Carboxylate Surface Groups†				
63,564-2	1.5	10 wt. % in methanol	$[NH_2(CH_2)_4NH_2]$:(G=1.5);dendri PAMAM$(NHCH_2CH_2COONa)_{16}$	16
63,563-4	2.5	10 wt. % in methanol	$[NH_2(CH_2)_4NH_2]$:(G=2.5);dendri PAMAM$(NHCH_2CH_2COONa)_{32}$	32
63,562-6	3.5	10 wt. % in methanol	$[NH_2(CH_2)_4NH_2]$:(G=3.5);dendri PAMAM$(NHCH_2CH_2COONa)_{64}$	64
63,561-8	4.5	10 wt. % in methanol	$[NH_2(CH_2)_4NH_2]$:(G=4.5);dendri PAMAM$(NHCH_2CH_2COONa)_{128}$	128
63,559-6	5.5	10 wt. % in methanol	$[NH_2(CH_2)_4NH_2]$:(G=5.5);dendri PAMAM$(NHCH_2CH_2COONa)_{256}$	256
Succinamic Acid Surface Groups†				
63,585-5	2	10 wt. % in water	$[NH_2(CH_2)_4NH_2]$:(G=2);dendri PAMAM$(NHCOCH_2CH_2COOH)_{16}$	16
63,586-3	3	10 wt. % in water	$[NH_2(CH_2)_4NH_2]$:(G=3);dendri PAMAM$(NHCOCH_2CH_2COOH)_{32}$	32
63,587-1	4	10 wt. % in water	$[NH_2(CH_2)_4NH_2]$:(G=4);dendri PAMAM$(NHCOCH_2CH_2COOH)_{64}$	64
63,589-8	5	10 wt. % in water	$[NH_2(CH_2)_4NH_2]$:(G=5);dendri PAMAM$(NHCOCH_2CH_2COOH)_{128}$	128
63,590-1	6	10 wt. % in water	$[NH_2(CH_2)_4NH_2]$:(G=6);dendri PAMAM$(NHCOCH_2CH_2COOH)_{256}$	256

Dendrimers from Aldrich (continued)

Aldrich Cat. No.	Generation	Form	Formula	Surface Groups
Tris(hydroxymethyl)amidomethane Surface Groups†				
64,812-4	2	10 wt. % in water	$[NH_2(CH_2)_4NH_2]$:(G=2);dendri PAMAM$[NHC(CH_2OH)_3]_{16}$	16
64,816-7	3	10 wt. % in water	$[NH_2(CH_2)_4NH_2]$:(G=3);dendri PAMAM$[NHC(CH_2OH)_3]_{32}$	32
64,813-2	4	10 wt. % in water	$[NH_2(CH_2)_4NH_2]$:(G=4);dendri PAMAM$[NHC(CH_2OH)_3]_{64}$	64
64,814-0	5	10 wt. % in water	$[NH_2(CH_2)_4NH_2]$:(G=5);dendri PAMAM$[NHC(CH_2OH)_3]_{128}$	128
64,817-5	6	10 wt. % in water	$[NH_2(CH_2)_4NH_2]$:(G=6);dendri PAMAM$[NHC(CH_2OH)_3]_{256}$	256
PAMAM Dendrimers with 1,6-Diaminohexane Core (6-Carbon Core)				
Amidoethanol Surface Groups†				
63,523-5	2	10 wt. % in methanol	$[NH_2(CH_2)_6NH_2]$:(G=2);dendri PAMAM$(NHCH_2CH_2OH)_{16}$	16
63,524-3	3	10 wt. % in methanol	$[NH_2(CH_2)_6NH_2]$:(G=3);dendri PAMAM$(NHCH_2CH_2OH)_{32}$	32
63,525-1	4	10 wt. % in methanol	$[NH_2(CH_2)_6NH_2]$:(G=4);dendri PAMAM$(NHCH_2CH_2OH)_{64}$	64
63,527-8	5	10 wt. % in methanol	$[NH_2(CH_2)_6NH_2]$:(G=5);dendri PAMAM$(NHCH_2CH_2OH)_{128}$	128
63,528-6	6	10 wt. % in methanol	$[NH_2(CH_2)_6NH_2]$:(G=6);dendri PAMAM$(NHCH_2CH_2OH)_{256}$	256
Amino Surface Groups†				
59,652-3	0	20 wt. % in methanol	$[NH_2(CH_2)_6NH_2]$:(G=0);dendri PAMAM$(NH_2)_4$	4
59,663-9	1	20 wt. % in methanol	$[NH_2(CH_2)_6NH_2]$:(G=1);dendri PAMAM$(NH_2)_8$	8
59,675-2	2	20 wt. % in methanol	$[NH_2(CH_2)_6NH_2]$:(G=2);dendri PAMAM$(NH_2)_{16}$	16
59,686-8	3	20 wt. % in methanol	$[NH_2(CH_2)_6NH_2]$:(G=3);dendri PAMAM$(NH_2)_{32}$	32
59,696-5	4	10 wt. % in methanol	$[NH_2(CH_2)_6NH_2]$:(G=4);dendri PAMAM$(NH_2)_{64}$	64
59,708-2	5	10 wt. % in methanol	$[NH_2(CH_2)_6NH_2]$:(G=5);dendri PAMAM$(NH_2)_{128}$	128
59,719-8	6	10 wt. % in methanol	$[NH_2(CH_2)_6NH_2]$:(G=6);dendri PAMAM$(NH_2)_{256}$	256
3-Carbomethoxypyrrolidinone Surface Groups†				
64,798-5	2	10 wt. % in methanol	$[NH_2(CH_2)_6NH_2]$:(G=2);dendri PAMAM$(PYR\text{-}COOMe)_{16}$	16
64,799-3	3	10 wt. % in methanol	$[NH_2(CH_2)_6NH_2]$:(G=3);dendri PAMAM$(PYR\text{-}COOMe)_{32}$	32
64,800-0	4	10 wt. % in methanol	$[NH_2(CH_2)_6NH_2]$:(G=4);dendri PAMAM$(PYR\text{-}COOMe)_{64}$	64
64,801-9	5	10 wt. % in methanol	$[NH_2(CH_2)_6NH_2]$:(G=5);dendri PAMAM$(PYR\text{-}COOMe)_{128}$	128
64,802-7	6	10 wt. % in methanol	$[NH_2(CH_2)_6NH_2]$:(G=6);dendri PAMAM$(PYR\text{-}COOMe)_{256}$	256
Hexylamide Surface Groups†				
64,095-6	4	10 wt. % in methanol	$[NH_2(CH_2)_6NH_2]$:(G=4);dendri PAMAM$(NHCO(CH_2)_4CH_3)_{64}$	64
64,096-4	5	10 wt. % in methanol	$[NH_2(CH_2)_6NH_2]$:(G=5);dendri PAMAM$(NHCO(CH_2)_4CH_3)_{128}$	128
64,097-2	6	10 wt. % in methanol	$[NH_2(CH_2)_6NH_2]$:(G=6);dendri PAMAM$(NHCO(CH_2)_4CH_3)_{256}$	256
Sodium Carboxylate Surface Groups†				
63,558-8	1.5	10 wt. % in methanol	$[NH_2(CH_2)_6NH_2]$:(G=1.5);dendri PAMAM$(NHCH_2CH_2COONa)_{16}$	16
63,556-1	2.5	10 wt. % in methanol	$[NH_2(CH_2)_6NH_2]$:(G=2.5);dendri PAMAM$(NHCH_2CH_2COONa)_{32}$	32
63,555-3	3.5	10 wt. % in methanol	$[NH_2(CH_2)_6NH_2]$:(G=3.5);dendri PAMAM$(NHCH_2CH_2COONa)_{64}$	64
63,554-5	4.5	10 wt. % in methanol	$[NH_2(CH_2)_6NH_2]$:(G=4.5);dendri PAMAM$(NHCH_2CH_2COONa)_{128}$	128
63,553-7	5.5	10 wt. % in methanol	$[NH_2(CH_2)_6NH_2]$:(G=5.5);dendri PAMAM$(NHCH_2CH_2COONa)_{256}$	256
Succinamic Acid Surface Groups†				
63,605-3	2	10 wt. % in water	$[NH_2(CH_2)_6NH_2]$:(G=2);dendri PAMAM$(NHCOCH_2CH_2COOH)_{16}$	16
63,606-1	3	10 wt. % in water	$[NH_2(CH_2)_6NH_2]$:(G=3);dendri PAMAM$(NHCOCH_2CH_2COOH)_{32}$	32
63,608-8	4	10 wt. % in water	$[NH_2(CH_2)_6NH_2]$:(G=4);dendri PAMAM$(NHCOCH_2CH_2COOH)_{64}$	64
63,609-6	5	10 wt. % in water	$[NH_2(CH_2)_6NH_2]$:(G=5);dendri PAMAM$(NHCOCH_2CH_2COOH)_{128}$	128
63,611-8	6	10 wt. % in water	$[NH_2(CH_2)_6NH_2]$:(G=6);dendri PAMAM$(NHCOCH_2CH_2COOH)_{256}$	256
Tris(hydroxymethyl)amidomethane Surface Groups†				
64,818-3	2	10 wt. % in water	$[NH_2(CH_2)_6NH_2]$:(G=2);dendri PAMAM$[NHC(CH_2OH)_3]_{16}$	16
64,819-1	3	10 wt. % in water	$[NH_2(CH_2)_6NH_2]$:(G=3);dendri PAMAM$[NHC(CH_2OH)_3]_{32}$	32
64,820-5	4	10 wt. % in water	$[NH_2(CH_2)_6NH_2]$:(G=4);dendri PAMAM$[NHC(CH_2OH)_3]_{64}$	64
64,821-3	5	10 wt. % in water	$[NH_2(CH_2)_6NH_2]$:(G=5);dendri PAMAM$[NHC(CH_2OH)_3]_{128}$	128
64,822-1	6	10 wt. % in water	$[NH_2(CH_2)_6NH_2]$:(G=6);dendri PAMAM$[NHC(CH_2OH)_3]_{256}$	256
PAMAM Dendrimers with 1,12-Diaminododecane Core (12-Carbon Core)				
Amidoethanol Surface Groups†				
63,529-4	2	10 wt. % in methanol	$[NH_2(CH_2)_{12}NH_2]$:(G=2);dendri PAMAM$(NHCH_2CH_2OH)_{16}$	16
63,530-8	3	10 wt. % in methanol	$[NH_2(CH_2)_{12}NH_2]$:(G=3);dendri PAMAM$(NHCH_2CH_2OH)_{32}$	32
63,531-6	4	10 wt. % in methanol	$[NH_2(CH_2)_{12}NH_2]$:(G=4);dendri PAMAM$(NHCH_2CH_2OH)_{64}$	64
63,532-4	5	10 wt. % in methanol	$[NH_2(CH_2)_{12}NH_2]$:(G=5);dendri PAMAM$(NHCH_2CH_2OH)_{128}$	128
63,533-2	6	10 wt. % in methanol	$[NH_2(CH_2)_{12}NH_2]$:(G=6);dendri PAMAM$(NHCH_2CH_2OH)_{256}$	256
Amino Surface Groups†				
59,730-9	0	20 wt. % in methanol	$[NH_2(CH_2)_{12}NH_2]$:(G=0);dendri PAMAM$(NH_2)_4$	4
59,741-4	1	20 wt. % in methanol	$[NH_2(CH_2)_{12}NH_2]$:(G=1);dendri PAMAM$(NH_2)_8$	8
59,763-5	2	20 wt. % in methanol	$[NH_2(CH_2)_{12}NH_2]$:(G=2);dendri PAMAM$(NH_2)_{16}$	16
59,774-0	3	20 wt. % in methanol	$[NH_2(CH_2)_{12}NH_2]$:(G=3);dendri PAMAM$(NH_2)_{32}$	32
59,785-6	4	10 wt. % in methanol	$[NH_2(CH_2)_{12}NH_2]$:(G=4);dendri PAMAM$(NH_2)_{64}$	64
59,795-3	5	10 wt. % in methanol	$[NH_2(CH_2)_{12}NH_2]$:(G=5);dendri PAMAM$(NH_2)_{128}$	128
59,807-0	6	10 wt. % in methanol	$[NH_2(CH_2)_{12}NH_2]$:(G=6);dendri PAMAM$(NH_2)_{256}$	256



Aldrich Cat. No.	Generation	Form	Formula	Surface Groups
3-Carbomethoxypyrrolidinone Surface Groups†				
64,803-5	2	10 wt. % in methanol	$[NH_2(CH_2)_{12}NH_2]$:(G=2);dendri PAMAM(PYR-COOMe)$_{16}$	16
64,805-1	3	10 wt. % in methanol	$[NH_2(CH_2)_{12}NH_2]$:(G=3);dendri PAMAM(PYR-COOMe)$_{32}$	32
64,807-8	4	10 wt. % in methanol	$[NH_2(CH_2)_{12}NH_2]$:(G=4);dendri PAMAM(PYR-COOMe)$_{64}$	64
64,808-6	5	10 wt. % in methanol	$[NH_2(CH_2)_{12}NH_2]$:(G=5);dendri PAMAM(PYR-COOMe)$_{128}$	128
64,809-4	6	10 wt. % in methanol	$[NH_2(CH_2)_{12}NH_2]$:(G=6);dendri PAMAM(PYR-COOMe)$_{256}$	256
Hexylamide Surface Groups†				
64,098-0	4	10 wt. % in methanol	$[NH_2(CH_2)_{12}NH_2]$:(G=4);dendri PAMAM(NHCO$(CH_2)_4CH_3)_{64}$	64
64,099-9	5	10 wt. % in methanol	$[NH_2(CH_2)_{12}NH_2]$:(G=5);dendri PAMAM(NHCO$(CH_2)_4CH_3)_{128}$	128
64,100-6	6	10 wt. % in methanol	$[NH_2(CH_2)_{12}NH_2]$:(G=6);dendri PAMAM(NHCO$(CH_2)_4CH_3)_{256}$	256
Sodium Carboxylate Surface Groups†				
63,552-9	1.5	10 wt. % in methanol	$[NH_2(CH_2)_{12}NH_2]$:(G=1.5);dendri PAMAM(NHCH$_2$CH$_2$COONa)$_{16}$	16
63,551-0	2.5	10 wt. % in methanol	$[NH_2(CH_2)_{12}NH_2]$:(G=2.5);dendri PAMAM(NHCH$_2$CH$_2$COONa)$_{32}$	32
63,548-0	3.5	10 wt. % in methanol	$[NH_2(CH_2)_{12}NH_2]$:(G=3.5);dendri PAMAM(NHCH$_2$CH$_2$COONa)$_{64}$	64
63,547-2	4.5	10 wt. % in methanol	$[NH_2(CH_2)_{12}NH_2]$:(G=4.5);dendri PAMAM(NHCH$_2$CH$_2$COONa)$_{128}$	128
63,546-4	5.5	10 wt. % in methanol	$[NH_2(CH_2)_{12}NH_2]$:(G=5.5);dendri PAMAM(NHCH$_2$CH$_2$COONa)$_{256}$	256
Succinamic Acid Surface Groups†				
63,612-6	2	10 wt. % in water	$[NH_2(CH_2)_{12}NH_2]$:(G=2);dendri PAMAM(NHCOCH$_2$CH$_2$COOH)$_{16}$	16
63,614-2	3	10 wt. % in water	$[NH_2(CH_2)_{12}NH_2]$:(G=3);dendri PAMAM(NHCOCH$_2$CH$_2$COOH)$_{32}$	32
63,613-4	4	10 wt. % in water	$[NH_2(CH_2)_{12}NH_2]$:(G=4);dendri PAMAM(NHCOCH$_2$CH$_2$COOH)$_{64}$	64
63,615-0	5	10 wt. % in water	$[NH_2(CH_2)_{12}NH_2]$:(G=5);dendri PAMAM(NHCOCH$_2$CH$_2$COOH)$_{128}$	128
63,616-9	6	10 wt. % in water	$[NH_2(CH_2)_{12}NH_2]$:(G=6);dendri PAMAM(NHCOCH$_2$CH$_2$COOH)$_{256}$	256
Tris(hydroxymethyl)amidomethane Surface Groups†				
64,824-8	2	10 wt. % in water	$[NH_2(CH_2)_{12}NH_2]$:(G=2);dendri PAMAM[NHC(CH$_2$OH)$_3]_{16}$	16
64,825-6	3	10 wt. % in water	$[NH_2(CH_2)_{12}NH_2]$:(G=3);dendri PAMAM[NHC(CH$_2$OH)$_3]_{32}$	32
64,827-2	4	10 wt. % in water	$[NH_2(CH_2)_{12}NH_2]$:(G=4);dendri PAMAM[NHC(CH$_2$OH)$_3]_{64}$	64
64,828-0	5	10 wt. % in water	$[NH_2(CH_2)_{12}NH_2]$:(G=5);dendri PAMAM[NHC(CH$_2$OH)$_3]_{128}$	128
64,829-9	6	10 wt. % in water	$[NH_2(CH_2)_{12}NH_2]$:(G=6);dendri PAMAM[NHC(CH$_2$OH)$_3]_{256}$	256
Phosphorus Dendrimers with Thiophosphoryl Chloride Core [PMMH= PhenoxyMethyl(MethylHydrazono)]				
Aldehyde Surface Groups				
55,176-7	0.5	powder	S=P(O(C$_6$H$_4$)CHO)$_3$	3
55,167-8	1.5	powder	S=P(Cl)$_3$:(G=1.5);dendri Thiophosphoryl-PMMH[O(C$_6$H$_4$)CHO]$_6$	6
55,169-4	2.5	powder	S=P(Cl)$_3$:(G=2.5);dendri Thiophosphoryl-PMMH[O(C$_6$H$_4$)CHO]$_{12}$	12
55,171-6	3.5	powder	S=P(Cl)$_3$:(G=3.5);dendri Thiophosphoryl-PMMH[O(C$_6$H$_4$)CHO]$_{24}$	24
55,173-2	4.5	powder	S=P(Cl)$_3$:(G=4.5);dendri Thiophosphoryl-PMMH[O(C$_6$H$_4$)CHO]$_{48}$	48
55,175-9	5.5	powder	S=P(Cl)$_3$:(G=5.5);dendri Thiophosphoryl-PMMH[O(C$_6$H$_4$)CHO]$_{96}$	96
Dichlorophosphinothioyl Surface Groups				
55,177-5	1	powder	S=P(O(C$_6$H$_4$)CH=NN(CH$_3$)P(S)(Cl)$_2)_3$	3
55,168-6	2	powder	S=P(Cl)$_3$:(G=2);dendri Thiophosphoryl-PMMH[O(C$_6$H$_4$)CH=NN(CH$_3$)P(S)(Cl)$_2]_6$	6
55,170-8	3	powder	S=P(Cl)$_3$:(G=3);dendri Thiophosphoryl-PMMH[O(C$_6$H$_4$)CH=NN(CH$_3$)P(S)(Cl)$_2]_{12}$	12
55,172-4	4	powder	S=P(Cl)$_3$:(G=4);dendri Thiophosphoryl-PMMH[O(C$_6$H$_4$)CH=NN(CH$_3$)P(S)(Cl)$_2]_{24}$	24
55,174-0	5	powder	S=P(Cl)$_3$:(G=5);dendri Thiophosphoryl-PMMH[O(C$_6$H$_4$)CH=NN(CH$_3$)P(S)(Cl)$_2]_{48}$	48
Phosphorus Dendrimers with Hexachlorocyclotriphosphazene Core [PMMH= PhenoxyMethyl(MethylHydrazono)]				
Aldehyde Surface Groups				
55,201-1	0.5	powder	N$_3$P$_3$(O(C$_6$H$_4$)CHO)$_6$	6
55,206-2	1.5	powder	N$_3$P$_3$(Cl)$_6$:(G=1.5);dendri Thiophosphoryl-PMMH[O(C$_6$H$_4$)CHO]$_{12}$	12
55,213-5	2.5	powder	N$_3$P$_3$(Cl)$_6$:(G=2.5);dendri Thiophosphoryl-PMMH[O(C$_6$H$_4$)CHO]$_{24}$	24
55,211-9	3.5	powder	N$_3$P$_3$(Cl)$_6$:(G=3.5);dendri Thiophosphoryl-PMMH[O(C$_6$H$_4$)CHO]$_{48}$	48
55,209-7	4.5	powder	N$_3$P$_3$(Cl)$_6$:(G=4.5);dendri Thiophosphoryl-PMMH[O(C$_6$H$_4$)CHO]$_{96}$	96
55,214-3	5.5	powder	N$_3$P$_3$(Cl)$_6$:(G=5.5);dendri Thiophosphoryl-PMMH[O(C$_6$H$_4$)CHO]$_{192}$	192
Dichlorophosphinothioyl Surface Groups				
55,205-4	1	powder	N$_3$P$_3$(O(C$_6$H$_4$)CHO)$_6$	6
55,207-0	2	powder	N$_3$P$_3$(Cl)$_6$:(G=2);dendri Thiophosphoryl-PMMH[O(C$_6$H$_4$)CH=NN(CH$_3$)P(S)(Cl)$_2]_{12}$	12
55,212-7	3	powder	N$_3$P$_3$(Cl)$_6$:(G=3);dendri Thiophosphoryl-PMMH[O(C$_6$H$_4$)CH=NN(CH$_3$)P(S)(Cl)$_2]_{24}$	24
55,210-0	4	powder	N$_3$P$_3$(Cl)$_6$:(G=4);dendri Thiophosphoryl-PMMH[O(C$_6$H$_4$)CH=NN(CH$_3$)P(S)(Cl)$_2]_{48}$	48
55,208-9	5	powder	N$_3$P$_3$(Cl)$_6$:(G=5);dendri Thiophosphoryl-PMMH[O(C$_6$H$_4$)CH=NN(CH$_3$)P(S)(Cl)$_2]_{96}$	96

* Manufactured by Dendritech, Inc. † Manufactured by Dendritic NanoTechnologies, Inc.

Dendrimers and Other Dendritic Polymers, J. Fréchet and D. Tomalia; John Wiley & Sons, 2002; Aldrich catalog number **Z51,403-9**

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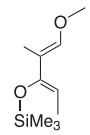
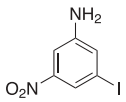
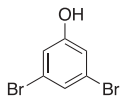
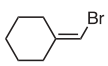
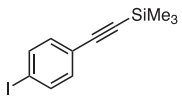
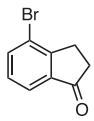
64,069-7
$C_{10}H_{20}O_2Si$

1g
5g

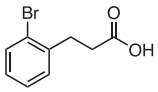
64,581-8
$C_6H_5IN_2O_2$

5g

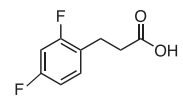
64,610-5
C_6H_4BrO

1g
10g

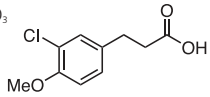
64,416-1
$C_7H_{11}Br$

1g
5g

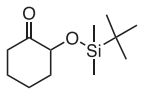
64,075-1
$C_{11}H_{13}ISi$

1g
5g

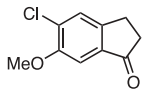
64,436-6
C_9H_7BrO

1g
5g

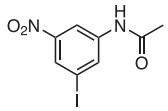
64,391-2
$C_9H_9BrO_2$

5g
25g

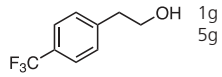
64,457-9
$C_9H_8F_2O_2$

1g
5g

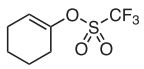
63,877-3
$C_{10}H_{11}ClO_3$

1g
5g

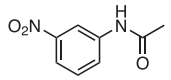
64,393-9
$C_{12}H_{24}O_2Si$

1g
10g

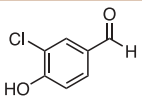
63,878-1
$C_{10}H_9ClO_2$

1g
5g

64,435-8
$C_8H_7IN_2O_3$

1g
10g

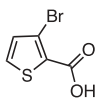
64,208-8
$C_9H_9F_3O$

1g
5g

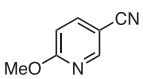
48,058-4
$C_7H_9F_3O_3S$

5g
25g

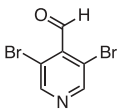
64,425-0
$C_8H_8N_2O_3$

5g
25g

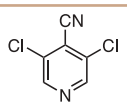
64,418-8
$C_7H_5ClO_2$

1g
5g

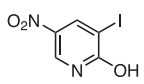
Heterocyclic Building Blocks

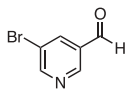
63,301-1
$C_5H_3BrO_2S$

5g
25g

64,225-8
$C_7H_6N_2O$

1g
5g

64,611-3
$C_6H_3Br_2NO$

1g
5g

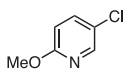
64,419-6
$C_6H_2Cl_2N_2$

1g
5g

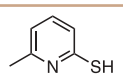
64,201-0
$C_5H_3IN_2O_3$

1g
10g

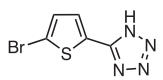
64,410-2
C_6H_4BrNO

1g
5g

63,985-0
$C_4H_5BrN_2$

1g
5g

64,296-7
C_6H_6ClNO

1g
10g

64,209-6
C_6H_7NS

1g
5g

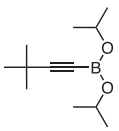
64,618-0
$C_5H_3BrN_4S$

1mL
5mL

50 wt. % solution in DMF

Boronic Acids and Esters

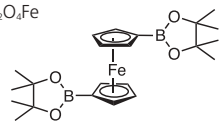
63,919-2

$C_{12}H_{23}BO_2$ 1g 5g



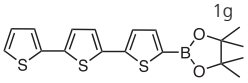
64,375-0

$C_{22}H_{32}B_2O_4Fe$ 1g 10g



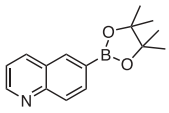
64,514-1

$C_{18}H_{19}BO_2S_3$ 500mg 1g



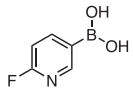
64,161-8

$C_{15}H_{18}BNO_2$ 1g 5g



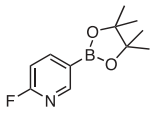
63,918-4

$C_5H_5BFNO_2$ 1g 5g



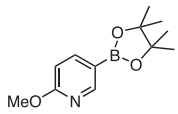
59,254-4

$C_{11}H_{15}BFNO_2$ 1g 5g



63,602-9

$C_{12}H_{18}BNO_3$ 1g 5g



63,805-6

$C_4H_9BO_2$ 1g 5g

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New Carbon Nanotubes from Aldrich

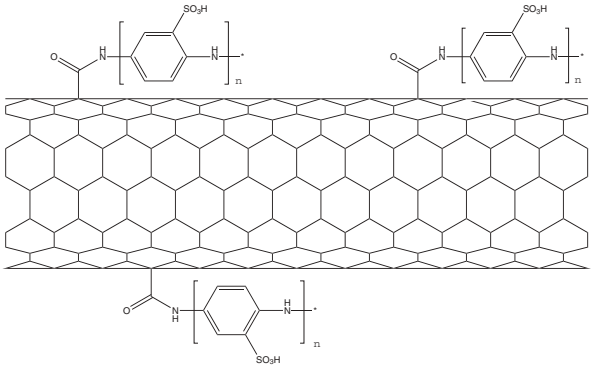
63,923-0 Polyaminobenzenesulfonic acid coated single-walled carbon nanotubes (35/65) 50mg

Single-walled carbon nanotubes coated in the water-soluble polymer polyaminobenzenesulfonic acid (PABS-SWNT)

- 65 wt. % polymer
- 70–85% SWNT purity (carbonaceous purity as determined in Itkis, M.E. et al. *Nano Lett.* **2003**, *3*, 309)
- Diam = 1.1 nm
- Length = 70–85 nm
- Solubility (determined by near-IR absorbance spectroscopy)
  - H_2O = 5.0 mg/mL
  - DMF = 0.1 mg/mL
  - Ethanol = 0.05 mg/mL

63,735-1 Double-walled carbon nanotubes (DWNT) 250mg 1g

- 50–80 wt. % DWNT
- 10–40 wt. % SWNT
- Outer diam = <5 nm
- Inner diam = 1.3–2.0 nm
- Length = 0.5–50 µm



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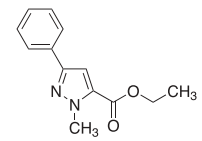
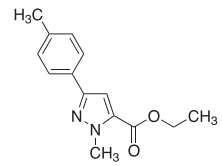
L20,136-7

$C_{13}H_{14}N_2O_2$
MW 230.27
250mg



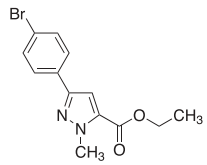
L20,137-5

$C_{14}H_{16}N_2O_2$
MW 244.30
250mg



L20,138-3

$C_{13}H_{13}BrN_2O_2$
MW 309.16
250mg



L23,277-7

$C_{14}H_{12}N_2O$
MW 224.26
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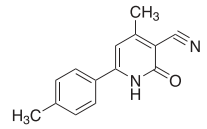

L23,279-3

$C_{13}H_9BrN_2O$
MW 289.13
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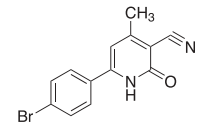
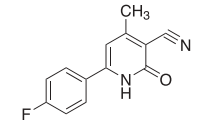


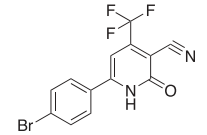
L23,280-7

$C_{13}H_9FN_2O$
MW 228.23
250mg



L23,285-8

$C_{13}H_6BrF_3N_2O$
MW 343.10
250mg



L23,287-4

$C_{14}H_9F_3N_2O_2$
MW 294.24
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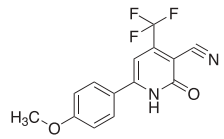

L23,306-4

$C_{11}H_9F_3N_2O$
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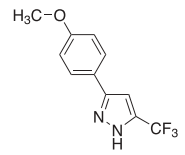
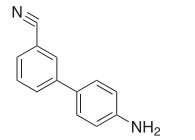


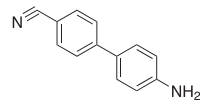
L30,068-3

$C_{13}H_{10}N_2$
MW 194.24
500mg



L30,069-1

$C_{13}H_{10}N_2$
MW 194.24
500mg



L30,070-5

$C_{13}H_{10}N_2$
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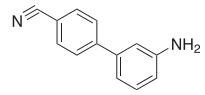
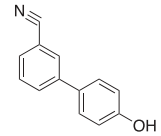
500mg



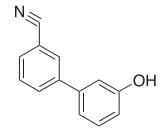
L30,071-3

$C_{13}H_9NO$
MW 195.22
500mg



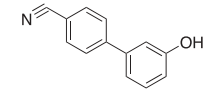
L30,072-1

$C_{13}H_9NO$
MW 195.22
500mg



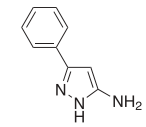
L30,074-8

$C_{13}H_9NO$
MW 195.22
500mg



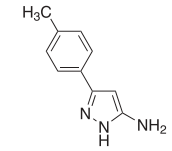
L31,783-7

$C_9H_9N_3$
MW 159.19
250mg



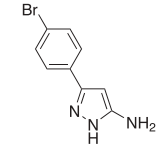
L31,784-5

$C_{10}H_{11}N_3$
MW 173.22
250mg



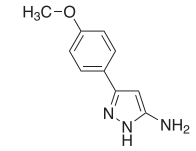
L31,786-1

$C_9H_8BrN_3$
MW 238.09
250mg



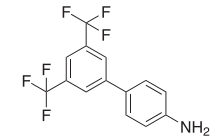
L31,788-8

$C_{10}H_{11}N_3O$
MW 189.22
250mg



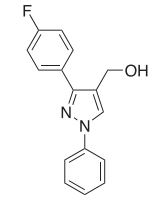
L44,655-6

$C_{14}H_9F_6N$
MW 305.22
250mg



L45,046-4

$C_{16}H_{13}FN_2O$
MW 268.29
250mg



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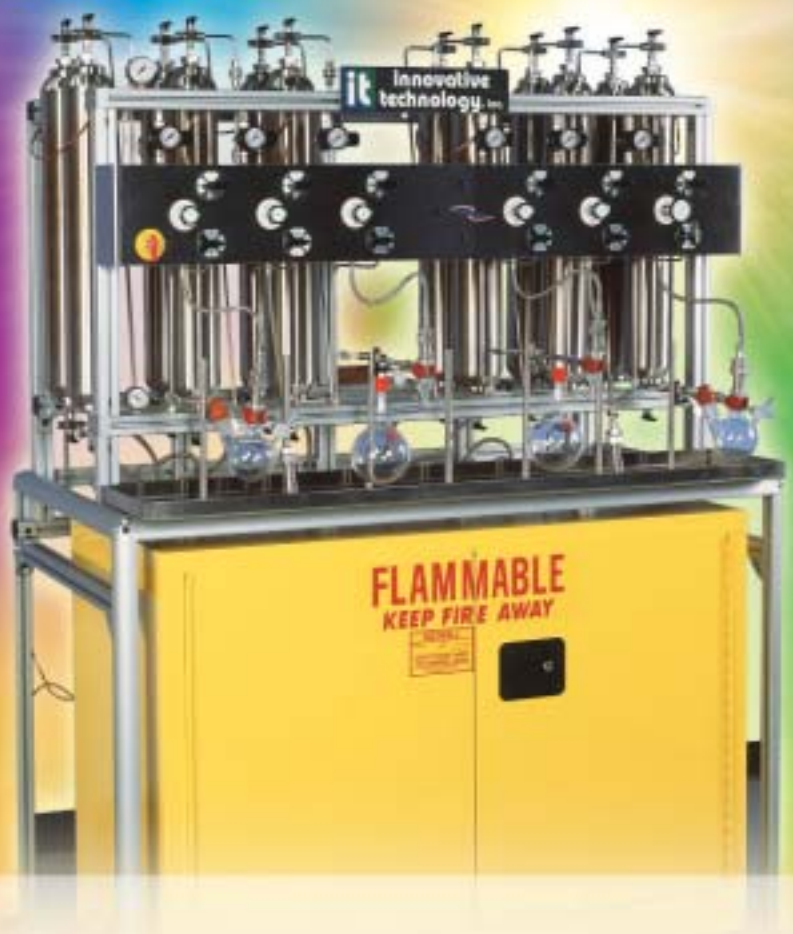

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Recent Advances in Microwave-Assisted Synthesis

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Outline

1. A Brief Review of Microwave Theory

The use of microwave irradiation in organic synthesis has become increasingly popular within the pharmaceutical and academic arenas, because it is a new enabling technology for drug discovery and development.[1] By taking advantage of this efficient source of energy, compound libraries for lead generation and optimization can be assembled in a fraction of the time required by classical thermal methods.

Presently, thermally driven organic transformations take place by either of two ways: conventional heating or microwave-accelerated heating. In the first way, reactants are slowly activated by a conventional external heat source. Heat is driven into the substance, passing first through the walls of the vessel in order to reach the solvent and reactants. This is a slow and inefficient method for transferring energy into the reacting system. In the second way, microwaves couple directly with the molecules of the entire reaction mixture, leading to a rapid rise in temperature. Since the process is not limited by the thermal conductivity of the vessel, the result is an instantaneous localized superheating of any substance that will respond to either dipole rotation or ionic conduction—the two fundamental mechanisms for transferring energy from microwaves to the substance(s) being heated.[1a]

The rate of a reaction is determined by the Arrhenius equation ($k = Ae^{-Ea/RT}$), where T is the absolute temperature that controls the kinetics of the reaction. In conventionally heated reactions, this temperature is a bulk temperature (T_B). Microwave-assisted reactions are different. Microwave irradiation will directly activate most molecules that possess a dipole or are ionic. Since energy transfer occurs in less than a nanosecond (10^{-9} s), the molecules are unable to completely relax (~ 10^{-5} s) or reach equilibrium. This creates a state of nonequilibrium that results in a high instantaneous temperature (T_i) of the molecules and is a function of microwave power input. The instantaneous temperature is not directly measurable, but it is much greater than the measured T_B ($T_i >> T_B$). Thus, the greater the intensity of microwave power being administered to a chemical reaction, the higher and more consistent T_i will be. A precedence exists where the concept of instantaneous temperatures has been used to explain reactions occurring at a lower bulk temperature than expected, while using microwave irradiation.[2] In addition, in ultrasonic chemistry, extremely high and immeasurable temperatures are created that enhance the rates of chemical reactions by up to 1 million times.[3] The instantaneous temperature (T_i), not T_B, ultimately determines the kinetics of microwave reactions.

Based on experimental data from numerous studies that have been performed over the past ten years, chemists have found that microwave-enhanced chemical reaction rates can be faster than those of conventional heating methods by as much as 1,000-fold.[1] Assuming a standard first-order rate law (rate = k[A]), the Arrhenius rate equation has been used to calculate the instantaneous temperatures required to get three different reaction enhancements (10-, 100-, and 1,000-fold). The assumption was based on a desired reaction bulk temperature of 150 °C and an activation energy of 50 kcal/mol for the transformation. For a 10-fold rate increase, it was determined that a temperature enhancement of only 17 °C would be needed, relative to a bulk temperature of 150 °C. Microwave energy can provide that temperature increase instantly. Likewise, for a 100-fold rate increase, the instantaneous temperature would have to reach 185 °C—approximately a 35 °C increase over the bulk temperature. A 1000-fold enhancement would need a 56 °C increase over T_B. These instantaneous temperatures are very consistent with the temperatures that would be expected in a microwave system and are directly responsible for the enhancements in reaction rates and yields.[1m]

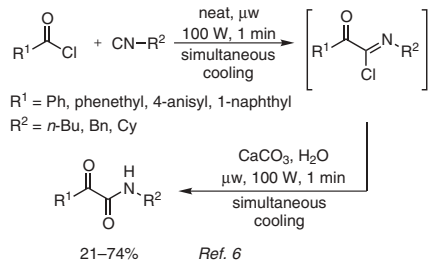
2. Enhanced Microwave Synthesis (EMS)

Recently, an alternative method for performing microwave-assisted organic reactions, termed "Enhanced Microwave Synthesis" (EMS), has been examined.[4] By externally cooling the reaction vessel with compressed air, while simultaneously administering microwave irradiation, more energy can be directly applied to the reaction mixture. In "Conventional Microwave Synthesis" (CMS), the initial microwave power is high, increasing the bulk temperature (T_B) to the desired set point very quickly. However, upon reaching this temperature, the microwave power decreases or shuts off completely in order to maintain the desired bulk temperature without exceeding it. When microwave irradiation is off, classical thermal chemistry takes over, losing the full advantage of microwave-accelerated synthesis. With CMS, microwave irradiation is predominantly used to reach T_B faster. Microwave enhancement of chemical reactions will only take place during application of microwave energy.[5] This source of energy will directly activate the molecules in a chemical reaction; therefore, it is not desirable to suppress its application. EMS ensures that a high, constant level of microwave energy is applied.

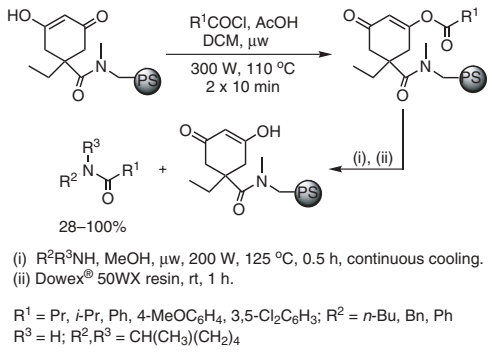
Research published very recently in leading organic synthesis journals supports the use of simultaneous cooling of reactions being heated by microwave energy.[6–8] Simultaneous cooling enables a greater amount of microwave energy to be introduced into a reaction, while keeping the reaction temperature low. This results in significantly greater yields and cleaner chemistries. EMS was employed in the synthesis of a variety of α-keto amides to support a protease inhibitor discovery project. This may eventually lead to improved treatments for stroke, Alzheimer's disease, and muscular dystrophy.[6] Following an earlier protocol from the 1960s, the authors coupled acyl chlorides with various isonitriles. α-Keto imidoyl chloride intermediates were formed, which were then converted to the α-keto amides upon hydrolysis **(Scheme 1)**. Under conventional heating conditions, this took between 2 to 6 hours for completion; whereas under optimized EMS conditions, the two steps were completed in 2 min and in 21–74% yields.

EMS has also been beneficial in producing higher release levels of the desired amides from the solid-phase resin, as compared with microwave heating alone **(Scheme 2)**.[7]

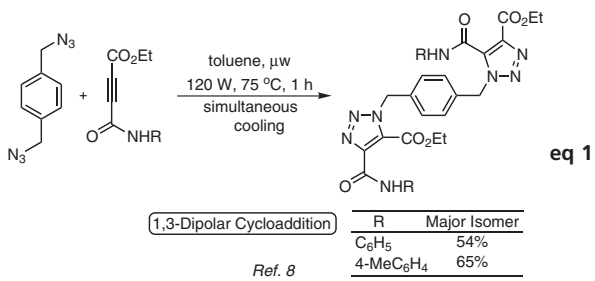
More recently, Katritzky et al. illustrated the advantages of EMS in preparing bistriazoles by the 1,3-dipolar cycloaddition reactions of 1,4-bis(azidomethyl)benzene with monoacetylenes.[8] When reacting the diazide with a carbamoylpropiolate at 120 W and 55 °C for 30 minutes, cycloaddition only occurred at one of the azido moieties. Higher temperatures and irradiation powers resulted in decomposition. By using EMS for the reaction between the diazide and butynoate at 120 W and 75 °C for 1 hour, the Katritzky group successfully synthesized the bistriazole **(eq 1)**. The major isomer was isolated in 54–65% yields.



Scheme 1. Improved Synthesis of α-Keto Amides by Enhanced Microwave Synthesis (EMS).

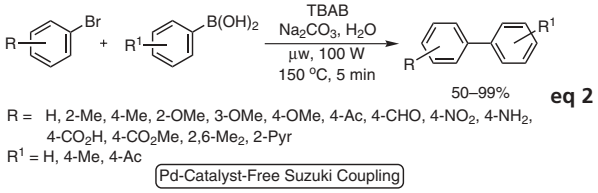


Scheme 2. Improved Release Levels of Amides from Resin by EMS.



R	Major Isomer
C_6H_5	54%
4-MeC_6H_4	65%

eq 1



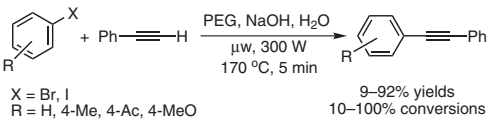
eq 2

3. New Synthetic Applications

The recent publication of several major reviews on microwave-assisted organic synthesis notwithstanding,[1a,b,l] a plethora of very recent articles describing a variety of new chemistries performed with microwave irradiation have appeared. This section will document many of these synthetic applications. **Table 1**, at the end of this section, provides an in-depth summary of the wide range of microwave-assisted applications that are not discussed here in detail.[2,4,5e,6–246]

In organometallic chemistry, two of the most phenomenal recent discoveries are transition-metal-free Suzuki and Sonogashira couplings.[9] Leadbeater and coworkers have shown that reacting an activated aryl bromide with an arylboronic acid in water, using tetrabutylammonium bromide (TBAB) as a phase-transfer catalyst, results in a successfully coupled biaryl Suzuki product without the aid of a palladium catalyst **(eq 2)**.[9b] In addition, a transition-metal-free Sonogashira reaction between an aryl bromide or iodide and phenylacetylene results in respectable yields **(eq 3)**.[9c] In this case, poly(ethylene glycol) is used as the phase-transfer agent.

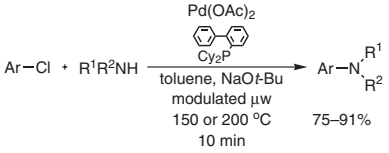
Buchwald–Hartwig chemistry has become a powerful method for synthesizing arylamines. Conventionally, this reaction requires high temperatures and long reaction times. Many fast and highly efficient applications have been developed in conjunction with



eq 3

Transition-Metal-Free Sonogashira Reaction

Ref. 9c

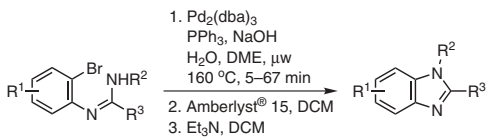


eq 4

R^1 = H, Me; R^2 = Ph, 4-tolyl; R^1R^2 = $(CH_2)_2O(CH_2)_2$
Ar = 2-pyridinyl, 3-pyridinyl, 2-quinolinyl, 2-pyrazinyl, 4-tolyl, 2-anisyl

Intermolecular Buchwald–Hartwig Amination of Aryl Chlorides

Ref. 11

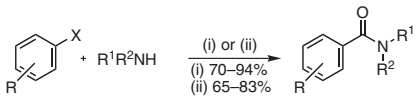


eq 5

R^1 = 3-Me, 5-H, 5-OMe, 5-NO_2
R^2 = Me, *i*-Pr, Ph
R^3 = Me, Ph

Intramolecular Buchwald–Hartwig Amination of Aryl Bromides

Ref. 10

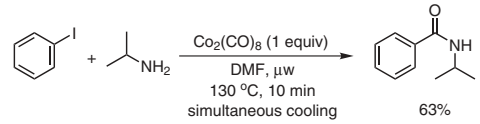


eq 6

(i) $Pd(OAc)_2$, dppf, imidazole, KO*t*-Bu, DMF
μw, 180–190 °C, 15–20 min (*Ref. 21*).
(ii) [Pd], K_2CO_3(aq), $Mo(CO)_6$, diglyme, μw, 150 °C, 15 min (*Ref. 19*).

(i) X = Br; R = H, 2-Me, 4-Me, 4-MeO
R^1R^2NH = aniline, benzylamine, morpholine.
(ii) X = Br, I; R = 4-Me, 4-MeO, 4-CF_3, 4-Ac
R^1R^2NH = *n*-$BuNH_2$, piperidine.

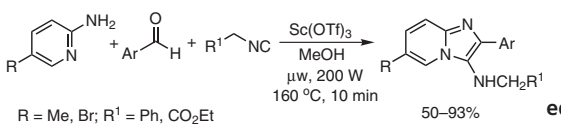
Pd-Catalyzed Amidation Using in situ Generated CO



eq 7

Palladium-Free Amidation Using $Co_2(CO)_8$ as the Only CO Source

Ref. 22a



eq 8

R = Me, Br; R^1 = Ph, CO_2Et
Ar = 2-pyridinyl, 2-naphthyl

A Three-Component Ugi Reaction

Ref. 24

microwave irradiation.[10–16] One interesting example is the palladium-catalyzed amination of (azahetero)aryl chlorides. Aryl chlorides are known to be quite unreactive due to the C–Cl bond strength, but with microwave heating for 10 minutes, these aminations proceed nicely **(eq 4)**.[11] **Equation 5** shows a microwave-assisted, improved intramolecular amination of aryl bromides to benzimidazoles.[10]

Another organometallics area of interest is carbonyl-insertion reactions. Multiple examples of palladium-catalyzed ester synthesis,[17] both palladium-[18–21] and nonpalladium[22]-facilitated amidations, and diaryl ketone synthesis[23] have been published. Carbon monoxide can be generated in situ by reaction of a formamide with potassium *t*-butoxide, or it can be generated from metal carbonyl complexes such as $Mo(CO)_6$ or $Co_2(CO)_8$. **Equation 6** illustrates palladium-catalyzed amidations using both carbon monoxide sources.[18–21] Using EMS, an amidation was successfully executed directly from an aryl halide and an amine with only $Co_2(CO)_8$ and no palladium catalyst or additional CO source **(eq 7)**.[22] To the author's knowledge, this has never been achieved with either CMS or conventional heating.

One-pot, multicomponent reactions receive much attention because of their efficient access to complex molecules. In the past year or so, there have been many different microwave-assisted multicomponent applications examined. Some of these include Ugi,[24,25] Mannich,[26–29] and other heterocycle-forming reactions.[30–51] The Ugi condensation can be either a three-component or a four-component, one-pot reaction. A three-component example—utilizing a 2-aminopyridine, an aldehyde, and an isocyanide—successfully leads to fused 3-aminoimidazoles in 10 minutes under microwave irradiation **(eq 8)**.[24] Ugi reaction products are generally difficult to purify at the end of the reaction because of the multiple reactants. When one reagent is attached to a solid-phase resin, however, the purification bottleneck is removed. **Scheme 3** shows a four-component Ugi reaction example in which the solid-phase resin acts as a protecting group for one of the amino groups on the diaminobenzene. After the condensation is completed, cleavage of the resin with trifluoroacetic acid (TFA) provides a primary amine that can then undergo cyclization to form the quinoxalinone ring system. By changing either the isocyanide or the aldehyde component, a diverse library can be synthesized.[25]

Mannich reactions are some of the best methods to synthesize β-amino ketones. This one-pot, three-component condensation traditionally utilizes a substituted methyl ketone, an aldehyde, and an amine. In the Petasis boronic-Mannich reaction, the methyl ketone is replaced with a boronic acid and the aldehyde components most commonly used are glyoxylic acid and salicylaldehyde. This yields α-amino acids and aminoalkylphenols, respectively. **Equation 9** illustrates a microwave-assisted, boronic-Mannich reaction run in dichloromethane at 120 °C for 10 minutes.[26] Reaction of glyoxylic acid with different boronic acids and amines provided moderate-to-good yields.

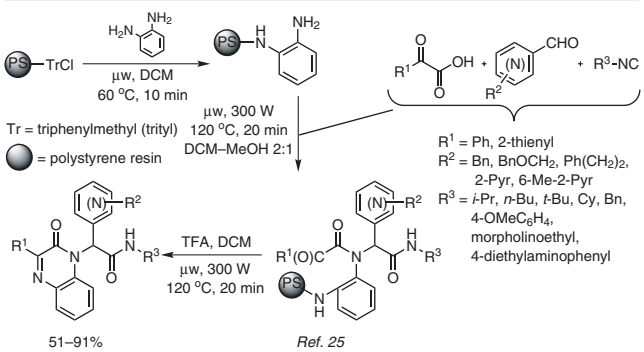
Ring-closing metathesis (RCM) has become a powerful synthetic tool for the construction of ring systems. Utilizing Grubbs' catalyst (a metal carbene complex) carbon-, oxygen-, nitrogen-, and sulfur-containing dienes can cyclize to form functionalized cycloalkenes. When carried out conventionally, this reaction can be plagued by long reaction times, and it can also have limited success due to unfavorable substitution patterns. Use of microwave irradiation has allowed greatly enhanced reaction and conversion rates, as well as opened up new, previously inaccessible, ring-system possibilities.[52–57] **Equation 10** illustrates a survey of microwave-assisted RCM reactions in both solvent and solvent-free conditions.[54]

Table 1. Recent Applications of Microwave-Assisted Organic Synthesis

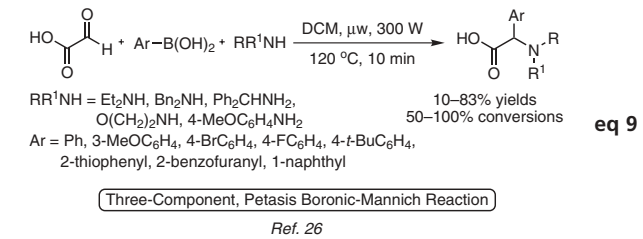
Reaction Type	Reference No.
Alkylations, Acetylations	36,60,83–93
Asymmetric Reactions	58–60,83,85,94
Carbohydrates	92,95–99
CO Insertions	17–24
Condensations	28–31,100–104
Cyanations	105–111
Cycloadditions	8,76,107,112–119,127c,g,128,224
Heterocycle Synthesis	5e,8,25–27,32–57,72,74,76,78,79,81,101,107,108, 112, 114,116,118,120–150
Reactions Involving Ionic Liquids	41,105c,127g,151–161
Michael Reactions	94,127f,162–165
Multicomponent Synthesis	25–51
Nucleoside Synthesis	49,166–169
General Organometallics	17–24,52–57,60,80,83,85,115,127d,170–179
Buchwald-Hartwig	10–16
Heck, Suzuki, Sonogashira	9,116,161,166b,180–184
Fischer Carbenes	185
Pauson-Khand	186–188
Oxidations	189–196
Peptides, Proteins	2,197–203
Photochemistry	65,170,204–205
Polymers	61,63,64,67,68,70,206–212
Protections/Deprotections	213–217
Radicals	61–70
Rearrangements	69,99,153,194,200b,218–223
Ring-Closing Metathesis (RCM)	52–57
Scavengers	7,73,127a,b,224
Simultaneous Cooling (EMS)	4,6,7,8
Solid-Phase Reactions	7,18,23,26,39,42,67,71–82,93b,100,123e,125, 127b,e,133,168,197,198a,b,202,225–231
Solvent-Free Reactions	31,33,34,48–50,84,89,91,98,102,104,122,128, 131,132,135,136,139,142,145,191,192,195,196
C–H Bond Activation	232
Dye Synthesis	233,234
Halide Exchange	235
Halogenation	166a,236–238
Macrocycles	58,59
Nitration	239,240
SNAr	241
Phosgenation	242
Polymerase Chain Reaction (PCR)	243
Trypsin Digestion	244
Wittig Reaction	245,246

Macrocyclic ring systems are of key interest to many natural product chemists. One emerging area for these chemists is library synthesis of diversity-oriented templates that resemble natural products. These molecules can have therapeutic potential that is greater than the natural products themselves. Microwave-assisted asymmetric macrocyclic syntheses provide a fast and efficient route to these compounds.[58–60] Utilizing a distannoxane catalyst, an effective, microwave-assisted (200 °C, 7 min) cyclodimerization of a chiral hydroxy ester led to a 60% yield of the macrodiolide product **(eq 11)**.[58]

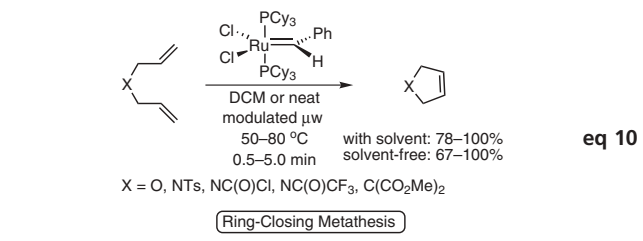
There are many organic transformations that proceed via radical chemistry. As chemists wonder if microwave irradiation can promote radical formation, microwave-assisted free-radical chemistry is increasingly being explored.[61–70] **Scheme 4** shows a microwave-assisted, tin-free, radical carboaminoxylation of substituted alkenes by the persistent radical effect (PRE).[62] Mechanistically, the alkoxyamine generates 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO) and a stable malonyl radical, which subsequently reacts with the alkene. Diverse malonates were synthesized in 10 minutes in DMF at 180 °C.



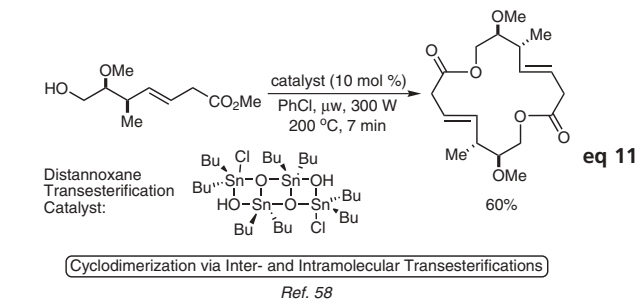
Scheme 3. A Four-Component Ugi Reaction Facilitated by Microwave Irradiation.



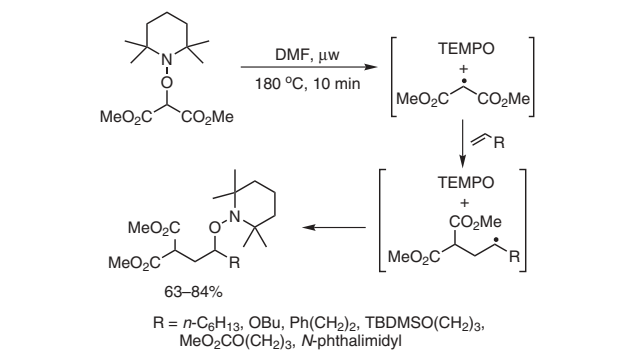
eq 9



eq 10



eq 11



Scheme 4. Tin-Free, Radical Carboaminoxylation of Substituted Alkenes.

As shown earlier in this section, microwave irradiation is very applicable not only to solution-phase chemistry, but also to solid-phase organic synthesis.[7,26,39,42,71–82] There are many different supports, including polystyrene (PS), polyamide, poly(ethylene glycol)–polystyrene (PEG-PS) graft resins, poly(ethylene glycol)–polyacrylamide (PEGA) resins, and even silica, to name a few. The choice of resin depends on its chemical and physical properties with respect to the particular chemistry to be performed. One interesting application is the use of cellulose beads for preparing pyrazole and isoxazole libraries. Cellulose swells nicely in both polar and aqueous solvents and is biodegradable. **Scheme 5** shows a two-step, open-vessel application, which produces excellent yields of the corresponding heterocycles.[74]

4. Use of Microwave Irradiation in Biochemical Applications

Microwave irradiation is fast becoming a source of energy for biochemical applications. The hesitancy of its onset, compared to organic synthesis, is most likely due to the high temperatures associated with microwave-assisted transformations. Many of the biochemical molecules are temperature-sensitive. Now, with current technology, temperatures as low as 35–40 °C can be maintained by precise power input (additional accessories allow temperatures as low as –100 °C[247]), which permits a much wider range of chemistries to be explored. At present, there have been relevant studies published on carbohydrates,[92,95–99] nucleosides[49,166–169] peptides,[197–200,203] proteins,[2,201] peptoids,[202] the polymerase chain reaction (PCR),[243] and trypsin digestion.[244]

It is well documented that microwave irradiation is applicable to solid-phase synthesis (see references in Table 1). The majority of peptide synthesis is performed on a solid phase, and it has been shown that microwave irradiation can enhance deprotection, coupling, and cleavage reactions.[197,198a,b] Traditionally, solid-phase peptide synthesis (SPPS) is run at room temperature and can be very time consuming. It is also plagued with inherent difficulties due to intermolecular aggregation, β-sheet formation, steric hindrance from protecting groups, and premature termination of the sequence. Microwave-assisted peptide synthesis, that is run at elevated temperatures up to 60 °C, enhances coupling rates and efficiency in difficult sequences due to the thermal disruption of peptide aggregation.[197] **Scheme 6** shows the microwave-assisted synthesis of the well-known acyl carrier peptide, ACP (65–74), which was initiated on a preloaded, glycine-functionalized, Fmoc-Wang resin.[197] After conventional cleavage, the peptide was recovered in greater than 95% yield.

The onset of proteomics has created a huge need for protein-binding molecules. Building libraries of protein-like compounds has become an increasingly important goal. Unlike native proteins, peptidomimetic compounds are resistant to proteases and other modifying enzymes. Peptoids, one class of these molecules, are oligo(*N*-alkylglycines). They differ from peptides in that the side chain is connected to the amide nitrogen rather than the α-carbon atom. Standard methods for peptoid synthesis require long coupling times. With microwave irradiation, each coupling is reduced to 1 minute (**Scheme 7**).[202] Upon cleavage, both homo- and hetero-oligomers are synthesized with respectable yields varying between 43 and 95%.

Another area of biochemical interest is nucleoside chemistry. These important monomers make up nucleic acids, or DNA and RNA. The synthesis of nucleosides can assist in the development of therapeutic drugs, be used as precursors to fluorescent compounds for automated DNA synthesis, and facilitate the determination of nucleic acid metabolism. The hydroxymethyl-

ation of uracil rings with paraformaldehyde is one microwave-assisted application, which gives excellent yields (> 93%) in only 3 minutes **(Scheme 8)**.[167]

Carbohydrate chemistry is another area that can benefit from microwave irradiation. Carbohydrates are notoriously heat-sensitive. Carbohydrate derivatives are valuable intermediates in the synthesis of diverse natural products and their analogues. **Scheme 9** shows an example of an efficient route to 1,6-anhydrosugars via microwave irradiation.[98] Performing this reaction under solvent-free conditions leads to respectable yields (45–80%) in 7 minutes.

5. Conclusions and Future Trends

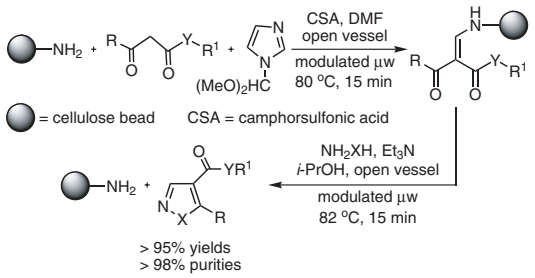
Microwave technology is emerging as an alternative energy source powerful enough to accomplish chemical transformations in minutes, instead of hours or even days. For this reason, microwave irradiation is presently seeing an exponential increase in acceptance as a technique for enhancing chemical synthesis. A growing number of investigators are adopting microwave-assisted synthesis as a means to increase their productivity.

Enhanced Microwave Synthesis (EMS) provides the ability to cool a reaction vessel externally while simultaneously administering microwave irradiation, allowing more energy to be directly applied to a chemical reaction. A higher microwave power input results in substantially enhanced chemistry while maintaining a desired bulk temperature (T_B). Reactions with large activation energies will benefit greatly from this new technology. In addition, as seen in the previous section, a whole new arena of biochemical applications can now be explored.

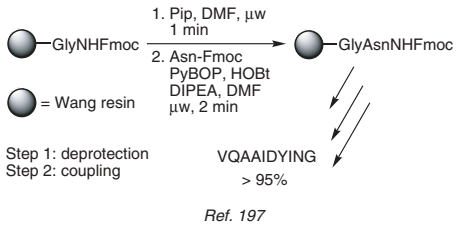
The obvious next step in microwave technology is scale-up for chemical development. Scaling up syntheses from gram quantities to kilograms is essential for drug development, as this is a discouraging bottleneck for present-day process chemists. Many milligram- and gram-scale syntheses cannot be replicated, or even attempted for safety reasons, on larger scales. Development chemists often must start from the beginning. Microwave technology provides the possibility that the same chemistries used in the initial route can be safely scaled up, enabling chemists to spend their valuable time creating novel synthetic methods, not recreating them.

Instrumentation is currently available for kilogram-scale synthesis. One application area that is being examined for scale-up microwave-assisted synthesis is flow-through technology. This allows for the continuous reaction of reagents and, therefore, the continuous on-line production of material. Another parallel technology involves a stop-flow process. Reagents are pumped into a vessel as a batch, reacted, and then pumped out into a collection container. This cycle is repeated as necessary to achieve the scale desired. This, too, allows for a continuous production of material. These two types of systems would allow the pharmaceutical laboratory to produce large quantities of final products in a safe and efficient manner. As a result, the process chemist would have access to all of the advantages of microwave synthesis without having to forfeit the scale of material production that is needed.

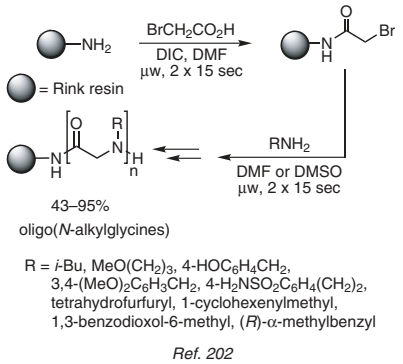
Clearly, microwave irradiation has emerged as a powerful tool for organic synthesis. In concert with a rapidly expanding applications base, microwave synthesis can be effectively applied to any type of chemistry, resulting in faster reaction times and improved product yields. In addition, microwave synthesis creates new possibilities in performing chemical reactions. Because microwaves can transfer energy directly to the reactive species, they can promote transformations that are currently not possible



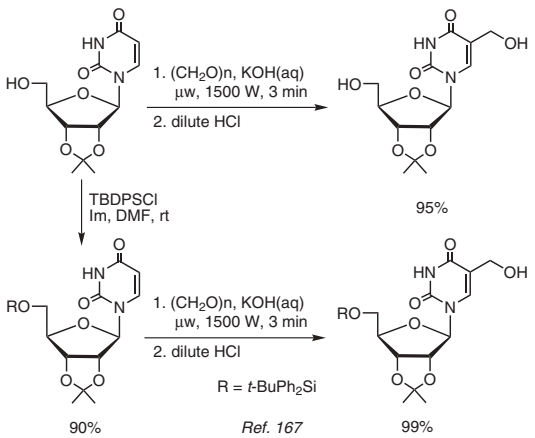
Scheme 5. Microwave-Assisted, Regiospecific, Solid-Phase Library Synthesis of Pyrazoles and Isoxazoles.



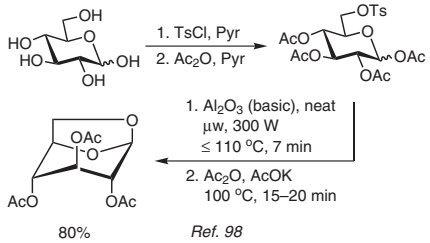
Scheme 6. Microwave-Assisted, Solid-Phase Synthesis of the Acyl Carrier Peptide, ACP (65-74).



Scheme 7. Microwave-Assisted, Solid-Phase Synthesis of Peptoids.



Scheme 8. Microwave-Assisted Hydroxymethylation of the Uracil Ring.



Scheme 9. Microwave-Assisted Synthesis of 1,6-Anhydrosugars.

using conventional heat, creating a new realm in synthetic organic chemistry.

6. Acknowledgement

The author would like to thank E. Keller Barnhardt and Michelle Horn for their editorial contributions.

7. References

(†) Current address: EMD Biosciences, Inc.; 10394 Pacific Center Court; San Diego, CA 92121.

(1) (a) Hayes, B. L. *Microwave Synthesis: Chemistry at the Speed of Light*; CEM Publishing: Matthews, NC, 2002. (b) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225. (c) Larhed, M.; Hallberg, A. *Drug Discovery Today* **2001**, *6*, 406. (d) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199. (e) Bradley, D. *Modern Drug Discovery*, August 2001, p 32. (f) Fini, A.; Breccia, A. *Pure Appl. Chem.* **1999**, *71*, 573. (g) Sridar, V. *Curr. Sci.* **1998**, *74*, 446. (h) Majetich, G.; Wheless, K. In *Microwave-Enhanced Chemistry: Fundamentals, Sample Preparation, and Applications*; Kingston, H. M., Haswell, S. J., Eds.; American Chemical Society: Washington, DC, 1997; Chapter 8. (i) Caddick, S. *Tetrahedron* **1995**, *51*, 10403. (j) Majetich, G.; Hicks, R. *Radiat. Phys. Chem.* **1995**, *45*, 567. (k) Majetich, G.; Hicks, R. *J. Microw. Power Electromagn. Energy* **1995**, *30*, 27. (l) *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2002. (m) Collins, M. J., Jr. CEM Corporation, Matthews, NC. Unpublished work, 2001.

(2) De Pomerai, D. I.; Smith, B.; Dawe, A.; North, K.; Smith, T.; Archer, D. B.; Duce, I. R.; Jones, D.; Candido, E. P. M. *FEBS Lett.* **2003**, *543*, 93.

(3) Ultrasonic chemistry references: (a) Maynard, B. J. Sonochemistry. *Chemistry*, Summer 2000, 17. (b) Suslick, K. S. The Chemistry of Ultrasound. In *The Yearbook of Science and the Future 1994*; Encyclopedia Britannica: Chicago, 1994; pp 138–55 (available online at the Suslick Research Group Home Page, http://www.scs.uiuc.edu/~suslick/britannica.html; accessed April 2004).

(4) Hayes, B. L.; Collins, M. J. World Patent WO 04002617, January 8, 2004.

(5) (a) Vass, A.; Dudás, J.; Varma, R. S. *Tetrahedron Lett.* **1999**, *40*, 4951. (b) Perreux, L.; Loupy, A.; Volatron, F. *Tetrahedron* **2002**, *58*, 2155. (c) Loupy, A.; Monteux, D.; Petit, A.; Aizpurua, J. M.; Domínguez, E.; Palomo, C. *Tetrahedron Lett.* **1996**, *37*, 8177. (d) Hajipour, A. R.; Mallakpour, S. E.; Afrousheh, A. *Tetrahedron* **1999**, *55*, 2311. (e) Frère, S.; Thiéry, V.; Besson, T. *Tetrahedron Lett.* **2001**, *42*, 2791. (f) Vega, J. A.; Vaquero, J. J.; Alvarez-Builla, J.; Ezquerra, J.; Hamdouchi, C. *Tetrahedron* **1999**, *55*, 2317. (g) Chatti, S.; Bortolussi, M.; Loupy, A. *Tetrahedron* **2000**, *56*, 5877. (h) Díaz-Ortiz, A.; Prieto, P.; Loupy, A.; Abenhaïm, D. *Tetrahedron Lett.* **1996**, *37*, 1695. (i) Limousin, C.; Cléophax, J.; Loupy, A.; Petit, A. *Tetrahedron* **1998**, *54*, 13567. (j) Bougrin, K.; Loupy, A.; Petit, A.; Daou, B.; Soufiaoui, M. *Tetrahedron* **2001**, *57*, 163. (k) Paul, S.; Gupta, M.; Gupta, R.; Loupy, A. *Tetrahedron Lett.* **2001**, *42*, 3827. (l) Kabza, K. G.; Chapados, B. R.; Gestwicki, J. E.; McGrath, J. L. *J. Org. Chem.* **2000**, *65*, 1210. (m) Laurent, R.; Laporterie, A.; Dubac, J.; Berlan, J.; Lefeuvre, S.; Audhuy, M. *J. Org. Chem.* **1992**, *57*, 7099.

(6) Chen, J. J.; Deshpande, S. V. *Tetrahedron Lett.* **2003**, *44*, 8873.

(7) Humphrey, C. E.; Easson, M. A. M.; Tierney, J. P.; Turner, N. J. *Org. Lett.* **2003**, *5*, 849.

(8) Katritzky, A. R.; Zhang, Y.; Singh, S. K.; Steel, P. J. *Arkivoc* [Online] **2003**(xv), 47; http://www.arkat-usa.org/ark/journal/2003/general_part(xv)/03-912A/03-912A.htm (accessed March 2004).

(9) (a) Leadbeater, N. E.; Marco, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1407. (b) Leadbeater, N. E.; Marco, M. *J. Org. Chem.* **2003**, *68*, 5660. (c) Leadbeater, N. E.; Marco, M.; Tominack, B. J. *Org. Lett.* **2003**, *5*, 3919.

(10) Brain, C. T.; Steer, J. T. *J. Org. Chem.* **2003**, *68*, 6814.

(11) Maes, B. U. W.; Loones, K. T. J.; Lemière, G. L. F.; Dommisse, R. A. *Synlett* **2003**, 1822.

(12) McCarroll, A. J.; Sandham, D. A.; Titcomb, L. R.; de K. Lewis, A. K.; Cloke, F. G. N.; Davies, B. P.; de Santana, A. P.; Hiller, W.; Caddick, S. *Mol. Diversity* **2003**, *7*, 115.

(13) Shi, L.; Wang, M.; Fan, C.-A.; Zhang, F.-M.; Tu, Y.-Q. *Org. Lett.* **2003**, *5*, 3515.

(14) Ullrich, T.; Giraud, F. *Tetrahedron Lett.* **2003**, *44*, 4207.

(15) Wang, T.; Magnin, D. R.; Hamann, L. G. *Org. Lett.* **2003**, *5*, 897.

(16) Weigand, K.; Pelka, S. *Mol. Diversity* **2003**, *7*, 181.

(17) Georgsson, J.; Hallberg, A.; Larhed, M. *J. Comb. Chem.* **2003**, *5*, 350.

(18) Wannberg, J.; Larhed, M. *J. Org. Chem.* **2003**, *68*, 5750.

(19) Kaiser, N.-F. K.; Hallberg, A.; Larhed, M. *J. Comb. Chem.* **2002**, *4*, 109.

(20) Wan, Y.; Alterman, M.; Larhed, M.; Hallberg, A. *J. Comb. Chem.* **2003**, *5*, 82.

(21) Wan, Y.; Alterman, M.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2002**, *67*, 6232.

(22) (a) Hayes, B. L.; Barnhardt, E. K. CEM Corporation, Matthews, NC. Unpublished work, 2002. (b) Hayes, B. L. The Synergistic Effect of Applied Microwave Energy with Simultaneous Cooling. Presented at the 1st International Microwaves in Chemistry Conference, Gainesville, FL, March 9, 2003; Presentation No. 12.

(23) Enquist, P.-A.; Nilsson, P.; Larhed, M. *Org. Lett.* **2003**, *5*, 4875.

(24) Ireland, S. M.; Tye, H.; Whittaker, M. *Tetrahedron Lett.* **2003**, *44*, 4369.

(25) (a) Hayes, B. L. CEM Corporation, Matthews, NC. Unpublished work, 2003. (b) Hayes, B. L. New Developments in Microwave Chemistry for Enhancing Library Synthesis and Design. Presented at the IBC Design and Synthesis of Target-Based Compound Libraries Conference, San Diego, CA, December 10, 2003; Presentation No. 26.

(26) McLean, N. J.; Tye, H.; Whittaker, M. *Tetrahedron Lett.* **2004**, *45*, 993.

(27) Leadbeater, N. E.; Torenius, H. M.; Tye, H. *Mol. Diversity* **2003**, *7*, 135.
(28) Lehmann, F.; Pilotti, Å.; Luthman, K. *Mol. Diversity* **2003**, *7*, 145.
(29) Wang, L.; Li, P.-H. *Chin. J. Chem.* **2003**, *21*, 710.
(30) Choudhary, V. R.; Tillu, V. H.; Narkhede, V. S.; Borate, H. B.; Wakharkar, R. D. *Catal. Commun.* **2003**, *4*, 449.
(31) Kidwai, M.; Saxena, S.; Mohan, R.; Venkataramanan, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1845.
(32) Coleman, C. M.; MacElroy, J. M. D.; Gallagher, J. F.; O'Shea, D. F. *J. Comb. Chem.* **2002**, *4*, 87.
(33) Yadav, L. D. S.; Singh, A. *Synthesis* **2003**, 2395.
(34) Yadav, J. S.; Reddy, B. V. S.; Rao, R. S.; Naveenkumar, V.; Nagaiah, K. *Synthesis* **2003**, 1610.
(35) Azizian, J.; Mohammadi, A. A.; Karimi, A. R. *Synth. Commun.* **2003**, *33*, 415.
(36) Azizian, J.; Fallah-Bagher-Shaidaei, H.; Kefayati, H. *Synth. Commun.* **2003**, *33*, 789.
(37) Balalaie, S.; Hashemi, M. M.; Akhbari, M. *Tetrahedron Lett.* **2003**, *44*, 1709.
(38) Bora, U.; Saikia, A.; Boruah, R. C. *Org. Lett.* **2003**, *5*, 435.
(39) Dandia, A.; Arya, K.; Sati, M.; Sharma, R. *Heterocycl. Commun.* **2003**, *9*, 415.
(40) Devi, I.; Kumar, B. S. D.; Bhuyan, P. J. *Tetrahedron Lett.* **2003**, *44*, 8307.
(41) Fraga-Dubreuil, J.; Bazureau, J. P. *Tetrahedron* **2003**, *59*, 6121.
(42) Hoener, A. P. F.; Henkel, B.; Gauvin, J.-C. *Synlett* **2003**, 63.
(43) Laskar, D. D.; Prajapati, D.; Sandhu, J. S. *Indian J. Chem.* **2003**, *42B*, 135.
(44) Mont, N.; Teixidó, J.; Kappe, C. O.; Borrell, J. I. *Mol. Diversity* **2003**, *7*, 153.
(45) Mont, N.; Teixidó, J.; Borrell, J. I.; Kappe, C. O. *Tetrahedron Lett.* **2003**, *44*, 5385.
(46) Tu, S.-J.; Fang, F.; Miao, C.-B.; Jiang, H.; Shi, D.-Q. *Chin. J. Chem.* **2003**, *21*, 706.
(47) Vasquez, T. E., Jr.; Nixey, T.; Chenera, B.; Gore, V.; Bartberger, M. D.; Sun, Y.; Hulme, C. *Mol. Diversity* **2003**, *7*, 161.
(48) Yadav, L. D. S.; Singh, S. *Synthesis* **2003**, 63.
(49) Yadav, L. D. S.; Kapoor, R. *Tetrahedron Lett.* **2003**, *44*, 8951.
(50) Yadav, L. D. S.; Dubey, S.; Yadav, B. S. *Tetrahedron* **2003**, *59*, 5411.
(51) Zbruyev, O. I.; Stiasni, N.; Kappe, C. O. *J. Comb. Chem.* **2003**, *5*, 145.
(52) Yang, C.; Murray, W. V.; Wilson, L. J. *Tetrahedron Lett.* **2003**, *44*, 1783.
(53) Grigg, R.; Martin, W.; Morris, J.; Sridharan, V. *Tetrahedron Lett.* **2003**, *44*, 4899.
(54) Thanh, G. V.; Loupy, A. *Tetrahedron Lett.* **2003**, *44*, 9091.
(55) Garbacia, S.; Desai, B.; Lavastre, O.; Kappe, C. O. *J. Org. Chem.* **2003**, *68*, 9136.
(56) Mayo, K. G.; Nearhoof, E. H.; Kiddle, J. J. *Org. Lett.* **2002**, *4*, 1567.
(57) Varray, S.; Gauzy, C.; Lamaty, F.; Lazaro, R.; Martinez, J. *J. Org. Chem.* **2000**, *65*, 6787.
(58) Su, Q.; Beeler, A. B.; Lobkovsky, E.; Porco, J. A., Jr.; Panek, J. S. *Org. Lett.* **2003**, *5*, 2149.
(59) Chebanov, V. A.; Reidlinger, C.; Kanaani, H.; Wentrup, C.; Kappe, C. O.; Kollenz, G. *Supramol. Chem.* **2004**, *16*, 121.
(60) Belda, O.; Lundgren, S.; Moberg, C. *Org. Lett.* **2003**, *5*, 2275.
(61) Chen, G.; Zhu, X.; Cheng, Z.; Xu, W.; Lu, J. *Radiat. Phys. Chem.* **2004**, *69*, 129.
(62) Wetter, C.; Studer, A. *Chem. Commun.* **2004**, 174.
(63) Wang, Y. Z.; Zheng, X. X.; Chen, Z. F.; Zheng, C. Y. *J. Macromol. Sci., Part A: Pure Appl. Chem.* **2003**, *40*, 739.
(64) Cheng, Z.; Zhu, X.; Chen, M.; Chen, J.; Zhang, L. *Polymer* **2003**, *44*, 2243.
(65) Horikoshi, S.; Hidaka, H.; Serpone, N. *Chem. Phys. Lett.* **2003**, *376*, 475.
(66) Lamberto, M.; Corbett, D. F.; Kilburn, J. D. *Tetrahedron Lett.* **2003**, *44*, 1347.
(67) Wisnoski, D. D.; Leister, W. H.; Strauss, K. A.; Zhao, Z.; Lindsley, C. W. *Tetrahedron Lett.* **2003**, *44*, 4321.
(68) Xu, W.; Zhu, X.; Cheng, Z.; Chen, G.; Lu, J. *Eur. Polym. J.* **2003**, *39*, 1349.
(69) Durand-Reville, T.; Gobbi, L. B.; Gray, B. L.; Ley, S. V.; Scott, J. S. *Org. Lett.* **2002**, *4*, 3847.
(70) Porto, A. F.; Sadicoff, B. L.; Amorim, M. C. V.; de Mattos, M. C. S. *Polym. Testing* **2002**, *21*, 145.
(71) Al-Obeidi, F.; Austin, R. E.; Okonya, J. F.; Bond, D. R. S. *Mini-Rev. Med. Chem.* **2003**, *3*, 449.
(72) Dai, W.-M.; Guo, D.-S.; Sun, L.-P.; Huang, X.-H. *Org. Lett.* **2003**, *5*, 2919.
(73) (a) Baxendale, I. R.; Lee, A.-L.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1850. (b) Baxendale, I. R.; Ley, S. V.; Piutti, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 2194. (c) Baxendale, I. R.; Ley, S. V.; Nessi, M.; Piutti, C. *Tetrahedron* **2002**, *58*, 6285.
(74) De Luca, L.; Giacomelli, G.; Porcheddu, A.; Salaris, M.; Taddei, M. *J. Comb. Chem.* **2003**, *5*, 465.
(75) Erdélyi, M.; Gogoll, A. *J. Org. Chem.* **2003**, *68*, 6431.
(76) Kaval, N.; Van der Eycken, J.; Caroen, J.; Dehaen, W.; Strohmeier, G. A.; Kappe, C. O.; Van der Eycken, E. *J. Comb. Chem.* **2003**, *5*, 560.
(77) Longobardo, L.; Fierro, O.; Grieco, P.; Campiglia, P.; Novellino, E. *Biopolym.* **2003**, *71*, 343.
(78) Westman, J.; Lundin, R. *Synthesis* **2003**, 1025.
(79) Martin, B.; Sekljic, H.; Chassaing, C. *Org. Lett.* **2003**, *5*, 1851.
(80) Organ, M. G.; Mayer, S.; Lepifre, F.; N'Zemba, B.; Khatri, J. *Mol. Diversity* **2003**, *7*, 211.
(81) Rostamizadeh, S.; Tajik, H.; Yazdanfarahi, S. *Synth. Commun.* **2003**, *33*, 113.
(82) Porcheddu, A.; Giacomelli, G.; De Luca, L.; Ruda, A. M. *J. Comb. Chem.* **2004**, *6*, 105.
(83) Belda, O.; Moberg, C. *Acc. Chem. Res.* **2004**, *37*, 159.
(84) Wang, C.; Hang, T.; Zhang, H. *Synth. Commun.* **2003**, *33*, 451.
(85) Belda, O.; Moberg, C. *Synthesis* **2002**, 1601.
(86) Marwah, P.; Marwah, A.; Lardy, H. A. *Tetrahedron* **2003**, *59*, 2273.
(87) Salazar, J.; Lopez, S. E.; Rebollo, O. *J. Fluorine Chem.* **2003**, *124*, 111.
(88) Ameta, K. L.; Verma, B. L. *J. Indian Chem. Soc.* **2002**, *79*, 840.

(89) Paul, S.; Nanda, P.; Gupta, R.; Loupy, A. *Tetrahedron Lett.* **2002**, *43*, 4261.

(90) Hon, Y.-S.; Hsu, T.-R.; Chen, C.-Y.; Lin, Y.-H.; Chang, F.-J.; Hsieh, C.-H.; Szu, P.-H. *Tetrahedron* **2003**, *59*, 1509.

(91) Saidi, M. R.; Rajabi, F. *Phosphorus, Sulfur Silicon Relat. Elem.* **2003**, *178*, 2343.

(92) Singh, V.; Tiwari, A.; Tripathi, D. N.; Malviya, T. *Tetrahedron Lett.* **2003**, *44*, 7295.

(93) (a) Crosignani, S.; White, P. D.; Linclau, B. *Org. Lett.* **2002**, *4*, 2961. (b) Crosignani, S.; White, P. D.; Linclau, B. *Org. Lett.* **2002**, *4*, 1035.

(94) Camara, C.; Keller, L.; Dumas, F. *Tetrahedron: Asymmetry* **2003**, *14*, 3263.

(95) Singh, V.; Sethi, R.; Tewari, A.; Srivastava, V.; Sanghi, R. *Carbohydr. Polym.* **2003**, *54*, 523.

(96) Mathew, F.; Jayaprakash, K. N.; Fraser-Reid, B.; Mathew, J.; Scicinski, J. *Tetrahedron Lett.* **2003**, *44*, 9051.

(97) Maugard, T.; Gaunt, D.; Legoy, M. D.; Besson, T. *Biotech. Lett.* **2003**, *25*, 623.

(98) Bailliez, V.; de Figueiredo, R. M.; Olesker, A.; Cleophax, J. *Synthesis* **2003**, 1015.

(99) (a) Das, S. K.; Reddy, K. A.; Abbineni, C.; Roy, J.; Rao, K. V. L. N.; Sachwani, R. H.; Iqbal, J. *Tetrahedron Lett.* **2003**, *44*, 4507. (b) Das, S. K.; Reddy, K. A.; Roy, J. *Synlett* **2003**, 1607.

(100) Yang, G.; Chen, Z.; Xu, G.; Nie, X. *Catal. Commun.* **2004**, *5*, 75.

(101) Alexandre, F.-R.; Berecibar, A.; Wrigglesworth, R.; Besson, T. *Tetrahedron* **2003**, *59*, 1413.

(102) (a) Mogilaiah, K.; Reddy, N. V. *Synth. Commun.* **2003**, *33*, 73. (b) Mogilaiah, K.; Prashanthi, M.; Reddy, G. R.; Reddy, C. S.; Reddy, N. V. *Synth. Commun.* **2003**, *33*, 2309. (c) Mogilaiah, K.; Kankaiah, G. *Indian J. Chem.* **2002**, *41B*, 2194.

(103) Nemes, P.; Vincze, Z.; Balázs, B.; Tóth, G.; Scheiber, P. *Synlett* **2003**, 250.

(104) Karchgaudhuri, N.; De, A.; Mitra, A. K. *J. Chem. Res. (S)* **2002**, 180.

(105) (a) Arvela, R. K.; Leadbeater, N. E.; Torenius, H. M.; Tye, H. *Org. Biomol. Chem.* **2003**, *1*, 1119. (b) Arvela, R. K.; Leadbeater, N. E. *J. Org. Chem.* **2003**, *68*, 9122. (c) Leadbeater, N. E.; Torenius, H. M.; Tye, H. *Tetrahedron* **2003**, *59*, 2253.

(106) Zhang, A.; Neumeyer, J. L. *Org. Lett.* **2003**, *5*, 201.

(107) Charmier, M. A. J.; Kukushkin, V. Y.; Pombeiro, A. J. L. *Dalton Trans.* **2003**, 2540.

(108) Csokai, V.; Parlagh, G.; Grofcsik, A.; Kubinyi, M.; Bitter, I. *Synth. Commun.* **2003**, *33*, 1615.

(109) Dewan, S. K.; Singh, R. *Synth. Commun.* **2003**, *33*, 3085.

(110) (a) Srinivas, K. V. N. S; Mahender, I.; Das, B. *Chem. Lett.* **2003**, *32*, 738. (b) Srinivas, K. V. N. S; Reddy, E. B.; Das, B. *Synlett* **2002**, 625.

(111) Hegedüs, A.; Cwik, A.; Hell, Z.; Horváth, Z.; Esek, A.; Uzsoki, M. *Green Chem.* **2002**, *4*, 618.

(112) Bashiardes, G.; Safir, I.; Mohamed, A. S.; Barbot, F.; Laduranty, J. *Org. Lett.* **2003**, *5*, 4915.

(113) Bentabed, G.; Derdour, A.; Benhaoua, H. *Synth. Commun.* **2003**, *33*, 1861.

(114) Dandia, A.; Singh, R.; Sharma, P. *Heteroat. Chem.* **2003**, *14*, 468.

(115) Desai, B.; Danks, T. N.; Wagner, G. *Dalton Trans.* **2003**, 2544.

(116) Harris, J. M.; Padwa, A. *Org. Lett.* **2003**, *5*, 4195.

(117) Hong, B.-C.; Shr, Y.-J.; Liao, J.-H. *Org. Lett.* **2002**, *4*, 663.

(118) (a) Katritzky, A. R.; Singh, S. K. *J. Org. Chem.* **2002**, *67*, 9077. (b) Katritzky, A. R.; Singh, S. K. *Arkivoc* [Online] **2003**(xiii), 68; http://www.arkat-usa.org/ark/journal/2003/Trofimov/BT-752R/752R.pdf (accessed April 2004)

(119) Longchar, M.; Bora, U.; Boruah, R. C.; Sandhu, J. S. *Synth. Commun.* **2002**, *32*, 3611.

(120) Katritzky, A. R.; Cai, C.; Suzuki, K.; Singh, S. K. *J. Org. Chem.* **2004**, *69*, 811.

(121) Minetto, G.; Raveglia, L. F.; Taddei, M. *Org. Lett.* **2004**, *6*, 389.

(122) Yadav, L. D. S.; Yadav, B. S.; Dubey, S. *Tetrahedron* **2004**, *60*, 131.

(123) (a) Alexandre, F.-R.; Berecibar, A.; Wrigglesworth, R.; Besson, T. *Tetrahedron Lett.* **2003**, *44*, 4455. (b) Alexandre, F.-R.; Domon, L.; Frère, S.; Testard, A.; Thiéry, V.; Besson, T. *Mol. Diversity* **2003**, *7*, 273. (c) Frère, S.; Thiéry, V.; Bailly, C.; Besson, T. *Tetrahedron* **2003**, *59*, 773. (d) Frère, S.; Thiéry, V.; Besson, T. *Synth. Commun.* **2003**, *33*, 3795. (e) Fînaru, A.; Berthault, A.; Besson, T.; Guillaumet, G.; Berteina-Raboin, S. *Org. Lett.* **2002**, *4*, 2613. (f) Fînaru, A.; Berthault, A.; Besson, T.; Guillaumet, G.; Berteina-Raboin, S. *Tetrahedron Lett.* **2002**, *43*, 787.

(124) (a) Bagley, M. C.; Hughes, D. D.; Taylor, P. H. *Synlett* **2003**, 259. (b) Bagley, M. C.; Singh, N. *Synlett* **2002**, 1718. (c) Bagley, M. C.; Lunn, R.; Xiong, X. *Tetrahedron Lett.* **2002**, *43*, 8331.

(125) Chang, W.-J.; Yeh, W.-B.; Sun, C.-M. *Synlett* **2003**, 1688.

(126) Crawford, K. R.; Bur, S. K.; Straub, C. S.; Padwa, A. *Org. Lett.* **2003**, *5*, 3337.

(127) (a) Dallinger, D.; Gorobets, N. Y.; Kappe, C. O. *Org. Lett.* **2003**, *5*, 1205. (b) Dallinger, D.; Gorobets, N. Y.; Kappe, C. O. *Mol. Diversity* **2003**, *7*, 229. (c) Kaval, N.; Dehaen, W.; Kappe, C. O.; Van der Eycken, E. *Org. Biomol. Chem.* **2004**, *2*, 154. (d) Kaval, N.; Bisztray, K.; Dehaen, W.; Kappe, C. O.; Van der Eycken, E. *Mol. Diversity* **2003**, *7*, 125. (e) Pérez, R.; Beryozkina, T.; Zbruyev, O. I.; Haas, W; Kappe, C. O. *J. Comb. Chem.* **2002**, *4*, 501. (f) Stiasni, N.; Kappe, C. O. *Arkivoc* [Online] **2002**(viii), 71; http://www.arkat-usa.org/ark/journal/2002/Padwa/AP374H/374H.asp (accessed April 2004). (g) Van der Eycken, E.; Appukkuttan, P.; De Borggraeve, W.; Dehaen, W.; Dallinger, D.; Kappe, C. O. *J. Org. Chem.* **2002**, *67*, 7904.

(128) Díaz-Ortiz, A.; de la Hoz, A.; Herrero, M. A.; Prieto, P.; Sánchez-Migallón, A.; Cossio, F. P.; Arrieta, A.; Vivanco, S.; Foces-Foces, C. *Mol. Diversity* **2003**, *7*, 175.

(129) Emtenäs, H.; Taflin, C.; Almqvist, F. *Mol. Diversity* **2003**, *7*, 165.

(130) (a) Evans, M. D.; Ring, J.; Schoen, A.; Bell, A.; Edwards, P.; Berthelot, D.; Nicewonger, R.; Baldino, C. M. *Tetrahedron Lett.* **2003**, *44*, 9337. (b) Nicewonger, R.; Fowke, A.; Nguyen, K.; Ditto, L.; Caserta, J.; Harris, M.; Baldino, C. M. *Mol. Diversity* **2003**, *7*, 247.

(131) Ferrett, R. R.; Hyde, M. J.; Lahti, K. A.; Friebe, T. L. *Tetrahedron Lett.* **2003**, *44*, 2573.

(132) (a) García-Tellado, F.; Loupy, A.; Petit, A.; Marrero-Terrero, A. L. *Eur. J. Org. Chem.* **2003**, 4387. (b) Pérez, E. R.; Loupy, A.; Liagre, M.; de Guzzi Plepis, A. M.; Cordeiro, P. J. *Tetrahedron* **2003**, *59*, 865. (c) Rodríguez, H.; Suarez, M.; Pérez, R.; Petit, A.; Loupy, A. *Tetrahedron Lett.* **2003**, *44*, 3709. (d) Dandia, A.; Sati, M.; Loupy, A. *Green Chem.* **2002**, *4*, 599. (e) Paul, S.; Gupta, M.; Gupta, R.; Loupy, A. *Synthesis* **2002**, 75.

(133) (a) Giacomelli, G.; De Luca, L.; Porcheddu, A. *Tetrahedron* **2003**, *59*, 5437. (b) Giacomelli, G.; Porcheddu, A.; Salaris, M.; Taddei, M. *Eur. J. Org. Chem.* **2003**, 537. (c) Porcheddu, A.; Ruda, G. F.; Sega, A.; Taddei, M. *Eur. J. Org. Chem.* **2003**, 907.
(134) Hazarkhani, H.; Karimi, B. *Tetrahedron* **2003**, *59*, 4757.
(135) Lee, J. C.; Choi, H. J.; Lee, Y. C. *Tetrahedron Lett.* **2003**, *44*, 123.
(136) Martinez-Palou, R.; de Paz, G.; Marín-Cruz, J.; Zepeda, L. G. *Synlett* **2003**, 1847.
(137) Martins, M. A. P.; Pereira, C. M. P.; Beck, P.; Machado, P.; Moura, S.; Teixeira, M. V. M.; Bonacorso, H. G.; Zanatta, N. *Tetrahedron Lett.* **2003**, *44*, 6669.
(138) Pottorf, R. S.; Chadha, N. K.; Katkevics, M.; Ozola, V.; Suna, E.; Ghane, H.; Regberg, T.; Player, M. R. *Tetrahedron Lett.* **2003**, *44*, 175.
(139) Ranu, B. C.; Hajra, A.; Dey, S. S.; Jana, U. *Tetrahedron* **2003**, *59*, 813.
(140) Savin, K. A.; Robertson, M.; Gernert, D.; Green, S.; Hembre, E. J.; Bishop, J. *Mol. Diversity* **2003**, *7*, 171.
(141) Sha, Y.; Dong, Y. *Synth. Commun.* **2003**, *33*, 2599.
(142) Song, S. J.; Cho, S. J.; Park, D. K.; Kwon, T. W.; Jenekhe, S. A. *Tetrahedron Lett.* **2003**, *44*, 255.
(143) Uchida, H.; Tanikoshi, H.; Nakamura, S.; Reddy, P. Y.; Toru, T. *Synlett* **2003**, 1117.
(144) (a) Villemin, D.; Liao, L. *Synth. Commun.* **2003**, *33*, 1575. (b) Villemin, D.; Bar, N.; Khalid, M.; Jaffrès, P.-A.; Santos, J. S. O. *J. Chem. Res. (S)* **2003**, 433.
(145) Wang, X.; Li, Z.; Quan, Z.; Lu, X.; Gou, R. *Synth. Commun.* **2003**, *33*, 2891.
(146) Xia, M.; Wang, Y.-g. *Synthesis* **2003**, 262.
(147) Wellner, E.; Sandin, H.; Pääkkönen, L. *Synthesis* **2002**, 223.
(148) Wu, T. Y. H.; Schultz, P. G.; Ding, S. *Org. Lett.* **2003**, *5*, 3587.
(149) Yeh, W.-B.; Lin, M.-J.; Lee, M.-J.; Sun, C.-M. *Mol. Diversity* **2003**, *7*, 185.
(150) Zhao, Z.; Leister, W. H.; Strauss, K. A.; Wisnoski, D. D.; Lindsley, C. W. *Tetrahedron Lett.* **2003**, *44*, 1123.
(151) Deetlefs, M.; Seddon, K. R. *Green Chem.* **2003**, *5*, 181.
(152) Hoffmann, J.; Nüchter, M.; Ondruschka, B.; Wasserscheid, P. *Green Chem.* **2003**, *5*, 296.
(153) Lee, J. K.; Kim, D.-C.; Song, C. E.; Lee, S.-g. *Synth. Commun.* **2003**, *33*, 2301.
(154) Nguyen, H.-P.; Matondo, H.; Baboulène, M. *Green Chem.* **2003**, *5*, 303.
(155) Berthold, H.; Schotten, T.; Hönig, H. *Synthesis* **2002**, 1607.
(156) Khadilkar, B. M.; Rebeiro, G. L. *Org. Process Res. Dev.* **2002**, *6*, 826.
(157) Law, M. C.; Wong, K.-Y.; Chan, T. H. *Green Chem.* **2002**, *4*, 328.
(158) Leadbeater, N. E.; Torenius, H. M. *J. Org. Chem.* **2002**, *67*, 3145.
(159) Namboodiri, V. V.; Varma, R. S. *Tetrahedron Lett.* **2002**, *3*, 5381.
(160) Swatloski, R. P.; Spear, S. K.; Holbrey, J. D.; Rogers, R. D. *J. Am. Chem. Soc.* **2002**, *124*, 4974.
(161) Vallin, K. S. A.; Emilsson, P.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2002**, *67*, 6243.
(162) Michaud, D.; Hamelin, J.; Texier-Boullet, F. *Tetrahedron* **2003**, *59*, 3323.
(163) Narasimhan, S.; Velmathi, S. *Synth. Commun.* **2002**, *32*, 3791.
(164) Rissafi, B.; El Louzi, A.; Loupy, A.; Petit, A.; Soufiaoui, M.; Tétouani, S. F. *Eur. J. Org. Chem.* **2002**, 2518.
(165) Sharma, U.; Bora, U.; Boruah, R. C.; Sandhu, J. S. *Tetrahedron Lett.* **2002**, *43*, 143.
(166) (a) Paolini, L.; Petricci, E.; Corelli, F.; Botta, M. *Synthesis* **2003**, 1039. (b) Petricci, E.; Radi, M.; Corelli, F.; Botta, M. *Tetrahedron Lett.* **2003**, *44*, 9181.
(167) Abdel-Rahman, A. A.-H.; El Ashry, E. S. H. *Synlett* **2002**, 2043.
(168) Andrzejewska, M.; Kaminski, J.; Kazimierczuk, Z. *Nucleosides, Nucleotides Nucleic Acids* **2002**, *21*, 73.
(169) Rao, N. S.; Kumar, P.; Chauhan, V. K.; Garg, B. S.; Gupta, K. C. *Nucleosides, Nucleotides Nucleic Acids* **2002**, *21*, 393.
(170) Dosa, P. I.; Whitener, G. D.; Vollhardt, K. P. C.; Bond, A. D.; Teat, S. J. *Org. Lett.* **2002**, *4*, 2075.
(171) Laskar, D. D.; Gohain, M.; Prajapati, D.; Sandhu, J. S. *New J. Chem.* **2002**, *26*, 193.
(172) Whittaker, A. G.; Mingos, D. M. P. *J. Chem. Soc., Dalton Trans.* **2002**, 3967.
(173) Stadler, A.; Kappe, C. O. *Org. Lett.* **2002**, *4*, 3541.
(174) Burton, G.; Cao, P.; Li, G.; Rivero, R. *Org. Lett.* **2003**, *5*, 4373.
(175) Villemin, D.; Elbilali, A.; Siméon, F.; Jaffrès, P.-A.; Maheut, G.; Mosaddak, M.; Hakiki, A. *J. Chem. Res. (S)* **2003**, 436.
(176) Zhang, W.; Lu, Y.; Chen, C. H.-T. *Mol. Diversity* **2003**, *7*, 199.
(177) Fürstner, A.; Seidel, G. *Org. Lett.* **2002**, *4*, 541.
(178) Kuhnert, N.; Danks, T. N. *J. Chem. Res. (S)* **2002**, 66.
(179) (a) Wu, Y.-J.; He, H.; L'Heureux, A. *Tetrahedron Lett.* **2003**, *44*, 4217. (b) Wu, Y.-J.; He, H. *Synlett* **2003**, 1789.
(180) (a) Andappan, M. M. S.; Nilsson, P.; Larhed, M. *Mol. Diversity* **2003**, *7*, 97. (b) Datta, G. K.; Vallin, K. S. A.; Larhed, M. *Mol. Diversity* **2003**, *7*, 107. (c) Vallin, K. S. A.; Zhang, Q.; Larhed, M.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **2003**, *68*, 6639. (d) Nilsson, P.; Gold, H.; Larhed, M.; Hallberg, A. *Synthesis* **2002**, 1611.
(181) Bai, L.; Wang, J.-X.; Zhang, Y. *Green Chem.* **2003**, *5*, 615.
(182) (a) Leadbeater, N. E.; Marco, M. *J. Org. Chem.* **2003**, *68*, 888. (b) Leadbeater, N. E.; Marco, M. *Org. Lett.* **2002**, *4*, 2973.
(183) Gong, Y.; He, W. *Org. Lett.* **2002**, *4*, 3803.
(184) Melucci, M.; Barbarella, G.; Sotgiu, G. *J. Org. Chem.* **2002**, *67*, 8877.
(185) Spinella, A.; Caruso, T.; Pastore, U.; Ricart, S. *J. Organomet. Chem.* **2003**, *684*, 266.
(186) Hayes, B. L. Syntheses of Cyclopentenones via Microwave-Assisted Pauson–Khand Reactions. Presented at the 224th National Meeting of the American Chemical Society, Boston, MA, August 18–22, 2002; Paper ORGN 0842.
(187) Iqbal, M.; Vyse, N.; Dauvergne, J.; Evans, P. *Tetrahedron Lett.* **2002**, *43*, 7859.
(188) Fischer, S.; Groth, U.; Jung, M.; Schneider, A. *Synlett* **2002**, 2023.
(189) Bogdal, D.; Lukasiewicz, M.; Pielichowski, J.; Miciak, A.; Bednarz, S. *Tetrahedron* **2003**, *59*, 649.
(190) Heravi, M. M.; Sangsefidi, L.; Oskooie, H. A.; Ghassemzadeh, M.; Tabar-Hydar, K. *Phosphorus, Sulfur Silicon Relat. Elem.* **2003**, *178*, 707.
(191) Kiasat, A. R.; Kazemi, F.; Rafati, M. *Synth. Commun.* **2003**, *33*, 601.

(192) Mogilaiah, K.; Prashanthi, M.; Reddy, G. R. *Synth. Commun.* **2003**, *33*, 3741.
(193) Takahashi, M.; Oshima, K.; Matsubara, S. *Tetrahedron Lett.* **2003**, *44*, 9201.
(194) Davis, C. J.; Moody, C. J. *Synlett* **2002**, 1874.
(195) Heravi, M. M.; Farhangi, N.; Beheshtiha, Y. S.; Assadolah, K.; Ghassemzadeh, M.; Tabar-Hydar, K. *Phosphorus, Sulfur Silicon Relat. Elem.* **2002**, *177*, 2883.
(196) Lee, J. C.; Park, H.-J.; Park, J. Y. *Tetrahedron Lett.* **2002**, *43*, 5661.
(197) Collins, J. M.; Collins, M. J.; Steorts, R. C. Novel Method for Solid-Phase Peptide Synthesis Using Microwave Energy. Presented at the 18th American Peptide Symposium, Boston, MA, July 22, 2003; Poster P267 (abstract published in *Biopolym*. **2003**, *71*, 361).
(198) (a) Erdélyi, M.; Gogoll, A. *Biopolym.* **2003**, *71*, 340. (b) Erdélyi, M.; Gogoll, A. *Synthesis* **2002**, 1592. (c) Erdélyi, M.; Langer, V.; Karlén, A.; Gogoll, A. *New J. Chem.* **2002**, *26*, 834.
(199) Luppi, G.; Villa, M.; Tomasini, C. *Org. Biomol. Chem.* **2003**, *1*, 247.
(200) (a) Patil, B. S.; Vasanthakumar, G.-R.; Suresh Babu, V. V. *J. Org. Chem.* **2003**, *68*, 7274. (b) Patil, B. S.; Vasanthakumar, G.-R.; Suresh Babu, V. V. *Lett. Peptide Sci.* **2002**, *9*, 231. (c) Vasanthakumar, G.-R.; Patil, B. S.; Suresh Babu, V. V. *Lett. Peptide Sci.* **2002**, *9*, 207.
(201) (a) Pramanik, B. N.; Ing, Y. H.; Bose, A. K.; Zhang, L.-K.; Liu, Y.-H.; Ganguly, S. N.; Bartner, P. *Tetrahedron Lett.* **2003**, *44*, 2565. (b) Bose, A. K.; Ing, Y. H.; Lavlinskaia, N.; Sareen, C.; Pramanik, B. N.; Bartner, P. L.; Liu, Y.-H.; Heimark, L. *J. Am. Soc. Mass Spectrom.* **2002**, *13*, 839.
(202) Olivos, H. J.; Alluri, P. G.; Reddy, M. M.; Salony, D.; Kodadek, T. *Org. Lett.* **2002**, *4*, 4057.
(203) Roy, I.; Gupta, M. N. *Tetrahedron* **2003**, *59*, 5431.
(204) (a) Literák, J.; Relich, S.; Kulhánek, P.; Klán, P. *Mol. Diversity* **2003**, *7*, 265. (b) Klán, P.; Literák, J.; Relich, S. *J. Photochem. Photobiol., A: Chem.* **2001**, *143*, 49.
(205) Rohrbaugh, D. K.; Longo, F. R.; Durst, H. D.; Munavalli, S. *Phosphorus, Sulfur Silicon Relat. Elem.* **2001**, *176*, 201.
(206) (a) Chatti, S.; Bortolussi, M.; Loupy, A.; Blais, J. C.; Bogdal, D.; Roger, P. *J. Appl. Polym. Sci.* **2003**, *90*, 1255. (b) Chatti, S.; Bortolussi, M.; Loupy, A.; Blais, J. C.; Bogdal, D.; Majdoub, M. *Eur. Polym. J.* **2002**, *38*, 1851.
(207) Bogdal, D.; Gorczyk, J. *Polymer* **2003**, *44*, 7795.
(208) (a) Zhu, X.; Chen, J.; Cheng, Z.; Lu, J.; Zhu, J. *J. Appl. Polym. Sci.* **2003**, *89*, 28. (b) Zhu, X.; Chen, J.; Zhou, N.; Cheng, Z.; Lu, J. *Eur. Polym. J.* **2003**, *39*, 1187.
(209) (a) Lu, J.-M.; Ji, S.-J.; Chen, N.-Y.; Sun, Z.-R.; Zhu, X.-L.; Shi, W.-P.; Wang, Z.-G. *J. Appl. Polym. Sci.* **2003**, *89*, 2611. (b) Lu, J.-M.; Ji, S.-J.; Chen, N.-Y.; Zhang, Z.-B.; Sun, Z.-R.; Zhu, X.-L.; Shi, W.-P. *J. Appl. Polym. Sci.* **2003**, *87*, 1739.
(210) (a) Faghihi, K.; Zamani, K.; Mirsamie, A.; Sangi, M. R. *Eur. Polym. J.* **2003**, *39*, 247. (b) Faghihi, K.; Hagibeygi, M. *Eur. Polym. J.* **2003**, *39*, 2307. (c) Faghihi, K.; Fouroghifar, N.; Hajibeygi, M.; Mallakpour, S.; Zamani, K. *Iran Polym. J. Eng. Ed.* **2003**, *12*, 339. (d) Mallakpour, S.; Kowsari, E. *J. Polym. Sci., Part A: Polym. Chem.* **2003**, *41*, 3974. (e) Mallakpour, S.; Hajipour, A.-R.; Zamanlou, M. R. *J. Polym. Sci., Part A: Polym. Chem.* **2003**, *41*, 1077. (f) Mallakpour, S.; Habibi, S. *Eur. Polym. J.* **2003**, *39*, 1823. (g) Mallakpour, S. E.; Hajipour, A.-R.; Habibi, S. *J. Appl. Polym. Sci.* **2002**, *86*, 2211. (h) Mallakpour, S. E.; Hajipour, A.-R.; Zamanlou, M. R. *Eur. Polym. J.* **2002**, *38*, 475.
(211) Hawley, M. C.; Kempel, L. C.; Sgriccia, N.; Zhou, S.; Zong, L. *J. Microw. Power Electromagn. Energy* **2003**, *38*, 49.
(212) Baudel, V.; Cazier, F.; Woisel, P.; Surpateanu, G. *Eur. Polym. J.* **2002**, *38*, 615.
(213) Ramesh, C.; Mahender, G.; Ravindranath, N.; Das, B. *Green Chem.* **2003**, *5*, 68.
(214) Saxena, I.; Deka, N.; Sarma, J. C.; Tsuboi, S. *Synth. Commun.* **2003**, *33*, 4185.
(215) Tajbakhsh, M.; Heravi, M. M.; Habibzadeh, S. *Phosphorus, Sulfur Silicon Relat. Elem.* **2003**, *178*, 361.
(216) Wettergren, J.; Minidis, A. B. E. *Tetrahedron Lett.* **2003**, *44*, 7611.
(217) Hajipour, A.-R.; Mallakpour, S. E.; Mohammadpoor-Baltork, I.; Khoee, S. *Synth. Commun.* **2002**, *32*, 611.
(218) Eshghi, H.; Gordi, Z. *Synth. Commun.* **2003**, *33*, 2971.
(219) Muccioli, G. G.; Wouters, J.; Poupaert, J. H.; Norberg, B.; Poppitz, W.; Scriba, G. K. E.; Lambert, D. M. *Org. Lett.* **2003**, *5*, 3599.
(220) Yamamoto, T.; Wada, Y.; Enokida, H.; Fujimoto, M.; Nakamura, K.; Yanagida, S. *Green Chem.* **2003**, *5*, 690.
(221) Gopalakrishnan, G.; Kasinath, V.; Pradeep Singh, N. D. *Org. Lett.* **2002**, *4*, 781.
(222) Shanmugasundaram, B.; Bose, A. K.; Balasubramanian, K. K. *Tetrahedron Lett.* **2002**, *43*, 6795.
(223) Sudrik, S. G.; Chavan, S. P.; Chandrakumar, K. R. S.; Pal, S.; Date, S. K.; Chavan, S. P.; Sonawane, H. R. *J. Org. Chem.* **2002**, *67*, 1574.
(224) Werner, S.; Curran, D. P. *Org. Lett.* **2003**, *5*, 3293.
(225) Crosignani, S.; Launay, D.; Linclau, B.; Bradley, M. *Mol. Diversity* **2003**, *7*, 203.
(226) Sauer, D. R.; Kalvin, D.; Phelan, K. M. *Org. Lett.* **2003**, *5*, 4721.
(227) Swamy, K. M. K.; Yeh, W.-B.; Lin, M.-J.; Sun, C.-M. *Curr. Med. Chem.* **2003**, *10*, 2403.
(228) Austin, R. E.; Okonya, J. F.; Bond, D. R. S.; Al-Obeidi, F. *Tetrahedron Lett.* **2002**, *43*, 6169.
(229) Clapham, B.; Lee, S.-H.; Koch, G.; Zimmermann, J.; Janda, K. D. *Tetrahedron Lett.* **2002**, *43*, 5407.
(230) Launay, D.; Booth, S.; Clemens, I.; Merritt, A.; Bradley, M. *Tetrahedron Lett.* **2002**, *43*, 7201.
(231) Yaylayan, V. A.; Siu, M.; Bélanger, J. M. R.; Paré, J. R. J. *Tetrahedron Lett.* **2002**, *43*, 9023.
(232) Tan, K. L.; Vasudevan, A.; Bergman, R. G.; Ellman, J. A.; Souers, A. J. *Org. Lett.* **2003**, *5*, 2131.
(233) Lee, C.-C.; Wang, J.-C.; Hu, A. T. *Mater. Lett.* **2004**, *58*, 535.
(234) (a) Han, J. W.; Castro, J. C.; Burgess, K. *Tetrahedron Lett.* **2003**, *44*, 9359. (b) Jiao, G.-S.; Castro, J. C.; Thoresen, L. H.; Burgess, K. *Org. Lett.* **2003**, *5*, 3675.
(235) Arvela, R. K.; Leadbeater, N. E. *Synlett* **2003**, 1145.
(236) Lee, J. C.; Bae, Y. H. *Synlett* **2003**, 507.
(237) Katritzky, A. R.; Majumder, S.; Jain, R. *Arkivoc* [Online] **2003**(xii), 74; http://www.arkat-usa.org/ark/journal/2003/Shine/HS-873J/HS-873J.asp (accessed April 2004).
(238) Inagaki, T.; Fukuhara, T.; Hara, S. *Synthesis* **2003**, 1157.
(239) Ganguly, N. C.; Datta, M.; De, P.; Chakravarty, R. *Synth. Commun.* **2003**, *33*, 647.
(240) Shackelford, S. A.; Anderson, M. B.; Christie, L. C.; Goetzen, T.; Guzman, M. C.; Hananel, M. A.; Kornreich, W. D.; Li, H.; Pathak, V. P.; Rabinovich, A. K.; Rajapakse, R. J.; Truesdale, L. K.; Tsank, S. M.; Vazir, H. N. *J. Org. Chem.* **2003**, *68*, 267.

(241) Rebeiro, G. L.; Khadilkar, B. M. *Synth. Commun.* **2003**, *33*, 1405.
(242) Trotzki, R.; Nüchter, M.; Ondruschka, B. *Green Chem.* **2003**, *5*, 285.
(243) Fermér, C.; Nilsson, P.; Larhed, M. *Eur. J. Pharm. Sci.* **2003**, *18*, 129.
(244) Pramanik, B. N.; Mirza, U. A.; Ing, Y. H.; Liu, Y.-H.; Bartner, P. L.; Weber, P. C.; Bose, A. K. *Protein Sci.* **2002**, *11*, 2676.
(245) Rama Rao, V. V. V. N. S.; Ravikanth, S.; Venkat Reddy, G.; Maitraie, D.; Yadla, R.; Shanthan Rao, P. *Synth. Commun.* **2003**, *33*, 1523.
(246) Yu, X.; Huang, X. *Synlett* **2002**, 1895.
(247) (a) Barnhardt, E. K. CEM Corporation, Matthews, NC. Unpublished work, 2003. (b) Barnhardt, E. K.; Hayes, B. L. Performing Microwave-Assisted Reactions at Low Temperatures. Presented at the 226th National Meeting of the American Chemical Society, New York, NY, Sep 7–11, 2003; Paper ORGN 0303.

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About the Author

Brittany L. Hayes was born in Lansing, MI, and raised in Palm Beach Gardens, FL. She received her B.S. degree in chemistry from Emory University in Atlanta, GA (1994). After continuing an undergraduate research project in the Department of Radiology at Emory's Medical School for an additional year, she headed off to graduate school at Wake Forest University in Winston-Salem, NC (1995). She received her Ph.D. degree in organic chemistry in 1999 under the direction of Mark E. Welker for research that focused on transition-metal-mediated cycloaddition reactions. She conducted her postdoctoral research at the Center for Pharmaceutical Biotechnology and Department of Medicinal Chemistry and Pharmacognosy of the University of Illinois at Chicago (UIC). At UIC, she was one of 15 people to be awarded an American Heart Association Postdoctoral Fellowship, Midwest Affiliate, in 2000. With this funding, she examined the design and synthesis of potential inhibitors of sickle cell hemoglobin polymerization. In addition, she helped develop a new homogeneous assay that combinatorially screens libraries of reactive isothiocyanate derivatives using electrospray mass spectrometry (ESMS).

Brittany is currently a Senior Scientist in the Life Sciences Division at CEM Corporation (Matthews, NC). In 2002, she authored the first educational text on microwave organic synthesis, *Microwave Synthesis: Chemistry at the Speed of Light*, and developed a patented microwave reaction technique that allows chemists to maximize microwave power while simultaneously removing latent thermal energy from the reaction vessel and cavity. Presently, she splits her time between developing new microwave applications, customer support, collaborative ventures with other leading technology companies, and traveling worldwide to support CEM's sales force.

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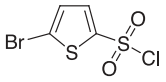
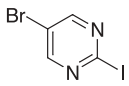
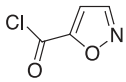
63,622-3
5-Bromothiophene-2-sulfonyl chloride
$C_4H_2BrClO_2S_2$
5g
25g



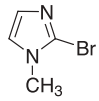
63,775-0
5-Bromo-2-iodopyrimidine, 97%
$C_4H_2BrIN_2$
250mg
1g



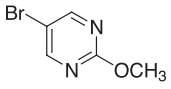
63,623-1
Isoxazole-5-carbonyl chloride, 97%
$C_4H_2ClNO_2$
1g
5g



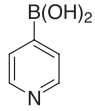
63,985-0
2-Bromo-1-methyl-1*H*-imidazole, 97%
$C_4H_5BrN_2$
1g
5g



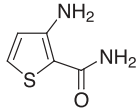
63,488-3
5-Bromo-2-methoxypyrimidine, 97%
$C_5H_5BrN_2O$
1g



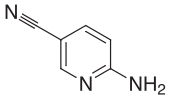
63,449-2
4-Pyridineboronic acid
$C_5H_6BNO_2$
1g
5g



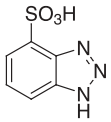
63,281-3
3-Aminothiophene-2-carboxamide, 97%
$C_5H_6N_2OS$
250mg
1g



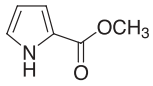
63,747-5
2-Amino-5-cyanopyridine, 97%
$C_6H_5N_3$
5g
25g



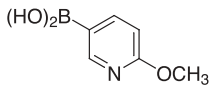
63,280-5
1*H*-Benzotriazole-4-sulfonic acid, 97%
$C_6H_5N_3O_3S$
1g
5g



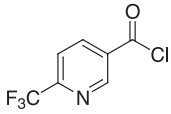
64,042-5
Methyl 2-pyrrolecarboxylate, 97%
$C_6H_7NO_2$
5g
25g



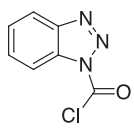
63,761-0
2-Methoxy-5-pyridineboronic acid
$C_6H_8BNO_3$
1g
5g



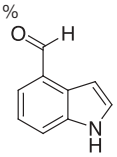
64,006-9
6-(Trifluoromethyl)nicotinoyl chloride, 97%
$C_7H_3ClF_3NO$
1g
5g



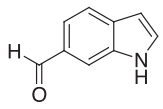
63,391-7
Benzotriazole-1-carbonyl chloride, tech.
$C_7H_4ClN_3O$
1g



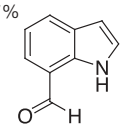
63,242-2
Indole-4-carboxaldehyde, 97%
C_9H_7NO
1g
5g



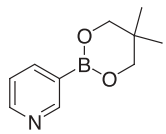
63,240-6
Indole-6-carboxaldehyde, 97%
C_9H_7NO
250mg
1g



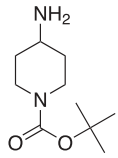
63,241-4
Indole-7-carboxaldehyde, 97%
C_9H_7NO
1g
5g



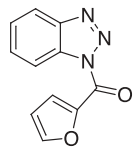
64,262-2
Pyridine-3-boronic acid neopentylglycol ester, 97%
$C_{10}H_{14}BNO_2$
1g
5g



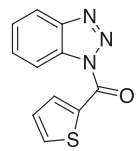
64,004-2
4-Amino-1-Boc-piperidine, 97%
$C_{10}H_{20}N_2O_2$
1g
5g



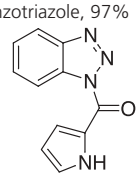
63,079-9
1-(2-Furoyl)-1*H*-benzotriazole, 97%
$C_{11}H_7N_3O_2$
1g



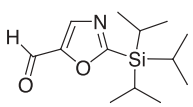
63,077-2
1-(2-Thienylcarbonyl)-1*H*-benzotriazole, 97%
$C_{11}H_7N_3OS$
1g



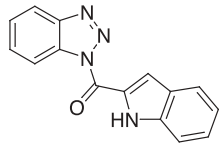
63,189-2
1-(2-Pyrrolecarbonyl)benzotriazole, 97%
$C_{11}H_8N_4O$
1g



64,110-3
2-Triisopropylsilyloxazole-5-carboxaldehyde, 96%
$C_{13}H_{23}NO_2Si$
1g
5g



63,060-8
1-(1*H*-Indol-2-ylcarbonyl)-1*H*-benzotriazole
$C_{15}H_{10}N_4O$
1g



TO ORDER: Contact your local Sigma-Aldrich office, call 1-800-558-9160 (USA), or visit sigma-aldrich.com.

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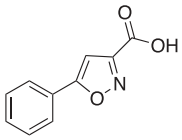
New Isoxazole Building Blocks

Aldrich is proud to bring you the following new building blocks. Each month, our chemists add a new set of building blocks that are suitable for your medicinal and synthetic chemistry needs. If you require a building block, but do not see it on the list, please contact bseitz@sial.com. To place an order for any of the items below, please call **800-558-9160** (USA) or contact your local Sigma-Aldrich office.

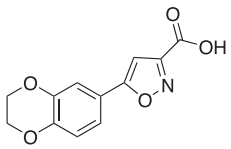
L48,252-8

$C_{10}H_7NO_3$
MW 189.17
250mg



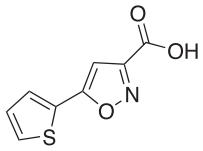
L48,257-9

$C_{12}H_9NO_5$
MW 247.21
250mg



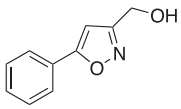
L48,258-7

$C_8H_5NO_3S$
MW 195.20
250mg



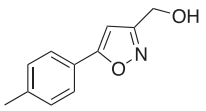
L48,269-2

$C_{10}H_9NO_2$
MW 175.19
250mg



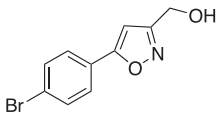
L48,270-6

$C_{11}H_{11}NO_2$
MW 189.22
250mg



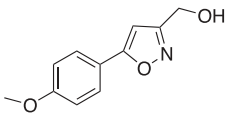
L48,272-2

$C_{10}H_8BrNO_2$
MW 254.08
250mg



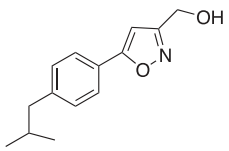
L48,273-0

$C_{11}H_{11}NO_3$
MW 205.22
250mg



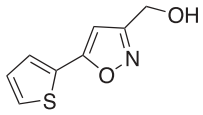
L48,274-9

$C_{14}H_{17}NO_2$
MW 231.30
250mg



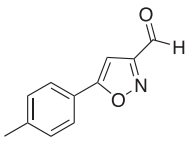
L48,276-5

$C_8H_7NO_2S$
MW 181.21
250mg



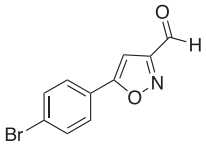
L48,277-3

$C_{11}H_9NO_2$
MW 187.20
250mg



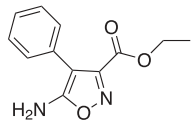
L48,280-3

$C_{10}H_6BrNO_2$
MW 252.07
250mg



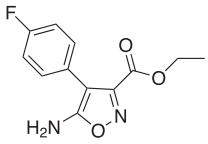
L48,281-1

$C_{12}H_{12}N_2O_3$
MW 232.24
250mg



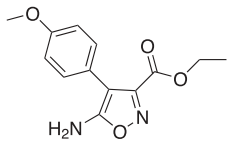
L48,284-6

$C_{12}H_{11}FN_2O_3$
MW 250.23
250mg



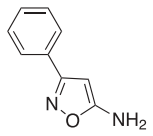
L48,285-4

$C_{13}H_{14}N_2O_4$
MW 262.27
250mg



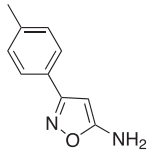
L48,289-7

$C_9H_8N_2O$
MW 160.18
250mg



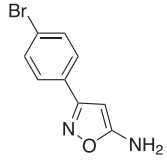
L48,290-0

$C_{10}H_{10}N_2O$
MW 174.20
250mg



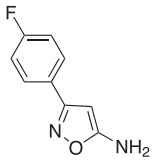
L48,291-9

$C_9H_7BrN_2O$
MW 239.07
250mg



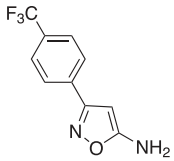
L48,292-7

$C_9H_7FN_2O$
MW 178.17
250mg



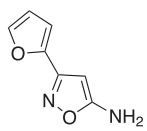
L48,293-5

$C_{10}H_7F_3N_2O$
MW 228.18
250mg



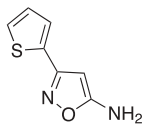
L48,298-6

$C_7H_6N_2O_2$
MW 150.14
250mg



L48,299-4

$C_7H_6N_2OS$
MW 166.20
250mg



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Aldrich Glass with SafetyBarb™ Hose Connectors!

For the safe connection and removal of heating, cooling, and vacuum tubing.

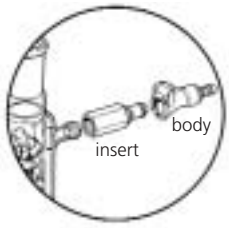
This new glassware features SafetyBarb™ removable connections for ¼ in. i.d. flexible tubing. The "barbed" polypropylene connector grips tubing firmly and can be safely detached from the glassware by unscrewing the PBT cap. Accidental glassware breakage is eliminated when installing or removing the tubing. A silicone rubber seal ensures a liquid- and vacuum-tight connection to the glass GL 24 thread.

Automatic Shutoff Quick-Disconnects

To install, unscrew tubing connector on glassware and replace with coupling insert. Chemically resistant acetal coupling insert and body are spring-loaded, locking, and have 316SS springs and EPR seals. Both sides seal automatically when pulled apart. One coupling insert and body needed for each glass connection. Use with ¼ in. i.d. flexible tubing.

Coupling insert, GL 14 inner thread
Z55,337-9

Coupling body, for ¼ in. i.d. tubing
Z55,338-7



Gas-Inlet Adapter

Joint	Cat. No.
14/20	Z55,193-7
19/22	Z55,194-5
24/40	Z55,195-3
29/32	Z55,196-1

Vacuum-Distilling Adapter

Joint	Cat. No.
14/20	Z55,283-6
19/22	Z55,284-4
24/40	Z55,285-2
29/32	Z55,286-0

Gas Bubbler

Description	Cat. No.
4 mL	Z55,185-6

Vacuum Adapter

Joint	*Inner joint* Cat. No.	*Inner joint w/ side-port* Cat. No.
14/20	Z55,198-8	Z55,210-0
19/22	Z55,199-6	Z55,276-3
24/40	Z55,200-3	Z55,277-1
29/32	Z55,201-1	Z55,279-8
34/45	Z55,203-8	Z55,280-1

Joint	*Outer joint* Cat. No.
14/20	Z55,204-6
19/22	Z55,205-4
24/40	Z55,206-2
29/32	Z55,207-0
34/45	Z55,209-7

Check-Valve Bubbler

Description	Cat. No.
Single-inlet, top outlet	Z55,186-4
T-inlet, side outlet	Z55,187-2

In-Line Oil Bubbler

Joint	Cat. No.
14/20	Z55,188-0
19/22	Z55,189-9
19/38	Z55,190-2
24/40	Z55,191-0
29/32	Z55,192-9

Reaction Vessel Bubbler

Joint	Cat. No.
14/20	Z55,287-9
19/22	Z55,288-7
24/40	Z55,289-5
29/32	Z55,290-9

Reverse-Flow Bubbler

Description	Cat. No.
25 mL	Z55,266-6

High-Efficiency Friedrichs Condenser

Overall length is 220 mm.

Joint	Cat. No.
24/40	Z55,262-3
29/32	Z55,263-1

High-Efficiency Liebig Condenser

Overall length is 220 mm.

Joint	Cat. No.
24/40	Z55,259-3
29/32	Z55,261-5

Büchner Funnel

With 24/40 bottom joint.

Capacity (mL)	Porosity (µm)	Cat. No.
60	4–8	Z55,308-5
	10–20	Z55,309-3
	25–50	Z55,310-7
	70–100	Z55,311-5
	145–175	Z55,414-6
140	4–8	Z55,415-4
	10–20	Z55,416-2
	25–50	Z55,417-0
	70–100	Z55,418-9
	145–175	Z55,419-7
350	4–8	Z55,420-0
	10–20	Z55,421-9
	25–50	Z55,422-7
	70–100	Z55,423-5
	145–175	Z55,424-3

Replacement SafetyBarb™ Hose Connectors

Reservoir Cap. (mL)	Overall L (mm)
Straight, GL 14	Z54,778-6
Bent, GL 14	Z54,788-3

Contact us for the new *Aldrich Glass with SafetyBarb™ Hose Connectors* brochure for a complete listing.
Call 800-558-9160 (USA) or email aldrich@sial.com.

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Sigma-Aldrich

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W600016 Beverage Study Kit

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CHEERS!

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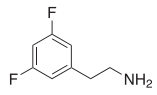
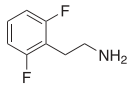
L30,017-9

$C_8H_9F_2N$
MW 157.16
1g



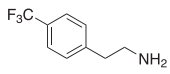
L30,018-7

$C_8H_9F_2N$
MW 157.16
1g



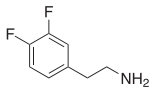
L30,022-5

$C_9H_{10}F_3N$
MW 189.18
1g



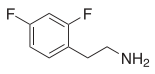
L30,023-3

$C_8H_9F_2N$
MW 157.16
1g



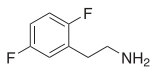
L30,024-1

$C_8H_9F_2N$
MW 157.16
1g



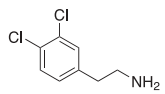
L30,027-6

$C_8H_9F_2N$
MW 157.16
1g



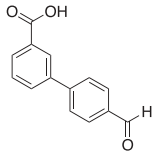
L30,029-2

$C_8H_9Cl_2N$
MW 190.07
250mg



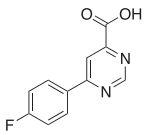
L48,018-5

$C_{14}H_{10}O_3$
MW 226.23
500mg



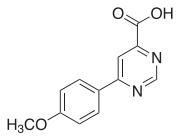
L30,036-5

$C_{11}H_7FN_2O_2$
MW 218.19
500mg



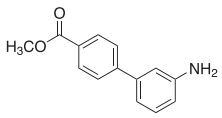
L30,037-3

$C_{12}H_{10}N_2O_3$
MW 230.23
500mg



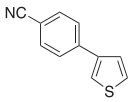
L48,020-7

$C_{14}H_{13}NO_2$
MW 227.27
500mg



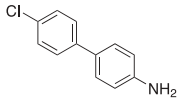
L30,065-9

$C_{11}H_7NS$
MW 185.25
500mg



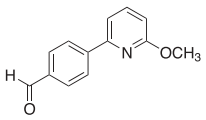
L30,082-9

$C_{12}H_{10}ClN$
MW 203.67
250mg



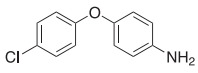
L30,013-6

$C_{13}H_{11}NO_2$
MW 213.24
1g



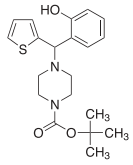
L30,084-5

$C_{12}H_{10}ClNO$
MW 219.67
250mg



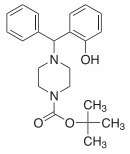
L30,034-9

$C_{20}H_{26}N_2O_3S$
MW 374.51
500mg



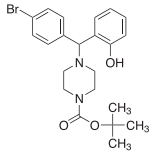
L30,038-1

$C_{22}H_{28}N_2O_3$
MW 368.48
500g



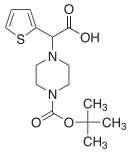
L48,023-1

$C_{22}H_{27}BrN_2O_3$
MW 447.38
500mg



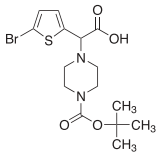
L48,026-6

$C_{15}H_{22}N_2O_4S$
MW 326.42
500mg



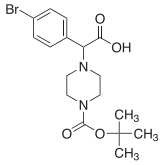
L48,027-4

$C_{15}H_{21}BrN_2O_4S$
MW 405.31
500mg



L48,028-2

$C_{17}H_{23}BrN_2O_4$
MW 399.29
500mg



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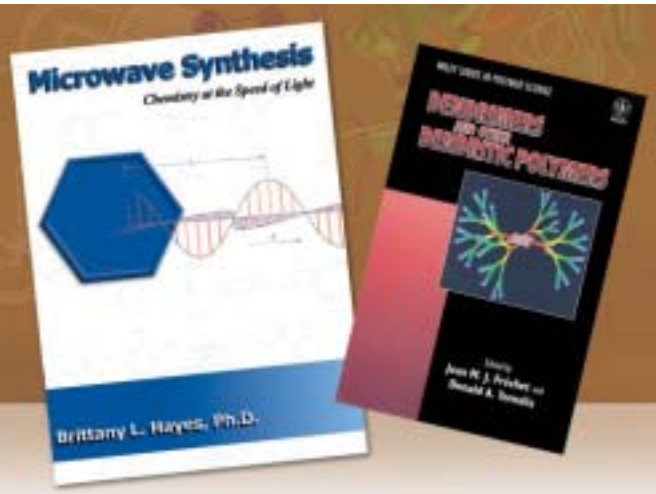

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Z55,550-9

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Z55,549-5

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S. Gronowitz and A. B. Hornfeldt, Elsevier Science, 2003, 960pp. Hardcover. Part of the *Best Synthetic Methods* series, this book allows the reader to rapidly review and select the best methods of performing a synthetic conversion to create or modify a specifically substituted thiophene. The large number of experimental recipes enables the user to prepare a thiophene derivative. Especially useful for physicists working in materials science and for organic and pharmaceutical chemists.

Z55,547-9

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L. Brandsma, Ed., Elsevier Science, 2003, 512pp. Hardcover. Part of the *Best Synthetic Methods* series, this book contains a valuable distillation and critical evaluation of the formation and reaction of molecules containing carbon–carbon triple bonds or cumulative carbon–carbon double bonds. The emphasis in all cases is on describing efficient practical methods to effect the transformations described.

Z55,548-7

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Z51,403-9

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H. S. Nalwa and S. Miyata, Eds., American Scientific Publishers, 1996, 885pp. Hardcover. Presents theoretical approaches, measurement techniques, materials, technologies, and applications of modern nonlinear optical (NLO) materials. It provides an excellent overview of the exciting advances in NLO materials and their applications in emerging photonics technologies. Discusses photonics technologies and applications, and covers basic optical physics through to advanced theoretical modeling and molecular engineering.

Z55,222-4

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B. L. Hayes, CEM Publishing, Matthews, NC, 2003, 289pp. Hardcover. Benefiting both the practicing chemist and student alike, this book discusses microwave-based chemistry for the organic laboratory. Topics include optimizing reactions, applications in microwave synthesis, atmospheric and pressurized reactions, choosing the best solvent for a microwave-assisted reaction, solvent-free reactions, and the fundamentals of microwave theory.

Z55,386-7

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H. Zollinger, John Wiley & Sons, 2004, 647pp. Hardcover. Following the success of the first and second editions, this book continues to be useful in the discussion of modern applications of color chemistry. Useful as a general reference textbook, and in physical-organic chemistry.

Z55,546-0

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Catalog No.	Product Name	Unit
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55,404-9	**Activator** (1*H*-Tetrazole, 3 wt. % solution in acetonitrile)	1L 2L
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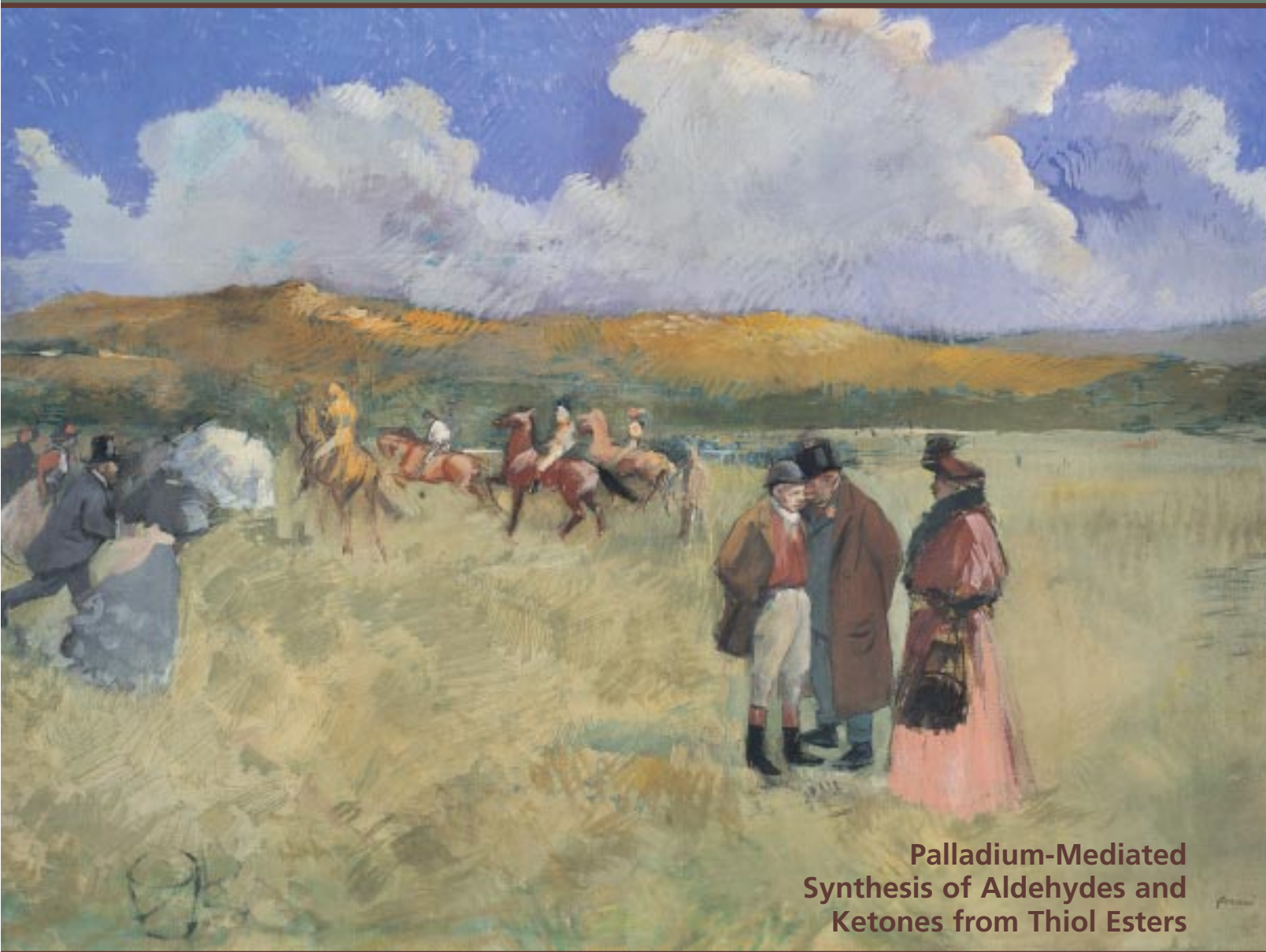

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(*S*)-(–)-2-Methyl-CBS-oxazaborolidine, 1*M* solution in toluene

45,770-1 — 5 mL, 25 mL

(*R*)-(+)-2-Methyl-CBS-oxazaborolidine

64,931-7 — 1 g, 10 g

(*R*)-(+)-2-Methyl-CBS-oxazaborolidine, 1*M* solution in toluene

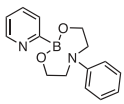
45,769-8 — 5 mL, 25 mL

Excellent catalysts for the asymmetric reduction of prochiral ketones.[1] Reduction of aralkyl ketones with borane sources such as BH_3–THF, BMS, amine-boranes, catecholborane, in the presence of these catalysts (0.02 to 0.1 mol %), provides the corresponding secondary alcohols in high (>95% ee) enantiomeric excesses.[2–5] These reagents are also effective for kinetic resolutions.[6]

(1) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986. (2) Corey, E. J. et al. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (3) Corey, E. J. et al. *J. Am. Chem. Soc.* **1987**, *109*, 7925. (4) Cho, B. T.; Kim, D. J. *Tetrahedron: Asymmetry* **2001**, *12*, 2043. (5) Cho, B. T. et al. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1204. (6) Lebsack, A. D. et al. *J. Am. Chem. Soc.* **2001**, *123*, 4851.

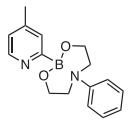
2-Pyridineboronic acid *N*-phenyldiethanolamine ester

64,728-4 — 1 g, 5 g, 10 g



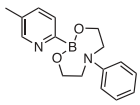
4-Methyl-2-pyridineboronic acid *N*-phenyldiethanolamine ester

64,884-1 — 5 g



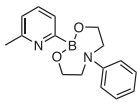
5-Methyl-2-pyridineboronic acid *N*-phenyldiethanolamine ester

64,882-5 — 500 mg, 1 g, 5 g



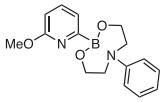
6-Methyl-2-pyridineboronic acid *N*-phenyldiethanolamine ester

64,881-7 — 1 g, 5 g



6-Methoxy-2-pyridineboronic acid *N*-phenyldiethanolamine ester

64,915-5 — 1 g, 5 g



Novel 2-pyridineboronic acid derivatives that are stable for storage and suitable for Suzuki–Miyaura cross-coupling.[1–3]

(1) Fischer, F. C.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 21. (2) Bouillon, A. et al. *Tetrahedron* **2003**, *59*, 10043. (3) Hodgson, P. B.; Salingue, F. H. *Tetrahedron Lett.* **2004**, *45*, 685.

2-Chloro-6-(methylamino)purine, 97%

64,459-5 — 5 g

Has been employed in the preparation of selective $P2Y_1$ receptor agonists and antagonists as pharmacological probes.[1–3]

(1) Kim, Y.-C. et al. *J. Med. Chem.* **2000**, *43*, 746. (2) Nandanan, E. et al. *J. Med. Chem.* **2000**, *43*, 829. (3) Kim, H. S. et al. *J. Med. Chem.* **2001**, *44*, 3092.

Benzofurazan, 97%

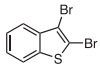
65,013-7 — 1 g, 10 g

Modifications around this key heterocyclic nucleus have led to the preparation of fluorescence probes[1] and inhibitors of nucleic acid and protein biosyntheses.[2,3]

(1) Uchiyama, S. et al. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2525. (2) Crampton, M. R. et al. *J. Chem. Soc., Perkin Trans. 2* **2002**, 257. (3) Ghosh, P. B. et al. *J. Med. Chem.* **1972**, *15*, 255.

2,3-Dibromobenzo[*b*]thiophene, 97%

64,737-3 — 1 g, 5 g



Served as a basic starting material for the synthesis of novel, chiral benzothiophene ligands via Pd-catalyzed allylation.[1] Selective displacement of each bromine makes this compound a very useful building block in Suzuki and Stille coupling reactions.[2,3]

(1) Tietze, L. F.; Lohmann, J. K. *Synlett* **2002**, 2083. (2) Heynderickx, A. et al. *Synthesis* **2002**, 213. (3) Yamamura, K. et al. *Org. Biomol. Chem.* **2004**, *2*, 1413.

2-Chloro-1,1,1-triethoxyethane

64,975-9 — 1 g, 10 g

An effective reagent for the large-scale preparation of 2-chloromethylbenzothiazoles and benzoxazoles.[1] Used also in the synthesis of 21-desoxy-21-chlorocorticosteroids with functionalized 17α-ester groups.[2]

(1) Mylari, B. L. et al. *Synth. Commun.* **1989**, *19*, 2921. (2) Ueno, H. et al. *J. Med. Chem.* **1991**, *34*, 2468.

(Chloromethyl)dimethylvinylsilane, 97%

64,911-2 — 1 g, 10 g

Utilized in the synthesis of silylated β-lactams possessing antibacterial properties.

Altamura, M. et al. *J. Org. Chem.* **1995**, *60*, 8403.

2-(Trimethylsilyl)pyridine, 98%

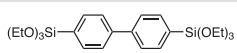
64,985-6 — 1 g, 10 g

Utilized in the preparation of a novel hydroxymethylating reagent, which was then used in the stereoselective synthesis of vinylsilanes.

Itami, K. et al. *Tetrahedron* **2001**, *57*, 5045.

4,4'-Bis(triethoxysilyl)biphenyl, 95%

63,810-2 — 1 g, 10 g



Employed in the preparation of arylene-bridged polysilsesquioxanes.[1,2]

(1) Kapoor, M. P. et al. *Chem. Lett.* **2003**, *32*, 914. (2) Schaefer, D. W. et al. *Chem. Mater.* **2004**, *16*, 1402.

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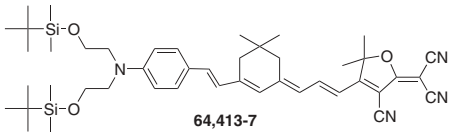

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Photograph © Board of Trustees, National Gallery of Art, Washington.

The Race Track (oil on canvas, 80.5 × 114.9 cm) was painted about 1891 by the French artist Jean-Louis Forain. Just to the right of center in the foreground of the painting, two men and a woman converse intently. A little further back and near the left edge of the picture, several figures appear to be rushing towards the horses and riders. The relative position and differing size—some larger, some smaller—of these groups of figures help to create a sense of space in the picture, which otherwise is dominated by large relatively flat areas of brilliant color, the light green of the grass, the white of the clouds, and the intense blue of the sky.

At first glance, one might identify the artist of this painting as Degas, an artist well known for horseracing subjects. Not only the subject, however, but also the style of the painting may remind us of Degas, as it exhibits the same casual, seemingly unplanned composition that is usual in the work of the more famous artist. It is as if the figures in the painting were caught unawares in a snapshot shortly before the beginning of the race. Indeed, Forain had a chameleon-like tendency to imitate other artists he admired. Not only did he paint racehorses and ballet dancers in a manner that reminds one of Degas, but his wily lawyers and scheming politicians can also be easily mistaken for those of Daumier. And like Daumier, he was a graphic artist as well as a painter. In fact, it was his etchings that brought Forain his greatest fame. He was what we now might call a political cartoonist. Fine as his graphic technique was, however, his paintings almost always remind us of other, better-known artists. All his life, he remained something of a follower, rather than an inventive and original creator of his own unique style.

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

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Palladium-Mediated Synthesis of Aldehydes and Ketones from Thiol Esters

Professor Tohru Fukuyama (right) receiving the *2004 ACS Award for Creative Work in Synthetic Organic Chemistry* from Dr. Chris D. Hewitt, Sigma-Aldrich Director of Chemistry Business Development.
Photo © James Tkatch.

Professor Hidetoshi Tokuyama

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Graduate School of Pharmaceutical Sciences
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Outline

1. Introduction

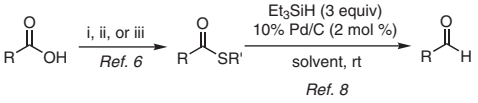
The conversions of carboxylic acids and their derivatives into aldehydes and ketones are important synthetic transformations. The development of mild and chemoselective reactions for effecting these transformations has been thoroughly investigated.[1] Because of the high reactivity of aldehydes under reducing conditions, the development of reagents, which can selectively reduce carboxylic acids or carboxylic acid derivatives to aldehydes without over-reduction to the primary alcohols, has been a challenging task.[1a] To date, several protocols have been utilized for the selective transformation of carboxylic acids and derivatives into aldehydes. These protocols include the reduction of acid chlorides, under Rosenmund conditions (H_2, $Pd/BaSO_4$) or with tributyltin hydride under palladium catalysis, and the reduction of esters or amides with reducing agents such as DIBAL-H or lithium aluminum hydride. However, the currently available protocols are insufficient with respect to functional group compatibility, since these reactions usually require unstable substrates, such as acyl halides or activated esters, or highly basic and nucleophilic reagents. In the course of synthetic studies on natural products, we unexpectedly encountered an exceptionally mild conversion of ethanethiol esters into the corresponding aldehydes with triethylsilane in the presence of palladium-on-carbon.[2] We later learned that the reductive transformation of thiol esters into aldehydes had been discovered in the mid-1940s.[3] However, the impractical procedure, namely heating an ethanethiol ester at reflux in ethanol for six hours with fifty equivalents of Raney® nickel, hampered further investigations. Following our disclosure of the mild Et_3SiH–Pd/C conditions, this transformation has enjoyed widespread use in the synthesis of highly functionalized aldehydes, ranging from α-amino aldehydes to complex natural products. Furthermore, we have also found that the reaction of thiol esters with appropriate organometallic reagents in the presence of transition-metal catalysts is effective for the mild synthesis of ketones.[4,5] In this account, we will discuss the scope and applications of these transformations of thiol esters.

2. Synthesis of Aldehydes by Reduction of Thiol Esters with Triethylsilane

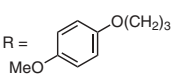
2.1. Reaction Conditions and Scope

Thiol esters can be easily prepared from the corresponding carboxylic acids via the acid chlorides or mixed anhydrides, or by utilizing various dehydrating agents such as DCC or WSCD **(Scheme 1)**.[6] Steglich's method (DCC, DMAP, EtSH)[7] is effective for the thioesterification of N-protected amino acids. Reduction of the resulting ethanethiol esters can be performed under argon with triethylsilane in the presence of palladium-on-carbon at room temperature. A survey of the optimal reaction conditions using simple thiol esters indicated that the reduction reaction rate depends on the choice of solvent (conversion rates are relatively faster in polar solvents) and the structure of the thiol ester moiety (a longer reaction time is required when the steric bulk of the R' group is increased, and no conversion is observed for the substrate derived from *t*-butylmercaptan even after eight hours at room temperature) (see Scheme 1). Reactions in various solvents provided the desired aldehydes in good-to-excellent yields.[8] Accordingly, we developed the following standard conditions: esters of ethanethiol are prepared and their reduction performed in acetone or dichloromethane at room temperature. Another important factor to consider is the concentration of the thiol ester substrate, which should be 0.5 M or higher in order to effect a complete conversion.[9]

A variety of functional groups—including amide, ester, acetonide, silyloxy, sulfide, keto, and even β-lactam—survive the essentially neutral reduction conditions **(Figure 1)**.[2a,b,10–12] However, when an olefin-bearing substrate is employed, reduction of the olefin moiety proceeds under the standard reaction conditions.[13a] Evans et al. reported that this undesired reduction was suppressed by use of Lindlar's catalyst ($Pd/CaCO_3/PbO$) in the presence of an excess amount of an auxiliary terminal alkene such as 1-hexene or 1-decene **(Scheme 2)**.[13]



(i) $ClCO_2Et$, Et_3N, CH_2Cl_2; R'SH, cat. DMAP.
(ii) DCC, R'SH, cat. DMAP, CH_2Cl_2.
(iii) $SOCl_2$, CH_2Cl_2, cat. DMF; R'SH, Et_3N, Et_2O.



R'	Solvent	Time (min)	Yield
Et	acetone	10	97%
Et	DMF	10	71%
Et	MeCN	30	98%
Et	THF	30	97%
Et	DCM	30	89%
Et	PhMe	60	98%
Et	EtOAc	120	78%
Me	acetone	15	91%
i-Pr	acetone	120	93%
Bn	acetone	600	74%
Ph	acetone	600	94%
t-Bu	acetone	480	no reaction

Scheme 1. Effect of Solvent and Thiol Residue Structure on the Rates and Yields of the Reduction Reaction.

2.2. Application to the Synthesis of Amino Aldehydes

α-Amino aldehydes are useful chiral starting materials for which several preparative methods have been developed.[14] Since α-amino aldehydes tend to racemize easily under both acidic and basic conditions, the mild conditions of the present reduction procedure should be suitable for the preparation of this class of compounds. The conversion of a wide range of α-amino acid ethanethiol esters to the corresponding α-amino aldehydes was effected in high yields and without racemization by using Et_3SiH–Pd/C **(Figure 2)**.[2b] In addition to simple α-amino acid derivatives, other amino acid derivatives such as aspartic acid, glutamic acid, lysine derivatives, and β-amino acid derivatives also behave well under the reduction conditions.[2b,15–29] Moreover, the widely used amine-protecting groups—Cbz, Boc,[30] Fmoc,[31] and phthaloyl (Phth)—are unaffected by the reaction conditions. The utility of the Ei_3SiH–Pd/C reduction has been clearly demonstrated in the case of a tetrapeptide **(eq 1)**[32] and a cyclosporin analogue **(eq 2)**.[33]

2.3. Application to the Total Synthesis of Structurally Complex Natural Products

The versatility of the mild Et_3SiH–Pd/C reduction has been fully demonstrated in the total synthesis of a number of structurally complex natural products.[10,13a,b,21,34–46] In a key step in the total synthesis of (+)-cyanocycline A,[47] *N*-Boc-L-glutamic ethanethiol ester was subjected to the standard Et_3SiH–Pd/C conditions on a 40-g scale to give the aldehyde in high yield. Treatment of the aldehyde in situ with $CSA/HC(OMe)_3$ furnished the desired dimethyl acetal without epimerization in 95% overall yield **(Scheme 3)**.[2a] The core skeleton of (+)-neothramycin A was similarly assembled by treating a suitably functionalized L-glutamic diethanethiol ester benzoylamide with Et_3SiH–Pd/C in dichloromethane **(Scheme 4)**.[2a] The intramolecular condensation of the resultant dialdehyde proceeded spontaneously to furnish the desired tricyclic intermediate. Subsequent functional group manipulation led to a concise total synthesis of (+)-neothramycin A.

Oxazolidinones are widely used auxiliaries in synthetic organic chemistry. This type of auxiliary can be easily removed

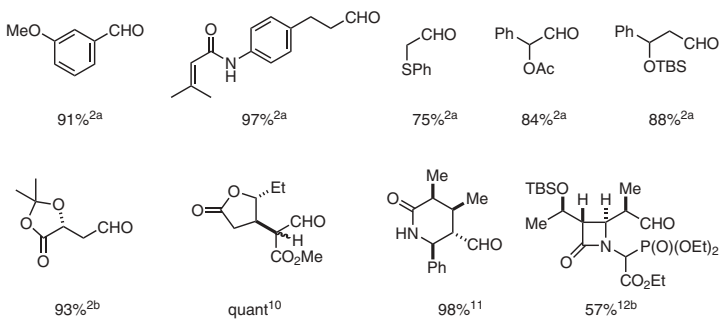


Figure 1. Functional-Group Tolerance of the Thiol Ester Reduction with Et_3SiH–Pd/C.

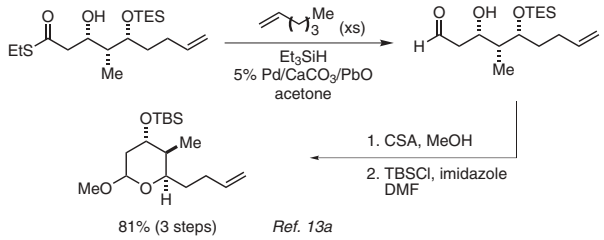
by a regioselective attack of the thiolate anion on the imide carbonyl carbon.[48,49] The sequence of reactions consisting of oxazolidinone cleavage with thiolate, followed by palladium-mediated reduction of the thiol ester with Et_3SiH, constitutes a facile and mild method for obtaining the corresponding aldehyde. This approach was employed by Evans and Johnson in their asymmetric total synthesis of the marine natural product (–)-isopulo'upone **(Scheme 5)**.[13b] The bicyclic core skeleton of (–)-isopulo'upone was effectively constructed by a catalytic, enantioselective, intramolecular Diels–Alder reaction with the chiral Cu(II)-bis(oxazoline) complex.[13c] Thioesterification of the hindered imide intermediate was achieved by addition of lithium ethylthiolate. Reduction of the resulting ethyl thiol ester, under the modified conditions developed for olefin-containing substrates, produced the corresponding aldehyde with complete suppression of the endocyclic-double-bond reduction.[13]

We performed the Et_3SiH–Pd/C reduction twice on highly functionalized substrates in our total synthesis of (+)-leinamycin, a potent antitumor agent **(Scheme 6)**.[36] Treatment of the β,γ-unsaturated thiol ester with Et_3SiH–Pd/C afforded the corresponding aldehyde without isomerization of the Z double bond, which was then migrated to the α,β position with Dabco®. The catalytic asymmetric aldol reaction developed by Mukaiyama[50] provided the anti α,β-dihydroxy thiol ester product. Protection of the allylic hydroxyl group as an MOM ether, followed by thiol ester reduction with Et_3SiH–Pd/C, afforded the corresponding protected dihydroxy aldehyde intermediate.

An asymmetric aldol reaction of a ketene silyl *O,S*-acetal and a subsequent Et_3SiH–Pd/C reduction of the resultant thiol ester[13a,36,40,41,43–46] constitute a powerful protocol for the construction of contiguous chiral centers. The utility of this protocol was demonstrated in Evans's elegant, enantioselective, total synthesis of altohyrtin C (also known as spongistatin 2), a potent in vitro antitumor agent **(Scheme 7)**.[40] The enantioselective Sn^{2+}-catalyzed aldol reaction of ethyl glyoxylate gave the anti aldol product.[51] Reduction of the benzenethiol ester under the standard Et_3SiH–Pd/C conditions took place smoothly to afford the corresponding aldehyde. This aldehyde was subjected to the Mukaiyama aldol reaction, which resulted in elongation of the carbon chain and the formation of an ethanethiol ester. Reduction of this second thiol ester with Et_3SiH–Pd/C, followed by treatment with camphorsulfonic acid (CSA) and silylation with TESCl, furnished the intermediate for the F-ring unit of altohyrtin C.

3. Synthesis of Ketones from Thiol Esters

The synthesis of ketones from carboxylic acids and their derivatives by nucleophilic addition has also been an important tool in synthetic organic chemistry.[1b] A number of protocols have been developed to improve this reaction by suppressing the formation of tertiary alcohols arising from further addition of the



Scheme 2. Suppression of Alkene Reduction by Use of Lindlar's Catalyst.

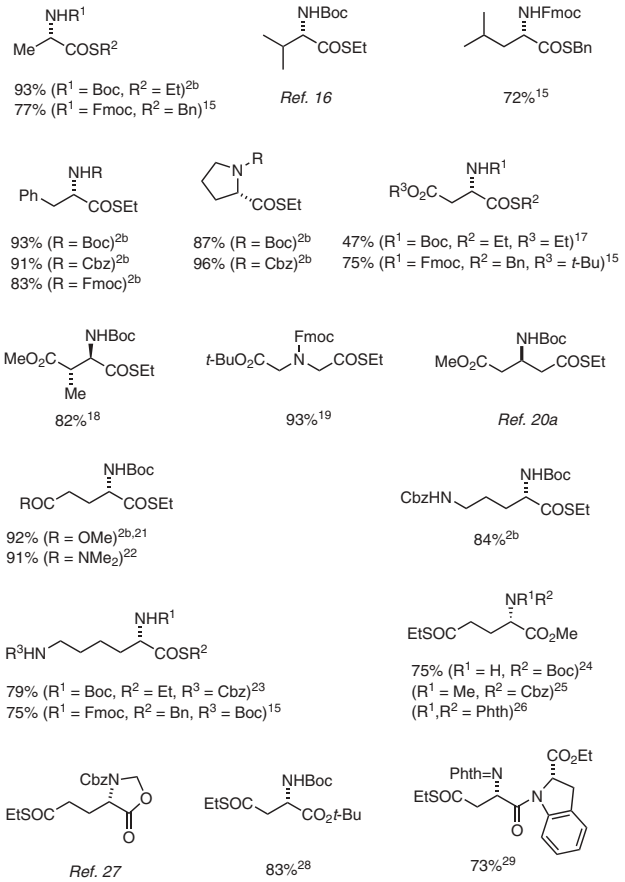
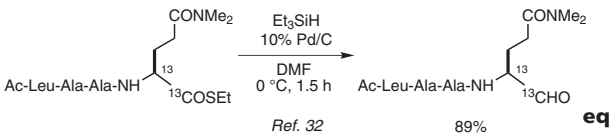
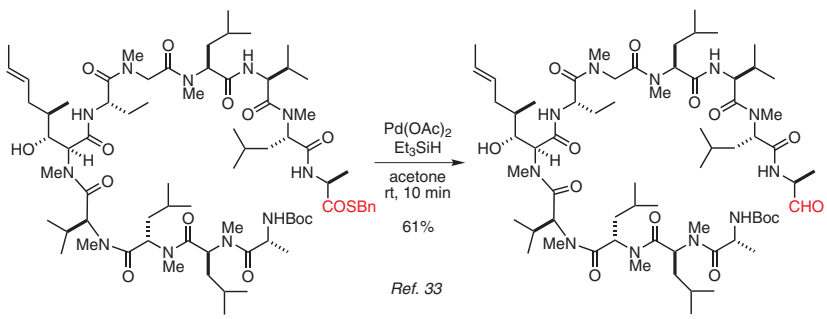


Figure 2. α-Amino Acid Thiol Esters as Precursors to α-Amino Aldehydes. Yields Shown Are of the Amino Aldehyde Products.



eq 1



eq 2

nucleophiles to the (initially formed) ketone products. These protocols include the addition of Grignard and organolithium reagents to heterosubstituted amides and esters, such as *N*-methoxy-*N*-methylamides (Weinreb's amides)[52] or *S*-(2-pyridyl)thiolates;[53] the reaction of organocopper reagents with acid chlorides,[54] *S*-(2-pyridyl)thiolates,[55] or thiol esters;[56] and the transition-metal-catalyzed reaction of acid halides with organotin[57] or organozinc reagents.[58]

Having successfully established the usefulness of the Et_3SiH–Pd/C reduction for the preparation of aldehydes, we then turned our attention to extending this chemistry to the synthesis of ketones. The proposed mechanism of aldehyde formation **(Scheme 8)** involves initial oxidative addition of Pd(0) to the C(sp^2)–S bond, followed by transmetallation of the resultant acylpalladium species[59] with Et_3SiH. Reductive elimination from the resulting acylpalladium hydride leads to the desired aldehyde and the regeneration of the Pd(0) species. On the basis of this mechanism, we surmised that substituting an appropriate organometallic reagent for Et_3SiH would provide the corresponding ketone after transmetallation and reductive elimination.

3.1. Palladium-Catalyzed Coupling of Thiol Esters with Organozinc Reagents

3.1.1. Reaction Conditions and Scope

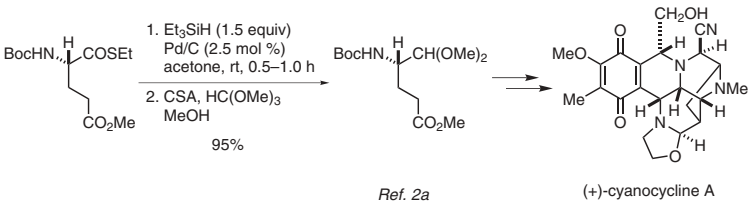
Extensive screening of various combinations of transition-metal catalysts and organometallic reagents revealed that the optimal conditions for generating ethyl ketones from thiol esters in high yields involve the use of an excess of EtZnI and catalytic amounts of $PdCl_2(PPh_3)_2$ in toluene at room temperature **(eq 3)**.[4,60] In addition to ethylzinc iodide, isobutyl-, phenyl-, β-phenethyl-, and vinylzinc iodides[61]—as well as benzylzinc bromide and functionalized alkylzinc reagents bearing ester[62] and protected amine groups[63]—could also be employed. The mildness and versatility of the reaction were demonstrated with a variety of substrates: alkyl, aryl, and α,β-unsaturated thiol esters bearing sensitive functional groups such as keto, α-acetyloxy, mercapto, aromatic bromo and chloro, and even aliphatic and aromatic aldehydo groups **(eq 4)**.[2c,4] This exceptionally high chemoselectivity is probably due to the facile oxidative addition of the palladium catalyst to the C–S bond and the relatively low nucleophilicity of the zinc reagents. These reaction conditions are also suitable for the synthesis of N-protected α-amino ketones without appreciable racemization **(eq 5)**.[4,64] Combinations of functionalized organozinc reagents and thiol esters—prepared from phenylalanine, glutamic acid, or proline—afforded structurally intriguing amino ketones in good yields.

Very recently, Seki and co-workers modified the reaction conditions in order to apply this reaction on an industrial scale.[65] They found that, unlike homogeneous catalysts, Pd/C[65a] and $Pd(OH)_2$/C[65b,c] are effective heterogeneous catalysts for the coupling reaction **(eq 6)**. In general, $Pd(OH)_2$/C possesses superior activity, providing the desired ketone product with only 0.15 mol % of the catalyst. A key to the facile coupling using these heterogeneous catalysts is to perform the reaction in a mixed solvent system, such as THF and toluene, in the presence of 4% (v/v) DMF.

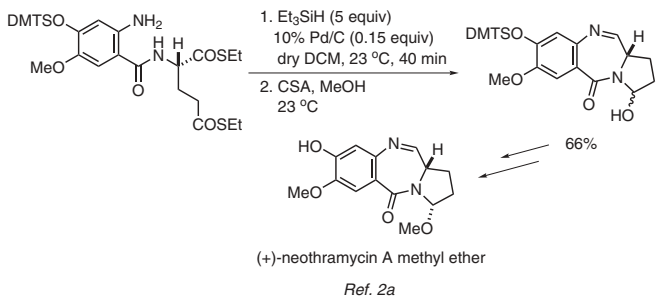
3.1.2. Application to the Total Synthesis of Natural Products

The exceptionally high chemoselectivity of this coupling reaction is particularly useful for the conversion of polyfunctionalized carboxylic acids into ketones via thiol esters. One example is the efficient synthesis of (+)-biotin **(Scheme 9)**,[65b,66] in which Seki's group applied this methodology to the cyclic thiolactone system. The coupling reaction was carried out on the known key thiolactone intermediate[67] using 4-ethoxycarbonylbutylzinc iodide. In situ acid-mediated dehydration of the thiohemiketal coupling product led to the known intermediate for biotin synthesis in 87% yield for the two steps. (+)-Biotin was obtained according to the method described by Gerecke et al.,[67] which included hydrogenation of the double bond from the convex face and deprotection reaction steps.

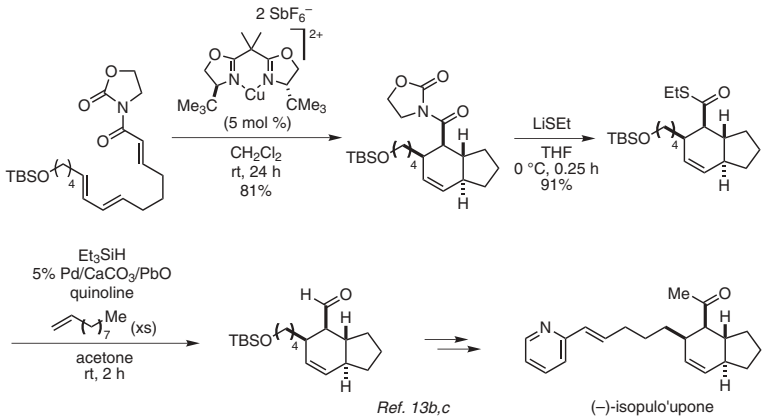
Our second-generation total synthesis of the squalene synthase inhibitor phomoidride B (also known as (–)-CP-263,114), utilized the Pd-catalyzed coupling reaction in the final stage of the synthesis **(Scheme 10)**.[68] Although our initial attempt to carry out the coupling reaction under the "standard" conditions resulted in the recovery of the starting material, a modified procedure—in which the THF solvent was pumped out and replaced by toluene—was successful. Thus, the reaction of the advanced intermediate **(M)**—which had all of the required functionalities including maleic anhydride, γ-lactone hemiketal, and thiol ester—proceeded



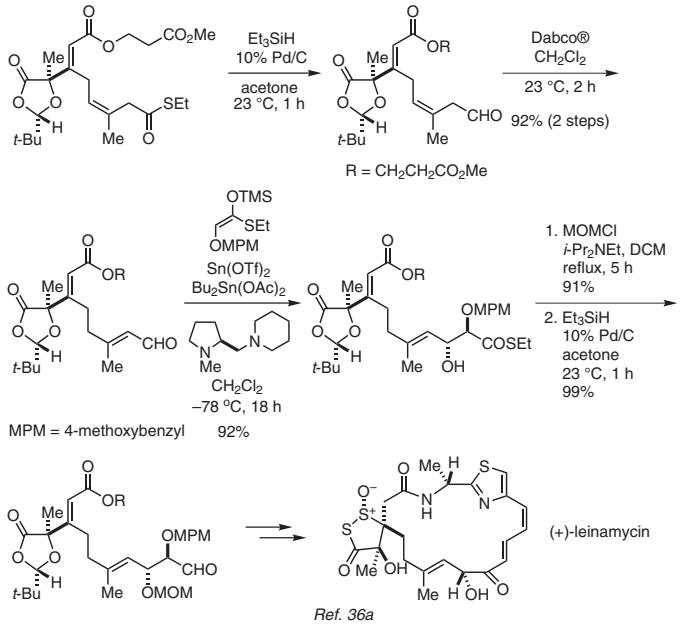
Scheme 3. Et_3SiH–Pd/C Reduction of a Thiol Ester as a Key Step in the Synthesis of the Natural Product (+)-Cyanocycline A.



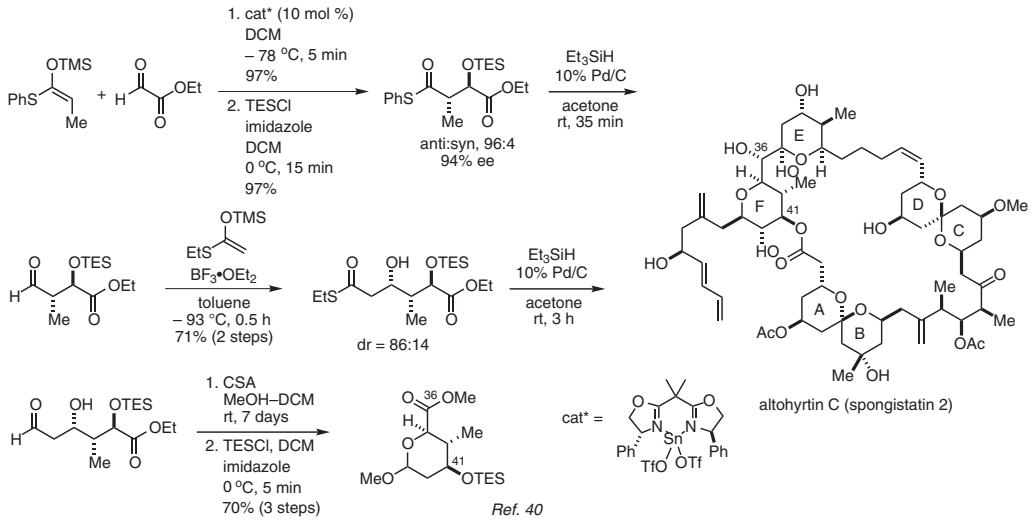
Scheme 4. Et_3SiH–Pd/C Reduction of a Di(ethanethiol ester) as a Key Step in Assembling the Core Skeleton of (+)-Neothramycin A.



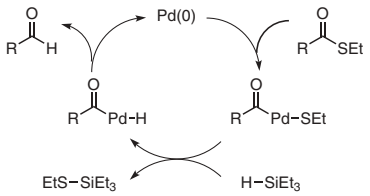
Scheme 5. Et_3SiH Reduction of an Ethanethiol Ester as a Key Step in the Asymmetric Total Synthesis of (–)-Isopulo'upone.



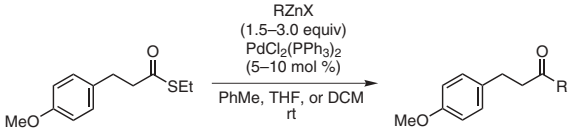
Scheme 6. The Reduction of Thiol Esters with Et_3SiH–Pd/C Used Twice in the Total Synthesis of (+)-Leinamycin.



Scheme 7. Thiol Ester Reduction as an Important Part of a Powerful Protocol for the Construction of Contiguous Chiral Centers.



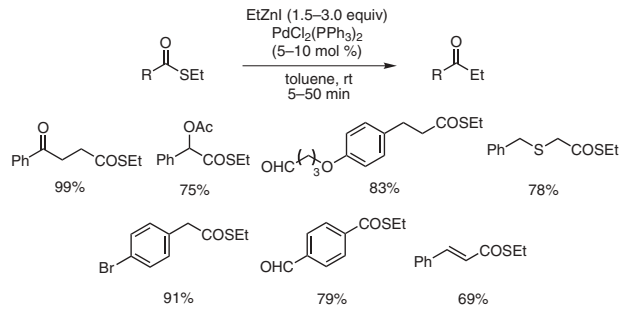
Scheme 8. Proposed Catalytic Cycle for the Pd-Catalyzed Reduction of Thiol Esters with Et_3SiH.



RZnX	Time (min)	Yield (%)
EtZnI	5	91
i-BuZnI	15	90
PhZnBr	60	86
PhZnI	60	50
EtO_2C–ZnI	15	92
–ZnI	120	79
PhthN–ZnI	40	83

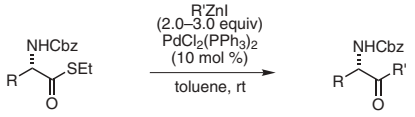
Ref. 4

eq 3



Ref. 2c,4

eq 4



Thiol Ester	R'	Time (min)	Yield (%)
	Et	15	88
NHCbz, Ph, SEt	$EtO_2C(CH_2)_3$	40	88
	Ph	90	58
	$PhthN(CH_2)_3$	90	64
NHCbz, MeO_2C, SEt	Et	90	82
	$EtO_2C(CH_2)_3$	90	82
NCbz, SEt	Et	180	73
	$EtO_2C(CH_2)_3$	110	64

Ref. 4

eq 5

smoothly in toluene to afford the desired coupling product without affecting the delicate functional groups. The fact that the coupling reaction with ethylzinc iodide (instead of 3-pentenylzinc iodide) provided the corresponding ethyl ketone analogue with equal ease should make this an attractive approach for the synthesis of phomoidride B analogues differing in the ketone side chain.

3.2. Palladium-Catalyzed Coupling of Thiol Esters with Terminal Alkynes

We have recently extended our methodology to the synthesis of α,β-acetylenic ketones[69] by the Pd-catalyzed coupling of thiol esters with terminal alkynes. The coupling reaction proceeded smoothly under modified Sonogashira-coupling conditions [$PdCl_2$(dppf), 0.10 equiv; P(2-furyl)$_3$, 0.25 equiv; and CuI (1.7 equiv) in DMF–NEt_3 (5:1)], in which an excess of CuI was required for complete conversion **(eq 7)**.[5] Various terminal acetylenes and functionalized thiol esters were successfully reacted under these conditions, demonstrating the versatility of this ynone synthesis **(eq 8)**.[5]

3.3. Related Coupling Reactions of Thiol Esters

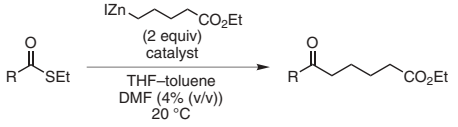
The formation of ketones by transition-metal-catalyzed coupling of thiol esters with other organometallic reagents has also been reported. Marchese and co-workers carried out the Fe(II)-catalyzed coupling of benzenethiol esters with Grignard reagents to smoothly furnish the corresponding ketones in high yields **(eq 9)**.[70] Recently, Liebeskind, Srogl, and Savarin established two conditions for the coupling reaction between thiol esters and boronic acids.[71] They used 4-halo-*n*-butylthiol esters as starting materials in one case **(eq 10)**,[71a] and found that the presence of Cu(I) thiophene-2-carboxylate (as co-catalyst) was crucial in the second case **(eq 11)**.[71b]

4. Odorless Protocol with 1-Dodecanethiol

The preceding conversions of ethanethiol esters into aldehydes or ketones are exceptionally mild and highly chemoselective transformations, and have a variety of applications, especially in the total synthesis of complex natural products. However, despite these advantages, ethanethiol and its byproducts are unpleasant compounds to work with because of their offensive odors. This drawback can be mitigated by using 1-dodecanethiol esters, since 1-dodecanthiol is reported to be odorless.[72]

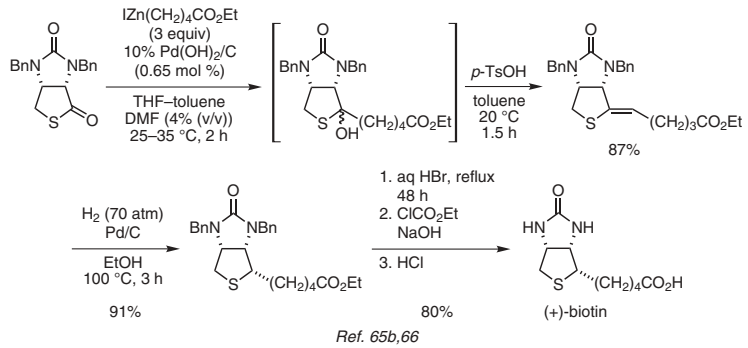
The dodecanethiol esters were prepared in the same manner as the ethanethiol esters by the mixed anhydride method, acylation with acid chlorides, or by the use of dehydrating reagents.[73] While dodecanethiol esters generally required longer reaction times than those of the corresponding ethanethiol esters, comparable yields of the desired products were obtained in the Et_3SiH–Pd/C reduction to aldehydes, ketone formation with organozinc reagents, and alkynyl ketone synthesis with terminal acetylenes **(Scheme 11)**.[73]

Lithium dodecanethiolate proved useful in the removal of oxazolidinone-type chiral auxiliaries **(Scheme 12)**.[73a] Thus, after Evans's diastereoselective aldol reaction, the imide was transformed into the dodecanethiol ester by the regioselective



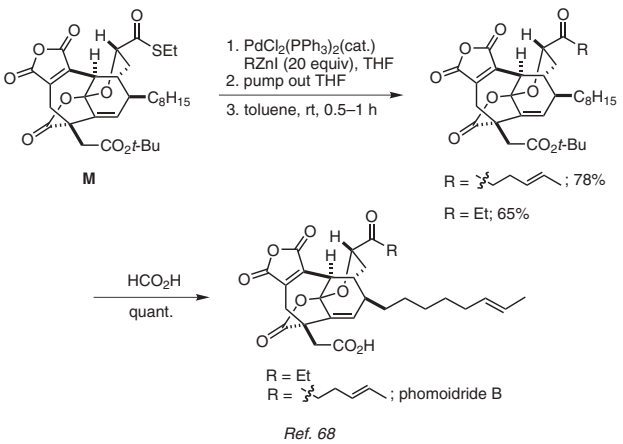
Ref. 65a,c

eq 6



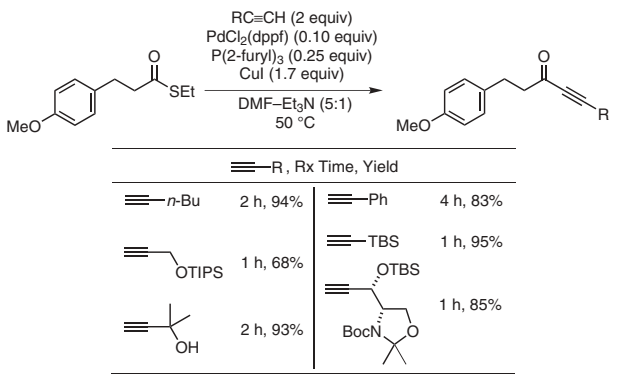
Ref. 65b,66

Scheme 9. Application of the Pd-Catalyzed Coupling of Thiol Esters with Organozinc Reagents to the Total Synthesis of (+)-Biotin.



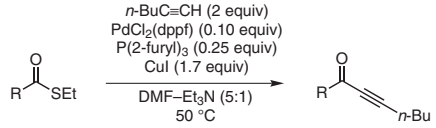
Ref. 68

Scheme 10. Application of the Pd-Catalyzed Coupling of Thiol Esters with Organozinc Reagents to the Total Synthesis of Phomoidride B.



Ref. 5

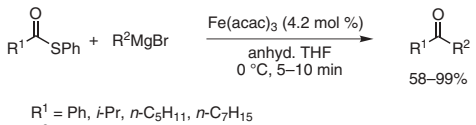
eq 7



R	Time	Yield
4-MeOC$_6$H$_4$CH$_2$CH$_2$	2 h	94%
PhC(=O)CH$_2$CH$_2$	3 h	80%
4-BrC$_6$H$_4$CH$_2$CH$_2$	1 h	80%
trans-*n*-C$_5$H$_{11}$CH=CH	2 h	64%
trans-PhCH=CH	4 h	64%
3-ClC$_6$H$_4$	1 h	74%

Ref. 5

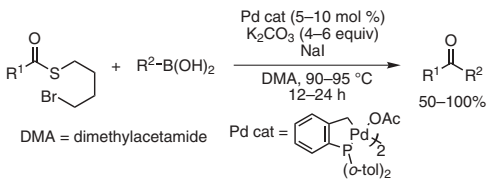
eq 8



R^1 = Ph, *i*-Pr, *n*-C$_5$H$_{11}$, *n*-C$_7$H$_{15}$
R^2 = Ph, Me, *i*-Pr, Bu, *n*-C$_5$H$_{11}$, *n*-C$_7$H$_{15}$

Ref. 70a

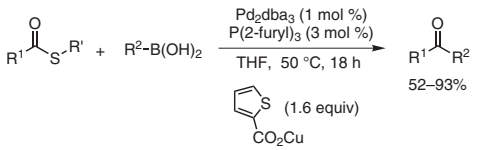
eq 9



R^1 = Ph, Me, *n*-C$_{11}$H$_{23}$
R^2 = Ph, 3-MeOC$_6$H$_4$, 2-naphthyl, 2-HCO-4-MeOC$_6$H$_3$

Ref. 71a

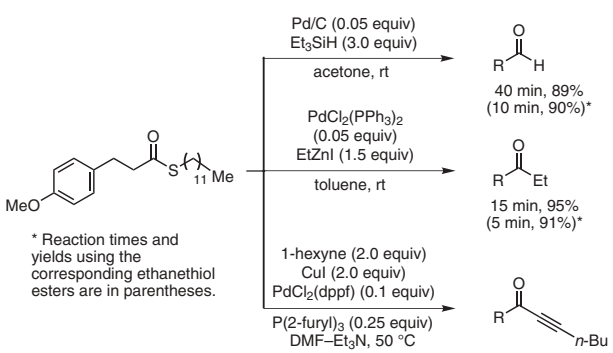
eq 10



R^1 = CF_3, $ClCH_2$, $AcOCH_2$, Ph, 4-$NO_2C_6H_4$, 4-HOC_6H_4, 2-pyrazyl, $C_{11}H_{23}$, adamantyl
R^2 = Ph, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 3-$NO_2C_6H_4$, 4-$MeO_2CC_6H_4$, 2-CHO-4-$MeOC_6H_3$, 3,4-methylenedioxyphenyl, (*E*)-β-styryl, 2-naphthyl
R' = Et, Ph, 4-MeC_6H_4, Me_2NOCCH_2

Ref. 71b

eq 11



Ref. 73a

Scheme 11. Reactivity of Dodecanethiol Esters vis-à-vis Ethanethiol Esters.

addition of lithium dodecanethiolate. The resulting dodecanethiol ester was converted into the corresponding aldehyde with Et_3SiH–Pd/C.

5. Conclusions

A number of complex aldehydes and ketones have been synthesized efficiently from thiol esters by the methods described in this review. The most attractive feature of these methods is their broad compatibility with sensitive and complex functional groups on the thiol ester, as well as with the coupling partners in the case of ketone synthesis. This is likely due to the unique nature of thiol esters, which serve as relatively stable precursors for the generation of acylpalladium species. Once the acylpalladium species is generated, reduction with the trialkylsilane or coupling with the organometallic reagent takes place under the mild reaction conditions. Because of its versatility, we expect this thiol ester based methodology will find many more useful applications in organic synthesis.

6. Acknowledgements

The generous financial support of the Ministry of Education, Culture, Sports, Science, and Technology of Japan; CREST and PRESTO, the Japan Science and Technology Agency (JST); the Mitsubishi Foundation; and the Uehara Memorial Foundation is gratefully acknowledged. We would like to thank our co-workers, who have contributed to these studies, and whose names appear in the cited publications.

7. References and Notes

(1) (a) For a review on the synthesis of aldehydes, see Parkes, K. E. B.; Richardson, S. K. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Pergamon: Oxford, 1995; Vol. 3, Chapter 3.01. (b) For a review on the synthesis of ketones, see O'Neill, B. T. Nucleophilic Addition to Carboxylic Acid Derivatives. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, Chapter 1.13, p 397.

(2) (a) Fukuyama, T.; Lin, S.-C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050. (b) Tokuyama, H.; Yokoshima, S.; Lin, S.-C.; Li, L.; Fukuyama, T. *Synthesis* **2002**, 1121. (c) Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Lin, S.-C.; Li, L.; Fukuyama, T. *J. Braz. Chem. Soc.* **1998**, *9*, 381. (d) Fukuyama, T. *J. Synth. Org. Chem. Jpn.* **2003**, *61*, 620. (e) Tokuyama, H. *Yakugaku Zasshi* **2003**, *123*, 1007.

(3) (a) Wolfrom, M. L.; Karabinos, J. V. *J. Am. Chem. Soc.* **1946**, *68*, 1455. (b) Wolfrom, M. L.; Karabinos, J. V. *J. Am. Chem. Soc.* **1946**, *68*, 724.

(4) Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 3189.

(5) Tokuyama, H.; Miyazaki, T.; Yokoshima, S.; Fukuyama, T. *Synlett* **2003**, 1512.

(6) For reviews on the synthesis of thiol esters, see: (a) Bauer, W.; Kühlein, K. In *Carboxylic Acids and Carboxylic Acid Derivatives*; Falbe, J., Ed.; Methoden Der Organischen Chemie (Houben-Weyl); Georg Thieme Verlag: Stuttgart, Germany, 1985; Vol. E5, p 832. (b) Voss, J. Synthesis of Thioesters and Thiolactones. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6, Chapter 2.5, p 435.

(7) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.

(8) Fukuyama, T.; Tokuyama, H.; Kuboyama, T. The University of Tokyo, Tokyo, Japan. Unpublished work, 2000.

(9) Even under these optimal conditions, we sometimes observed that consumption of the starting thiol ester stopped. In such cases, effective reactions were achieved in the presence of (a) ca. 2 equivalents of anhydrous $MgSO_4$ (Fukuyama, T.; Tokuyama, H.; Yamagishi, H. The University of Tokyo, Tokyo, Japan. Unpublished work, 2004), or (b) 4 Å molecular sieves as described by Estiarte, M. A.; de Souza, M. V. N.; del Rio, X.; Dodd, R. H.; Rubiralta, M.; Diez, A. *Tetrahedron* **1999**, *55*, 10173.

(10) Takayama, H.; Fujiwara, R.; Kasai, Y.; Kitajima, M.; Aimi, N. *Org. Lett.* **2003**, *5*, 2967.

(11) Jnoff, E.; Ghosez, L. *J. Am. Chem. Soc.* **1999**, *121*, 2617.

(12) For applications to β-lactams, see: (a) Sakurai, O.; Horikawa, H. *Tetrahedron Lett.* **1996**, *37*, 7811. (b) Seki, M.; Kondo, K.; Iwasaki, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 3. (c) Sakurai, O.; Takahashi, M.; Ogiku, T.; Hayashi, M.; Horikawa, H.; Iwasaki, T. *Tetrahedron Lett.* **1994**, *35*, 6317.

(13) (a) Evans, D. A.; Trotter, B. W.; Côté, B.; Coleman, P. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2741. (b) Evans, D. A.; Johnson, J. S. *J. Org. Chem.* **1997**, *62*, 786. (c) Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; von Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582.

(14) For reviews on α-amino aldehydes, see: (a) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149. (b) Gryko, D.; Chalko, J.; Jurczak, J. *Chirality* **2003**, *15*, 514.

(15) Ho, P. T.; Ngu, K.-y. *J. Org. Chem.* **1993**, *58*, 2313.

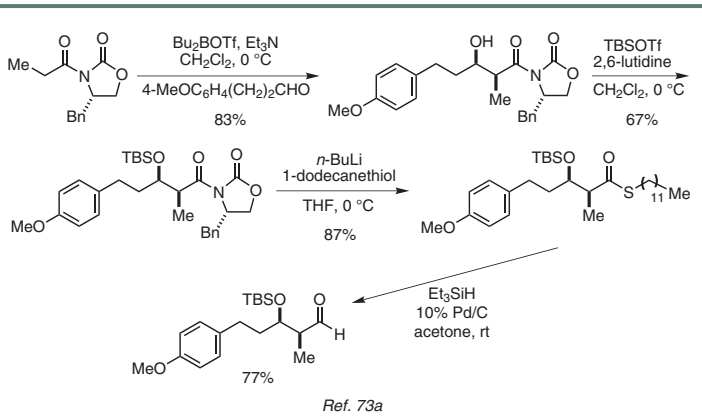
(16) Plake, H. R.; Sundberg, T. B.; Woodward, A. R.; Martin, S. F. *Tetrahedron Lett.* **2003**, *44*, 1571.

(17) Ede, N. J.; Rae, I. D.; Hearn, M. T. W. *Int. J. Pept. Protein Res.* **1994**, *44*, 568.

(18) D'Aniello, F.; Mann, A.; Taddei, M. *J. Org. Chem.* **1996**, *61*, 4870.

(19) Han Y.; Giragossian, C.; Mierke, D. F.; Chorev, M. *J. Org. Chem.* **2002**, *67*, 5085.

(20) (a) Fujiwara, A.; Kan, T.; Fukuyama, T. *Synlett* **2000**, 1667. (b)



Ref. 73a

Scheme 12. Application of the Et_3SiH Reduction of Dodecanethiol Esters in Synthesis.

Kan, T.; Fujiwara, A.; Kobayashi, H.; Fukuyama, T. *Tetrahedron* **2002**, *58*, 6267.
(21) Taschner, M. J.; Huang, Y.; El-Alali, A.; Chen, L.; Youngs, W. J. *Tetrahedron Lett.* **1992**, *33*, 2765.
(22) Ramtohul, Y. K.; James, M. N. G.; Vederas, J. C. *J. Org. Chem.* **2002**, *67*, 3169.
(23) Iwanowicz, E. J.; Lin, J.; Roberts, D. G. M.; Michel, I. M.; Seiler, S. M. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1607.
(24) Tamura, S. Y.; Goldman, E. A.; Brunck, T. K.; Ripka, W. C.; Semple, J. E. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 331.
(25) (a) Aurelio, L.; Brownlee, R. T. C.; Hughes, A. B. *Org. Lett.* **2002**, *4*, 3767. (b) Aurelio, L.; Box, J. S.; Brownlee, R. T. C.; Hughes, A. B.; Sleebs, M. M. *J. Org. Chem.* **2003**, *68*, 2652.
(26) Robl, J. A. *Tetrahedron Lett.* **1994**, *35*, 393.
(27) Fukuyama, T.; Liu, G.; Linton S. D.; Lin, S.-C.; Nishino, H. *Tetrahedron Lett.* **1993**, *34*, 2577.
(28) Bergmeier, S. C.; Cobás, A. A.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 2369.
(29) Robl, J. A.; Karanewsky, D. S.; Asaad, M. M. *Tetrahedron Lett.* **1995**, *36*, 1593.
(30) For some Boc-protected substrates, we observed the formation of a byproduct, which was completely suppressed by addition of 1.5 equivalents of 2,6-lutidine (see reference 2b).
(31) Ho and Ngu (reference 15) observed an undesired loss of Fmoc from ethanethiol esters. This side reaction was suppressed by using the corresponding benzylthiol esters.
(32) Malcolm, B. A.; Lowe, C.; Shechosky, S.; McKay, R. T.; Yang, C. C.; Shah, V. J.; Simon, R. J.; Vederas, J. C.; Santi, D. V. *Biochemistry* **1995**, *34*, 8172.
(33) Eberle, M. K.; Jutzi-Eme, A.-M.; Nuninger, F. *J. Org. Chem.* **1994**, *59*, 7249.
(34) (+)-A83543A (lepicidin) aglycon: (a) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1992**, *114*, 2260. (b) Evans, D. A.; Black W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497.
(35) Rutamycin B: (a) Evans, D. A.; Ng, H. P. *Tetrahedron Lett.* **1993**, *34*, 2229. (b) Evans, D. A.; Ng, H. P.; Rieger, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 11446.
(36) (+)-Leinamycin: (a) Kanda, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **1993**, *115*, 8451. (b) Fukuyama, T.; Kanda, Y. *J. Synth. Org. Chem. Jpn.* **1994**, *52*, 888.
(37) (+)-Acutiphycin and (+)-*trans*-20,21-didehydroacutiphycin: Smith, A. B., III; Chen, S. S.-Y.; Nelson, F. C.; Reichert, J. M.; Salvatore, B. A. *J. Am. Chem. Soc.* **1995**, *117*, 12013.
(38) Smith, A. B., III; Chen, S. S.-Y.; Nelson, F. C.; Reichert, J. M.; Salvatore, B. A. *J. Am. Chem. Soc.* **1997**, *119*, 10935.
(39) (–)-Stenine: Morimoto, Y.; Iwahashi, M.; Nishida, K.; Hayashi, Y.; Shirahama, H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 904.
(40) Altohyrtin C (spongistatin 2): Evans, D. A.; Trotter, B. W.; Coleman, P. J.; Côté, B.; Carlos Dias, L.; Rajapakse, H. A.; Tyler, A. N. *Tetrahedron* **1999**, *55*, 8671.
(41) (+)-Methyl pederate: (a) Toyota, M.; Hirota, M.; Nishikawa, Y.; Fukumoto, K.; Ihara, M. *J. Org. Chem.* **1998**, *63*, 5895. (b) Toyota, M.; Ihara, M. *J. Synth. Org. Chem. Jpn.* **1998**, *56*, 818.
(42) Garsubellin A: (a) Usuda, H.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2002**, *4*, 859. (b) Usuda, H.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 3621.
(43) Cyclic hexadepsipeptide GE3: Makino, K.; Henmi, Y.; Hamada, Y. *Synlett* **2002**, 613.
(44) Pectenotoxins-4 and 8: (a) Evans, D. A.; Rajapakse, H. A.; Chiu, A.; Stenkamp, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 4573. (b) Evans, D. A.; Rajapakse, H. A.; Stenkamp, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 4569.
(45) (+)-Cystothiazole A: DeRoy, P. L.; Charette, A. B. *Org. Lett.* **2003**, *5*, 4163.
(46) Octalactin B: Shiina, I.; Oshiumi, H.; Hashizume, M.; Yamai, Y.-s.; Ibuka, R. *Tetrahedron Lett.* **2004**, *45*, 543.
(47) Fukuyama, T. In *Advances in Heterocyclic Natural Product Synthesis*; Pearson, W. H., Ed.; JAI Press: Greenwich, CT, 1992; pp 189–249.
(48) Damon, R. E.; Coppola, G. M. *Tetrahedron Lett.* **1990**, *31*, 2849.
(49) Narasaka, K.; Saitou, M.; Iwasawa, N. *Tetrahedron: Asymmetry* **1991**, *2*, 1305.
(50) Mukaiyama, T.; Uchiro, H.; Shiina, I.; Kobayashi, S. *Chem. Lett.* **1990**, 1019.
(51) Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10859.
(52) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
(53) Mukaiyama, T.; Araki, M.; Takei, H. *J. Am. Chem. Soc.* **1973**, *95*, 4763.
(54) For a review, see Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; Wiley: New York, 1980.
(55) Onaka, M.; Matsuoka, Y.; Mukaiyama, T. *Chem. Lett.* **1981**, 531.
(56) Anderson, R. J.; Henrick, C. A.; Rosenblum, L. D. *J. Am. Chem. Soc.* **1974**, *96*, 3654.
(57) Milstein, D.; Stille, J. K. *J. Org. Chem.* **1979**, *44*, 1613.
(58) Negishi, E.-i.; Bagheri, V.; Chatterjee, S.; Luo, F. -T.; Miller, J. A.; Stoll, A. T. *Tetrahedron Lett.* **1983**, *24*, 5181.
(59) For the generation of acylpalladium species from carboxylic acid derivatives, see: (a) Kakino, R.; Yasumi, S.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 137. (b) Nagayama, K.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1803. (c) Wang, D.; Zhang, Z. *Org. Lett.* **2003**, *5*, 4645. (d) Falorni, M.; Giacomelli, G.; Porcheddu, A.; Taddei, M. *J. Org. Chem.* **1999**, *64*, 8962.
(60) The Suzuki-coupling reaction (thiol ester, *p*-benzyloxyphenylboronic acid, $Pd(PPh_3)_4$, Ag_2CO_3, in toluene-water) gave the desired aryl ketone in low yield. When a commercially available THF solution of Et_2Zn was used instead of EtZnI, a small amount of the corresponding aldehyde was isolated (see footnotes 10 and 11 in reference 4).
(61) (a) For a general review on the preparation of organozinc reagents, see Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117 and references therein. (b) β-Phenethylzinc iodide: Grondin, J.; Hajjad, F.; Vottero, P.; Blancou, H.; Commeyras, A. *C. R. Acad. Sci. Paris Ser. II* **1988**, *307*, 1699. (c) Benzylic zinc bromides: Berk, S. C.; Knochel, P.; Yeh, M. C. P. *J. Org. Chem.* **1988**, *53*, 5789. (d) Arylzinc iodides: Majid, T. N.; Knochel, P. *Tetrahedron Lett.* **1990**, *31*, 4413.
(62) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z.-i. In *Organic Syntheses*; Freeman, J. P., Ed.; Wiley: New York, 1993; Collect. Vol. VIII, p 274.
(63) Yeh, M. C. P.; Chen, H. G.; Knochel, P. *Org. Synth.* **1992**, *70*, 195.
(64) Estiarte, M. A.; Diez, A.; Rubiralta, M.; Jackson, R. F. W. *Tetrahedron* **2001**, *57*, 157.
(65) (a) Shimizu, T.; Seki, M. *Tetrahedron Lett.* **2001**, *42*, 429. (b) Mori, Y.; Seki, M. *Heterocycles* **2002**, *58*, 125. (c) Mori, Y.; Seki, M. *J. Org. Chem.* **2003**, *68*, 1571. (d) Shimizu, T.; Seki, M. *Tetrahedron Lett.* **2002**, *43*, 1039.
(66) Shimizu, T.; Seki, M. *Tetrahedron Lett.* **2000**, *41*, 5099.
(67) Gerecke, M.; Zimmermann, J.-P.; Aschwanden, W. *Helv. Chim. Acta* **1970**, *53*, 991.
(68) Hayashi, Y.; Itoh, T.; Fukuyama, T. *Org. Lett.* **2003**, *5*, 2235.
(69) For a review on α,β-unsaturated ketones, see: Ebenezer, W. J.; Wight, P. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Reeds, C. W., Eds.; Pergamon: Cambridge, U.K., 1995; Vol. 3, Chapter 3.05, pp 205–276.
(70) (a) Cardellicchio, C.; Fiandanese, V.; Marchese, G.; Ronzini, L. *Tetrahedron Lett.* **1985**, *26*, 3595. (b) Fiandanese, V.; Marchese, G.; Naso, F. *Tetrahedron Lett.* **1988**, *29*, 3587.
(71) (a) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2000**, *2*, 3229.

(b) Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260.

(72) (a) Node, M.; Kumar, K.; Nishide, K.; Ohsugi, S.-i.; Miyamoto, T. *Tetrahedron Lett.* **2001**, *42*, 9207. (b) Nishide, K.; Ohsugi, S.-i.; Fudesaka, M.; Kodama, S.; Node, M. *Tetrahedron Lett.* **2002**, *43*, 5177. (c) 1-Dodecanethiol is commercially available and inexpensive.

(73) (a) Miyazaki, T.; Han-ya, Y.; Tokuyama, H.; Fukuyama, T. *Synlett* **2004**, 477. (b) Separation of the product from the reaction mixture was carried out rather easily. After removal of the palladium catalyst by filtration through a pad of Celite® and concentration of the filtrate, the less polar byproduct, $Et_3SiS(CH_2)_{11}Me$, was separated by passing the material through a short column of silica gel with hexanes as eluent.

About the Authors

Professor Tohru Fukuyama was born in Anjo, Aichi, in 1948, and received his B.A. in 1971 and M.A. in 1973 from Nagoya University. He then moved to Harvard University and received his Ph.D. in 1977 under the direction of Professor Y. Kishi. After a year of postdoctoral study at Harvard, he joined the faculty of Rice University as assistant professor, and rose to the rank of full professor in 1988. In 1995, he moved to the University of Tokyo, where he is currently professor of pharmaceutical sciences. He is the recipient of the 1993 ACS Arthur C. Cope Scholar Award; the 2001 Synthetic Organic Chemistry, Japan, Award; the 2003 ISHC Senior Award in Heterocyclic Chemistry; and the 2004 ACS Award for Creative Work in Synthetic Organic Chemistry. His research interest is in the area of total synthesis of complex natural products.

Professor Hidetoshi Tokuyama was born in Yokohama in 1967. He received his Ph.D. in 1994 from the Tokyo Institute of Technology under the direction of Professor Ei-ichi Nakamura. He spent one year (1994–1995) at the University of Pennsylvania as a postdoc with Professor Amos B. Smith, III. He joined the group of Professor Tohru Fukuyama at the University of Tokyo in 1995, and was appointed associate professor in 2003. He is the recipient of the 2001 Sankyo Award in Synthetic Organic Chemistry, Japan; and the 2003 Pharmaceutical Society of Japan Award for Young Scientist. His current research interest is centered on the development of protocols for synthesizing heterocyclic compounds and the total synthesis of natural products.

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- Palladium contamination of reaction vessels and associated cleanup costs
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- Cost of catalyst lost during reaction workup

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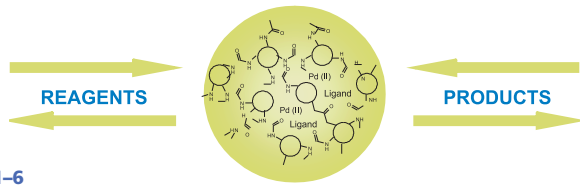
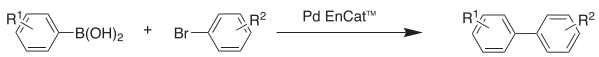
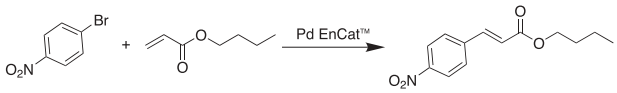
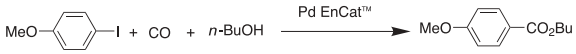
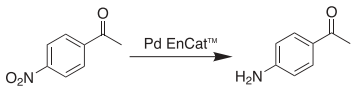


What Can Pd EnCat™ Do?[1–6]

Suzuki Coupling	
Heck Reaction	
Carbonylation	
Transfer Hydrogenation	

References: (1) Yu, J.-Q. et al. *Chem Commun.* **2003**, 678. (2) Bremeyer, N. et al. *Synlett* **2002**, 1843. (3) Ley, S. V. et al. *Chem Commun.* **2002**, 1134. (4) Chandrashekar, R. et al. *Chem Commun.* **2002**, 1132. (5) Vickerstaffe, E. et al. *Org. Biomol. Chem.* **2003**, *1*, 2419. (6) Ley, S. V. et al. *Org. Lett.* **2003**, *5*, 4665.

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Cat No.	Name	Matrix Content (%)	Pd (mmol/g)	P (mmol/g)	Ligand	Units		
64,472-2	Pd EnCat™ 40	40	3.9–4.6	N/A	N/A	1 g	10 g	100 g
64,471-4	Pd EnCat™ 30	30	3.9–4.6	N/A	N/A	1 g	10 g	100 g
64,470-6	Pd EnCat™ TPP30	30	3.9–4.6	0.26–0.35	Ph_3P	1 g	10 g	100 g
64,469-2	Pd EnCat™ TOTP30	30	3.9–4.6	0.15–0.20	$(o\text{-toyl})_3P$	1 g	10 g	100 g

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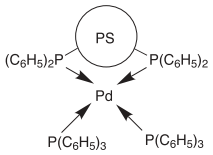
References: (1) Kim, J.-H. et al. *Tetrahedron Lett.* **2004**, *45*, 5827. (2) Churruca, F. et al. *Tetrahedron* **2004**, *60*, 2393. (3) Akiyama, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 3412. (4) Yamazaki, K.; Kondo, Y. *J. Comb. Chem.* **2002**, *4*, 191.

Palladium Reagents

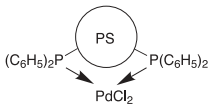
51,157-9
Tetrakis(triphenylphosphine)palladium(0), polymer-bound
1% DVB, 100–200 mesh, 0.5–1.5 mmol Pd/g

1 g
5 g



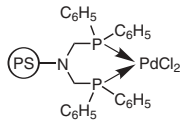
59,693-0
Bis(triphenylphosphine)palladium(II) dichloride, polymer-bound
1% DVB, 100–200 mesh, 1.0–2.0 mmol Pd/g

1 g
5 g



64,655-5
Bis[(diphenylphosphanyl)methyl]aminepalladium(II) dichloride, polymer-bound

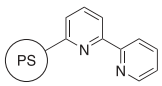
1 g
5 g



Palladium-Scavenging Resins

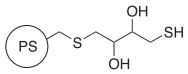
58,999-3
Bipyridine, polymer-bound
1% DVB, 100–200 mesh, 1.0–2.0 mmol N/g

5 g
25 g
100 g



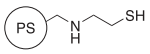
64,194-4
Dithiothreitol, polymer-bound
1% DVB, 100–200 mesh, 2.0–3.0 mmol S/g

5 g
25 g



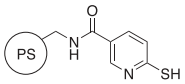
64,102-2
2-Mercaptoethylamine, polymer-bound
1% DVB, 70–90 mesh, 1.0–1.5 mmol S/g

5 g
25 g



64,390-4
6-Thionicotinamide, polymer-bound
1% DVB, 70–90 mesh, 2.0–3.0 mmol S/g

5 g
25 g



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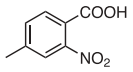
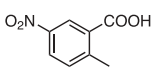
63,829-3
$C_8H_7NO_4$ — 1 g, 5 g

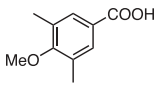


63,830-7
$C_8H_7NO_4$ — 1 g, 5 g

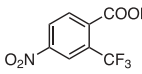


63,832-3
$C_8H_7FO_2$ — 1 g, 5 g

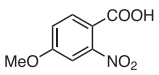
63,869-2
$C_{10}H_{12}O_3$ — 1 g, 5 g



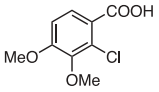
63,870-6
$C_8H_4F_3NO_4$ — 1 g, 5 g



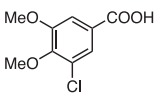
63,872-2
$C_8H_7NO_5$ — 1 g, 5 g



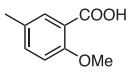
63,873-0
$C_9H_9ClO_4$ — 1 g, 5 g



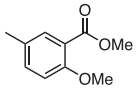
63,874-9
$C_9H_9ClO_4$ — 1 g, 5 g



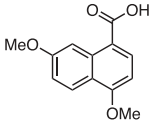
64,289-4
$C_9H_{10}O_3$ — 1 g, 5 g



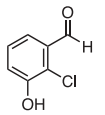
64,441-2
$C_{10}H_{12}O_3$ — 5 g



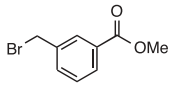
64,715-2
$C_{13}H_{12}O_4$ — 1 g



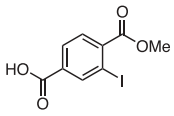
64,736-5
$C_7H_5ClO_2$ — 1 g, 10 g



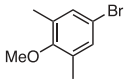
64,811-6
$C_9H_9BrO_2$ — 5 g, 25 g



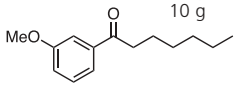
65,006-4
$C_9H_7IO_4$ — 5 g, 10 g



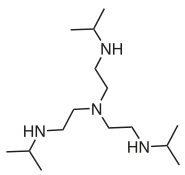
63,880-3
$C_9H_{11}BrO$ — 1 g, 5 g



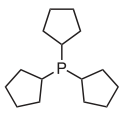
64,989-9
$C_{14}H_2O_2$ — 1 g, 10 g



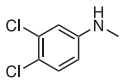
64,509-5
$C_{15}H_{36}N_4$ — 1 g, 5 g



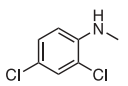
64,907-4
$C_{15}H_{27}P$ — 1 g, 5 g



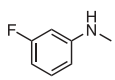
56,926-7
$C_7H_7Cl_2N$ — 1 g, 10 g



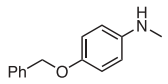
63,095-0
$C_7H_7Cl_2N$ — 1 g, 5 g



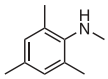
63,096-9
C_7H_8FN — 1 g, 5 g



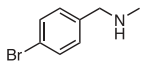
63,103-5
$C_{14}H_{15}NO$ — 1 g, 10 g



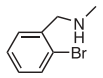
63,104-3
$C_{10}H_{15}N$ — 1 g, 5 g



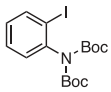
63,114-0
$C_8H_{10}BrN$ — 1 g, 5 g



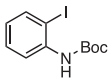
63,116-7
$C_8H_{10}BrN$ — 1 g, 5 g



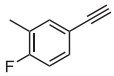
64,424-2
$C_{16}H_{22}INO_4$ — 1 g, 10 g



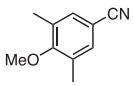
64,731-4
$C_{11}H_{14}INO_2$ — 1 g, 10 g



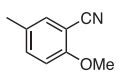
52,120-5
C_9H_7F — 1 g, 10 g



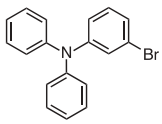
63,881-1
$C_{10}H_{11}NO$ — 1 g, 5 g



64,290-8
C_9H_9NO — 1 g, 5 g

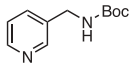


64,752-7
$C_{18}H_{14}BrN$ — 1 g, 5 g

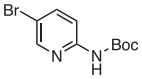


Heterocyclic Building Blocks

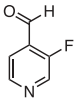
63,444-1
$C_{11}H_{16}N_2O_2$ — 1 g, 5 g



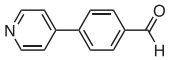
64,638-5
$C_{10}H_{13}BrN_2O_2$ — 5 g



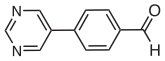
64,431-5
C_6H_4FNO — 1 g, 5 g



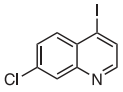
64,598-2
$C_{12}H_9NO$ — 1 g, 5 g



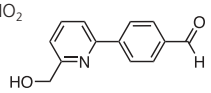
64,713-6
$C_{11}H_8N_2O$ — 1 g, 5 g



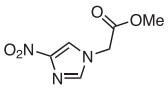
64,738-1
C_9H_5ClIN — 1 g, 5 g



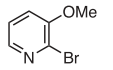
64,849-3
$C_{13}H_{11}NO_2$ — 1 g, 5 g



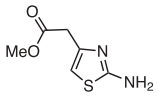
64,970-8
$C_6H_7N_3O_4$ — 1 g, 10 g



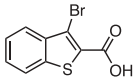
64,971-6
C_6H_6BrNO — 1 g, 10 g



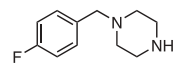
64,972-4
$C_6H_8N_2O_2S$ — 1 g, 5 g



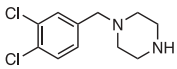
64,973-2
$C_9H_5BrO_2S$ — 1 g



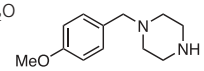
64,616-4
$C_{11}H_{15}FN_2$ — 1 g, 5 g



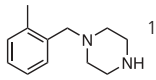
64,426-9
$C_{11}H_{14}Cl_2N_2$ — 1 g, 5 g



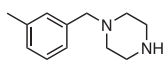
64,615-6
$C_{12}H_{18}N_2O$ — 1 g, 5 g



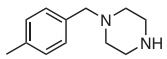
64,422-6
$C_{12}H_{18}N_2$ — 1 g, 10 g



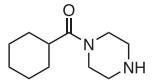
64,852-3
$C_{12}H_{18}N_2$ — 1 g, 5 g



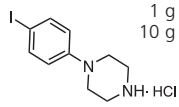
64,617-2
$C_{12}H_{18}N_2$ — 1 g, 5 g



64,712-8
$C_{11}H_{20}N_2O$ — 1 g, 5 g

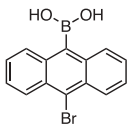


64,726-8
$C_{10}H_{13}IN_2 \cdot HCl$ — 1 g, 10 g

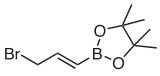


Boronic Acids and Esters

59,575-6
$C_{14}H_{10}BBrO_2$ — 1 g, 10 g

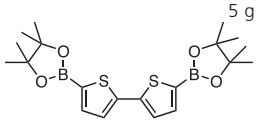


64,378-5
$C_9H_{16}BBrO_2$ — 1 g, 5 g

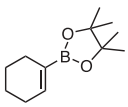


64,659-8
$C_4H_9BO_2$ — 500 mg, 2 g

64,702-0
$C_{20}H_{28}B_2O_4S_2$ — 1 g, 5 g

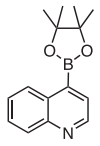


65,027-7
$C_{12}H_{21}BO_2$ — 500 mg, 1 g

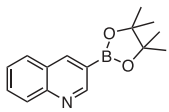


64,878-7
$C_3H_9BO_2$ — 1 g, 10 g

64,879-5
$C_{15}H_{18}BNO_2$ — 1 g, 5 g



64,795-0
$C_{15}H_{18}BNO_2$ — 1 g, 5 g



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For competitive quotes on larger quantities, please contact **safcglobal.com.**

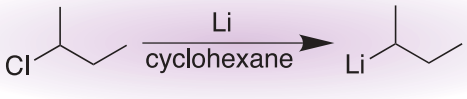
Stabilized Lithium Powder

Finely powdered lithium metal is widely used in a variety of reactions, notably the formation of alkyllithium reagents from organic halides. Caution should be used, however, since lithium is a flammable metal that reacts violently with water yielding flammable hydrogen gas.

Aldrich offers stabilized lithium metal:

59,058-4	Lithium, stabilized powder, 50–150 micron	10 g 50 g

- Nonpyrophoric
- Chemically stable under typical atmospheric conditions[1]
- Retains high reactivity with organic halides[2]
- Free-flowing, high-surface area powder



sec-Butyllithium is readily prepared from easy-to-use stabilized lithium.[2]

Also available:

24,882-7	Lithium, ca. 30 wt. % dispersion in mineral oil	100 g
59,518-7	Lithium, ca. 40 wt. % dispersion in mineral oil	100 g

References and Notes:

(1) Can be handled in air for a short period of time. A dry, argon atmosphere should be used for long-term storage.
(2) Dieter, R. K. et al. *J. Org. Chem.* **2001**, *66*, 2302.

2005 ACS Award Recipients

Aldrich, a proud sponsor of three ACS awards, congratulates the following recipients for their outstanding contributions to chemistry.

ACS Award for Creative Work in Synthetic Organic Chemistry
Professor Chi-Huey Wong, *The Scripps Research Institute*

ACS Award in Inorganic Chemistry
Professor William J. Evans, *University of California, Irvine*

Herbert C. Brown Award for Creative Research in Synthetic Methods
Professor Emeritus Gilbert Stork, *Columbia University*

Congratulations to each and all!

2004 Young Chemist in Industry Prizes

Sigma-Aldrich is pleased to announce the names of the prize winners for the top three presentations at the *Young Chemist in Industry XIII* meeting that was held in London on April 27, 2004.

Group photograph of some of the attendees. Alasdair Smith is 7th from the left, David Wightman 4th from the right, and Sarah Kelly 5th from the right. Photo courtesy of Janette Niccolls of SCI.

This annual, one-day meeting is organized by the Society of Chemical Industry (SCI), and showcases organic chemistry research undertaken in an industrial setting by chemists under the age of 30 who do not hold a Ph.D. It represents a unique opportunity for younger chemists to present their research to an industry-wide audience. The presentation topics span a wide range of areas that include medicinal, combinatorial, and process chemistry. This year's gathering was attended by 95 delegates, and featured 10 presentations by participants and one invited lecture.

Sigma-Aldrich applauds the work of these talented young scientists. It is our honor to recognize the important contributions being made by young chemists throughout the industry.

We congratulate the winners and commend all those who participated in the meeting.

First Place Winner:	Alasdair Smith, Organon (Newhouse) *Opioid Receptor Like (ORL-1) Agonists as Novel Analgesics*
Second Place Winner:	David Wightman, AstraZeneca (Macclesfield) *AZD2563 Coupled Ketal: A Mixed Anhydride Approach*
Third Place Winner:	Sarah Kelly, Merck, Sharp and Dohme (Harlow) *Novel Ligands for the $GABA_A$ Receptor as Potential Anxiolytics*

Hydroalumination Reactions in Organic Chemistry†

Professor Herbert W. Roesky (right) receiving the *2004 ACS Award in Inorganic Chemistry* from Dr. Geoff Irvine, President of Aldrich-APL. Photo © James Tkatch.

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D-37077 Göttingen, Germany
Email: hroesky@gwdg.de

Outline

1. Introduction

Aluminum is the most abundant metal in the earth's crust (82 g•kg^{-1}) and is extensively used in daily life, thus making it an ideal choice for use in organometallic compounds. Since the discovery of Ziegler and Natta that aluminum compounds play a crucial role in polymerization reactions, many aluminum compounds have become available on an industrial scale. As a result, the chemistry of organoaluminum compounds has found widespread use for a variety of such materials. In particular, methylalumoxane (MAO), an important polymerization cocatalyst, has been the subject of recent interest and its chemistry has been reviewed.[1] The present article will give a brief overview of the chemistry of R_2AlH and $RAlH_2$ compounds, but will concentrate on hydroalumination reactions.

2. Synthetic Routes to Diorganoaluminum Hydrides (R_2AlH)

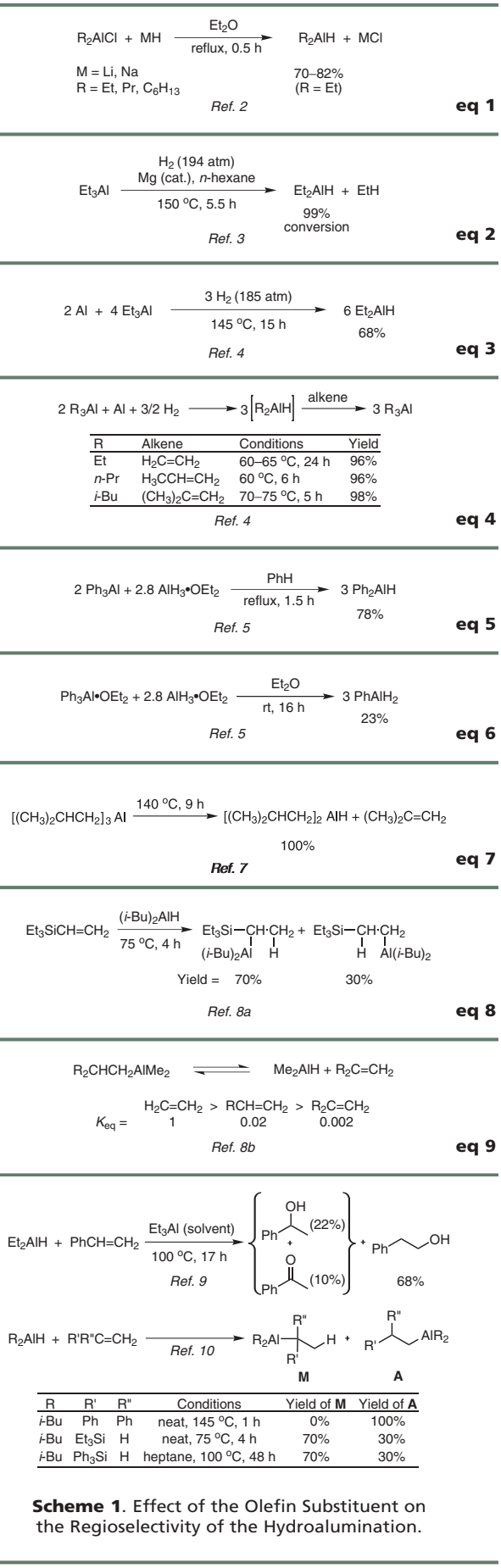
The most commonly used synthesis of R_2AlH compounds is the metathesis of R_2AlX (X = halide) with lithium or sodium hydride **(eq 1)**.[2] The reaction of MH with organoaluminum dihalides does not yield the corresponding dihydrides in a pure form. In general, a mixture of mono- and dihydrides is obtained. Hydrogenolysis of triorganoaluminum compounds is another route to diorganoaluminum hydrides **(eq 2)**.[3] This method generally gives high yields of R_2AlH, although an autoclave operating at 194 atm and 150 °C has to be used. Ziegler's method uses aluminum and hydrogen directly in the presence of R_3Al **(eq 3)**,[4] and, in most cases, the R_2AlH generated is used without isolation in insertion reactions with alkenes **(eq 4)**.[4] The redistribution of R_3Al and aluminum hydride (prepared in situ) in different stoichiometries is yet another method for the preparation of R_2AlH **(eq 5** and **6)**.[5,6]

Finally, the loss of alkene from an aluminum trialkyl is an interesting route to R_2AlH compounds. The ease of departure of the alkene decreases in the following order: $CH_2{=}CR_2$ > $H_2C{=}CHR$ > $CH_2{=}CH_2$. Therefore, the higher-substituted alkyl is used for the preparation of R_2AlH compounds **(eq 7)**.[7]

3. Hydroalumination with R_2AlH

The reverse of the reaction shown in equation 7 can be used for the hydroalumination of alkenes **(eq 8)**.[8a] The relative stability of the C–Al bond can be estimated by thermodynamic and kinetic studies of the reactions of R_2AlH with alkenes. A determination of the equilibrium constant (*K*) for the system depicted in **equation 9** would indicate the thermodynamic stability of a given C–Al bond in the presence of a given alkene.[8] However, it is assumed that the olefinic exchange takes place through a preformed "L_2AlH" and, therefore, the rate of exchange is closely related to the reaction of L_2AlH with the olefin.

It was found that for a given $RAlL_2$, *K* decreases in the order $H_2C{=}CH_2$ > $H_2C{=}CHR$ > $H_2C{=}CR_2$. In general, hydroalumination reactions with R_2AlH are highly syn stereoselective and, although anti-Markovnikov addition is favored, substituents on the olefin can greatly influence product formation **(Scheme 1)**.[9,10]



Scheme 1. Effect of the Olefin Substituent on the Regioselectivity of the Hydroalumination.

The addition of R_2AlH to alkynes can result in principle in four stereoisomeric products **(Scheme 2)**. However, the product formed highly depends on the nature of the substituents R^1, R^2, and AlR_2. The kinetically controlled mode of addition generally gives the syn products. The anti products are formed at higher temperatures through rearrangement or by a double addition–elimination reaction **(eq 10)**.[11]

4. Preparations and Reactions of $RAlH_2$ Compounds

A compound of composition $(RAlH_2)_2$, **1**, where R = *t*-Bu_2pz (*t*-Bu_2pz = 3,5-di-*tert*-butylpyrazolato), resulted from the reaction of H[*t*-Bu_2pz] with AlH_3•NMe_3 and concomitant elimination of hydrogen and trimethylamine **(eq 11)**.[12]

The reaction of **1** with an excess of HC≡CPh smoothly leads to [(μ-η': η'-3,5-*t*-Bu_2pz)(μ-Al)(C≡CPh)$_2$]$_2$ **(2)** in 59% yield **(eq 12)**.[13] The X-ray structural analysis of **2** reveals that the six-membered ring is in a twisted conformation and the four phenylethynyl groups are in terminal positions. Most interesting, two of the terminal AlC≡C units are markedly deviated from the linearity expected for the *sp*-hybridized carbon atom (AlC≡C, 160.2°).

In contrast to its reaction with PhC≡CH, **1** reacts with an excess of HC≡C$SiMe_3$ to give the heterocycle **3** in 51% yield **(eq 13)**.[13] The formation of **3** is surprising. We assume that all four hydrides in **1** are initially replaced by C≡C$SiMe_3$ groups to yield an intermediate similar to **2**. Insertion of two molecules of HC≡C$SiMe_3$ into the Al–N bonds of this intermediate then takes place and affords **3**.

The reaction of **1** with the congeners of molecular oxygen yields the chalcogenide hydrides **4**–**6** that contain a bridging chalcogen atom **(eq 14)**.[14] Complexes **4**–**6** are easily prepared as long as strictly stoichiometric amounts of starting materials are used; otherwise, the formation of polymeric materials is observed. It is quite surprising that compounds **4**–**6** are stable, since one Al–H and one Al–E bond are both attached to each of the aluminum atoms. The two hydrides in **4**–**6** can easily be replaced by C≡CR groups with concomitant elimination of H_2, when **4**–**6** are reacted with H-C≡CR compounds.

The aluminum dihydride **7** was obtained in 86% yield by reaction of β-diketimine ArN=C(Me)CH=C(Me)NHAr (Ar = 2,6-diisopropylphenyl) with AlH_3•NMe_3 at room temperature in hexane **(eq 15)**.[15] The heterogeneous reaction of **7** with elemental selenium proceeds at room temperature in toluene to give $RAl(SeH)_2$ **(8)**—the first aluminum compound with two SeH groups—in 58% yield.[15] At room temperature, **8** is slowly converted to **9** with elimination of H_2Se **(eq 16)**.[15] An alternative route to **9** is the reaction of **7** with selenium at 60 °C. Compounds **8** and **9** are useful starting materials for the preparation of bimetallic systems containing Al–Se–M linkages.

The corresponding reaction of **7** with elemental sulfur under the same conditions yielded a mixture of products with trace amounts of $RAl(SH)_2$, **10**. Pure **10**, the first structurally characterized aluminum compound with two SH groups, was obtained when a catalytic amount of $P(NMe_2)_3$ was added to the reaction mixture of **7** and sulfur **(eq 17)**.[16a] The role of $P(NMe_2)_3$ in the reaction was investigated by ^1H and ^{31}P NMR spectroscopy. The NMR measurements showed that $P(NMe_2)_3$ is immediately converted into $SP(NMe_2)_3$. However, an independent experiment indicated that $SP(NMe_2)_3$ is not functioning as a catalyst. The system becomes catalytic when $SP(NMe_2)_3$ and sulfur are used. Obviously, the reactive intermediate $S_2P(NMe_2)_3$ is responsible for the conversion of **7** into **10 (Scheme 3)**.[16a] Formation of $S_2P(NMe_2)_3$ is also favored from theoretical calculations on the model compound SPH_3 using the RHF/3-21 G* method.[16b]

5. Reactions of AlH_3 Compounds with Alkynes

AlH_3•NMe_3 is best prepared from $LiAlH_4$ and Me_3N•HCl **(eq 18)**.[17] The trimethylamino group in AlH_3•NMe_3 can be easily replaced by an N-heterocyclic carbene (e.g., **11**) to yield **12 (eq 19)**.[18a] AlH_3•NMe_3 reacts with excess HC≡CPh in boiling hexane to give **13** in 73% yield **(eq 20)**.[18b] Due to the filled octet shell at the aluminum in **13**, dimerization of **13** is not observed. The N-heterocyclic carbene adduct **14** is available in 91% yield directly from $AlCl_3$, *t*-BuC≡CLi, and the stable N-heterocyclic carbene :C[N(Me)CMe]$_2$ **(eq 21)**.[18b] Adduct **14** is the first example of an N-heterocyclic-carbene-stabilized aluminum alkynyl containing three terminal alkynyl groups.

In contrast, when the HC acidic alkynes HC≡CR (R = Ph, CH_2SiMe_3) are treated with an excess of AlH_3•NMe_3 in boiling toluene, carbaalanes [$(AlH)_6(AlNMe_3)_2(CCH_2R)_6$], **15** and **16**, are formed in 85% and 93% yields, respectively **(eq 22)**.[19]

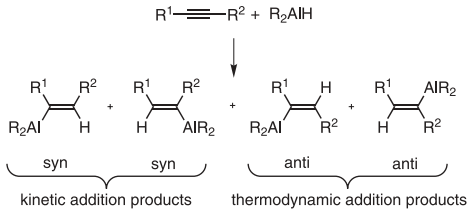
The crystal structure of **15** is a rhombic dodecahedron containing a cube of eight aluminum atoms with six carbon atoms and attached organic groups at each face of the cube **(Figure 1)**.[19] Each carbon atom of the dodecahedron core is connected to three AlH and one Al(NMe_3) unit. The bonding in these cores can be regarded as three-dimensional surface aromaticity. Four bonds are formed using three electron pairs on the closed Al_4C faces of the cube and, consequently, lead to a strong delocalization of the electrons. Ab initio (RHF and DFT) calculations, carried out on the modified structure [$(AlH)_6(AlNH_3)_2(CMe)_6$], indicate that the molecular orbital localized at one Al_4C cubic face has a sextet with a large HOMO–LUMO gap (8.8 eV) that is consistent with an aromatic character.[19]

Most important in compounds **15** and **16** are six reactive Al–H bonds attached to the dodecahedron core. In fact, compound **16** reacts stepwise with BCl_3 to yield the metathesis product [$(AlCl)_6(AlNMe_3)_2(CCH_2CH_2SiMe_3)_6$] (**17**) in 84% yield **(Scheme 4)**.[19] Surprisingly, when an excess of BCl_3 is used, one methyl group of the $SiMe_3$ unit is replaced by a chlorine atom to generate [$(AlCl)_6(AlNMe_3)_2(CCH_2CH_2SiMe_2Cl)_6$] (**18**). These results clearly demonstrate that cluster **16** can be functionalized stepwise both in its inner and outer spheres.

The synthesis of a nanosized, ferrocenylmethylene-substituted carbaalane, **19**, was achieved when an excess of AlH_3•NMe_3 was treated with ferrocenylacetylene **(eq 23)**.[20] Compound **19** is a model for the fixation of an organometallic fragment onto a carbide surface; its structure was established by single-crystal, X-ray analysis.

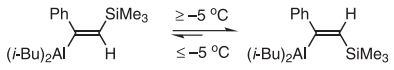
Wilke and Schneider were the first to investigate the reaction of R_2AlH with R_2AlC≡CR (R = Me, Et) leading to carbaalanes.[21] The structural characterization of these carbaalane products was reported by Uhl and Breher.[22]

In boron chemistry, the carbaborane dianions are a well-established class of compounds. In contrast, the first carbaalane dianion, [{*t*-$BuCH_2C(AlH_2$•$NMe_3)_3Li\}_2\{(AlH)_8(CCH_2$*t*-$Bu)_6\}$] (**20**), was prepared in 62% yield only recently **(eq 24)**.[23] $ClAlH_2$•NMe_3, one of the starting materials used for the synthesis of **20**, was obtained in situ from the reaction of AlH_3•NMe_3 with Me_3SiCl. The central part of the 3-D structure of **20 (Figure 2)** is the carbaalanate cluster $[(AlH)_8(CCH_2t\text{-}Bu)_6]^{2-}$, which is isoelectronic with [$(AlH)_6(AlNMe_3)_2(CCH_2Ph)_6$] (**15**) and, therefore, implies the same aromatic stabilization. In each of the two cationic parts, a lithium is coordinated through three hydrogen atoms to the neutral [*t*-$BuCH_2C(AlH_2$•$NMe_3)_3$] moiety. In the latter species, three AlH_2•NMe_3 groups are bound covalently to one carbon atom. DFT calculations on the simplified model [$MeC(AlH_2$•$NH_3)_3Li]^+$ showed that the Li cation fits nicely

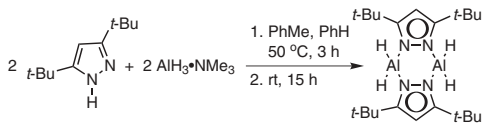


Ref. 11

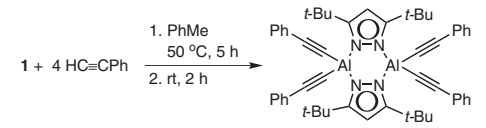
Scheme 2. The Four Possible Stereoisomers Resulting from Addition of R_2AlH to Alkynes.



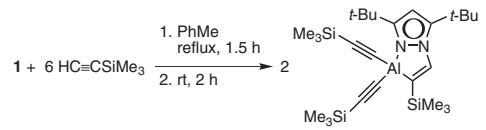
Ref. 11b ≥ 99% **eq 10**



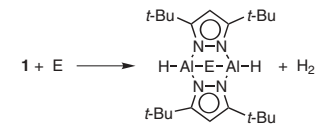
Ref. 12 76% **eq 11**



Ref. 13 59% **eq 12**

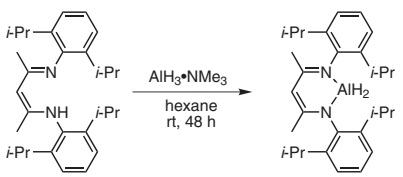


Ref. 13 51% **eq 13**

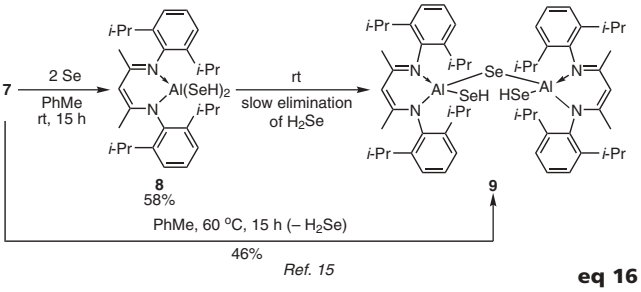


E	Solvent	Temp.	Time	Prdt	Yield
S	PhMe–THF	50 °C	15 h	**4**	58%
Se	PhMe	reflux	2–3 h	**5**	62%
Te	PhMe	reflux	4 days	**6**	54%

Ref. 14 **eq 14**

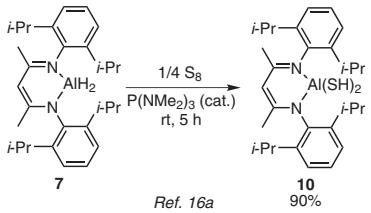


Ref. 15 86% **eq 15**



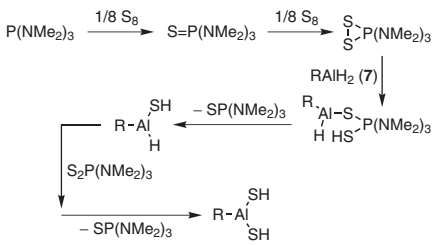
Ref. 15

eq 16



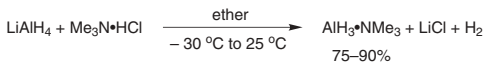
Ref. 16a

eq 17



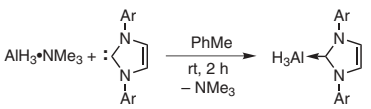
Ref. 16a

Scheme 3. Proposed Mechanism for the $P(NMe_2)_3$-Promoted Conversion of **7** to **10**.



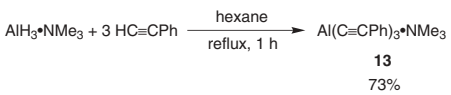
Ref. 17

eq 18



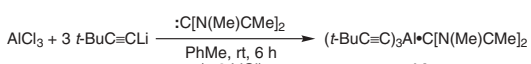
Ref. 18a

eq 19



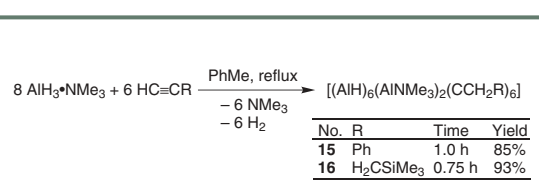
Ref. 18b

eq 20



Ref. 18b

eq 21



No.	R	Time	Yield
15	Ph	1.0 h	85%
16	H_2CSiMe_3	0.75 h	93%

Ref. 19

eq 22

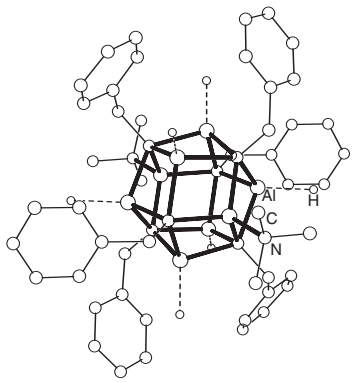
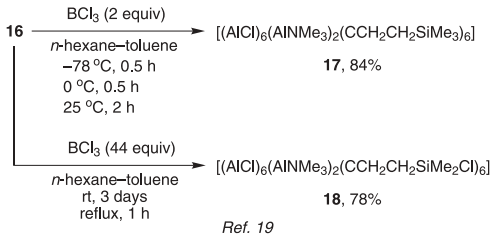
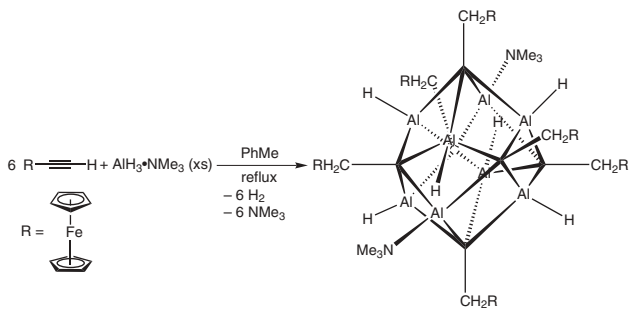


Figure 1. The Crystal Structure of Carbaalane $[(AlH)_6(AlNMe_3)_2(CCH_2Ph)_6]$ (**15**).



Ref. 19

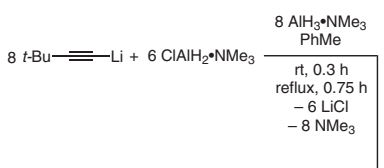
Scheme 4. The Stepwise Functionalization of Cluster **16** in Its Inner and Outer Spheres.



Ref. 20

19, 67%

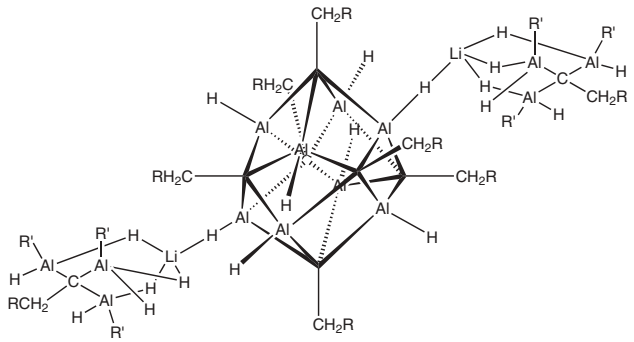
eq 23



20, 62%

Ref. 23

eq 24



[{*t*-BuCH$_2$C(AlH$_2$•NMe$_3$)$_3$Li}$_2${(AlH)$_8$(CCH$_2$*t*-Bu)$_6$}]

20; R = *t*-Bu, R' = NMe$_3$

Ref. 23

Figure 2. The 3D Structure of the Carbaalane Dianion [{*t*-BuCH$_2$C(AlH$_2$•NMe$_3$)$_3$Li}$_2${(AlH)$_8$(CCH$_2$*t*-Bu)$_6$}] (**20**).

$$AlH_3•NMe_3 + 2\ Et_2NH \xrightarrow[\text{reflux, 24 h}]{\text{benzene}} HAl(NEt_2)_2 + 2\ H_2 + NMe_3$$

Ref. 24 **eq 25**

$$AlH_3•NMe_3 + Et_2NH \xrightarrow[\text{rt, 0.5 h}]{\text{benzene}} H_2AlNEt_2 + H_2 + NMe_3$$

~100%

Ref. 24 **eq 26**

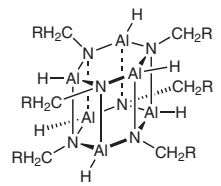
$$2\ AlH_3•NMe_3 \xrightarrow[\text{80 °C, 2 h}]{Al(NMe_2)_3} 3\ H_2AlNMe_2 + 2\ NMe_3$$

~100%

Ref. 25 **eq 27**

$$AlH_3•NMe_3 + RCN \xrightarrow[\text{reflux*}]{\text{PhMe}}$$

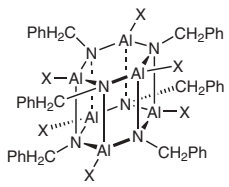
(*) Heated at reflux until evolution of NMe$_3$ ceased.



No.	R	Yield	Ref.
21	Ph	46%	*30a*
22	4-MeC$_6$H$_4$	65%	*30a*
23	4-CF$_3$C$_6$H$_4$	63%	*30a*
24	2-thienyl	64%	*30b*

eq 28

21 (R = Ph) + Me$_3$SiBr or PhC≡CH $\xrightarrow[\text{reflux, 1 h}\ -\ 6\ H_2]{\text{PhMe}}$

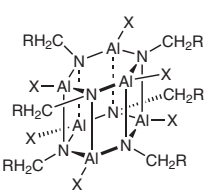


X	Yield
PhC≡C	70%
Br	83%

Ref. 30a **eq 29**

24 + 6 R'C≡CH $\xrightarrow[\text{reflux}\ -\ 6\ H_2]{\text{PhMe}}$

R = 2-thienyl
R' = ferrocenyl
X = C≡CR'



25, 52%

Ref. 31 **eq 30**

into the pocket, where it interacts with the three Al–H groups. The resulting Li^+ binding energy to the free [MeC(AlH$_2$•NH$_3$)$_3$] species of 77.5 kcal/mol stabilizes the whole complex.[23]

6. Reactions of AlH$_3$•NMe$_3$ with Amines

Aluminum compounds containing the (AlN)$_n$ skeleton are potential precursors for a variety of applications. Depending on stoichiometry, the reaction of AlH$_3$•NMe$_3$ with secondary amines leads to either HAl(NR$_2$)$_2$ or H$_2$AlNR$_2$ (e.g., **eq 25** and **eq 26**).[24] Alternatively, H$_2$AlNMe$_2$ can be prepared from AlH$_3$•NMe$_3$ and Al(NMe$_2$)$_3$, when used in a molar ratio of 2:1 **(eq 27)**.[25] A few of these compounds are obviously good precursors for the preparation of aluminum nitride (AlN).

7. Hydroalumination of the RC≡N and *t*-BuNC Systems with AlH$_3$•NMe$_3$

Aluminum imides and amides can be prepared by reaction of alanes and alanates with amines.[26,27] An insoluble Al–N polymer was obtained from MeNH$_2$ and alane,[28] but its structure was not characterized. The reaction of trialkylalanes with acetonitrile and propionitrile was reported but, again, no structural evidence was presented for the products.[29] More recently, the reaction of various nitriles with AlH$_3$•NMe$_3$ was investigated **(eq 28)**.[30] Compounds **21**–**24** were characterized by single-crystal X-ray structural analysis. Each structure contains a drum-like Al$_6$N$_6$ core made up of two, almost planar, six-membered Al$_3$N$_3$ rings. The hydrogen atoms in **21**–**24** can be replaced by nucleophiles **(eq 29** and **30)**.[30a,31]

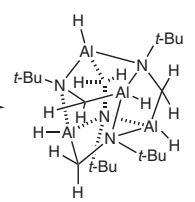
Equation 23 showed that the hydroalumination of ferrocenylacetylene (η^5-C$_5$H$_5$)Fe(η^5-C$_5$H$_4$C≡CH) yields **19**, a compound with ferrocenylmethylene groups attached to an aluminum carbide surface. Similarly, six ferrocenylacetylene groups bind to an aluminum nitride surface in **25**. Compounds **19** and **25** are the first examples of carbides and nitrides functioning to fix organometallic fragments on surfaces.

Treatment of *t*-BuNC with AlH$_3$•NMe$_3$ in refluxing toluene results in the formation of compound **26** with an Al$_4$C$_4$N$_4$ core in 75% yield **(eq 31)**.[32] Compound **26** could be considered as a fused carbaaminolane. The carbon atoms in the Al$_4$C$_4$N$_4$ cage configuration may be formally viewed as having inserted into four Al–N bonds of an Al$_4$N$_4$ cube. The molecular symmetry of **26** is quite close to S_4, but no other elements of symmetry exist in the molecule. The core of **26** consists of six faces formed by two boat-shaped, six-membered Al$_2$C$_2$N$_2$ rings and four puckered, five-membered Al$_2$CN$_2$ rings. Recently, we have been able to show that the hydrogen atoms on aluminum in **26** can be replaced by terminal fluorine atoms without destroying the core of **26**.[33] Terminal fluorine atoms on the surface of a cluster compound are so far very rare. In general, fluorine atoms prefer bridging positions.

8. Conclusions

The AlH$_3$•NMe$_3$ adduct is a very useful hydrogen-transfer agent for C≡C, N≡C, and C≡N multiple-bond systems. It is easily

$$AlH_3•NMe_3 + t\text{-BuNC} \xrightarrow[\text{reflux, 0.5 h}]{\text{PhMe}}$$



[{(μ_3-AlH)(μ_3-CH$_2$N-*t*-Bu)}$_4$]

Ref. 32 **26**, 75% **eq 31**

available and allows the synthesis of carbaalanes, functionalized aluminum nitrides, and carbaaminoalanes. The successful synthesis of aluminum polyhedra will undoubtedly promote future applications of AlH_3•NMe_3, and result in a chemistry that is similar to that of carboranes.

9. Acknowledgements

The author is very thankful to his students and postdocs, whose names appear in the references, for their contributions to this research program. Financial support for this research from the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the Göttinger Akademie der Wissenschaften is gratefully acknowledged. I am grateful to Dr. Ganapathi Anantharaman for drawing the schemes and equations. Moreover, I am very thankful to S. Shravan Kumar for proofreading the manuscript and making many suggestions for improvement.

10. References and Notes

(†) Dedicated to Professor Alan Herbert Cowley on the occasion of his 70th birthday.

(1) Chen, E. Y.-X.; Marks, T. J. *Chem. Rev.* **2000**, *100*, 1391.

(2) Ziegler, K. Br. Patent 774,516, May 8, 1957; *Chem. Abstr.* **1958**, *52*, 2050b.

(3) Podall, H. E.; Petree, H. E.; Zietz, J. R. *J. Org. Chem*. **1959**, *24*, 1222.

(4) Ziegler, K.; Gellert, H.-G.; Lehmkuhl, H.; Pfohl, W.; Zosel, K. *Liebigs Ann. Chem.* **1960**, *629*, 1.

(5) Surtees, J. R. *Chem. Ind.* **1964**, 1260.

(6) Eisch, J. J.; Rhee, S. G. *J. Organomet. Chem.* **1975**, *86,* 143.

(7) Ziegler, K.; Nagel, K.; Pfohl, W. *Liebigs Ann. Chem.* **1960**, *629*, 210.

(8) (a) Eisch, J. J.; Husk, G. R. *J. Org. Chem.* **1964**, *29*, 254. (b) Ziegler, K.; Kroll, W.-R.; Larbig, W.; Steudel, O.-W. *Liebigs Ann. Chem.* **1960**, *629*, 53. (c) Eisch, J. J. Aluminum. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon: Elmsford, NY, 1982; Vol. 1, pp 555–682.

(9) Natta, G.; Pino, P.; Mazzanti, G.; Longi, P.; Bernardini, F. *J. Am. Chem. Soc.* **1959**, *81*, 2561.

(10) Eisch, J. J.; Husk, G. R. *J. Organomet. Chem.* **1974**, *64*, 41.

(11) (a) Eisch, J. J. Aluminum. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Elsevier Science: Tarrytown, NY, 1995; Vol. 1, pp 431–502. (b) Eisch, J. J.; Rhee, S.-G. *J. Am. Chem. Soc.* **1975**, *97*, 4673.

(12) Zheng, W.; Roesky, H. W.; Noltemeyer, M. *Organometallics* **2001**, *20*, 1033.

(13) Zheng, W.; Mösch-Zanetti, N. C.; Roesky, H. W.; Hewitt, M.; Cimpoesu, F.; Schneider, T. R.; Stasch, A.; Prust, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3099.

(14) Zheng, W.; Mösch-Zanetti, N. C.; Roesky, H. W.; Noltemeyer, M.; Hewitt, M.; Schmidt, H.-G.; Schneider, T. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 4276.

(15) Cui, C.; Roesky, H. W.; Hao, H.; Schmidt, H.-G.; Noltemeyer, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1815.

(16) (a) Jancik, V.; Peng, Y.; Roesky, H. W.; Li, J.; Neculai, D.; Neculai, A. M.; Herbst-Irmer, R. *J. Am. Chem. Soc.* **2003**, *125*, 1452. (b) The Restricted Hartree–Fock (RHF) calculations with STO-3G basis set were performed with Spartan '02 program: Hehre, W. J.; Stewart, R. F.; Pople, J. A. *J. Chem. Phys.* **1969**, *51*, 2657.

(17) Ruff, J. K. *Inorg. Synth.* **1967**, *9*, 30.

(18) (a) Arduengo, A. J., III; Rasika Dias, H. V.; Calabrese, J. C.; Davidson, F. *J. Am. Chem. Soc.* **1992**, *114*, 9724. (b) Schiefer, M.; Reddy, N. D.; Ahn, H.-J.; Stasch, A.; Roesky, H. W.; Schlicker, A. C.; Schmidt, H.-G.; Noltemeyer, M.; Vidovic, D. *Inorg. Chem.* **2003**, *42*, 4970.

(19) Stasch, A.; Ferbinteanu, M.; Prust, J.; Zheng, W.; Cimpoesu, F.; Roesky, H. W.; Magull, J.; Schmidt, H.-G.; Noltemeyer, M. *J. Am. Chem. Soc.* **2002**, *124*, 5441.

(20) Kumar, S. S.; Rong, J.; Singh, S.; Roesky, H. W.; Vidovic, D.; Magull, J.; Neculai, D.; Chandrasekhar, V.; Baldus, M. *Organometallics* **2004**, *23*, 3496.

(21) Wilke, G.; Schneider, W. *Bull. Soc. Chim. Fr.* **1963**, 1462.

(22) Uhl, W.; Breher, F. *Eur. J. Inorg. Chem.* **2000**, *1* and references therein.

(23) Stasch, A.; Roesky, H. W.; von Ragué Schleyer, P.; Magull, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5507.

(24) Kovar, R. A.; Callaway, J. O. *Inorg. Synth.* **1977**, *17*, 36.

(25) Ruff, J. K. *J. Am. Chem. Soc.* **1961**, *83*, 2835.

(26) (a) Al-Wassil, A.-A. I.; Hitchcock, P. B.; Sarisaban, S.; Smith, J. D.; Wilson, C. L. *J. Chem. Soc., Dalton Trans.* **1985**, 1929. (b) Cesari, M.; Perego, G.; Del Piero, G.; Cucinella, S.; Cernia, E. *J. Organomet. Chem.* **1974**, *78*, 203. (c) Del Piero, G.; Cesari, M.; Perego, G.; Cucinella, S.; Cernia, E. *J. Organomet. Chem.* **1977**, *129*, 289. (d) Del Piero, G.; Perego, G.; Cucinella, S.; Cesari, M.; Mazzei, A. *J. Organomet. Chem.* **1977**, *136*, 13.

(27) (a) Wehmschulte, R. J.; Power, P. P. *J. Am. Chem. Soc.* **1996**, *118*, 791. (b) Heine, A.; Stalke, D. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 854 and references therein.

(28) Wiberg, V. E.; May, A. *Z. Naturforsch., Part B* **1955**, *10*, 232.

(29) Cucinella, S.; Salvatori, T.; Busetto, C.; Cesari, M. *J. Organomet. Chem.* **1976**, *121*, 137.

(30) (a) Reddy, N. D.; Roesky, H. W.; Noltemeyer, M.; Schmidt, H.-G. *Inorg. Chem.* **2002**, *41*, 2374. (b) Reddy, N. D.; Kumar, S. S.; Roesky, H. W.; Vidovic, D.; Magull, J.; Noltemeyer, M.; Schmidt, H.-G. *Eur. J. Inorg. Chem.* **2003**, 442.

(31) Kumar, S. S.; Reddy, N. D.; Roesky, H. W.; Vidovic, D.; Magull, J.; Winter, R. F. *Organometallics* **2003**, *22*, 3348.

(32) Zheng, W.; Stasch, A.; Prust, J.; Roesky, H. W.; Cimpoesu, F.; Noltemeyer, M.; Schmidt, H.-G. *Angew. Chem., Int. Ed.* **2001**, *40*, 3461.

(33) Peng, Y.; Rong, J.; Vidovic, D.; Roesky, H. W.; Labahn, T.; Magull, J.; Noltemeyer, M.; Schmidt, H.-G. *J. Fluorine Chem.* **2004**, *125*, 951.

About the Author

Professor Herbert W. Roesky was born in 1935 in Laukischken, Germany. He studied chemistry at the University of Göttingen, Germany, where he obtained his diploma in 1961 and doctoral degree in 1963. After one year of postdoctoral work at Du Pont in Wilmington, DE, he achieved his "Habilitation" at the University of Göttingen. In 1971, he became full professor at the Johann Wolfgang Goethe-Universität in Frankfurt am Main and, since 1980, he has been a full professor and director of the Institute of Inorganic Chemistry at the University of Göttingen. He has been a visiting professor at Jawaharlal Nehru Centre for Advanced Scientific Research in Bangalore, at the Tokyo Institute of Technology, and Kyoto University. He has also been a frontier lecturer at Texas A&M University at College Station, the University of Texas at Austin, and the University of Iowa at Iowa City. He is a member of the Academy of Sciences of Göttingen, the New York Academy of Sciences, the Academy of Scientists "Leopoldina" in Halle, L'Académie des Sciences in Paris, and the Academia Europaea in London. He served as the vice president of the German Chemical Society in 1995, and is presently the president of the Academy of Sciences of Göttingen. In addition to the 2004 ACS Inorganic Chemistry Award, he has received many others, e.g., the Leibniz Award, the Stock Preis, the Alexander von Humboldt Award, and the Fluorine Award of the American Chemical Society. More than 900 publications, articles, patents, and books have recorded his research activity in the areas of inorganic chemistry and materials science.

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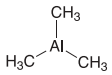

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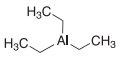
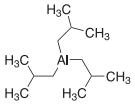


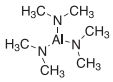
Triisobutylaluminum*

25,720-6		100 g 1 kg



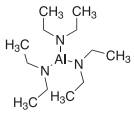
Tris(dimethylamido)aluminum*

46,994-7		10 g



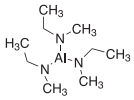
Tris(diethylamido)aluminum

J10,003-0	**99.99+%** Ultrapure for electronic applications	



Tris(ethylmethylamido)aluminum

J10,002-9	**99.99+%** Ultrapure for electronic applications	



Aluminum trichloride

56,391-9	**99.999%**, anhydrous powder Electronic grade	5 g 25 g
20,691-1	**98%**	5 g 100 g 1 kg

Aluminum tribromide

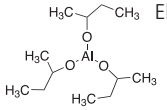
44,960-1	**99.999%**, anhydrous powder Electronic grade	5 g 25 g
21,007-2	**98+%**	5 g 25 g 100 g

Diethylaluminum ethoxide*

25,674-9	**97%**	100 g

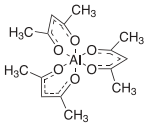
Aluminum tri-*sec*-butoxide*

51,160-9	**99.99%** Electronic grade	5 g



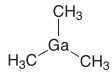
Aluminum acetylacetonate*

20,824-8	**99%**	5 g 100 g 500 g



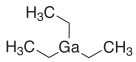
Trimethylgallium

J10,001-5	**99.999%** Ultrapure for electronic applications	



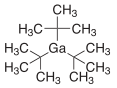
Triethylgallium

J10,001-7	**99.99+%** Ultrapure for electronic applications	



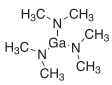
Tri-*tert*-butylgallium

J10,003-4	**99.99+%** Ultrapure for electronic applications	



Tris(dimethylamido)gallium*

54,653-4	**98%**	1 g 5 g



Gallium trichloride

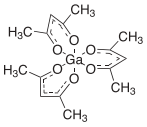
42,712-8	**99.999+%**, anhydrous beads Electronic grade	5 g 25 g 100 g

Gallium tribromide

45,086-3	**99.999%**, anhydrous powder Electronic grade	1 g 5 g 25 g

Gallium acetylacetonate*

39,354-1	**99.99%**	5 g 25 g



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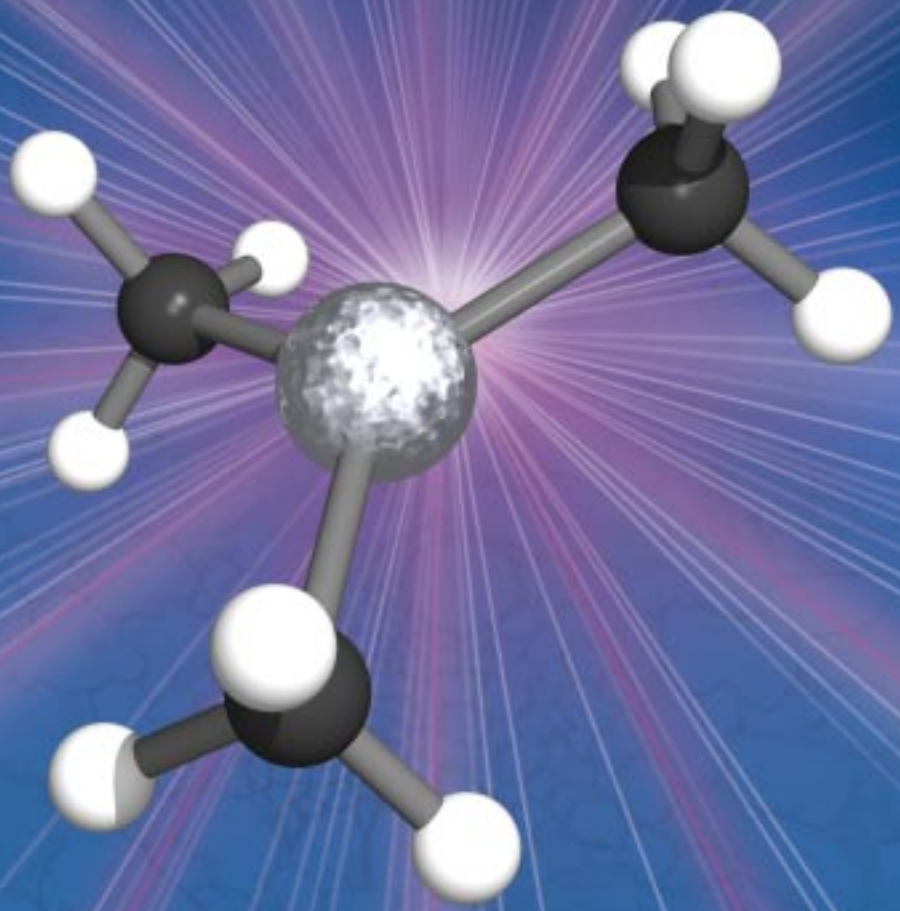

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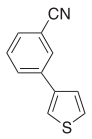
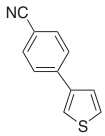
64,653-9
3-(3-Thienyl)benzonitrile, 97%

1 g
5 g



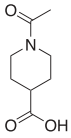
64,652-0
4-(3-Thienyl)benzonitrile, 97%

1 g
5 g



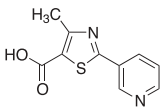
64,775-6
1-Acetylpiperidine-4-carboxylic acid, 97%

5 g
25 g



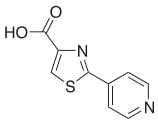
64,604-0
2-(3-Pyridyl)-4-methylthiazole-5-carboxylic acid, 97%

1 g
5 g



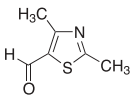
64,603-2
2-(4-Pyridyl)thiazole-4-carboxylic acid, 97%

1 g
5 g



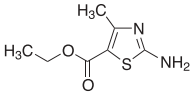
64,602-4
2,4-Dimethylthiazole-5-carboxaldehyde

1 g
5 g



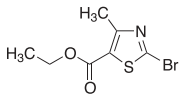
64,601-6
Ethyl 2-amino-4-methylthiazole-5-carboxylate, 97%

1 g
5 g



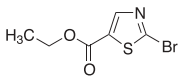
64,599-0
Ethyl 2-bromo-4-methylthiazole-5-carboxylate, 97%

1 g
5 g



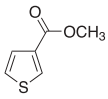
64,249-5
Ethyl 2-bromothiazole-5-carboxylate, 97%

1 g
5 g



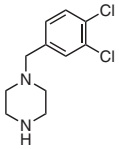
64,555-9
Methyl 3-thiophenecarboxylate, 97%

1 g
5 g



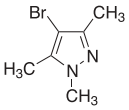
64,426-9
1-(3,4-Dichlorobenzyl)piperazine, 97%

1 g
5 g



64,766-7
4-Bromo-1,3,5-trimethylpyrazole

1 g
5 g

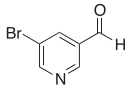


64,887-6
2-Hydroxy-4-(trifluoromethyl)pyridine

250 mg

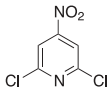
64,410-2
5-Bromo-3-pyridinecarboxaldehyde, 97%

1 g
5 g



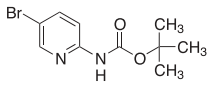
64,741-1
2,6-Dichloro-4-nitropyridine

1 g
5 g



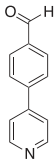
64,638-5
2-(Boc-amino)-5-bromopyridine, 97%

5 g



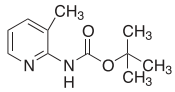
64,598-2
4-(4-Formylphenyl)pyridine, 97%

1 g
5 g



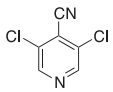
64,392-0
2-(Boc-amino)-3-methylpyridine, 97%

5 g
25 g



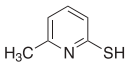
64,419-6
3,5-Dichloro-4-pyridinecarbonitrile, 97%

1 g
5 g



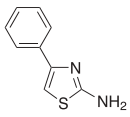
64,209-6
2-Mercapto-6-methylpyridine, 97%

1 g
5 g



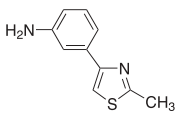
64,275-4
2-Amino-4-phenylthiazole, 97%

1 g
5 g



64,263-0
2-Methyl-4-(3-aminophenyl)thiazole, 97%

1 g
5 g



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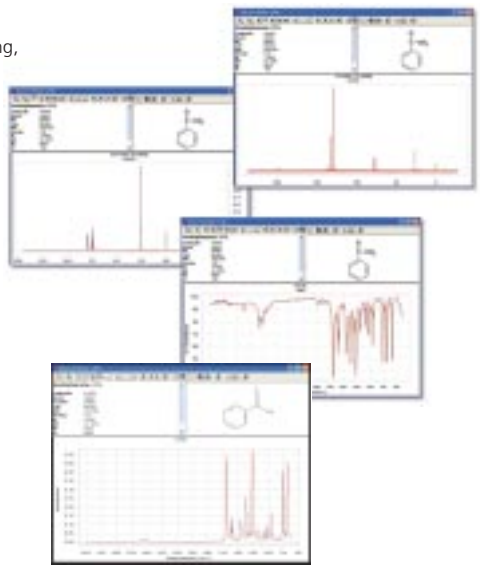

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No Reactives	Simplify your screening results by reducing the number of false positives.

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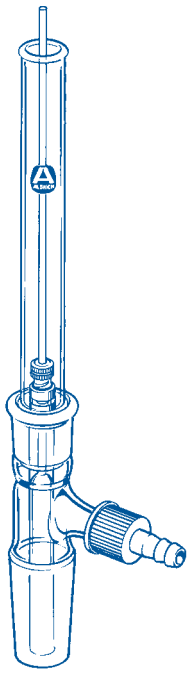
New Aldrich Glassware with SafetyBarb™ Hose Connectors

This new glassware features SafetyBarb™ removable connections for ¼ in. i.d. flexible tubing. The "barbed" polypropylene connector grips tubing firmly and can be safely detached from the glassware by unscrewing the PBT [poly(butylene terephthalate)] cap. Accidental glassware breakage is eliminated when installing or removing the tubing. A silicone rubber seal ensures a liquid- and vacuum-tight connection to the glass GL 14 thread.

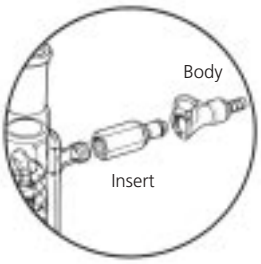


NEW!
Aldrich SafetyBarb™ NMR Tube Cleaner

Inner PTFE wash tube with Luer connection prevents NMR tube breakage during the cleaning process. Detaches for thorough cleaning or replacement. SafetyBarb™ vacuum connection. Washes 3, 5, and 10mm NMR tubes in both 7 and 8 inch lengths.

Joint	Cat. No.
24/40	**Z55,836-2**
29/32	**Z55,837-0**

Automatic Shutoff Quick-Disconnects



To install, unscrew SafetyBarb™ connector on glassware and replace with coupling insert. Chemically resistant acetal coupling insert and body are spring-loaded, locking, and have 316SS springs and EPR seals. Both sides seal automatically when pulled apart. One coupling insert and body needed for each glass connection. Use with ¼ in. i.d. flexible tubing.

Coupling insert, GL 14 inner thread
Z55,337-9

Coupling body, for ¼ in. i.d. tubing
Z55,338-7

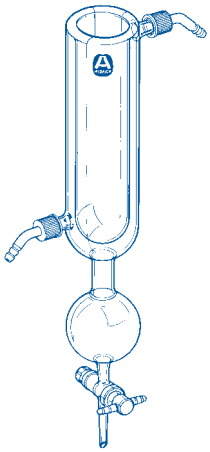
Request a copy of the *New Aldrich Glass with SafetyBarb™ Hose Connectors (GXW)* brochure for a complete listing of these products.

SafetyBarb is a trademark of Sigma-Aldrich Biotechnology, L.P.

Dry Ice Condenser Trap

4 mm PTFE stopcock. Use with or without dry ice to condense and collect material in trap.

Reservoir Cap. (mL)	Overall L (mm)	Cat. No.
250	450	**Z55,355-7**
500	470	**Z55,356-5**
1,000	490	**Z55,357-3**

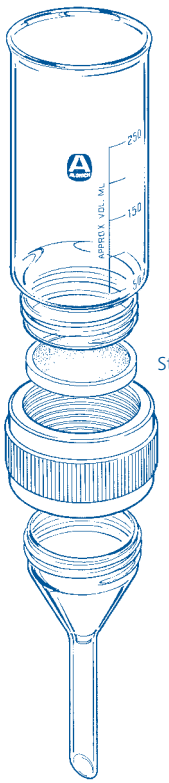


New Glassware for Organic Synthesis

Büchner Funnel with Removable Frit

Style A has integral, cup-style PTFE gasket on a glass frit.
Style B has flat, removable PTFE gaskets on a glass frit.

Capacity (mL)	Porosity (µm)	Style A Cat. No.	Style B Cat. No.
30	4–8	**Z55,425-1**	**Z55,455-3**
	10–20	**Z55,427-8**	**Z55,456-1**
	25–50	**Z55,428-6**	**Z55,458-8**
	70–100	**Z55,429-4**	**Z55,459-6**
	145–175	**Z55,430-8**	**Z55,461-8**
60	4–8	**Z55,431-6**	**Z55,462-6**
	10–20	**Z55,432-4**	**Z55,463-4**
	25–50	**Z55,433-2**	**Z55,464-2**
	70–100	**Z55,434-0**	**Z55,465-0**
	145–175	**Z55,435-9**	**Z55,466-9**
140	4–8	**Z55,436-7**	**Z55,467-7**
	10–20	**Z55,437-5**	**Z55,468-5**
	25–50	**Z55,438-3**	**Z55,469-3**
	70–100	**Z55,439-1**	**Z55,470-7**
	145–175	**Z55,440-5**	**Z55,471-5**
350	4–8	**Z55,441-3**	**Z55,472-3**
	10–20	**Z55,442-1**	**Z55,473-1**
	25–50	**Z55,444-8**	**Z55,475-8**
	70–100	**Z55,445-6**	**Z55,476-6**
	145–175	**Z55,446-4**	**Z55,477-4**
600	10–20	**Z55,447-2**	**Z55,478-2**
	25–50	**Z55,448-0**	**Z55,479-0**
	70–100	**Z55,449-9**	**Z55,480-4**
	145–175	**Z55,450-2**	**Z55,481-2**
1,500	10–20	**Z55,451-0**	**Z55,482-0**
	25–50	**Z55,452-9**	**Z55,483-9**
	70–100	**Z55,453-7**	**Z55,484-7**
	145–175	**Z55,454-5**	**Z55,485-5**



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Aqueous-Phase Organometallic Catalysis: Concepts and Applications, 2nd Edition, Revised and Enlarged

B. Cornils and W. A. Herrmann, Eds., Wiley–VCH, 2004, 780pp. Hardcover. This is a method that facilitates separation in an efficient and "green" way, thus saving time and money. The application of this technology on a large scale in the chemical industry clearly underlines its practicability for anyone working in this field.

Z55,841-9

Main Group Metals in Organic Synthesis (2-Volume Set)

H. Yamamoto and K. Oshima, Eds., Wiley–VCH, 2004, 901pp. Hardcover. Covers all aspects of this fascinating field of chemistry. It is structured according to the individual metals in the main groups, and is focused on the modern transformations in organic synthesis that are closely linked to main group elements—both stoichiometric and catalytic.

Z55,773-0

One-Dimensional Metals: Conjugated Polymers, Organic Crystals, Carbon Nanotubes, 2nd Edition, Revised and Extended

S. Roth and D. Carroll, Wiley–VCH, 2004, 264pp. Hardcover. Low-dimensional solids are of fundamental interest in materials science due to their anisotropic properties. This book explains the important concepts behind their physics. It surveys the most interesting one-dimensional systems and discusses their present and emerging applications in molecular-scale electronics.

Z55,847-8

Carbon Nanotubes: Basic Concepts and Physical Properties

S. Reich, C. Thomsen, and J. Maultzsch, Wiley–VCH, 2004, 224pp. Hardcover. Many concepts of one-dimensional physics have been verified experimentally such as electron and phonon confinement, or the one-dimensional singularities in the density of states. For this reason, they open up new perspectives for various applications, such as nanotransistors in circuits, field-emission displays, artificial muscles, or added reinforcements in alloys. This text is an introduction to the physical concepts needed for investigating carbon nanotubes and other one-dimensional solid-state systems.

Z55,139-2

DRUG DISCOVERY TITLES

Lipases and Phospholipases in Drug Development

G. Müller and S. Petry, Eds., John Wiley & Sons, 2004, 354pp. Hardcover. Lipases and phospholipases are key control elements in mammalian intermediary metabolism. They share many common features that set them apart from other metabolic enzyme classes, most importantly their association with "two-dimensional" substrates. Their potential as drug targets for the treatment of metabolic diseases is increasingly recognized, and the first lipase inhibitor drugs have been successfully introduced.

Z55,849-4

ANALYTICAL CHEMISTRY TITLES

Modern Practice of Gas Chromatography, 4th Edition

R. L. Grob and E. F. Barry, Eds., Wiley–Interscience, 2004, 1056pp. Hardcover. Incorporates the most recent developments in the field, including gas chromatography/mass spectrometry (GC/MS), optimization of separations and computer assistance, high speed or fast gas chromatography, mobile phase requirements, qualitative and quantitative analysis by GC, validation and QA/QC of chromatographic methods, and useful hints for carrying out good gas chromatographic analyses.

Z55,844-3

Dean's Analytical Chemistry Handbook, 2nd Edition

P. Patnaik, McGraw-Hill, 2004, 1280pp. Hardcover. This one-of-a-kind resource presents fundamental data on subjects such as: volumetric and gravimetric analysis; chromatographic methods; electronic absorption and luminescence spectroscopy; optical activity and rotary dispersion; nuclear magnetic resonance spectroscopy and electron spin resonance; electroanalytical methods; thermal analysis; detection and determination of functional groups in organic compounds; and water analysis. It also contains new chapters on pesticide and herbicide analysis and environmental analysis, and includes updates on processes, tools, and techniques.

Z70,256-0

ORGANIC SYNTHESIS TITLES

Fiesers' Reagents for Organic Synthesis, Volume 22

T.-L. Ho, John Wiley & Sons, 2004, 608pp. Hardcover. The format of the series continues with its concise descriptions, good structural formulas, and selected examples of application, providing references to new reagents as well as to reagents included in previous volumes. Helpful information includes how to make a reagent, where it can be bought, what it is good for, and so on.

Z55,839-7

Dean's Handbook of Organic Chemistry, 2nd Edition

G. W. Gokel, McGraw-Hill, 2004, 1000pp. Hardcover. Updates biopolymers, electronegativity, nomenclature, properties tables, and structural drawings, thus making the data easier for the researcher to access and use.

Z55,842-7

CRC Handbook of Chemistry and Physics, 85th Edition

D. R. Lide, Ed., CRC Press, 2004, 2712pp. Hardcover. This edition features a foreword by author Oliver Sacks, a free facsimile of the 1913 first edition of the handbook, and thumb tabs that make it easier to locate particular data. New tables in this edition include index of refraction of inorganic crystals, upper and lower azeotropic data for binary mixtures, critical solution temperatures of polymer solutions, and density of solvents as a function of temperature. Several tables omitted from recent editions are back. The fundamental physical constants section has been updated with the latest CODATA/NIST values, and the mathematical tables appendix now features several new sections that include orthogonal polynomials and Clebsch–Gordon coefficients.

Z55,808-7

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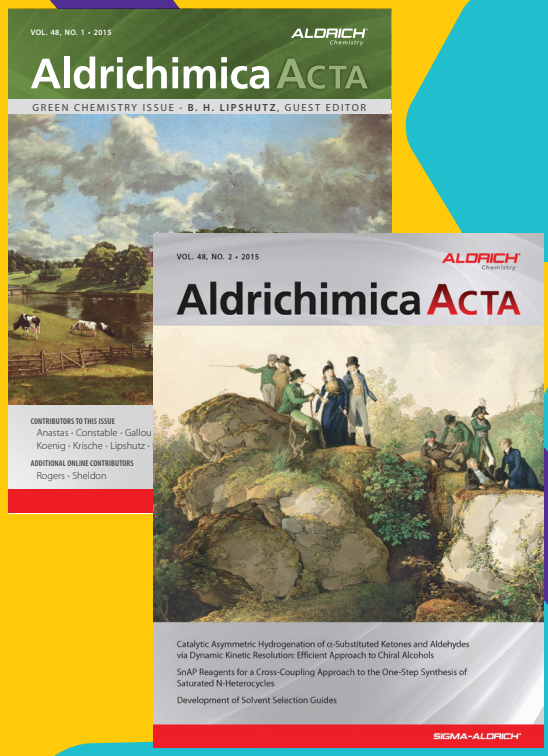

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