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Aldrichimica ACTA

VOL. 34, NO. 1 • 2001

Preparation of Optically Active α-Amino Acids

Alkoxymethylenemalonates in Organic Synthesis

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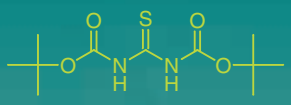
NEW PRODUCTS

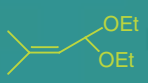
53,182-0 ***N,N′*-Di-(*tert*-butoxycarbonyl)thiourea**, 97%



This diprotected thiourea is widely used in the synthesis of heterocycles, including a pentacyclic guanidine system as an intermediate to ptilomycalin A,[1] and, recently, in the preparation of *p*-*N,N′*-bis-Boc-guanidophenol, a key intermediate for the preparation of a series of aryl *o*-aroylbenzoates as serine protease inhibitors.[2]

(1) Nagasawa, K. et al. *Tetrahedron* **2000,** *56,* 187. (2) Jones, P.B.; Porter, N.A. *J. Am. Chem. Soc.* **1999,** *121,* 2753.

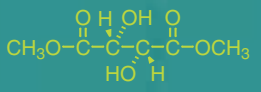
54,036-6 **1,1-Diethoxy-3-methyl-2-butene**, 97%



This acetal has been utilized in the synthesis of the related 1-alkoxy-3-phenylselenoalkenes and 3-phenylselenoalkanals,[1] and in the preparation of 2,2-dimethylchromenes from electron-deficient phenols.[2]

(1) Nishiyama, Y. et al. *Tetrahedron Lett.* **1998**, *39,* 8685 (2) North, J.T. et al. *J. Org. Chem.* **1995,** *60,* 3397.

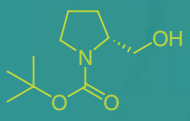
16,345-7 **Dimethyl L-tartrate**, 99% (99+% ee/GLC)



Recent citations for this versatile chiral building block include the enantioselective synthesis of α-bromo carbonyl and carboxylic acid derivatives,[1] and the synthesis of enantiomerically pure spirane porphyrazines.[2]

(1) Boyes, S.A.; Hewson, A.T. *J. Chem. Soc., Perkin Trans.1* **2000,** 2759. (2) Hachiya, S.-i. et al. *Tetrahedron* **2000,** *56,* 6565.

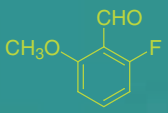
46,944-0 **(*R*)-(+)-1-(*tert*-Butoxycarbonyl)-2-pyrrolidinemethanol**, 97%



This protected pyrrolidinemethanol was used in a recent study of 3-substituted indoles as potential antimigraine drugs.[1] It was also utilized in the preparation of a novel, potent, and selective 5-HT_7 antagonist via elongation of the side chain followed by transformation into the protected piperidinylethylpyrrolidine, subsequent deprotection and arylsulfonylation.[2]

(1) Sternfeld, F. et al. *J. Med. Chem.* **1999,** *42,* 677. (2) Lovell, P.J. et al. *ibid.* **2000,** *43,* 342.

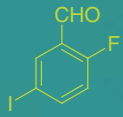
53,673-3 **2-Fluoro-6-methoxybenzaldehyde**, 98%



On conversion to a dinitro ester, the aryl fluorine acts as a useful leaving group early in the synthesis of the macrolactam portion of the ansamycin antibiotic (+)-thiazinotrienomycin E.

Smith, A.B., III; Wan, Z. *J. Org. Chem.* **2000,** *65,* 3738.

54,331-4 **2-Fluoro-5-iodobenzaldehyde**, 97%

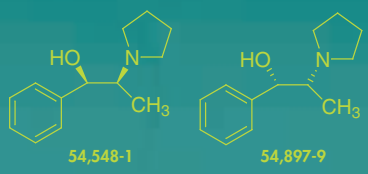


The related iodobenzo[b]thiophenecarboxylate ester has been synthesized in moderate yield from this dihalo aldehyde.

Bridges, A.J. et al. *Tetrahedron Lett.* **1992,** *33,* 7499.

54,548-1 **(1*R*,2*S*)-1-Phenyl-2-(1-pyrrolidinyl)-1-propanol**, 98%

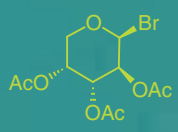
54,897-9 **(1*S*,2*R*)-1-Phenyl-2-(1-pyrrolidinyl)-1-propanol**, 98%



These norephedrine derivatives are useful chiral mediators and have applications in the enantioselective addition of acetylides to carbonyl compounds. Examples include the synthesis of the HIV-1 reverse transcriptase inhibitor DMP 266[1] and the enantioselective addition of diethylzinc to aldehydes.[2]

(1) Pierce, M.E. et al. *J. Org. Chem.* **1998,** *63,* 8536. (2) Soai, K. et al. *ibid.* **1991,** *56,* 4264.

54,174-5 **Tri-*O*-acetyl-β-D-arabinosylbromide**, 95%



Among the many applications for this protected bromosugar, the solid-state reaction to make glycopyranosyl pyrimidine nucleosides,[1] the novel synthesis of thioglycosides,[2] and the high-yield preparation of pyranoid glycals[3] are some of the ones that have been cited.

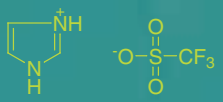
(1) Im, J. et al. *Tetrahedron Lett.* **1997**, *38,* 451. (2) Pakulski, Z. et al. *Tetrahedron* **1994,** *50,* 2975. (3) Kovács, G. et al. *ibid.* **1999,** *55,* 5253.

52,869-2 **2-(6-Bromohexyloxy)tetrahydro-2*H*-pyran**, 97%

This THP-protected bromoalcohol is an important building block used in the synthesis of alkaloids,[1] symmetrical olefins,[2] and 14-membered macrocyclic ethers.[3]

(1) Kaiser, A. et al. *J. Org. Chem.* **1999,** *64,* 3778. (2) Poulain, S. et al. *Tetrahedron Lett.* **1996,** *37,* 7703. (3) Clyne, D.S.; Weiler, L. *Tetrahedron* **1999,** *55,* 13659.

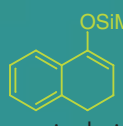
51,587-6 **Imidazole, trifluoromethanesulfonate salt**, 97%



This triflate has been used as a coupling agent for oligonucleotide synthesis[1] and as a reagent for the synthesis of aryl triflates.[2]

(1) Hayakawa, Y.; Kataoka, M. *J. Am. Chem. Soc.* **1998,** *120,* 12395. (2) Effenberger, F.; Mack, K.E. *Tetrahedron Lett.* **1970,** 3947.

54,039-0 **(3,4-Dihydro-1-naphthyloxy)trimethylsilane**, 97%



The titanium tetrachloride promoted reaction of this trimethylsilyl enol ether with ethylene oxide affords the homoaldol-type product in moderate yield.[1] In other studies, C_2-symmetric copper complexes have been shown to catalyze the enantioselective amination of,[2] or ketomalonate addition to,[3] this enol silane.

(1) Lalic, G. et al. *Tetrahedron Lett.* **2000,** *41,* 763. (2) Evans, D.A.; Johnson, D.S. *Org. Lett.* **1999,** *1,* 595. (3) Reichel, F. et al. *J. Chem. Soc., Chem. Commun.* **1999,** 1505

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About Our Cover

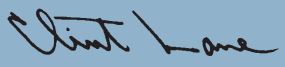
Edgar Degas's *Ballet Scene* (pastel on cardboard, 30¼ in. x 43¾ in.) was executed ca. 1907 when the artist was in his seventies, and not long before his career was cut short by his growing blindness. The subject of the picture is one indelibly identified with Degas who, unlike his impressionist friends, more often chose to represent urban scenes than the country landscapes they preferred. Life in the cafés, at the racetrack, in the theatre, at the opera, and in particular at the ballet, was what most attracted him.

However, it was not the glamour, the drama, and the sumptuous spectacle of a ballet performance that interested him, but the behind-the-scenes work that goes on before the dancers go on stage. His goal was to distill from the constantly changing movements and postures of the dancers a single moment which would capture the essence of motion, and it was the exercises, the rehearsals, the minutes before a performance that gave him the opportunity to do this.

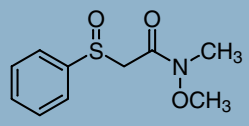
This goes some way towards explaining the medium he used for this work, which is not an oil painting on canvas but a picture executed in pastel chalks, a dry medium similar to the charcoal he often used to sketch quickly the varied life of the city of Paris all around him. Through his depiction of varied postures and gestures, Degas leads the eye along a curving line from the lower right corner of the picture to the left, contrasting the more static attitudes of the three figures in the right foreground with the animated movements of the dancers further back on the left, to capture in an essentially motionless work of art a sense of the dynamic actions of a group of dancers at work.

This painting is in the Chester Dale Collection at the National Gallery of Art, Washington, D.C.

"Please Bother Us."



Clint Lane, President



Professor Ahcène Boumendjel of the Université Joseph Fourier (La Tronche, France) kindly suggested that we make *N*-methoxy-*N*-methyl-2-(phenylsulfinyl)-acetamide.[1] This amide is useful for the homologation of alkyl halides to α,β-unsaturated *N*-methoxy-*N*-methyl-amides, which are valuable intermediates in the synthesis of natural products and therapeutics.[2]

(1) Beney, C.; Boumendjel, A.; Mariotte, A.-M. *Tetrahedron Lett.* **1998**, *39*, 5779. (2) Sibi, M. P. *Org. Prep. Proced. Int.* **1993**, *25*, 15.

51,139-0
***N*-Methoxy-*N*-methyl-2-(phenyl-sulfinyl)acetamide**, 96%

Naturally, we made this useful reagent. 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.

Table of Contents

Lab Notes

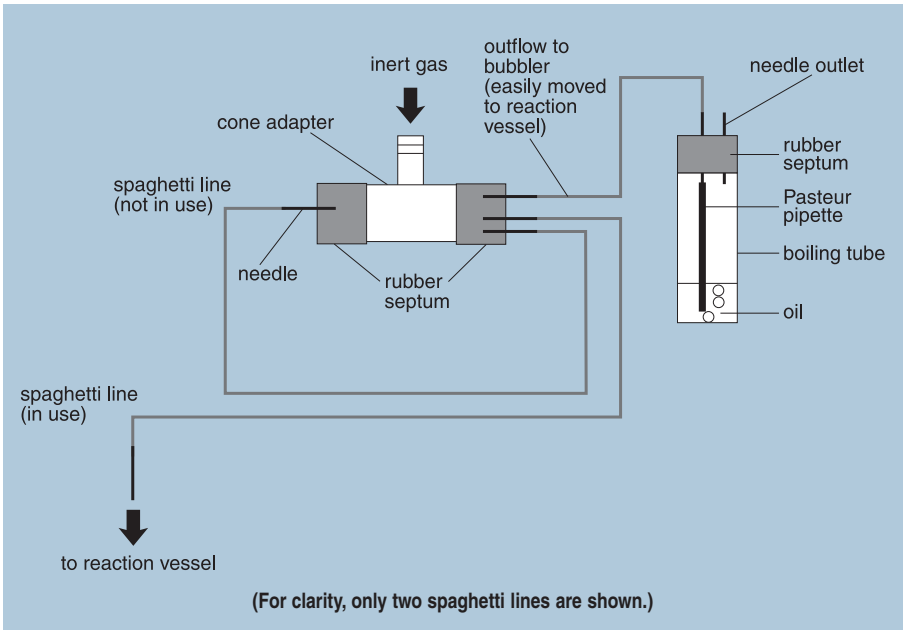
Inexpensive and Easily Constructed Space-Saving "Spaghetti Tubing Apparatus" for Creating Inert Atmospheres within a Large Number of Reaction Vessels

I read a recent Lab Notes article,[1] which prompted me to share another innovative method for creating and maintaining inert atmospheres within a large number of reaction vessels or reagent bottles. The setup is easily constructed from inexpensive equipment generally found in a laboratory, and occupies less space than a conventional manifold line.

The system has been used in our laboratories for several years with great success, supplying inert atmospheres to multiple reactions and easily coping with the higher pressures required for cannulation. Based on the "spaghetti tubing" manifold described by Casey et al.,[2] this apparatus consists of a single source of inert gas connected to the side-arm of a B29/32 cone adapter, which has been fitted at each end with rubber septa. The single source of inert gas is split into multiple supplies (comfortably up to six) by needle-tipped, 3-mm (o.d.) spaghetti lines piercing the septa. A positive pressure of inert gas in the apparatus is maintained by means of an outflow passing through a bubbler assembled from a boiling tube, an inverted Pasteur pipette, a needle and a rubber septum. The various outflow supply lines are easily moved to individual reaction vessels allowing each reaction to be individually purged with inert gas.

The present trend toward the efficient synthesis of compounds via parallel synthesis should make this apparatus invaluable for the pharmaceutical chemist. In addition, its cost effectiveness and small size make it ideal for university chemistry departments, where restricted space within fume cupboards and tight budgetary constraints may exist.

References: (1) Flemer, S., Jr. *Aldrichimica Acta* **1998**, *31*, 34. (2) Casey, M.; Leonard, J.; Lygo, B.; Procter, G. *Advanced Practical Organic Chemistry*; Blackie & Son: London, UK, 1990; pp 108-109.



(For clarity, only two spaghetti lines are shown.)

Materials for Constructing the Spaghetti Line and Bubbler:

- B29/32 socket/cone adapter with "T" connection (equivalent to Aldrich cat. no. **Z41,580-4**) (fitted with detachable plastic connector for easy coupling of tubing)
- Suba•Seal® No. 45 (Aldrich cat. no. **Z16,732-0**)
- Suba•Seal® No. 57 (Aldrich cat. no. **Z16,735-5**)
- Silicone tubing (Versilic) (o.d. 3 mm; bore x wall, 1x1 mm)
- Pasteur pipette (9.0 in. long) (Aldrich cat. no. **Z19,061-6**)
- Disposable needles (16 ga. x 1 in.). Using grips to hold the metal needle, pliers are used to remove the purple plastic sheath. The blunt end of the needle is then pushed into the spaghetti tubing) (Aldrich cat. no. **Z19,256-2**).

Suba•Seal is a registered trademark of William Freeman & Co., Ltd.

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The Preparation of Optically Active α-Amino Acids from the Benzophenone Imines of Glycine Derivatives

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Outline

1. Introduction

New methods for the synthesis of both natural and unnatural α-amino acids, the "building blocks of life", have been the focus of numerous studies over the past quarter century.[1] Our efforts in this field date from 1978, when we reported the first general synthesis of α-amino acids by phase-transfer catalysis.[2] The key starting substrates for this endeavor have been the benzophenone imines of glycine alkyl esters (**1**),[3,4] which have been used as glycine anion equivalents and as starting materials for the preparation of the complementary glycine cation equivalents.

The following section will outline the development of benzophenone imines of glycine derivatives for the synthesis of α-amino acids in which the newly created stereogenic center at the α carbon is not controlled. Sections 3, 4, and 5 will then discuss the preparation of optically active amino acids, either by enantio- or diasteriocontrolled synthesis, or by the resolution of racemic or enriched products derived from reactions of substrates of general structure **1**. Section 6 will briefly discuss methods for the removal of the benzophenone imine group.

2. Background

2.1. Starting Material Preparation

The condensation of glycine alkyl esters and benzophenone under forcing conditions (refluxing toluene or xylene, BF_3•Et_2O, Dean–Stark trap) was used as an early route to the corresponding benzophenone imines (**4**).[2a,5] In addition to the harsh reaction conditions and the need for extensive purification of the crude product, this procedure requires initial conversion of the stable glycine ester salt into the free amino ester. This can be problematic with the lower glycine esters (e.g., Me and Et), which readily undergo self-condensation to the corresponding diketopiperazines.

A much milder route involves the transimination reaction of the glycine alkyl ester *salt* with benzophenone imine,[3b] a more reactive benzophenone equivalent (**eq 1**).[6] This room-temperature procedure has been used for the preparation of a variety of benzophenone imines of glycine and higher amino acid derivatives as well as peptide esters.

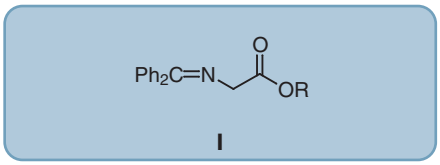
Several of the benzophenone imines of glycine alkyl esters (**4**) as well as the benzophenone imine of aminoacetonitrile ($Ph_2C{=}NCH_2CN$),[2b,3c] another useful glycine anion equivalent, are commercially available. Other routes to benzophenone imines of amino acid derivatives are noted.[7]

2.2. Glycine Anion Equivalents

Substrates **4** are active methylene compounds that can be deprotonated using mildly basic conditions. Phase-transfer-catalyzed (PTC) reactions of **4** with electrophiles provide an attractive route to the higher amino acid derivatives **5**, because of the easy reaction procedure, mild conditions, safe and inexpensive solvents and reagents, and the ability to conduct the reactions on a large scale (**Scheme 1**).[1e,1g,8] A variety of mild basic systems (e.g., NaOH, KOH, K_2CO_3), either in aqueous solution (liquid–liquid PTC) or as the solid

(solid–liquid PTC), can be used in conjunction with either a catalytic amount (PTC) or a full equivalent (ion–pair extraction) of a quaternary ammonium phase-transfer reagent. For the small-scale rapid preparation of products, these reactions can also be conveniently accomplished with strong base (e.g., *n*-BuLi, LDA, NaH, KOtBu, LiHMDS, NaHMDS, KHMDS) under anhydrous conditions by preparing the anion of **4** at low temperature and then adding the electrophilic reagent.

An important aspect of the alkylation reactions of **4** under mild conditions is the selective formation of only the monoalkylated product, **5**, without concomitant production of the undesired dialkylated derivative, **6**.[9,10] This results from the much lower acidity of products **5** as compared to the starting material, **4** (e.g., **5b** is about 10^4 less acidic than **4b**) (**eq 2**).[11] In addition to controlling the alkylation, this acidity-weakening effect is also key in the stereoselective introduction of the R group under mildly basic reaction conditions, since it is possible to deprotonate **4** without deprotonating **5**, which would result in racemization of the newly created stereogenic center.



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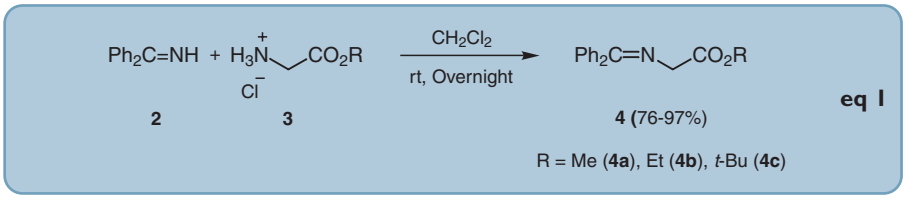
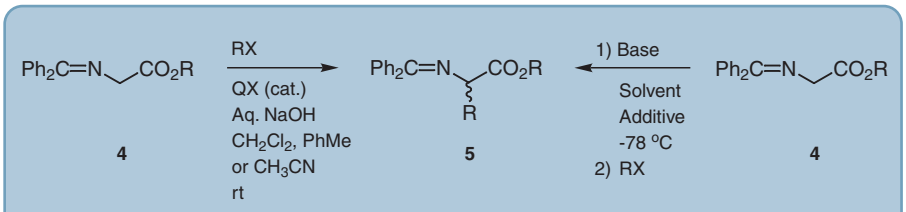
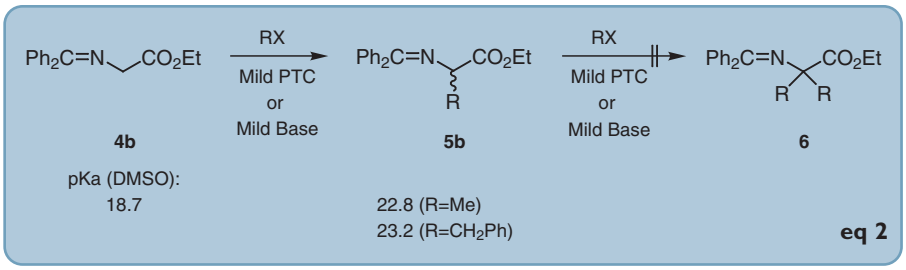


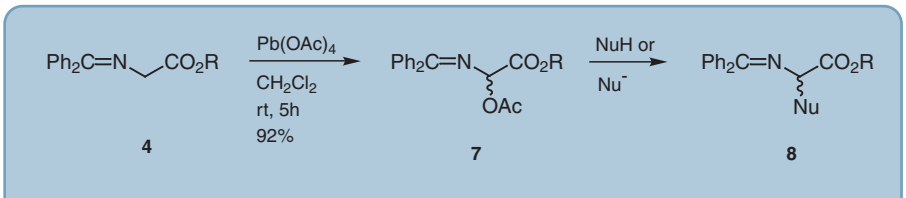
eq 1



Scheme 1. PTC and Anhydrous Alkylations of Benzophenone Imine Derivatives.



eq 2



Nucleophile	Conditions	Nu in **8**	Product No.	Reference
RXH	--	RX	**9**	12a
ArH	$TiCl_4$	Ar	**10**	12d, 13d
9-Ar-9-BBN	ArOK	Ar	**10**	12c
$Ar_2Cu(CN)Li_2$	--	Ar	**10**	12b
Ar_2Zn	--	Ar	**10**	13c
$AllylSiR_3$	$TiCl_4$	CH_2=$CHCH_2$	**11**	12d
RCH=CHM	Pd(0)	RCH=CH	**12**	12f
Z_2CHM	Pd(0)	Z_2CH	**13**	12e, 12g
9-R-9-BBN	ArOK	R	**5**	12c, 13a
$R_2Cu(CN)Li_2$	--	R	**5**	12b, 13b, 13f
RZnCl	Pd(0)	R	**5**	13e

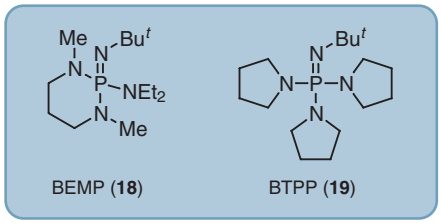
Scheme 2. Preparation and Reactions of Glycine Cation Equivalent **7**.

2.3. Glycine Cation Equivalents

The benzophenone imines of glycine alkyl esters (**4**) can also be used as starting materials to prepare the α-acetoxy derivatives, **7**, which serve as glycine cation equivalents.[12] Thus, reaction of **7** with a variety of either neutral or charged nucleophiles leads to the monosubstituted amino acid derivatives **8** (**Scheme 2**). This provides a complementary route to several classes of products that are often not available by the anionic method: other α-heteroatom-substituted derivatives (**9**),[12a] aryl glycines (**10**),[12b-12d,13c,13d] vinyl glycines (**12**),[12f] derivatives from coupling to other active methylene compounds (**13**),[12e,12g] and other alkyl derivatives.[12b-12d,13a,13b,13e,13f]

2.4. Solid-Phase Organic Synthesis

In 1996, in collaboration with Dr. William L. Scott of Eli Lilly and Company in Indianapolis, we reported the solid-phase synthesis of unnatural amino acids and peptides, termed "Unnatural Peptide Synthesis" ("UPS").[14] This methodology involves the introduction of the amino acid side chain during a normal Solid-Phase Peptide Synthesis (SPPS) (**Scheme 3**). Three key steps are added to a normal SPPS to accomplish UPS: (i) activation of the *N*-terminal glycine residue as the benzophenone imine (**14** to **15**), (ii) deprotonation and alkylation of the resulting active methylene substrate (**15** to **16**), and (iii) hydrolysis of the imine (**16** to **17**) to liberate the free *N*-terminal residue for further reactions such as another cycle of UPS or cleavage of the product from the resin. Since solid-phase synthesis already involves a second phase, the use of normal PTC types of reactions in the UPS sequence was expected to be problematic. The organic-soluble, nonionic phosphazene bases ("Schwesinger bases", **18** and **19**)[15] used in the UPS alkylation step function in a manner similar to that of typical phase-transfer base systems. Since the Schwesinger bases do not react at an appreciable rate with alkyl halides, it is possible to first add the electrophile and then the Schwesinger base to the reaction mixture. These reactions can



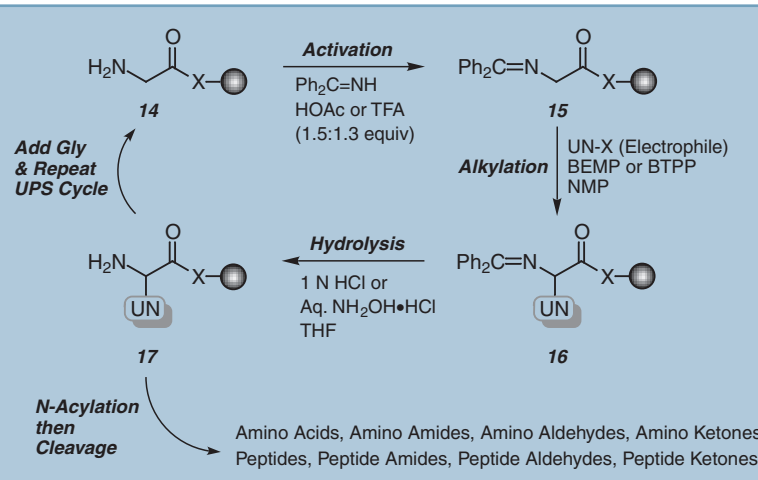
also typically be accomplished at room temperature, because only a small amount of the substrate anion is formed and then trapped by reaction with the electrophile.

In addition to normal alkylations of both resin-bound amino acid and peptide derivatives, several other types of products are also available by UPS methodology. Relatively unreactive alkyl halides or those prone to elimination can be employed by increasing the stoichiometry of the reagents (i.e., base and electrophile) or by converting an unreactive alkyl chloride or bromide into the more reactive iodide by an in situ Finkelstein reaction.[14c] Tandem dialkylation, which involves a typical UPS mono-alkylation with a base such as BEMP (**18**) followed by a second alkylation using a stronger base (KHMDS) under anhydrous conditions, allows the preparation of unsymmetrical α,α-disubstituted products.[14d] Reaction of Michael acceptors by UPS leads to a variety of glutamic acid derivatives.[14e] Other types of products can be prepared using different resins: amino amides or peptide amides using Rink amide resin;[14h] amino aldehydes, amino ketones, peptide aldehydes, or peptide ketones using Weinreb amide resin.[14g] A resin-bound glycine cation equivalent reacts with organoboranes to yield various α-substituted amino acids.[14f]

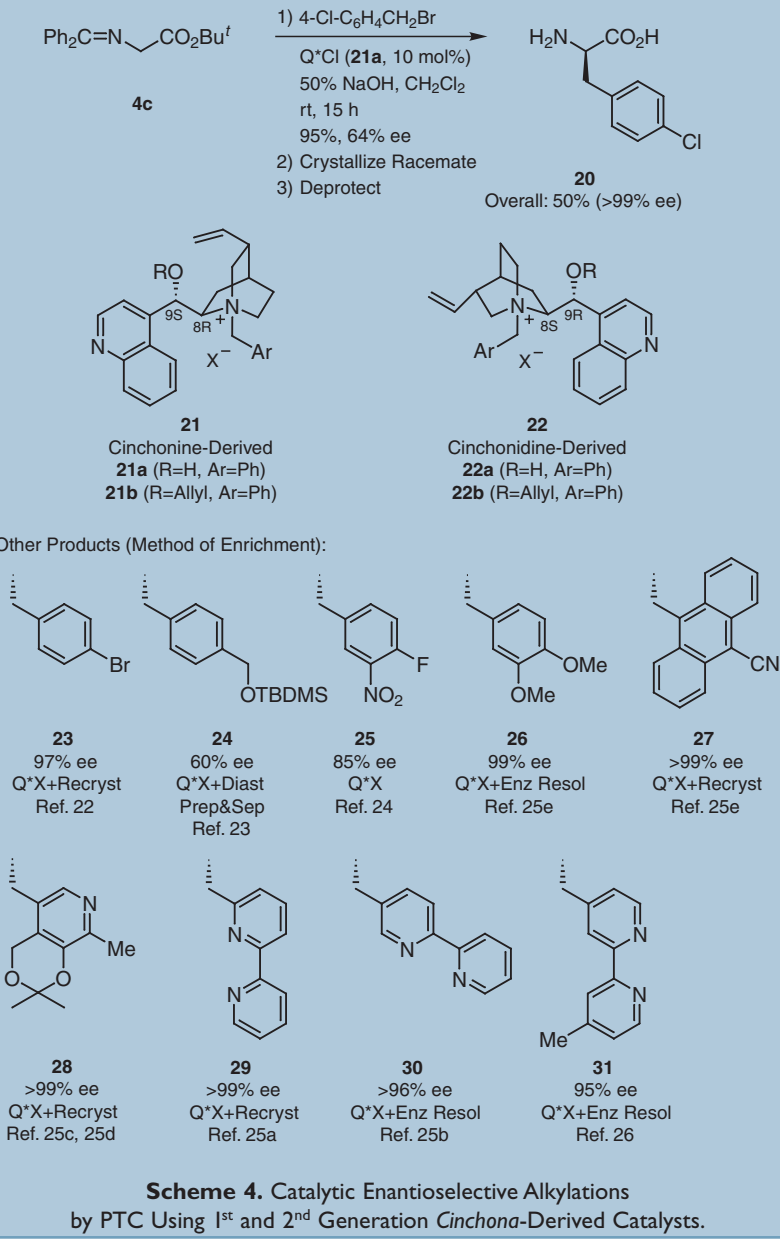
Recently, the alkylation of soluble, PEG polymer-supported benzophenone imines of glycine has been reported by Martinez and co-workers.[16]

2.5. Purification and Analysis of Products

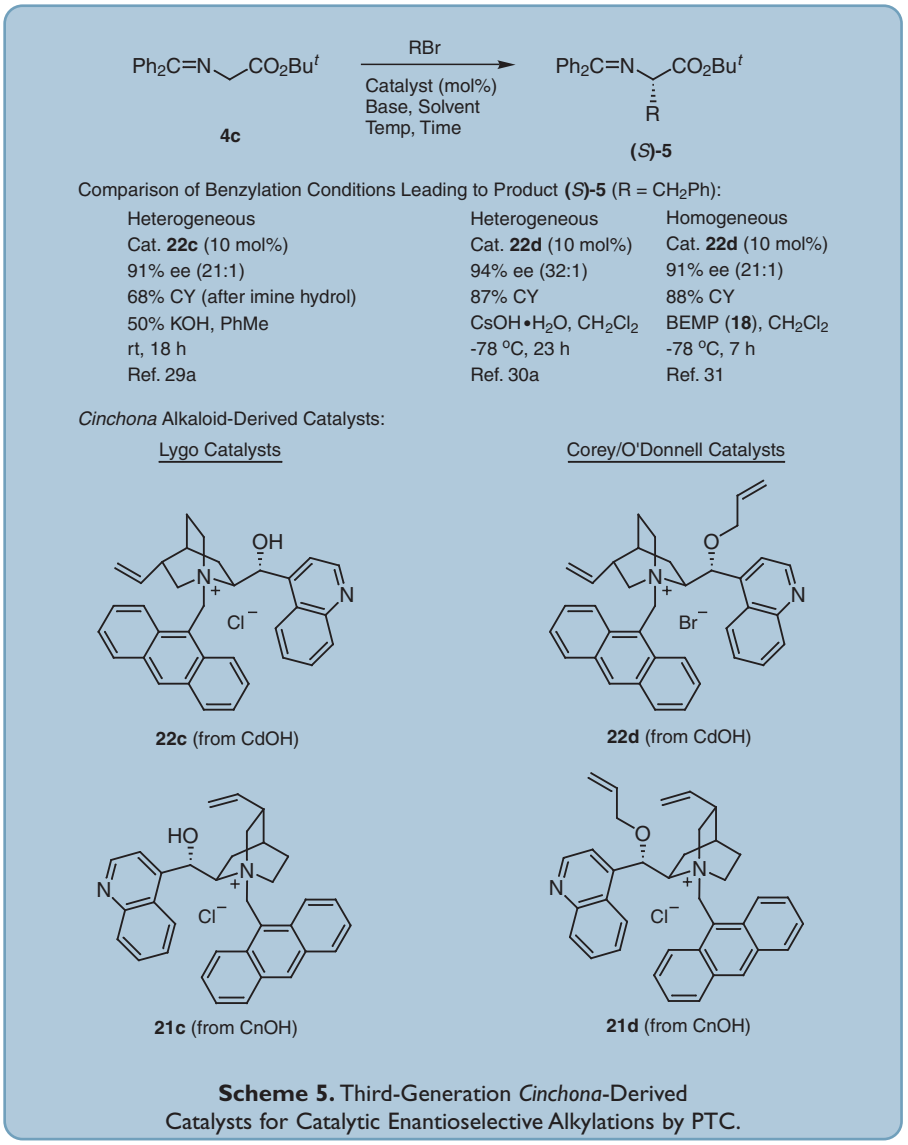
Products containing the benzophenone imine group are normally more stable to hydrolytic and chromatographic conditions than their aldimine counterparts. The benzophenone imine is, however, removed under mildly acidic aqueous conditions. Thus, care must be taken in the purification of these compounds to avoid acidic conditions or long residence times on chromatography columns. Typically, the products from the benzophenone imine of glycine derivatives (**1**) can be purified by normal flash chromatography.[17] In cases where the products are labile to such conditions, it is recommended that silica gel be deactivated by removal of water and triethylamine be used in the eluent solvent, as



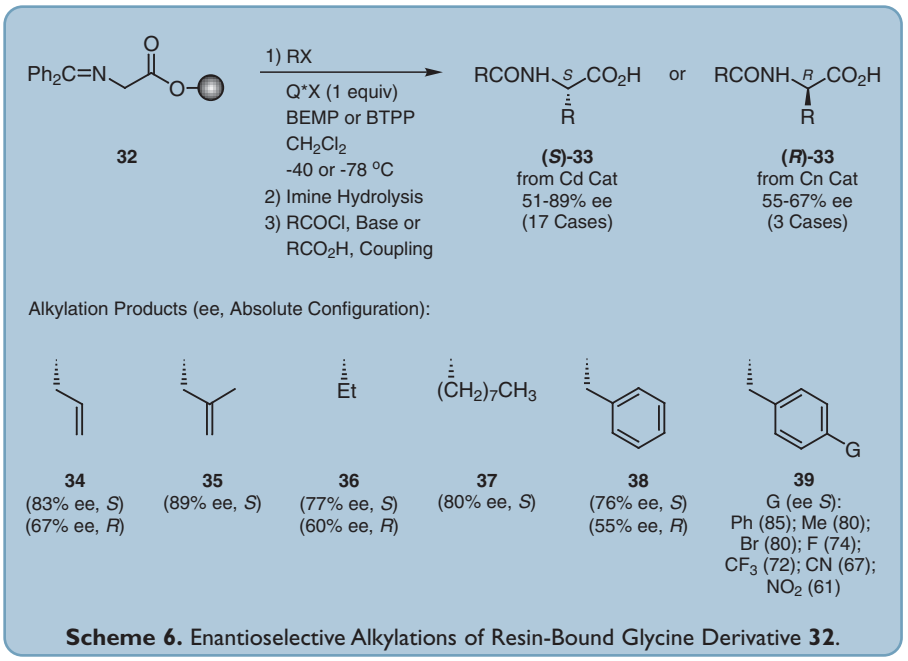
Scheme 3. Unnatural Amino Acid and Peptide Synthesis (UPS).



Scheme 4. Catalytic Enantioselective Alkylations by PTC Using 1st and 2nd Generation *Cinchona*-Derived Catalysts.



Scheme 5. Third-Generation *Cinchona*-Derived Catalysts for Catalytic Enantioselective Alkylations by PTC.



Scheme 6. Enantioselective Alkylations of Resin-Bound Glycine Derivative **32**.

reported by de Meijere and co-workers.[18] If decomposition of the benzophenone imine products is still problematic, the crude reaction products can be hydrolyzed directly to the amine salt or the free amine for purification and analysis.

Measurements of the enantioselectivities of the optically active products derived from Schiff bases **1** have been accomplished using a variety of HPLC methods.[19] The two main methods are (i) direct separation by chiral HPLC, or (ii) conversion to diastereomeric derivatives for analysis using normal achiral HPLC methods.

3. Catalytic Enantioselective Reactions

3.1. Alkylations

Our contribution in this area followed the pioneering work of the Merck group using phase-transfer catalysts, derived by N-alkylation of the *Cinchona* alkaloids, for the preparation of alkylated indanone derivatives.[20] In 1989, we reported the catalytic enantioselective PTC alkylation of imine **4c** using the pseudoenantiomeric catalysts (**21a** or **22a**) derived from cinchonine (CnOH) or cinchonidine (CdOH) (**Scheme 4**).[21] While modest enantioselectivities (up to 66% ee) were obtained, it was possible in some cases to prepare optically pure, higher α-amino acids by recrystallization of these enriched products (**4c** to **20**). Scheme 4 shows examples of the use of this chiral PTC methodology in combination with enrichment by recrystallization, by preparation and separation of diastereomeric derivatives, or by enzymatic resolution.[22-26,27]

An improvement of the catalyst was reported in 1994, when we proposed that the active catalyst species in these alkylations was derived by in situ O-alkylation of the *Cinchona* quat.[28] The *O*-allyl group was shown to be the optimal substituent in this new second-generation of catalysts (**21b** or **22b**, Scheme 4). Enantioselectivities of up to 81% were obtained using these catalysts.

A further major improvement in catalyst performance was reported simultaneously in late 1997 by the groups of Lygo at Salford[29] and Corey at Harvard.[30] Enantioselectivities of 91–94% were obtained for the model benzylation using third-generation catalysts containing the *N*-9-anthracenylmethyl group either with a free OH (**22c** or **21c**, converted in situ to the active *O*-alkyl catalyst) or with an *O*-allyl group (**22d**), respectively (**Scheme 5**). The highest enantioselectivities reported were 94% ee (with benzyl bromide) for the Lygo system and 99.5% ee (with either *n*-hexyl iodide or benzhydryl bromide) using catalyst **22d** as reported by Corey.

Table 1. Comparison of Various Enantioselective Alkylations

(*S*)-Products: $Ph_2C{=}N$ (*S*) CO_2Bu^t, R — **5** (Solution-Phase); $RCONH$ (*S*) CO_2H, R — **33** (Solid-Phase)

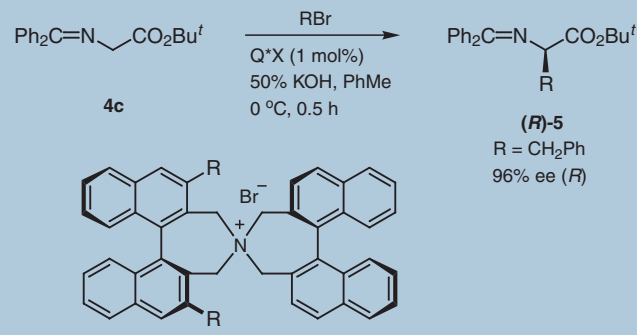
Side-Chains: / Method			 Ph	Me	Et	C_nH_{2n+1}		Ref.
PTC (Lygo):	88% ee (*S*) 88% ee (*R*)	-- --	91% ee (*S*) 89% ee (*R*)	89% ee (*S*) 86% ee (*R*)	-- --	88% ee (*S*) (C_4) 87% ee (*R*) (C_4)	-- --	29a
PTC (Corey):	97% ee (*S*) --	92% ee (*S*) --	94% ee (*S*) --	97% ee (*S*) --	98% ee (*S*) --	99.5% ee (*S*) (C_6) --	-- --	30a,30b
Homogeneous (O'Donnell):	90% ee (*S*) 87% ee (*R*)	94% ee (*S*) --	91% ee (*S*) 83% ee (*R*)	94% ee (*S*) --	89% ee (*S*) 85% ee (*R*)	93% ee (*S*) (C_8) --	97% ee (*S*) 87% ee (*R*)	31
Solid-Phase (O'Donnell):	83% ee (*S*) 67% ee (*R*)	89% ee (*S*) --	76% ee (*S*) 55% ee (*R*)	86% ee (*S*) --	77% ee (*S*) 60% ee (*R*)	80% ee (*S*) (C_8) --	80% ee (*S*) --	32
PTC (Maruoka):	-- 94% ee (*R*)	-- 93% ee (*R*)	-- 96% ee (*R*)	-- 90% ee (*R*)	-- 95% ee (*R*)	-- --	-- --	34

We showed that it was possible to carry out these catalytic enantioselective reactions in *homogeneous* solution by using the Schwesinger bases, BEMP (**18**) or BTPP (**19**), in conjuction with catalyst **22d** or its pseudoenantiomer **21d**.[31] The highest enantioselectivity (97% ee) was obtained using isobutyl bromide as the alkyl halide.

We have also reported the enantioselective solid-phase synthesis of α-amino acid derivatives using the *Cinchona*-derived reagents, **22d** and **21d**, together with the Schwesinger bases, BEMP (**18**) or BTPP (**19**), and resin-bound glycinate **32** (**Scheme 6**).[32] Enantioselectivities of up to 89% ee (with methallyl bromide) were obtained using normal Wang resin bound substrates. It is interesting to note that there is a considerable erosion of enantioselectivity in the preparation of the *R* enantiomer using catalyst **21d**.

The use of a resin-bound, *Cinchona*-derived, phase-transfer catalyst gave only a poor induction (27% ee) for the alkylation of **4c**.[33]

The Maruoka group recently reported a new class of quaternary ammonium catalysts (**40**) that are derived from the BINAP system.[34] Excellent enantioselectivity (96% ee) was achieved with only 1 mol% catalyst at 0 °C in 30 minutes for the model benzylation reaction (**eq 3**). The highest enantioselectivities (96% ee) were obtained with various benzylic bromides. Although these catalysts are expected to be relatively expensive—since they are not derived from the chiral pool—they should also be more stable to the basic reaction conditions than β-hydrogen-containing quat salts, which can suffer degradation by the Hofmann elimination.



eq 3

Enantioselectivities for various types of alkyl halides using the five different enantioselective routes just described are compared in **Table 1**.[29-32,34] Side-chain structures for the various products formed using these methodologies are given in **Table 2**.[29-31,34,35]

A number of different groups have studied the catalytic enantioselective allylic substitution of **4** using Pd(0) and various chiral phosphines (**eq 4**).[36-39] Of note is the research of the Genet group in Paris using DIOP and other related bisphosphines.[36] In general, the enantioselectivities have been modest with this type of reaction. An exception is the excellent enantioselectivity (97% ee) obtained by Williams and co-workers, who used the phosphorus-containing oxazole ligand **68** with a diphenyl-substituted allylic acetate.[39] However, the same reaction with the parent allyl acetate gave only poor enantioselectivity (17% ee in DMF, 5% ee in THF). Taken together, these

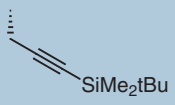
Table 2. Optically Active Amino Acid Derivatives Prepared Using PTC Catalysts 22c, 22d, or 40

41
97% ee
Ref. 31

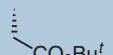
42
99% ee
Ref. 30a

43
99% ee
Ref. 30b

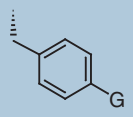
44
95% ee
Ref. 34a



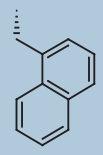
45
95% ee
Ref. 30a



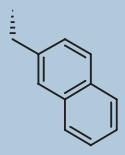
46
83% (84%) ee
Ref. 29a
56% ee
Ref. 31



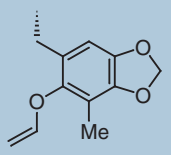
47 - 52
G (% ee):
Me (91); NO_2 (89);
CF_3 (88); Ph (86);
CN (85); F (84)
Ref. 31



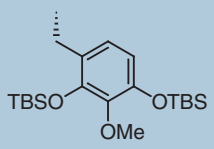
53
96% ee
Ref. 34



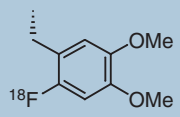
54
86% (82%) ee
Ref. 29a



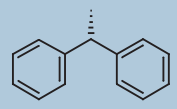
55
96% ee
Ref. 30a



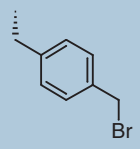
56
97% ee
Ref. 30a



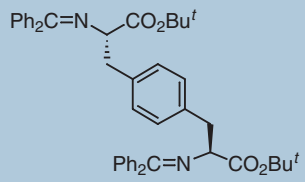
57
90% ee
Ref. 35



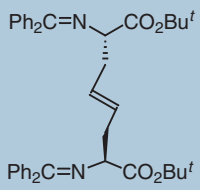
58
99.5% ee
Ref. 30a



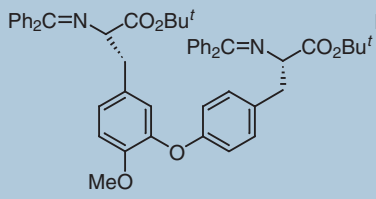
59
86% ee
Ref. 29b



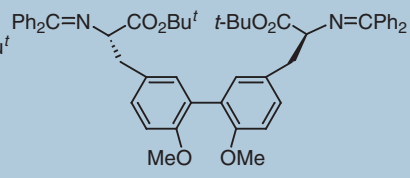
60
≥95% ee, 72% de
Ref. 29b



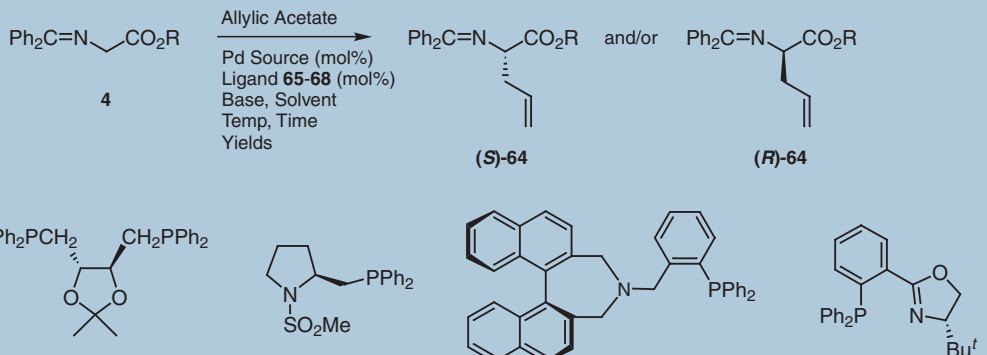
61
≥95% ee, 82% de
Ref. 29b



62
≥95% ee, 80% de
Ref. 29c



63
≥95% ee, 80% de
Ref. 29c



65

AllylOAc, R=Me
$Pd(OAc)_2$ (3%)
Cat. **65** (6%)
LiHMDS, THF
-60 °C, 3h
68% (70% ee, *R*)
Ref. 36

66

AllylOAc, R=Me
$PdCl(C_3H_5)_2$ (3%)
Cat. **66** (12%)
LDA, THF
-50 °C, 1 h
82% (62% ee, *S*)
Ref. 37

67

AllylOAc, R=Me
$(PdC_3H_5Cl)_2$ (1%)
Cat. **67** (2%)
BSA, PhMe
-20 °C, 110 h
81% (51% ee, *S*)
Ref. 38

68

PhCH=CHCH(Ph)OAc, R=*t*-Bu
$(PdC_3H_5Cl)_2$ (2.7%)
Cat. **68** (10%)
BSA, CsOAc, THF
rt, 10 h
89% (97% ee, *S*)
Ref. 39

eq 4

results imply that the choice of electrophilic partner is key to obtaining high stereoselectivities in these palladium-catalyzed allylic substitutions.

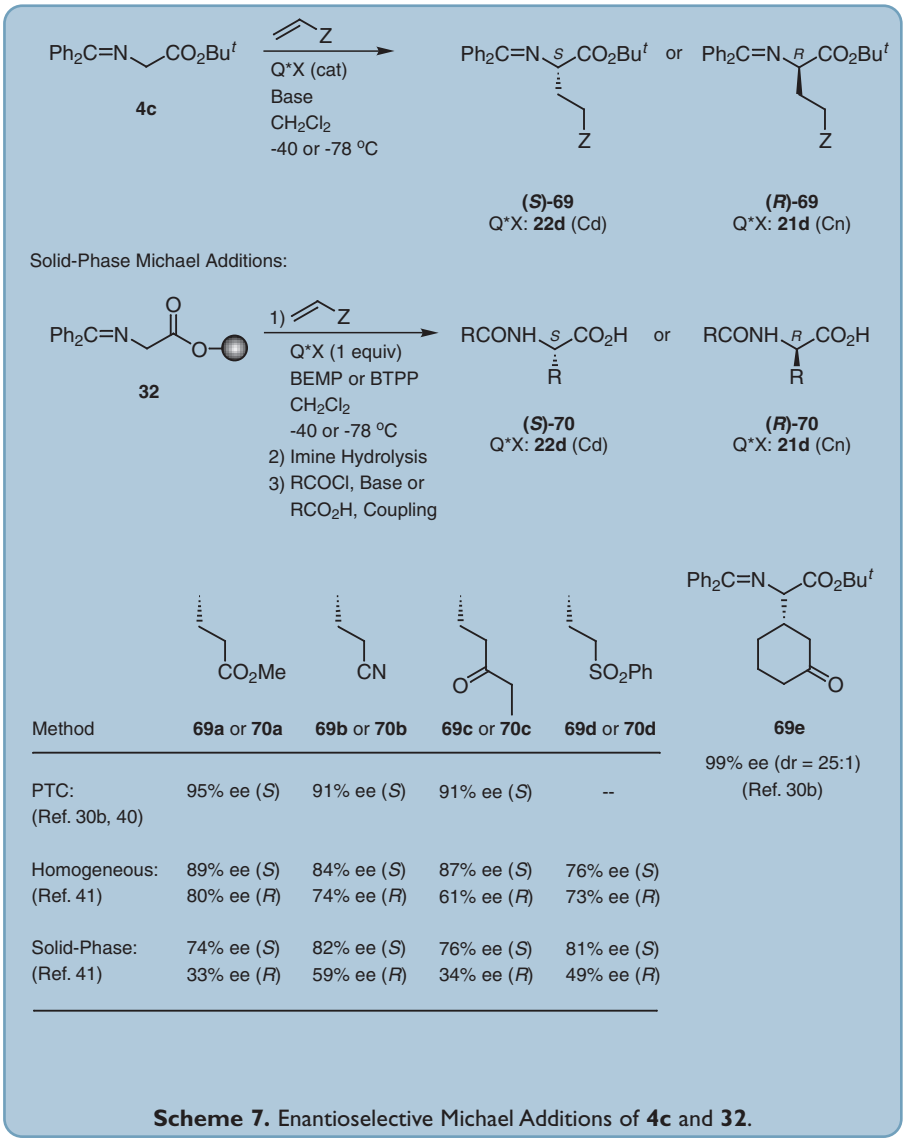
3.2. Michael Additions

Catalytic enantioselective conjugate additions of **4c** and Michael acceptors have been reported by the Corey group as a route to various glutamic acid derivatives (**Scheme 7**).[30b,40] The reactions can be accomplished either by the Corey PTC route[30b,40] (up to 99% ee) or by our homogeneous reaction utilizing Schwesinger bases[41] (up to 89% ee) (see Scheme 5 for related alkylations). The natural (*S*)-**69** is prepared using catalyst **22d**, while (*R*)-**69** is available, generally with lower enantioselectivity, using catalyst **21d**. Solid-phase synthesis (UPS) on Wang resin has also been used as a route to optically active Michael adducts **70** in up to 82% ee using a full equivalent of the quaternary ammonium salts **22d** or **21d**.[41] The considerable erosion of stereoselectivity for the (*R*)-**70** products is noteworthy.

3.3. Aldol Reactions

β-Hydroxy amino acid derivatives have been prepared by the Corey group in high enantioselectivity and good diastereoselectivity by a catalytic enantioselective aldol reaction (**Scheme 8**).[42] Silyl ketene acetal **71** was reacted with sterically demanding aliphatic aldehydes in the presence of quaternary ammonium bifluoride catalyst **22e** to give the syn diastereomer as the major product. The initial reaction products consisted of a mixture of the isomeric oxazolidine, **72**, and the open-chain β-hydroxy product, **73**.[43] Lower syn/anti ratios were observed with unbranched aldehydes (RCH_2CH_2CHO), while the highest syn/anti ratio (13:1, 86% de) was obtained with cyclohexanecarboxaldehyde. Ketene silyl acetal **71** was prepared from **4c** (LDA, THF, -78 °C, 1h; TMSCl; unstable in CH_2Cl_2 solution at room temperature). The bifluoride catalyst, **22e**, was prepared from the corresponding quaternary ammonium bromide, **22d**, which was converted to the hydroxide and then neutralized with 2 equiv of 1 N HF.[42]

Further transformations of product **76** demonstrate the utility of this reaction for the preparation of structurally diversified products.[42] Treatment of **76** with a mild base leads directly to β-hydroxypipecolic acid derivatives, **77**, by intramolecular nitrogen-to-carbon alkylation, while initial protection of the nitrogen followed by an in situ Finkelstein reaction gives the cyclic ether, **78**, by intramolecular oxygen-to-carbon alkylation. While the initial aldol reaction to form **76** occurred without diastereoselectivity, each of the products **77** and **78** was readily purified by column chromatography.



Method	69a or 70a	69b or 70b	69c or 70c	69d or 70d
PTC: (Ref. 30b, 40)	95% ee (*S*)	91% ee (*S*)	91% ee (*S*)	--
Homogeneous: (Ref. 41)	89% ee (*S*) 80% ee (*R*)	84% ee (*S*) 74% ee (*R*)	87% ee (*S*) 61% ee (*R*)	76% ee (*S*) 73% ee (*R*)
Solid-Phase: (Ref. 41)	74% ee (*S*) 33% ee (*R*)	82% ee (*S*) 59% ee (*R*)	76% ee (*S*) 34% ee (*R*)	81% ee (*S*) 49% ee (*R*)

Scheme 7. Enantioselective Michael Additions of **4c** and **32**.

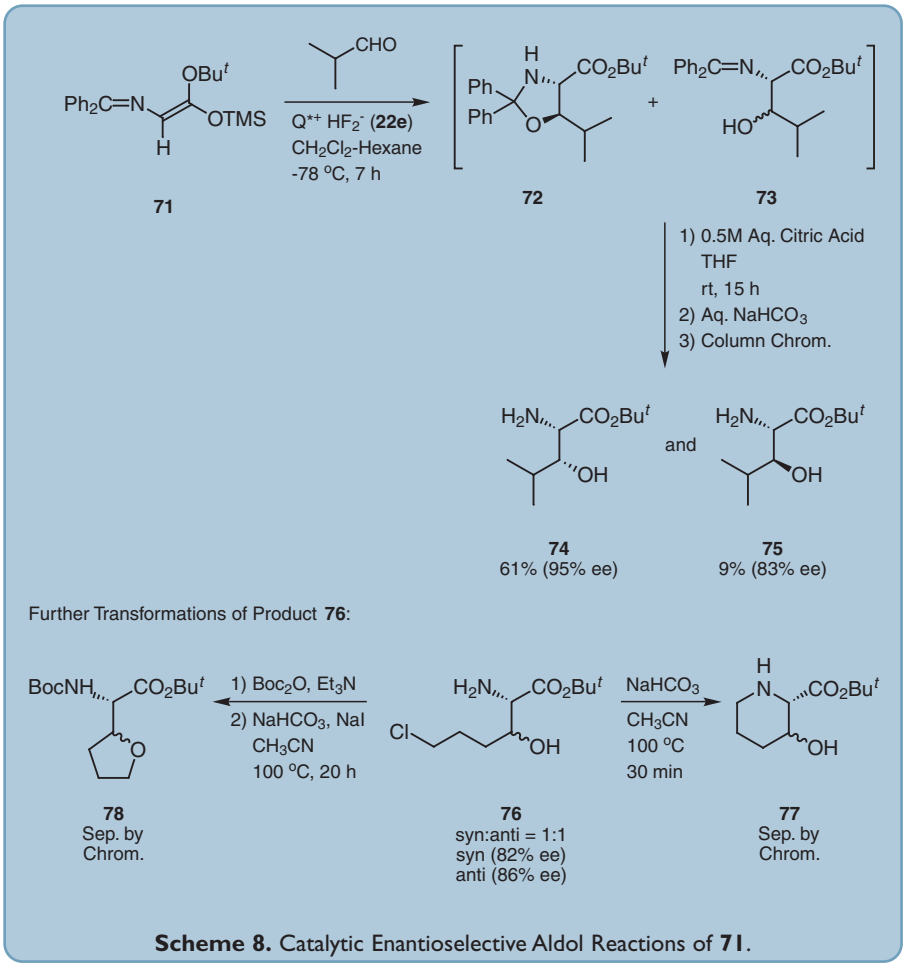
3.4. Glycine Cation Equivalents

The catalytic enantioselective reaction of glycine cation equivalent **7** with malonate anions occurred at room temperature in one hour in the presence of Pd(0) and the chiral bisphosphine ligand BINAP (**eq 5**).[12g,44] The product, **79**, a protected derivative of β-carboxyaspartic acid, was formed in up to 85% ee from a (2-aza-π-allyl)palladium intermediate. A number of variables were optimized in this system: substrate ester, imine, and leaving group; base, solvent, counterion, and additive; and steric factors in the nucleophilic partner. The best results were obtained with the benzophenone imine of glycine *tert*-butyl ester (**7**), and the stereoselectivity was shown to be sensitive to the nature of the nucleophile. The reaction was run on a scale of up to 10 mmoles, and the optical purity of the product was improved to 95.5% ee by simple recrystallization of the initial reaction product, **79**.[12g]

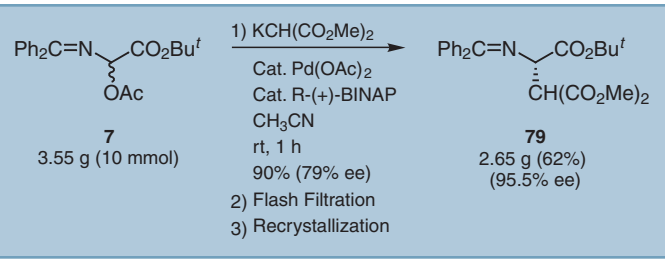
4. Stereoselective Reactions Involving Chiral Auxiliaries

The use of either an ester or an amide as a chiral auxiliary, in conjunction with nitrogen protection using the benzophenone imine, has been studied by a number of groups. Two methods are presented in some detail (**Scheme 9** and **eq 6**).

Chassaing's group first reported the preparation (by the trimethylaluminum-mediated acylation of sultam **80** with **4a**) and use of substrate **81**, which contains the Oppolzer sultam auxiliary.[45] Their typical alkylation conditions (**81** → **82**) involved the formation of the lithium enolate at low temperature followed by addition of the alkyl halide, often with added HMPA (or DMPU[46]), and alkylation at either low temperature or room temperature.



Scheme 8. Catalytic Enantioselective Aldol Reactions of **71**.



eq 5

In addition to a number of alkylation products such as **83**–**87**, this route was also used to prepare various labeled amino acids (Ala, Val, Ser, Asn, Gln, Asp, Trp, Cys) from labeled starting materials **88**–**90**. The authors noted that the major limitations of the method were the preparation of electrophiles (for Arg, Lys, His, and Tyr) and control of chirality at the β-carbon center (for Ile and Leu).[45] Other labeling studies using this route include the preparation of compounds **91**[46] and **92**.[47] Roques and coworkers have also used the sultam route to introduce a number of interesting amino acid side chains (**93**–**96**).[48] Palladium-catalyzed allylations to prepare compounds such as **97** and **98**, as well as regular alkylation to form **99**, have been reported by de Meijere's[49] and Salaün's[49a] groups. These workers have made extensive use of both anionic and cationic benzophenone imine derivatives of glycine to prepare various cyclopropyl-substituted amino acid derivatives.[49,13e,13f] López and Pleixats have reacted **81** with active halides or Michael acceptors under solid–liquid phase-transfer catalysis conditions (K_2CO_3, Bu_4NBr, CH_3CN at either rt or reflux) to prepare products such as **100** and **101**.[50] These conditions avoid the anhydrous, low-temperature conditions and the use of HMPA as reported above.

An interesting glycine imine substrate, **102**, containing an imidazolidinone chiral auxiliary derived from ephedrine, has been reported by Nájera's group (**eq 6**).[51] This system has considerable potential for the rapid and convenient synthesis of various optically active α-amino acid derivatives. A key to the successful diastereoselective reactions of **102** was the addition of LiCl to the alkylation and Michael addition reactions. Several different base systems were studied. In general, better yields and stereoselectivities were obtained with DBU than with PTC using solid LiOH. Allylation occurred in high diastereoselectivity with both DBU (1 h, 86%, 98% de) and BEMP (3.5h, 60%, 98% de). However, with the less expensive DBU, the reaction was faster and resulted in a better chemical yield. While Michael additions to form **109** occurred with excellent diastereoselectivities, the chemical yields were poor (25–32%). Because of partial decomposition during purification of products **103**, the crude products were normally hydrolyzed directly to the amino-imidazolidinones (0.5 N HCl, THF; K_2CO_3).

Several other starting Schiff bases containing chiral auxiliaries will be briefly summarized. ^{11}C-Labeled alanine and phenylalanine were prepared by Långström's group for positron emission tomography (PET) studies.[5a] Because of the short lifetime of ^{11}C ($t_{1/2}$ = 20.4 min), the preparation of such compounds must be accomplished in the shortest possible time. Alkylation of an 8-phenylmenthol-derived ester with a ^{11}C-labeled alkyl halide, followed by imine deprotection by transimination (NH_2OH) and ester saponification, gave the labeled amino acids in 15–40% decay-corrected radiochemical yields, with higher than 98% radiochemical purity, and in 52–55% ee in a total synthesis time of 35–55 minutes. Double asymmetric induction with a chiral ester and a chiral catalyst was used in a Pd(0) catalyzed allylation.[52] A chiral sultam was used as the starting material for an asymmetric benzylation (>91% de).[53] An asymmetric anti-selective aldol reaction of a titanium enolate containing a chiral auxiliary gave products with diastereomeric ratios of 95:5 to ≥99:1[54] (compare with Corey's system[42] that gave mainly *syn*-aldol products; see Scheme 8). An axially chiral binaphthol-derived ester was alkylated with active halides in 69–86% de,[55a] and an α,β-dide-hydro-8-phenylmenthyl ester Schiff base was alkylated at the γ carbon in up to 64% de.[55b]

Other reactions with chiral nonracemic reaction partners or reagents are noted. These include chiral electrophiles for alkylations,[56,57] Michael additions,[58] and aldol reactions;[59] a chiral proton source;[56] a chiral base;[60] and chiral, nonracemic Schiff base derived ligands with transition metals for use as potential catalysts.[61]

5. Resolutions

Whitesides's group reported the racemic alkylation of **4b** to form **110**. Hydrolysis and acylation of **110** led to **111**, which were

subjected to kinetic enzymatic resolution using acylase I to yield the natural L-amino acids, (*S*)-**112**, together with the unreacted, unnatural D-enantiomers, (*R*)-**111**.[62] Excellent enantioselectivities for both enantiomers (typically >90–95% ee) were obtained in this comprehensive study (**Scheme 10**).

Enzymatic resolutions of racemic or enriched phenylalanine-type substrates, prepared from benzophenone imines of glycinates, have been reported (**Figure 1**).[23,25,27,63-66] Långström and coworkers reported a synthesis of [3-^{11}C]-labeled alanine and phenylalanine that involved resolution using immobilized D-amino acid oxidase, which selectively destroys the D-enantiomer.[64] Conversely, Pirrung and Krishnamurthy used L-amino acid oxidase to prepare a variety of unnatural D-amino acids.[65] The Imperiali group[25b,25e] and others[66] have employed alkaline protease, which converts the L-enantiomer of an amino acid methyl ester into the amino acid without affecting the D-enantiomer, to prepare a number of interesting phenylalanine analogs. Of note in the Imperiali studies is the use of catalytic enantioselective alkylations with early-generation, chiral, phase-transfer catalysts to obtain optically enriched products (Scheme 4), which were then resolved to obtain the desired pure enantiomers.[25b,25e]

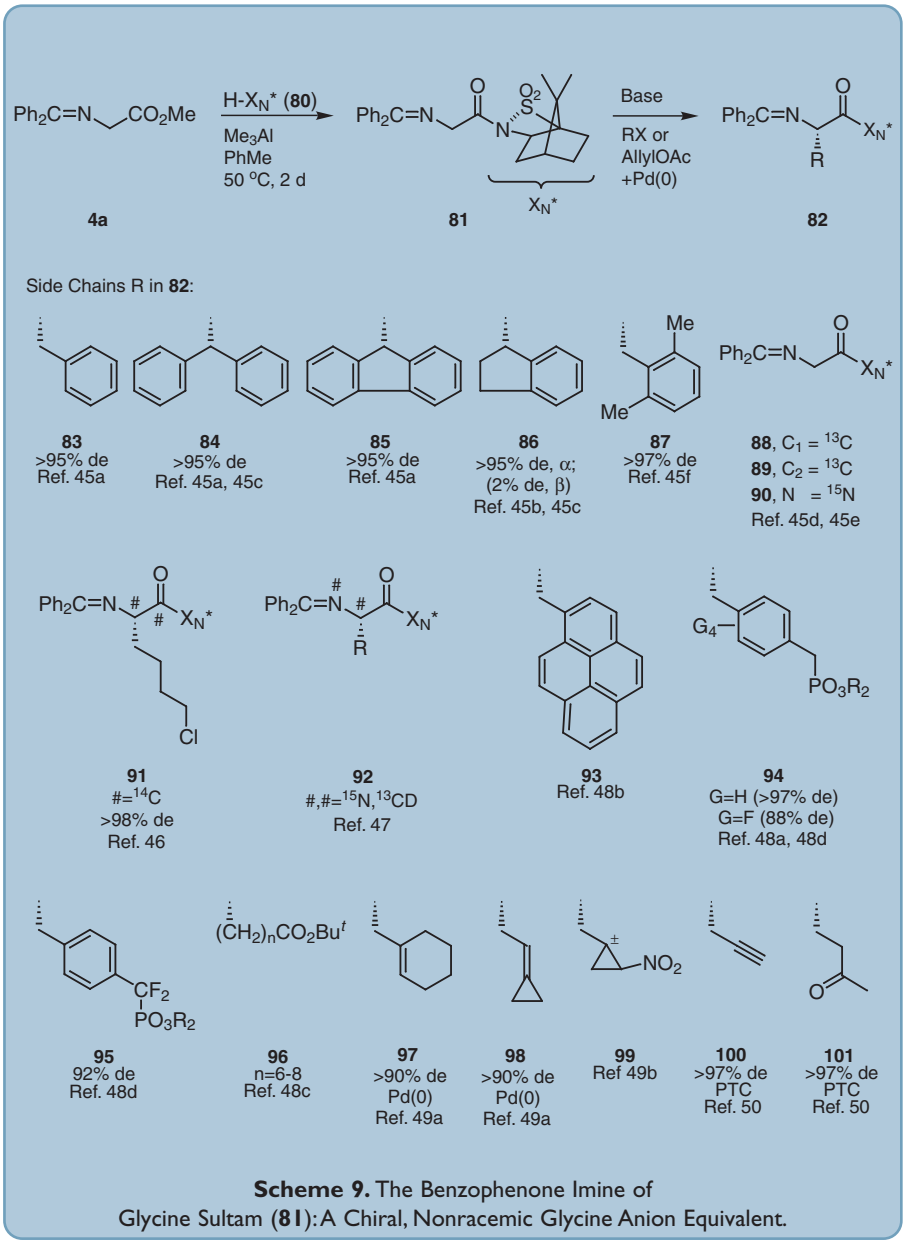
Groups at DSM and the University of Amsterdam have made extensive use of aminopeptidase for the enzymatic resolution of various types of amino amides.[67] Several representative examples, which make use of prior alkylation chemistry of benzophenone imines, are given in **Scheme 11**.

6. Removal of the Benzophenone Imine Group

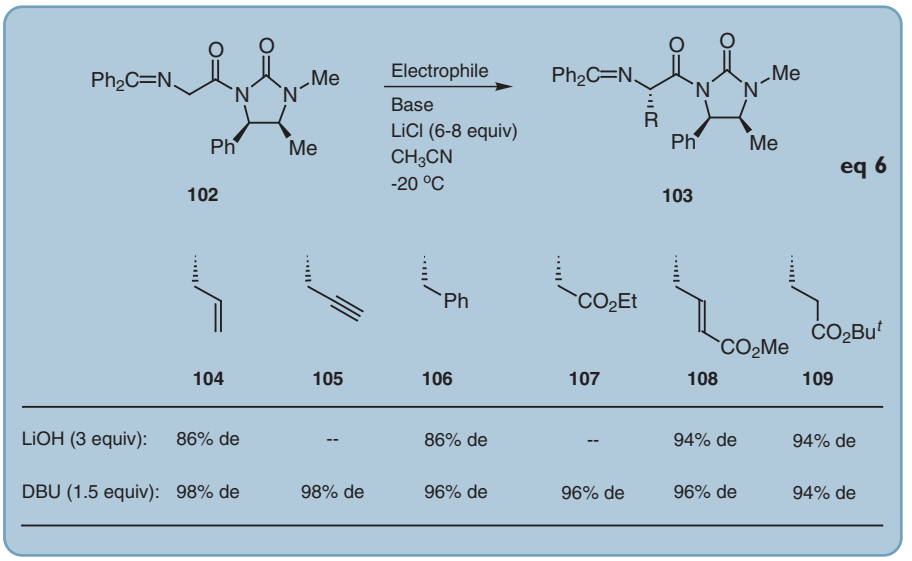
The three most common methods for removing benzophenone imine groups are: treatment with mild acid, hydrogenolysis, or transimination. By carefully controlling the conditions, it is possible to accomplish the deprotection in the presence of various other functionalities. On the other hand, it is also possible to remove multiple protecting groups in the same reaction. A number of either optically active or racemic products, that have been subjected to various methods of deprotection, are given in **Figure 2**.[68-70]

7. Conclusions

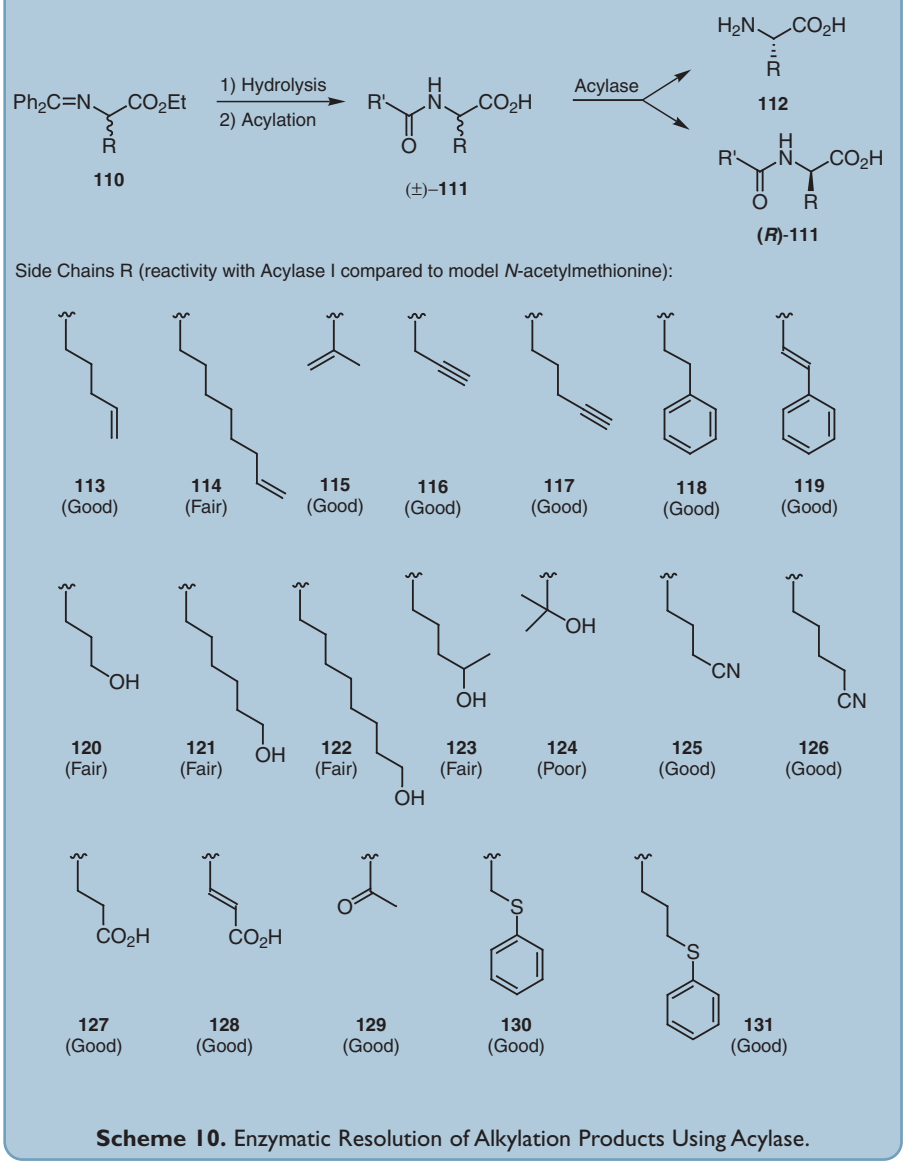
The use of benzophenone imines of glycine derivatives to prepare optically active α-amino acids has been reviewed. Recent advances in the area of new chiral catalysts for enantioselective, phase-transfer reactions will doubtless lead to the increased use of



Scheme 9. The Benzophenone Imine of Glycine Sultam (**81**): A Chiral, Nonracemic Glycine Anion Equivalent.



	104	105	106	107	108	109
LiOH (3 equiv):	86% de	--	86% de	--	94% de	94% de
DBU (1.5 equiv):	98% de	98% de	96% de	96% de	96% de	94% de



Scheme 10. Enzymatic Resolution of Alkylation Products Using Acylase.

this methodology for the preparation of the α-amino acids. Further improvements in the use of various chiral auxiliaries, as well as enzymatic methods for the resolution of racemic or optically enriched products, are also expected. The benzophenone imine is also being developed as an attractive protecting group for primary amines in other, non-amino acid applications.[69] To realize the full potential of this group, it will be important to optimize the conditions under which it will act solely as a protecting group and won't be affected by the particular reaction conditions employed. Continued utilization of this protecting and activating group in synthesis will also require further development of the processes for its introduction and selective removal.

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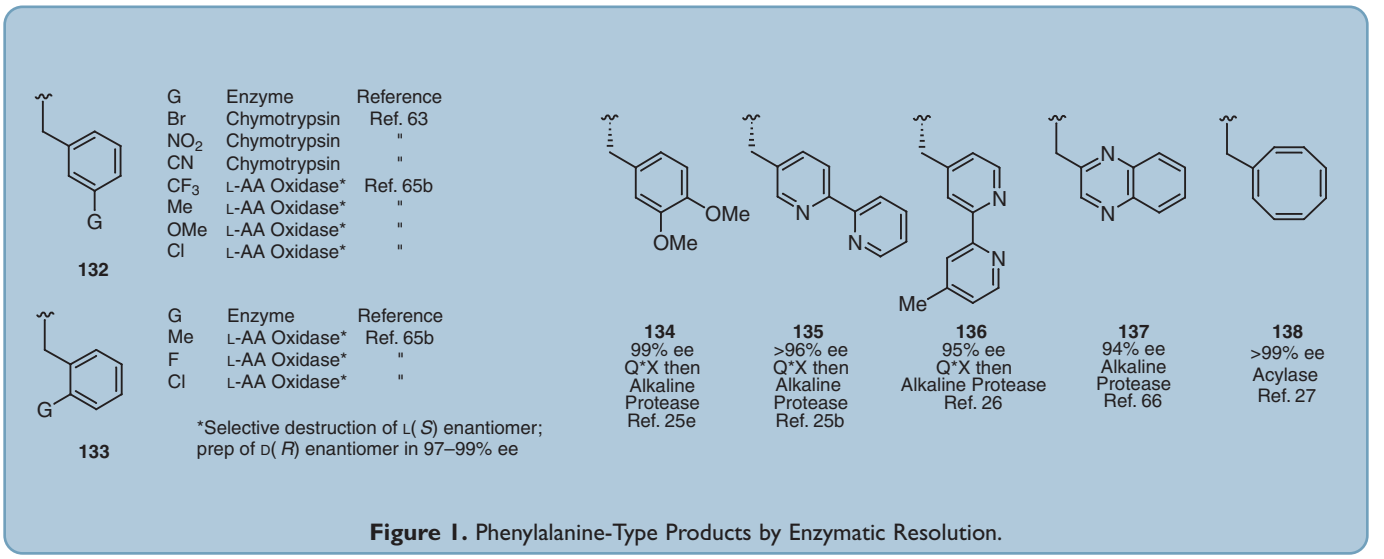

Figure 1. Phenylalanine-Type Products by Enzymatic Resolution.

at Lilly-Spain; and Dr. R. Schwesinger at Universität Freiburg.

I want to thank all of the members of my research group, whose names appear in our publications, for their skill and dedication, without which none of our chemistry would have been realized. Finally, I wish to thank my family for their love and understanding.

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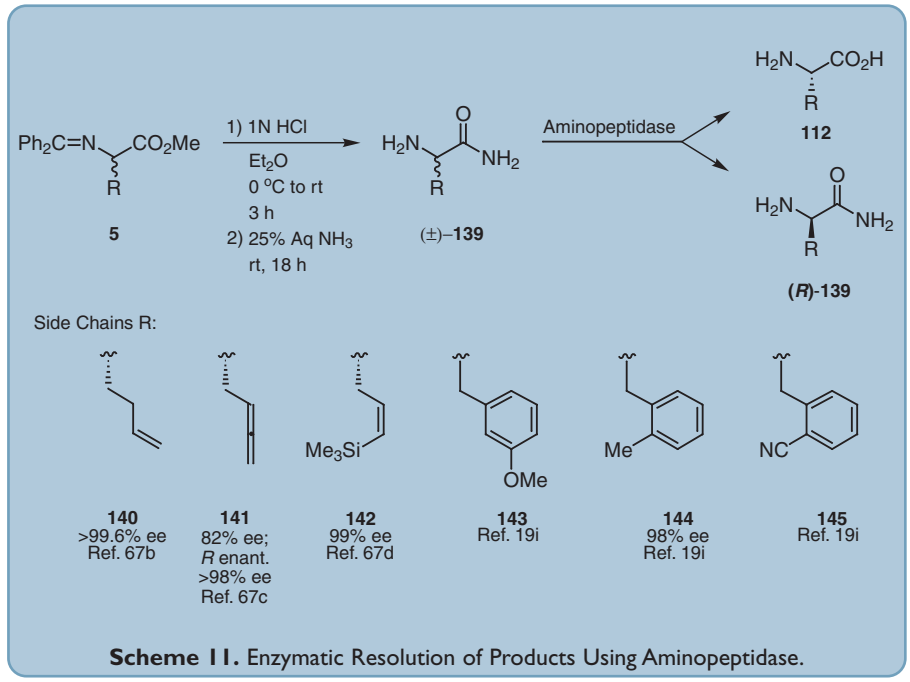

Scheme 11. Enzymatic Resolution of Products Using Aminopeptidase.

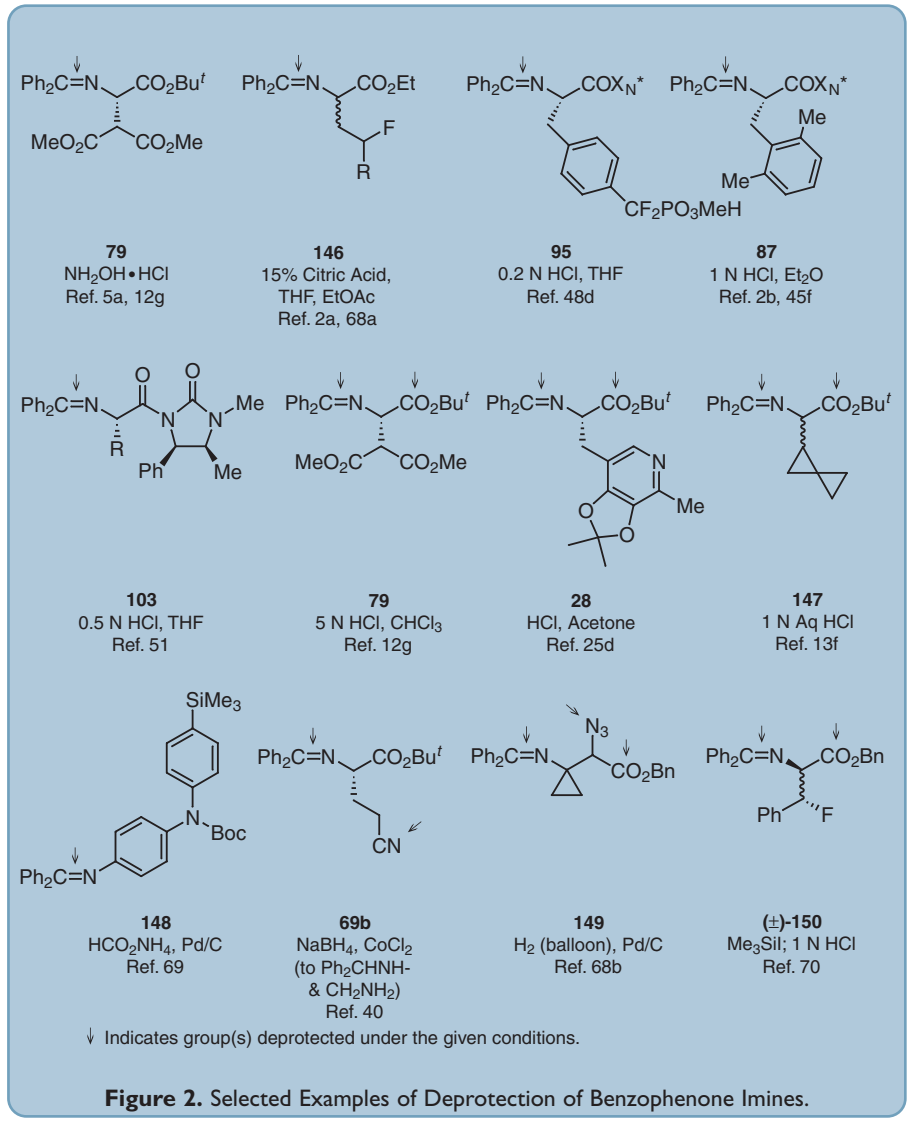

Figure 2. Selected Examples of Deprotection of Benzophenone Imines.

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About the Author

Marty O'Donnell obtained his B.S. degree in chemistry from the University of Iowa in 1968. He received his Ph.D. in 1973 with Professor Kenneth B. Wiberg at Yale, and then did a postdoctoral fellowship with Professor Léon Ghosez at the Université Catholique de Louvain in Belgium. He started at IUPUI in 1975 and was promoted to Professor in 1984. He is the recipient of several teaching and research awards at IUPUI, including the 1995 Chancellor's Award for Excellence in Teaching, which is given annually to a single faculty member in the University. He is the author of 60 research publications and was an editor of *Annual Reports in Organic Synthesis* from 1978 to 1985. His research interests include the development of new synthetic methodology for amino acids and peptides, combinatorial chemistry and solid-phase organic synthesis, the application of phase-transfer reactions to synthesis, and asymmetric syntheses using catalytic enantioselective phase-transfer reactions as well as organometallic catalysis.

Optically Active α-Amino Acids

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36,448-7	***N*-(Diphenylmethylene)glycine *tert*-butyl ester**, 98%
22,254-2	***N*-(Diphenylmethylene)glycine ethyl ester**, 98%
34,795-7	**Glycine *tert*-butyl ester hydrochloride**, 97%
G650-3	**Glycine ethyl ester hydrochloride**, 99%
G660-0	**Glycine methyl ester hydrochloride**, 99%

Bases

53,649-0	**2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine on polystyrene**, 2.0-2.5 mmol base/g, (BEMP on polystyrene)
20025F	**2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine**, 98+% (BEMP)
18,617-1	**Butyllithium**, 1.6*M* solution in hexanes
23,070-7	**Butyllithium**, 2.5*M* solution in hexanes
13,900-9	**1,8-Diazabicyclo[5.4.0]undec-7-ene**, 98% (DBU)
22,577-0	**Lithium bis(trimethylsilyl)amide**, 1.0*M* solution in tetrahydrofuran (LiHMDS)
36,179-8	**Lithium diisopropylamide**, 2.0*M* solution in heptane/tetrahydrofuran/ethylbenzene
79432F	**Phosphazene Base P_1-*t*-Bu-tris(tetramethylene)**, 98+% (BTPP)
15,667-1	**Potassium *tert*-butoxide**, 95%
22,344-1	**Sodium hydride**, dry, 95%
47,128-3	**Triethylamine**, 99.5%

Reagents

18,524-8	**Allyl acetate**, 99%
49,961-7	***O*-Allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide**, 95%
51,427-6	***O*-Allyl-*N*-benzylcinchonidinium bromide**
22,238-0	**Allylpalladium chloride dimer**
15,626-4	**Ammonium formate**, 97%
51,570-1	***N*-(9-Anthracenylmethyl)cinchonidinium chloride**, 90%
52,443-3	***N*-Benzylcinchonidinium bromide**, 97%
13285F	***N*-Benzylcinchonidinium chloride**, 98.0% (BCDC)
13288F	***N*-Benzylcinchoninium chloride**, 98.0% (BCNC)
29,581-7	**(*R*)-(+)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl**, 97% [(R)-(+)-BINAP]
29,582-5	**(*S*)-(-)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl**, 97% [(S)-(-)-BINAP]
12,891-0	***N*,*O*-Bis(trimethylsilyl)acetamide (BSA)**
17,550-1	**Boron trifluoride diethyl etherate**
30,580-4	**(1*R*)-(+)-2,10-Camphorsultam**, 98%
29,835-2	**(1*S*)-(-)-2,10-Camphorsultam**, 98%
32,982-7	**Cesium acetate**, 99.9%
38,652-9	**Chlorotrimethylsilane**, redistilled, 99+%
20,524-9	**Di-*tert*-butyl dicarbonate**, 99%
25,156-9	**1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone**, 98% (DMPU)
H1,160-2	**Hexamethylphosphoramide**, 99% (HMPA)
25,558-0	**Hydroxylamine hydrochloride**, 98%, A.C.S. reagent
19,552-9	**Iodotrimethylsilane**, 97%
41,811-0	**Isobutyraldehyde**, redistilled, 99.5+%
23,766-3	**(+)-2,3-*O*-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane**, 98% [(+)-DIOP]
18,519-1	**Lead(IV) acetate**, 95%
20,586-9	**Palladium(II) acetate**, 98%
21,346-2	**Sodium borohydride**, 99%
25,722-2	**Trimethylaluminum**, 97%

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47659F	**Fmoc-Gly-Wang resin**
83885F	**Rink amide (aminomethyl)polystyrene**, 100-200 mesh, ~1.1 mmol/g
53,394-7	**Rink amide MBHA resin**, 1% cross-linked, 50-100 mesh
86391F	**TentaGel™ S PHB-Gly-Fmoc**

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25,636-6	2-Butoxyethanol, 99+%
15,470-9	Carbon Disulfide, 99+%
36,691-9	Chloroform, 99.8%, A.C.S.
15,473-3	Chloroform, 99.8%, A.C.S.
15,474-1	Cyclohexane, 99+%, A.C.S.
15,479-2	Dichloromethane, 99.6%, A.C.S.
15,482-2	1,4-Dioxane, 99+%,
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15,485-7	Ethyl Acetate, 99.5+%, A.C.S.
45,982-8	Ethyl Alcohol, 200 Proof, HPLC
29,323-7	Ethylene Glycol, 99+%
29,587-6	Formamide, 99+%
19,161-2	Glycerol, 99.5+%
15,487-3	Heptane, 99%
24,887-8	Hexane, 95+%
15,490-3	Methyl Alcohol, 99.9%, A.C.S.
24,279-9	1-Methyl-2-Pyrrolidinone, 99+%
15,493-8	Methyl Sulfoxide, 99.9%, A.C.S.
25,969-1	Methylcyclohexane, 99%
15,495-4	Pentane, 99+%
26,173-4	Petroleum Ether
25,640-4	1-Propanol, 99+%
15,497-0	2-Propanol, 99.5+%, A.C.S.
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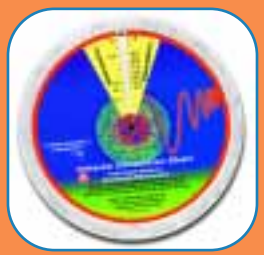

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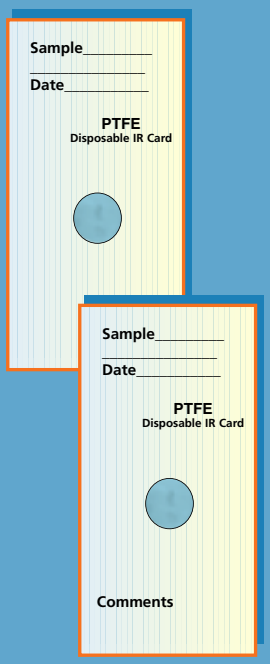

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Series 500	500+	Ultra-high resolution	535-PP	897240
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	8	0.0010	0.0006	**Z41,293-7**
Series 500	7	0.0005	0.00025	**Z41,294-5**
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	8	0.0010	0.0006	**Z41,285-6**
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25/13	528-TR-7	**Z27,194-2**
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	white	**Z15,328-1**
	yellow	**Z15,330-3**
	green	**Z15,331-1**
	blue	**Z15,333-8**
Set 5mm (100 each color, with case)		**Z15,326-5**
8	white	**Z27,208-6**
10	red	**Z11,808-7**

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Self-laminating, vinyl labels with white, write-on surface resist oil, water, and solvent. 38 L x 8.7mm W. Label wraps around 5mm tube for positive sample identification. Temp. range: -40 to 150°F. Supplied with 26 labels on a card, 25 cards per pack.

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Number of positions	Ŧ Joint	Cat. No.
Single	24/40	**Z42,156-1**
Single	29/32	**Z42,158-8**
Three	24/40	**Z41,417-4**
Three	29/32	**Z42,159-6**
Reservoir flask	24/40	**Z41,418-2**
	29/32	**Z42,161-8**

Five-position NMR tube cleaner system

Washes up to five 5mm, 7 or 8in. L NMR tubes at once (Figure 1). NMR tube caps can be used to plug holes if less than five tubes are to be cleaned. Cleaning solvent is pulled from an external container via PTFE tube, eliminating repetitious filling of side-mounted reservoirs. Note: bottle for cleaning solvent is not included.

Features:

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Simple to use:

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2) **Insert NMR tubes into top adapter.**
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4) **Open solvent valve to wash tubes.**
5) **Turn solvent valve 90° to air dry tubes.**

Description	Cat. No.
NMR tube cleaner system, complete	**Z42,284-3**

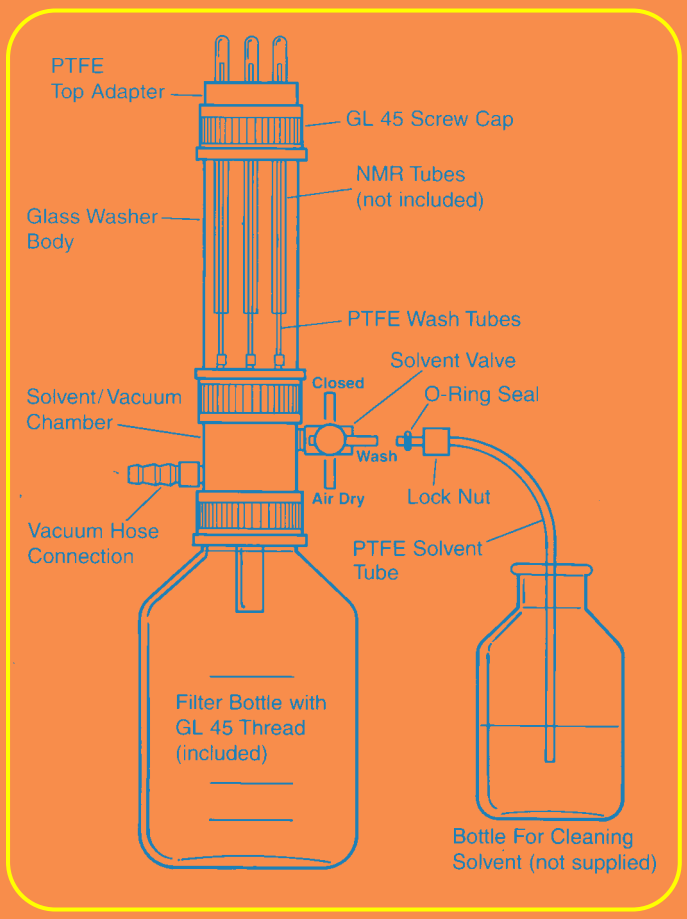

Figure 1

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Version	Cat. No.
Pro version	**Z40,699-6**
Pro version (Academic)	**Z40,701-1**
Standard version	**Z40,700-3**
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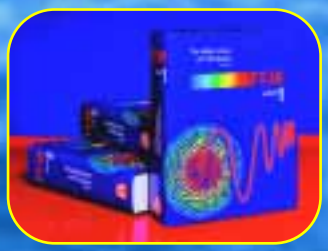

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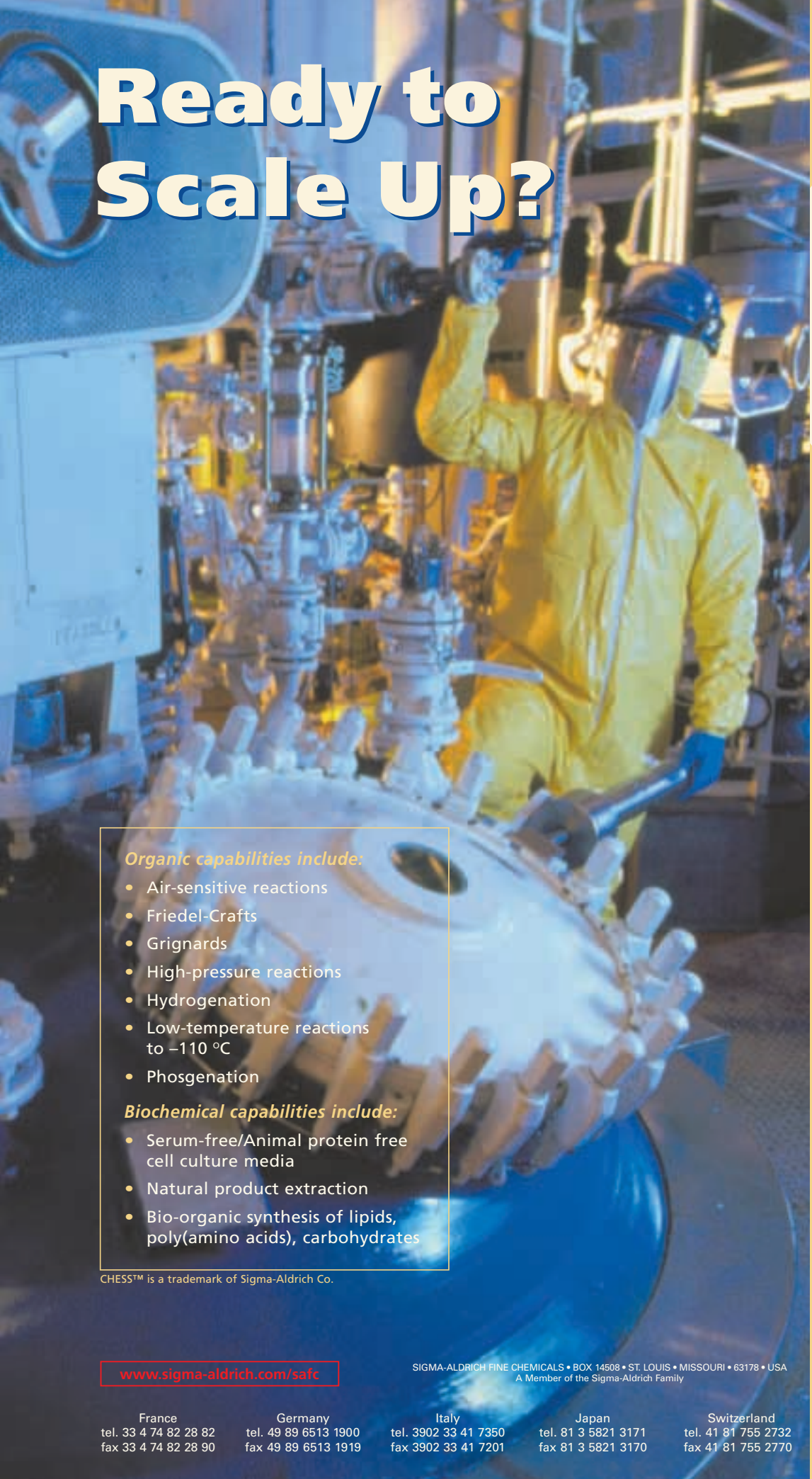

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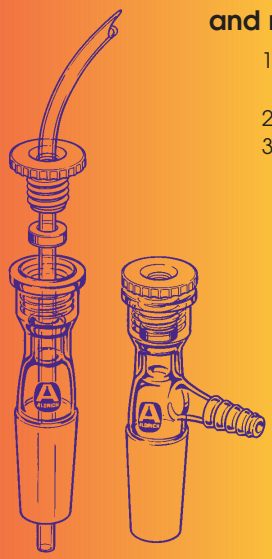

1. Hard-wall transfer tubing (e.g. PP or PTFE) is inserted through the threaded polypropylene bushing and PTFE-coated sealing ring of the adapter.
2. Turn the bushing to make an airtight compression seal with the tubing.
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Tubing o.d. (in.)	Inner ⅀ joint	*Straight* Cat. No.	*With hose barb* Cat. No.
3/16	14/20	**Z53,162-6**	**Z53,172-3**
3/16	19/22	**Z53,163-4**	**Z53,173-1**
5/16	14/20	**Z53,164-2**	**Z53,175-8**
5/16	19/22	**Z53,165-0**	**Z53,176-6**
5/16	24/40	**Z53,166-9**	**Z53,177-4**
5/16	29/32	**Z53,167-7**	**Z53,178-2**
1/2	24/40	**Z53,168-5**	**Z53,179-0**
1/2	29/32	**Z53,169-3**	**Z53,180-4**
1/2	34/45	**Z53,170-7**	**Z53,181-2**
1/2	45/50	**Z53,171-5**	**Z53,182-0**

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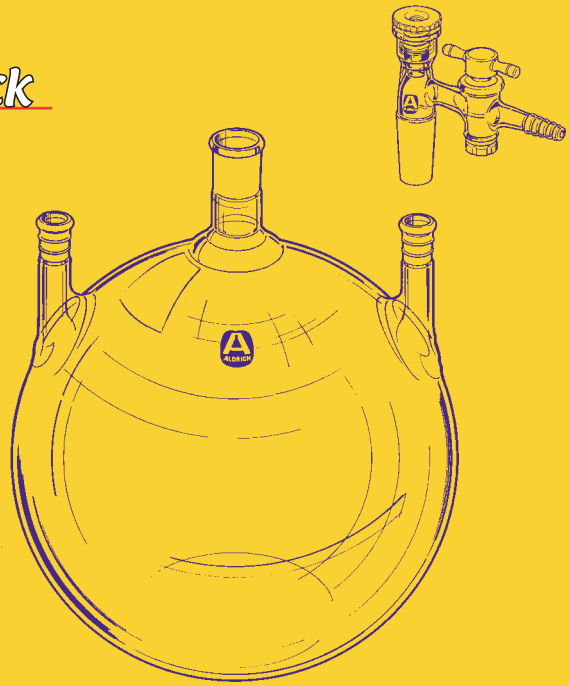
Glass and PTFE stopcocks are threaded for additional safety and have a 2mm bore for 3/16 in. tubing connection and 4mm bore for 5/16 in. and 1/2 in. tubing connections.

Tubing o.d. (in.)	Inner ⅀ joint	*PTFE stopcock* Cat. No.	*Glass stopcock* Cat. No.
3/16	14/20	**Z53,183-9**	**Z53,195-2**
3/16	19/22	**Z53,184-7**	**Z53,196-0**
5/16	14/20	**Z53,185-5**	**Z53,197-9**
5/16	19/22	**Z53,186-3**	**Z53,198-7**
5/16	24/40	**Z53,187-1**	**Z53,199-5**
5/16	29/32	**Z53,189-8**	**Z53,200-2**
1/2	24/40	**Z53,190-1**	**Z53,201-0**
1/2	29/32	**Z53,192-8**	**Z53,202-9**
1/2	34/45	**Z53,193-6**	**Z53,203-7**
1/2	45/50	**Z53,194-4**	**Z53,204-5**



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Replace transfer tubing with this plug to make a leakproof Torion™ seal.

Plug o.d. (in.)	Cat. No.
3/16	**Z53,205-3**
5/16	**Z53,206-1**
1/2	**Z53,208-8**

Replacement PTFE-Coated Sealed Rings

I.d. (in.)	Cat. No.
3/16	**Z53,209-6**
5/16	**Z53,211-8**
1/2	**Z53,212-6**

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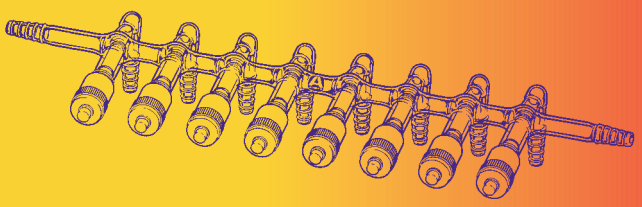

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Positions	Overall L (mm)	Cat. No.
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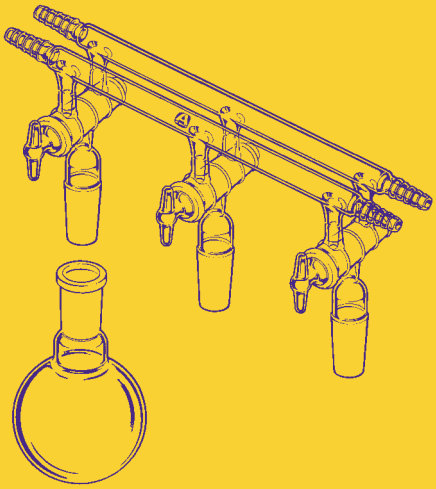
8	420	**Z53,074-3**



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Positions	Overall L (mm)	*Ŧ14/20* Cat. No.	*Ŧ24/40* Cat. No.
3	**300**	**Z53,066-2**	**Z53,069-7**
4	**400**	**Z53,067-0**	**Z53,070-0**
5	**500**	**Z53,068-9**	**Z53,071-9**

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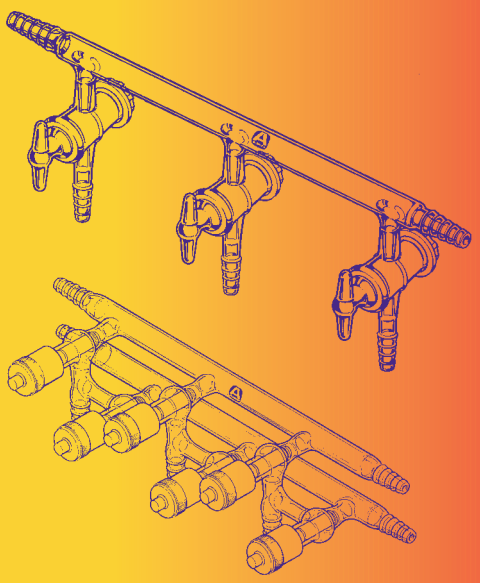

Positions	Overall L (mm)	*Single-bank* Cat. No.	*Dual-bank* Cat. No.
Glass stopcock, 4mm bore			
3	300	**Z53,213-4**	**Z20,268-1**
4	400	**Z53,214-2**	**Z20,270-3**
5	500	**Z53,215-0**	**Z24,357-4**
High-vacuum, PTFE J. Young valves			
3	300	**Z53,219-3**	**Z41,413-1**
4	400	**Z53,220-7**	**Z41,415-8**
5	500	**Z53,221-5**	**Z41,416-6**

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Alkoxymethylenemalonates in Organic Synthesis

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Faculty of Chemical Technology
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Outline

1. Introduction

Alkoxymethylenemalonates represent a very reactive group of enol ethers, which are widely used in the synthesis of heterocyclic or carbocylic compounds.[1,2] Other derivatives bearing an electron-withdrawing group, such as cyano, acetyl, trifluoroacetyl, benzoyl, nitro, sulfonyl, amido, and formyl, in the β position of the double bond, also belong to this group of α,β-unsaturated compounds. They have been known for over a hundred years, ever since **1b** was prepared by Claisen.[3] However, the greatest synthetic exploitation came only in the last 40 years in connection with the discovery of nalidixic acid, an antibacterial drug.[4] In spite of this, only one review of alkoxymethylenemalonates has been published thus far.[5]

Sardesai published a four-page, relatively inaccessible review,[5] while the applications of the related aminomethylenemalonates in heterocyclic synthesis have been surveyed by Hermecz et al.[6] Selected aspects of their chemistry have also been highlighted in reviews concentrating on the preparation of nalidixic acid derivatives and analogs.[7]

The present review covers the literature until 1999, and highlights only representative examples of alkoxymethylenemalonates. It must be mentioned, that these compounds have often been given different names, such as alkoxymethylenemalonates, propanedioates, and 2,2-dimethyl-4,6-dioxo-1,3-dioxane (Meldrum's acid) derivatives. The compound types covered in this review are principally **1–3**.

The higher esters and alkoxymethylene derivatives are not so common; however, the alkoxy,[1g,8] dibutyl,[9] bis(isopropyl),[10] benzyl,[11] bis[2-(acetyloxy)ethyl],[12] or aryloxymethylene derivatives[13,14] have been described. Also known are ethoxymethylenemalonates with different ester alkyl groups, such as methyl/ethyl,[1j,15] ethyl/butyl,[16] methyl/benzyl,[17] ethyl/*t*-butyl,[18] ethyl/carboxymethyl, ethyl/2-oxo-2-(benzyloxy)ethyl,[19] or monoethyl.[20]

2. Preparation

The most convenient method for the preparation of alkoxymethylenemalonates is the condensation of trialkyl orthoesters[1a,1c,3,21–26] with dialkyl malonates or with Meldrum's acid[27,28] in acetic anhydride in the presence of a catalyst (e.g., zinc chloride, zinc acetate). Recently, an improved method for the preparation of **3b** was published by Saloň et al.[29] Dialkoxymethyl acetates and dialkoxyethanes are intermediates in these reactions (**eq 1**).[24,30]

Another preparative method, alkylation of the sodium salts of hydroxymethylenemalonates (enol forms of 2-formylmalonates, obtained by formylation of malonates) with dialkyl sulfates, has been covered by a patent

reporting the preparation of **1a** and **2b**.[31] A third approach, alcoholysis of chloromethylenemalonates also leads to the title compounds.[13]

3. Reactions with Nucleophiles

Alkoxymethylenemalonates are regarded as vinylogous malonates and are thus expected to react as mono- and bifunctional electrophiles, similarly to 3-alkoxyacroleins.[1i] It is no surprise then that most of their reported reactions are with nucleophiles. Generally, the first step is nucleophilic substitution of the alkoxy group, followed by cyclization. Products of the first step can be isolated, but both steps can also be carried out in a one-pot fashion. These two reaction steps result in the incorporation of three additional carbons into the starting material and frequently form a new fused ring. Sometimes, when bifunctional nucleophiles are used, products lacking the methylene moiety are also observed; such products incorporate one "orthoformate"carbon.[32–34]

3.1. Monofunctional Nucleophiles

The monofunctional nucleophiles used are not only the traditional ones, but also anilines, (thio)phenols, and similar compounds. These permit the preparation and isolation of the products of the first step, nucleophilic substitution, since the second step, cyclization, requires elevated temperatures of up to 250 °C or the use of a catalyst.

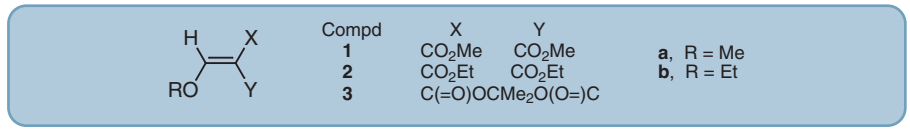
3.1.1. Nitrogen Nucleophiles

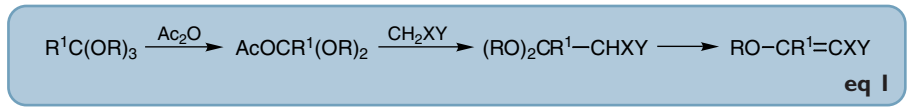
Nitrogen nucleophiles, especially anilines, are the most frequently used nucleophiles. They displace the alkoxy group to produce anilinomethylene derivatives of malonic esters, which could be formally considered as aminoethylene derivatives with substituents in the β position(s). Their preparations, properties, and reactions have been comprehensively reviewed.[6]

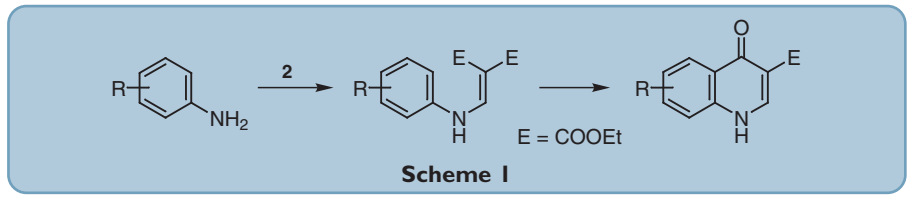
3.1.1.1. Anilines and Related Compounds

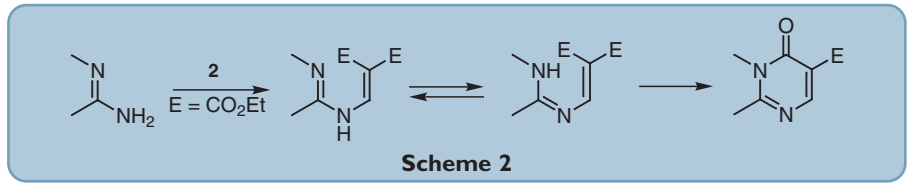
Claisen was the first to react aniline with **2b** to produce the corresponding diethyl anilinomethylenemalonate.[3] Although the substitution step was reported in 1897, it took 4 years before the thermal cyclization step, leading to the first 4-quinolone, was reported by Camps (**Scheme 1**).[35] In 1939, Gould and Jacobs first used the tandem of these two reactions to prepare quinolines and benzoquinolines.[36] The Gould–Jacobs reaction was rediscovered in the sixties in connection with the synthesis of the antibacterial drug nalidixic acid and its analogs.[37] Nalidixic acid analogs can also be prepared by another method.[4,7a] Anilinomethylene Meldrum's acids have been prepared by a similar procedure.[27a] Many anilinomethylene derivatives are biologically active (e.g., as herbicides), or exhibit photosynthetic inhibitory activity.[27b]

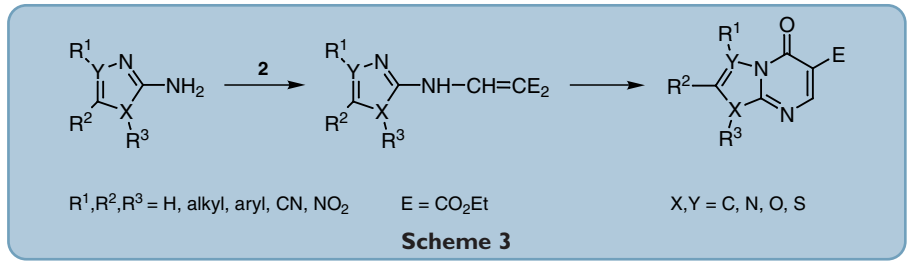
Not only have other types of alkoxymethylene derivatives been used in the Gould–Jacobs reaction, but so have substituted anilines, since substitution on the benzene ring does not affect the outcome of this reaction.[23,38] The second step, cyclization to a 4-quinolone, can be carried out under thermal or catalytic conditions. When N-substituted anilines were used, only cyclization using PPA, PPE, or other Lewis acids was successful; thermal cyclization did not take place.[39,40] The same conditions, applied to derivatives of anilinomethylene Meldrum's acid, led to 4-quinolone-3-carboxylic acids, while thermal cyclization only gave 4-quinolones.[41,42] In the case of 3-substituted anilines, two products, 5- or 7-substituted-4-oxo-1,4-dihydroquinolines were formed.[38b] Aminobenzazoles or amino-

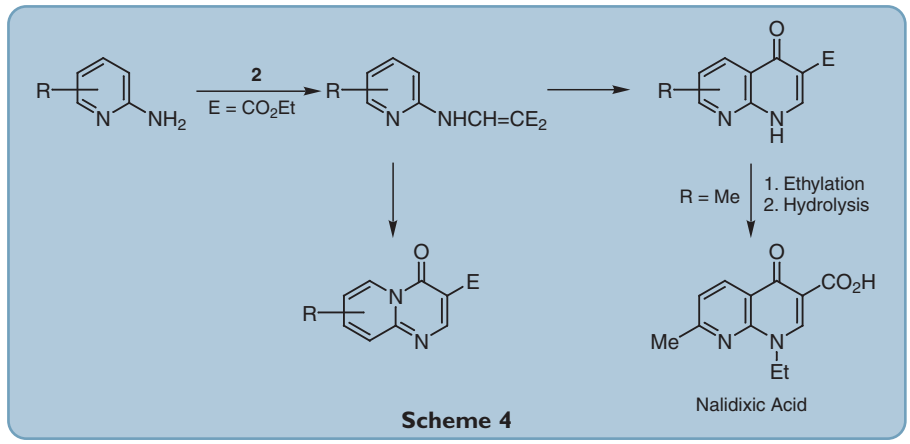












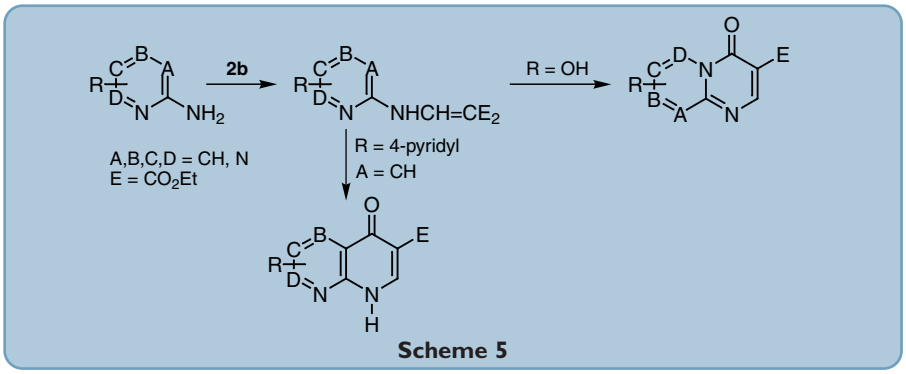
benzocondensed heterocycles, with an amino group on the benzene ring, are regarded as disubstituted anilines, while the ones with an amino group on the heterocyclic ring belong to the family of 5- or 6-membered heterocyclic amines or other nucleophiles.[6,37]

3.1.1.2. Heterocyclic Amines

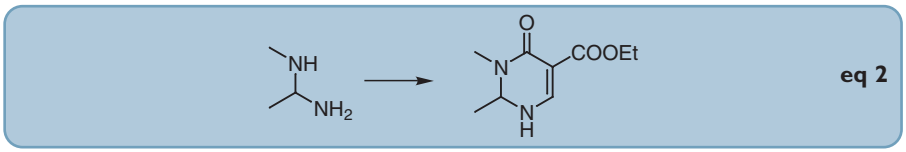
Heterocyclic amines exhibit a lower reactivity than anilines, because of the reduced nucleophilicity caused by the presence of the heteroatom(s) in the ring. On the other hand, when the ring nitrogen is in the α position with respect to the amino group, cyclization products arise under mild conditions due to an amidine-type tautomerism; simultaneously, a pyrimidine ring fused to the starting amine is formed (**Scheme 2**).

3.1.1.2.1. Five-Membered Heterocyclic Amines

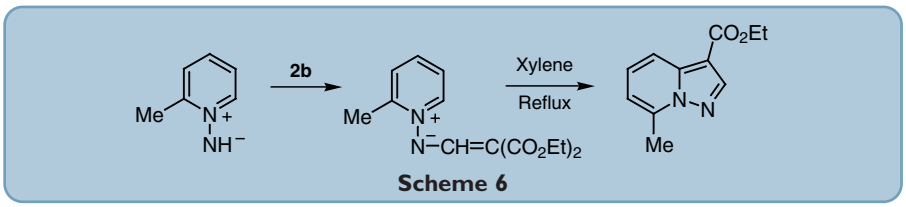
5-Aminoimidazoles, treated with **2b**, afforded mainly N-adducts, while treatment with ethoxymethylenemalononitrile led to C-adducts.[43]



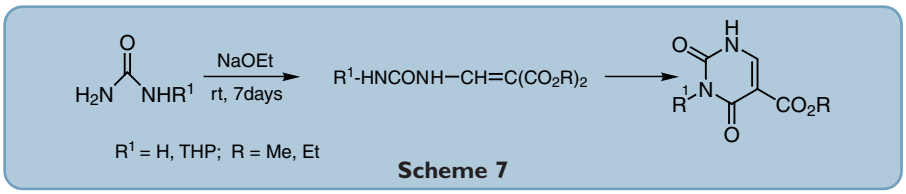
Scheme 5



eq 2



Scheme 6



Scheme 7

2-Aminothiophenes react with **2b** to yield thieno[3,2-*b*]pyridines, while 3-aminothiophenes give the [3,4-*b*] isomers.[44]

Nitrogen-containing heterocycles, azoles or isoazoles, especially those with an amino group in the ortho position to the nitrogen atom, give rise to "*a*"-fused pyrimidino heterocycles (**Scheme 3**).[45–47]

In many cases, cyclization occurred not on a ring α-nitrogen atom, as anticipated, but on a carbon atom.[48] In this regard, the work of Ramsden on 4-/5-aminoimidazoles and their C-/N-substitution is especially valuable.[49]

3.1.1.2.2. Six-Membered Heterocyclic Amines

The reactions of 2-aminopyridines with **2b**, **3a**, and **3b** have been intensively studied,[38f,50] since the antibacterial activity of nalidixic acid derives from the presence of the 6-methyl-2-aminopyridine moiety of the 1,8-naphthyridine skeleton (**Scheme 4**).[4,7a] Other authors have reported that cyclization occurs on the nitrogen atom and leads to pyrido[1,2-*a*]pyrimidine derivatives.[7a,51] When **3a** is used instead of **2b**, it is observed that, following thermal cyclization, the final product lacks the ethoxycarbonyl group (E) at C–3.[41,52]

3-Aminopyridines can yield two products resulting from cyclization at positions 2 or 4.[7a,53,54] In contrast, 4-aminopyridines give only 1,6-naphthyridines.[7a,53]

While 2,6-diaminopyridine, treated with 1 equivalent of **2b**, afforded ethyl 7-amino-4-hydroxy-1,8-naphthyridine-3-carboxylate,[53] 3,5-diaminopyridine yielded, with 2 equivalents of **2b**, tricyclic 1,8,10-triazaanthracene derivatives.[55]

Aminopyrazines, pyrimidines, or pyridazines behave similarly as pyridines, and yield the corresponding condensed 4-oxopyrimidinones under relatively mild conditions.[56] 2-Substituted-4-aminopyrimidines afford pyrimido[1,6-*a*]pyrimidine or pyrido[2,3-*d*]pyrimidine after cyclization to nitrogen or to carbon (**Scheme 5**).[56c,57]

A similar reaction is observed with 4-aminobenzo[*h*]quinazolines[58] or aminopyrazines that results in the formation of pyrido[2,3-*b*]pyrazines.[56b] Aminobenzothiadiazine dioxides lead to pyrimido[1,2-*b*][1,2,4]benzothiadiazine dioxides.[59]

3.1.1.3. Other Nitrogen Nucleophiles

Ammonolysis of **2b** or **3a** afforded diethyl aminomethylenemalonate or aminomethylene Meldrum's acid,[27] the latter was decomposed by barium hydroxide or futher ammonolyzed to malondiamide.[60] The corresponding alkylaminomethylene derivatives were obtained from reactions of alkylamines with **3a**.[27,61] The protection of the amino group in amino sugars and amino acids using **2b** or **3a**, and the removal of the protecting group with bromine in $CHCl_3$, chlorine, ammonia, or Amberlite® IRA-400 (HO^-) resin have been reported.[62,63] Partially hydrogenated nitrogen heterocycles, with an NH group attached to the aromatic ring, are secondary amines that are similar to N-alkylated anilines, and are frequently used to prepare ortho–peri condensed tricyclic 4-quinolones.[7,64,65] Saturated heterocycles bearing both an NH group and an amino group in the α position form products that are similar to those of aromatic heterocycles; however, products of initial attack on the secondary amino group have also been observed (**eq 2**).[66]

The product of nucleophilic substitution of **2b** with 2-methylpyridium-*N*-imide cyclized under reflux in xylene to afford ethyl 7-methyl-pyrazolo[1,5-*a*]pyridine-3-carboxylate (**Scheme 6**).[33]

A similar reaction of 2,2-dialkylsulfur diimide with **3b** has been reported.[67]

Urea reacted with **2b** in 35% hydrochloric acid and ethanol at room temperature over three days to give only a product of nucleophilic substitution in 87% yield.[68] On the other hand, tetrahydropyranylurea reacted with NaOEt at room temperature over seven days to form the corresponding uracil derivative (**Scheme 7**).[69]

The reaction of Schiff bases with **1a** leads to substitution on the nitrogen or the α carbon, or yields *N*-substituted-2-oxopyridine-3-carboxylates.[70,71] The title compounds also react with various amino derivatives such as 2-aminoazulenes.[72]

3.1.2. Sulfur Nucleophiles

Sulfur nucleophiles, when treated with **1b,** produce the fragment -S-CH=C<; thus, thioglycolic acid esters give a substitution intermediate, which, under alkaline conditions, undergoes cyclization and hydrolysis to 3-hydroxy-2,4-thiophenedicarboxylic acid (**Scheme 8**). Monodecarboxylation of the diacid leads to 4-hydroxy-3-thiophenecarboxylic acid, while treatment with diazomethane followed by hydrolysis and decarboxylation yields 3-methoxythiophene (**Scheme 8**).[73]

The reaction of thiophenols with **2b** gives rise to sulfur analogs of chromones (**eq 3**), while their reaction with **3a** under flash vacuum pyrolysis conditions affords phenylthioacetylene and benzothiophene.[74–75]

Reaction of 3-mercapto-1,2,4-triazole with **2b** afforded 6-ethoxycarbonyl-[1,2,4]triazolo[3,2-*b*][1,3]thiazin-5-one (X=N) in 58% yield, and a small amount of [1,2,4]triazolo[3,2-*b*][1,3]thiazin-5-one, the latter arising from ester hydrolysis and decarboxylation. 2-Mercaptoimidazole afforded 6-ethoxycarbonylimidazolo[2,1-*b*][1,3]thiazin-5-one (X = CH) in 29 % yield. Its structure was confirmed by ^{1}H and ^{13}C NMR spectroscopy in the presence of $Eu(fod)_3$ (**eq 4**).[76]

3.1.3. Oxygen Nucleophiles

Hydroxides react with **2b** in ethanol and diethyl ether to produce salts of the enol form of ethyl 2-formylmalonate.[3,77] The enol is stabilized by intramolecular hydrogen bonding between the hydroxyl group and the ester carbonyl group.[78] Similar results were obtained from the acidic hydrolysis of **3b**.[27]

2b adds a molecule of ethanol in the presence of sodium ethoxide to give $(EtO)_2CH\text{-}CH(COOEt)_2$,[3] but undergoes an ester interchange when heated with *l*-menthol in the presence of sodium.[79] When substituted phenols are used, the corresponding chromones are formed (**eq 5**).[26,74a]

1,4 addition was observed in the oxymercuration–demercuration reaction of **1a** with 2,4-hexadienol (**eq 6**).[80,81]

3.1.4. Carbon Nucleophiles

Grignard reagents react with **2b** to yield not only the desired products, as in the Knoevenagel reaction of aldehydes with dialkyl malonates, but also products of bisaddition.[82,83]

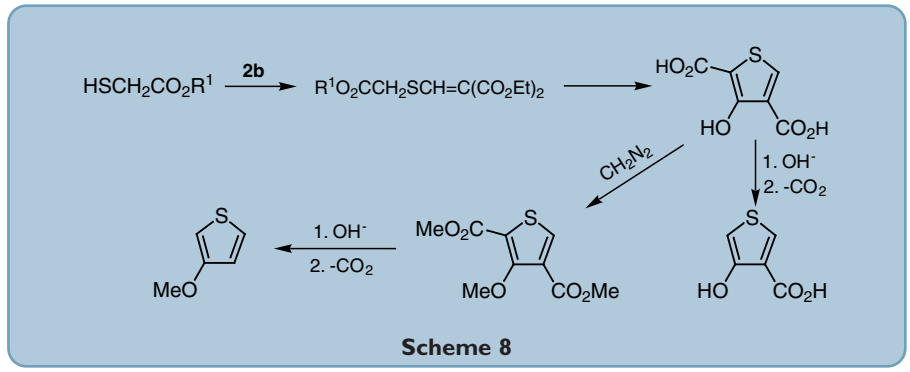
The cyclopentadienylide anion reacts similarly,[84] as do *o*-alkoxyphenylithiums, which, after cyclization in acidic media, afford substituted coumarins (**eq 7**).[85] Similar products are prepared from enolizable ketones and **1a**.[86]

In contrast to Grignard reagents, only 1,4 addition is observed with organometallic compounds at low temperature.[81,87–89]

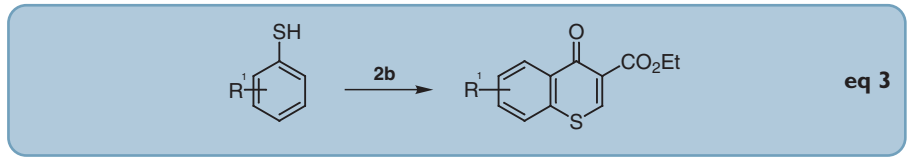
5-Hydroxy-3,6,8-trimethoxycarbonyl-coumarin is formed under Lewis acid catalysis as a by-product in the preparation of **1a** (**Scheme 9**).[90] **1a** reacts with dimethyl malonate to produce a tetraester, which undergoes a Claisen condensation followed by cyclization. Under alkaline conditions (NaH), the reaction stops at the tetraester stage.[1c,91]

The anion generated from 2-benzothiazolyl acetate yields the pyrido[2,1-*b*]benzothiazolone derivative.[92]

The ethoxy group of **3b** can be replaced by a carbon moiety stemming from enamino-activated, exocyclic methylene heterocycles (prepared in situ from 2-methyl-*N*-heterocycles).[93]



Scheme 8



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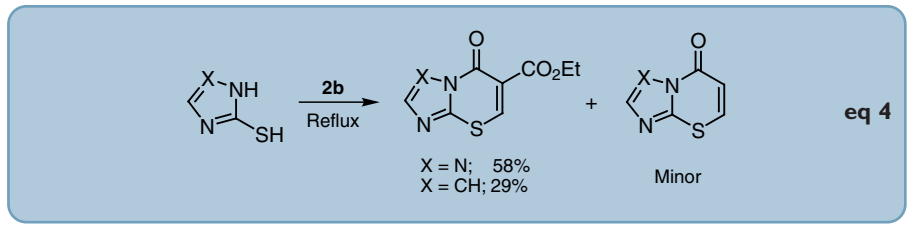

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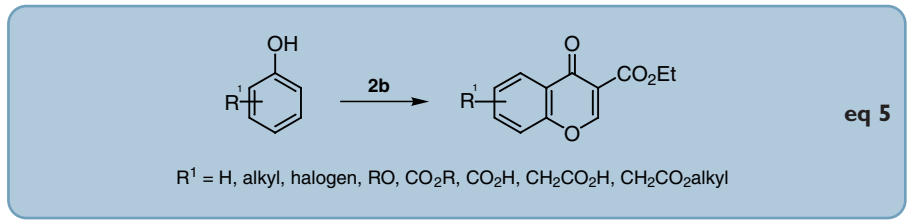

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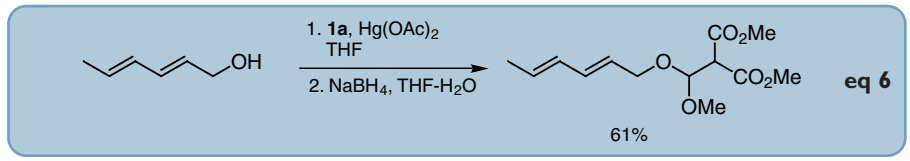

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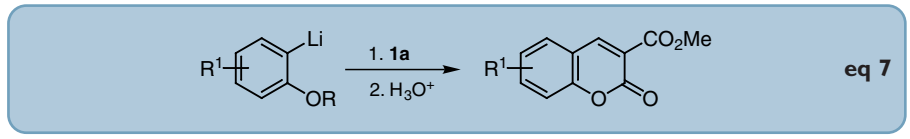
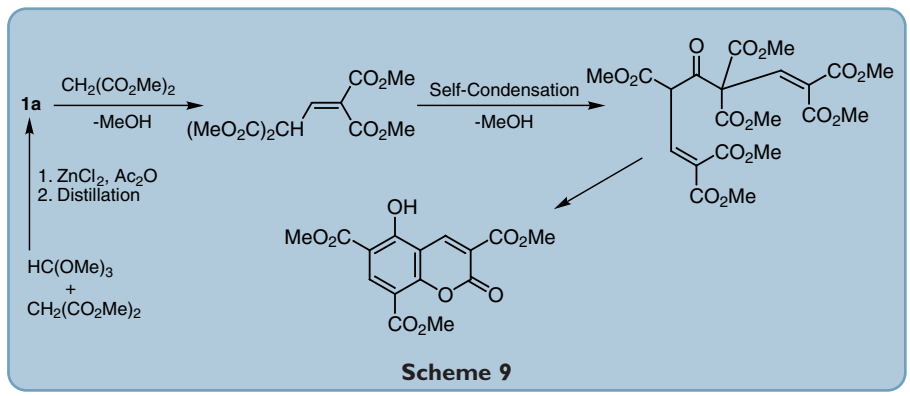
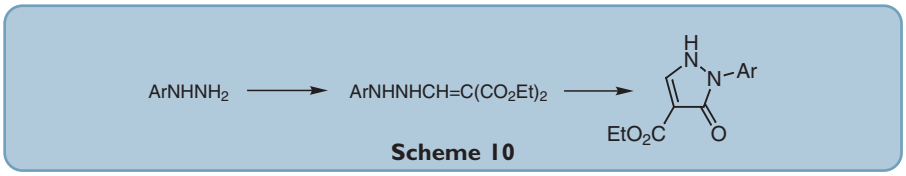


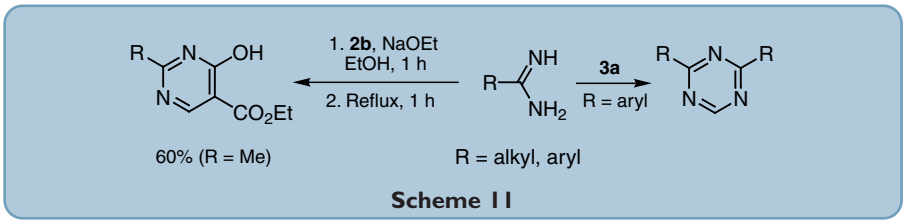
eq 7



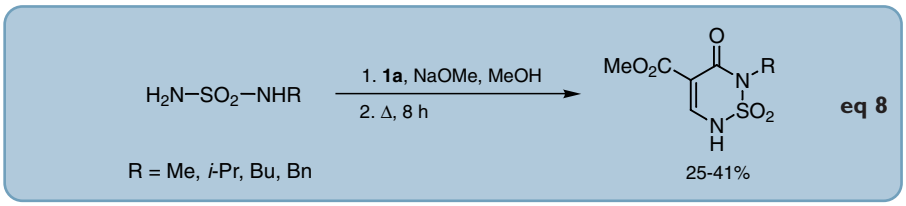
Scheme 9

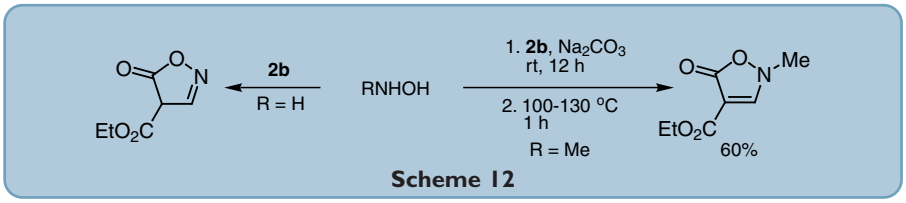


Scheme 10

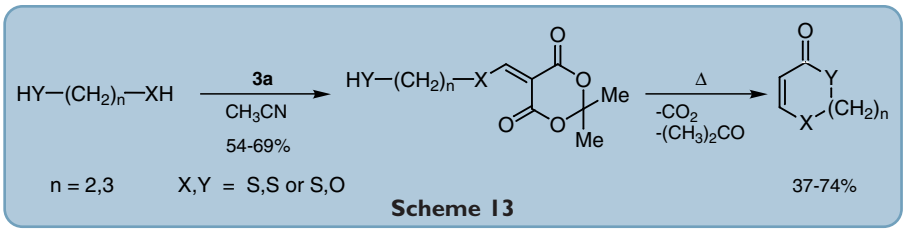


Scheme 11





Scheme 12



Scheme 13

3.2. Di- and Polyfunctional Nucleophiles

3.2.1. Dinitrogen Nucleophiles

The reaction of phenylenediamines with **2b** in a 1:2 molar ratio led directly, or via substitution products, to angularly annelated phenanthrolines. No linearly annelated products were observed. Equimolar amounts of starting materials gave no N,N´-disubstituted intermediates or benzimidazoles;[94–96] however, 1,8-diaminonaphthalene gave rise to pterimidine.[32]

Aryl- and benzylhydrazines react with **2b** to yield ethyl 1-aryl/benzyl-5-oxopyrazol-4-carboxylates (**Scheme 10**).[3,60,97]

6-Chloro-3-hydrazinopyridazine did not yield the corresponding pyrazolone; instead, the product of elimination of diethyl malonate, 6-chlorotriazolo[4,3-*b*]pyridazine, was formed.[34] 1,1-Disubstituted hydrazines afforded enhydrazino esters, which, upon thermolysis at 330–360 °C, gave chiefly oxopyrazolinium ylides and pyrazolinones in variable proportions that depended on the experimental conditions. At higher temperatures, hydroxypyrazoles were also produced and could be isolated. The proposed mechanism involves the formation of hydrazonoketenes as intermediates; cyclization of these gives pyrazolinium ylides and then pyrazolinones by an intramolecular [1,4] sigmatropic alkyl shift.[98]

Aliphatic and aromatic amidines were reacted with **2b** to prepare 2-alkyl-4-hydroxypyrimidine-5-carboxylates.[99] The use of **3a** and arylamidine led to aminomethylene derivatives and then to 1,3,5-triazines (**Scheme 11**).[100] Morpholinoformamidine yielded the corresponding 2-morpholinopyrimidines.[101] In the case of N,N´-disubstituted formamidines, only substitution products were prepared and used as pesticides.[102] Similarly, urea, *N*-(2-tetrahydropyranyl)urea[68,103] and thiourea[104] gave with **2b** the corresponding substitution products in good yields. In the case of N,N´-disubstituted urea, the corresponding 2,4-dioxo-*N*,*N*´-disubstituted uracils were formed.[103]

Analogs of urea, N-monoalkylsubstituted sulfonyldiamines, react with **1a** preferentially on the unsubstituted amino group to yield 3-oxo-1,2,6-thiadiazine-1,1-dioxides (**eq 8**).[33]

3.2.2. Mixed Mononitrogen, Sulfur, Oxygen, and Other Nucleophiles

Hydroxylamine and *N*-methylhydroxylamine react with **2b** and lead to 5-isoxazolone derivatives (**Scheme 12**).[105] Aldoximes or ketoximes react with methoxymethylene Meldrum's acid to give 4,5-dihydroisoxazoles in 35-79% yield.[106]

While phenylenediamines did not produce benzimidazole, 2-aminothiophenol reacted with **3a** at room temperature over a 3-hour period to afford the N-substituted (kinetic) product, which, after 10 hours at room temperature or thermolysis at 250 °C, was converted into the S-substituted isomer (thermodynamic product). Thermolysis at 500 °C gave benzothiazole and the undesired 7-membered benzolactam.[107] Different amino alcohols favored N-substitution in the reaction with **3b**.[28]

Thermolysis of the substitution products of **3a** with ω-dithiols or mercaptoalcohols yielded 7- or 8-membered heterocycles containing the S-CH=CH-CO- moiety (**Scheme 13**).[107]

4. Cycloadditions

In an effort to prepare β-ribofuranosylpropanedioates stereoselectively, the $LiClO_4$ catalyzed Diels–Alder reaction of cyclopentadiene with acetoxymethylenemalonates was examined (**eq 9**), and the results were compared with those obtained under high pressure in the absence of a catalyst.[108] It was found that the $LiClO_4$ catalyzed cycloaddition afforded the [4+2] adduct as a 2:1 mixture of the endo and exo isomers, irrespective of solvent or catalyst concentration. $LiClO_4$ caused a remarkable acceleration of the asymmetric Diels–Alder reaction of the di-*l*-menthyl derivative.

Cyclopentenes were formed in a [3+2] cycloaddition of **1a** and cyclopropenone acetals (**eq 10**),[109] while cyclopentanes were formed from trimethylenemethane acetals.[17]

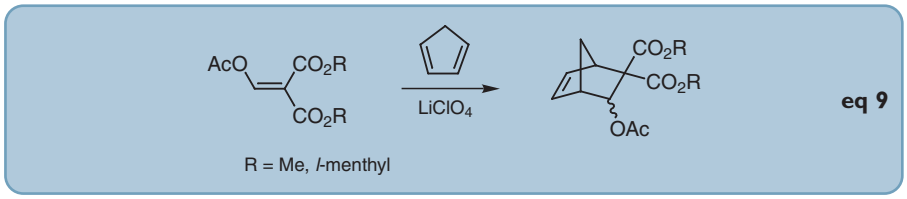
Similarly, the reaction of **2b** with benzonitrilium isopropylide (generated in situ by a photoinduced cleavage of the corresponding azirine) leads to pyrrolines,[110] while reaction of **1a** with diazo compounds leads to pyrazolines.[111] Diazomethane was used to convert **1a** to dimethyl methoxy-

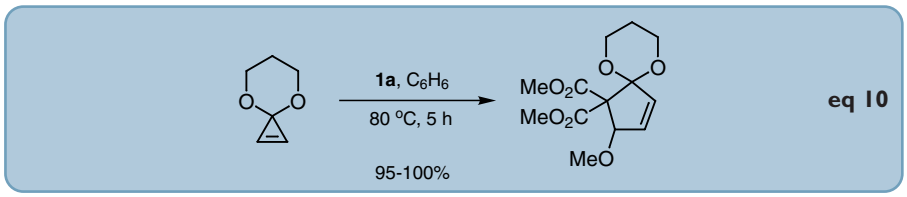
ethylidenemalonate,[112] while azides reacted with **2b** to give a mixture of diethyl 2,4-diethoxycarbonyl-2-pentenedioate and diethyl 2-hydroxypyrrole-3,5-dicarboxylate.[113,114] Ozonolysis of **2b** or **3a** yielded diethyl oxomalonate or oxo-Meldrum's acid after workup with PCl_3.[115]

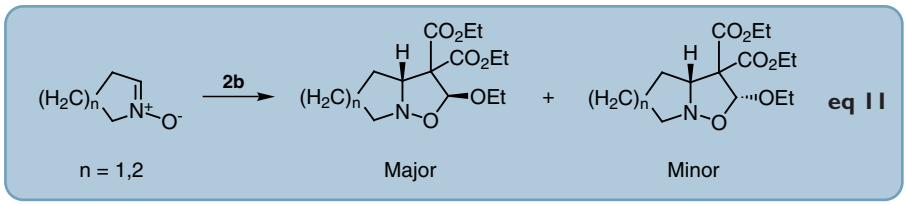
The 1,3-dipolar cycloaddition of cyclic nitrones with **2b** gives a mixture of stereoisomers in which the 2-(*S*) isomer prevails (**eq 11**).[116]

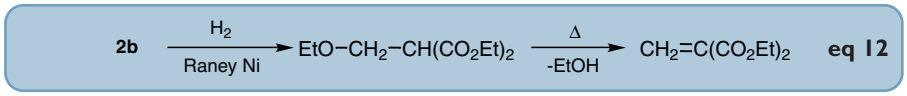
5. Reductions

Catalytic reduction of **2b**, followed by elimination of ethanol, afforded the unstable diethyl methylenemalonate (**eq 12**).[117] Malonate **2b** was not reduced by hydrogen in the presence of colloidal palladium,[118] but hydrogenation over Raney nickel furnished two products, namely 2-methyl-1,3-propanediol and diethyl methylmalonate.[119] On the other hand, **1a** was successfully reduced using palladium on carbon to yield dimethyl methoxymethylmalonate in 75% yield.[117,120]









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About the Author

Viktor Milata was born in 1957 in Bratislava (Slovak republic) and completed his undergraduate (1981) and graduate studies (1987) at the Faculty of Chemical Technology of the Slovak University of Technology, where he is currently an Associate Professor (since 1996). During the last decade, he has spent short periods of time (up to 12 months) at the Université de Paris-Sud (Orsay), the Technical University of Vienna, Cambridge University, and, last year, at the National University of Distance Study in Madrid. A common thread throughout his work has been an interest in organic chemistry, which has included the relationship between heterocyclic chemistry (especially nitrogen-containing heterocycles such as 4-quinolones, benzazoles, 1,4-dihydropyridines; and the applied Gould–Jacobs reaction) and spectral methods (especially NMR). He is a member of the Slovak Chemical Society and of the editorial boards of the electronic journals *Molecules* and *Arkivoc,* and has co-authored nearly fifty papers and 2 reviews: Tricyclic Azoloquinolines in *Advances in Heterocyclic Chemistry,* and 4-Quinolines in *Targets in Heterocyclic Chemistry*.

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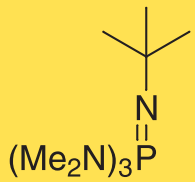
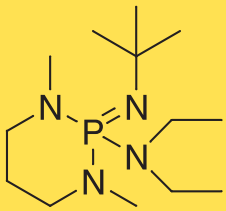
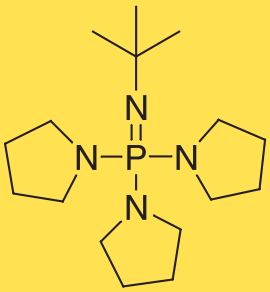
P_1 Bases



79408 P_1-*t*-Bu



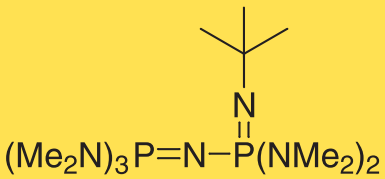
20025 BEMP



79432 P_1-*t*-Bu-tris(tetramethylene) (BTPP)

pK_{BH^+} = ~ 26

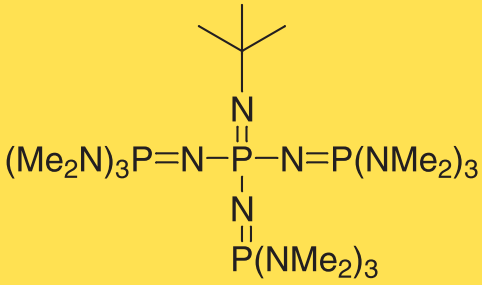
P_2 Base



79416 P_2-*t*-Bu Solution, ~2.0M in THF

pK_{BH^+} = ~ 33

P_4 Base



79421 P_4-*t*-Bu Solution, ~1.0M in *n*-hexane

pK_{BH^+} = ~ 42

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52,410-7
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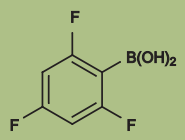
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5g

51,404-7
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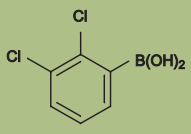
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25g

51,403-9
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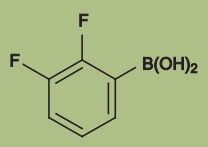
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51,786-0
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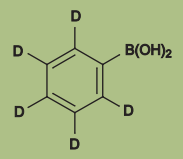
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52,401-8
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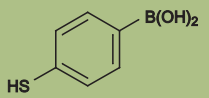
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52,396-8
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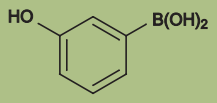
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52,635-5
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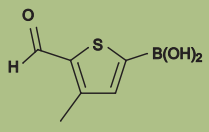
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43,203-2
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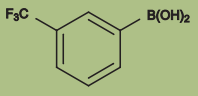
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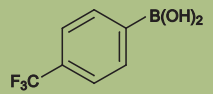
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51,270-2
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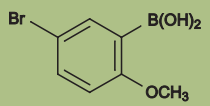
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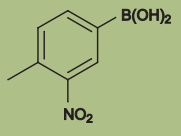
$C_7H_8BNO_4$

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52,636-3
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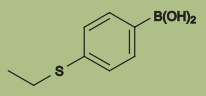
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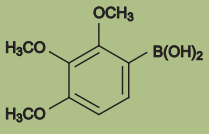
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52,366-6
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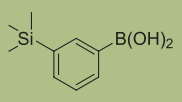
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52,367-4
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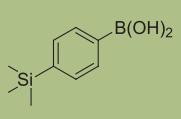
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52,151-5
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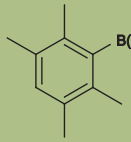
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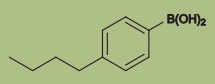
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52,404-2
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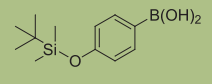
1g
5g

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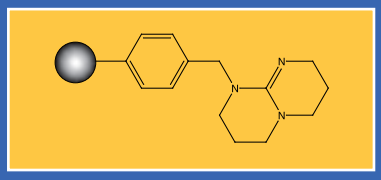
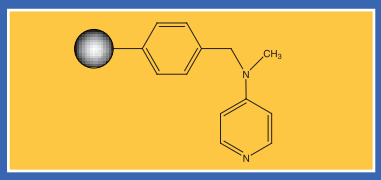
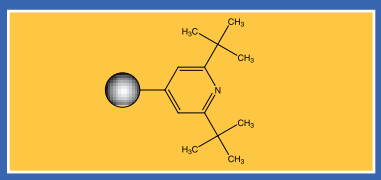


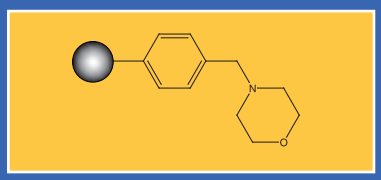
35,875-4 **1,3,4,6,7,8-Hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine, polymer-bound,* 8.0-8.5 mmol base/g**
***1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD), polymer-bound**
Used in the preparation of aryl ethers. O- and N-alkylations, and O-arylations were conducted using this resin both as a reagent for the deprotonation of phenols and as a scavenger of excess starting phenol.[2]



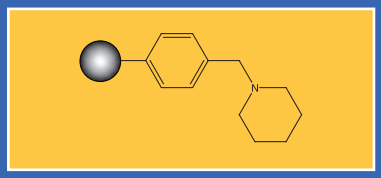
35,988-2 **Dimethylaminopyridine, polymer-bound, dry, *ca.* 5.5-6.0 mmol "DMAP"/g**
Used as a catalyst for the esterification of tertiary alcohols.[3]
Also used in acylation and sulfonylation reactions.[4]



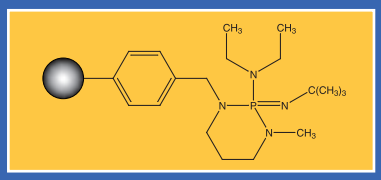
37,782-1 **2,6-Di-*tert*-butylpyridine, polymer-bound, 1% DVB, 200-400 mesh, *ca.* 1.8 mmol base/g**



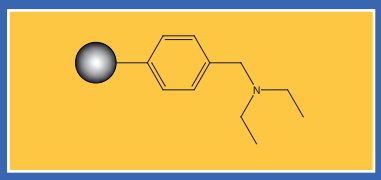
49,381-3 **Morpholine, polymer-bound, 1% DVB, 200-400 mesh, 2.5-4.0 mmol/g**
Used in the preparation of sulfonamides and amides.[5,6]
Also utilized as an acid scavenger in the synthesis of acyl-aminopiperidines.[7]



49,461-5 **Piperidine, polymer-bound, 1% DVB, 200-400 mesh, 3.0-4.0 mmol/g**
This tertiary amine simplifies reactions requiring a tertiary base, since it eliminates the need to separate final products from ammonium salts.



53,649-0 **2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine, polymer-bound (BEMP resin), 100-200 mesh, 1% DVB, 2.0-2.5 mmol/g**
A polymer-supported base used for the N-alkylation reactions of weakly acidic heterocycles.[8]
Utilized in the synthesis of unnatural peptides.[9]



53,733-0 **Diethylamine, polymer-bound, 100-200 mesh, 1% DVB, 1.0-1.5 mmol/g**
Polymer-bound tertiary amine eliminates the need to separate ammonium salts from final products.

REFERENCES: (1) Lam, K.S. et al. *Tetrahedron Lett.* **1997**, *38*, 411. (2) Xu, W. *ibid.* **1997**, *38*, 7337. (3) Guendouz, F. et al. *Tetrahedron* **1988**, *44*, 7095. (4) Shai, Y. et al. *J. Am. Chem. Soc.* **1985**, *107*, 4249. (5) Booth, R.J.; Hodges, J.C. *ibid.* **1997**, *119*, 4882. (6) Blackburn, C. et al. *Tetrahedron Lett.* **1998**, *39*, 3635. (7) Creswell, M.W. et al. *Tetrahedron* **1998**, *54*, 3983. (8) Xu, W. et al. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1089. (9) O'Donnell, M.J. et al. *J. Am. Chem. Soc.* **1996**, *118*, 6070.

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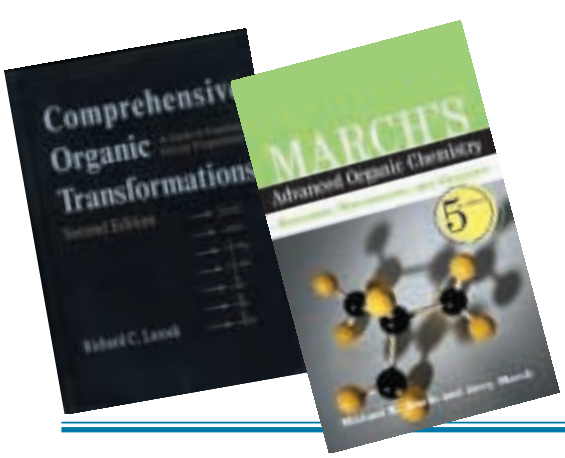

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5th ed., M. B. Smith & J. March, John Wiley & Sons, New York, NY, 2001, 1,824pp. Hardcover. Contains over 600 reactions, including 40 new sections with detailed descriptions of the basic principles underlying those reactions. Describes the structure of organic compounds, including chemical bonding and stereochemistry. Features a reaction index classified by type of compound synthesized. Contains more than 20,000 references to original papers—5,000 new to this edition.

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Z41,242-2

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F. Z. Dorwald, John Wiley & Sons, New York, NY, 2000, 474pp. Hardcover. In recent years, solid-phase synthesis has become a valuable alternative to traditional organic synthesis in solution. This book provides readers with a practical guide to solid-phase synthesis, including numerous examples with reaction conditions and hundreds of references to the original literature.

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Z42,249-5

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Z33,824-9

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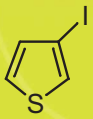
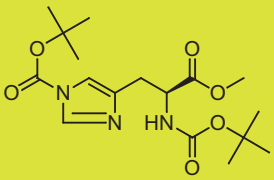
21,502-3 3-Iodothiophene, 97%



Has been used recently in the stereoselective synthesis of (*E*)-(3-thienyl)vinylgermanes via a Stille coupling reaction,[1] and in the preparation and study of 3-(diacetoxyiodo)thiophene.[2]

(1) David-Quillot, F. et al. *Tetrahedron Lett.* **2000,** *41,* 9981. (2) Togo, H. et al. *J. Org. Chem.* **2000,** *65,* 8391.

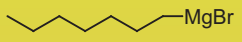
55,075-2 Nα,*N*-(im)-Di-Boc-L-histidine methyl ester, 97%



Was employed in the preparation of the corresponding imidazole-2-thione during the development of the first synthesis of L-(+)-ergothioneine.

Xu, J.; Yadan, J.C. *J. Org. Chem.* **1995,** *60,* 6296.

55,065-5 Heptylmagnesium bromide, 1.0*M* solution in diethyl ether



In situ generation of the corresponding organozinc compound was a key step in the recent use of this Grignard reagent in the stereoselective synthesis of protected alkylhydroxypyrrolidinones.[1] In another report, this reagent was used in the enantioselective opening of an epoxide en route to (*S*)-(+)-8-hydroxyhexadecanoic acid.[2]

(1) Huang, P.Q. et al. *Synth. Commun.* **2000,** *30,* 2259. (2) Shimojo, M. et al. *Tetrahedron* **2000,** *56,* 9281.

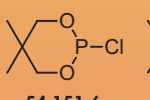
54,330-6 2,7-Di-*tert*-butylfluorene, 98%

Two recent examples of the use of this building block include the preparation of new group 4 metal complexes containing aminofluorenyl ligands,[1] and a novel, soluble analog of the Fmoc group.[2]

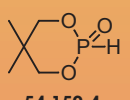
(1) Miller, S.A.; Bercaw, J.E. *Organometallics* **2000,** *19,* 5608. (2) Stigers, K.D. et al. *J. Org. Chem.* **2000,** *65,* 3858.

54,151-6 2-Chloro-5,5-dimethyl-1,3,2-dioxaphosphorinane, 97%

54,152-4 5,5-Dimethyl-1,3,2-dioxaphosphorinan-2-one, 96%



54,151-6

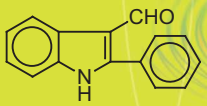


54,152-4

Reaction of the chlorophosphorinane with Cp_2NbH_3 proceeds via a carbene-like insertion mechanism to give a derived cationic diphosphite complex in high yield.[1] Other workers have prepared tungsten (*Z*)-1,2-diphosphite–alkene tetracarbonyl and (*E*)-vinyl–phosphite pentacarbonyl complexes from this reagent via phosphite Fischer carbene complexes.[2]

(1) Nikonov, G.I. et al. *J. Organomet. Chem.* **1997,** *547,* 183. (2) Barluenga, J. et al. *Organometallics* **1997,** *16,* 3732.

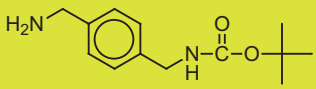
54,332-2 2-Phenylindole-3-carboxaldehyde, 97%



Has been employed in a study of the inhibition of tubulin polymerization and the growth of breast cancer cells.

Gastpar, R. et al. *J. Med. Chem.* **1998,** *41,* 4965.

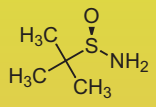
53,944-9 1-(*N*-Boc-aminomethyl)-4-(aminomethyl)benzene, 97%



Has been utilized for the solid- and solution-phase syntheses of oligomeric thioureas,[1] the preparation of a bipyrrole-based [2]catenane,[2] and, very recently, for the synthesis of model receptors for dicarboxylates and monosaccharides.[3]

(1) Smith, J. et al. *J. Org. Chem.* **1996,** *61,* 8811. (2) Andrievsky, A. et al. *J. Am. Chem. Soc.* **1998,** *120,* 9712. (3) Benito, J.M. et al. *J. Org. Chem.* **2001,** *66,* 1366.

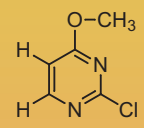
49,740-1 (*R*)-(+)-2-Methyl-2-propanesulfinamide, 98%



Developed by Ellman, this chiral sulfinamide has found widespread use in diastereoselective enolate alkylations,[1] the synthesis of protected chiral amines,[2] the Strecker synthesis of α-alkyl α-amino acids,[3] and the preparation of novel ligands for asymmetric Lewis acid catalysis.[4]

(1) Backes, B.J. et al. *J. Org. Chem.* **1999,** *64,* 5472. (2) Borg, G. et al. *Tetrahedron Lett.* **1999,** *40,* 6709. (3) Davis, F.A. et al. *J. Org. Chem.* **2000,** *65,* 8704. (4) Owens, T.D. et al. *J. Am. Chem. Soc.* **2001,** *123,* 1539.

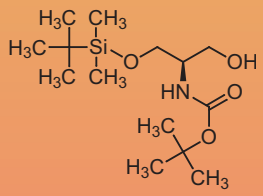
53,645-8 2-Chloro-4-methoxypyrimidine, 98%



The introduction of the 2-pyrimidinyl functionality, in the synthesis of methylene phosphonate analogs of thymidine 3′-phosphate, was achieved via a nucleophilic substitution reaction by an intermediate thioglycoside on this chloropyrimidine.[1] A number of related pyrazolylpyrimidines were prepared for study as potential cytoprotective antiulcer agents.[2]

(1) Yokomatsu, T. et al. *Heterocycles* **1999,** *50,* 21. (2) Ikeda, M. et al. *Chem. Pharm. Bull.* **1996,** *44,* 1700.

52,007-1 (*R*)-(+)-*N*-(Boc)-*O*-(TBDMS)serinol, 97%



The TEMPO oxidation of this protected serinol yields the α-amino aldehyde in good yield and without racemization.[1] This amino alcohol has also been employed in the diastereoselective synthesis of 1,2-diamines.[2]

(1) Jurczak, J. et al. *Tetrahedron* **1998,** *54,* 6051. (2) Gonda, J. et al. *Synthesis* **1993,** 729.

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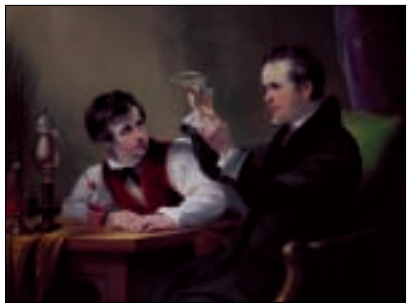

Paintings of all kinds have graced the covers of our *Aldrichimica Acta* over the years. Most were old masters, a few (like the one on the cover of Vol. 1, No. 1) were alchemical, and a few others were modern. Perhaps, none has a more direct connection to chemistry than the one reproduced on the cover of this issue. It (oil on canvas, 40 in. x 50 in.) was painted by Thomas Phillips in London in 1816, and depicts a 24-year-old Michael Faraday watching his teacher, Professor W. T. Brande, make **Prussian Blue**. At the time, Faraday was not yet the great chemist and physicist he later became—arguably the ablest British scientist of the 19th century.

What a fitting cover for the *Acta* issue celebrating Aldrich's 50th birthday!

The interested reader can learn more about this painting in: (a) Bader, A. End of the Mystery. *Chem. Br.*, July 2001, in press. (b) Bader, A. Out of the Blue. *Chem. Br.*, November 1997, p 24.

This painting is in the collection of Alfred Bader Fine Arts, Milwaukee, WI.

Full-color reproductions (11 in. x 14 in.) of this painting are available for a nominal fee to cover postage and handling. Please call 800-558-9160 (USA) and specify the Prussian Blue painting (Z52,866-8) from the cover of Aldrichimica Acta*, Volume 34, Number 2.*

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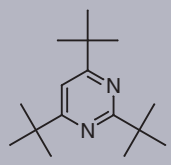

Professor David Crich of the Department of Chemistry, University of Illinois at Chicago, kindly suggested that we offer the highly sterically hindered base, 2,4,6-tri-*tert*-butylpyrimidine (TTBP), as an alternative to 2,6-di-*tert*-butylpyridine, and its 4-methyl and 4-*tert*-butyl derivatives, in glycosylation reactions and in the preparation of vinyl triflates.

Crich, D.; Smith, M.; Yao, Q.; Picione, J. *Synthesis* **2001**, 323.

54,996-7
2,4,6-Tri-*tert*-butylpyrimidine, 97% **1g $21.15; 5g $70.50**

Naturally, we made this useful reagent. 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.

Table of Contents

Lab Notes

1-Chlorobutane—A Useful Solvent for Recrystallizations

When carrying out a recrystallization, there are sometimes problems with the choice of solvent and recourse is made to mixed solvents. Of these, the combination ethyl acetate–petroleum ether is perhaps the most common pairing. Usually, one obtains a hot solution by addition of the more polar solvent to a hot suspension of the would-be solute in the less polar solvent. However, on cooling there is frequently development of two phases followed by precipitation of the solute as a solid mass rather than as crystals of good texture.

After some experiences as outlined above, we sought an alternative approach. What we were seeking was a solvent of low but definite polarity, with a convenient boiling point. We chose 1-chlorobutane, bp 77–78 °C, and we have found this to be a convenient solvent for the recrystallization of oxime ethers;[1] nitrogen ylides, such as $Me_3N^+–N^-–CN$ (with no butylation of the ylide);[2] and 3-pyrrolylpentanoic acid.[3] In unpublished work, we have used 1-chlorobutane to advantage in the recrystallization of the nitrogen ylide $Me_3N^+–N^-–C(=O)Me$ (again without butylation), and the bicyclic compounds 1-nitrocamphene and camphor-4-carboxylic acid.

Although the bulk dielectric constant does not tell the whole story about a solvent, 1-chlorobutane, interestingly, has a higher dielectric constant (7.28) than ethyl acetate (6.08); that of *n*-hexane is 1.89.[4] Specific solute–solvent interactions also need to be taken into account.

We recommend that 1-chlorobutane be considered as a solvent for recrystallization in appropriate cases subject to a couple of caveats: (a) manipulations with the solvent be carried out in a fume cupboard, and (b) one is mindful that 1-chlorobutane may be attacked by nucleophiles, though its reactivity is, at best, sluggish.

For recrystallizations that require a higher temperature, 1-chloropentane is worth consideration.

References: (1) Bradley, G. W.; Morris, D. G. *J. Chem. Res. (S)* **1993**, 220. (2) Chardin, A.; Berthelot, M.; Laurence, C.; Morris, D. G. *J. Phys. Org. Chem.* **1995**, *8*, 626. (3) Ryder, K. S.; Morris, D. G.; Cooper, J. M. *Langmuir* **1996**, *12*, 5681. (4) *CRC Handbook of Chemistry and Physics*, 79th ed.; Lide, D. R., Ed.; CRC Press LLC: Boca Raton, FL, 1998–1999; Section 6, pp 139–161.

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Making Optimal Use of Peristaltic Pumps

Laboratories involved in process development (e.g., fermentation research) frequently need to pump liquids at constant rates for specified periods of time. These liquids may be culture media, acids, alkalis, or special feed supplements. Peristaltic pumping is the chief means by which this is achieved. However, it may occasionally happen that the rate at which a liquid needs to be delivered is much lower than what can be achieved with the available pump head and tubing. This is especially the case if the pump head cannot accommodate tubings of different diameters. One simple and inexpensive solution is to pass a tubing of a smaller diameter through a short length of the pump head tubing and fix this tube-in-a-tube arrangement into the pump head. The pressure that is applied to the outer tubing by the pump rollers is transferred to the outer walls of the inner tubing, facilitating peristaltic action. Sometimes, the inner tubing may slip out of the pump head tubing when the pump is operating. To prevent this, the inner tubing may be fastened to physical supports using rubber bands or pieces of string near the two points where it emerges from the pump head.

If it is found difficult to pass the thinner tubing through the pump head tubing, smearing its outer walls with a lubricant (an oil, for instance) may help. Furthermore, the thinner tubing may be easily passed through the thicker one if twisting motions are used. If suction of liquid does not occur, a slight adjustment of the gap between the rollers and the wall of the pump head may be required.

We have successfully used this arrangement in our laboratory. It does not appear to have any drawbacks, either with regard to the pump or the tubing. In fact, it has a distinct advantage: the wear on the inner tubing is reduced, since it is shielded by the thicker pump head tubing.

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Outline

1. Introduction

This August, Aldrich Chemical Company turns fifty. What a remarkable fifty-year period this has been! While it is today a "household" name among chemical scientists and practitioners worldwide, it is hard to imagine that Aldrich is only a half century old. On the following pages, I will take a brief look back at the past fifty years. While the story of Aldrich has been told and retold in one form or another many times,[1,2,3] it is my sincere hope that the fresh approach I am using will prove to be of most interest to our *Aldrichimica Acta* readers. This approach traces the development of Aldrich through the key chemical products and business ventures that played a crucial role in the uninterrupted success that the company has enjoyed over the past fifty years. Since the success of any great enterprise is dependent immensely on the contributions of a legion of dedicated individuals who believe in its mission, the roles that key people played in the development of Aldrich will also be highlighted.[4]

2. What's in a Name?

2.1. Alfred R. Bader

Alfred Robert Bader, a young Austrian immigrant and a chemistry graduate student at Harvard University, first entertained the idea of starting a company to sell research chemicals in 1949—on the suggestion of Warren Stockwood, the storeroom supervisor at Harvard's Department of Chemistry[5]—after being disappointed with the service he received from the leading supplier of research chemicals at the time. Acting on the premise that chemists needed a wider array of research chemicals and better service, he and Jack Nathan Eisendrath, a Milwaukee attorney, founded Aldrich Chemical Company, Inc. on August 17, 1951. Jack became the company's first president.[6] In a curious twist of fate, the company was named following a coin toss,

not after either of the founders, but after Eisendrath's fiancée, Bettie Mae Aldrich.[7] Had Bader won the coin toss, the company would have been named Daniels Chemical Company, after Helen Ann Daniels, Bader's fiancée and future wife.[2]

2.2. Aldrich Chemical Company, Inc.

In 1951, the company operated first from Eisendrath's office on 161 W. Wisconsin Avenue and, later that year, from a rented garage located on N. Farwell Avenue in Milwaukee's East Side. It had three part-time employees: Alfred, Jack, and Lorraine Worby (née Neau). Lorraine first worked for Aldrich part-time, 4–5 hours on Wednesday nights, then became the first full-time Aldrich employee in August of 1954.[8] From 1951 to 1954, Alfred sowed the seeds of what later became very important collaborations and acquisitions through visits to small chemical producers in Continental Europe and the United Kingdom. Noteworthy are two visits in 1952 to Fluka AG Chemische Fabrik in St. Gallen, Switzerland, and Heidenheimer Chemisches Laboratorium (HCL) in Heidenheim, Germany. These two companies as well as many others served as

Photo courtesy of A. R. Bader

Alfred R. Bader, cofounder of Aldrich (mid-1980s).

Photo courtesy of Bettie Aldrich Eisendrath

Jack N. Eisendrath, cofounder and first president of Aldrich (1951).

important suppliers to Aldrich in this period and for years thereafter. **Table 1** summarizes the fledgling company's vital statistics for this period.

2.3. MNNG and Other Products

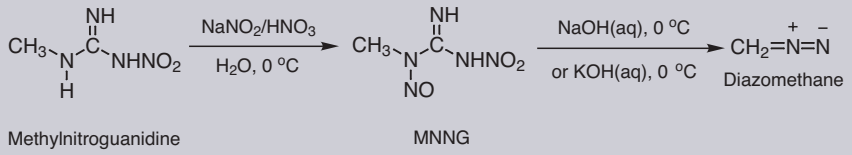
Aldrich offered 1-methyl-3-nitro-1-nitrosoguanidine (MNNG) as its first product. MNNG is a convenient, small-scale precursor to diazomethane, a widely used methylating reagent (**Scheme 1**).[9,10] Perhaps foretelling of the vital role that suppliers would subsequently play in helping Aldrich grow and prosper, Aldrich did not at the time produce MNNG but sourced it from two companies, one in Milwaukee and the other in Canada.

Some of the other interesting products offered in the early fifties include 3-hydroxypyridine (**1**), which later became one of the company's best-selling products; ethyl diazoacetate (**2**); tetranitromethane (**3**); and ethanedithiol (**4**) (**Figure 1**). The addition of new products was guided by the beliefs that production should be combined with resale and that the company should not offer products that were also sold by its main competitor, Eastman Kodak's Fine Chemicals Division, which dominated the fine chemicals market at that time. In addition, Aldrich recognized very early on the vital role of suppliers in its growth and worked diligently to establish mutually beneficial relationships with them. Suppliers continue to be important to the growth of the company to the present day.

Table 1. Aldrich's Vital Statistics for the First Four Years

Year	Sales	Products Offered	Catalog Number	Catalog Pages	Employees[a]
1951	$1,705	1	1	1	Alfred, Jack, Lorraine
1952	$5,400	12	2	1	Alfred, Jack, Lorraine
1953	$15,000	>100	3 & 4[b]	4	Alfred, Jack, Lorraine
1954	$45,000	>1,200	5	32	Alfred, Jack, Lorraine, Anthony

[a] All part-time employees except for Anthony D. Kontowicz. In August 1954, Alfred and Lorraine became full-time employees; Lorraine was the first non-owner employee. [b] Two catalogs were produced for 1953, one came out in October 1952 (No. 3) and the other in May 1953 (No. 4). Each consisted of 4 pages and listed over 100 products. Sources: references 1 and 8 and company catalogs.



Scheme 1. Preparation of MNNG and Generation of Diazomethane.

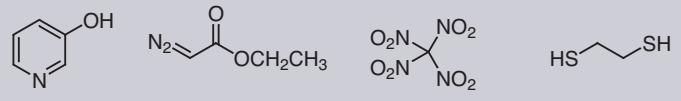


Figure 1. Some of the Interesting Products Offered in the Early Fifties.

3. Critical Years: 1954 and 1955

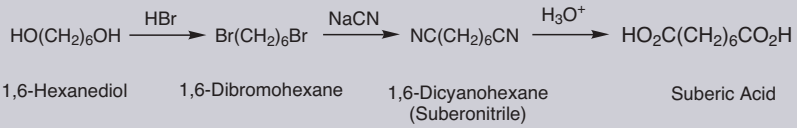
3.1. A Crucial Decision

First, Alfred Bader elected not to relocate to the Pittsburgh area, where The Pittsburgh Plate Glass Co. (PPG), his employer at the time, was relocating the research laboratories of its Milwaukee paint division. Alfred had been working for PPG-Milwaukee since January 1950. Instead, he left PPG in August 1954 to dedicate his time and energy fully to the fledgling company, which he had cofounded only three years earlier. He also became convinced that products should not only be sourced but also sold overseas, e.g., in Western Europe, in spite of the potential stiff competition from well-established fine chemicals companies. This conviction would later have important consequences for the future of Aldrich.

Second, William Kesselman, a Milwaukee businessman, bought one-third of Aldrich for $25,000, but bowed out seven months later, with the company owing him $12,000.[11] In August 1954, after Kesselman bought into the company, Aldrich moved out of the N. Farwell Avenue garage into a 1,000-sq ft, rented laboratory at 3747 N. Booth Street, one block south of Capitol Drive, still in Milwaukee.

Third, Aldrich hired a second full-time employee, Anthony D. Kontowicz, a former laboratory technician at PPG. Anthony was thus the first full-time laboratory technician hired; however, he worked at Aldrich for only a short period of time (ca. 1 year).[8a,12,13]

1955 was no less critical for Aldrich. The Eisendraths sold their 50% stake in the company for $15,000.[14,15,16] Alfred and Helen Bader became the sole and equal owners of the company,[17] and Alfred became the second president of Aldrich in May 1955.[18] In August 1955, Alfred met Marvin E. Klitsner, a Milwaukee attorney, at a religious retreat.



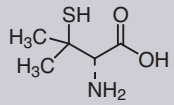
Scheme 2. Large-Scale Preparation of Suberic Acid.

Later on, Marvin was instrumental in guiding the growth of Aldrich, both as legal counsel and director of Aldrich and of Sigma-Aldrich. As Alfred put it, Marvin "was the moving spirit in the growth of Aldrich".[19] Marvin also played a key role in the negotiations leading up to the merger of Aldrich Chemical Company, Inc. and Sigma International, Ltd. in 1975; but more on that later! Beginning in January 1955, Helen Bader, Alfred's wife since July 1952, began working full-time for Aldrich.[20,21] On September 01, 1955, George Skeff, also a former PPG laboratory technician, was hired as a full-time laboratory technician, following the departure of Anthony D. Kontowicz. George retired from Aldrich on April 14, 1989, after close to 34 years of employment!

3.2. Suberic Acid and D-Penicillamine

More importantly, Aldrich delivered its first bulk order, 500 lb of suberic acid, to Du Pont toward the end of 1955 (**Scheme 2**).[3a]

Furthermore, one of the important products that Aldrich began to offer that same year was D-penicillamine or 3-mercapto-D-valine (**5**), an antirheumatic α-amino acid and, at the time, a promising orphan drug, which chelates and removes the copper accumulated in the liver of patients suffering from the rare disorder known as Wilson's Disease.[22]



D-Penicillamine (**5**)

4. The Remainder of the 1950s

4.1. Rapid Growth

The remainder of the 1950s was characterized by rapid growth in sales and the number of products offered. This growth in sales led to the expansion of the physical facilities and the hiring of additional staff. In February 1956, Beverly Horick, the fourth non-owner employee, was hired on a part-time basis.[23] The next employee hired was Stella Ward. By 1958, Aldrich had about a dozen employees. In the same year, Aldrich purchased and moved to a three-story, 27,000-sq ft building at 2369 N. 29th Street in Milwaukee's inner city. Two years later (1960), a larger, 70,000-sq ft building was purchased nearby at 2371 N. 30th Street. The 29th Street building housed the R&D and Production departments, while the 30th Street building had administrative offices and the QC, Packaging, and Warehousing departments.[24] The 29th and 30th Street buildings remained Aldrich's headquarters until 1969, when they were condemned by the Milwaukee County Expressway and Transportation Commission in preparation for building the east–west Park Freeway (which was never built). In 1969, Aldrich relocated to 940 W. St. Paul Avenue into an eight-story building that previously belonged to General Electric Company.[25]

The 7th edition of the Aldrich catalog (December 1955) and its supplements featured over 1,600 products.[26] Some of the products offered in the late fifties became success stories. Among the most interesting ones are dicyclohexylcarbodiimide (DCC, **6**), a useful reagent in peptide coupling reactions; *p*-tolylsulfonylmethylnitrosamide (Diazald®, **7**), a diazomethane precursor that is safer than MNNG; and *p*-phenyl-azomaleinanil (**8**), a reagent employed for the characterization of conjugated dienes (**Figure 2**). Other interesting products from this period include lithium borohydride ($LiBH_4$), sodium tetraphenyl boron ($NaBPh_4$), diketene ($C_4H_4O_2$), and triallylamine ($C_9H_{15}N$).

The births of several important company entities, as well as other significant developments, also took place in the late fifties.

4.2. The Rare Chemical Library

The Rare Chemical Library (RCL) grew out of the collecting and salvaging of valuable research samples of retiring or deceased academic researchers and from other sources. While the RCL was initially part of a separate company, the Alfred Bader Chemical Corporation, it was sold to Aldrich Chemical Co. on December 20, 1965, just prior to a public offering of 100,000 Aldrich shares.[27] Over the years, large-scale contributions of samples to the library came from, among others, the personal collection of Joe Karabinos (who founded Carbolabs,

Photo courtesy of the Helen Bader Foundation

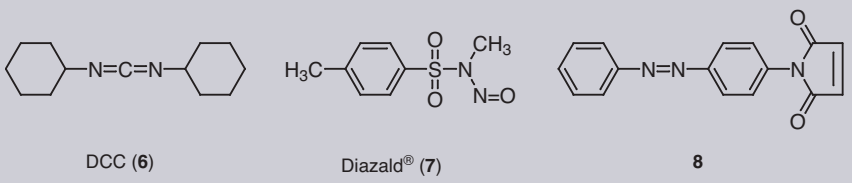
Helen A. Bader (née Daniels), 1982.

Photo courtesy of Bettie Aldrich Eisendrath

Bettie Aldrich Eisendrath (née Aldrich), 1951.

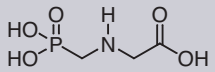
Photo courtesy of A.R. Bader

Left to right: Lorraine, George, Stella, and Beverly—1st, 3rd, 5th, and 4th Aldrich employee, respectively (1978).



DCC (**6**) Diazald® (**7**) **8**

Figure 2. Best-Selling Products from the Period 1955–1959.



N-(Phosphonomethyl)glycine
(*Active Ingredient in Roundup®*)

Sigma-Aldrich facility in Gillingham, Dorset, United Kingdom.

Sigma-Aldrich facility in Steinheim am Albuch, Germany.

Inc.) and from the laboratories of such chemical luminaries as Henry Gilman, George Wittig, Robert Woodward, and Louis and Mary Fieser. The RCL currently boasts over 90,000 listings of hard-to-find chemicals. Over the years, the RCL has been invaluable to researchers in the chemical sciences and has led to the discovery and commercialization, by others, of some very valuable chemical commodities, e.g., Roundup® (Monsanto Co.), based on lead compounds obtained from the RCL.

4.3. Aldrich Chemical Co Ltd

In 1959, Aldrich's British subsidiary formally began as Ralph N. Emanuel, Ltd., and was equally owned by the Emanuel and Bader families. It had less than $1,000 in sales in its first year,[28] but sales grew briskly leading to a rapid expansion of the physical facilities and the number of employees. Between 1969 and 1973, Aldrich began gradually acquiring Ralph N. Emanuel, Ltd., and turning it into a wholly owned subsidiary. It was then renamed Aldrich Chemical Co. Ltd. Ralph Emanuel became an Aldrich and, afterwards, a Sigma-Aldrich director. Business growth led to the company moving to the current site in Gillingham, Dorset, U.K., where a distribution center and a new cGMP manufacturing facility are presently located. In 1986, Sigma-Aldrich purchased Bristol Organics, a small manufacturer and long-time Aldrich supplier of fluoro-aromatics, and shortly thereafter integrated its operations with those of the larger British subsidiary. Three years after the acquisition of Fluka Chemie by Sigma-Aldrich Corp., the operation of Fluka's subsidiary in Glossop, Derbyshire, was transferred to the Gillingham facility in September 1992. The British subsidiary has a special significance to the corporation, not only because it has become Britain's largest supplier of research chemicals, but also because it has been a source of a number of individuals in corporate leadership positions. Moreover, success of the British subsidiary encouraged the company to open other branches in Continental Europe, where strong competition from well-established fine chemicals companies had been a concern.

4.4. Aldrich Chemie KG

The story of Aldrich's subsidiary in Germany is somewhat different. It starts out with Heidenheimer Chemisches Laboratorium (HCL) in Heidenheim, Germany, acting as Aldrich's best supplier for most of the 50s. HCL was then operated by Dr. Ernst Reif, a chemist, and Gerhard Keppler, a businessman. Following, an industrial accident at HCL and a legal setback for the company, Aldrich became involved in the restructuring and refinancing of its operations. It was renamed EGA-Chemie KG[29] and moved to Steinheim am Albuch—with Aldrich owning about 80% of it. Later (1971),[30] Aldrich bought the remaining 20% of EGA and renamed it Aldrich-Chemie GmbH & Co. KG. Like its British counterpart, the German subsidiary has been a tremendous success story, and has grown steadily in capabilities, personnel, and facilities. It now manufactures a range of products [e.g., 2,4-dimethylbenzaldehyde (**9**), 6-hydroxydihydrotheaspirane (**10**), and 6-acetoxydihydrotheaspirane (**11**)—all three are important flavoring raw materials for the food industry (**Figure 3**).] and serves a corporate warehousing function for all markets in Continental Europe from warehouses in three German towns: Schnelldorf, Steinheim, and Seelze. In 1975, it started producing a full German language edition of the Aldrich catalog concurrently with the English language editions. Two decades later, the activities of all Sigma-Aldrich brands in Germany were combined in one legal entity, Sigma-Aldrich Chemie GmbH, in order to streamline their operations. Perhaps one name stands out more than any other and is credited for most of the early success of Aldrich Chemie—that of Dr. Alfred Griesinger. Dr. Griesinger joined the company in March 1963, owned an interest in EGA-Chemie (1965–1970), and served in various important capacities. He later became a director of Aldrich-Chemie KG, and remained with the company until his untimely death in August 1997.[31]

4.5. Custom Synthesis

The late fifties and early sixties also witnessed the growing importance of custom synthesis and bulk sales. In these early days, custom synthesis was formally one of the business activities of the separate corporation, Alfred Bader Chemical Corp., which was sold to Aldrich on December 20, 1965.[27] Over the years, custom synthesis became an important function within the Aldrich Production department, and, together with bulk sales, evolved into Sigma-Aldrich Fine Chemicals (SAFC), currently one of four strategic business units within Sigma-Aldrich Corporation. SAFC concentrates on worldwide large-scale manufacturing and sales. Past and present custom synthesis customers are some of the best-known chemical and pharmaceutical companies in the world. Perhaps some of the more interesting custom synthesis projects that Aldrich worked on in the sixties involved the preparation of *tert*-butoxycarbonyl azide (**12**), BSA (**13**), and acryloyl chloride (**14**).[32] Some of the hard-to-find products offered in bulk (100–1,000 lb) in the late fifties included several dimethylphenols (**15**),

trimethylphenols (**16**), 2-methylresorcinol (**17**), and dihydroxybenzoic acids (**18**) (**Figure 4**). Along with the R&D group, the custom synthesis team routinely carries out significant process improvement and scale-up projects as well as the manufacture of newly introduced products.

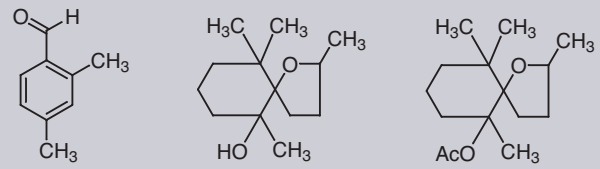
5. The 1960s: A Decade of Transformation

Firstly, Aldrich went from being a privately owned company to being a publicly traded one. Secondly, the growth in sales began to occur, not only as a result of the addition of new products, but also as a result of joint ventures and acquisitions. Finally, important developments took place within the company, such as the birth of this magazine (1967) and the transformation of the Aldrich catalog from a simple list of products and prices into a "handbook", as a consequence of the inclusion of useful factual information about the compounds being offered.

5.1. Early to Mid-1960s

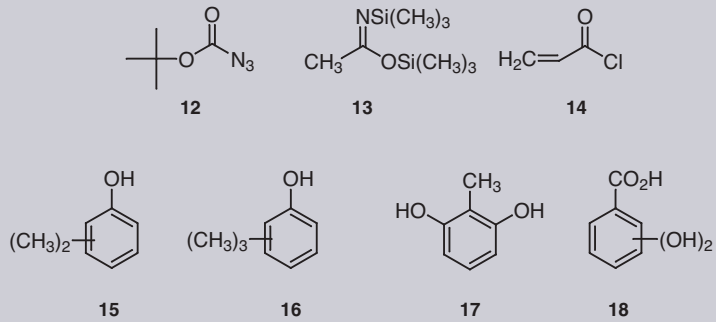
1962 was, in many respects, a watershed year for the young company. Annual sales reached the $1 million mark for the first time, and the Aldrich catalog grew to 303 pages, as the number of products offered swelled to 10,000. Aldrich became Janssen Pharmaceutica's sales agent in the US, and started ALFA Inorganics, a joint venture with Metal Hydrides, Inc. Dr. John Biel joined the company as Director of Research, replacing Edmund (Pete) J. Eisenbraun, Harvey B. Hopps was hired as an R&D group leader, and Bernard (Bernie) E. Edelstein joined as a chemist. Bernie went on to become one of the company's directors, its secretary, and then its first Executive Vice President (1974). In 1962, William Buth was Aldrich's General Manager; he later became the first Aldrich Vice President. In the same year (1962), J. T. Baker Chemical Co. attempted to buy Aldrich for $1.5 million, but was rebuffed.[33]

In the mid-sixties, the prior practice of listing only products that were not offered by Eastman Kodak's Fine Chemicals division was abandoned in favor of listing products based on their usefulness and marketability. An interesting offering from this period is 9-amino-1,2,3,4-tetrahydroacridine hydrochloride hydrate (Tacrine hydrocloride; **19**), which was first introduced as an Aldrich product in 1963, and is now sold by Warner–Lambert, a division of Pfizer Inc., under the trade name COGNEX® for the treatment of mild to moderate dementia of the Alzheimer's type.[34,35]



9 10 11

Figure 3. Important Flavoring Raw Materials Manufactured by the German Subsidiary.



12 13 14 15 16 17 18

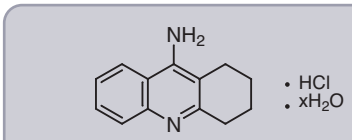
Figure 4. Custom Synthesis (**12**–**14**) and Hard-to-Find Products Offered in Bulk (**15**–**18**) in the Late Fifties.

5.2. Business, Art, and Chemistry

In 1965 and then in 1966, the Bader family sold some of their shares in the company first to a select group of chemists and friends and then to the public at large. By 1965, sales had almost doubled to about $1.8 million, from $1 million in 1962, and the number of employees had grown to over 100, of which 15 were chemists (7 with a Ph.D.).[33] The Aldrich Catalog/Handbook took on its now familiar name and look, as the 1967/1968 edition was the first to have a painting, *The Quill Cutter* by Paulus de Lesire, on its cover. Contrary to popular belief, the idea for placing a painting on the cover of the catalog came, not from Bader—the art lover and collector—but from Bernie Edelstein, an Aldrich employee.[36]

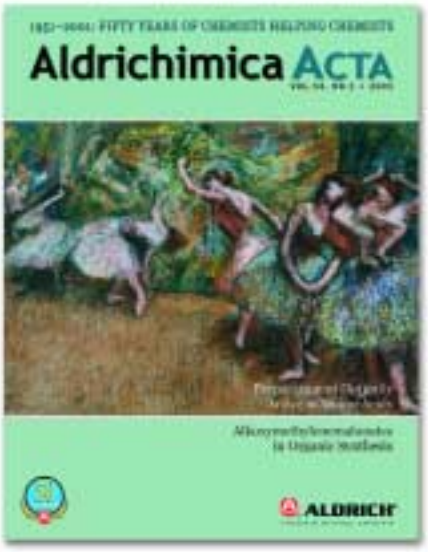
Following the public offerings, sales and the share price rose steadily as Aldrich grew by expanding into new lines of business and entering into (exclusive) distributorship agreements with a number of commodity chemical producers and other companies. Aldrich also acquired stakes in a number of U.S. based, small chemical producers, such as Hexagon and Kaplop Laboratories, but later divested itself of these stocks after the companies ran into business difficulties.

The *Aldrichimica Acta* evolved from the *Kardindex Sheets* that Aldrich used to mail to its best customers to keep them informed of its newest product offerings.[37] A preview issue was printed in the fall of 1967, and then



Tacrine Hydrochloride (**19**)

publication on a regular basis started in 1968. Richard K. Vitek, Aldrich's Director of Marketing at the time, became its first editor—albeit for a very short period of time. A classical alchemical Dutch painting by



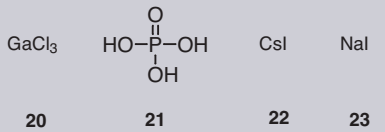


Figure 5. Ultrahigh-Purity Products Manufactured by AAPL™.

Aldrich's manufacturing site near Sheboygan, Wisconsin.

Thomas Wyck (17th century) from the Alfred Bader art collection was reproduced on the cover of the first issue of 1968. Of this very same issue, 10,000 copies were printed, whereas, today, over 130,000 copies of each issue are distributed worldwide free of charge. Alfred Bader, who coined the name *Aldrichimica Acta*, came up with the idea of placing a painting on its cover,[17] following the precedent-setting reproduction of a painting on the cover of the 1967/1968 edition of the Aldrich Catalog/Handbook (vide supra).

5.3. Joint Ventures

5.3.1. ALFA Inorganics, Inc.

This 50/50 joint venture with Metal Hydrides, Inc. (later became Ventron, Inc. and then a part of Thiokol Corp.) began in 1962 and ended in 1967. It was created to market inorganics, organometallics, and others such as organoboron and organoarsenic reagents.[38] Even though the joint venture lasted only five years, it helped Aldrich learn a great deal about inorganics and set the stage for Aldrich to expand into this market sector in the 1970s.

5.3.2. Aldrich-Europe

In the late fifties and early sixties, Janssen Pharmaceutica (JP) of Beerse, Belgium, had become one of Aldrich's better suppliers. It was no surprise then that, in 1962, Aldrich became JP's sales agent in the United States. Thus started the good relationship between the two companies. It led in May of 1970 to the creation of Aldrich-Europe, a wholly owned division of JP, charged with distributing Aldrich products in Continental Europe. The joint venture lasted until June 1982. Its dissolution opened the way for Sigma-Aldrich to start subsidiaries and sales offices in many countries in Continental Europe. Today, these number 18.

5.3.3. Riedel-deHaën® Laboratory Chemicals

Fast-forwarding to the present, Sigma-Aldrich first formed a joint venture, Riedel-deHaën® Laborchemikalien GmbH & Co. KG, with Allied Signal in 1997 to market and sell mainly analytical reagents and solvents carrying the Riedel-deHaën® brand name. Three years later, the joint venture became a wholly owned subsidiary of Sigma-Aldrich Corporation and is currently offering close to 4,000 products belonging to three general types: Karl Fischer reagents for water determination, standards for environmental analysis, and high-purity solvents.

5.3.4. Aldrich-APL, L.L.C. (AAPL™)

Also in the present, Aldrich has a majority stake in a joint venture with APL Engineered Materials to produce select inorganics of extremely high purity and low moisture content (ultradry) intended for the high-tech market. This collaboration began in September 1995 and presently operates from a manufacturing facility in Urbana, Illinois. Dr. John Long, who had been hired by Aldrich in the 1970s to head the inorganics production laboratories in Milwaukee, was initially charged with managing the Urbana facility. Some of the more popular, ultrahigh-purity products that are presently manufactured by AAPL™ include anhydrous gallium(III) chloride (**20**), phosphoric acid (**21**), anhydrous cesium iodide (**22**), and anhydrous sodium iodide (**23**) (**Figure 5**).

6. Great Opportunities and Profound Changes (1970s)

6.1. Aldrich-Boranes, Inc.

The greatest opportunity came when Professor H. C. Brown of Purdue University convinced Aldrich to further develop and commercialize the hydroboration technology and organoborane chemistry that he had developed and patented. This led, in May 1972, to the establishment of Aldrich-Boranes, Inc., a wholly owned Aldrich subsidiary, created to manufacture, among others, hydroboration reagents and products. Aldrich-Boranes, Inc. began operation in September 1972, with Dr. Harvey B. Hopps as its manager, Professor Brown as one of its directors, and a small development group of chemists headed by Clinton F. Lane, an enthusiastic young Ph.D., who had trained with Professor Brown at Purdue. Some of the first compounds manufactured by Aldrich-Boranes were borane–THF (**24**), 9-BBN (**25**), borane–methyl sulfide (**26**), and compounds **27–30** (**Figure 6**).[39] A multitude of others followed in rapid succession. The early development of this chemistry has been described in several reviews by Lane.[40] In the early 80s, Aldrich-Boranes, Inc. was integrated into Aldrich.

In the first five years, Aldrich-Boranes, Inc. operated from the production laboratories on West St. Paul Avenue in Milwaukee's city center. Following the purchase, in December 1977, of a laboratory building and a property in the town of Wilson, Sheboygan County, Wisconsin, its operations were moved to this site in March 1978.[41] This became the nucleus of Sigma-Aldrich's current 513-acre manufacturing site at 5485 County Road V. The range of products manufactured at the site has long expanded to include pharmaceutical intermediates, air-sensitive reagents, various organometallics, cGMP products, high-purity solvents, and many other compound types.

6.2. Stable Isotopes

Also in 1972, Aldrich acquired Diaprep, an Atlanta based manufacturer of deuterated solvents, and with it two experienced chemists—Tom Wickersham and Bob Askins. Tom remained with Aldrich until his retirement in 1999; he spent most of his career in the Stains & Dyes division, which he helped grow into an important part of the business (vide infra). With the acquisition of Diaprep, Aldrich started the production of

deuterated solvents; this production has expanded rapidly and considerably to the point that Aldrich is presently perhaps the world's largest producer of deuterated solvents. Moreover, through special agreements with companies such as Isotec Inc., Aldrich has also been able to significantly expand its offerings of products labeled with other stable isotopes, such as ^{6}Li, ^{7}Li, ^{10}B, ^{11}B, ^{12}C, ^{13}C, ^{15}N, and ^{18}O. In February 2001, Sigma-Aldrich purchased Isotec, Inc., thus becoming the leader in the stable isotopes market.

6.3. Sigma-Aldrich Corporation

The other profound event occurred three years later, in August 1975, when Aldrich Chemical Co. merged with Sigma International, Ltd. of St. Louis, Missouri, to form Sigma-Aldrich Corporation. At the time, both companies were publicly owned, with Aldrich the leading supplier of organic research chemicals and Sigma the leading supplier of research biochemicals. Having dodged several takeover attempts, Aldrich had, in 1967, approached Sigma—then a privately owned company—with an offer to merge, but was rebuffed. By 1975, however, changing trends in chemical research and the synergy to be realized from their complementary business practices and product offerings convinced the two companies to finally merge.

Dan Broida, Sigma's president at the time of the merger, became chairman of the board, while Alfred Bader, Aldrich's president, became president of Sigma-Aldrich Corp. At the time, the new company did not have a CEO. As anticipated, the merged companies drew on each other's strengths—Sigma's emphasis on quality and service and Aldrich's emphasis on introducing new products and maintaining good relationships with suppliers.

A little over a year prior to the merger (April 23, 1974), four Aldrich departmental managers—Robert Gorzek, Irwin (Ike) Klundt, Charles (Chuck) Pouchert, and Edward Segrin—were promoted to vice presidents. On the same date, Vice President Bernard Edelstein was promoted to Executive Vice President.[42] The first and second Aldrich vice presidents, William Buth and John Biel, had left the company in 1973 and 1968, respectively.[43] Also in 1974, David R. Harvey (see Section 7.1) became Aldrich's Vice President of European Operations.[44]

6.4. Floyd Green's Stains and Dyes

In 1973, Dr. Floyd J. Green, a widely respected authority on biological stains and dyes, founded Aristo Custom Chemicals, Inc. in Cincinnati, Ohio, to manufacture biological stains. He sold Aristo to Sigma-Aldrich in 1977 and moved to Milwaukee to become an Aldrich vice president in charge of the company's newly created Stains and Dyes division. This division currently boasts ca. 1,300 products, and offers an attractive handbook on stains, dyes, and indicators that was originally prepared by Dr. Green.[45] Two of the early dyes sold by the division were pararosaniline chloride and acetate. Presently, the Stains and Dyes division operates from a 110,000-sq ft facility, at 230 S. Emmber Lane in Milwaukee, that was purchased in the early seventies.

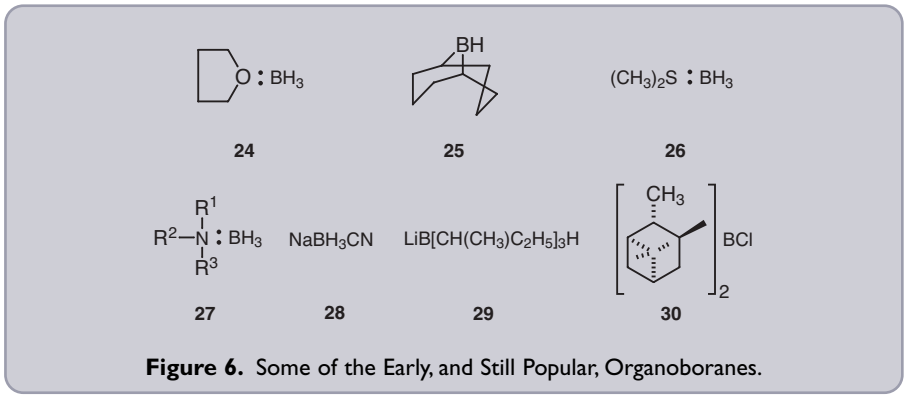


Figure 6. Some of the Early, and Still Popular, Organoboranes.

6.5. Nonchemical Products

6.5.1. Laboratory Equipment (Techware)

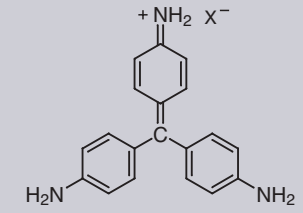
Charles J. Pouchert, a long-time Aldrich employee and Manager of its Quality Control department in the early 70s, promoted the idea that Aldrich should sell books that are useful to chemists. Not surprisingly, the first nonchemical item that Aldrich offered (cat. no. Z10,000-5)[46] was the first edition (1970) of *The Aldrich Library of Infrared Spectra*, that Pouchert edited. The idea of offering a laboratory equipment item was advanced by Dr. Harvey B. Hopps, at the time Aldrich's Manager of Technical Services. This first laboratory equipment item was a Diazald® kit (cat. no. Z10,025-2) and was listed for sale for the first time in the very early 70s.[24] Thus started the Techware division of Aldrich—with much input and encouragement from Edward J. Segrin, Aldrich's Sales Manager at the time. This division expanded rapidly over the years into such product areas as books, electronic media products, and glassware. It currently offers over 13,000 nonchemical items[47]—everything the practicing chemist needs in addition to chemicals.

6.5.2. The Aldrich Glass Shop

The Aldrich glass shop grew simply enough from the need to repair laboratory glassware in-house. In the early 70s, and by arrangement with Daytime Vacuum Products, a glass shop was set up on the 4th floor of the 940 W. St. Paul Avenue building. When the lone glass blower retired, Aldrich purchased the shop and looked to hire a glass blower to operate it. An early hire in 1974 left after a few months.[48] However, in 1975, an able

2001 edition of the Aldrich Stable Isotopes catalog.

SIGMA-ALDRICH
CORPORATION



X = Cl; Pararosaniline chloride (Basic Red 9)
X = OAc; Pararosaniline acetate

Techware CD-ROM product.


Sophisticated piece of glassware manufactured by the Aldrich Glass Shop.

Company logo from the early days.

glass blower, Dieter Damrow, was hired to operate the glass shop. Dieter stayed with the shop until his retirement in 1999, and has had a greater impact on the growth and development of the shop than anyone else. During Dieter's tenure, the glass shop grew steadily and its mission expanded to include the manufacture of new glass apparatus and custom glassware, and the taking on of outside repair jobs. Back in 1985, the glass shop was relocated to newer quarters in the 2905 W. Hope Avenue facility.

6.6. New Lines of Business

As is clearly evident from the preceding discussion, the 70s were an exciting period for Aldrich. In addition to those mentioned in the previous sections, Aldrich availed itself of other business opportunities. Thus, in 1971, Aldrich launched its line of biochemical products with Irwin Klundt as its technical manager.[42] However, this line of products had a brief, independent existence up until Aldrich's merger with Sigma in 1975. In 1978—free from the restrictions of the separation agreement that led to the dissolution of the Aldrich–Ventron joint venture (see Section 5.3.1)—Aldrich hired Dr. John Long, a promising young inorganic chemist, to spearhead its development and production of inorganic products. It wasn't long before Aldrich was competing successfully with ALFA Inorganics, Inc. The inorganic line of products is thriving today, enhanced by the establishment of the joint venture with APL Engineered Materials in 1995 (see Section 5.3.4). Together with the line of organometallics, it offers close to 10,000 products for, among others, the high-technology markets.

6.7. Craftsmen in Chemistry?

Just as many other companies have had to, Aldrich also had to change with the times. The "Craftsmen in Chemistry" slogan, which was in use in the late 60s, was abandoned a few years later (1975), since it was deemed politically incorrect. It wasn't until early 1978 that a new slogan, "chemists helping chemists in research and industry", began appearing in company literature. Presently, this motto is slowly being phased out in favor of its shorter version, "chemists helping chemists". Aldrich's logo also underwent a face-lift; an earlier version is depicted here. Fortunately, and unlike many other prominent chemical companies, Aldrich did not succumb to the pressure of dropping the word "chemical" from its name, during a period of time when this word had become a public relations liability.

7. Post-Merger Era

7.1. The Succession

With Aldrich now a company within Sigma-Aldrich Corporation, Alfred Bader became President of the merged company and remained President of Aldrich until early 1981. He was succeeded as President of Aldrich by Dr. David R. Harvey (1981–1986), Dr. Jai P. Nagarkatti (1987–1999), and Dr. Clinton F. Lane (1999–Present).[49]

David R. Harvey, an Oxford University graduate, started out in Aldrich-UK in August 1974 as Vice President of European Operations. As president of Aldrich, he oversaw, among others, the relocation of the distribution center to the Hope Avenue facility and the construction of the laboratory building at the Sheboygan County site. He is also credited with starting the company's Flavors & Fragrances division. David went on to become President of Sigma-Aldrich Corp. and then, in 2000, its Chairman, President, and CEO.

A graduate of East Texas State University, Jai P. Nagarkatti started his career at Aldrich in 1976 as a Process Development Chemist in the Production Laboratory. He progressed through the ranks to become Vice President of Production in 1985 and President of Aldrich in 1987. Late in 1999, he was promoted to President of Sigma-Aldrich Fine Chemicals, one of four strategic business units of Sigma-Aldrich Corp. During his tenure as president, Aldrich experienced a substantial growth in business. He oversaw a major expansion of the manufacturing plant (Pro II) at the Sheboygan County site, and worked tirelessly to integrate Aldrich more closely into Sigma-Aldrich Corp.

Clinton F. Lane, the current president, is a Purdue University graduate who was the first chemist hired for the Aldrich-Boranes, Inc. venture back in September 1972. After working as a bench chemist in Milwaukee, he moved, along with Aldrich-Boranes, Inc. to the Sheboygan County site soon after its purchase in 1977. After 13 years as Plant Manager of the Sheboygan County site, he was promoted to Vice President, Executive Vice President, and then President of Aldrich in 1999. Clint is credited with the substantial growth that both the Sheboygan County site and the line of boron-containing products have experienced. The interested reader should review Section 6.1 for more details.

7.2. The 80s and 90s

Following the merger of Aldrich and Sigma, business expectations for the merged company were soon realized. Annual double-digit growth has since been the norm, and other companies[50,51]—Floyd Green's Aristo Custom Chemicals (USA, 1977), Makor Chemicals (Israel, 1978), Pathfinder (USA, 1984), Bio Yeda (Israel, 1986), Bristol Organics (UK, 1986), Fluka Chemie AG (Switzerland, 1989), Supelco (USA, 1993), LabKemi AB (Sweden, 1994), Research

David R. Harvey, Aldrich President (1981–1986).

Jai P. Nagarkatti, Aldrich President (1987–1999).

Clinton F. Lane, Aldrich President (1999–Present).

Biochemicals International (USA, 1997), Carbolabs (USA, 1997), Genosys Biotechnologies, Inc. (USA, 1998), Riedel-deHaën® Laborchemikalien GmbH & Co. KG (Germany, 1999), ARK Scientific GmbH (Germany, 2000), First Medical, Inc. (USA, 2000), Amelung GmbH (Germany, 2000), Isotec, Inc. (USA, 2001)—have also become part of Sigma-Aldrich Corp. In 2000, Sigma-Aldrich corporate sales were over one billion dollars![52] The brands that make up Sigma-Aldrich Corp. are now well-known and trusted worldwide. The total number of products they offer is about 85,000 of which about 40,000 are poduced.

Aldrich continued its spectacular growth in these two decades as evidenced by the purchase of several large buildings in the mid-1980s: 2905 W. Hope Avenue (currently holds the RCL collection), 1101 W. St. Paul Avenue (contains the Flavors & Fragrances products), and 1001 W. St. Paul Avenue (houses administrative offices and support departments). In 1986, Aldrich added 284 acres to the Sheboygan County site, and, in the early 90s, purchased and then added to a site at 6000 N. Teutonia Avenue in Milwaukee. In the 1990s, groupings of products, that Aldrich had offered since its early days, evolved into distinct product lines with their own technical managers, e.g., chiral, nonracemic products (~2,400 listings) and monomers & polymers (~3,100 products).

7.3. The Present and the Future

7.3.1. "A Member of the Sigma-Aldrich Family"

Today, Aldrich continues to thrive within Sigma-Aldrich Corp. and has expanded into new market sectors—such as combinatorial chemistry, active high-purity metals and inorganics, and high-purity gases—and new overseas markets. In the past decade, it has also upgraded and enlarged its Milwaukee and East Coast distribution centers to enable the company to become even more responsive to its customers.

What does the future hold for Aldrich? Aldrich's future is intimately tied to that of Sigma-Aldrich. In December 2000, Sigma-Aldrich launched a new strategic plan clearly focusing the company on "leadership in Life Science and High Technology". In fact, 75% of the company's current sales are for Life Science applications, while the remaining 25% are in a variety of High Technology areas. The other key initiatives undertaken focus on service and process improvements.[53] The strategic plan made Aldrich a part of the Scientific Research business unit of Sigma-Aldrich Corp. The startup of a state-of-the-art, $25 million production plant (Pro I) near Sheboygan Falls, WI, a combinatorial chemistry product line, a wide array of active and high-purity metals, and a strong Internet presence are but a few of the ways in which Aldrich is implementing this strategy and is continuing to evolve.

Aldrich's Teutonia Avenue site.

Pro I building at Aldrich's Sheboygan County site.

Sigma-Aldrich's corporate vision is embodied in its motto: "We Are Committed to the Success of Our Customers, Employees and Shareholders through Leadership in Life Science, High Technology and Service."

7.3.2. www.sigma-aldrich.com/aldrich

Over the past five years, Sigma-Aldrich Corp. has been implementing its strategic plan for a strong, independent presence on the Internet with the goal of eventually transacting at least 50% of sales via the Internet. In 2000, corporate Internet sales represented over 10% of sales in the USA and about 5% of sales worldwide.[52] Ongoing updates and a vast array of useful information, coupled with a focus on ease of use and visual appeal, have characterized the corporation's Web site.

Aldrich has vigorously participated in this effort by making available free of charge not only its catalog/handbook and various specialty catalogs and promotional materials,

Photo courtesy of H.C. Brown

Professor Herbert C. Brown (1999).

Photo courtesy of B.J. Horick

Beverly J. Horick (2001), recently retired Aldrich employee with the most years of service (February 17, 1956 to February 28, 2001).

but also its vast store of MSDSs, CofAs, and product technical data. One of its goals for the near future is to make available, free of charge, its IR, UV, and NMR spectral libraries on its Web site.

8. The Role of Science and Scientists

This is a topic that is so dear to the "heart" of the company that it merits a separate treatment.

8.1. Scientists' Contributions

Aldrich is a science-based company. It was cofounded by a Ph.D. chemist, currently employs several dozen Ph.D. chemists and many hundreds of college-educated chemistry professionals. Most of its customers are scientists of all walks of life. Early on, Aldrich recognized the importance of scientists to the growth and health of the company: Scientists were the originators of many of the successful Aldrich products, as well as the main consumers of its products. As discussed in Section 4.2, a large portion of the company's collection of hard-to-find research samples, known as the Rare Chemical Library, comes from the laboratories of these scientists.

Aldrich has been fortunate to have had long-standing professional collaborations with many of the leading chemists of the second half of the twentieth century. These relationships proved advantageous not only to the company, but also to the community of chemists by making available reagents that are now indispensable for chemistry research: $Me_2S{\bullet}BH_3$, $NaBH_3CN$, and the family of Selectride® reducing agents, to name a few. In the early days, it was natural for Alfred Bader to turn to Louis Fieser, his Ph.D. advisor at Harvard, or Martin Ettlinger, his graduate school contemporary, for ideas on what compounds would be of interest to researchers. Subsequently, Aldrich has had significant collaborations with many other leading chemists. What follows is only a partial list (in alphabetical order):[54] E. J. Corey, Henry Gilman (deceased), Eric N. Jacobsen, Kim D. Janda, Richard Lerner, Andrew G. Myers, K. C. Nicolaou, Martin J. O'Donnell, David O'Hagan, Siegfried Pickholz (deceased), Reuben Rieke, Ian P. Rothwell, I. Herbert Scheinberg, Barry K. Sharpless, John C. Sheehan (deceased), Gilbert Stork, and Robert B. Woodward (deceased).

Perhaps more than any other factor, it was the development of ideas and technologies, invented by researchers and developed or commercialized by Aldrich, that propelled Aldrich (and later Sigma-Aldrich) to the prominent position that it is presently in. It is unquestionably the vigorous pursuit of these contacts and collaborations that will keep Sigma-Aldrich a leading technology company.

8.2. Herbert C. Brown

Aside from Alfred Bader, perhaps no other single chemist has had a greater impact on the success of Aldrich than Professor Herbert C. Brown of Purdue University. A Nobel laureate and a towering figure in chemistry, Brown not only was the catalyst and a driving force for Aldrich–Boranes, Inc., as explained in Section 6.1, but he also served on the Aldrich Board of Directors (1972–1975) and the Sigma–Aldrich Board of Directors (1975–1979). In recognition of his lasting contributions, Aldrich not only pays royalties to the Purdue Research Foundation, but also co-sponsors the *Herbert C. Brown Award for Creative Research in Synthetic Methods* that is administered by the American Chemical Society.

8.3. Rewarding Excellence

Aldrich has also had a tradition of rewarding excellence in chemistry research by sponsoring or co-sponsoring prestigious professional awards, symposia, and student fellowships. A few examples come to mind: *ACS Award for Creative Work in Synthetic Organic Chemistry*, *ACS Award in Inorganic Chemistry*, *Herbert C. Brown Award for Creative Research in Synthetic Methods*, Project SEED, 32nd Organosilicon Symposium (Milwaukee, 1999), Asymmetric Synthesis Symposium (Milwaukee, 1998), Boron–USA meetings, and various Gordon Conferences. Moreover, Alfred Bader, Aldrich's cofounder, personally sponsors the *Alfred Bader Award in Bioinorganic or Bioorganic Chemistry*, and has helped over the years many deserving academic chemists by underwriting some of their research.[2]

9. Valued Customers, Dedicated Employees

Aldrich recognized very early on the importance of establishing strong relationships with its customers, and the necessity to provide them with valuable information related to the products that they were purchasing. Thus, it was no surprise that the Aldrich catalog was transformed from a listing of available products and prices to a "handbook" containing a wealth of information, which has made it an indispensable desk reference in many academic and industrial laboratories and libraries. Chemists active in research were not only customers, but also partners in the chemical enterprise, who were also invited to share their insights with others through such widely circulated and *free* Aldrich publications as the *Aldrichimica Acta* (which has been in existence for 34 years). It is also no secret that ideas for new products often

Table 2. Present and Former Aldrich Employees with 25 or More Years of Continuous Service [a,b]

Adler, Wayne J.	Gorzek, Robert J.	Leitner, Lorraine	Rochwerger, Leonard L.
Ahmed, Waheeduddin	Griesinger, Alfred	Lenga, Robert E.	Roper, Mattie D.
Bader, Alfred R.	Griffiths, David W.	Lent, Mary A.	Saladin, Barbara L.
Benson, Christine F.	Gunther, Patricia A.	Lewis, Robert J.	Schreiber, Peter L.
Borenstein, Mark	Harvey, David R.	Lisztwan, Emilia M.	Settingsgaard, Jacqueline L.
Bourgeois, Shirley R.	Helmin, William T.	Malone, Rosie L.	Shortridge, Nelgene
Branski, Robert A.	Holm, Phillip L.	Mehta, Milan N.	Shuder, Diane L.
Brien, Diana M.	Horick, Beverly J.	Metz, Marian E.	Siegel, Brian S.
Brien, James J.	Jenkins, Dolores H.	Mititch, Jacqueline	Skeff, George
Bruesewitz, Richard J.	Kasprzak, Russell J.	Nagarkatti, Jai P.	Smith, Andrew P.
Creighton, Anthony J.	Kett, Jeffrey A.	Napiorkowski, Anna M.	Smith, Robert W.
Daniels, John J.	Koppel, Henry C.	Podd, Rodney L.	Stanton, Genevieve L.
Edelstein, Sara	Kopperud, Cynthia A.	Poth, Donna L.	Wallace, Kenneth J.
Farrell, Richard T.	Korthoff, Kristine L.	Pouchert, Charles J.	Ward, Stella L.
Feustel, Barbara L.	Kratzer, Phyllis C.	Pruss, Judith R.	Weber, Roger O.
Fox, Lyle G.	Kreinus, Timothy M.	Pykett, Jonathan R.	Wells, Sheila E.
Freeman, Roland P.	Kurzynski, Alice J.	Rebarchik, Joseph A.	Wickersham, Thomas W.
Gallaspy, Barbara A.	Lane, Clinton F.	Riedmaier, John E.	Wondra, Carl T.

[a] As of June 2001. [b] Admittedly, length of service is an imperfect measure of an employee's contribution to the company; however, this author was at a loss to come up with a fair, objective way of recognizing those employees who have given so much to the company, but may not be mentioned in the text. I offer my apologies to those employees, whose names belong in the table, but were inadvertently left out.

came from customers. To appreciate this fact more fully, it is sufficient to consult the "Please Bother Us." section of any recent *Aldrichimica Acta* issue.

Aldrich's phenomenal success is a tribute to the vision and determination of its cofounder, Dr. Alfred R. Bader, and the dedication and hard work of thousands of former and present employees. **Table 2** is only a modest attempt at acknowledging their contributions.

10. Acknowledgments

In addition to the sources cited, I wish to acknowledge the specific assistance of (in alphabetical order): (i) Bettie Aldrich Eisendrath, Gerd Backes, Alfred Bader, Jim Brien, Tom Gandia, David Harvey, Don Hobbs, Harvey Hopps, Beverly Horick, Peter Hyland, Linda Kehren, Clinton Lane, Lorraine Leitner, Edward Niemiec, Judith Pruss, Robert Smith, Joan Suda, Robert Wandler, Tom Wickersham, and LaShannon Wilson, who provided me with valuable information and recollections either via personal communications or via source materials that they supplied to me; (ii) Brian Case, Robert Gorzek, David Harvey, Chris Hewitt, Harvey Hopps, Peter Hyland, Anthony J. La Loggia, Clinton Lane, Jai Nagarkatti, and Craig Recatto, who proofread the manuscript or sections thereof, and offered helpful comments; (iii) Jennifer L. Botic, who laid out the manuscript and this issue of the *Acta*, and who assisted me in locating some of the photographs used; and (iv) Rebecca Zelenka, who helped with contacting former Aldrich employees. Finally, I would like to thank my wife for her patience and understanding while I was preparing the manuscript.

11. References and Notes

(1) This brief tour of the past fifty years cannot possibly do justice to the topic. For more details and anecdotes, the interested reader is directed to the very readable book by one of the founders of Aldrich: Bader, A. *Adventures of a Chemist Collector*; Weidenfeld and Nicolson: London, U.K., 1995.

(2) Cori, T.; Emanuel, R. N.; Harvey, D.; Klitsner, M. E. *Aldrichimica Acta* **1984**, *17*, 3.

(3) (a) Bader, Alfred. The Building of Aldrich. My Advice to Entrepreneurs. *The Chemist,* November/December 1997, pp 1–5. (b) Buchan, P. Bruce. Three Boards and "A Bet Against the Company". *The Chemical Intelligencer,* October 1996, pp 24–29 and 41. (c) Edward, J. T. *Can. Chem. News* **1992**, *44*(6), 23. (d) Bohning, James J. Crystallizing Hamburger: Alfred Bader and the Aldrich Chemical Company, Part I. *Beckman Center News,* Spring 1991, pp 1 and 8–9. (e) Bohning, James J. Crystallizing Hamburger: Alfred Bader and the Aldrich Chemical Company, Part II. *Beckman Center News,* Fall 1991, pp 3–4. (f) Bader, A. R. *CHEMTECH* **1990** (March), 138. (g) A Chemical Company in Your Garage. An Interview with Dr. Alfred Bader. *The DEL–CHEM BULLETIN,* May 1974, pp 5–10.

(4) While it is unquestionably the contributions of a great many dedicated employees that have made Aldrich what it is today, it is not possible in such a short overview to mention them all. The author regrets any inadvertent or necessary omissions.

(5) Reference 1, pp 70, 101, and 185.

(6) (a) The 500 shares of stock issued were owned 50% by Alfred R. Bader and 50% by Jack N., Frank N., and Bettie Mae Eisendrath. Professor A. F. McKay of the University of Toronto, Canada, owned only one share of stock: Bader, A. R. Alfred Bader Fine Arts, Milwaukee, WI. Personal communication, April 09, 2001. (b) Prior to cofounding Aldrich, Jack Eisendrath had attempted to start and run a number of mail order/catalog businesses (e.g., selling moccasins): Eisendrath, B. A. Washington, DC. Personal communication, April 03, 2001.

(7) (a) Reference 1, p 70. (b) Up until the Eisendraths sold their 50% stake in the company, Bettie acted as the company's (unpaid) secretary. As of the writing of this review, Bettie was still a remarkably energetic and socially active octogenarian living in Washington, DC.

(8) (a) Leitner, L. (née Neau; retired) Aldrich Chemical Co., Inc., Milwaukee, WI. Personal communication, March 16, 2001. (b) Horick, B. J. (retired) Aldrich Chemical Co., Inc., Milwaukee, WI. Personal communication, February 01, 2001.

(9) (a) McKay, A. F.; Wright, G. F. *J. Am. Chem. Soc.* **1947**, *69*, 3028. (b) McKay, A. F. *J. Am. Chem. Soc*. **1948**, *70*, 1974. (c) McKay, A. F.; Ott, W. L.; Taylor, G. W.; Buchanan, M. N.; Crooker, J. F. *Can. J. Res., Sec. B* **1950**, *28*, 683.

(10) Aldrich Chemical Co., Inc. *Diazald®, MNNG, and Diazomethane Generators*. Aldrich Technical Information Bulletin No. AL-180; Milwaukee, WI, 1993.
(11) Reference 1, pp 71–72.
(12) Bader, A. R. Alfred Bader Fine Arts, Milwaukee, WI. Personal communication, March 19, 2001.
(13) While at PPG, Anthony co-authored a paper with Alfred Bader on the easy preparation of phenyl esters of carboxylic acids by heating the acid and phenol in the presence of PPA: Bader, A. R.; Kontowicz, A. D. *J. Am. Chem. Soc.* **1953**, *75*, 5416.
(14) Reference 1, p 74.
(15) Jack Eisendrath continued his practice of general, family, and consumer law in Milwaukee for about 40 years. He died on November 06, 1997 at the age of 85: Knoche, Eldon. Consumers Had Advocate in Attorney Eisendrath. *The Milwaukee Journal Sentinel* [Online], November 9, 1997, main page (www.jsonline.com).
(16) For a glimpse of Eisendrath's perspective of these events, see: (a) Lank, Avrum D. Chemist Mixes Knowledge, Savvy. *The Milwaukee Sentinel*, October 01, 1985, Part 4, pp 1–2. (b) Gillespie, Scott. Alfred Bader's Diverse Talents Led Firm to International Role. *The Business Journal Special Report* (Milwaukee), Week of September 22, 1986, p 9.
(17) Bader, A. R. Alfred Bader Fine Arts, Milwaukee, WI. Personal communication, March 09 and April 09, 2001.
(18) Kenney, Ray. Aldrich Firing Up All Burners. *The Milwaukee Sentinel*, September 02, 1974, Part 2, p 9.
(19) Reference 1, p 77.
(20) Bader, A. R. Alfred Bader Fine Arts, Milwaukee, WI. Personal communication, March 23, 2001.
(21) Helen Bader (née Daniels) worked for Aldrich in various capacities on and off for over twenty years, whenever her family obligations permitted her to. In addition to being one of the owners of Aldrich, she was also a company director and treasurer for several years and the third company president for a very short period of time (1964). Following her death in 1989, her family established the Helen Bader Foundation, Inc. to honor her memory and continue the charitable work that she had started. The interested reader can find out more by accessing the Foundation's Web site at *www.hbf.org*.
(22) Reference 1, pp 80–81.
(23) Horick, Beverly J. Then & Now. *The Aldrich Reporter*, January 2001, p 10. When Beverly J. Horick retired from Aldrich on February 28, 2001 (after a little over 45 years of continuous service!) she set a record as the employee with the longest service to the company.
(24) Hopps, H. B. Amarillo College, Amarillo, TX. Personal communication, February 21, 2001.
(25) (a) Aldrich Chemical Co., Inc. The Aldrich Annual Report; Milwaukee, WI, September 03, 1969. (b) Aldrich Chemical Co., Inc. Annual Report; Milwaukee, WI, September 30, 1970.
(26) Reference 1, p 98.
(27) Aldrich Chemical Co., Inc. Prospectus; Milwaukee, WI, December 30, 1965; p 2.
(28) Reference 1, p 79.
(29) EGA from the names **E**rnst, **G**erhard, and **Al**fred.
(30) Aldrich Chemical Co., Inc. Annual Report 1971; Milwaukee, WI, March 24, 1972.
(31) (a) Mack, H. Sigma-Aldrich Chemie GmbH, Steinheim, Germany. Personal communication, March 06, 2001. (b) Backes, G. Sigma-Aldrich Chemie GmbH, Steinheim, Germany. Personal communication, March 09, 2001.
(32) Koppel, H. *Aldrichimica Acta* **1968**, *1*, 3.
(33) Reference 1, p 88.
(34) Medical Economics Company, Inc. *Physicians' Desk Reference*, 52nd ed.; Montvale, NJ, 1998; pp 2082–2086.
(35) The statements in this paragraph should not be construed to imply that COGNEX® is formulated with a material obtained from Aldrich. Aldrich brand products are sold mainly for research or industrial applications and are not intended for drug or household use, unless specifically designated for that purpose.
(36) Reference 1, pp 82–83.
(37) Aldrich Chemical Co., Inc. *Aldrichimica Acta* (Preview Issue); Milwaukee, WI, Fall 1967.
(38) Reference 1, p 133.
(39) Lane, Clinton F. Greetings from the Future Leaders in Organoborane Chemicals! *Aldrich-Boranes, Inc. Newsletter*, February 1973, p 2.
(40) For some examples, see: (a) Lane, C. F. *Aldrichimica Acta* **1973**, *6*, 21. (b) Lane, C. F. *Aldrichimica Acta* **1973**, *6*, 51. (c) Lane, C. F. *Aldrichimica Acta* **1974**, *7*, 7. (d) Lane, C. F. *Aldrichimica Acta* **1974**, *7*, 32. (e) Lane, C. F. *Synthesis* **1975**, 135. (f) Lane, C. F. *Aldrichimica Acta* **1975**, *8*, 3. (g) Lane, C. F. *Aldrichimica Acta* **1975**, *8*, 20. (h) Lane, C. F.; Kabalka, G. W. *Tetrahedron* **1976**, *32*, 981. (i) Lane, C. F. *Chem. Rev.* **1976**, *76*, 773. (j) Lane, C. F. *Aldrichimica Acta* **1976**, *9*, 31. (k) Lane, C. F.; Kramer, G. W. *Aldrichimica Acta* **1977**, *10*, 11. (l) Brown, H. C.; Lane, C. F. *Heterocycles* **1977**, *7*, 453. (m) Lane, C. F. *Aldrichimica Acta* **1977**, *10*, 41.
(41) Aldrich Chemical Co., Inc. *Welcome to Aldrich Sheboygan Site*. Aldrich Informational Bulletin; Sheboygan Falls, WI, 1999.
(42) Aldrich Chemical Co., Inc. The Aldrich Semimonthly Newsletter (Extra); Milwaukee, WI, April 25, 1974.
(43) (a) Aldrich Chemical Co., Inc. Annual Report 1973; Milwaukee, WI, February 15, 1974. (b) Reference 1, p 167.
(44) Aldrich Chemical Co., Inc. Annual Report 1974; Milwaukee, WI, February 21, 1975.
(45) Green, F. J. *The Sigma-Aldrich Handbook of Stains, Dyes and Indicators*; Aldrich Chemical Co., Inc.: Milwaukee, WI, 1990.
(46) Has since been replaced by the third edition, cat. no. Z10,750-6: Pouchert, C. J. *The Aldrich Library of Infrared Spectra*, 3rd ed.; Aldrich Chemical Co., Inc.: Milwaukee, WI, 1981.
(47) Brien, J. J. Aldrich Chemical Co., Inc., Milwaukee, WI. Personal communication, March 08, 2001.
(48) Damrow, D. (retired) Aldrich Chemical Co., Inc., Milwaukee, WI. Personal communication, February 22, 2001.
(49) For the record, Aldrich has had the following presidents in the following order: Jack Eisendrath, Alfred Bader, Helen Bader, Alfred Bader, David Harvey, Jai Nagarkatti, and Clinton Lane.
(50) Suda, Joan. *The Sigma-Aldrich Story. Overview of a Multinational Family of Companies*. Sigma-Aldrich Bulletin; Sigma-Aldrich Corp.: St. Louis, MO, 2001.
(51) Sigma-Aldrich Corp. *Sigma-Aldrich Acquires Isotec to Enhance Life Science Capabilities*. Press Release; St. Louis, MO, February 16, 2001.
(52) Suda, Joan. *An Interview with David R. Harvey*. Sigma-Aldrich Bulletin; Sigma-Aldrich Corp.: St. Louis, MO, January 2001; p 1.
(53) Harvey, D. R. Sigma-Aldrich Corp., St. Louis, MO. Personal communication, May 05, 2001.
(54) Many more scientists have had fruitful collaborations or a significant impact on the growth of Aldrich. The author regrets not being able to acknowledge all of them.

Monsanto Company: Roundup®; **Riedel-deHaën GmbH**: Riedel-deHaën®; **Rieke Metals**: Rieke®; **Sigma-Aldrich Co.**: AAPL™, ALDRICH®, Diazald®, FLUKA®, Selectride®, SIGMA®; **Warner-Lambert Co**.: COGNEX®.

Happy 50th Anniversary Aldrich!

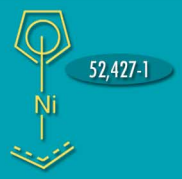
About the Author

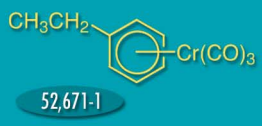
Sharbil J. Firsan was born and raised in Lebanon. He completed his undergraduate studies at the American University of Beirut and his graduate work on acyclic imidate and thioimidate *N*-oxides with Professor Robert M. Coates at the University of Illinois in Urbana-Champaign (Ph.D., 1986). He did postdoctoral work at the University of Oregon in Eugene, OR, and then moved to Oklahoma State University in Stillwater, OK, to become a Research Associate and then a Visiting Assistant Professor. In 1996, he joined Aldrich Chemical Co., Milwaukee, WI, as a Promotions and Publications Specialist. He is currently a Senior Promotions and Publications Specialist and Editor of the *Aldrichimica Acta*. With his wife, Leah (Leila), Sharbil enjoys outdoor activities, gardening, and travel.

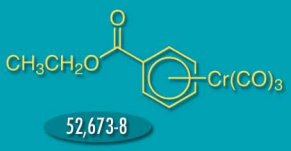
THE OLD AND THE NEW

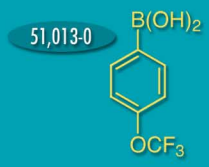
Dr. Firsan's review of the past fifty years of Aldrich's history identified a number of products as having had a historical significance for the company; for example, diazomethane precursors, organoboranes, phenols, dyes, and ultrahigh-purity inorganics. Aldrich still sells these and has expanded its list of products to about 40,000. Fifty years have passed and Aldrich has changed in many ways, but our unwavering commitment to serve you, our customer, has not changed! One way we demonstrate this commitment is by continuously introducing new products and reagents to save you money and to free up your valuable research time. The list below is only a small sample of some recently introduced products.

NEW ORGANOMETALLICS



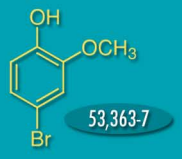


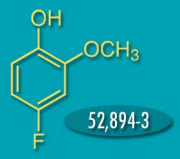


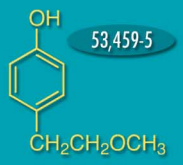


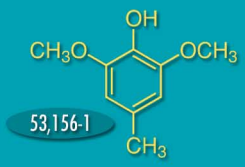
52,427-1 **Allyl(cyclopentadienyl)nickel**, 97%
52,671-1 **(Ethylbenzene)tricarbonylchromium**
52,673-8 **(Ethyl benzoate)tricarbonylchromium**, 96%
51,013-0 **4-(Trifluoromethoxy)phenylboronic acid**

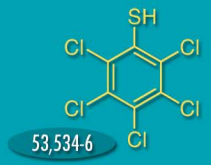
NEW PHENOLS











53,363-7 **4-Bromo-2-methoxyphenol**, 98%
52,894-3 **4-Fluoro-2-methoxyphenol**, 97%
53,459-5 **4-(2-Methoxyethyl)phenol**, 97%
53,156-1 **4-Methyl-2,6-dimethoxyphenol**, 97%
53,534-6 **Pentachlorothiophenol**, 96%

NEW HIGH-PURITY INORGANICS

51,065-3 **Copper(I) sulfide**, anhydrous, powder, 99.99%
51,438-1 **Titanium(III) chloride**, 99.999%

As in the past, suggestions for new products are always welcome. If you have questions about any of our products, or would like to suggest new ones, please call our Technical Services department at **800-231-8327 (USA)**. If you would like to place an order, please contact our Customer Services department at **800-558-9160 (USA)**. International customers, please contact your local Sigma-Aldrich office or visit our website at **www.sigma-aldrich.com**.

*Larger quantities are available through **Sigma-Aldrich Fine Chemicals**. Please call **800-336-9719** or **314-534-4900 (USA)**, your local office or visit us on the web at **www.sigma-aldrich.com/safc** for competitive quotes and availability.*

Sigma-Aldrich is pleased to announce the winners of the Young Chemist in Industry awards, presented on May 8, 2001, at the 10th Young Chemists Meeting in London

This annual, one-day meeting 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. This year's gathering was attended by over 80 young scientists and featured 10 presentations by participants and an invited lecture by Dr. Simon Campbell of Pfizer Inc.

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 symposium.

Nick Devereux of Novartis (left) and Gordon Shearer of Glaxo Wellcome (right). Simon Goodacre was unavailable at the time this photo was taken.

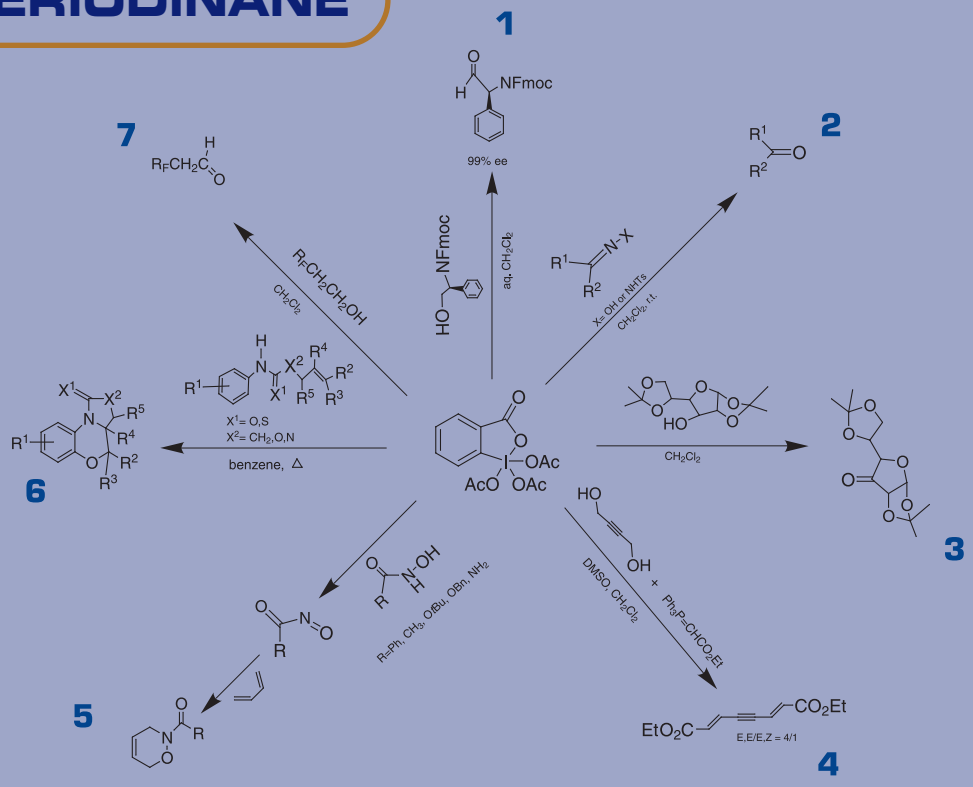
First Prize: **Gordon Shearer**, Glaxo Wellcome
Application of On-Line Mid-IR Spectroscopy to Process Development

Runner-Up: **Nick Devereux**, Novartis
C-8 Aryl Xanthines, Novel Potent PDE5 Inhibitors

Runner-Up: **Simon Goodacre**, Merck Sharp & Dohme
Neighbouring Group Participation of the Indole Nucleus—An Unusual DAST-Mediated Rearrangement Reaction

DESS-MARTIN PERIODINANE

Dess–Martin periodinane is widely used for the mild oxidation of alcohols to aldehydes and ketones.[1] This reagent is especially useful for substrates containing sensitive functional groups and offers an alternative to other mild reagents (e.g., TPAP*). Other advantages such as selectivity, rapid rates, avoiding the use of toxic (e.g. chromium–based) chemicals, using stoichiometric amounts of reagent, and ease of workup, make the Dess–Martin periodinane a reliable and easy-to-use oxidant in organic synthesis.



1. Useful in the preparation of epimerization-sensitive, optically active, N-protected α-amino aldehydes with high enantiomeric excess.[2]
2. Oximes and tosylhydrazones are converted into the corresponding carbonyl compounds without overoxidation of the product.[3]
3. Oxidation of sugar hydroxyls in good yields with periodinane avoids the use of ruthenium dioxide.[4]
4. A highly unstable dialdehyde was prepared by oxidation with periodinane and trapped in situ with a preformed Wittig ylide.[5]
5. A convenient route to the preparation of highly reactive acyl nitroso compounds. These products can be trapped by dienes to form cycloadducts.[6]
6. Rapid production of complex and diverse natural product-like polycycles. A proposed mechanism starts with an ortho oxidation followed by an intramolecular hetero-Diels–Alder reaction.[7]
7. Neutral and mild workup conditions avoid the formation of dehydrofluorinated by-products in the oxidation of polyfluorinated primary alcohols to aldehydes.[8]

27,462-3 **Dess–Martin periodinane**, 97%
(1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one)

Additional Hypervalent Iodine Reagents

23,213-0 **[Bis(trifluoroacetoxy)iodo]benzene**, 97%
30,103-5 **Hydroxy(tosyloxy)iodobenzene**, 96%
17,872-1 **Iodobenzene diacetate**, 98%

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References: (1) Dess, D.B; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (2) Myers, A.G. et al. *Tetrahedron Lett.* **2000**, *41*, 1359. (3) Bose, D.S.; Narsaiah, A.V. *Synth. Commun.* **1999**, *29*, 937. (4) Rao, H.S.P. et al. *Indian J. Chem., Sect. B* **1997**, *36B*, 816. (5) Barrett, A.G.M. et al. *J. Org. Chem.* **1997**, *62*, 9376. (6) Jenkins, N.E. et al. *Synth. Commun.* **2000**, *30*, 947. (7) Nicolaou, K.C. et al. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 622. (8) Lévêque, L. et al. *Tetrahedron Lett.* **1998**, *39*, 8857.

***TPAP= Tetrapropylammonium perruthenate,** 97% **(Aldrich catalog number 33,074-4).**

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Activated 2*H*-Azirines as Dienophiles and Electrophiles

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Liverpool L69 7ZD, United Kingdom
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Outline

Introduction

Many derivatives of the unsaturated nitrogen heterocycle 2*H*-azirine (**1**) have been synthesized.[1] The ring system also occurs naturally. Both enantiomers of dysidazirine (**2**) have been found as constituents of marine sponges,[2] and an antibiotic, azirinomycin (**3**), has been isolated from *Streptomyces aureus* cultures.[3] The biosynthetic origin of these compounds is unknown. Asymmetric syntheses of dysidazirine[4] and of *ent*-azirinomycin methyl ester[5] have been reported. 2*H*-Azirines behave as strained imines, and much of their chemistry was discovered as a result of extensive investigations during the 1960s and 1970s.[1] A special class of 2*H*-azirines, the 3-amino derivatives, are cyclic amidines. Largely as a result of the investigations of Heimgartner and his coworkers, these aminoazirines have been shown to be very useful substrates for the synthesis of unnatural amino acids, peptides, and other nitrogen heterocycles.[6] An example of peptide synthesis using a prolinylazirine, **4**, is shown in **eq 1**.[7]

The impetus for our recent investigations of 2*H*-azirine chemistry was a search for imines that could participate readily in Diels–Alder reactions. Imines are usually rather poor dienophiles unless they are substituted by one, or preferably two, electron-withdrawing groups, or are activated by the presence of acid or Lewis acid catalysts.[8] With nucleophilic dienes such as Danishefsky's diene as reaction partners, activated imines undergo highly selective Diels–Alder reactions in the presence of chiral catalysts (**eq 2**).[9] 2*H*-Azirines are inherently more reactive than acyclic imines as a consequence of ring strain, and there are several literature examples of 2*H*-azirines participating in Diels–Alder reactions with highly reactive dienes such as tetraphenylcyclopentadienone and 1,3-diphenylisobenzofuran.[10] Recorded attempts to achieve reaction with simpler dienes such as cyclopentadiene were unsuccessful. Cycloaddition reactions of azirines **5** with cyclopentadiene (**eq 3**) were the only exception.[11] The reactions were reported to take place exothermically at room temperature to give single products of unspecified stereochemistry; this observation formed the starting point for our own investigations.

2. Activated Azirines as Dienophiles

Undoubtedly, the structural feature that distinguishes azirines **5** from others, that had been used as partners in Diels–Alder reactions, is the aroyl group. This group provides additional activation of the C=N bond. We found that there were about 40 such 2*H*-azirines in the literature with a conjugating, activating substituent at C-3. Most of these compounds are esters, the majority of which bear an additional aryl substituent at C-2. These azirine esters are synthesized by the thermolysis of α-azidocinnamic esters.[12] However, under more vigorous thermal conditions, the azidocinnamic esters are converted into indole-2-carboxylic esters (the Hemetsberger indole synthesis) (**Scheme 1**).[13] The corresponding 2*H*-azirines are probably intermediates in this conversion. There are also a few other types of activated azirines in the literature. Besides compounds **5**, a number of other 3-acylazirines have been reported, but their reactivity as dienophiles has not been investigated.[14] A chiral azirinyl-3-phosphonate has been isolated from the Swern oxidation of aziridine **6** (**eq 4**).[15]

Two of the known azirine-3-carboxylic esters, **8a** and **8b**, were selected for the initial

study. These were found to react smoothly with cyclopentadiene, 1,3-cyclohexadiene, or 2,3-dimethylbutadiene at room temperature.[16] The reactions gave products that were single stereoisomers in each case (**Scheme 2**). The products are consistent with a cycloaddition transition state in which the three-membered ring is endo to the diene. The reaction was then investigated with a range of other simple dienes.[17] The more stable crystalline azirine, **8c**, was used in many of these reactions. Again, the reactions were highly stereoselective and, with unsymmetrical dienes, completely regioselective. The structure of aziridine **9**, formed from **8b** and 1-acetoxybutadiene, was determined by X-ray crystallography. This structure is consistent with endo addition with respect to the three-membered ring and with the regiochemistry expected from bonding of the more nucleophilic terminus of the diene to the electrophilic carbon of the azirine (**Scheme 3**). The Diels–Alder adducts are isolable by column chromatography, and are resistant to hydrolytic ring cleavage.

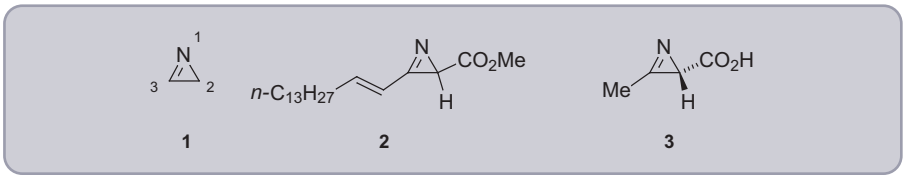
An interesting exception is the reaction of azirine **8c** with furan (**Scheme 4**). A crystalline adduct, **10**, was isolated in quantitative yield after several days at room temperature. The structure of **10** was later

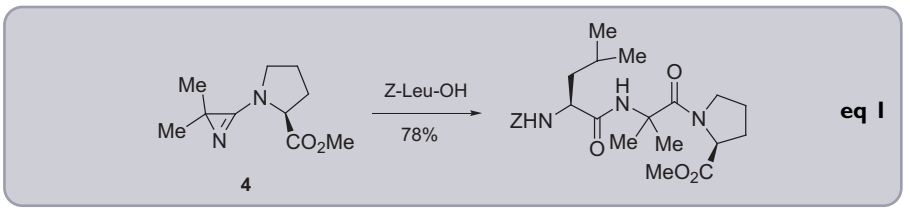
confirmed by an X-ray crystal determination, which clearly showed that the product has the opposite stereochemistry of that observed in adducts of all the other dienes; here, the 3-membered ring system is exo to the diene! Although furan is a very commonly used diene, the literature contains very few examples of cycloadducts formed from reactions of furan with heterodienophiles, and some of these cycloadducts are unstable.[18] For example, reaction of furan with diethyl azodicarboxylate leads to the formation of an unstable adduct that has never been fully characterized.[19] The furan adduct, **10**, similarly proved to be very susceptible to hydrolysis. Its crystal structure shows that the nitrogen lone pair is antiperiplanar to the bridging C–O bond; this structural feature is probably the reason for the instability of this and of other adducts formed from heterodienophiles.

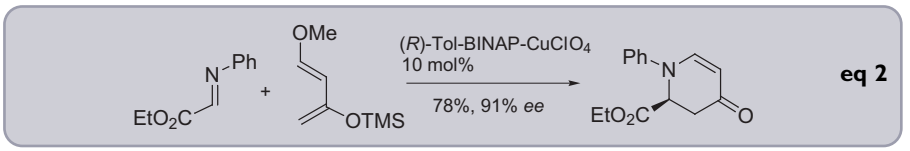
Explanations for the stereochemical outcomes of these reactions are only speculative. It is known that cyclopropenes (which are also good dienophiles due to ring strain) show a similar preference for endo addition with many dienes, and theoretical calculations have been carried out to determine the reasons for this preference.[20] Calculations also indicate that there is a preference for exo orientation of nitrogen lone pairs in Diels–Alder reactions of imines.[21] Furan is known to show a greater tendency to form exo cycloadducts in the Diels–Alder reaction than other common dienes, and, in such cases, the products often result from thermodynamic control.

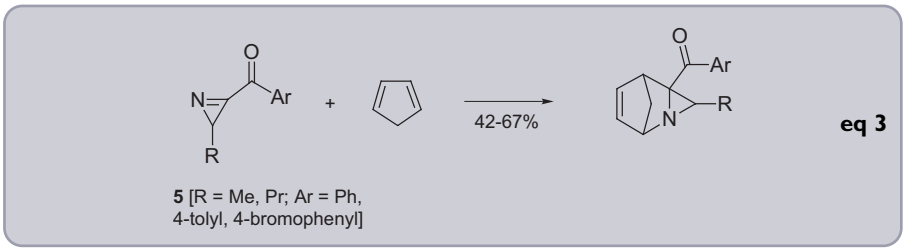
The dense functionality in these adducts and the potential for further reactions (for example, as precursors to unnatural amino acids) led us to extend the reaction to other, simpler azirines. There were no known azirine-3-carboxylic esters that were unsubstituted at C-2, but we found that they could be formed from readily available acrylate esters by way of the α-azido esters (**Scheme 5**). The *tert*-butyl ester, **11a**,[22] and the benzyl ester, **11b**,[23] have been prepared in this way. Ester **11a** is too unstable to allow its isolation and must be used in solution; benzyl ester **11b** can be isolated and stored below 0 °C for short periods of time. These azirines react with a range of nucleophilic dienes at room temperature in exactly the same way as their aryl-substituted counterparts, **8**. Some examples of the diene addition products that have been characterized are shown in **Figure 1** (yields have not been optimized). The adduct formed from **11a** and Danishefsky's diene rearranges on silica to dihydroazepinone **12** (**eq 5**). Furan and 2-methylfuran both react readily with azirine **11b** and, again, they give exclusively the exo cycloadducts that are analogous to compound **10**. These compounds are also very susceptible to acid-catalyzed cleavage of the oxygen bridge.[24] Along with the expected diols, dihydrofuranol **13** has been characterized as a major component of the mixture produced by hydrolysis of the Diels–Alder adduct from furan (**Scheme 6**).

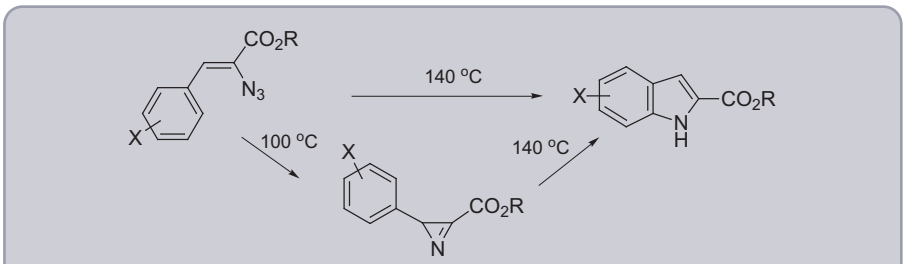
Asymmetric versions of these cycloaddition reactions are in principle achievable by incorporating a chiral auxiliary into either the azirine or the diene, or by asymmetric catalysis. A cycloaddition of ester **11a** to chiral diene **14** was highly regio- and diastereoselective: only one product, **15**, resulting from endo addition to the less hindered face of the diene, was detected (**eq 6**).[22] A chiral azirine ester, **16**, was also generated, but its cycloaddition reaction with cyclopentadiene showed poor diastereoselectivity.[25] Obviously, the chiral auxiliary is too far away from the reaction center and the free rotation of the ring precludes any good stereoselectivity. Azirine-3-carboxamides **17** have been synthesized in the same way as the



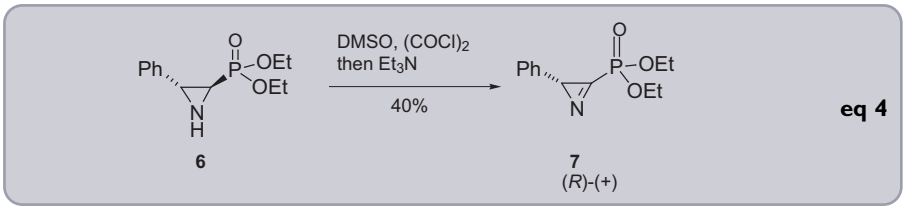








Scheme 1. The Hemetsberger Indole Synthesis.



Sigma Aldrich Laboratory Equipment

❖Summer 2001❖

Aldrich Kugelrohr
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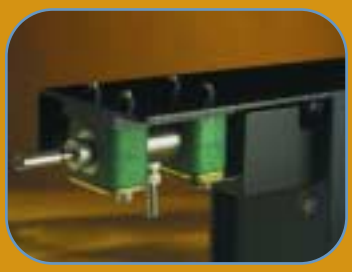
Kugelrohr apparatus shown with KNF Laboport vacuum pump.

"Distills the Most Difficult Materials"

Step 1

Oven flask is filled one-third full with distillable material, placed carefully in oven, and connected to the horizontal receiving flasks outside the oven.

Step 2



Connect the glassware to the rotary drive and the drive to a vacuum pump.* Switch the vacuum drive on to turn the distillation train 360° to speed distillation, ensure even heating, and prevent bumping. Start the vacuum pump.

*Use of a vacuum trap between the rotary drive and the pump is recommended to protect the pump. See the Equipment Section of the 2000-2001 Aldrich Handbook for vacuum traps.

Step 3

When the correct vacuum is attained, set the distillation temperature on the air-bath oven and begin distillation. The digital temperature controller displays both "set" and "actual" air-bath temperature.

Step 4

Collect distillate in the horizontal ball-tubes outside of oven. An ice-filled polypropylene cooling tray quickly condenses distillate in receiving ball-tubes.

Specifications

Micro to macro distillation capability

- Accommodates flask sizes 10mL to 1L

Air-bath oven

- SS wall with leakproof seal at the base contains spills
- Grounded heating element prevents electrical shock
- Detachable power cord, on/off switch, adjustable rubber feet, and interchangeable PTFE bearing set for flasks with ₹14/40 and ₹24/40 joints

Distill under vacuum to 0.05mm Hg

- Single-speed rotary drive is optimized for Kugelrohr distillations
- Detachable power cord, on/off switch, adjustable rubber feet, built-in stabilizing clamp

Automatic temperature controller

- Maintains oven temperature up to 220°C, ±1°C
- Type-K thermocouple ensures fast, accurate temperature measurements inside of oven
- Automatically turns off power to oven if thermocouple fails or disconnects

CE Compliant

Kugelrohr Short-Path Distillation Apparatus

Includes the following components:

air-bath oven with digital temperature controller, glassware set consisting of a straight tube with hose connection, 25 and 100mL round-bottom oven flasks, 25 and 100mL single bulb ball-tube flasks with ₹14/20 joints, and rotary drive.

Volts	Cat. No.
115	**Z40,113-7**
230	**Z40,114-5**

Please see the Equipment Section of the 2000-2001 Aldrich Handbook for a complete listing of Kugelrohr accessory glassware and parts.

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CAUTION: Never operate dry. Be certain that heat exchange medium is in bath before applying current.

Use with Ace multiple output (20, 40, 120V AC) proportional temperature controllers (see below) to get precise, accurate, and safe heating since the output voltage is automatically limited. Single output (120V AC) controllers may be used to manually control temperature, but care must be taken not to exceed the maximum voltage rating of the individual bath.

Low form oil baths

Diam. x H (mm)	Cap. (mL)	Volt/Amp	Cat. No.
70 x 50	160	20/5	**Z25,932-2**
100 x 50	340	40/6	**Z25,933-0**
125 x 65	700	40/8	**Z25,934-9**
150 x 75	1,200	120/5	**Z25,935-7**
190 x 100	2,600	120/10	**Z25,936-5**

High form oil baths

Diam. x H (mm)	Max. flask size (mL)	Volt/Amp	Cat. No.
100 x 100	300	40/10	**Z25,937-3**
150 x 150	1,000	120/8	**Z25,938-1**
190 x 180	3,000	120/10	**Z25,940-3**

Replacement connecting cord for all Instatherm oil baths

Z25,941-1

Silicone bath oil

Stable. Temp. range: -40 to 350°F (-40 to 175°C). May also be used for melting point and boiling point apparatus.

14,615-3

Ace temperature controllers

Time proportional; analog set. Dial in desired temperature. Controllers include an RTD sensor [318 L x 6mm (¼ in.) o.d.]. Units measure 15.9 H x 14 W x 20.1cm D (6¼ x 5½ x 7 29/32 in.).

Multiple output controller

20-, 40-, 120V AC. Recommended for use with Instatherm oil baths and other heating equipment. Wt: 5.9kg (14lb).

Z25,943-8

Single output controller

120V AC. Wt: 1.8kg (5lb). **Z25,944-6**

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Specifications:

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Temp. accuracy: ± 5°C (in center of oven at 300°C)
Warm-up time: from 20 to 300°C in approx. 10 min
CE compliant

Suitable for drying 100 to 250mL sample volumes, under inert gas or vacuum if required. Drying tube assembly consists of tube which enters oven and end cap fitted with stopcock with vacuum and atmosphere/inert gas connections. Sample is placed in drying tube, which attaches to end cap with vacuum-tight flange. End cap is designed to hold desiccant to absorb water driven off by heat. Oven may also be used for sublimation using optional sublimation insert.

Volts	Cat. No.
115	**Z40,765-8**
230	**Z31,915-5**
Sublimination Insert for drying tube	**Z31,926-0**

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Volts	Cat. No.
100-120	**Z25,198-4**
210-240	**Z25,199-2**

CHEM-DRY drying-tube assemblies

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Z22,271-2

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Provides precise melting points up to 500°C on one to three samples. Insert charged capillaries and adjust the heating rate. When the sample melts, record the temperature.

Use with glass mercury thermometers (**Z15,061-4** or **Z15,062-2** listed below) or digital thermometer and thermocouple kit (**Z17,354-1** and **Z16,037-7** listed below) for improved temperature resolution.

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- New integrated heat guard with glass viewport
- Castings conduct and radiate heat uniformly to capillaries and thermometer without the use of oils or volatile heat transfer fluids
- Precision 6X viewing lens and integrated light improves sample observation
- Compact heater housing, rugged aluminum top panel, etched panel markings
- CE compliant

MEL-TEMP Specifications:

Temp. range:	*ambient to 500°C*
Temp. resolution:	*0.1°C with low mass thermocouple and precision digital thermometer. One-half the smallest graduation with glass thermometer.*
Reproducibility:	*1°C*
Heat up time: (full power)	*25 to 400°C in 5min* *400 to 500°C in 4min*
Dim.:	*14 L x 11 W x 22cm H*
Weight:	*2.3kg*

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0 to 400°C **Z15,061-4**
100 to 500°C **Z15,062-2**

Digital thermometer, 0.1°C resolution, readout in °C or °F, hold button freezes display. Kit Z17,354-1 required for installation. **Z16,037-7**

Thermocouple kit, Type K probe, Includes extendable cord and mounting hardware in storage box. Use with digital thermometer **Z16,037-7** above. **Z17,354-1**

Volts AC	Cat. No.
110 - 120	**Z28,905-1**
210 - 230	**Z28,907-8**

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Window	Aperture (mm)	Cat. No.
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	15	**Z52,710-6**
	19	**Z52,713-0**
Crystal cover slips for **Z52,713-0**		**Z52,716-5**
KBr	9.5	**Z52,708-4**
	15	**Z52,711-4**
	19	**Z52,714-9**
Crystal cover slips for **Z52,714-9**		**Z52,717-3**
KCl	9.5	**Z52,709-2**
	15	**Z52,712-2**
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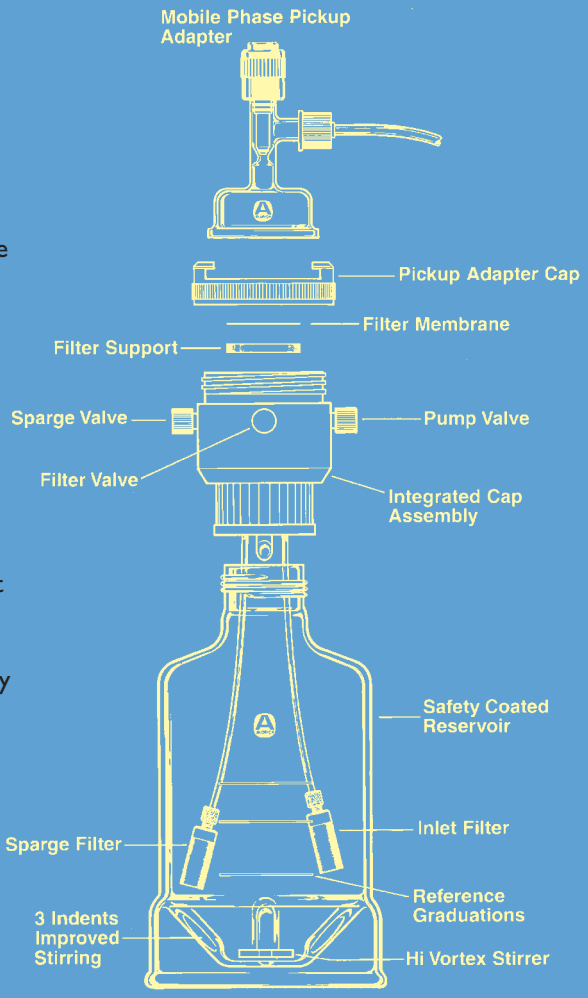

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10ft	PTFE tubing, ⅛ in. o.d.
2	2-Micron Stainless Steel filters
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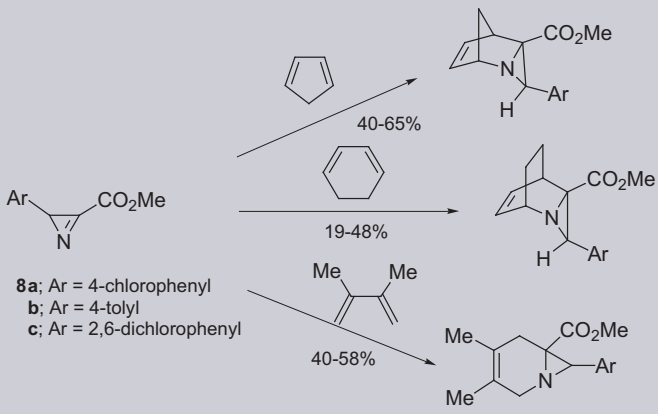
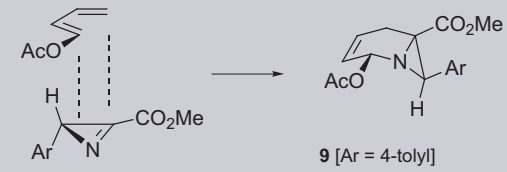
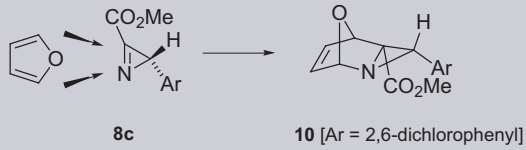


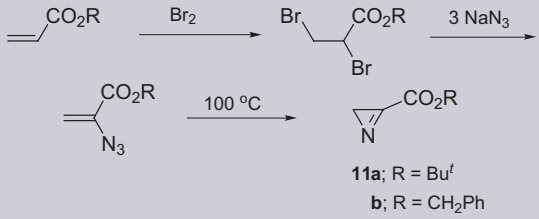
Scheme 2. Cycloaddition of Azirine Esters **8** to Symmetrical Dienes.



Scheme 3. Regio- and Stereoselective Addition to 1-Acetoxybutadiene.



Scheme 4. Exo Addition to Furan.



Scheme 5. Preparation of Azirine Esters **11** (Unsubstituted at C-2).

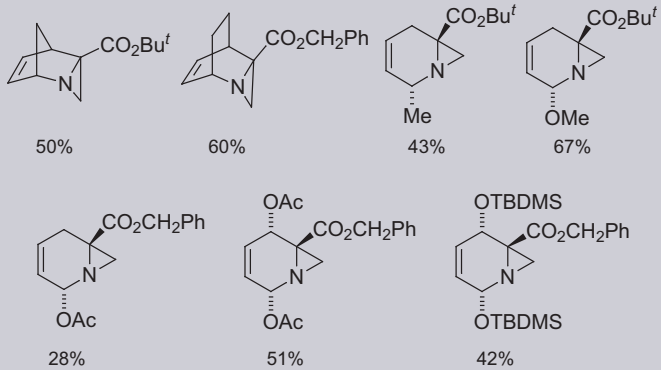


Figure 1. Adducts Formed from Azirines **11** and Dienes.

esters, by starting with readily available acrylamides and converting these into α-azidoacrylamides.[26] The azirine amides are somewhat more stable than the azirine esters, but they still participate readily in Diels–Alder reactions with cyclopentadiene and 1,3-cyclohexadiene. Chiral azirine **17c** showed no diastereoselectivity in its addition to cyclopentadiene.

In general, the most attractive approach to an asymmetric Diels–Alder reaction is to use a chiral catalyst. In comparison with acyclic imines, 2*H*-azirines appear to be ideal candidates for complexation to a chiral Lewis acid because of the fixed orientation of the lone pair. Our experiments aimed at achieving this with azirine-3-carboxylate esters have so far been unsuccessful, because the azirine esters are extremely susceptible to acid-catalyzed decomposition.

There are also isolated examples in the literature of other modes of cycloaddition of activated azirine esters: 1,3-dipolar addition reactions[27] and [2 + 2] addition reactions with enamines[28] have been described.

3. Activated Azirines as Electrophiles

Many examples of nucleophilic addition to the C=N bond of 2*H*-azirines are known[1] and, not surprisingly, azirine-3-carboxylic acid esters are particularly susceptible to nucleophilic attack. When adsorbed on silica, they dimerize to 1,2-dihydropyrazines (**18**) in a process which is probably initiated by acid-catalyzed hydrolysis (**eq 7**).[17] They also react rapidly with a wide variety of nucleophiles, including alcohols, thiols, and amines.[29] The simple addition products, **19** and **20**, are obtained from the addition of propargyl alcohol and thiophenol to azirine **8c**. Thiophenol adds to chiral azirine **16** with high facial selectivity,[25] but this selectivity does not generally extend to other nucleophilic additions to this azirine.

Intramolecular addition of the carboxylate function in azirine ester **21** leads to the formation of aziridine **22**.[30] Azirine ester **21** is the presumed intermediate in the thermolysis of ethyl 2-azido-3-(*o*-carboxyphenyl)propenoate (**Scheme 7**). Secondary amines, such as piperidine and morpholine, react rapidly with azirine **8c**, but the isolated products are enamines resulting from cleavage of the ring. The reactions of azirine **8c** with NH-acidic compounds, such as five-membered aromatic heterocycles and lactams, are more interesting since the aziridine addition products can be isolated.[31] A series of aziridine esters, such as **23**, are obtained from the base-catalyzed addition of heterocycles, such as pyrazole and 1,2,4-triazole, to azirine **8c** (**eq 8**). When

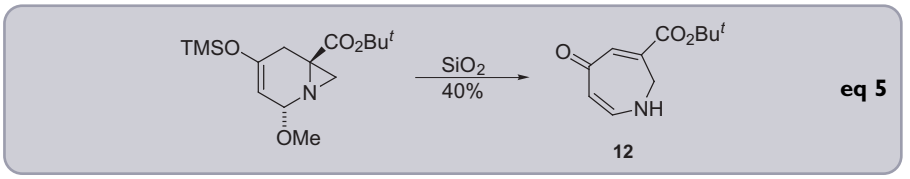
nucleophiles of this kind are added to other types of 2*H*-azirines, they usually cause cleavage of the three-membered ring.[6,32] Analogous addition products can be obtained from the simpler azirine esters, **11a** and **11b**. Reaction of the azirine benzyl ester, **11b**, with thymine gives adduct **24** regioselectively; similar adducts, **25** and **26**, are isolated in low-to-moderate yield from reactions with uracil and cytosine (**Scheme 8**).[23] The aziridine also reacts with adenine but, uncharacteristically for an alkylation reaction of this compound, only the 7-substituted adenine derivative, **27**, is isolated. In these reactions, a competitive decomposition of the azirine takes place and accounts for the observed low yields. A closer investigation revealed that the expected 9-substituted isomer was formed, but was then consumed during the course of the reaction, possibly by further reaction with adenine. Activated aziridines are well known as alkylating agents, and it seems possible that others among these aziridine esters are capable of acting in this way.

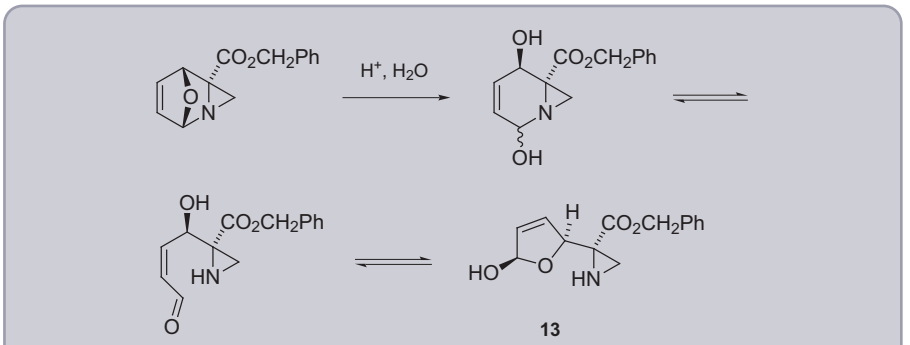
4. Conclusions

Activated 2*H*-azirines represent a new class of electrophilic building blocks. Azirine esters **11** are particularly attractive in this respect, since they can be generated in a few simple steps from readily available acrylate esters. Their high reactivity and high selectivity in Diels–Alder reactions make them very useful dienophiles, and their reactions with lactams and aromatic heterocycles provide routes to novel aziridine esters. There is obviously scope to extend this pattern of reactivity to other activated azirines. A major challenge is to achieve asymmetric reactions of these azirines by finding suitable chiral catalysts.

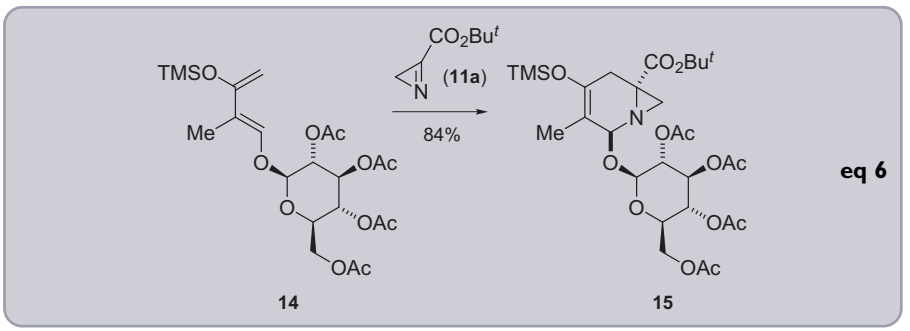
5. Acknowledgements

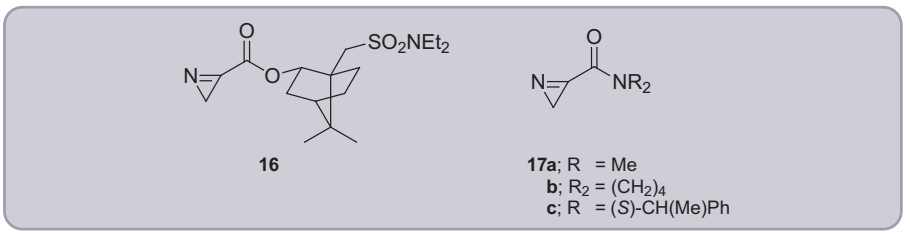
I am most grateful to my colleagues who have carried out the research described here. In particular, Dr. Maria José Alves (University of Minho, Portugal) performed much of the initial research during visits to Liverpool, and has continued the work in Portugal; and Ricardo Mendonça has greatly extended the earlier work during his Ph.D. studies at Liverpool. Jamie Bickley has produced X-ray crystal structures of several of the reaction products. The first experiments were carried out by Pamila Bhullar in the Wellcome Labs at Dartford, Kent; financial support has since been provided by the EPSRC (UK) and by JNICT (Portugal).

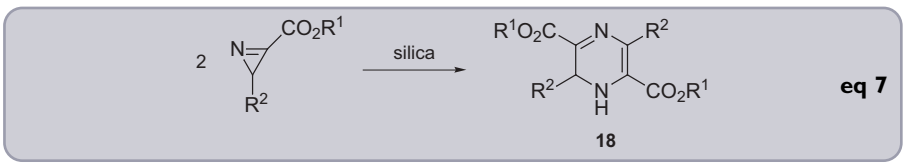


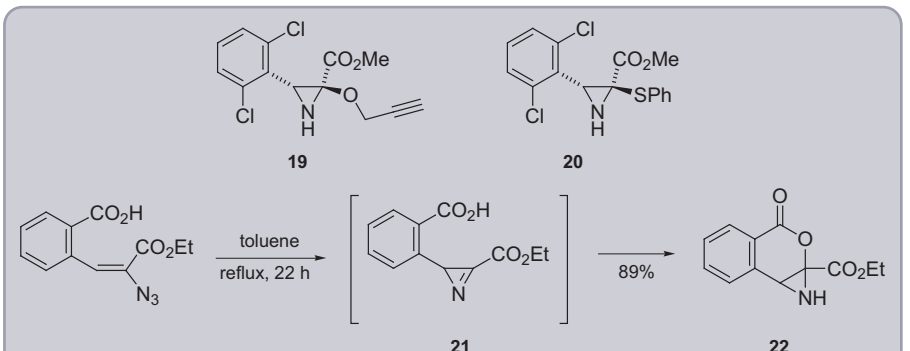


Scheme 6. Hydrolysis of a Furan Adduct.

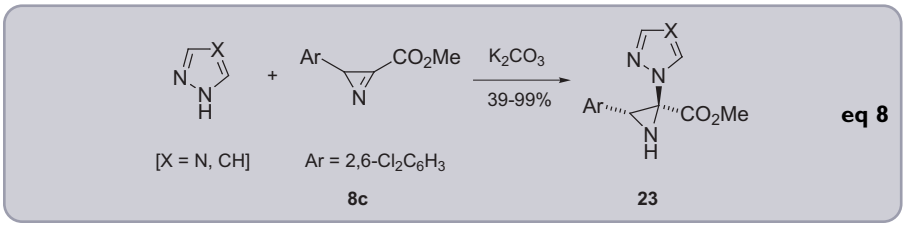


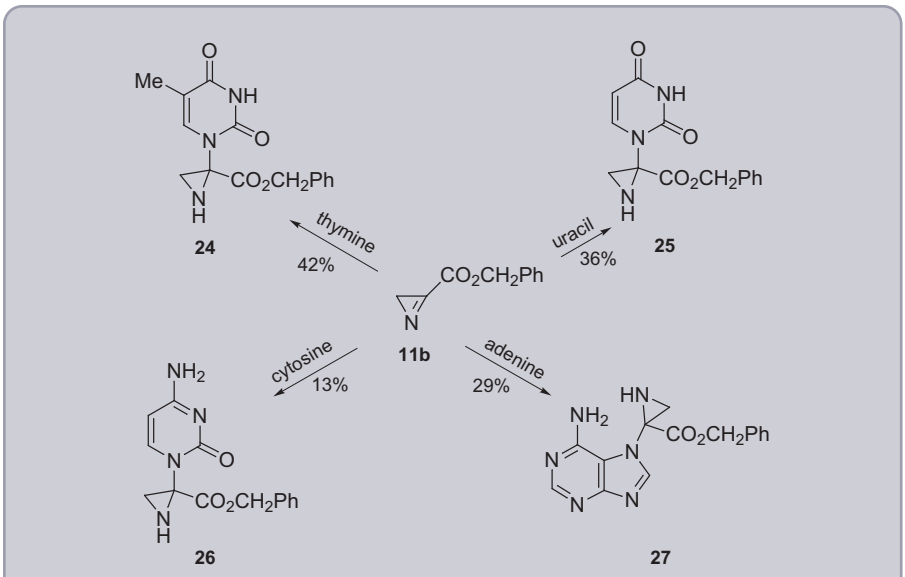






Scheme 7. Examples of Inter- and Intramolecular Nucleophilic Additions to 2*H*-Azirines.





Scheme 8. Addition of Azirine **11b** to Pyrimidines and Purines.

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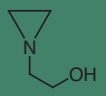
About the Author

Tom Gilchrist studied for his Ph.D. (1964) at King's College, University of London. His thesis, under the supervision of Professor Charles Rees, was on the synthesis and chemistry of Feist's acid and methylenecyclopropanes. He lectured for four years at the University of Leicester then moved to the University of Liverpool, where he has spent most of his career and is currently a Reader in Organic Chemistry. Most of his research has been in the area of heterocyclic chemistry, particularly on the use of new heterodienes and heterodienophiles for the synthesis of six-membered heterocycles. He has published several reviews and books, including *Organic Reactions and Orbital Symmetry* (with Richard Storr) and *Heterocyclic Chemistry*. He is the coeditor (with Gordon Gribble) of *Progress in Heterocyclic Chemistry*. He was awarded a 2000 Royal Society of Chemistry prize, endowed by Dr. Alfred Bader, for his contributions to heterocyclic chemistry.

Of Azirines, Aziridines, and Dienes



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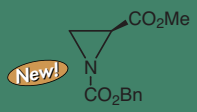

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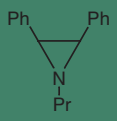

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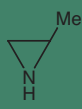
45,208-4; trans

45,204-1; cis
45,206-8; trans



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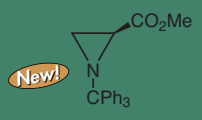

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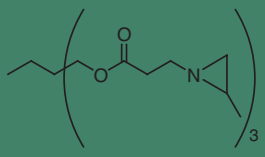

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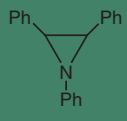

45,202-5; cis

Professor Gilchrist's review highlighted the interesting and highly useful chemistry of **2*H*-azirines**, in particular their use as imine dienophiles in the Diels–Alder reaction. The closely related aziridines also have many applications including, for example, the preparation of β-substituted α-amino acids from optically active aziridine 2-carboxylates (see Aldrich cat. no. 51,601-5 and 51,603-1 below).[1] In some cases, as mentioned in the review, aziridines can also serve as precursors to 2*H*-azirines.[2,3]

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51,603-1 New! **1-Benzyl 2-methyl (*S*)-(–)-1,2-aziridinedicarboxylate**, 97%

46,401-5 **(*S*)-(+)-2-Benzyl-1-(*p*-tolylsulfonyl)aziridine**, 98%

45,207-6 ***cis*-2,3-Diphenyl-1-propylaziridine**, 97%

45,208-4 ***trans*-2,3-Diphenyl-1-propylaziridine**

45,204-1 ***cis*-1-Isopropyl-2,3-diphenylaziridine**, 97%

45,206-8 ***trans*-1-Isopropyl-2,3-diphenylaziridine**, 97%

29,416-0 **2-Methylaziridine**, tech., 90%

51,601-5 New! **Methyl (*S*)-(–)-1-trityl-2-aziridinecarboxylate**, 98%

40,544-2 **Trimethylolpropane tris(2-methyl-1-aziridinepropionate)**

45,202-5 ***cis*-1,2,3-Triphenylaziridine**, 98%

Dienes

The following are some of the dienes described in the preceding review.

22,086-8 **1-Acetoxy-1,3-butadiene**, mixture of *cis* and *trans*

C10,000-5 **1,3-Cyclohexadiene**, 97%

45,433-8 **Dicyclopentadiene** (stabilized with BHT)

14,549-1 **2,3-Dimethyl-1,3-butadiene**, 98%

18,592-2 **Furan**, 99+%

21,283-0 ***trans*-1-Methoxy-3-(trimethylsilyloxy)-1,3-butadiene**, 90% (Danishefsky's diene)

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Have you tried our improved DMSO-d_6 and chloroform-*d*?

We have recently made process improvements in the manufacture of these two commonly used deuterated solvents to make them better than ever before. DMSO-d_6 is notorious for picking up moisture from the air. We dry our DMSO-d_6 using the latest technology to effectively get water levels below 200ppm just before packaging. You can be assured that regardless of whether you receive an ampule, a screw-cap bottle, or a Sure/Seal™ bottle, our DMSO-d_6 has undergone extensive drying to make it the driest possible.

Our chloroform-*d* is closely measured for acidity. We monitor acidity levels to make sure our deuterated chloroform is acid free just before packaging. Remember that there is a natural tendency for chloroform-*d* to degrade over time resulting in acidic impurities; but the less acidic impurities you have initially, the less you will have later.

If you are not currently an Aldrich customer for these products, we invite you to give us a chance to win your business. We are confident that, after trying our improved DMSO-d_6 and chloroform-*d*, you will be impressed.

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Sigma-Aldrich Synthetic Chemistry Symposium
March 1–2, 2001
Burg Schlaining, Austria

A beautiful, historic castle was the setting for the first, Sigma-Aldrich sponsored, Austria-wide synthetic chemistry symposium. The symposium attracted 55 participants from universities and high schools from across Austria. It was divided into 5 different sessions and consisted of 20 oral and 32 poster presentations. An award committee comprised of 6 well-known chemistry professors from across Austria chose one oral and one poster presentation as the best. The winning oral and poster presentations received award certificates and monetary prizes.

Best Oral Presentation

Application of Bacterial Epoxide Hydrolases in Asymmetric Synthesis: Scope and Limitations

Andreas Steinreiber, Sandra F. Mayer, Silvia M. Glück, and Kurt Faber
Department of Chemistry, Organic and Bio-organic Chemistry
Karl-Franzens-Universität Graz
Graz, Austria

Best Poster Presentation

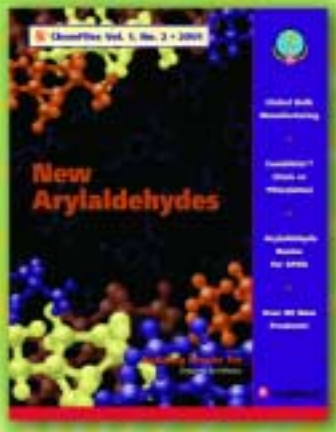
Oxidation Products of Abietic Acid

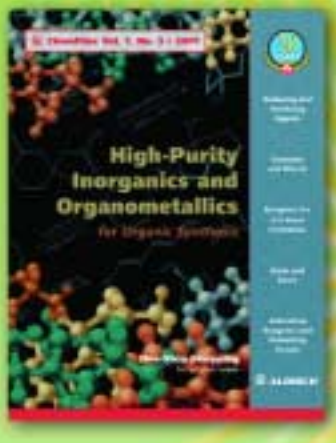
S. Prinz, A. Hüfner, U. Müllner, and E. Haslinger
Institute of Pharmaceutical Chemistry
Karl-Franzens-Universität Graz
Graz, Austria

Congratulations to the winners and a special thank-you to the employees of the Sigma-Aldrich Austria office for their efforts in organizing this symposium.

Special Interest Groups

In an effort to better serve our customer base, Aldrich is offering a number of specialty catalogs and brochures. These pieces highlight specific groupings of products with relevant references and technical information. Please visit our website at **www.sigma-aldrich.com** for more information on Aldrich products.





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- ❒ Combinatorial Chemistry Catalog (EDZ)
- ❒ Electronic Polymers & Precursors (EEL)
- ❒ High-Purity Inorganics & Organometallics for Organic Synthesis (DVV)
- ❒ New Arylaldehydes (DUG)
- ❒ Products for NMR (DTW)
- ❒ Products for Suzuki Coupling (DTK)

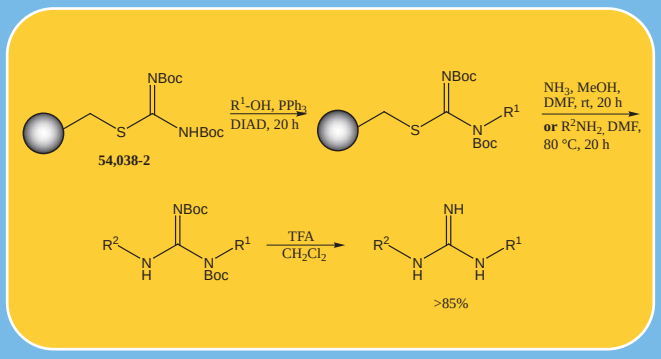
Oxidizing Reagents

FOR SOLUTION-PHASE SYNTHESIS

54,038-2 **Bis(*tert*-butoxycarbonyl)thiopseudourea, polymer-bound,** ~100-200 mesh, 1% cross-linked

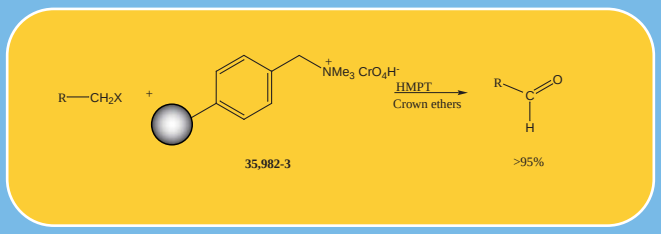
New!

This resin has been used as a masked guanidine scaffold for the parallel synthesis of mono-N-alkylated guanidines and N,N′-bisalkylated guanidines. Reaction of this resin with various alcohols under Mitsunobu conditions yields polymer-bound alkylated thiopseudoureas. Guanidines are cleaved from the resin in high yield and purity using methanolic ammonia in DMF or primary amines in DMF.[1]



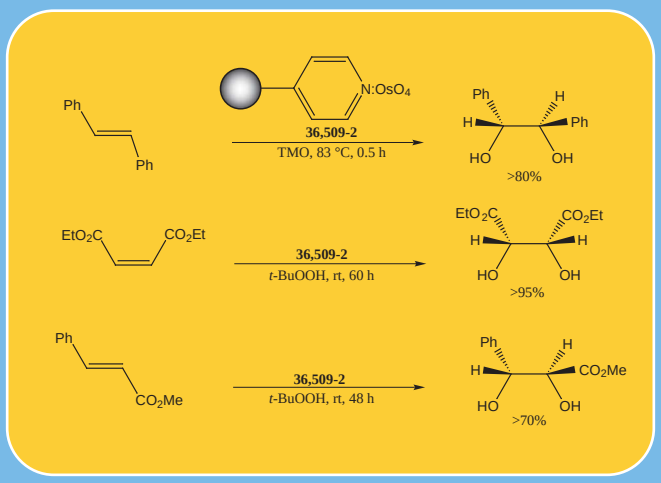
35,982-3 **Chromic acid, polymer-supported**

Has been utilized for the clean oxidation of primary and secondary alcohols to carbonyl compounds in high yields.[2,3] This resin has also been used as a reagent for the synthesis of aldehydes and ketones from allylic and benzylic halides.[4]

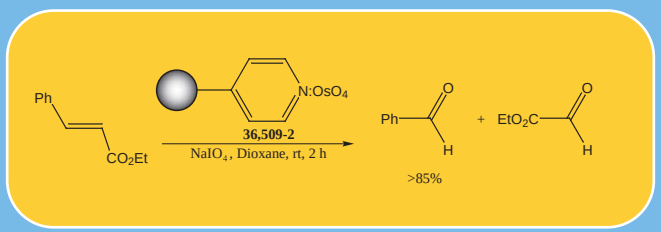


36,509-2 **Osmium tetroxide,** ~1 wt. % on poly(4-vinylpyridine)

This resin catalytically dihydroxylates olefins in the presence of a co-oxidant, such as hydrogen peroxide, *tert*-butyl hydroperoxide (*t*-BuOOH), or trimethylamine *N*-oxide (TMO).[5] Polymer-bound osmium tetroxide offers the advantage of easy workup without the need to decompose residual osmium tetroxide.



Furthermore, this resin has been used with $NaIO_4$ to oxidatively cleave olefins to produce carbonyls. This method provides an alternative to the double-bond cleavage by ozone.[6]



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REFERENCES: (1) Dodd, D.S.; Wallace, O.B. *Tetrahedron Lett.* **1998**, *39*, 5701. (2) Cainelli, G. et al. *J. Am. Chem. Soc.* **1976**, *98*, 6737. (3) Wade, L.G.; Stell, L.M. *J. Chem. Educ.* **1980**, *57*, 438. (4) Cardillo, G. et al. *Tetrahedron Lett.* **1976**, *44*, 3985. (5) Cainelli, G. et al. *Synthesis* **1989**, 45. (6) Cainelli, G. et al. *ibid.* **1989**, 47.

NEW PHOSPHORUS DENDRIMERS NEW

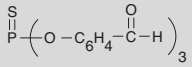
In recent years, a new structural class of macromolecules, the dendritic polymers, has attracted the attention of the scientific community. Dendrimers, the most regular members of the class, are characterized by nearly spherical structures, nanometer sizes, large numbers of reactive end-group functionalities, and shielded interior voids. This unique combination of properties makes them ideal candidates for nanotechnology applications in both biological and materials sciences. Applications highlighted in the recent literature include drug delivery, gene transfection, catalysis, energy harvesting, photoactivity, molecular weight and size determination, rheology modification, and nanoscale science and technology.[1]

Aldrich is pleased to offer two new families of **phosphorus-based dendrimers**. In addition to the properties mentioned above, the **Thiophosphoryl Dendrimers** and **Cyclotriphosphazene Dendrimers** exhibit high solubility, air stability, and large dipole moments (10–300 Debyes). For our complete list of dendrimer products, including PAMAM dendrimers up to Generation 10, with different surface modifications, please contact our Technical Services Department at **aldrich@sial.com.** If you have not already received the ***Aldrich Polymer Products CD–Catalog & Reference Guide***, please request your **FREE CD** today by emailing **sams-usa@sial.com** or request one from your local office.

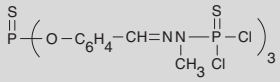
(1) *Functional Polymers and Dendrimers: From Synthesis to Application.* Proceedings of the American Chemical Society Division of Polymeric Materials: Science & Engineering, San Diego, CA, April 1-5, 2001; American Chemical Society: Washington, DC, 2001.

THIOPHOSPHORYL DENDRIMERS

22,429-4
Thiophosphoryl chloride, Gen. 0.0

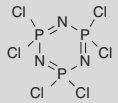


55,176-7
Thiophosphoryl-PMMH-3
Dendrimer, Gen. 0.5

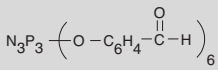


55,177-5
Thiophosphoryl-PMMH-3
Dendrimer, Gen. 1.0

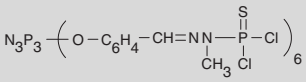
CYCLOTRIPHOSPHAZENE DENDRIMERS



23,028-6
Hexachlorocyclotriphosphazene,
Gen. 0.0



55,201-1
Cyclotriphosphazene-PMMH-6,
Gen. 0.5



55,205-4
Cyclotriphosphazene-PMMH-6,
Gen. 1.0

THIOPHOSPHORYL-PMMH DENDRIMERS*

Catalog No.	Generation	No. of Surface Groups	Unit Size
Surface Group: Aldehyde			
55,176-7	0.5	3	1g
55,167-8	1.5	6	500mg
55,169-4	2.5	12	500mg
55,171-6	3.5	24	500mg
55,173-2	4.5	48	500mg
55,175-9	5.5	96	300mg
Surface Group: Dichlorophosphinothioyl			
55,177-5	1.0	3	500mg
55,168-6	2.0	6	500mg
55,170-8	3.0	12	500mg
55,172-4	4.0	24	500mg
55,174-0	5.0	48	300mg

CYCLOTRIPHOSPHAZENE-PMMH DENDRIMERS*

Catalog No.	Generation	No. of Surface Groups	Unit Size
Surface Group: Aldehyde			
55,201-1	0.5	6	1g
55,206-2	1.5	12	500mg
55,213-5	2.5	24	500mg
55,211-9	3.5	48	500mg
55,209-7	4.5	96	500mg
55,214-3	5.5	192	300mg
Surface Group: Dichlorophosphinothioyl			
55,205-4	1.0	6	500mg
55,207-0	2.0	12	500mg
55,212-7	3.0	24	500mg
55,210-0	4.0	48	500mg
55,208-9	5.0	96	300mg

**PMMH = PhenoxyMethyl(MethylHydrazono)*

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Reactive Chemical Hazard Evaluation in the Scale-Up of Chemical Processes

Gordon Amery
Production Department
Sigma-Aldrich Company Ltd.
Gillingham, Dorset SP8 4XT, UK
E-mail: gamery@eurnotes.sial.com

Outline

1. Introduction

Chemical reactions either release heat (exothermic) or absorb heat (endothermic), with the majority of chemical reactions carried out in industry being exothermic. If the rate of heat production for an exothermic reaction exceeds the rate of heat removal, then a thermal runaway may result. As the surplus heat begins to raise the temperature of the reaction mass, the rate of reaction starts to increase. This in turn accelerates the rate of heat production. A thermal runaway can occur because, as the temperature increases, the rate of heat removal increases only linearly, whereas the rate of heat production increases exponentially (**Figure 1**). Once control of the reaction is lost, the temperature can rise rapidly leaving little time for correction. The reaction vessel may be at risk from overpressurization due to violent vaporization or rapid gas generation, and the elevated temperatures may initiate secondary, more hazardous decomposition reactions.

It is also worthy of note that hazards can arise from endothermic processes, which may bring about rapid crystallization and/or give rise to rapid gas evolution. Therefore, this type of reaction cannot be discounted during the risk assessment procedure.

One factor that has a significant effect on the balance between the heat generated and the heat lost is the scaling up of a reaction from the laboratory to the pilot or full-scale plant. The heat produced in a reaction mass increases with volume, which is proportional to the cube of the reactor diameter. The heat removed to the surroundings depends on the surface area available for heat transfer, which is proportional only to the square of the diameter. As the reaction scale and the ratio of reactor volume to surface area increase, cooling may become inadequate and the reaction tends towards the adiabatic (i.e., no heat loss).

An analysis of thermal runaways in the UK chemical industry[1] has indicated that incidents occur due to one or more of the following factors:

- Inadequate understanding of process chemistry and thermochemistry
- Inadequate design for heat removal
- Inadequate control systems and safety systems
- Inadequate operational procedures, including training

A detailed discussion of these points is beyond the scope of this article. However, I would like to outline the approach taken in the evaluation of reaction hazards at Sigma-Aldrich's new cGMP production facility in Gillingham, including the methods we use to obtain data on the thermal stability of raw materials, intermediates, products, and by-products; reaction thermochemistry; and the rate and quantity of gas evolution. I will describe the instrumentation used in our laboratories and give some examples taken from actual projects that we have carried out for customers.

2. Reactive Chemical Hazard Evaluation

Clearly, it is not safe to test unknown reactions in a full-size reactor. Therefore, various techniques have been developed to provide predictive data. Applicable methods used in our Hazard Evaluation Laboratory at Gillingham are outlined below. Further information on these and other hazard evaluation techniques can be obtained from a number of sources.[2–7]

2.1. Desk Screening

The existing literature is no substitute for chemical hazard testing, but it often makes a good starting point for assessing the hazards of an unknown reaction. *Bretherick's Handbook of Reactive Chemical Hazards*[8] and the National Fire Protection Association's *Manual of Hazardous Chemical Reactions*[9] are useful texts. They give accounts of previous incidents with many surprising and unexpected exothermic runaway reactions. However, the absence of a particular information does not necessarily imply that no hazards exist.

Thermochemical calculations are often useful for initial screening, and heat-of-reaction data are available in the literature for many standard reactions including nitration, sulfonation, and hydrogenation. The approximate exothermicity of chemical reactions can be predicted by other methods, including calculations which sum-average bond energies. We use the CHETAH computer program,[10] which allows us to readily perform this type of calculation. The estimated heat of reaction can then be used to predict the maximum temperature rise expected in the reaction mass under conditions of no heat loss (adiabaticity). The Maximum Temperature of the Synthesis Reaction (MTSR) is the sum of this adiabatic temperature rise and the maximum expected operating temperature. MTSR is an important value, because if it is below the temperature at which additional chemistry (e.g., decomposition), physical transitions (e.g., boiling or gas generation), or overpressurization from increased vaporization can occur, then there would be little hazard due to the heat released by the reaction. However, it should be noted that there may be dramatic effects on product yield or quality, even if the MTSR is not exceeded.

In addition, it is possible to obtain a preliminary estimate of the reactivity and stability of chemicals from their molecular structure. Examples of molecular groupings that are likely to introduce hazards into a process are double- and triple-bonded hydrocarbons, epoxides, hydrides, metal acetylides, nitrogen-containing compounds (e.g., amides; imides; nitrides; azides; azo, diazo, and diazeno compounds; halogen–nitrogen-bonded compounds; hydrazine-derived nitrogen compounds; nitrates; nitrites; nitroso and nitro compounds; and nitrogen–metal derivatives) and oxygenated compounds of halogens and peroxides. Many of these molecular groupings can cause materials to have explosive or highly energetic properties, and this may lead us to send such compounds out to a specialist testing agency to conduct screening tests for shock sensitivity, deflagration, and so on.

2.2. Basic Screening Tests

Differential Scanning Calorimetry (DSC) is used in our laboratory as a screening method to examine the thermal stability of a reactant, reaction mixture, or product, and the heat of reaction or decomposition. For a DSC test, a small amount of sample (1–20 mg) is placed in a sealed capsule and heated from ambient to, e.g., 400 °C at a constant rate (usually 5 K.min^{-1} in our tests). The temperature trace of the sample indicates exothermic or endothermic activity by means of peaks and troughs. The area under the trace gives the total amount of energy released, and the slope of the trace an estimate of the rate of release. The measured 'onset' temperature (i.e., the temperature at which the trace deviates from the baseline), the total energy, and the maximum rate of energy release are indicators of the degree of hazard. Some of the disadvantages of DSC are: (i) the measured 'onset temperature' is a function of sample loading and heating rate, (ii) representative sampling on such a small scale is difficult, (iii) no agitation of reaction mixtures is possible, (iv) no pressure data can be obtained, and (v) the technique has a relatively low sensitivity (1 to 20 W.kg^{-1}). For these reasons, a safety margin (60–100 °C) is normally applied to DSC data.

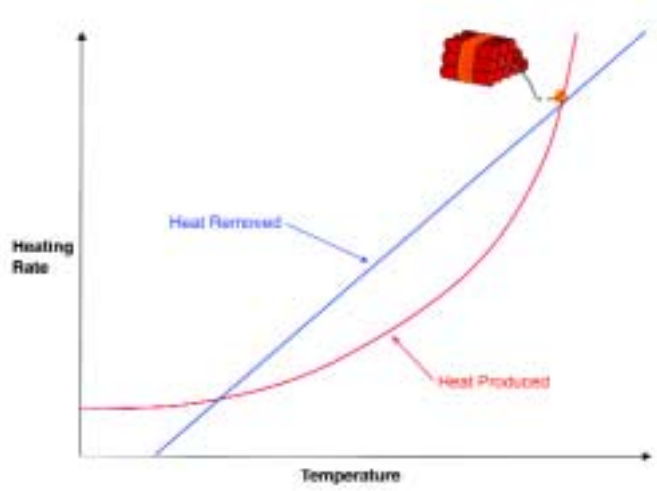


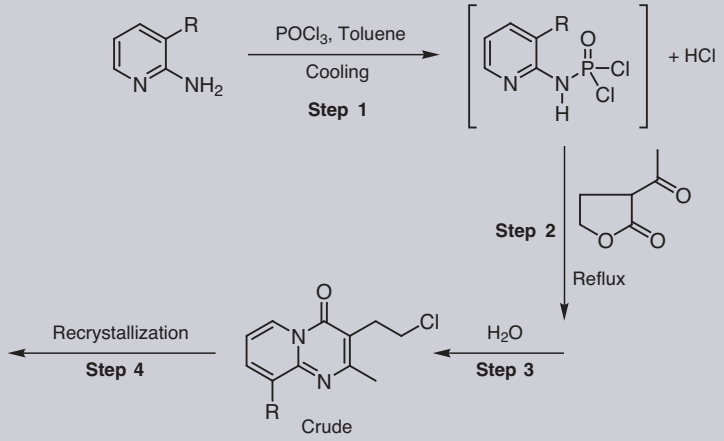
Figure 1. Effect of Temperature on Heat Production and Removal Rates.

Figure 2. RC1e Reaction Calorimeter in Use at Gillingham.

The instrument used in our laboratory is a Mettler® DSC821*e*. The DSC allows a screening test as outlined above to be carried out in about 1 hour. It also allows subambient operation down to approximately –70 °C for samples that may display thermal instability below ambient temperature.

2.3. Adiabatic Calorimetry

Adiabatic Calorimetry is employed mainly to examine the runaway potential of reaction mixtures and individual compounds. The Accelerating Rate Calorimeter (ARC™) is an adiabatic calorimeter that can be utilized to test small samples. Its use was pioneered in the 1970s by DOW Chemical Company, and it has become the best-known and most widely used adiabatic calorimeter. A sensitivity of <0.5 W.kg^{-1} can be obtained with an operating temperature of



Scheme 1. Phosphoryl Chloride Reaction as Proposed Initially.

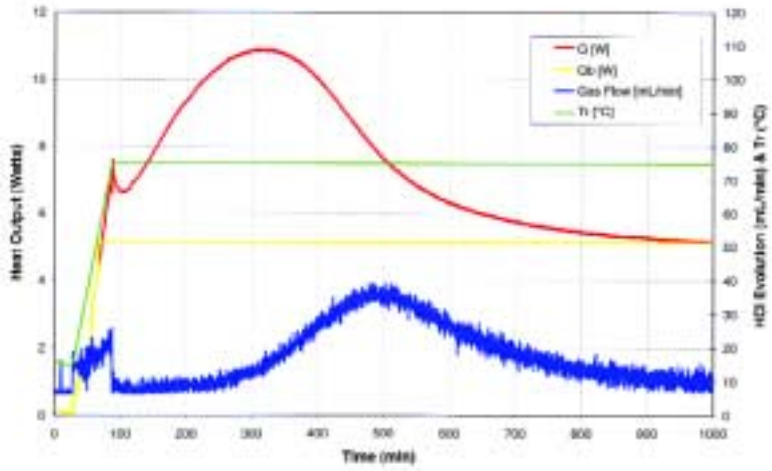


Figure 3. RC1e Trace for the Second Step of the Reaction Depicted in Scheme 1: Heating up to, and Reaction at, 75 °C.

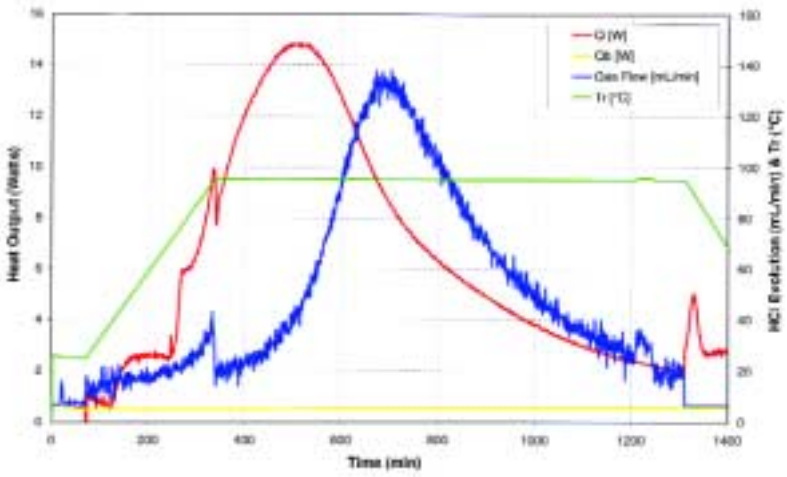


Figure 4. RC1e Trace for the Second Step of the Reaction Depicted in Scheme 1: Heating up to, and Reaction at, 95 °C.

up to 400 °C. A standard Heat-Wait-Search test can be completed in 1 day, although tests involving isothermal aging of the sample can take much longer.

2.4. Reaction Calorimetry

Reaction calorimetry is principally used to measure heats of reaction and reaction kinetics for 'desired' reactions along with thermal conversion; specific heats of reaction mixtures; and heats of mixing, dissolution, and crystallization. The heat of reaction obtained, along with the heat capacity, can be utilized to calculate the potential adiabatic temperature rise of a reaction mixture and, subsequently, the all-important MTSR (as defined above). *This is the single, most important parameter required for specifying a safe operating envelope.*

There are a number of different types of reaction calorimeters available from different manufacturers, but the Mettler® RC1*e* Low Temp (**Figure 2**) appears to have become the industry standard. Typically, we use it with a 2-L jacketed glass reactor, but a number of other reactors are available, including a Hastelloy® 60 barg pressure vessel (HP60).

In a typical experiment, starting materials and solvent are charged into the reaction calorimeter, and calibrations to obtain the heat transfer coefficient (U) and the heat capacity (Cp) of the mixture are performed. The reaction is then initiated by dosing in a second reagent, heating, or by addition of a catalyst, and the heat output profile is recorded. A further set of calibrations is then performed when the reaction is complete. Experiments are not limited to working hours: in automatic mode, the instrument can be used as a powerful Automated Laboratory Reactor (ALR). It can, therefore, have a wider role in the area of process development and scale-up.

2.5. Gas Evolution Measurement

Heat evolution data alone does not always give a full picture of potential reaction hazards. When a reaction goes out of control, it is the gas formed—either non-condensable or from vaporization of any solvent present—that causes vessel pressurization and possible explosion. It is, therefore, important to measure the gas evolution rate during the normal reaction. This information is required to design the venting or scrubbing system in order for the reactor not to become pressurized, or, if a flammable gas is evolved, the head space not to enter a flammable range. In our laboratory, we use thermal mass flow meters/controllers for this purpose. These allow precise measurement and control of

gas flow rates in the range of 0.001 L.min^{-1} to 2.0 L.min^{-1}. In our particular meters, supplied by Bronkhörst, all parts in contact with the gas stream are fabricated from Monel® and are thus relatively resistant to the corrosive gases routinely encountered. The gas flow rate data can be fed to the RC1*e* and combined with the heat data for final evaluation.

2.6. Other Tests

Recently, specialized equipment has been developed to provide data for vent sizing. This is currently outside the remit of our laboratory, and the work is sent off-site if required. Similarly, dust explosivity testing is handled externally.

3. Example One: Reaction with Phosphoryl Chloride

In this first example, the objective of a four-stage project was to supply a major customer with 10 kg of final product, prepared under cGMP conditions. Initial assessment of the chemistry showed that only the second stage of the process gave any cause for concern on safety grounds. This stage involved the reaction of a substituted pyridine ring with phosphoryl chloride to form the corresponding phosphorylamide, followed by reaction with acetylbutyrolactone and subsequent quenching to give the Stage Two product (**Scheme 1**).

The reaction procedure, as received from the customer, called for adding phosphoryl chloride to the substituted pyridine in toluene with cooling. It then intended to charge acetylbutyrolactone and heat the mixture at reflux until the reaction was complete. A water quench followed by recrystallization of the crude product would complete the project.

Addition of water to a mixture containing $POCl_3$ is potentially very dangerous owing to the possibility of a delayed exothermic hydrolysis reaction. Prior experience had shown us that reactions with phosphoryl chloride proceed well if $POCl_3$ is used as a solvent as well as a reagent. We thought that this would overcome the problem of the sticky oil formed as an intermediate when toluene is used as the solvent. Therefore, the customer's procedure was considerably altered during development work: the reaction was performed at 95 °C in an excess of $POCl_3$, and the resulting mixture quenched by adding it to aqueous sodium acetate. At this point, the project was passed on to the Calorimetry Laboratory for reactive hazard evaluation.

Initial reaction calorimetry work showed that, as expected, the formation of the

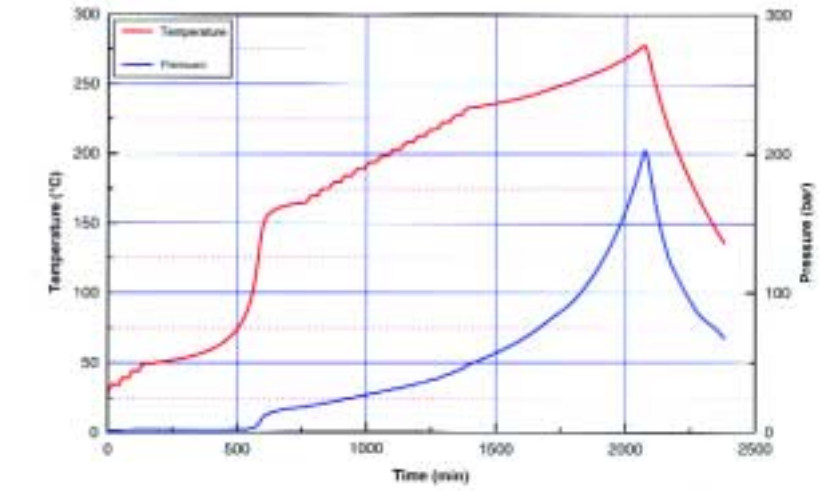


Figure 5. ARC™ Plots of Temperature and Pressure vs Time for the Second Step of the Reaction Depicted in Scheme 1.

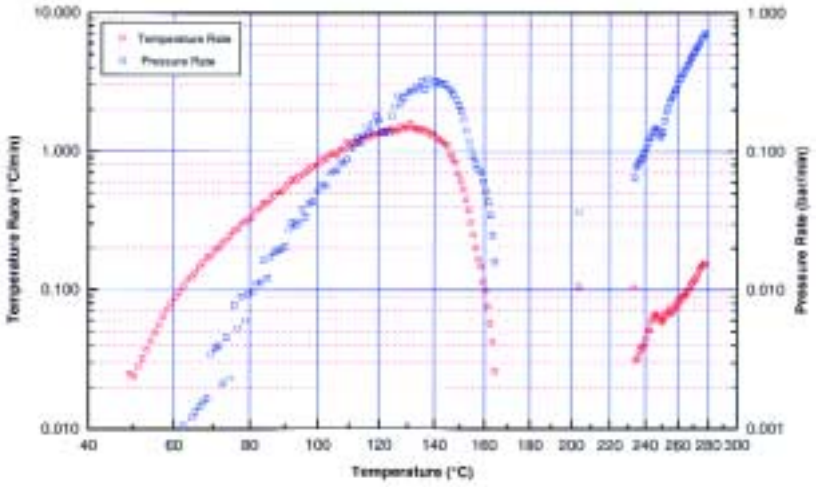


Figure 6. ARC™ Plots of Temperature and Pressure Rates vs Temperature for the Second Step of the Reaction Depicted in Scheme 1.

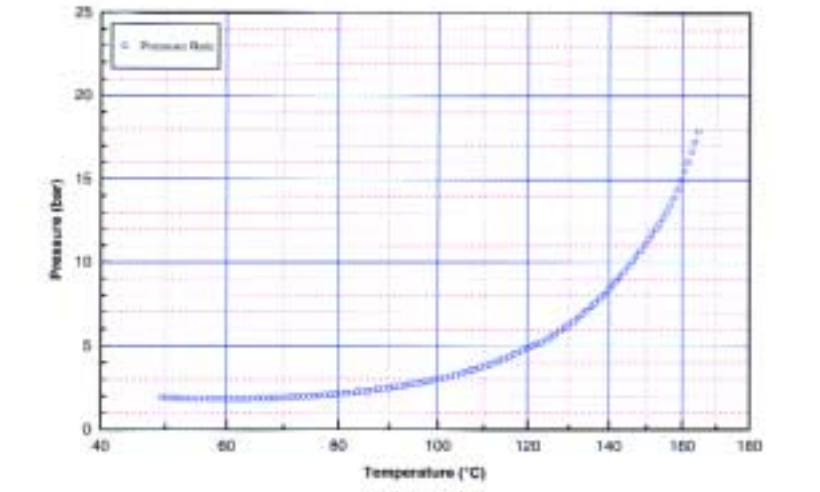


Figure 7. ARC™ Plot of Pressure vs Temperature for the Second Step of the Reaction Depicted in Scheme 1.

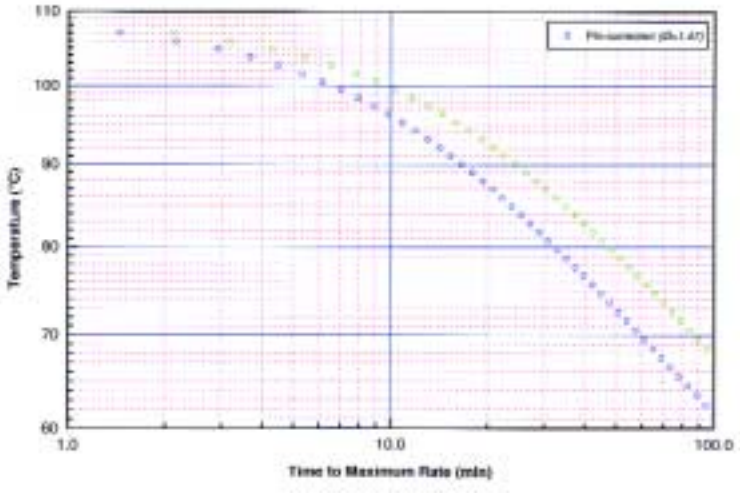
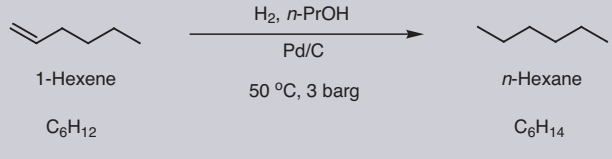


Figure 8. Time to Maximum Rate vs Temperature Plot for the Second Step of the Reaction Depicted in Scheme 1.

Figure 9. 400L Biazzi Hydrogenator.

and the heat evolution could be easily controlled by the rate of addition.

However, the second step of the reaction, which involved heating with acetyl-butyrolactone, gave cause for concern. RC1*e* traces for this reaction, performed at 75 °C and 95 °C, are shown in **Figures 3** and **4**. The reaction was slow, especially at 75 °C, and the maxima in the gas evolution curves did not correspond to the maxima in the heat evolution curves. An overall gas evolution of ~0.71 moles HCl per mole of substrate was recorded. The heat of reaction measured in the RC1*e* for this 'all on board' reaction was –148 kJ**.**mol^{-1}, and this figure, coupled with a relatively low heat capacity of some 1100



eq 1

intermediate phosphorylamide using neat phosphoryl chloride was a fast and addition-rate-controlled reaction with no apparent gas evolution. The measured heat of reaction (–61 kJ**.**mol^{-1}) was such that the MTSR would only be ~90 °C, even if the pyridine starting material were to be charged rapidly. This value is below the reflux temperature of phosphoryl chloride and the reaction is therefore inherently thermally safe.

Similarly, the quench step was found to be inherently safe, provided aqueous sodium acetate, not water, is used for the quench. It was also found that, if the initial quench temperature were greater than 30 °C, the accumulation of $POCl_3$ would be minimal, J**.**kg^{-1}**.**K^{-1}, would represent an adiabatic temperature rise of >133 °C, if control were to be lost.

It was evident that the plant could not control this reaction in the event of cooling failure, and that the potential consequence of the reaction going out of control would be a loss of $POCl_3$ to the vents and possibly the scrubbing system. There, it could react violently with the aqueous scrubbing liquors causing further uncontrolled evolution of heat and gas.

Additional (adiabatic) calorimetry was therefore performed in order to quantify this runaway potential, and a selection of the temperature/pressure/time plots for these ARC™ runs is presented in **Figures 5–7**. These graphs show that the ARC™ instrument detected the onset of reaction at ~50 °C and then followed the reaction adiabatically, reaching a maximum rate at ~131 °C and ending at ~165 °C. The overall heat of reaction, as measured by the ARC™, was –152 kJ**.**mol^{-1}, which compares well with that measured by the reaction calorimeter. A further decomposition reaction was also detected from ~230 °C, and, after making allowance for the thermal inertia of the sample holder, it was theoretically possible for this temperature to be reached by the initial runaway reaction. Additionally, the Time to Maximum Rate plot in **Figure 8** shows that, at the proposed reaction temperature of 95 °C, the time taken to reach reflux (~110 °C) would be of the order of 10 minutes. This means that, during heating up to the reaction temperature, the operator would have an unfeasibly short time to reconfigure the vessel from heating to cooling mode in an attempt to control the exotherm.

Ultimately, several recommendations were made to increase the safety of this process. These included:

(1) Performing the reaction at 75 °C, as opposed to the originally specified 95 °C. This increased the time available to switch from heating to cooling mode. It also prolonged the reaction time which, however, was not found to be critical.

(2) Not leaving the reaction unattended at any time during the critical period.

(3) Charging a suitable amount of toluene into an adjacent vessel, to be dumped into the reaction vessel by nitrogen pressure in the event of a cooling failure. Preliminary calculations, backed up by reaction calorimetry, showed that the reaction could be stopped completely if the reaction vessel were to be completely filled with dry toluene.

This work is an excellent example of the value of the combination of the three techniques: reaction calorimetry, adiabatic calorimetry, and gas evolution measurement.

4. Example Two: Qualification of Hydrogenation Equipment

From the outset, one of the primary design intents for our new hydrogenation facility at Gillingham was to always ensure full heat- and mass-transfer equivalence from 2L and 20L laboratory-scale Büchi hydrogenators to the 400L Biazzi hydrogenator (**Figure 9**). Another intent was to ensure that development reaction times

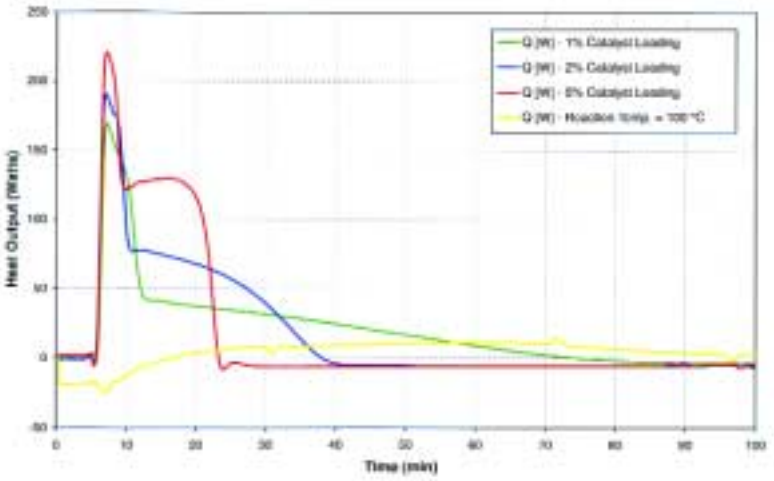


Figure 10. Heat Output vs Catalyst Loading During the Hydrogenation of 1-Hexene.

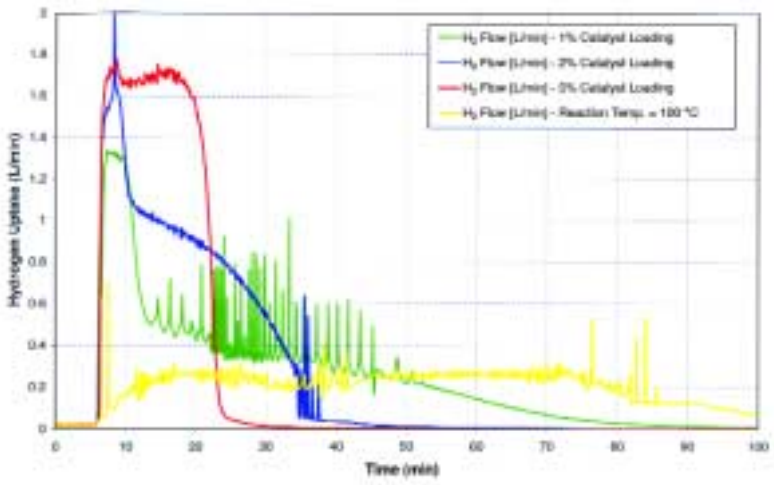


Figure 11. H_2 Uptake vs Catalyst Loading During the Hydrogenation of 1-Hexene.

were directly scalable. Equivalence in control philosophy and unit operations was also designed in to allow a high level of consistency between laboratory operation and full-scale production.

For the initial qualification runs, the catalytic hydrogenation of 1-hexene was chosen for its relative simplicity (**eq 1**). In a typical HP60 run, 0.1 kg of 1-hexene was dissolved in 1-propanol, 5% Pd/C catalyst added, and the mixture hydrogenated at 3 barg and 50 °C until the reaction was complete. The RC1*e* allowed us to examine the heat evolution during this reaction and, of course, any other side reactions that may have been taking place simultaneously. Use of a mass flow meter/controller also allowed the monitoring of the hydrogen uptake during the reaction.

The heat output vs time traces for several of the RC1*e* runs (**Figure 10**) and the corresponding hydrogen uptake curves (**Figure 11**) show that, as expected, the rate of hydrogenation increased with increased catalyst loading. The reaction run with 1% w/v catalyst loading (taken as dry catalyst weight) took >90 minutes to reach completion, whereas a run with 5% w/v loading took less than 25 minutes. The initial 'spike' in heat output and hydrogen absorption is believed to be an indication of the 'true' rate of reaction before the catalyst sites begin to be blocked by the hexane product.

A further reaction, run for comparison purposes at 100 °C, showed little or no heat evolution or hydrogen uptake. At first sight, this may seem surprising, but it is likely that, at elevated temperatures, the reverse dehydrogenation reaction of the hexane product to re-form 1-hexene becomes competitive. The overall reaction would of course be thermoneutral and not involve uptake of hydrogen.

Ultimately, the results of these RC1*e* runs were compared with the data obtained from similar experiments performed in the Büchi and Biazzi hydrogenators, and this comparison showed that the original design intentions have been realized in practice.

The chemistry described in the preceding paragraphs is very simple, but it does illustrate the usefulness of reaction calorimetry in facilitating the qualification of equipment, such as the Biazzi hydrogenator, in addition to its normal role in the evaluation of chemical reaction hazards.

5. Conclusion

There is no doubt that thorough reaction hazard assessments should be carried out prior to production at scale, and the depth of these assessments should reflect the complexity of the reaction system and the magnitude of the hazards identified. The ultimate goal should be to eliminate or reduce the reaction hazards by designing inherently safer processes. However, this is not always possible and a means of evaluating the hazards is therefore required. The information gained from such assessments does not need to be confined to making processes safer, since much of it can also be utilized in ensuring rapid and efficient scale-up. Reactive hazard evaluation, therefore, plays an integral part in our overall development effort at Gillingham through direct contact with development chemists, chemical engineers, and project managers.

6. Acknowledgments

I would like to thank all my friends and colleagues in the Production facility at Sigma-Aldrich, Gillingham, UK, for their assistance in the preparation of this article. Thanks also to my wife, Lia, for her support, patience, and editorial skills.

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Gordon Amery was born in 1957 in Wirral, Merseyside, UK. He received a Bachelor of Science degree from the University of Manchester Institute of Science and Technology (U.M.I.S.T.) in 1978. After spending some time as a research chemist with Roche Products Ltd., he moved to Sterling Organics Ltd. (now Rhodia ChiRex), where he later headed up the hazard evaluation laboratory. In 1997, he joined Sigma-Aldrich in Gillingham as Hazard Evaluation Manager. He is credited with setting up the hazard evaluation laboratory in the new cGMP production facility in Gillingham.

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250	14/20	**Z51,591-4**
250	24/40	**Z51,592-2**
250	29/32	**Z51,593-0**
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50	29/32	**Z51,556-6**
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1,000	24/40	**Z51,563-9**
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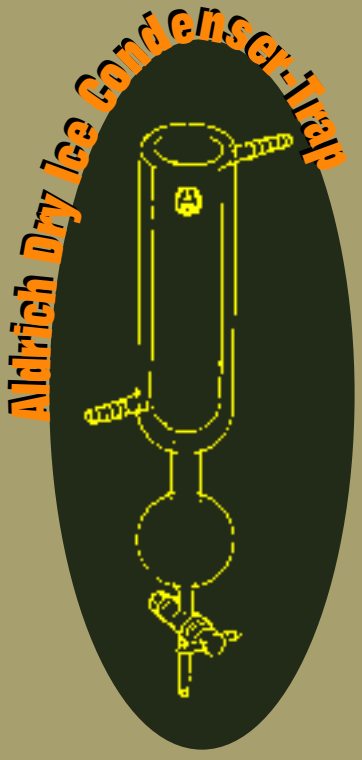

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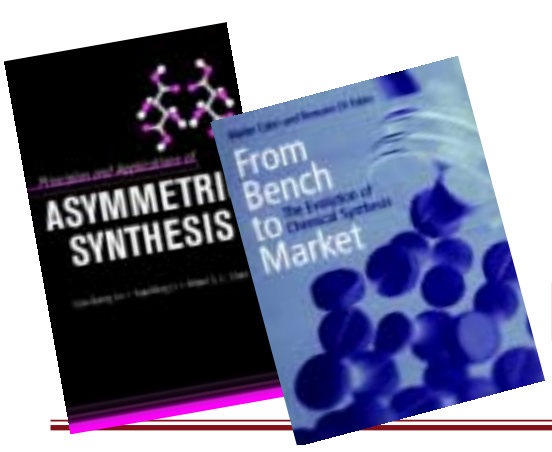

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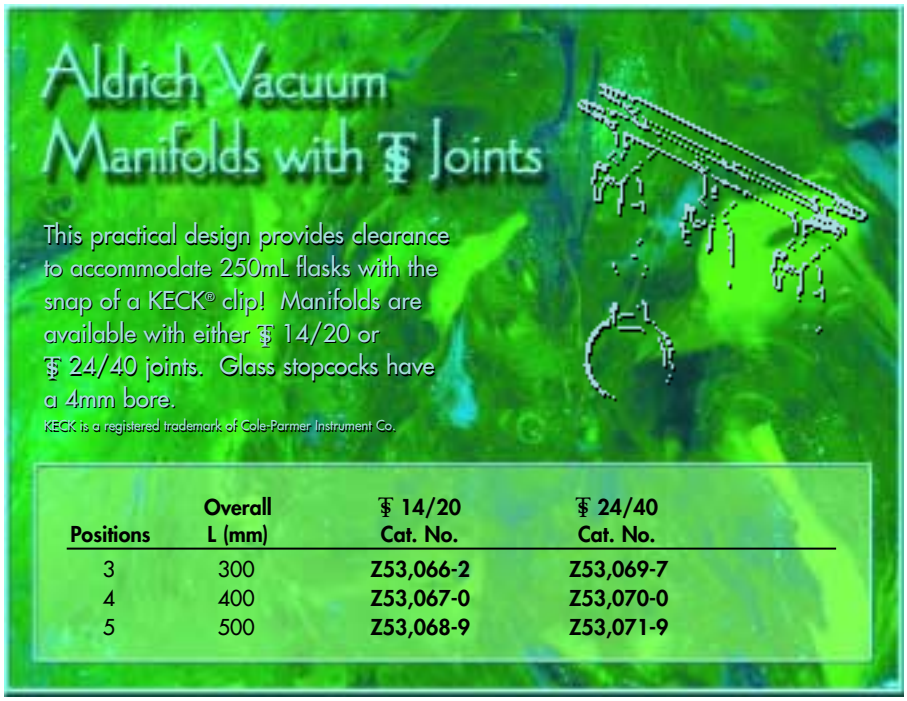

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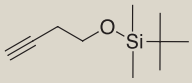
Aldrichimica ACTA

VOL. 34, NO. 3 • 2001
(Last issue in 2001)

Solid-Phase Dendrimer Chemistry

[Hydroxy(tosyloxy)-iodo]benzene

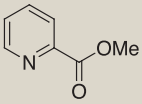
54,167-2 4-(*tert*-Butyldimethylsilyloxy)-1-butyne, 97%



Has been utilized for a transition-metal-catalyzed regioselective cyclotrimerization with enones[1] and as a starting material in the synthesis of (±)-asteriscanolide.[2]

(1) Ikeda, S.-I. et al. *Chem. Commun*. **2000**, 815. (2) Krafft, M. E. et al. *Synthesis* **2000**, 1020.

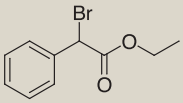
55,628-9 Methyl picolinate, 99%



Useful as a ligand for the formation of metal complexes[1] and as a starting material for the synthesis of biologically active aza-anthraquinones.[2]

(1) Britovsek, G. et al. *J. Mol. Catal. A: Chem.* **1996**, *110*, 77. (2) Epsztajn, J. et al. *Tetrahedron* **1996**, *52*, 11025.

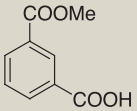
55,406-5 Ethyl α-bromophenylacetate, 97%



This versatile alkylating reagent has been utilized in the preparation of multifunctional phosphonates,[1] oxazinones,[2] and α-alkoxycarbonyl compounds.[3]

(1) Prager, R. H. et al. *Aust. J. Chem.* **1997**, *50*, 813. (2) Remuzon, P. et al. *Tetrahedron* **1997**, *53*, 17711. (3) Berglund, P. et al. *Tetrahedron: Asymmetry* **1999**, *10*, 4191.

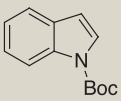
55,540-1 Monomethyl isophthalate, 97%



Was recently used to introduce structural variations in benzazepines,[1] and to synthesize a monomer for the preparation of an authentic H–T poly(amide–ester).[2]

(1) Murakami, Y. et al. *J. Med. Chem.* **1999**, *42*, 2621. (2) Li, L. et al. *Macromolecules* **1999**, *32*, 3851.

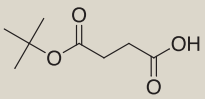
51,810-7 *tert*-Butyl 1-indolecarboxylate, 97%



Allows the easy preparation of indole-2-boronic acid[1] and the corresponding 3-nitroindole.[2]

(1) de Koning, C. B. et al. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1705. (2) Pelkey, E. T.; Gribble, G. W. *Synthesis* **1999**, 1117.

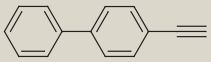
54,735-2 Mono-*tert*-butyl succinate, 97%



Key building block for the construction of a chiral lactone that is a versatile intermediate for possible HIV-1 protease inhibitors,[1] and for the construction of the carbacephem β-lactam framework.[2]

(1) Solladié-Cavallo, A. et al. *Tetrahedron: Asymmetry* **1996**, *7*, 1797. (2) Guzzo, P.R.; Miller, M. J. *J. Org. Chem.* **1994**, *59*, 4862.

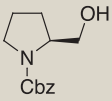
52,117-5 4-Ethynylbiphenyl, 97%



This terminal acetylene has been converted to enamines with resin-bound 2° amines.[1] It is also suitable for Pd(0)-mediated coupling on solid supports.[2]

(1) Aznar, F. et al. *Tetrahedron Lett.* **2000**, *41*, 5683. (2) Berteina, S. et al. *Synlett* **1998**, 676.

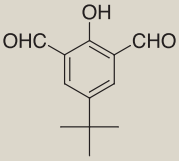
51,296-6 Z-L-prolinol, 97%



Useful for synthesizing peptidomimetics. A relatively recent application is in the synthesis of an ester mimic for the generation of catalytic antibodies.

Anderson, G. T. et al. *J. Org. Chem.* **1996**, *61,* 125.

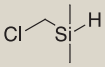
55,415-4 4-*tert*-Butyl-2,6-diformylphenol, 96%



Reported applications for this diformylphenol include the synthesis of binucleating macrocyclic ligands[1] and homooxocalix[*n*]arenes.[2]

(1) Lindoy, L. F. et al. *Synthesis* **1998**, 1029. (2) Komatsu, N. *Tetrahedron Lett.* **2001**, *42*, 1733.

55,587-8 Chloromethyl(dimethyl)silane, 97%

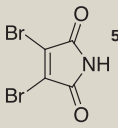


Hydrosilylation of olefins using this reagent provides the corresponding chloromethyl(dimethyl)silyl (CMDMS) derivatives.[1,2] This method was employed to introduce CMDMS groups on the terminal branches of carbosilane dendrimers.[2]

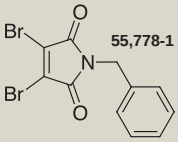
(1) Thibon, J. et al. *J. Org. Chem.* **1997**, *62*, 4635. (2) Krska, S. W.; Seyferth, D. *J. Am. Chem. Soc.* **1998**, *120*, 3604.

55,360-3 2,3-Dibromomaleimide, 97%

55,778-1 *N*-Benzyl-2,3-dibromomaleimide, 97%



55,360-3



55,778-1

Dihalogenated maleimides have applications in a broad spectrum of synthetic transformations, such as mono- or disubstitutions, Suzuki-type couplings, Grignard reactions, and Diels–Alder cyclizations. They are key intermediates in the synthesis of arcyriarubin,[1] staurosporine,[2] and pyrroloquinoxaline systems.[3]

(1) Mahboobi, S. et al. *Pharmazie* **1999**, *54*, 820. (2) Joyce, R. P. et al. *J. Org. Chem.* **1987**, *52*, 1177. (3) Hanaineh-Abdelnour, L. et al. *Tetrahedron* **1999**, *55*, 11859.

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About Our Cover

Edouard Manet's *Masked Ball at the Opera* (oil on canvas, 23¼ in. x 28½ in.), signed and dated 1873, is a reminder of one of the many sophisticated entertainment forms available to Parisians in the third quarter of the nineteenth century: the balls held at the opera on Saturday nights in March during Lent. The foyer of the old Opera House in the Rue Le Peletier is shown crowded with figures. The flowing line of the silk hats of a large group of elegantly dressed gentlemen creates a graceful rhythm across the center of the scene, helping to unify an otherwise somewhat fragmented composition. The informality and great variety of poses of the figures and the seemingly random cropping on either side and across the top of the image give a sense of immediacy and realism to the scene. The figures of Polichinelle on the left, of the gentleman on the right edge of the canvas, and of those on the balcony are all cut off by the frame, suggesting that only a small part of what is going on is visible in the picture. Manet included portraits of himself and several of his friends in the painting, which is remarkable for the absence of color. Manet saw the men's silk hats and evening clothes as a unique opportunity to depict every variation of ebony.

This painting is a gift of Mrs. Horace Havemeyer to the National Gallery of Art in Washington, D.C.

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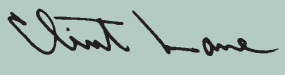

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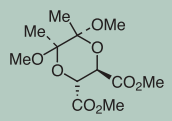

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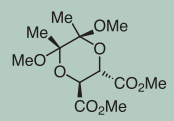

55,693-9

Professor Steven V. Ley of the University of Cambridge, U.K., kindly suggested that we offer these enantiomeric 2,3-butanediacetal-protected dimethyl tartrates. These compounds have been used in the synthesis of protected chiral tetrol derivatives[1] and for the transfer of chirality in enantioselective reactions.[2]

(1) Dixon, D. J.; Foster, A. C.; Ley, S. V.; Reynolds, D. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1635. (2) Barlow, J. S.; Dixon, D. J.; Foster, A. C.; Ley, S. V.; Reynolds, D. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1627.

55,692-0
(2*R*,3*R*,5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-[1,4]dioxane-2,3-dicarboxylic acid dimethyl ester, 98%

55,693-9
(2*S*,3*S*,5*S*,6*S*)-5,6-Dimethoxy-5,6-dimethyl-[1,4]dioxane-2,3-dicarboxylic dimethyl ester

Naturally, we made these useful 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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Lab Notes

Rapid-Dry TLC Spotter

Flash chromatography can very quickly generate a lot of samples that may require spotting on a TLC plate for analysis. If you want to get small spots at the origin you have to add the solvent slowly while blowing on the spot to evaporate the solvent. This can lead to hyperventilation or solvent inhalation and, depending on the number of fractions, can take longer than running the column.

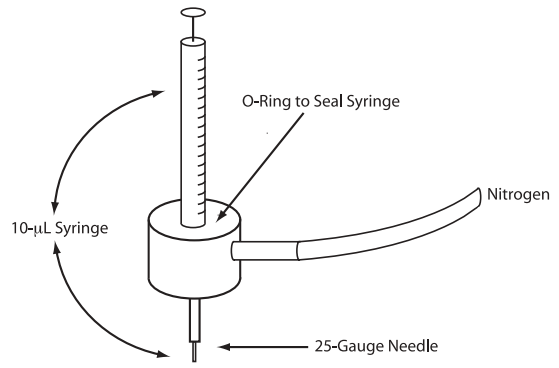

Figure 1

To simplify this operation and speed up the process, I devised a simple apparatus (**Figure 1**) to facilitate spotting of the TLC plate. The device is made from a cylinder of polymer in which the top is bored out to receive a flat-nosed, 10-microliter syringe, which is held in place by an O-ring (a trace of silicone grease on the O-ring facilitates the insertion and removal of the syringe barrel). A hose connector is attached to the side of the cylinder and used as an inlet for nitrogen. A hole in the bottom of the cylinder is fitted with a 25-gauge needle through which the tip of the 10-microliter syringe just emerges when inserted through the top. Nitrogen flows into the body of the device, down through the 25-gauge annulus and around the syringe needle, where it evenly and quickly evaporates the solvent as it is applied by depression of the syringe plunger.

This device has saved me countless hours while spotting TLC plates with flash chromatography fractions, especially those in higher boiling solvents. You also get narrower spots and thus achieve better resolution upon development of the TLC plate.

Dennis K. Klipa, Ph.D.
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Midland, MI 48674
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Solid-Phase Dendrimer Chemistry: Synthesis and Applications

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Outline

1. Introduction

Dendrimers or "cascade-type molecules" are, if synthesized correctly, highly ordered, hyperbranched, and polyfunctional macromolecules.[1] There are two fundamentally different approaches for constructing dendrimers (**Figure 1**).[2] Both methods are based on the repetition of a sequence of reactions, with each sequence creating a new dendrimer generation. The divergent method, first reported by Vögtle for the synthesis of poly(propyleneimine) dendrimers, is based on the successive attachment of branching units to the core molecule.[3] As a result of this growth, each subsequent reaction is characterized by the generation of an exponentially increasing number of functional groups on the periphery. In contrast, the convergent approach involves the synthesis of dendrimeric fragments followed by their subsequent addition to the core. This method was initially described by Hawker and Fréchet for the preparation of the poly(aryl ether) architecture.[4] Since the emergence of dendrimers, a growing variety of structures with different cores, branching units, and end groups have been synthesized;[1,5] examples of such structures include Tomalia's polyamidoamine (PAMAM) dendrimers[6] and Newkome's arborol systems.[7] As a class of structurally fascinating molecules, these new materials have a wide spectrum of potential applications, ranging from drug-delivery systems to catalyst carriers.[1]

In a similar way, the last decade has seen the rapid development of solid-phase and combinatorial chemistry methodologies.[8] The application of combinatorial organic synthesis, especially toward drug discovery processes, has encompassed an increasing number of synthetic transformations[9] as well as a wider choice of solid supports and linkers.[10] The present review deals with the synthesis and applications of dendrimers synthesized on solid supports. Considerable progress has been made over the last 5 years in research in the area of solid-phase dendrimer synthesis. The following areas are now of growing interest: (i) *high-loading resin beads, (ii) multivalent compound construction, and (iii) solid-phase dendrimer synthesis.*

2. High-Loading Supports

Since it was first introduced, Split-and-Mix synthesis[11] remains the most efficient and cost-effective method of producing large numbers of compounds (up to one million compounds is readily achievable). This method is rendered even more powerful by the fact that each single bead (in essence a microreactor) carries a unique/single compound.[12] Unfortunately, the full potential of this technique has not been completely exploited for two main reasons: the small amount of compound that is linked to a single bead, and the need for an encoding strategy or a time-consuming deconvolution

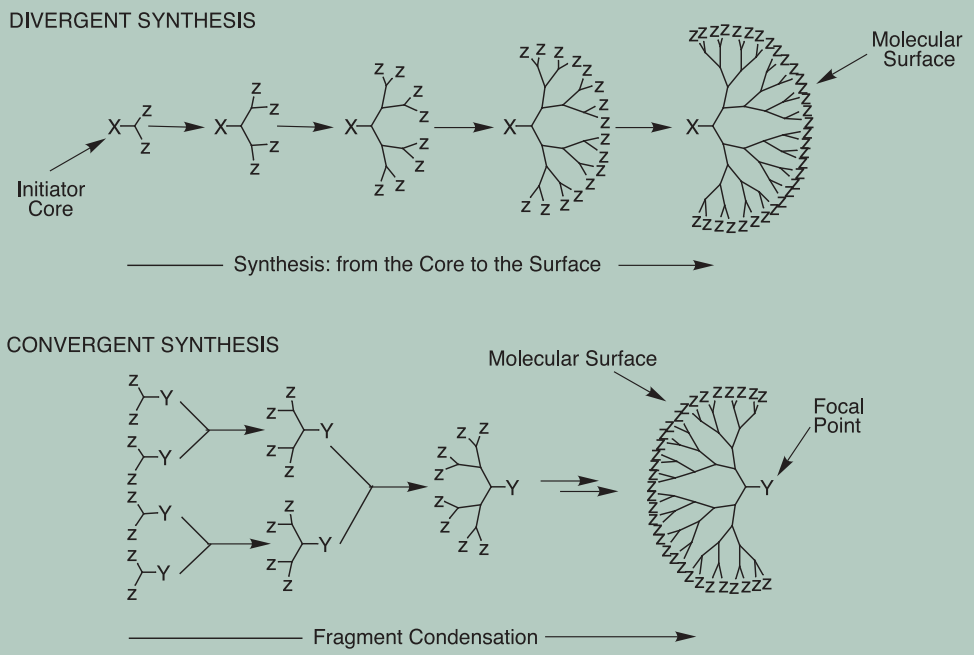


Figure 1. The Divergent and Convergent Methods of Dendrimer Synthesis.

analysis to identify the active compound following screening.[13] As a consequence, finding novel polymer beads with high-loading capacities for single-bead screening is proving to be of great interest.[14] Another area of concern for combinatorial chemistry is the need to optimize bead loading, yet maintain small volumes with suitable reaction kinetics. An additional advantage of high-loading beads is their application as resin supports or carriers for reagents or scavengers in parallel solution-phase synthesis.

2.1. Solid-Phase PAMAM Dendrimer Synthesis

In 1997, we described the synthesis of PAMAM dendrimers on the solid phase starting from TentaGel™ resin (**Figure 2**).[15] An acid-labile linker attached to a polyamine scaffold[16] was used to allow cleavage of the dendrimer from the resin in order to monitor the synthesis. Dendrimer synthesis was carried out by cyclic treatment with methyl acrylate in methanol and 1,3-diamino-propane in methanol. Generation 3.0 dendrimer-linked TentaGel™ was found to have a loading of approximately 2.3 mmol NH_2 per gram of resin, with each bead having between 5 and 6 nanomoles of free amino groups. This material was converted to a generation 4.0 dendrimer with a resin loading of 2.8 mmol/g and a single-bead loading of approximately 9.6 nmol/bead.

A generation 2.0 dendrimer was also synthesized on large polystyrene beads (250–300 μm, 1.02 mmol/g). A small inert polyethylene glycol (PEG) spacer was first introduced to allow efficient PAMAM dendrimer synthesis.[17] The high-loading resin beads were found to be physically robust and compatible with a wide range of solvents. Material from a single bead was sufficient to permit analysis by 500 MHz ^{1}H NMR. HPLC analysis revealed that approximately 32 nanomoles of essentially pure peptide was prepared from one bead. A small library based on Leu-enkephalin-Lys (Tyr-Gly-Gly-Phe-Leu-Lys) was synthesized, with cleavage and analysis from single beads possible by ES/MS and reverse phase HPLC (C-18, 15-cm column).

As the loading of the dendrimerized resin beads was considered satisfactory, the synthesis of a variety of small organic compounds was investigated to evaluate the resin beads (**Figure 3**).[18] It was believed that the resins would be inert towards a wide range of chemistries, as the dendrimers consist of only amide bonds and tertiary amino groups. Synthetic procedures involving strong bases or strong reducing agents were, however, not considered.

Starting with generation 3.0 PAMAM dendrimer linked to TentaGel™, a small library of aryl ethers was prepared via the Mitsunobu reaction in a semiautomated fashion on an Argonaut QUEST™ 210.[19] Results demonstrated that better yields were obtained with the dendrimer beads than with TentaGel™ alone, although high purity was found in all cases.

The synthesis of a small library of amidines as potential GP IIb-IIIa antagonists on TentaGel™ generation 2.0 and 3.0 PAMAM dendrimers was also carried out.[20] Analysis indicated purities greater than 40% in most cases; very encouraging since the final amidines were obtained in eight synthetic steps.

The reductive amination of (1-naphthylmethyl)amine using the Backbone Amide Linker (BAL)[21] attached to the PAMAM generation 3.0 TentaGel™ resin was carried out.[18] The resulting imine was reduced to the amine with tetrabutylammonium borohydride/acetic acid. Acylation with benzoic acid was followed by cleavage of the compound from the resin. A loading of 2.0 nmol/bead, half of the theoretical value, was found in accordance with the overall yield of the synthesis.

The reaction between an iodoaryl or iodoalkenyl derivative and a boronic acid (Suzuki coupling) is a commonly used reaction in solid-phase synthesis.[22] A Suzuki coupling, using 0.1 equivalent of $Pd(PPh_3)_4$ and 2 equivalents of potassium carbonate in DMF, was performed on the dendrimerized beads at 100 °C for 24 hours.[18] Although the resin was completely black at the end of the reaction, the desired compound was isolated

with a 90% purity and in 80% overall yield. The PAMAM dendrimer thus proved to be temperature-resistant and stable in the presence of potassium carbonate—an important observation as bases could induce retro-Michael reactions leading to leakage of dendrimer branches into solution.

2.2. Symmetrical 1→3 C-Branched Isocyanate Monomers

In an effort to produce resin beads with higher loadings, we became interested in AB_3-type dendrimers. In 1998, Newkome et al. reported the synthesis of AB_3-type isocyanate monomers **1** and **2** for dendritic construction (**Figure 4**).[23] The advantages of such an architecture over PAMAM dendrimers lie in the presence of a third branch for dendrimeric amplification and the possibility of direct solid-phase synthesis on polystyrene resins.

Monomer **1** was coupled with aminomethyl polystyrene resin (250–300 µm, 0.7 mmol/g) using *N*,*N*-diisopropylethylamine (DIPEA) and a catalytic amount of 4-(dimethylamino)pyridine (DMAP) in dichloromethane.[24] Displacement of the methyl ester with propane-1,3-diamine was followed by further coupling with the isocyanate monomer, and diamine treatment to afford generation 2.0 dendrimerized resin (**Figure 5**). These beads had a loading of 85% of the theoretical maximum (36 nmol per bead). They swelled to a much greater degree in more polar solvents than the starting aminomethyl polystyrene resin due to the nature of the dendrimer itself. Dendrimer synthesis was also carried out on 400–500 µm aminomethyl polystyrene beads, giving a loading of 116 nmol/bead for generation 1.0, and 230 nmol/bead for generation 2.0. The beads were successfully used for the synthesis of a tripeptide and for biaryl synthesis via Suzuki coupling. The cleaved product from a single bead gave good NMR data and a single peak by HPLC.

Although the structure afforded high-loading polystyrene resin beads, one limitation came from possible macrocyclization during ester displacement. This is more likely to occur at high generations, as steric hindrance and site-to-site interactions at the outer functional shell increase.[25] In order to prevent these undesired cross-coupling reactions, dendrimer synthesis using AB_3-type isocyanate monomers **2** and **3** was investigated. These types of monomers can easily be coupled to an amine via urea bond formation, followed by amine deprotection to afford the next generation with no danger of cross-coupling reactions.[26] Dendrimer synthesis was carried out on both aminomethyl polystyrene (0.7 nmol/bead, 75–150 µm) and aminomethyl TentaGel™ (0.7 nmol/bead, 160 µm) by reacting the isocyanate monomer, **2**, with DIPEA and DMAP, followed by removal of the *tert*-butoxycarbonyl group with 50% trifluoroacetic acid (TFA) in dichloromethane. The process was repeated until generation 3.0 was reached (**Figure 6**). The loadings were found to be 6.6 and 6.9 nmol/bead for polystyrene and TentaGel™, respectively, corresponding to an approximately 10-fold increase over the initial loading.[27] These resins swelled to a much greater degree in polar solvents. The same process was repeated with 250–300 µm polystyrene resin beads (initial loading 18 nmol/bead), and the first-generation dendrimer formed had a loading of 40.6 nmol/bead. However, most of the beads were observed to break when the *tert*-butoxycarbonyl groups were removed with 40% TFA in DCM. The damage was caused by the growing bubbles within the beads as a result of the formation of carbon dioxide and isobutylene during the deprotection reaction, as well as by the branches trying to position themselves as far apart as possible in order to minimize electronic repulsions (the so-called "umbrella effect"). In order to reduce potential

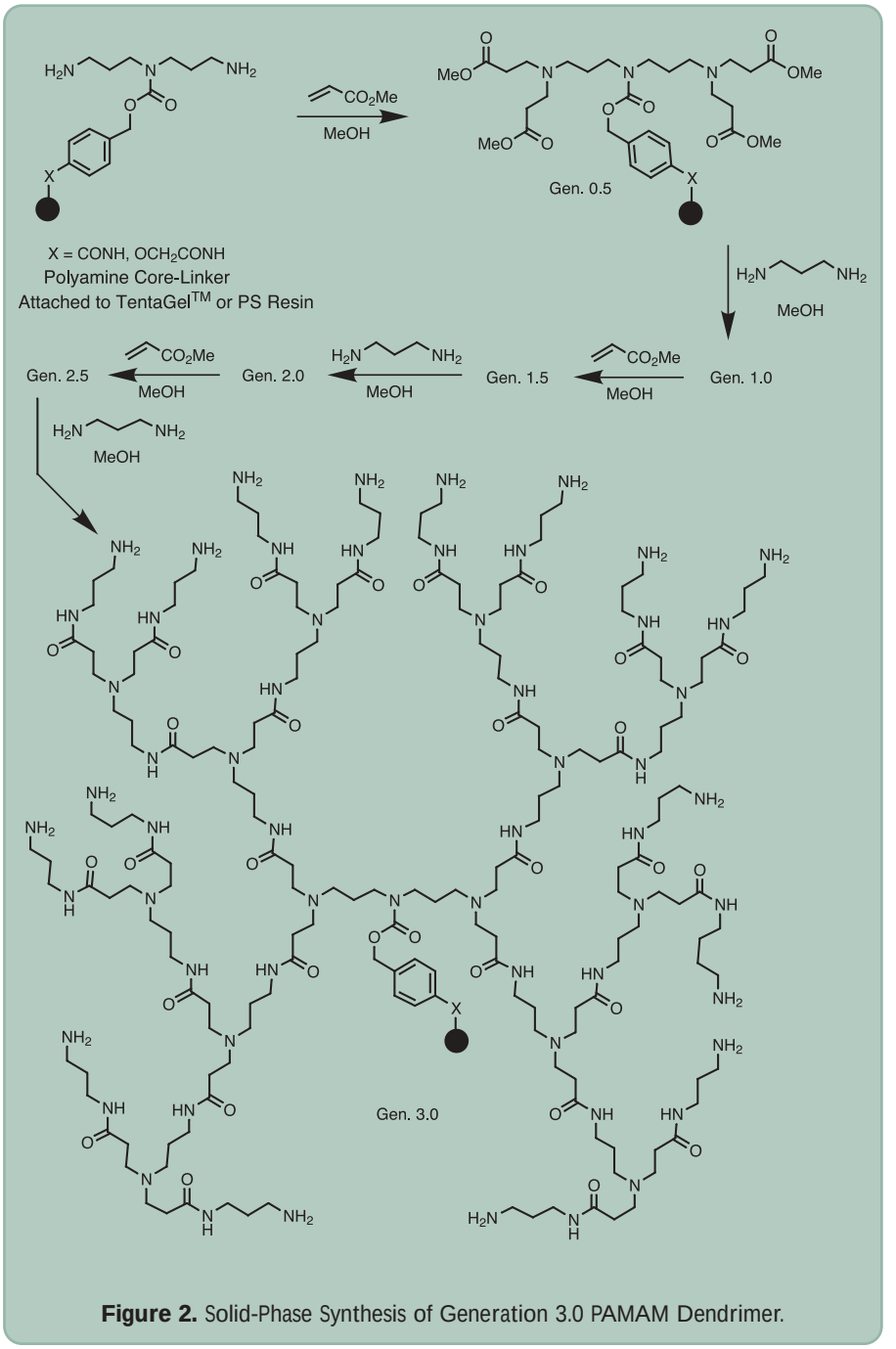


Figure 2. Solid-Phase Synthesis of Generation 3.0 PAMAM Dendrimer.

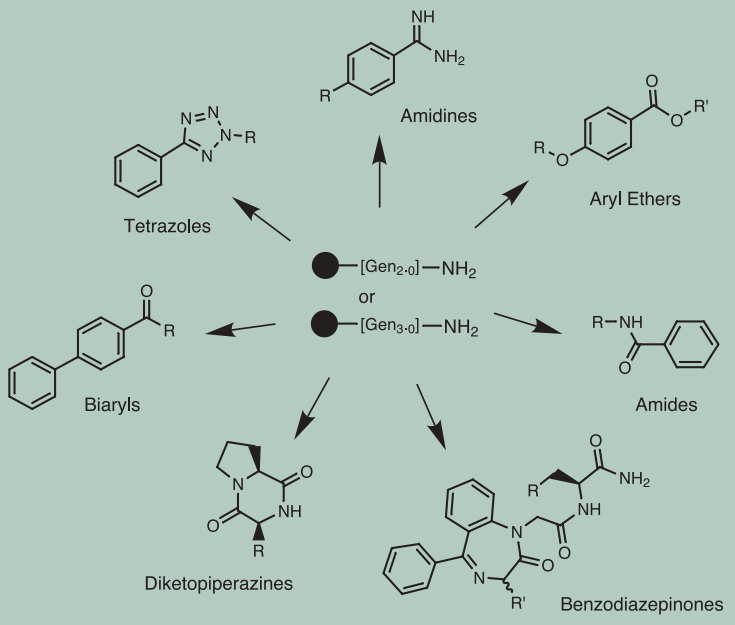


Figure 3. Different Chemistries Applied to Generation 2.0 or 3.0 PAMAM Resins.

electronic repulsions, we designed the isocyanate-type monomer, **3**, in which the distance between the branching point and the protected amino groups was increased from three to five atoms. Solid-phase dendrimer synthesis afforded generation 3.0 dendrimers on polystyrene (75–150 μm) and TentaGel™ (160 μm) with high loading capacities, 12.5 and 9.0 nmol/bead, respectively. 250–300-μm polystyrene resin beads were dendrimerized up to the second generation without breaking and with a loading of 120 nmol/bead.[27] These beads were robust and stable under a wide variety of solvent and reaction conditions.

2.3. Poly(aryl ether) Dendrimers

Due to the limitations of PAMAM dendrimers, such as the incompatibility of the dendrimer with strong reducing agents or bases and the possible occurrence of the retro-Michael reaction, a more inert dendrimeric scaffold was sought. Fréchet-type polyether dendrimers were therefore chosen and their solid-phase synthesis was investigated.[28] In dendrimer synthesis, ether

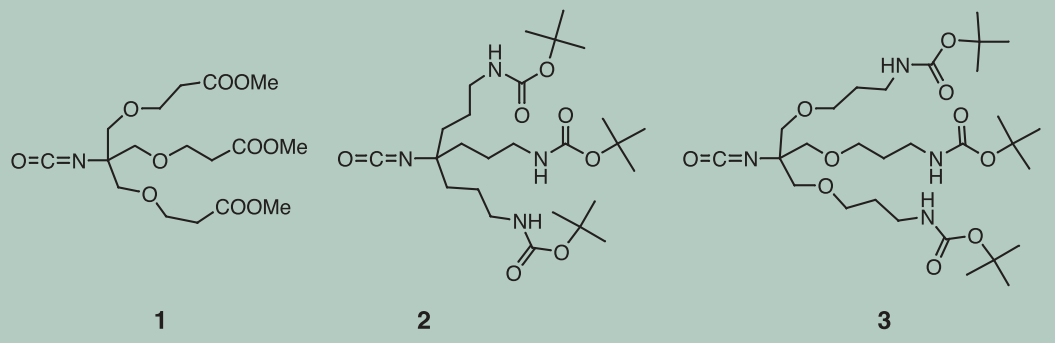


Figure 4. AB_3-Type Isocyanate Monomers.

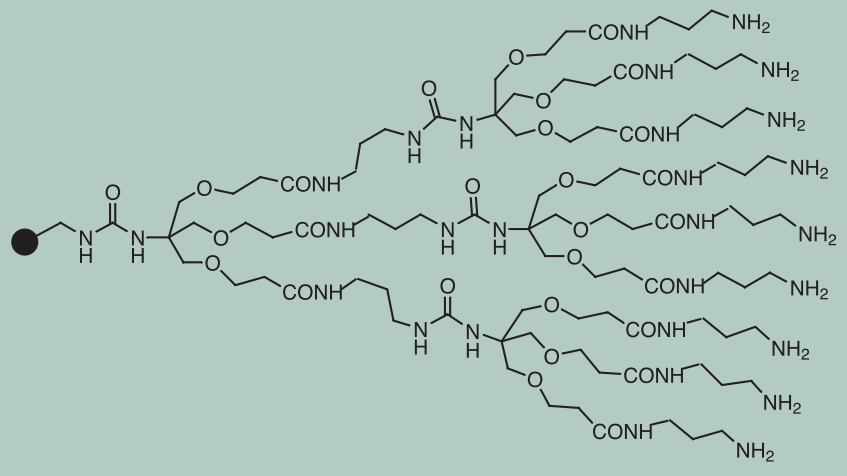


Figure 5. Generation 2.0 AB_3-Type Polyurea Resin-Bound Dendrimer.

bond formation is usually carried out via benzylic bromination followed by phenolic O-alkylation; however, it was believed that Mitsunobu condensation between a benzyl alcohol and a phenol would be more appropriate for the solid-phase. 3,5-Bis(acetoxymethyl)phenol was chosen as the building block for dendrimer construction. The synthesis was carried out on hydroxymethyl polystyrene in a two-step iterative procedure consisting of a Mitsunobu reaction using diisopropyl azodicarboxylate (DIAD) and triphenylphosphine followed by ester hydrolysis (**Scheme 1**). The resulting generation 3.0 dendrimer had a loading of 2.85 mmol/g or 3.0 nmol/bead, which corresponded to a 7-fold increase over that of the initial resin. The versatility of this resin was demonstrated by coupling methyl 4-hydroxybenzoate via the Mitsunobu reaction followed by reduction of the resin-bound methyl ester using $LiAlH_4$. This two-step procedure was found to be an efficient method to introduce the Wang linker, and the polyether dendrimer resin was perfectly stable to $LiAlH_4$ reduction. This new resin was used to synthesize the hexapeptide Leu-enkephalin-Lys. Following cleavage and purification, the peptide was isolated in 66% yield relative to the loading of the initial hydroxymethyl polystyrene resin.

2.4. Other High-Loading Supports

In 1999, Barrett et al. reported the use of ring-opening metathesis polymerization (ROMP) for the generation of high-loading resins (**eq 1**).[29] The cross-metathesis between vinyl polystyrene and different norbornene derivatives afforded "ROMP-spheres" with loadings of approximately 3 mmol/g. The synthesis of a biphenyl derivative by palladium-catalyzed coupling reaction was carried out to demonstrate the utility of the resin beads.

An alternate route was reported by Hodges et al.[30] Living free-radical polymerization, using TEMPO-methyl polystyrene resin with **4** and styrene, was carried out at 130 ˚C and afforded so-called "Rasta resins" with a loading level of approximately 2.5 mmol NCO/g (**eq 2**). This novel architecture is characterized by long, straight-chain polymers bearing isocyanates that emanate from the phenyl rings of a cross-linked polystyrene core. This resin has found applications in the scavenging of amines. Using a similar approach, "Rasta silane" resins were prepared from different silyl styrenes, **5**, (**eq 3**).[31] Loading capacities of these silane resins were up to 3.8 mmol/g. These beads appeared to be physically robust, similarly to polystyrene resin.

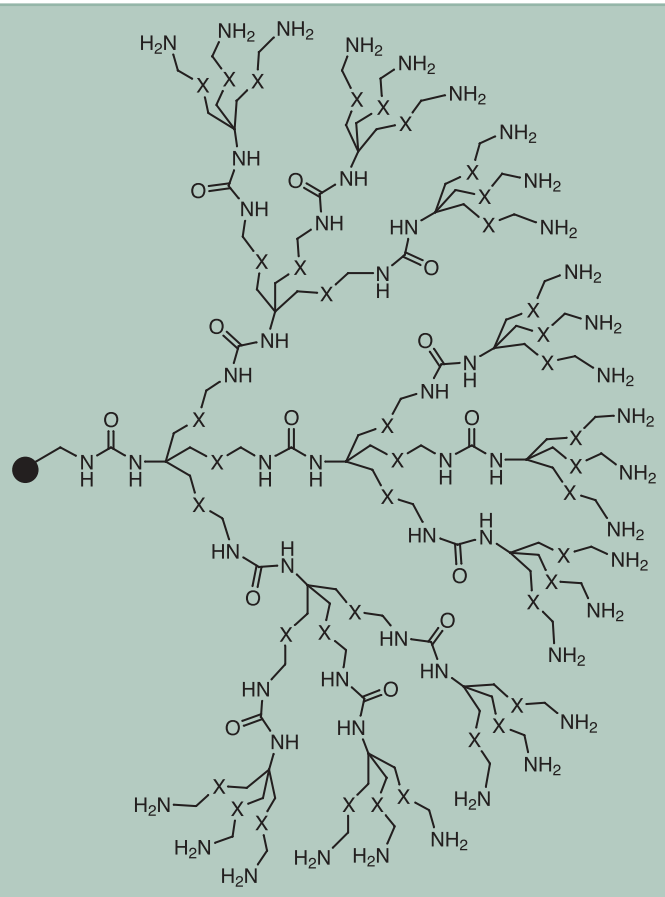
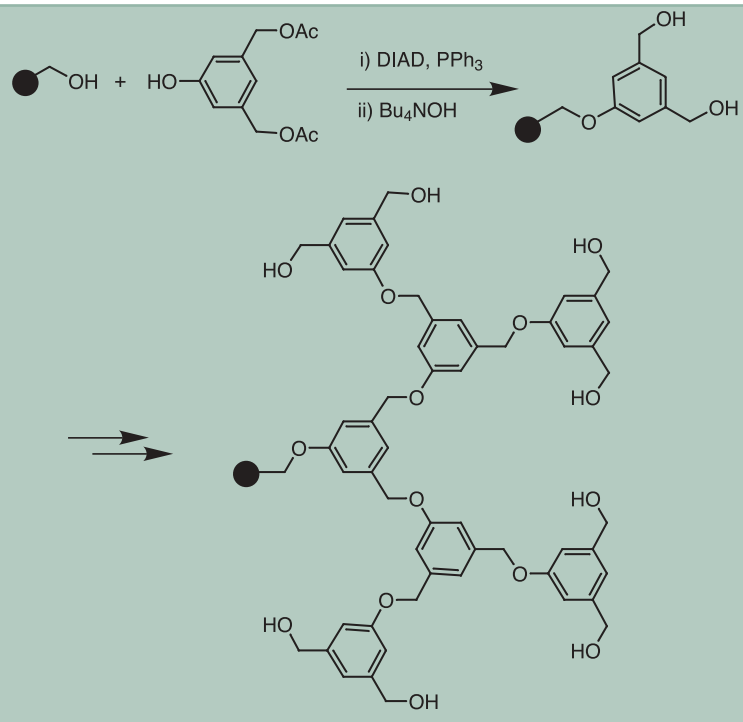
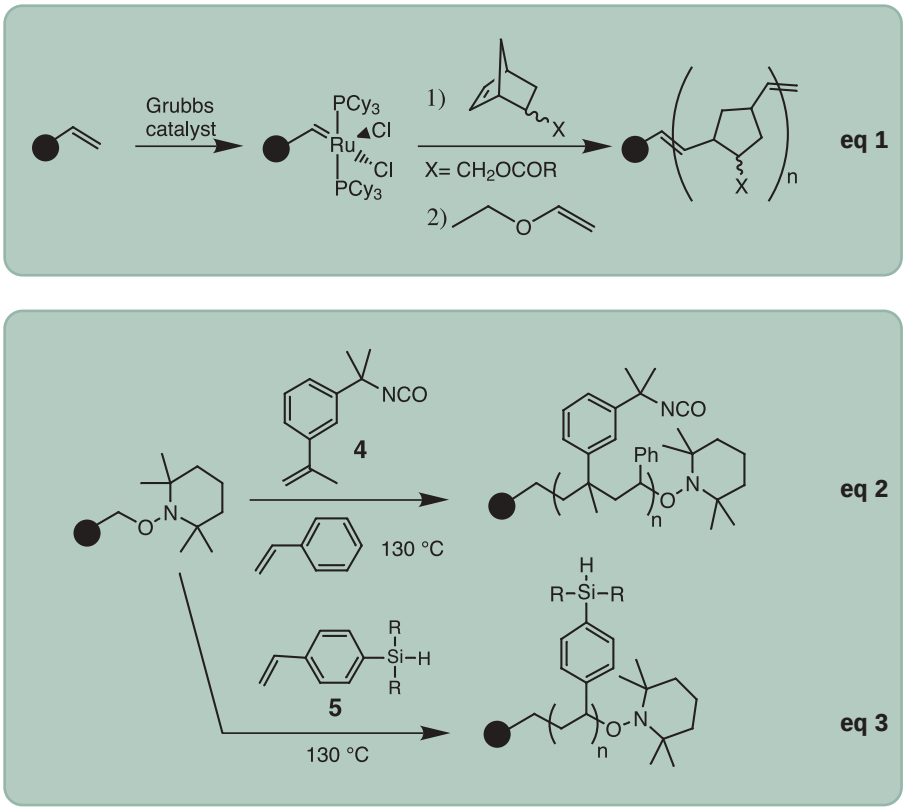


Figure 6. Generation 3.0 AB_3-Type Polyurea Resin-Bound Dendrimers (X = CH_2; OCH_2CH_2).



Scheme 1. Synthesis of Generation 3.0 Poly(aryl ether) Dendrimer.



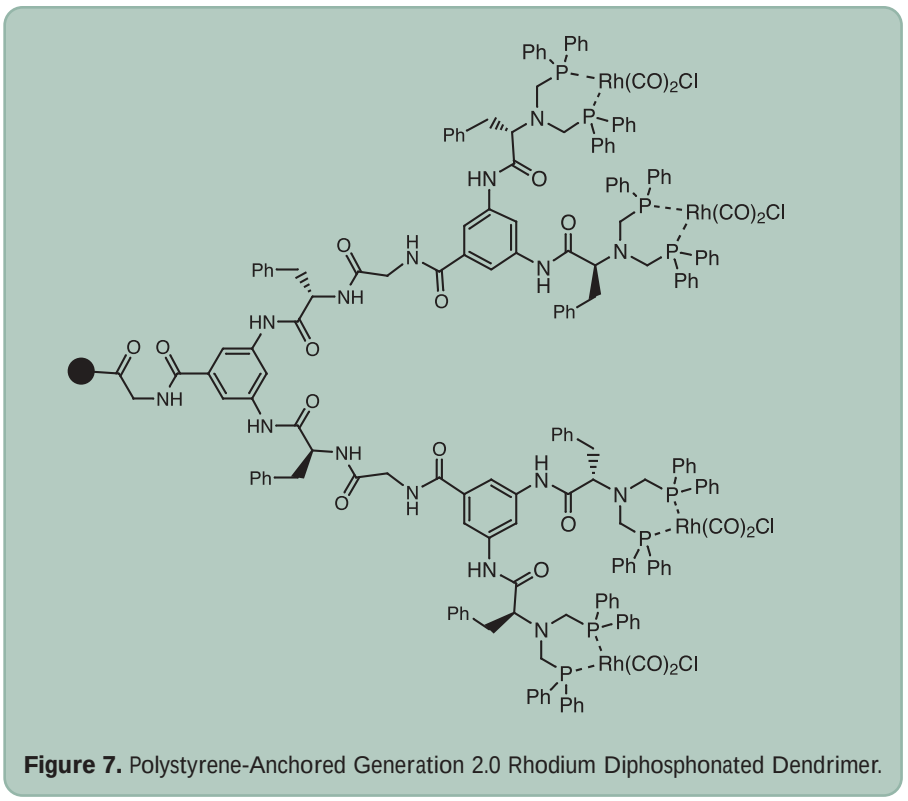


Figure 7. Polystyrene-Anchored Generation 2.0 Rhodium Diphosphonated Dendrimer.

Interest in high-loading resins as novel supports for parallel synthesis continues to increase. These resins have been successfully employed in the synthesis of small organic compounds and, increasingly, as scavengers and supported reagents.[32]

3. Multivalency

3.1. Multivalent Catalysts

Solid-phase dendrimer synthesis allows dendrimers to be readily conjugated to a variety of ligands and to offer multiple sites for metal coordination. The introduction of transition metals into dendrimers has been a recent trend and can be achieved either by surface modification, where metal complexation takes place at the periphery of the dendrimer, or by incorporating the metal within the dendritic infrastructure. Several groups have utilized the hyperbranched nature of dendritic materials to obtain multivalent ligands, and have tested them for homogeneous catalysis.[33] Arya and co-workers reported the solid-phase synthesis of rhodium-complexed PAMAM diphosphonated dendrimers anchored onto silica, and their application in the hydroformylation of olefins.[34] Aryl olefins and vinyl esters afforded branched-chain aldehydes in high regioselectivity. The heterogeneous catalyst was also recycled and reused without significant loss of selectivity or activity. A similar approach was then carried out using polystyrene beads, only using a pseudopeptide-based building block for solid-phase synthesis.[35] The building block, based on 3,5-diaminobenzoic acid, had two Fmoc-protected phenylalanine and one glycine unit coupled to the two amino groups and to the carboxylic acid, respectively. Dendrimer assembly on polystyrene resin was easily achieved by traditional peptide chemistry. Amino groups at each generation were then modified to obtain multivalent phosphine ligands at the surface of the beads (**Figure 7**). These dendritic phosphine ligands proved to be excellent catalysts for the hydroformylation of olefins.

3.2. Multivalent Compounds

Many biological binding events are enhanced by the operation of multivalent interactions. The adhesion of the influenza virus to epithelial cells,[36] the attachment of neutrophils to cells close to a site of inflammation,[37] and the attachment of antibodies to antigens[38] are just a few examples of such events.

It is evident from the sheer number of papers in the area of carbohydrate multivalent compounds, that the enhancement of weak nonbonding interactions of sugar ligands can be improved by the "cluster effect". Roy and co-workers have developed several types of neoglycoconjugates, including random-coil glycoconjugates, hyperbranched polymers, glycodendrons, and glycodendrimers **6** (**Figure 8**).[39] Kiessling and collaborators favored the linear polymer approach and have used ROMP to produce defined-length polymers with active *N*-hydroxysuccinimide esters, which were subsequently displaced by α-D-mannose derivatives to give polymers of type **7**.[40]

Whitesides's group generated linear polymers derivatized from poly(acrylic acid) and having multiple units of *N*-acetylneuraminic acid (NeuAc-Leu-NH_2) on the side chain, **8**.[41] The polymers were found to have affinities 10^6 times that of the monomer.

Despite growing interest, the multivalency approach has not been widely extended to the recognition of complex natural products or peptides. An example of a multivalent polymer of vancomycin, synthesized by ROMP, has shown significant 6- to 8-fold enhancements of antibacterial activity against vancomycin-resistant enterococci (VRE).[42]

Multivalent effectors have an application in understanding signal transduction pathways.[43] This approach has been used in the mimicry of erythropoeitin (EPO), which, upon binding, induces activation of many intracellular signalling molecules.[44] However, the most common synthetic effectors have been those that provoke an immune response; much synthetic effort has been put into attempts to produce an anticancer vaccine with carbohydrate antigens.[45]

3.3. Solid-Phase Synthesis of Multivalent Compounds

We have attempted to extend the cluster effect idea to peptide–protein interactions and to introduce a combinatorial aspect in both dendrimer and ligand synthesis. Cell–cell and cell–matrix interactions are involved in many disease states and entail a number of cell adhesion proteins, including integrins, which appear to be the major receptors by which cells attach to the extracellular matrix.[46] The integrin $\alpha_4\beta_1$ is found on numerous cell types including tumor cells, lymphocytes, and eosiniphils. The counterligand for $\alpha_4\beta_1$ is found in the CS-1 region of fibronectin, a cell adhesion protein, and the minimal peptide sequence for recognition is LDV (Leu-Asp-Val)[47] [the LDV motif is analogous to the RGD (Arg-Gly-Asp) motif, which is also found in fibronectin and has an extremely low affinity for the receptor compared to fibronectin]. This has led us to an investigation of the effect of the multivalent presentation of LDV on integrin binding.

Exploiting the solid-phase methodology developed in our laboratories, LDV-containing peptide–dendrimer conjugates have been synthesized on resin **9** (**Figure 9**) using standard peptide chemistry. The compound resulting from the synthesis of peptide EILDVPST on dendrimer scaffold **9** was found to be 12-fold more potent than the monomeric peptide.[48] In order to discover the best short-sequence peptide ligand for dendrimeric presentation, a small library of

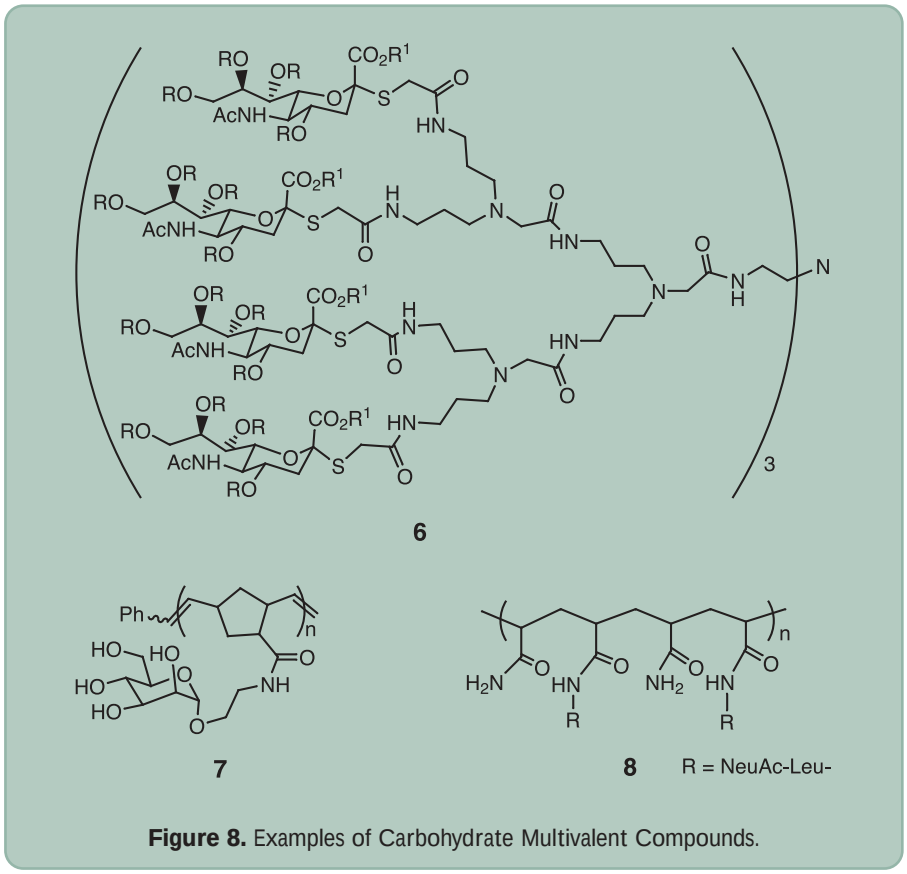


Figure 8. Examples of Carbohydrate Multivalent Compounds.

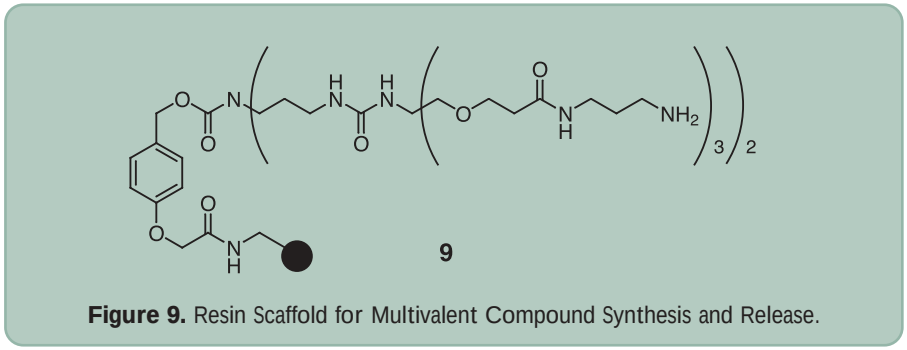


Figure 9. Resin Scaffold for Multivalent Compound Synthesis and Release.

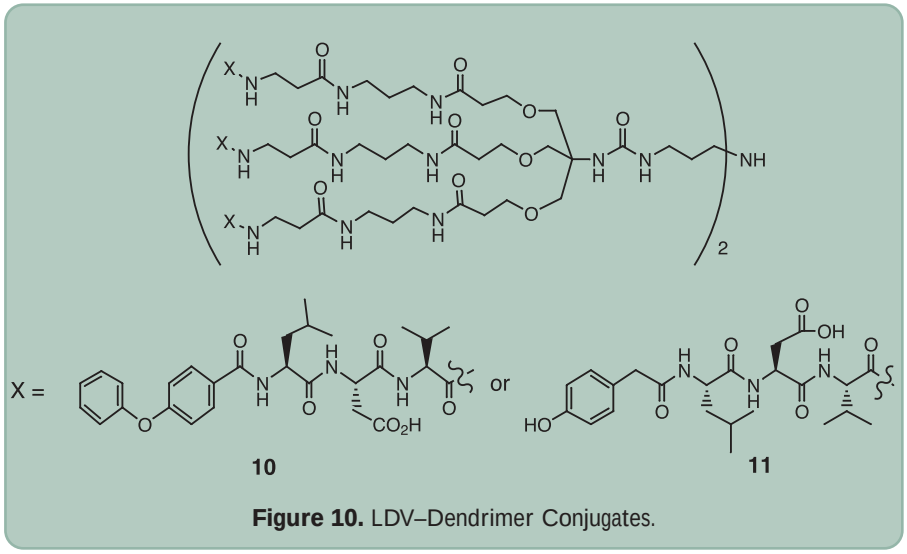


Figure 10. LDV–Dendrimer Conjugates.

divalent compounds with different capping groups on the LDV sequence was synthesized. Ligands **10** and **11** (**Figure 10**) were chosen for further dendrimeric presentation, and it was again found that the affinity of the ligands could be increased by dendrimeric presentation.[48]

Solid-phase synthesis of peptide–dendrimer conjugates has proved to be an efficient method for investigating the increases in affinity observed in multivalent ligand receptor interactions. We have observed that dendrimeric compounds are more potent than their monovalent forms, although not to the extent expected.

4. Conclusion and Prospects

Dendrimers have certainly caught the imagination of the chemical community, and their utility has now begun to be exploited. Solid-phase synthesis and conjugation is one very appealing means to this end, and offers an attractive route to homogeneous dendrimer materials. It allows the straightforward conjugation of biological ligands or catalysts to the dendrimers, an important concept in the areas of multiple valency and catalyst cooperativity. The solid-phase synthesis of dendrimers also offers a unique entry to high-loading supports for potential use in a range of reactions. Solid-phase dendrimer chemistry appears to have a bright and exploitable future.

5. Acknowledgments

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About the Authors

Sylvain Lebreton was born in France in 1974. After receiving his B.S. degree in 1997 from the University of Kingston, UK, he went to work for Selectide Corporation in Tucson, Arizona, and then Rhone-Poulenc Rorer in France, where he was introduced to combinatorial chemistry. His interests in solid-phase chemistry led him to work towards a Ph.D. degree with Professor Bradley at Southampton University, where he is focusing on solid-phase dendrimer chemistry and single-bead screening.

Seán Monaghan was born in 1975 in Enniskillen, N. Ireland. He received his first degree, "chemistry with extended studies in Europe", from Queens University in Belfast. In September 1998, he joined Professor Bradley's group. His Ph.D. research is centered on the synthesis of

peptide–dendrimer conjugates in an investigation of the multivalent effect of integrins.

Mark Bradley was born in the UK in 1962. He received his first degree from the University of Oxford in 1986 and his D.Phil., in the area of penicillin biosynthesis, from the same institution three years later under the supervision of Professor Sir Jack Baldwin. In 1989, he moved to the USA to work with Professor Chris Walsh at Harvard Medical School. In 1992, he joined Southampton University as a Royal Society University Research Fellow. He was made a Professor of Combinatorial Chemistry in 1997, and has published in excess of 50 papers in the combinatorial chemistry field. In January 2000, he became Director of the Combinatorial Centre of Excellence now housed in Southampton. His research interests span the whole spectrum of combinatorial high-throughput synthesis, screening, and analysis from an academic viewpoint. This includes interests in solid-phase and small-molecule synthesis as well as combinatorial activities in the area of catalysts, dendrimers, fluorophores, and polymers. He is also active in the area of enzyme inhibition, including research on proteases, antibacterial agents, and antiparasitics.

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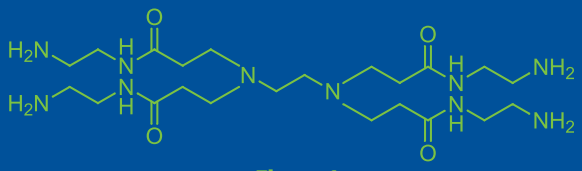

Figure 1

Generation	Aldrich Cat. No.*	Form	No. of Surface Groups	Unit Size	Unit Size
PAMAM Dendrimers with Primary Amino Surface Groups					
0.0	41,236-8	20 wt. % solution in methyl alcohol	4	5g	25g
1.0	41,238-4	20 wt. % solution in methyl alcohol	8	5g	25g
2.0	41,240-6	20 wt. % solution in methyl alcohol	16	5g	25g
3.0	41,242-2	20 wt. % solution in methyl alcohol	32	5g	25g
4.0	41,244-9	10 wt. % solution in methyl alcohol	64	2.5g	10g
5.0	53,670-9	5 wt. % solution in methyl alcohol	128	5g	
6.0	53,671-7	5 wt. % solution in methyl alcohol	256	5g	
7.0	53,672-5	5 wt. % solution in methyl alcohol	512	2.5g	
8.0	53,674-1	5 wt. % solution in methyl alcohol	1024	2.5g	
9.0	53,676-8	5 wt. % solution in methyl alcohol	2048	2g	
10.0	53,677-6	5 wt. % solution in methyl alcohol	4096	2g	
PAMAM Dendrimers with Carboxylate Surface Groups					
-0.5	52,614-2	Neat powder	4	1g	5g
0.5	41,237-6	20 wt. % solution in methyl alcohol	8	5g	25g
1.5	41,239-2	20 wt. % solution in methyl alcohol	16	1g	5g
2.5	41,241-4	10 wt. % solution in methyl alcohol	32	2.5g	10g
3.5	41,243-0	10 wt. % solution in methyl alcohol	64	2.5g	10g
4.5	47,045-7	5 wt. % solution in methyl alcohol	128	2.5g	10g
5.5	53,678-4	5 wt. % solution in methyl alcohol	256	5g	
6.5	53,679-2	5 wt. % solution in methyl alcohol	512	2.5g	
7.5	53,680-6	5 wt. % solution in methyl alcohol	1024	2.5g	
PAMAM Dendrimers with Hydroxyl Surface Groups					
2.0	47,783-4	20 wt. % solution in methyl alcohol	16	5mL	25mL
3.0	47,784-2	20 wt. % solution in methyl alcohol	32	5mL	25mL
4.0	47,785-0	10 wt. % solution in methyl alcohol	64	2.5g	10g
5.0	53,681-4	5 wt. % solution in methyl alcohol	128	5g	
6.0	53,682-2	5 wt. % solution in methyl alcohol	256	5g	
7.0	53,683-0	5 wt. % solution in methyl alcohol	512	2.5g	
PAMAM Dendrimers with 75% Primary Amino and 25% [*N*-(2-hydroxydodecyl)] Surface Groups					
2.0	53,684-9	20 wt. % solution in methyl alcohol	16	10g	
3.0	53,686-5	20 wt. % solution in methyl alcohol	32	10g	
4.0	53,696-2	10 wt. % solution in methyl alcohol	64	5g	
PAMAM Dendrimers with 50% Primary Amino and 50% [*N*-(2-hydroxydodecyl)] Surface Groups					
2.0	53,685-7	20 wt. % solution in methyl alcohol	16	10g	
3.0	53,687-3	20 wt. % solution in methyl alcohol	32	10g	
4.0	53,697-0	10 wt. % solution in methyl alcohol	64	5g	

*Manufactured by Dendritech, Inc.

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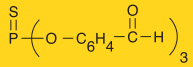
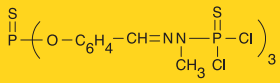
(1) *Functional Polymers and Dendrimers: From Synthesis to Application.* Proceedings of the American Chemical Society, Division of Polymeric Materials: Science & Engineering, San Diego, CA, April 1–5, 2001; American Chemical Society: Washington, DC, 2001.

THIOPHOSPHORYL DENDRIMERS

22,429-4
Thiophosphoryl chloride, Gen. 0.0

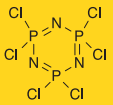


55,176-7
Thiophosphoryl-PMMH-3
Dendrimer, Gen. 0.5

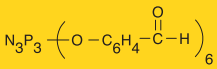


55,177-5
Thiophosphoryl-PMMH-3
Dendrimer, Gen. 1.0

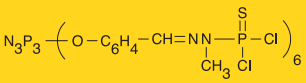
CYCLOTRIPHOSPHAZENE DENDRIMERS



23,028-6
Hexachlorocyclotriphosphazene,
Gen. 0.0



55,201-1
Cyclotriphosphazene-PMMH-6,
Gen. 0.5



55,205-4
Cyclotriphosphazene-PMMH-6,
Gen. 1.0

Thiophosphoryl-PMMH Dendrimers*

Catalog No.	Generation	No. of Surface Groups	Unit Size
Surface Group: Aldehyde			
55,176-7	0.5	3	1g
55,167-8	1.5	6	500mg
55,169-4	2.5	12	500mg
55,171-6	3.5	24	500mg
55,173-2	4.5	48	500mg
55,175-9	5.5	96	300mg
Surface Group: Dichlorophosphinothioyl			
55,177-5	1.0	3	500mg
55,168-6	2.0	6	500mg
55,170-8	3.0	12	500mg
55,172-4	4.0	24	500mg
55,174-0	5.0	48	300mg

Cyclotriphosphazene-PMMH Dendrimers*

Catalog No.	Generation	No. of Surface Groups	Unit Size
Surface Group: Aldehyde			
55,201-1	0.5	6	1g
55,206-2	1.5	12	500mg
55,213-5	2.5	24	500mg
55,211-9	3.5	48	500mg
55,209-7	4.5	96	500mg
55,214-3	5.5	192	300mg
Surface Group: Dichlorophosphinothioyl			
55,205-4	1.0	6	500mg
55,207-0	2.0	12	500mg
55,212-7	3.0	24	500mg
55,210-0	4.0	48	500mg
55,208-9	5.0	96	300mg

**PMMH = PhenoxyMethyl(MethylHydrazono)*

2002 ACS Award Recipients

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

Professor Myers has had a remarkable career and an enviable record as a synthetic organic chemist. In a relatively short period of time, he has established himself as a leader in the field, as attested to by the more than 90 publications and patents he has published and the dozen or so prestigious professional awards he has received. Examples of the latter include the Presidential Young Investigator Award, the Arthur C. Cope Scholar Award, and the current ACS award. Originality, keen insight, and practicality have characterized his research, which has spanned a range of areas: synthesis of natural products and biologically active compounds (e.g., tunicamycins, dynemicins, saframycin A), synthetic methodology and new-reagent development (e.g., lithium amidotrihydroborate, pseudoephedrine amides, silicon-directed aldol condensations), and mechanistic studies.

ACS Award for Creative Work in Synthetic Organic Chemistry:
Professor Andrew G. Myers, Harvard University

Exceptional creativity and deep insight have characterized the approaches that Professor Rauchfuss has used in tackling challenging research problems. While he has made significant contributions to several areas of inorganic and organometallic chemistry, he is perhaps better known for his accomplishments in the areas of sulfur ligand chemistry (hydrodesulfurization catalysis, modeling of the active sites of hydrogenases), synthesis of new Ru–S clusters, and the development of organometallic "containers" (e.g, $\{K[Mo_6(\mu\text{-}CN)_9(CO)_{18}]\}^{8-}$). Professor Rauchfuss is also a popular, sought-after lecturer and has received professional recognition from several sources, including the J.S. Guggenheim Memorial Foundation, the Alfred P. Sloan Foundation, and the Alexander von Humboldt Foundation.

ACS Award in Inorganic Chemistry:
Professor Thomas B. Rauchfuss, University of Illinois at Urbana-Champaign

This award recognizes Professor Heathcock's exceptional accomplishments in synthetic organic chemistry, principally his studies of stereoselectivity in the aldol and Michael reactions and his elegant total syntheses of numerous complex natural products (e.g., daphnilactone A, lycopodine, methyl homodaphniphyllate, and methyl homosecodaphniphyllate). His outstanding contributions to the field of organic chemistry have also been acknowledged with several other awards (e.g., the A. C. Cope Scholar Award, the ACS Award for Creative Work in Synthetic Organic Chemistry, and the RSC Centenary Medal). In addition to being one of the leading figures in organic synthesis, Professor Heathcock is also a distinguished teacher, lecturer, and editor. Noteworthy are his decade-long tenure as Editor-in-Chief of the Journal of Organic Chemistry and his many significant contributions to chemistry teaching and research.

Herbert C. Brown Award for Creative Research in Synthetic Methods:
Professor Clayton H. Heathcock, University of California, Berkeley

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20,559-1	**Sodium borodeuteride**, 98 atom % D	**1g** **5g**
19,002-0	**Sodium cyanoborodeuteride**, 96 atom % D	**1g**

Deuterium

36,840-7	**Deuterium**, 99.96 atom % D (Packaged in lecture bottle with CGA 110/170 outlet)	**10L** **25L**
36,186-0	**Deuterium**, 99.8 atom % D (Packaged in lecture bottle with CGA 110/170 outlet)	**10L** **25L**

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40,422-5	**Lithium aluminum deuteride**, 96 atom % D (1.0*M* solution in tetrahydrofuran)	**25mL** **50mL**
55,536-3	**Lithium deuteride**, 98 atom % D	**1g** **10g**
34,745-0	**Lithium deuteroxide**, 98 atom % D (9 wt. % solution in D_2O)	**25g** **100g**
46,090-7	**Lithium tri-*tert*-butoxyaluminodeuteride**, 97 atom % D	**250mg** **1g**

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[Hydroxy(tosyloxy)iodo]benzene† and Closely Related Iodanes: The Second Stage of Development

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Outline

1. Introduction

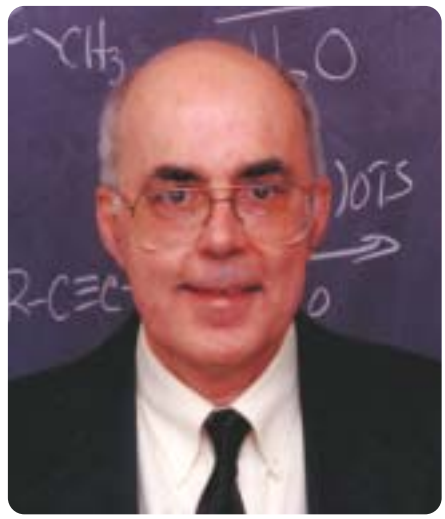
The history of the aryl λ^3-iodanes[1a] originates with the first reported syntheses of (dichloroiodo)benzene (**1**, 1885, 1886), iodosylbenzene (**2**, 1892), and (diacetoxyiodo)benzene (**3**, 1892) and follow-up preparations of numerous ring-substituted analogs of these compounds. The cyclic congener, '*o*-iodosylbenzoic acid' (**4**), was reported in 1892. The work of the classical period, including the synthesis of iodylarenes ($ArIO_2$) and iodonium salts and the derivatization of iodosylarenes at the iodosyl function with inorganic acids, is documented in a comprehensive 1914 monograph by C. Willgerodt.[1b]

Although aryl λ^3-iodanes attracted some attention as oxidants and were extensively employed for the synthesis of iodonium salts and iodonium ylides during the intervening years,[2,3] it is primarily during the last two decades that they have entered the mainstream of organic synthesis. This was stimulated in the 1970s and early 1980s by the development of aryl λ^3-iodanes, such as [hydroxy(tosyloxy)iodo]benzene (**5**)[4] and [bis(trifluoroacetoxy)iodo]benzene (**6**),[5] possessing weakly basic oxygen ligands; the appearance of several timely reviews;[3] and the disclosure of new applications of classical iodanes, especially in combination with other reagents. Early examples of the last-named development include the functionalization of carbonyl compounds with (diacetoxyiodo)benzene in KOH/MeOH[6] and the activation of iodosylbenzene with $Et_2O{\bullet}BF_3$ or $Et_3O^+\ BF_4^-$.[7] In some measure, the current state of hypervalent iodine chemistry reflects a gradual change in emphasis from the preparation of novel polyvalent iodine structures to their efficacy in organic synthesis, including the custom design of new iodine reagents.[8]

In this review, we highlight the chemistry of [hydroxy(tosyloxy)iodo]benzene (HTIB) from the 1990s and into the year 2000, and discuss closely related iodanes. Although HTIB was not the first unsymmetrical aryl λ^3-iodane to be described in the literature, it was the first such iodane to be systematically employed with organic substrates, and it served as an important guide for the general development of iodine(III)-sulfonate reagents. HTIB continues to find new applications in organic chemistry and is now firmly established as a versatile synthetic reagent.

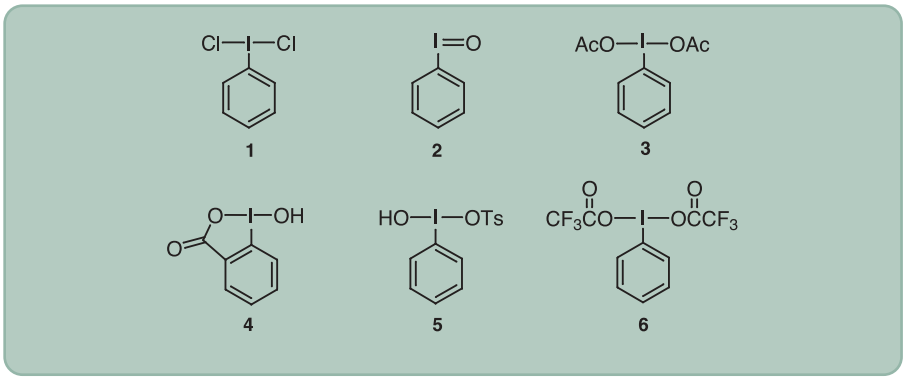
2. [Hydroxy(tosyloxy)iodo]-benzene (HTIB)

[Hydroxy(tosyloxy)iodo]benzene (HTIB), first reported by Neiland and Karele in1970,[4a] is a stable, nonhygroscopic crystalline solid that can be handled under atmospheric conditions without special precautions. It is readily prepared from



(diacetoxyiodo)benzene and *p*-TsOH•H_2O in organic solvents and can be recrystallized from acetonitrile. The solid-state structure of HTIB has been determined by single-crystal X-ray analysis,[9] and, as expected for an aryl λ^3-iodane, HTIB is T-shaped at iodine and best understood as a pseudotrigonal bipyramidal (ψ-TBP) system. However, unlike symmetrical aryl λ^3-iodanes such as (diacetoxyiodo)benzene,[10] HTIB contains mixed apical heteroligands of substantially different basicity. This results in disparate I–O bond distances and unsymmetrical electronic polarization of the O–I–O triad (**Figure 1**). In this respect, HTIB resembles an iodonium salt.

HTIB is moderately electrophilic at iodine and delivers the phenyliodonium and/or tosylate groups to a range of organic substrates. Whether such reactions stop at the phenyliodination stage or lead to oxytosylation depends on the tendency of the first-formed iodonium species to undergo nucleophilic collapse with reductive loss of iodobenzene. For example, *tert*-butylacetylene affords a stable alkynyliodonium salt with HTIB,[11] while acetophenone is



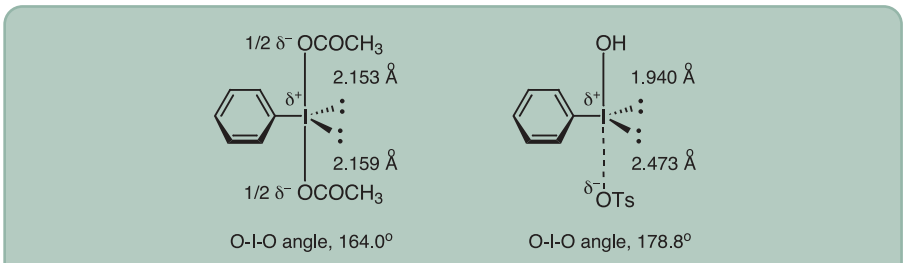
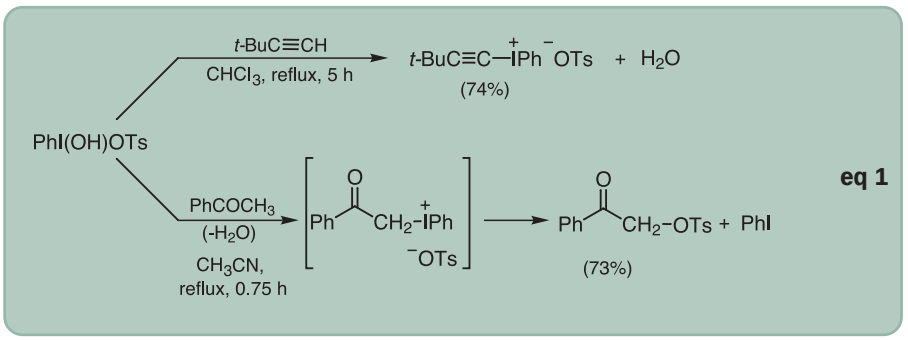


Figure 1. Schematic Structures of (Diacetoxyiodo)benzene[10b] and [Hydroxy(tosyloxy)iodo]benzene.[9]



eq 1

converted to its α-tosylate derivative (**eq 1**).[12] HTIB can also be employed for various oxidative transformations, including oxidative rearrangements, that do not eventuate in iodonium salts or tosylate esters.

During the discovery phase of HTIB chemistry, reviewed in 1990,[13] the reactivity patterns of HTIB with various classes of monofunctional and simple bifunctional compounds were elucidated. Some of the most important transformations, documented with primary references in the earlier review, are illustrated with general and specific examples in **Table 1**.

2.1. Mediation of HTIB Reactions

Acetonitrile and dichloromethane are the most popular solvents for the mediation of HTIB reactions. Although HTIB is not very soluble in either of these solvents at room temperature, many reactions proceed readily under these conditions and can be followed by noting the disappearance of the crystalline HTIB phase. In several studies, ultrasound has been employed to accelerate reactions in such two-phase mixtures, and for certain applications, such as the preparation of alkynyliodonium salts,[14] desiccants may be introduced to minimize side reactions and improve product yields. HTIB readily dissolves in acetonitrile near the reflux temperature to give intense yellow solutions; under these conditions, reactions can sometimes be followed as the color is discharged. The yellow color is probably due to the reversible formation of the μ-oxo anhydride **7**, the *o*-tolyl[15] and *o*-phenylene[16] analogs of which have been isolated and characterized.

Other solvents that have been employed for HTIB reactions include chloroform, ethyl acetate, and methanol. HTIB is quite soluble in methanol at room temperature and affords nearly colorless solutions, but in this medium oxidative rearrangements and/or solvohydroperiodination[17] reactions may be dominant. Finally, acetone and dimethyl sulfoxide react with HTIB, and their use as solvents should be avoided.

2.2. Aqueous Solutions of HTIB and [Hydroxy(mesyloxy)iodo]benzene (HMIB)

The moderate solubility of HTIB in water (ca. 1 g/42 mL at 22 °C) and acidity of such solutions were noted some years ago.[4a,16] More recently, it has been concluded that dissolution of HTIB, and the more soluble mesylate analog (HMIB), in water proceeds with the formation of fully solvated ('free') ion pairs (**eq 2**).[18] The hydroxy(phenyl)-iodonium ion (**8**), presumably ligated with at least one molecule of water, exhibits a pK_a of 4.30 ± 0.05 at 20 °C. Equilibrium concentrations of μ-oxodiiodine(III) mono- and dications **9** and **10** are also present in such aqueous solutions and originate from condensations of **8** with its conjugate base **11** or with itself. In very acidic solutions (pH < 1), dication **10** is the major dimeric species, but at higher pH, monocation **9** is favored and achieves maximum concentrations at pH levels near the pK_a of **8**. For example, at pH 4.25, the concentrations of **8**, **11**, **9**, and **10** in a 2.00 mmol•dm^{-3} solution of HMIB are 0.762, 0.679, 0.280, and 0.005 mmol•dm^{-3}, respectively.

3. Oxysulfonylation of Carbonyl Compounds at the α Carbon

The direct oxytosylation of ketones at the α carbon is among the most popular applications of HTIB (Table 1, entry 1).[13] This is primarily because of the ease and generality of ketol tosylate (i.e., α-tosyloxy ketone) synthesis by the HTIB method, which does not require prior availability of α-hydroxy ketones, and because of the parallel development of ketol tosylates as useful synthetic intermediates, especially as replacements for α-halo ketones. By comparison, α-halo ketones traditionally employed, for example, in the Hantzsch thiazole synthesis, have been variously described in the literature as lachrymatory, toxic, unstable, and not readily available.

Recent applications of the HTIB method include oxytosylations of bi- and tricyclic ketones,[19] pyridyl ketones and pyridyl esters,[20] β-diketones containing one perfluoroalkyl group[21] (i.e., structures **12**–**15**), and a range of aryl and heteroaryl alkyl ketones. The tosylate derivatives of perfluoroalkyl β-diketones were isolated as stable hydrates and converted with potassium carbonate into simple ketol tosylates.

In the area of natural product chemistry, oxytosylation with HTIB was described as the "method of choice" for activation of C-11

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- ❑ 33% Smaller footprint than previous models
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- ❑ Same as R-200, plus digital vapor temperature display

Specifications:

Rotation speed	20 to 280rpm
Weight	16 to 18kg
Approvals	UL, CSA, CE conformity

3-Step Selection Guide

Step 1
Choose Glassware

Diagonal condenser (A)

Vertical condenser (V)

Cold-trap condenser (C)

Step 2
Choose Evaporator Model

R-200 Fully-equipped base model

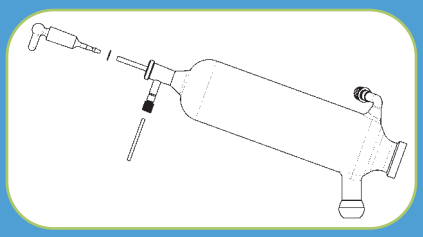
R-205 Base model, plus digital vapor temperature display

Step 3
Choose Level

BASIC Features of the selected evaporator model.

ADVANCED Features of the selected evaporator model, plus integrated, semi-automatic V-800 vacuum controller. Remote rotation speed and Servo-jack control optional.

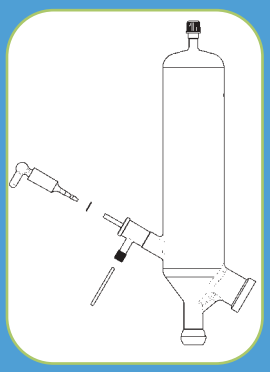
PROFESSIONAL Features of the selected evaporator model, plus integrated, programmable V-805 vacuum controller. Remote rotation speed and Servo-jack control optional.



Evaporators with Diagonal Condenser (A) Assemblies

For simple distillation of solvents and general use. Tap water cooled. Inlet feed tube for continuous feed of volumes exceeding flask capacity.

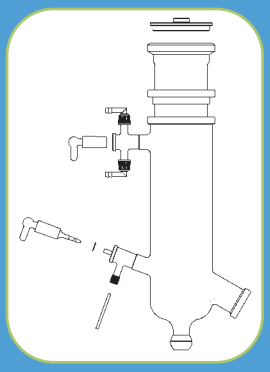
	Model R-200		*Model R-205*	
	120V	*230V*	*120V*	*230V*
Level	**Cat. No.**	**Cat. No.**	**Cat. No.**	**Cat. No.**
Basic	**Z52,662-2**	**Z60,364-3**	**Z52,671-1**	**Z60,371-6**
Advanced	**Z52,665-7**	**Z60,457-7**	**Z52,675-4**	**Z60,465-8**
Professional	**Z52,667-3**	**Z61,816-0**	**Z52,678-9**	**Z61,817-9**



Evaporators with Vertical Condenser (V) Assemblies

For distilling high-boiling solvents (>100ºC). Tap water cooled. Inlet feed tube for continuous feed of volumes exceeding flask capacity.

	Model R-200		*Model R-205*	
	120V	*230V*	*120V*	*230V*
Level	**Cat. No.**	**Cat. No.**	**Cat. No.**	**Cat. No.**
Basic	**Z52,663-0**	**Z60,365-1**	**Z52,673-8**	**Z60,372-4**
Advanced	**Z52,666-5**	**Z60,458-5**	**Z52,676-2**	**Z60,466-6**
Professional	**Z52,668-1**	**Z61,818-7**	**Z52,679-7**	**Z61,819-5**



Evaporators with Cold-trap Condenser (C) Assemblies

Two-piece cold-trap condenser style is ideal for low-boiling solvents. Uses mechanical refrigeration or dry ice and acetone.

	Model R-200		*Model R-205*	
	120V	*230V*	*120V*	*230V*
Level	**Cat. No.**	**Cat. No.**	**Cat. No.**	**Cat. No.**
Basic	**Z52,664-9**	**Z60,367-8**	**Z52,674-6**	**Z60,373-2**
Advanced	**Z52,666-5**	**Z60,459-3**	**Z52,677-0**	**Z60,467-4**
Professional	**Z52,670-3**	**Z61,820-9**	**Z52,680-0**	**Z61,821-7**

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Remote Control

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- ❑ Starting and stopping the distillation process
- ❑ Rotational speed
- ❑ Raising and lowering evaporation flask

Z52,869-2

R-200/R-205 Safety shield

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A Diagonal Condenser Assembly

For simple distillation of solvents and general use. Tap water cooled, or use coolant from ROTACOOL chiller.

Display/Series	*115V AC* Cat. No.	*230V AC* Cat. No.
Analog/4000	**Z41,440-9**	**Z33,486-3**
Digital/4002	**Z41,443-3**	**Z33,533-9**

B Vertical Condenser Assembly

For simple distillation of solvents and general use. Has the smallest space requirements. Tap water cooled, or use coolant from ROTACOOL chiller. Optional temperature sensor T*(auto)* (for Series 4002 only).

Display/Series	*115V AC* Cat. No.	*230V AC* Cat. No.
Analog/4000	**Z41,441-7**	**Z33,487-1**
Digital/4002	**Z41,444-1**	**Z33,534-7**
Temperature sensor T*(auto)* for Series 4002 digital evaporators		**Z33,595-9**

C Cold-Trap Condenser Assembly

Two-piece, cold-trap condenser style is ideal for low-boiling solvents. Use dry ice/acetone mix or similar coolant.

Display/Series	*115V AC* Cat. No.	*230V AC* Cat. No.
Analog/4000	**Z41,442-5**	**Z33,490-1**
Digital/4002	**Z41,446-8**	**Z33,536-3**

Replacement PTFE/graphite seal *for Series 4000 and 4002 evaporators* **Z33,585-1**

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Volts	Cat. No.
115	**Z21,944-4**
230	**Z40,574-4**

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Specifications:

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Temperature accuracy	+/-0.7K
Cooling capacity at 20ºC	240W
Pump capacity:	
Max. pressure	300mbar
Max. flow rate	12L/min.
Bath volume	3L
Dimensions:	
Base area	7.9 x 13.4in. (200 x 340mm)
Height	19.3in (490mm)
Weight	22kg
Total wattage	450VA

Volts	Cat. No.
115	**Z52,948-6**
230	**Z61,631-1**

Optional temperature and liquid level indicator **Z52,949-4**

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Features:

- pH meter uses both stainless steel probes with durable silicon chip sensors as well as any traditional glass pH electrode with BNC connector
- Model IQ400 pH system includes the Handspring Visor handheld computer, USB cradle, and SS pH probe
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Description	Cat. No.
pH/mV/ORP Temperature System w/Handspring Visor	**I 4656**
Accessories	
pH module only	**I 4781**
pH system recharging station with NiMH batteries, 115V	**I 5031**
pH system carrying case and calibration kit	**I 4906**
3.5mm NMR tube micro probe	**I 5156**

SPECIFICATIONS

		IQ400 pH System
Meter		pH/mV/ORP Temperature System complete with Handspring Visor handheld computer and USB cradle.
Range:	pH	0.00 to 14.00
	mV	± 1999 mV
	Temperature, ºC	-5 to +105 ºC Display either ºC or ºF
Resolution:	pH	0.1/0.01 pH
	mV	0.1/1 mV
	Temperature, ºC	0.1 ºC
Accuracy:	pH	± 0.01 pH
	mV	± 0.1mV
	Temperature, ºC	± 0.5
Display		160 x 160 touch screen
Temp. Compensation		Automatic -5 ºC to +105 ºC
Buffers		Automatic Recognition. 18 buffers in memory. 1.68, 2.00, 3.00 4.00, 4.01, 5.00, 6.00, 6.86, 7.00, 7.41, 8.00 9.00, 9.18, 9.21, 10.00, 10.01, 12.00, 12.45. User selectable to any other value.
Save/Recall		Save up to 9999 readings with attached notes and drawings
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GLP Functions		Stores last 50 calibrations
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Battery Life		150 hours on pH module Visor™: Approximately 10 hours continuous. Low battery warning.
Dimensions		3.0" x 6.0" (76mm x 152 mm) Visor™ with pH module attached
Shipping Weight		3.0 lbs. (1.3 kg)

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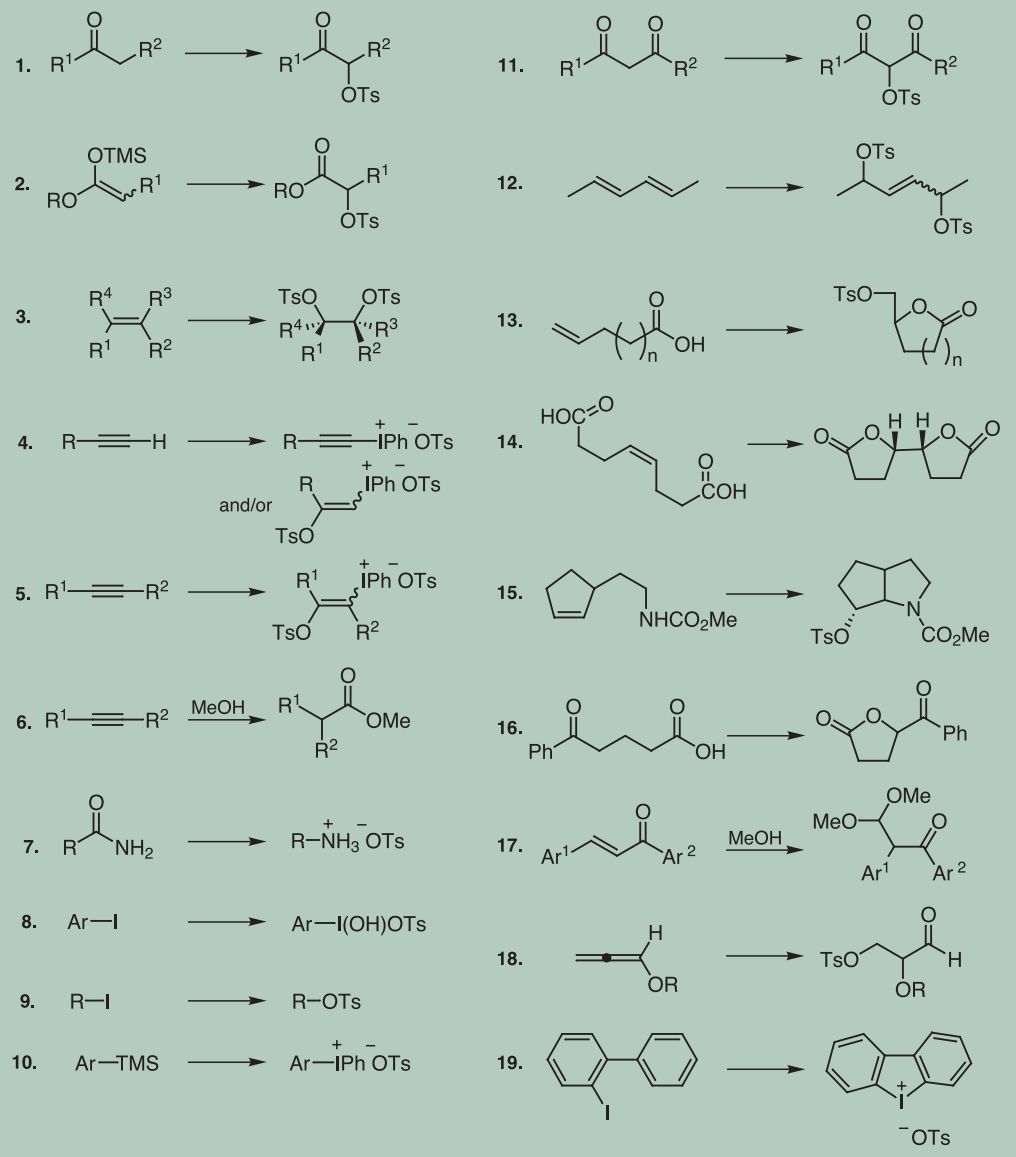
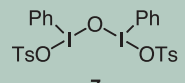
Table 1. Selected Transformations of Organic Substrates from the "Discovery Period" of HTIB Chemistry[13]





7

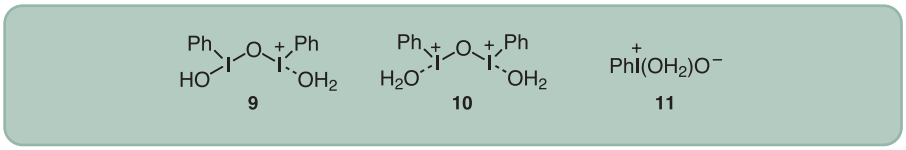
$$PhI(OH)OSO_2R \xrightarrow[R = p\text{-tolyl, Me}]{H_2O} PhI^{+}(OH_2)OH\ (aq) + RSO_3^{-}(aq) \qquad \textbf{eq 2}$$

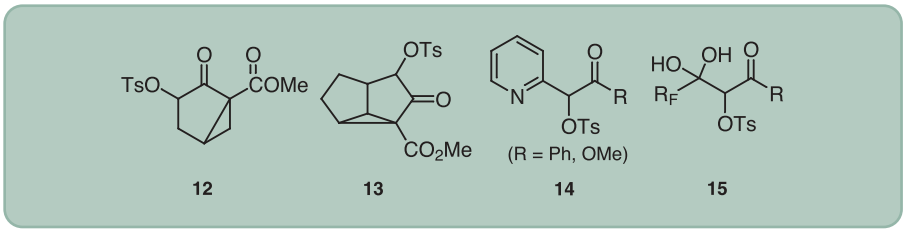
8

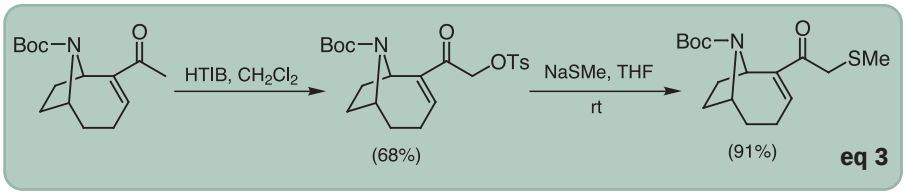
in the N-Boc derivative of the potent nicotinic agonist, anatoxin-a, the ketol tosylate being employed for the introduction of thioether linkages at C-11 of the protected alkaloid (**eq 3**).[22] Efforts to halogenate *N*-Boc-anatoxin-a and its silyl enol ether derivative at C-11 were unsuccessful.

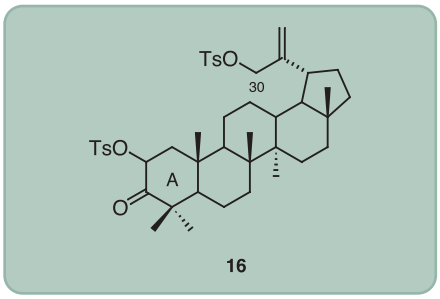
Treatment of the triterpenic ketone, lupenone, with two molar equivalents of HTIB results in oxytosylation of the α and allylic positions of lupenone to give ditosylate **16** in 34% yield.[23] Three other products, corresponding to elimination (ring A) and/or hydrolysis (C-30), were also obtained, perhaps, in part, because of the aqueous workup.

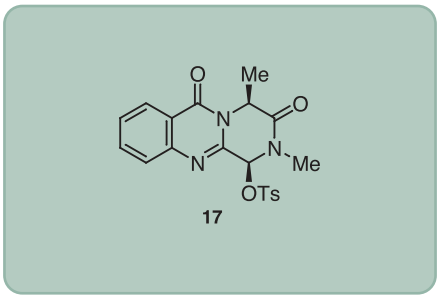
N-Acetylardeemin, a fungal metabolite and potent inhibitor of multidrug resistance to antitumor agents, is of interest, partially because of its peptidomimetic substructure. In one seven-step synthesis of didehydro-*N*-acetylardeemin from tryptamine, HTIB was employed in ethyl acetate to effect the final stereoselective cyclization step (**eq 4**).[24] This transformation is thought to proceed via oxytosylation of the α-carbon atom of the imino group of the substrate, followed by formation and cyclization of an intermediate iminium tosylate. In a related study, (4*S*)-2,4-dimethyl-2,4-dihydro-(1*H*)-pyrazino[2,1-*b*]quinazoline-3,6-dione was converted stereospecifically into the (1*S*,4*S*)-tosylate derivative **17** with HTIB in ethyl

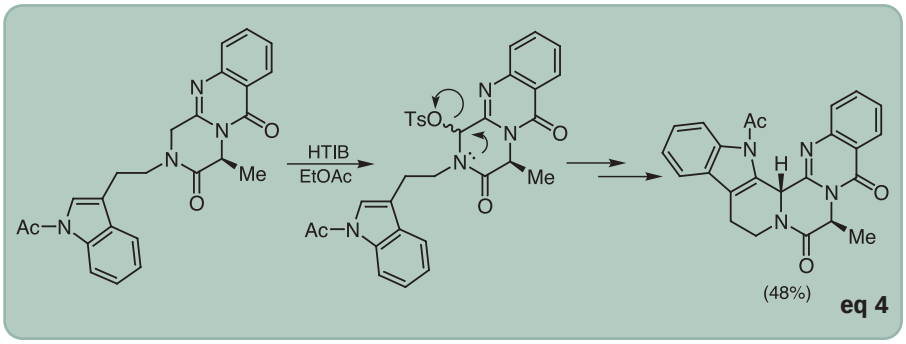


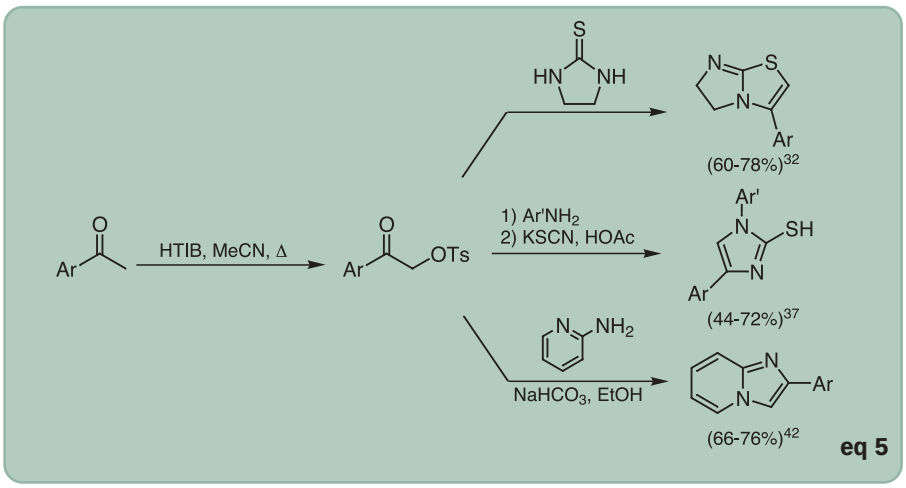












acetate (71% yield).[25] Hydrolysis of **17** with aqueous ammonium chloride occurred with retention of configuration to give the corresponding alcohol, shown to be an electrophilic glycine template.

The availability of ketol tosylates from ketones with HTIB and their reactivity with sulfur,[26] nitrogen,[27] and oxygen nucleophiles have been exploited rather extensively for the synthesis of heterocyclic compounds,[28-46] early developments in this area having been reviewed in 1994.[28c] A considerable range of heterocyclic structures, including bridgehead heterocycles, have been assembled by intra- and intermolecular condensations of ketol tosylates with appropriate nucleophilic partners, especially multidentate nucleophiles. In most studies of the intermolecular approach, two procedures are given: one in which the ketol tosylates are isolated prior to coupling, and another in which they are generated in situ and employed without isolation. Examples of the synthesis of heterocyclic compounds with HTIB are shown in **eq 5**.

A useful modification of the HTIB synthesis of ketol tosylates in two-phase mixtures entails the use of ultrasound. Sonication of a series of HTIB/ketone–acetonitrile mixtures for 10–30 minutes at 55 °C gives ketol tosylates in yields ranging from 42 to 92% (**eq 6**).[47] When ultrasound was not applied, presumably under the same conditions, ketol tosylates were not detected. High-yield HTIB conversions of various acetophenones, including solids, to their α-tosylate derivatives in the absence of solvents have also been documented. This was accomplished either by heating neat HTIB/ketone mixtures in a water bath[48] or by a 30-second exposure of such mixtures to microwave radiation[45] (**eq 6**).

HTIB has recently been employed in the presence of cupric bromide for mild, high-yield monobrominations of β-dicarbonyl compounds (**eq 7**).[49] Such reactions probably involve interception of the α-phenyliodonium intermediates by bromide ion prior to oxytosylation, perhaps assisted by Cu(II). The α-bromo-β-dicarbonyl compounds were utilized for the preparation of tricarbonyl compounds.

The preparation of ketol mesylates[50] and ketol (+)-10-camphorsulfonates[51] from ketones and β-dicarbonyl compounds with HMIB and [hydroxy(((+)-10-camphorsulfonyl)oxy)iodo]benzene (HCIB) was documented over ten years ago. More recently, similar preparations of ketol *p*-nitrobenzenesulfonates **18** and **19** with [hydroxy(*p*-nitrobenzenesulfonyloxy)-iodo]benzene (HNIB) have been reported.[52] The treatment of cyclic and acyclic ketol

p-nitrobenzenesulfonates in acetonitrile, either with potassium iodide in the presence of 18-crown-6 or with samarium iodide, provides a general synthesis of α-iodo ketones.[53]

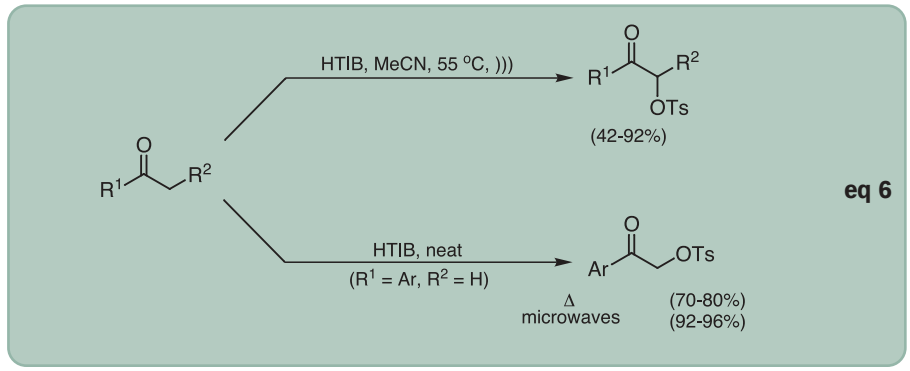
Although β-keto esters and α-pyridyl esters afford tosylate derivatives with HTIB, oxytosylations of unactivated monoesters have not been reported. However, the overall transformation has been accomplished with HTIB and silyl ketene acetals (Table 1, entry 2).[54] It has recently been found that aliphatic carboxylic anhydrides undergo oxytosylation at the α carbon, when an excess of the anhydride is heated (ca. 100 °C) with HTIB.[55] Treatment of the product mixtures with methanol and *p*-TsOH•H_2O affords methyl 2-tosyloxycarboxylate esters (**eq 8**).

4. Phenyliodination

The preparation of diaryliodonium tosylates by direct reactions of HTIB or its ring-substituted analogs with aromatic compounds is limited to activated substrates such as anisole, mesitylene, *p*-xylene, and variously substituted thiophenes.[56] Toluene, benzene, and bromobenzene do not give iodonium salts with HTIB. However, trimethylsilylbenzene, trimethylsilyltoluenes, and bis(trimethylsilyl)benzenes undergo aryliodination at the carbon–silicon bond with various [hydroxy(tosyloxy)iodo]arenes in acetonitrile at reflux, resulting in a regiospecific synthesis of diaryliodonium tosylates (Table 1, entry 10).[57]

A recent demonstration that diaryliodonium salts are useful precursors of ^{18}F-labeled fluoroarenes,[58] compounds of interest for positron emission tomography, prompted extensions of the HTIB methodology to arylstannanes and arylboronic acids. Various aryltributylstannanes, when mixed with HTIB in dichloromethane at room temperature, gave the corresponding aryl(phenyl)iodonium tosylates in yields ranging from 18 to 58% (**eq 9**).[59] Although product yields were moderate, the mild reaction conditions and the inclusion of deactivating F and CF_3 substituents in the arylstannane nucleus are noteworthy. Conversions of arylboronic acids to aryl(phenyl)iodonium triflates with the more robust reagent, PhI(OAc)$_2$•2TfOH, was preferred over the HTIB approach, but furyl- and thienylboronic acids gave iodonium salts with highly colored contaminants under these conditions.[60] For best results with heteroarylboronic acids, HTIB is the reagent of choice (**eq 10**).[60]

The synthesis and chemistry of alkynyliodonium salts is an exceptionally active area of research and has been thoroughly reviewed elsewhere.[61] Recent



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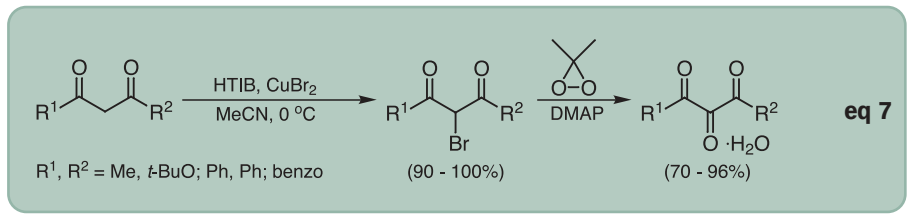

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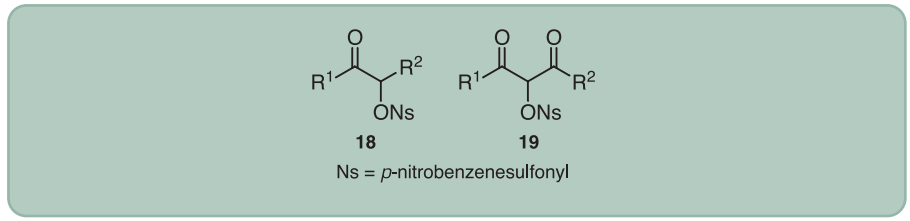

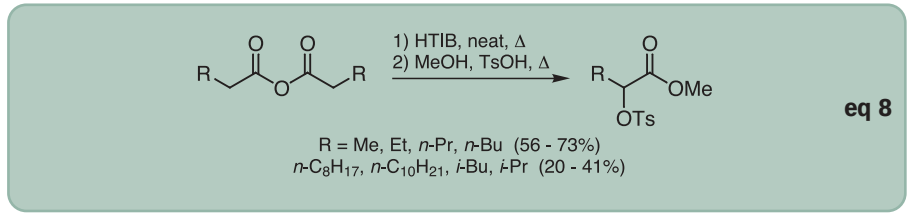

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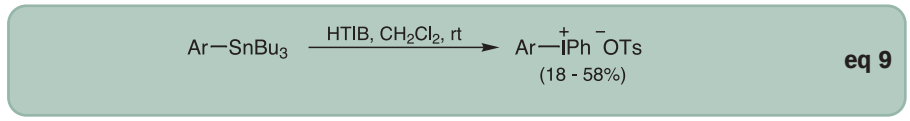

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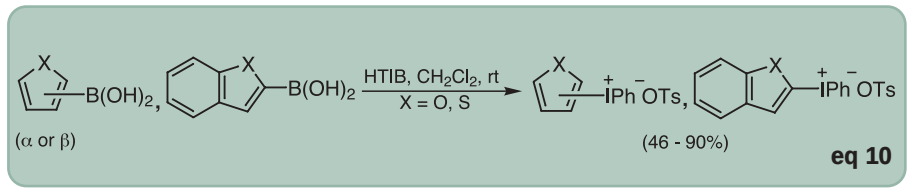

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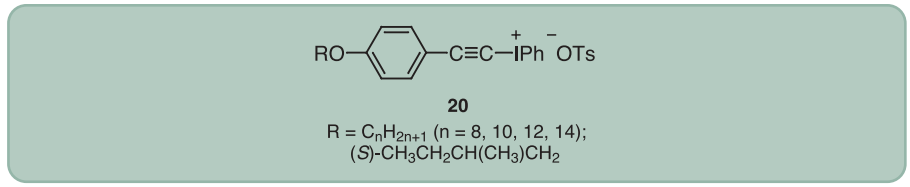

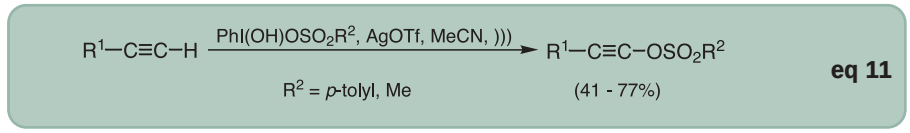

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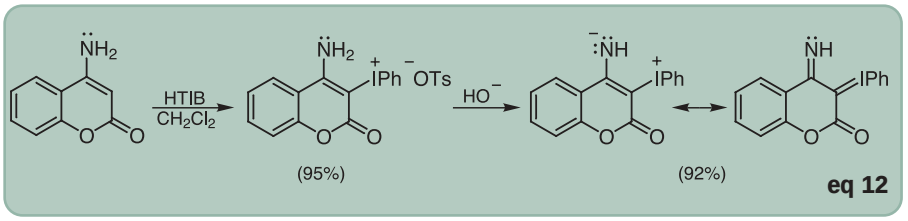
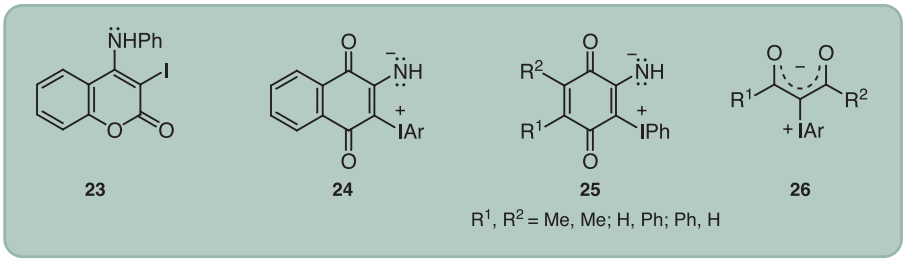
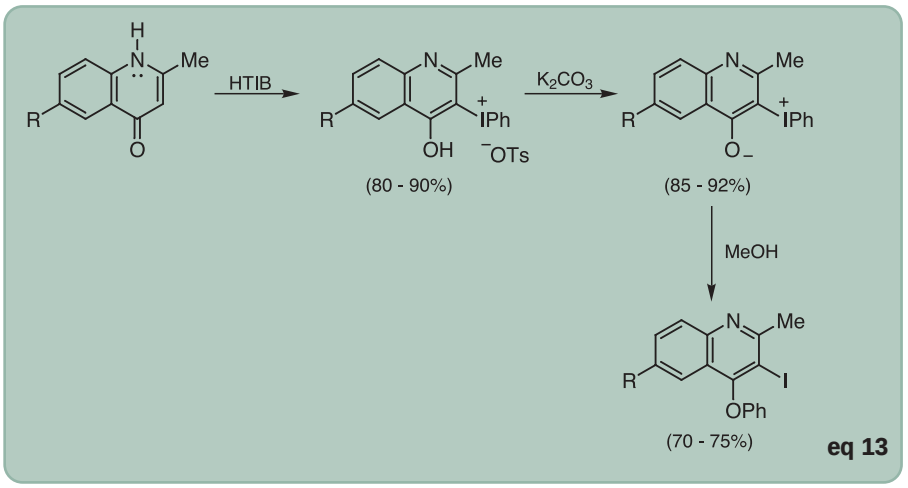
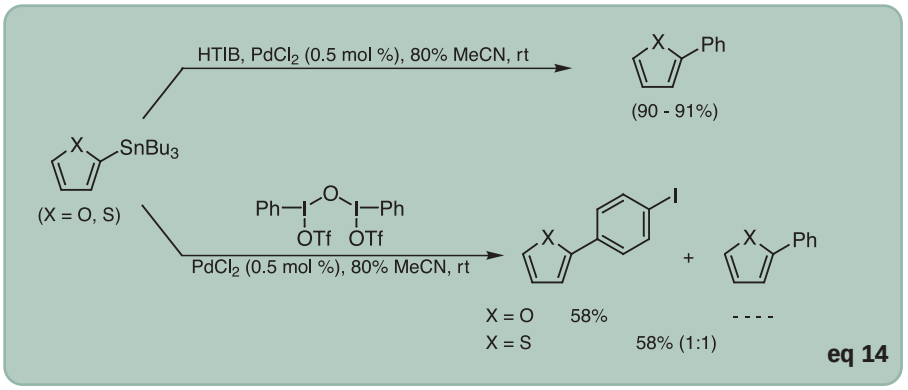
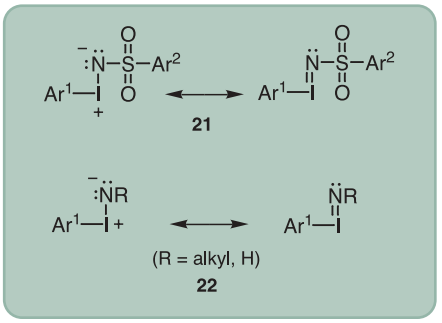










applications of HTIB in this context include the synthesis of several 4-alkoxyphenylethynyl(phenyl)iodonium tosylates (**20**), possessing long carbon chains in the alkoxy moiety,[62] and one analog with a chiral alkoxy group.[63] These compounds were employed for the preparation of liquid crystalline diacetylenes.[62-64]

The synthesis of the first alkynyl sulfonate esters, documented in the mid-1980s,[14] was accomplished by the initial conversion of terminal alkynes to alkynyliodonium sulfonates with HTIB or HMIB (Table 1, entry 4). Treatment of the alkynyliodonium salts with catalytic quantities of cuprous triflate or silver triflate in acetonitrile at 25 °C gave the corresponding alkynyl tosylates or mesylates as "stable, pale yellow, viscous oils".[14] More recently, ultrasound has been utilized to effect the overall transformation in a single step and in higher overall yield (**eq 11**).[65] Thus, sonication of a series of HTIB(HMIB)/AgOTf/alkyne mixtures in acetonitrile for 10–25 minutes at 25–45 °C gave alkynyl sulfonates in yields ranging from 41 to 77%.

4.1. Iodonium Ylides

Iodonium ylides possessing a negatively charged nitrogen atom are rare, the best-known examples being the arenesulfonyliminoiodanes, **21**.[66] Unstabilized 1,2-iminoiodanes such as **22**, nitrogen analogs of iodosylbenzene, have not been described. Recently, HTIB has been employed for two-step syntheses of 1,4-iminoiodanes from appropriately constructed enamines. For example, treatment of 4-aminocoumarin with HTIB in dichloromethane gave 4-amino-3-phenyliodonium coumarin tosylate in 95% yield (**eq 12**).[67] Deprotonation of the iodonium salt in aqueous sodium hydroxide delivered a 92% yield of the coumarin-1,4-iminoiodane. When the ylide was heated in acetonitrile, phenyl migration occurred and 3-iodo-4-(phenylamino)coumarin (**23**) was obtained. 1,4-Iminoiodanes **24** and **25** were similarly prepared and isolated as stable solids from the reactions of 2-amino-naphthoquinones and 2-aminobenzoquinones with HTIB and its ring-substituted analogs.[68,69] The stability of these 1,4-iminoiodanes is noteworthy, especially because they contain an unsubstituted nitrogen center, and must originate, at least in part, from charge delocalization in the enolate moiety, analogous to that in the well-known iodonium enolates **26** derived from aryl λ^3-iodanes and β-dicarbonyl compounds.

Iodonium betaines have also been prepared from a series of 2-methyl-4-quinolones, by sequential treatment with HTIB and potassium carbonate, and employed in methanol for the synthesis of 2-methyl-3-iodo-4-phenoxyquinolines (**eq 13**).[70]

5. Palladium-Catalyzed Cross-Couplings with HTIB

Although arylstannanes and arylboronic acids undergo phenyliodination with HTIB and afford aryl(phenyl)iodonium tosylates,

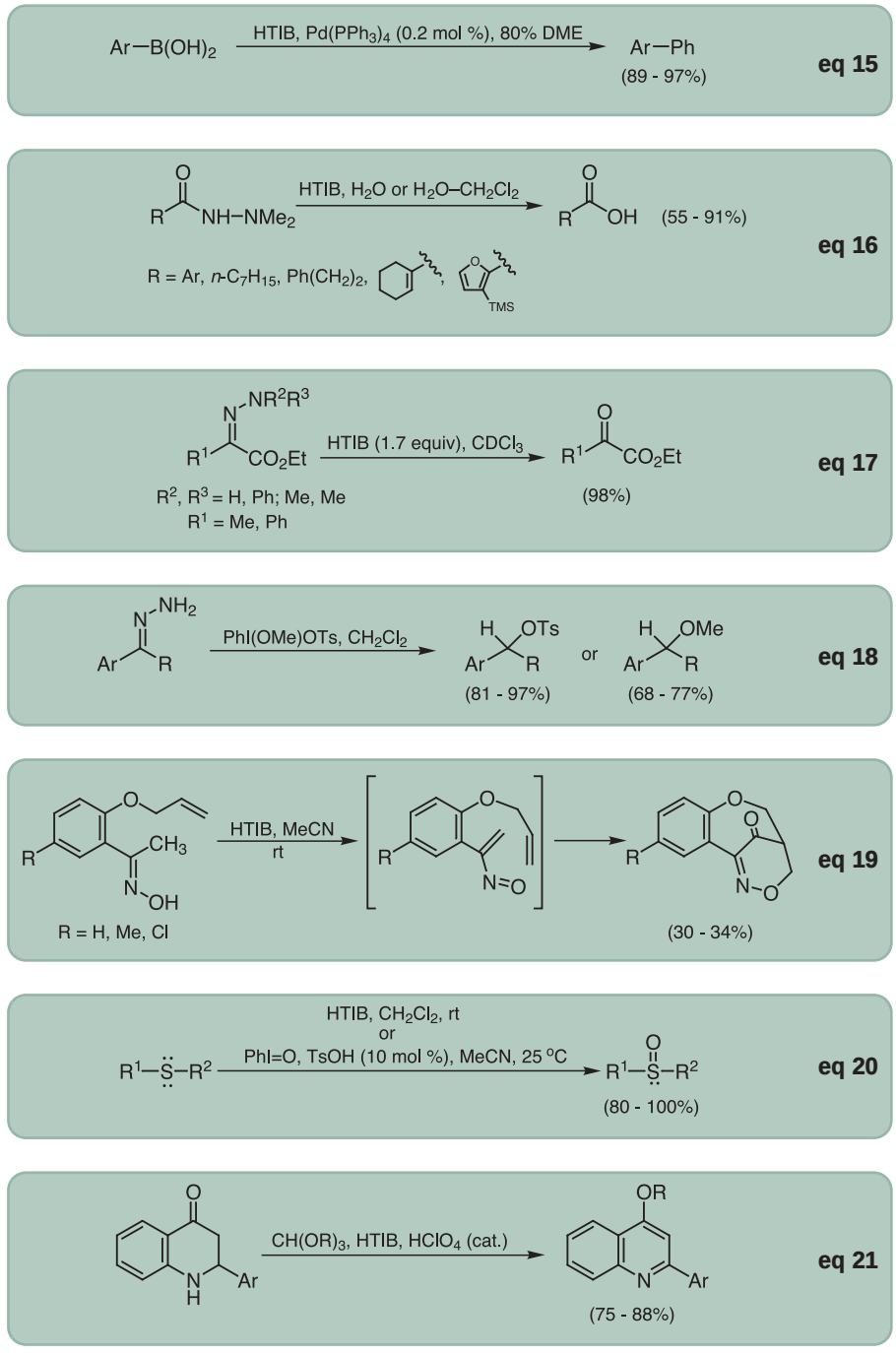
the presence of palladium catalysts in such mixtures results in Stille- and Suzuki-type cross-coupling reactions. For example, when tributylstannane derivatives of benzene, furan, and thiophene were mixed with HTIB and 0.5 mol % palladium(II) chloride in aqueous acetonitrile, high yields of the corresponding phenyl(hetero)arenes were produced (**eq 14**).[71] The use of Zefirov's reagent in place of HTIB gave (4-iodophenyl)arenes as well and is an interesting complementary system.[71] The treatment of a series of arylboronic acids with HTIB and 0.2 mol % $Pd(PPh_3)_4$ in aqueous DME under basic conditions has also been reported and affords high yields of the corresponding phenylarenes (**eq 15**).[72]

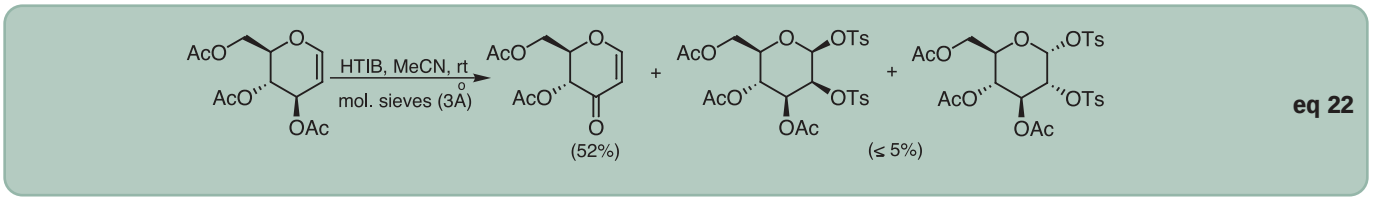
In an interesting variant of Suzuki-type cross-couplings of iodonium compounds, potassium aryltrifluoroborates ($ArBF_3^-$ K^+) were utilized without base as the organoboron component. Application of this approach to HTIB was limited to two examples, but in both cases, efficient production of biaryls was reported.[73] Other examples of palladium-catalyzed reactions of HTIB include cross-couplings with one alkynylstannane,[71] one arylboronate,[72] two vinylboronates,[72,74] and two vinylboranes.[72]

6. Oxidations and Oxidative Rearrangements

HTIB continues to find application in diverse oxidative transformations of synthetic importance. Recent demonstrations of functional group deprotection include conversions of dimethylhydrazides to carboxylic acids with HTIB in aqueous media (**eq 16**),[75] and the regeneration of α-keto esters from their phenyl- and dimethylhydrazones with HTIB in deuterochloroform (**eq 17**).[76] Hydrazones of aryl ketones are converted to benzylic tosylates or benzylic ethers with [methoxy(tosyloxy)iodo]benzene (MTIB) in dichloromethane (**eq 18**).[77] Tosylate formation is favored when electron-withdrawing substituents are present in the arene nucleus of the hydrazones. Oximes of *o*-allyloxyacetophenones afford tricyclic derivatives of 5,6-dihydro-1,2-oxazine-4-one with HTIB in acetonitrile (**eq 19**).[78] Such reactions proceed by oxidation of the oxime function to a nitrosoalkene, followed by an intramolecular [4 + 2] cycloaddition step. HTIB is particularly useful for room temperature oxidations of sulfides to sulfoxides without overoxidation to sulfones. This has been accomplished with stoichiometric quantities of HTIB in dichloromethane,[79] or with iodosylbenzene and 10 mol % TsOH (i.e., in situ generation of HTIB) in acetonitrile (**eq 20**).[80] Oxidation of *p*-tolyl disulfide to the corresponding thiosulfonic ester with two equivalents of HTIB has also been reported.[81] The preparation of a series of 4-alkoxy-2-arylquinolines, including two natural products, has been achieved by treatment of aryl(tetrahydro)quinolones with HTIB in the presence of trialkyl orthoformates (**eq 21**).[82] The initial formation of enol ethers and their phenyliodination at nitrogen is probably responsible for the overall transformation.

In the area of carbohydrate chemistry, Kirschning and co-workers have employed HTIB in **anhydrous** acetonitrile for allylic oxidations of fully protected glycals to hydroxy-differentiated 2,3-dihydro-4*H*-pyranones.[83-86] This is illustrated in **eq 22** with the oxidation of tri-*O*-acetyl-D-glucal to the corresponding di-*O*-acetyldihydropyranone.[84] Such oxidations proceed independently of relative stereochemistry in the starting glycal and are compatible with a range of protecting groups (i.e., Ac, Bz, Bn, MOM, TMS, TBDMS, $SnBu_2$) and combinations thereof. For example, in one publication,[84b] allylic HTIB oxidations of twenty-one variously protected glycals,





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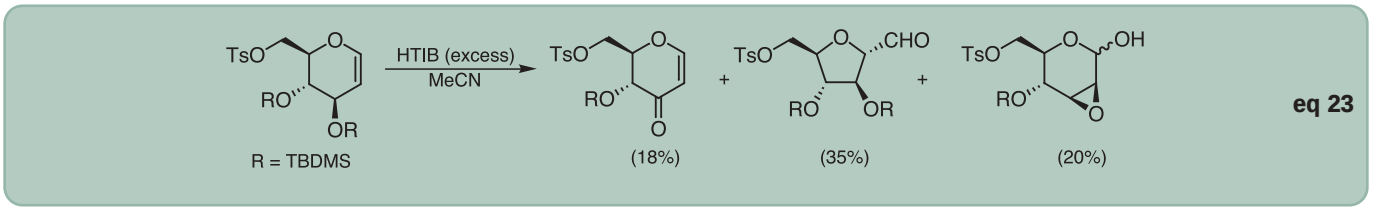

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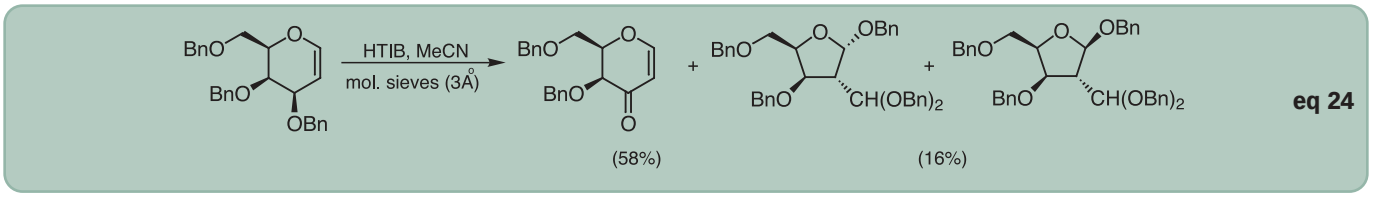

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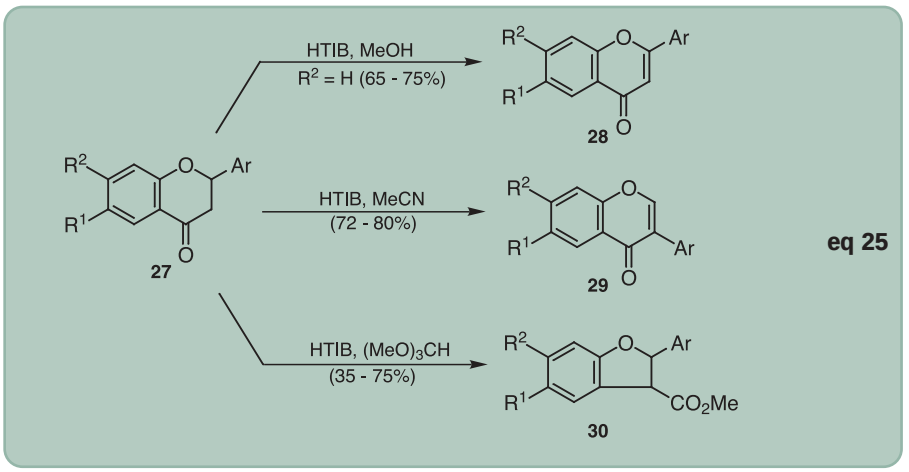

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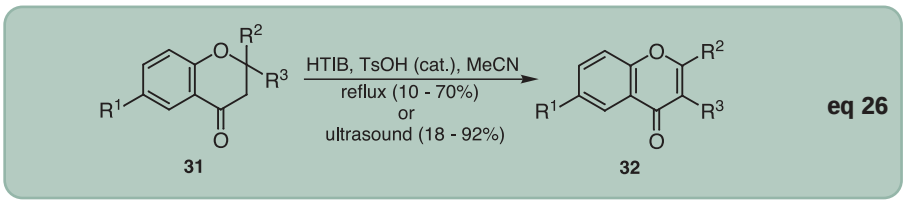


eq 26

divided among several stereochemical groups, to protected dihydropyranones in 32–74% yields are documented. The identity of the protecting group at O-3 in the starting glycal does, however, influence the efficiency of allylic oxidation, the highest product yields typically resulting with O-3 silyl protection. Other aryl λ^3-iodanes, including $PhI(OAc)_2$, $PhI(OCOCF_3)_2$, PhI(OMe)OTs, $PhI(CN)_2$, and PhI=O/$Et_2O{\bullet}BF_3$ were found to be ineffective oxidants in this context.[84,86b]

The mechanistic aspects of glycal oxidations with HTIB were clarified by the identification of by-products from selected substrates.[85] For example, HTIB oxidation of tri-*O*-acetyl-D-glucal (**eq 22**) gave low yields of products resulting from cis dioxytosylation (Table 1, entry 3) of the double bond,[84b] while prolonged treatment of 3,4-bis(*O*-*tert*-butyldimethylsilyl)-6-*O*-tosyl-D-glucal with excess HTIB led to products of ring contraction and epoxide formation (**eq 23**).[85a] HTIB oxidation of the perbenzylated glycal shown in **eq 24** gave the corresponding di-*O*-benzyldihydropyranone in 58% yield, but also led to products containing the tetrahydrofuran ring.[85b]

An interesting outcome of these investigations is the identification of '$PhI(OAc)_2$-Me_3SiN_3' as an important complementary reagent for glycal oxidations.[86] While HTIB is the reagent of choice with O-3 protecting groups such as acyl, benzyl, and methoxymethyl, the azide reagent affords higher yields of pyranones when O-3 silyl protection is employed.

HTIB oxidations of flavanones **27** occur with or without rearrangement, depending on the reaction medium (**eq 25**). In methanol, flavones **28** are obtained,[87] but in acetonitrile, migration of the C-2 aryl group accompanies oxidation, and isoflavones **29** are produced.[88] When HTIB is added to solutions of **27** in trimethyl orthoformate (TMOF), the major products are methyl 2-aryl-2,3-dihydrobenzofurancarboxylates, **30**.[89] The latter transformation probably involves phenyliodination of intermediate enol ethers, generated in situ from **27** and TMOF, and ring contraction of 2-phenyliodonio dimethyl ketals of **27** with loss of iodobenzene. The structurally related dialkylchromanones, **31**, rearrange to chromones **32** with HTIB in acetonitrile (**eq 26**), and, when spiroannulated chromanones **33** are employed, tetrahydroxanthones and their higher homologs, **34**, are obtained (**eq 27**).[90] The chromanone/HTIB rearrangement has recently been exploited for the conversion of spirochromanone **35** to the dehydrorotenoid core **36** (**eq 28**).[91]

HTIB-promoted conversions of 1,1-diphenylethylene to deoxybenzoin (CH_2Cl_2),[92] styrene to 1,1-dimethoxy-2-phenylethane (MeOH),[17] and α-methylstyrene to 2,2-dimethoxy-1-phenylpropane (MeOH)[17] were

noted over fifteen years ago. Recently, oxidative rearrangements of this type have been developed into a general regiospecific synthesis of α-phenyl ketones from cyclic and acyclic arylalkenes with HTIB in 95% methanol (**eq 29**).[93] Under these conditions, benzoannulated exocyclic alkenes undergo ring expansions and afford β-benzocycloalkanones (**eq 30**).[93] Because arylalkenes are readily available by Wittig olefination and alcohol dehydration methods, the synthesis of α-phenyl ketones and benzoannulated ketones by this approach is broad and flexible, and environmentally advantageous when compared with similar thallium(III)-induced transformations.[94]

When employed in acetonitrile at reflux, HTIB is an excellent Hofmann reagent for the conversions of aliphatic carboxamides to alkylammonium tosylates (Table 1, entry 7).[13] Recent applications of HTIB in this context include the preparation of 4-fluorocubanylammonium tosylate **37** from 4-fluorocubane-1-carboxamide,[95] and the conversions of several diethyl β-amidophosphonates to β-aminophosphonic acids **38** (i.e., after hydrolysis).[96] As part of a multistep asymmetric synthesis of an azanoradamantane benzamide target, described as a 'potent serotonin 5-HT_4 agonist/5-HT_4 antagonist', HTIB was employed for the preparation of the amino lactone shown in **eq 31** from the corresponding amide.[97] This reaction was driven to completion by addition of (diacetoxyiodo)benzene, which is believed to regenerate HTIB in situ.

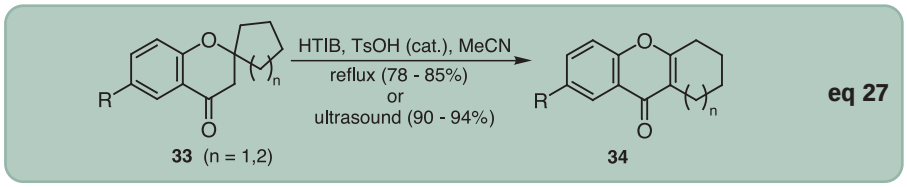
7. Conversion of Haloethynylcarbinols to β,β-Dihaloenones: the McNelis Rearrangement

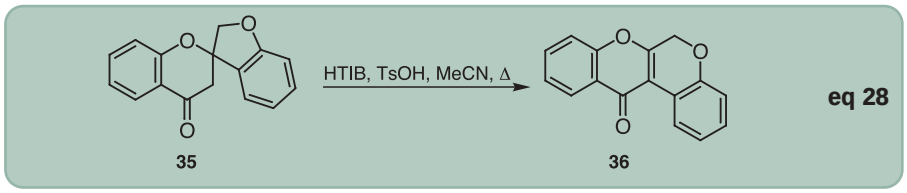
McNelis and his coworkers have utilized HTIB in conjunction with molecular iodine or *N*-iodosuccinimide (NIS) for the oxidative rearrangement of haloethynylcarbinols to β,β-dihaloenones. In their procedure, HTIB is employed stoichiometrically with I_2 or catalytically with NIS, and appears to function as a Lewis acid (e.g., **39**) thereby activating I_2 and NIS as I^+ donors.

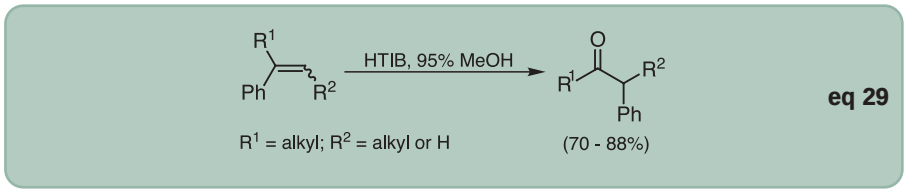
The treatment of acylic 2° and 3° bromoethynyl(phenyl)carbinols with the HTIB/iodine(I) reagents affords (*Z*)-β-bromo-β-iodoenones (**eq 32**).[98,99] The preference for a trans relationship between the phenyl and iodo substituents in the mixed dihaloenones presumably results from the intermediate formation of bridged iodonium species **40**.

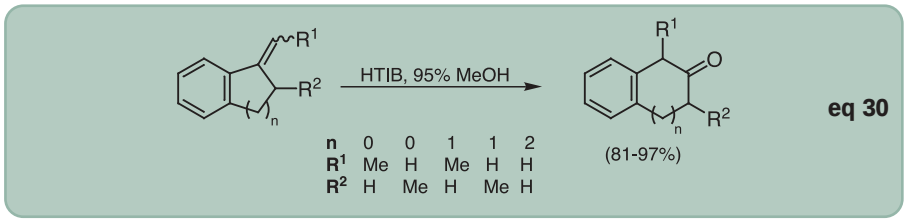
Reactions of bromoethynylcarbinols with HTIB/iodine(I) reagents are generally cleaner and more stereoselective than reactions of iodoethynylcarbinols with HTIB/bromine(I) reagents. For example, treatment of 4-iodo-2-phenyl-3-butyn-2-ol with HTIB-Br_2 in acetonitrile gave 4-bromo-4-iodo-3-phenylbutenone in lower yield. Furthermore, the *E* isomer was not preferred: a 5.9:1 *Z*/*E* mixture was obtained instead.

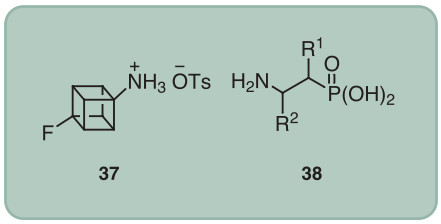
Rearrangements of haloethynylcarbinols to β,β-dihaloenones with HTIB-I_2 in

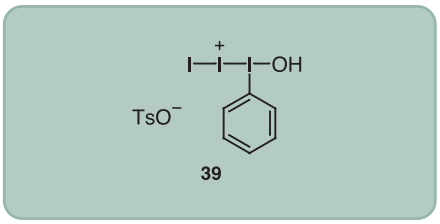


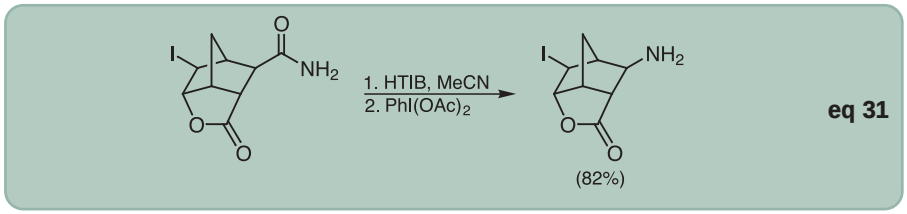


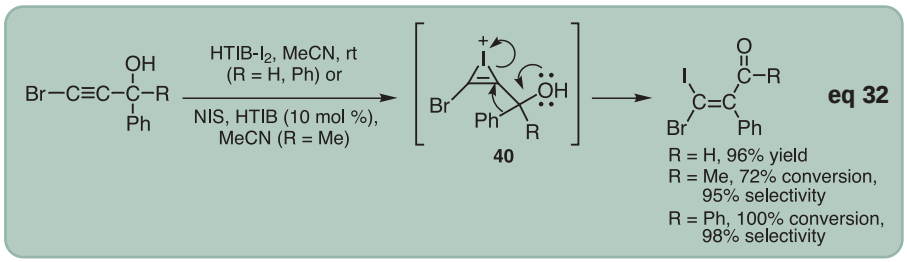


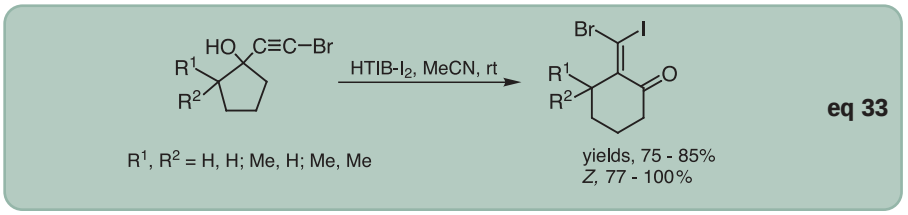












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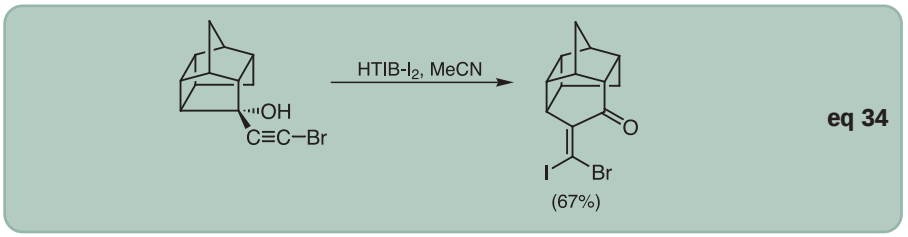

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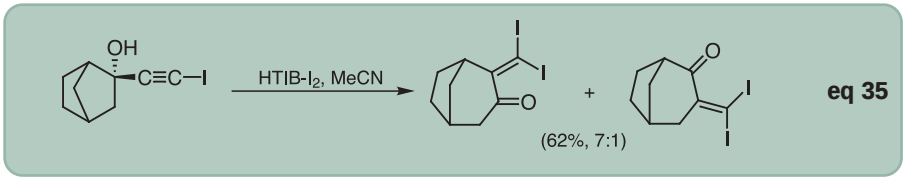

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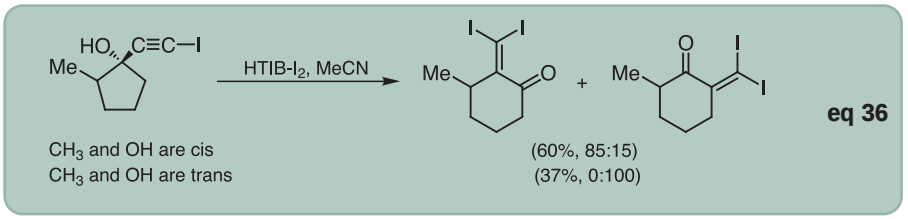

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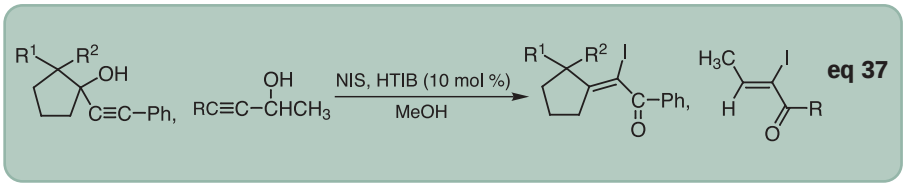

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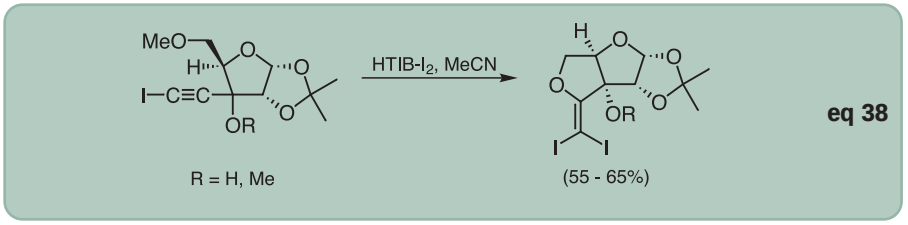
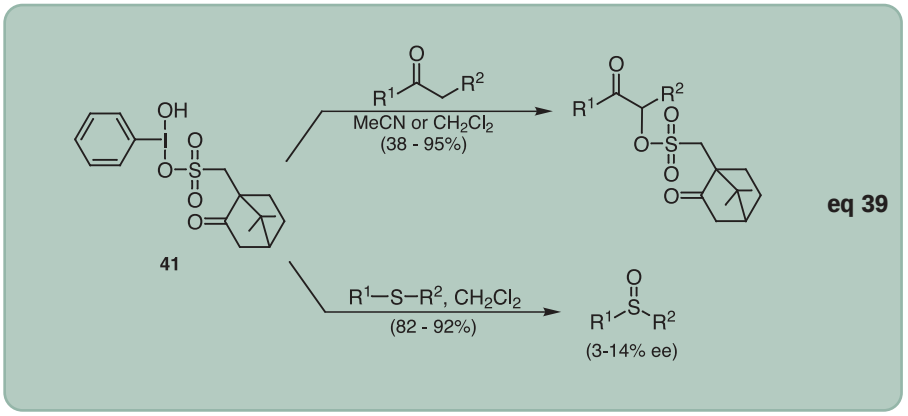


eq 38



eq 39

acetonitrile have been applied with great success to cyclic systems. This was first demonstrated with ring expansions of several 1-(bromoethynyl)cyclopentanols to 2-(dihalomethylidene)cyclohexanones in yields ranging from 75 to 85% (**eq 33**).[100] As with acyclic substrates, there is a high preference for the *Z* configuration in the enone products. Similar oxidations of bromoethynylcarbinols derived from camphor,[101] fluorenone,[102] and adamantanone[103] gave the *Z* isomers of the corresponding ring-expanded dihaloenones.

A complete reversal of the usual stereochemistry of the McNelis rearrangement was documented with the bromoethynylpentacycloundecyl alcohol shown in **eq 34**.[104] Exposure of this compound to HTIB-I_2 in acetonitrile gave a 67% yield of the ring-expanded (bromoiodomethylidene)cycloalkanone, determined by X-ray analysis to have exclusively the *E* configuration.

In principle, the production of β,β-dihaloenone regioisomers might be expected from rearrangements of cyclic haloethynylcarbinols possessing unsymmetrical structures, and has been demonstrated with haloethynylcarbinols derived from norcamphor (**eq 35**).[105] Upon treatment with HTIB-I_2, the norbornyl(iodoethynyl)carbinol gave a 7:1 mixture of isomeric (diiodomethylidene)bicyclo[3.2.1]octanones in 62% overall yield. The bromoethynylcarbinol behaved similarly, but in this case, a 1.5:1 mixture of regioisomeric bromoiodoenones was produced. A more thorough investigation of 1-haloethynyl-2-methylcyclopentanols revealed a similar behavior and a striking dependence of regioselectivity on the stereochemical disposition of the hydroxy and methyl groups in the starting alcohols.[106] This is shown in **eq 36** for the reactions of *cis*- and *trans*-1-iodoethynyl-2-methylcyclopentanols with HTIB-I_2 in acetonitrile. Thus, migration of the tertiary carbon (C-2) is largely preferred in the cis alcohol, while migration of the secondary carbon (C-5) is completely preferred in the trans alcohol. Similar, but slightly less dramatic, results were obtained with 1-bromoethynyl-2-methylcyclopentanols.

Rearrangements of nonhalogenated ethynylcarbinols with NIS or NBS and 10 mol % HTIB in methanol follow a different course and eventuate in α-haloenones (**eq 37**).[107] In such reactions, a "1,3-oxygen shift" appears to be required. Treatment of the iodoethynylcarbinol of the protected xylofuranose system shown in **eq 38** with HTIB-I_2 in acetonitrile does not lead to rearrangement.[108] In this case, capture of the intermediate iodonium species with the

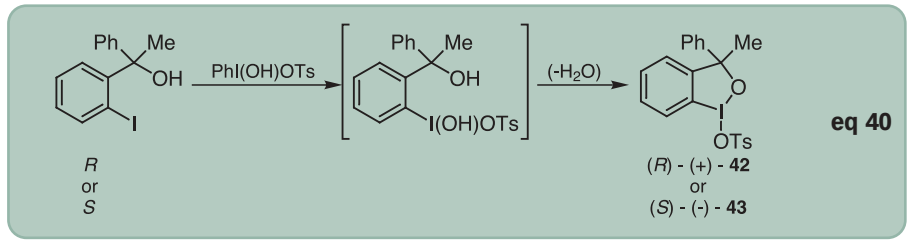
methoxy group at C-5 results in the formation of a (diiodomethylidene)furan ring.

8. Chiral Analogs of HTIB

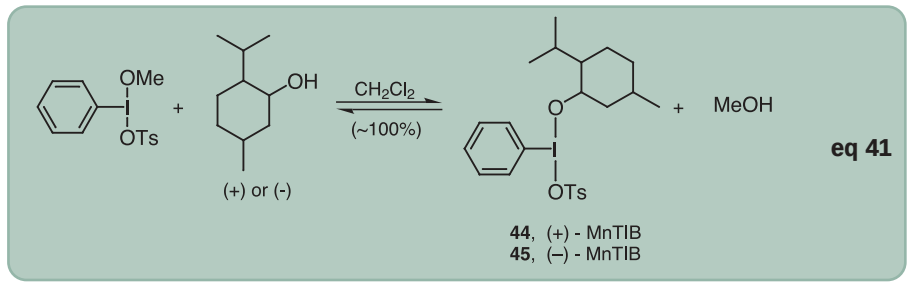
The development of chiral analogs of HTIB for applications in asymmetric synthesis is still at the rudimentary stage and a challenging direction for future research. [Hydroxy(((+)-10-camphorsulfonyl)oxy)-iodo]benzene (**41**, HCIB), an analog of HTIB with a chiral sulfonate ligand, was first reported in 1990[51] and employed with a series of ketones and β-dicarbonyl compounds for the oxysulfonylation of α carbons (**eq 39**). Among the prochiral substrates examined, only the camphorsulfonate of benzoylacetone displayed diastereomeric enrichment (50% de), but changed to a 1:1 mixture of diastereomers during column chromatography. Oxidations of unsymmetrical sulfides with HCIB have also been reported and gave sulfoxides in yields of 82 to 92% (**eq 39**),[79] but enantioselectivities were low (ee, 2.7 to 13.7%).

HTIB analogs possessing chiral alkoxy ligands include (*R*)-(+)- and (*S*)-(-)-1-tosyloxy-1,3-dihydro-3-methyl-3-phenylbenziodoxoles (**42** and **43**),[109] and homochiral [menthyloxy(tosyloxy)iodo]-benzenes (**44** and **45**) [(+)- and (-)-MnTIB)].[110] The benziodoxoles were prepared from enantiomeric 2-iodo-α-methylbenzhydrols by ligand-transfer oxidations with HTIB (**eq 40**), while the menthyloxyiodanes were obtained by ligand-exchange of [methoxy(tosyloxy)iodo]-benzene with (+)- and (-)-menthols (**eq 41**).

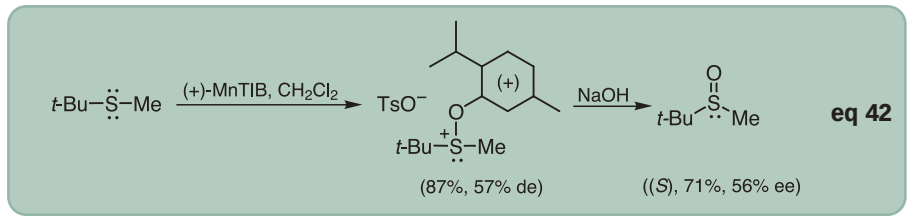
Although the use of benziodoxoles **42** and **43** for asymmetric synthesis has not yet been explored, the MnTIBs have been employed for the oxidation of unsymmetrical sulfides.[110] The MnTIBs behave analogously to [methoxy(tosyloxy)iodo]benzene[111] and transfer the formal equivalent of the menthyloxenium ion to sulfur. For example, methyl *t*-butyl sulfide gave the corresponding menthyloxysulfonium tosylate (87% yield, 57% de) with (+)-MnTIB in dichloromethane (**eq 42**). Hydrolysis of the sulfonium salt delivered methyl *t*-butyl sulfoxide in 71% yield, enriched (56% ee) in the *S* enantiomer. The (*R*)-enriched sulfoxide (49% ee) was similarly prepared with (-)-MnTIB. Oxidation of methyl *p*-tolyl sulfide with (+)-MnTIB gave a 92% yield of the corresponding menthyloxysulfonium salt, but with low diastereoselectivity (16% de). However, separation of the major diastereomer by fractional recrystallization, enabled the preparation of (*S*)-methyl *p*-tolyl sulfoxide in high optical purity (ca. 99% ee).



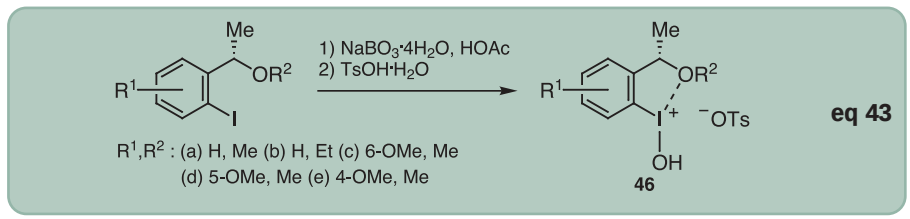
eq 40



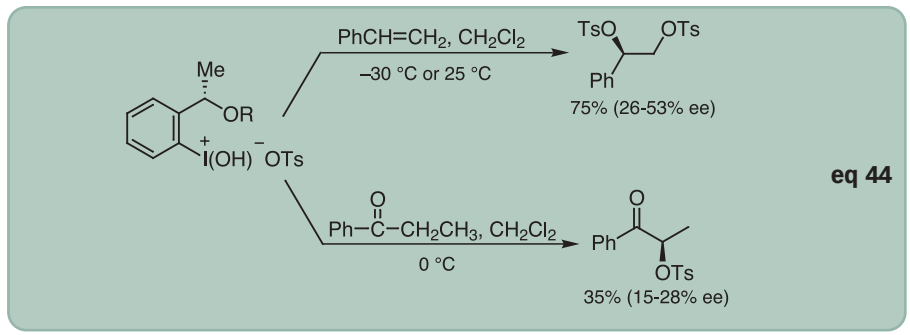
eq 41



eq 42



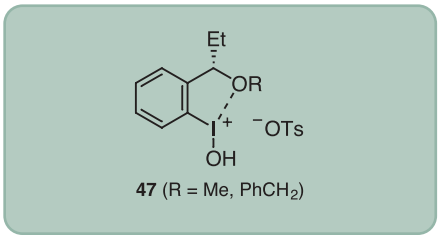
eq 43



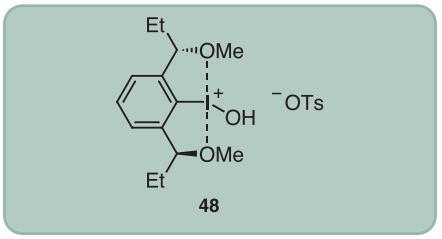
eq 44

A series of HTIB analogs, **46a**–**46e**, possessing chiral 1-alkoxyethyl groups in the ortho position of the arene ligand have recently been reported (**eq 43**).[112, 113] A single-crystal, X-ray structure determination of **46a** revealed a remarkable structural difference between this iodane and HTIB.[113] Whereas the hydroxy and tosyloxy ligands of HTIB are colinear (O-I-O angle = 179°) and occupy apical sites of the ψ-TBP, the tosylate ligand in **46a** is displaced by the oxygen atom of the *o*-(methoxy)ethyl substituent, and the O-I-O angle described by the apical ligands is 166°.

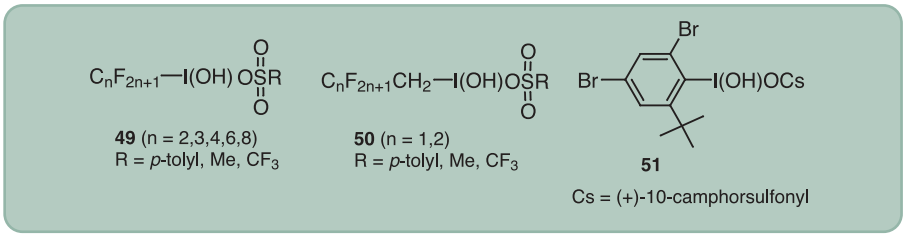
The capacity of **46a**–**46e** to effect asymmetric oxytosylations of organic substrates was tested with styrene and propiophenone (**eq 44**). Enantioselectivities of the dioxytosylation and α-oxytosylation reactions ranged from 26 to 53% and 15 to 28%, respectively, and, in both cases, the highest ee's were found with iodane **46c**. Chiral HTIB analogs **47** and **48**, containing a (methoxy)propyl or (benzyloxy)-propyl group at one ortho position and (methoxy)propyl groups at both ortho positions of the arene nucleus, were also



47 (R = Me, $PhCH_2$)



48



49 (n = 2,3,4,6,8)
R = *p*-tolyl, Me, CF_3

50 (n = 1,2)
R = *p*-tolyl, Me, CF_3

51

Cs = (+)-10-camphorsulfonyl

examined, but did not provide higher enantioselectivities.

Aliphatic analogs of HTIB with chiral alkyl ligands have not been reported, presumably because of the instability of most aliphatic iodanes. However, the stabilizing properties of perfluoroalkyl groups have recently been exploited for the preparation of stable [hydroxy(tosyloxy)iodo]perfluoroalkanes **49**[114] and 1*H*,1*H*-perfluoroalkanes **50**.[115] The reactivity patterns of **50** with organic substrates are similar to those of HTIB and suggest that chiral aliphatic analogs of HTIB might be prepared from such commercially available starting materials as (*R*)- and (*S*)- $PhCH(OH)CF_3$.

The possibility that unsymmetrical aryl λ^3-iodanes, possessing bulky substituents at both ortho positions, might be chiral by virtue of restricted rotation about the carbon–iodine bond has been tested with (+)-10-camphorsulfonyloxyiodane **51**.[109b] Because the rotational isomers of **51** are diastereomeric, a doubling of NMR resonances, especially those of the exocyclic methylene group of the camphorsulfonate ligand, was anticipated. However, this phenomenon was not observed, even at –40 °C. Thus, either C–I bond rotation, perhaps via an ion pair, and/or pseudorotation[116] of the heteroligands at iodine appears to be fast on the NMR time scale.

9. Conclusions

Prior to 1990, research on [hydroxy(tosyloxy)iodo]benzene (**5**) was largely focused on the systematic development of new reactions. The general modes of reactivity of HTIB, including oxytosylation, dioxytosylation, phenyliodination, solvohyperiodination, and a variety of other oxidative transformations, sometimes resulting in cyclizations or rearrangements, were clarified with mono- and bifunctional organic substrates. Related aryl λ^3-iodanes, including ring-substituted analogs of HTIB and analogs with other sulfonate ligands, were also developed, the chemistry of HTIB serving as a standard for comparison.

During the past decade, HTIB has become an established reagent. While new applications continue to emerge, HTIB is often employed because it is a convenient reagent for the preparation of useful compounds. In the future, the further development of chiral analogs of HTIB and the use of HTIB in conjunction with chiral catalysts can be expected. The solubility and oxidizing power[117] of HTIB in water, and its relatively benign nature, also suggest future applications in "green chemistry", especially for solvohyperiodination processes in that medium. The design of HTIB analogs that give water-soluble iodoarenes on reduction is an interesting challenge and should facilitate such research.

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11. References and Notes

(1) (a) In this review, the name "λ^3-iodane" refers to trivalent iodine compounds in which the ligands are attached to the iodine(III) center by means of covalent and polar covalent bonds. The term "aryl λ^3-iodane" is employed to identify λ^3-iodanes of general structure $ArIL^1L^2$ that contain at least one aryl ligand and achieve greatest stability when L^1 and L^2 are electronegative heteroatom ligands. Iodonium salts, such as $Ar_2I^+ L^-$, are distinguished from λ^3-iodanes in that they possess one ionic iodine–ligand bond. Actually, there is a continuum of iodine (III) structures between λ^3-iodanes and iodonium salts. (b) Willgerodt, C. *Die organischen Verbindungen mit mehrwertigem Jod*; F. Enke Verlag: Stuttgart, 1914.

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(†) *Editor's Note:* [Hydroxy(tosyloxy)-iodo]benzene is widely referred to as 'Koser's reagent'.

About the Author

Gerald F. Koser was born in 1942 in Sandusky, Ohio, and graduated from Sandusky High School in 1960. He received the B.S. degree (1964) from The Ohio State University and the M.S. (1966) and Ph.D. (1968) degrees from the University of Illinois (Urbana-Champaign), where he worked under the direction of Professor William H. Pirkle. After a year of postdoctoral study with Professor Jack Hine at The Ohio State University, he joined (1969) the Department of Chemistry at The University of Akron, where he has spent his entire professional career, including a period of service as Department Chair, and is now Distinguished Professor. The research of Gerald and his students has been focused primarily on various aspects of hypervalent iodine chemistry, with emphasis on reagent development, and includes a joint effort with Professor Kim C. Calvo on bisketol phosphates. Gerald's wife, Linda, teaches first grade in the Akron Public Schools. They have one son, Matthew.

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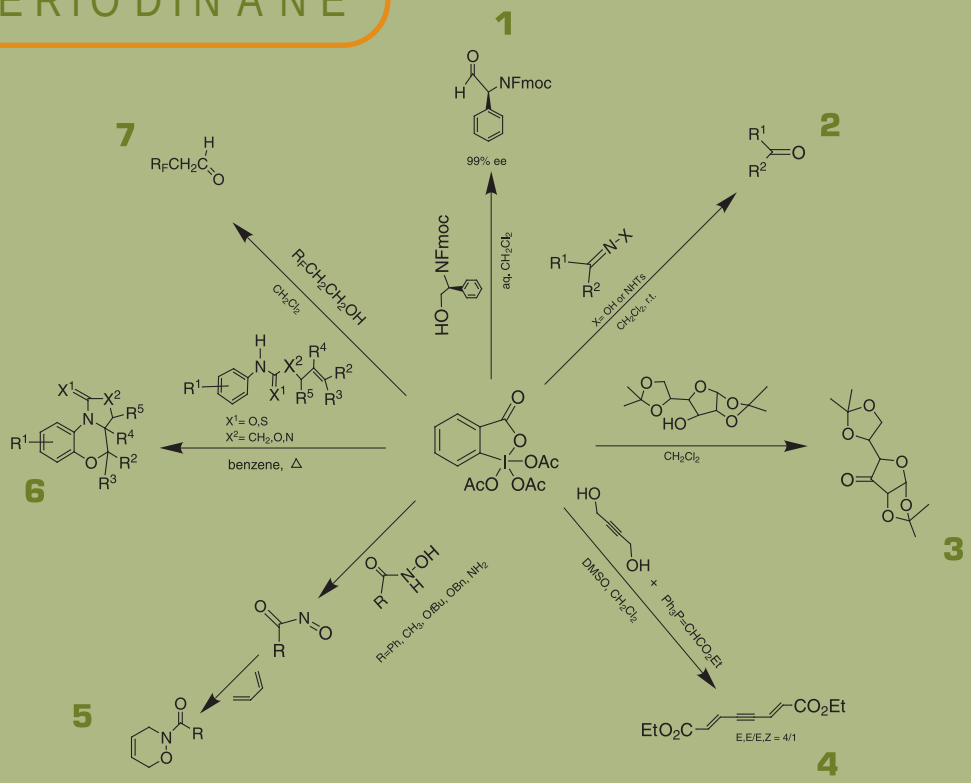

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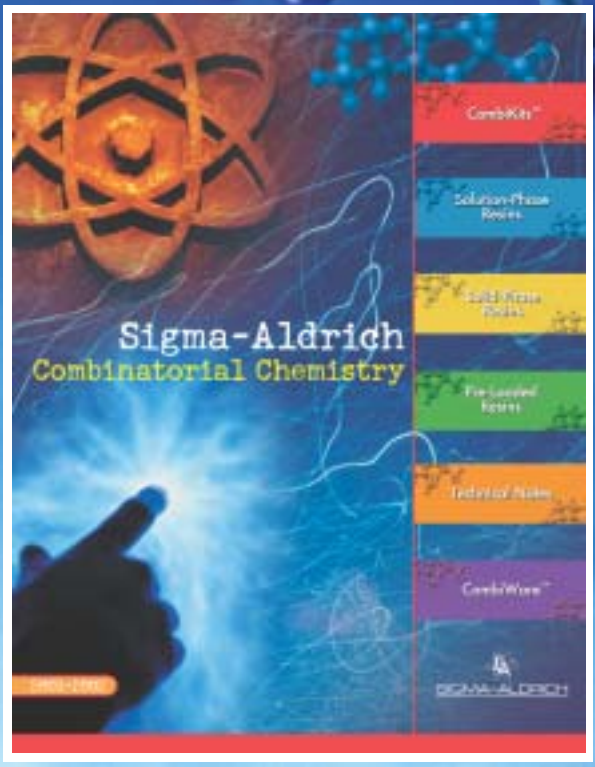

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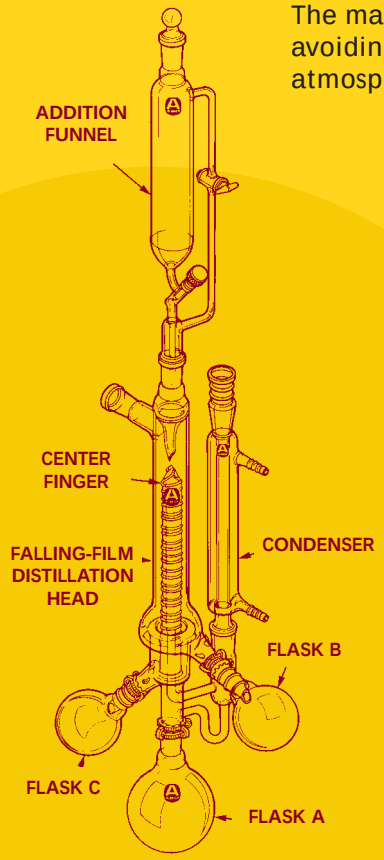
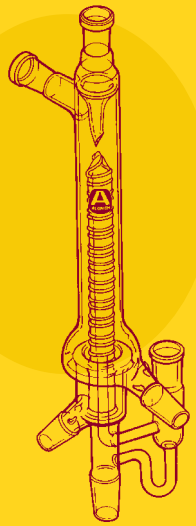


Figure 1

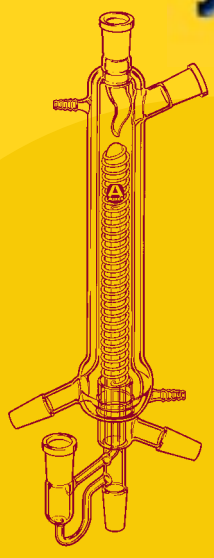
Falling-Film Technique (See Figure 1)

- **Flask A** is filled with the desired solvent and heated to reflux. The boiling solvent vapor maintains a constant temperature at the center finger. The temperature is the boiling point of the solvent.
- The material to be distilled is placed in the addition funnel and allowed to drip slowly onto the heated center finger. The volatilized material will condense on the outer, air-cooled wall and collect in **Flask B**. The high-boiling material will remain on the center finger and flow down the spiral into **Flask C**.
- Any pressure-equalizing funnel, standard condenser, and flasks can be used.



Size	Overall L (mm)	O.D. (mm)	Joints	Cat. No.
Micro	325	28	14/20	**Z25,024-4**
Small	420	42	24/40	**Z25,023-6**
Standard	570	42	24/40	**Z15,660-4**

Jacketed Falling-Film Distillation Head



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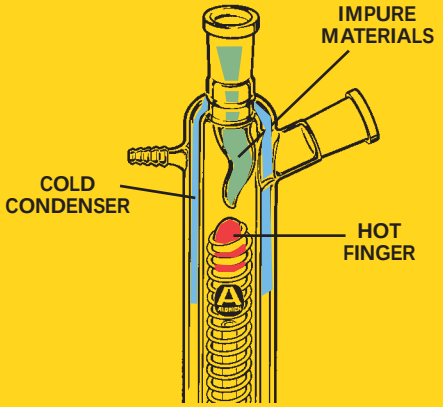

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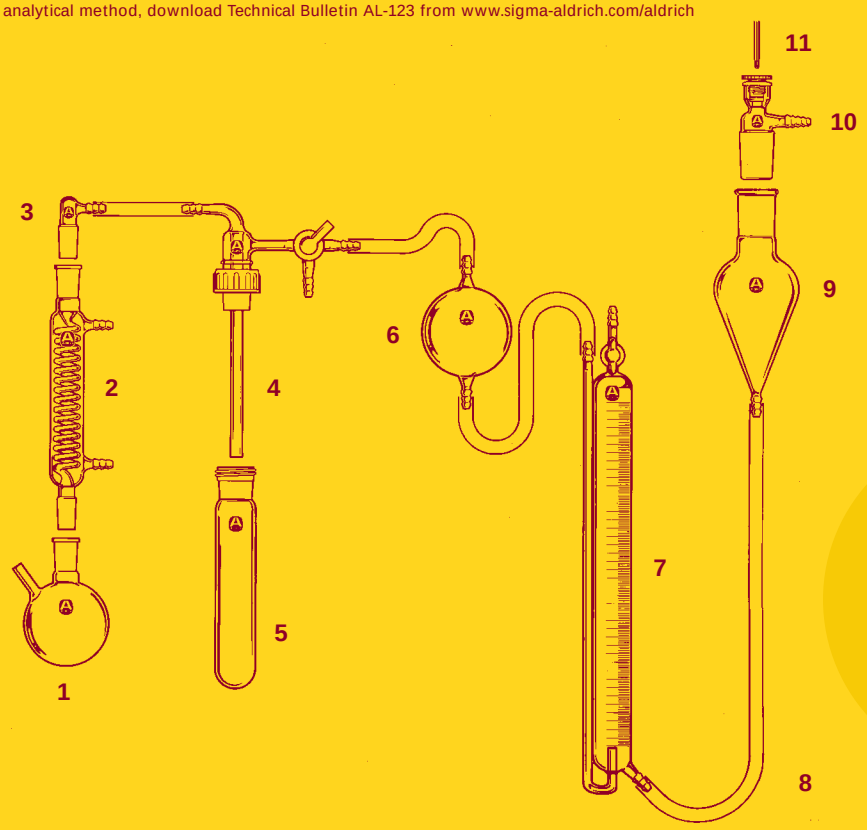

Hydrogen gas displaces water in the graduated burette, thus allowing a quantitative measurement to be made.

Components:

1. Septum-inlet flask, 250mL
2. Graham condenser, 300mm
3. Vacuum adapter
4. Cold-trap top with stopcock
5. Cold-trap bottom (dry ice/acetone)
6. Trap flask, 250mL
7. Graduated burette, 250mL with 1mL graduations
8. PVC flexible tubing
9. Leveling bulb, 250mL
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Z51,619-8

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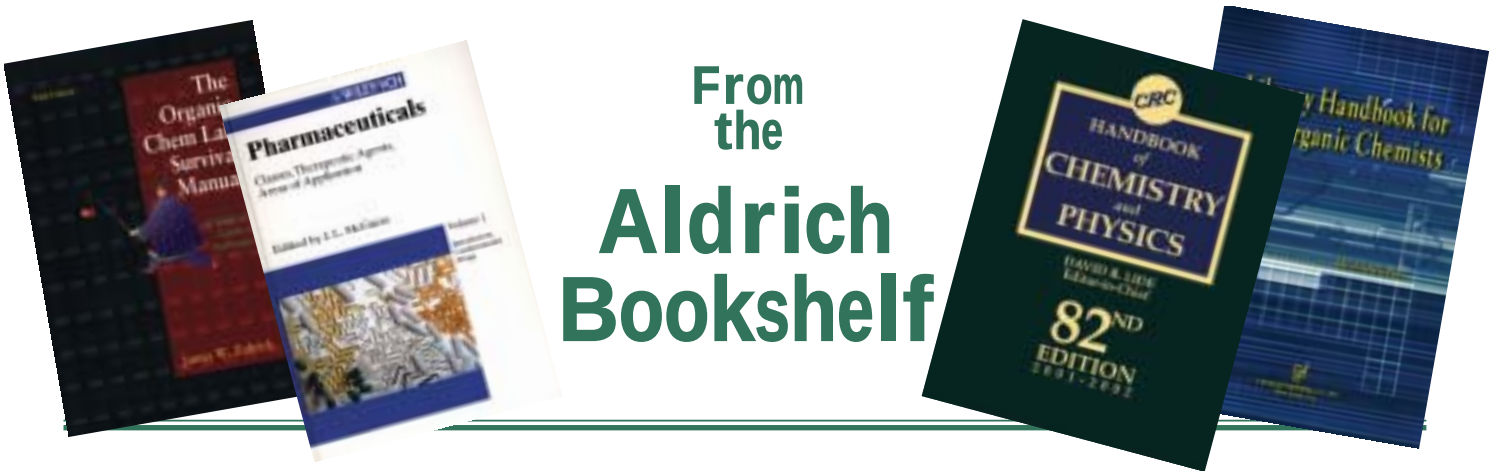

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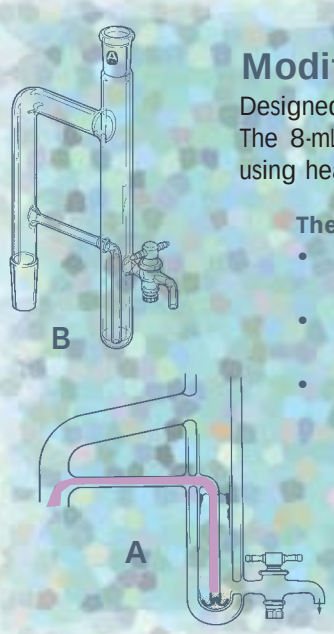

Modified Dean-Stark Apparatus

Designed specifically for azeotropic distillation using solvents heavier than water (e.g., chloroform). The 8-mL reservoir is specifically designed for small-scale azeotropic distillation of valuable solvents using heavy water. 2mm bore PTFE stopcock, 300mm overall height.

The modified Dean-Stark technique

- Solvent vapors condense and collect in the receiver.
- The modified Dean-Stark trap separates the two components.
- The heavier-than-water layer sinks to the bottom of the trap leaving the water on top.
- The solvent is forced back through the inside tube and returned to the boiling flask.
- The upper water layer is drained out through the 2mm PTFE stopcock.

	Reservoir Cap.	₹ 24/40 Cat. No.	₹ 29/32 Cat. No.
A.	8mL	Z51,617-1	Z51,629-5
B.	35mL	Z24,959-9	Z51,630-9

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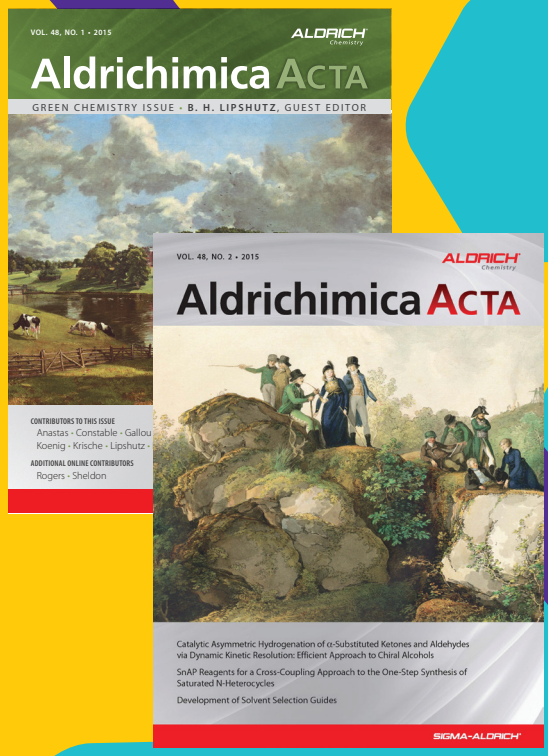

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