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The Chemical Vapor Deposition of Metal Nitride Films Using Modern Metalorganic Precursors

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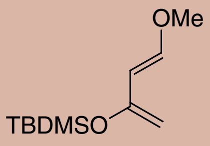
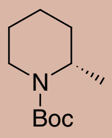
The *tert*-butyldimethylsilyl analog of Danishefsky's diene is now available. It has been used to prepare a variety of bicyclic enones and 2,3-dihydro-4*H*-pyran-4-ones.[1-3]



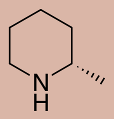
(1) Uchida, H. et al. *Tetrahedron Lett.* **1999**, *40*, 113. (2) Pudukulathan, Z. et al. *J. Am. Chem. Soc.* **1998**, *120*, 11953. (3) Annunziata, R. et al. *J. Org. Chem.* **1992**, *57*, 3605.

51,536-1 ***trans*-3-(*tert*-Butyldimethylsilyloxy)-1-methoxy-1,3-butadiene**, 95%

Building blocks for *trans*-2-methyl-6-substituted piperidines via deprotonation with *sec*-butyllithium followed by reaction with an electrophile.[1-3]



52,288-0



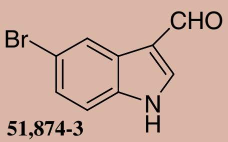
52,290-2

(1) Chackalamannil, S. et al. *J. Am. Chem. Soc.* **1996**, *118*, 9812. (2) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109. (3) Idem *ibid.* **1990**, *55*, 2578.

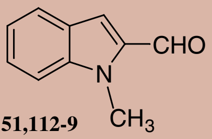
52,288-0 **(*S*)-(+)-*N*-(*tert*-Butoxycarbonyl)-2-methylpiperidine**, 98%

52,290-2 **(*S*)-(+)-2-Methylpiperidine**, 97%

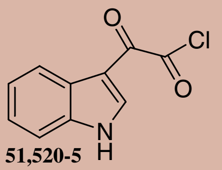
Precursors for a wide variety of substituted indoles.[1-3]



51,874-3



51,112-9



51,520-5

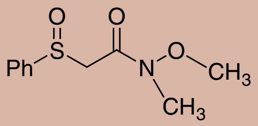
(1) Battaglia, S. et al. *Eur. J. Med. Chem.* **1999**, *34*, 93. (2) Joseph, B. et al. *J. Heterocycl. Chem.* **1997**, *34*, 525. (3) Le Borgne, M. et al. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 333.

51,874-3 **5-Bromoindole-3-carboxaldehyde**, 98%

51,112-9 **1-Methylindole-2-carboxaldehyde**, 97%

51,520-5 **3-Indoleglyoxylyl chloride**, 98%

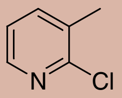
α,β-Unsaturated *N*-methoxy-*N*-methylamides are prepared from this reagent through deprotonation with sodium hydride, reaction with an alkyl halide, and in situ heating.



Beney, C. et al. *Tetrahedron Lett.* **1998**, *39*, 5779.

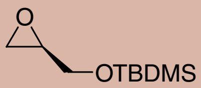
51,139-0 ***N*-Methoxy-*N*-methyl-2-(phenylsulfinyl)acetamide**, 96%

2-Substituted picolines have been prepared from this compound. Examples include (2-pyridyl)indoles and endothelin receptors.[1,2]

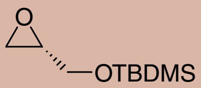


(1) Amat, M. et al. *J. Org. Chem.* **1997**, *62*, 3158. (2) Kourounakis, A. et al. *Biorg. Med. Chem. Lett.* **1997**, *7*, 2223.

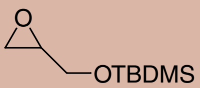
51,894-8 **2-Chloro-3-methylpyridine**, 97%



52,599-5



52,490-5



52,613-4

A variety of nucleophiles have been used to open the oxirane ring of these compounds. Examples include lithium acetylides[1,2] and lithium dithianes.[3]

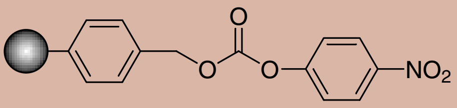
(1) Arista, L. et al. *Heterocycles* **1998**, *48*, 1325. (2) Maguire, R. J. et al. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2853. (3) Smith, A. B., III; Boldi, A. M. *J. Am. Chem. Soc.* **1997**, *119*, 6925.

52,599-5 ***tert*-Butyldimethylsilyl (*R*)-(+)-glycidyl ether**, 98%

52,490-5 ***tert*-Butyldimethylsilyl (*S*)-(–)-glycidyl ether**, 98%

52,613-4 ***tert*-Butyldimethylsilyl glycidyl ether**, 98%

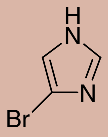
This carbonate resin is used to bind amines or amino acids as urethanes. Dipeptides and hydantoins have been prepared from these polymer-bound urethanes.[1-3]



(1) Dixit, D. M.; Leznoff, C. C. *J. Chem. Soc., Chem. Commun.* **1977**, 798. (2) Dressman, B. A. et al. *Tetrahedron Lett.* **1996**, *37*, 937. (3) Gouilleux, L. et al. *ibid.* **1996**, *37*, 7031.

51,529-9 **4-Nitrophenyl carbonate, polymer-bound on Wang Resin**

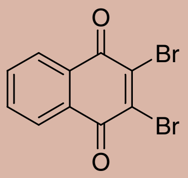
Starting material for the preparation of 4-substituted imidazoles.[1,2]



(1) Lange, J. H. M. et al. *Tetrahedron* **1995**, *51*, 13447. (2) Singh, B. et al. *J. Med. Chem.* **1992**, *35*, 4858.

47,869-5 **4-Bromo-1*H*-imidazole**, 97%

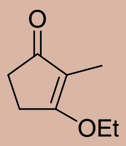
Naphthoquinones are prepared from this compound via palladium-catalyzed coupling reactions with tributylstannylheteroaromatics or by nucleophilic displacement of one or both bromides.[1,2]



(1) Yoshida, S. et al. *Chem. Lett.* **1996**, 139. (2) Falling, S. N.; Rapoport, H. *J. Org. Chem.* **1980**, *45*, 1260.

52,342-9 **2,3-Dibromo-1,4-naphthoquinone**, 97%

Precursor for 3-substituted-2-methyl-2-cyclopenten-1-ones.[1,2]



(1) Cossy, J. et al. *Tetrahedron Lett.* **1997**, *38*, 4069. (2) Junga, H.; Blechert, S. *ibid.* **1993**, *34*, 3731.

51,440-3 **3-Ethoxy-2-methyl-2-cyclopenten-1-one**, 97%

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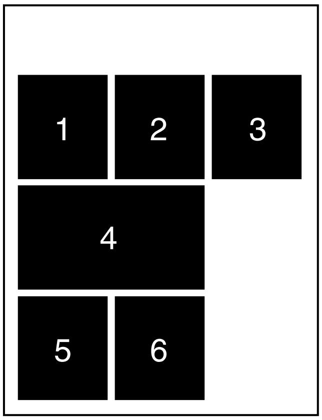

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Clint Lane, President

Dear Fellow Chemists:

It is a great pleasure for me to again provide a contribution to our *Aldrichimica Acta*, this time as President of Aldrich. During the years 1973–1977, I contributed nine reviews to this publication. Now, 23 years later, I am back on these pages. Much has changed over the years, but we never stopped publishing what we here at Aldrich simply call "the ACTA".

Year 2000 was viewed as a perfect time to roll out a new look for our classic. However, we have not deleted any of the features that you have come to expect. Art on the cover (reprints available), excellent and timely reviews, lab notes, featured new products, etc. are all here for you to enjoy. Our goal is to continue to be *Chemists Helping Chemists* as we move into the new millennium. We know you will continue to find new ideas and information to help you in your research efforts.

Thank you for staying with us over all these years. This is the first issue in the year 2000. We are up to Volume 33 (33 years) and still counting. As always, "Please Bother Us" with comments or contributions.

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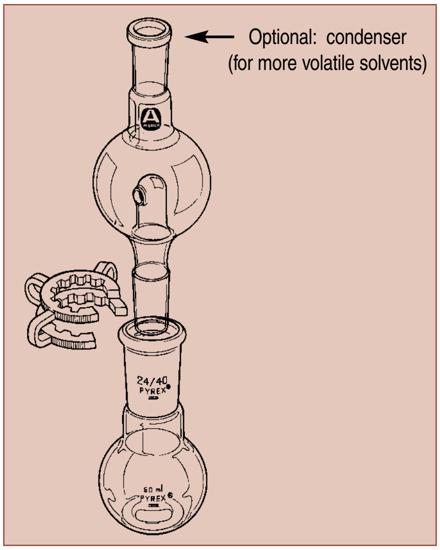
Lab Notes

Aldrich Rotary Evaporator Antisplash Adapters as Solvent Traps in Recrystallizations

For practicing synthetic chemists, recrystallization of reaction intermediates is routine. For maximal product recovery, it is important to prepare a saturated solution of the compound. In many instances, this is difficult to judge, since excess solvent is sometimes needed to completely dissolve the solute, or since filtration subsequent to charcoal treatment is followed by washing of the residue with hot solvent. These steps result in dilution of the crystallizing solution, and, therefore, concentration of such a solution has to be performed. This is usually accomplished by simply heating the solution to evaporate some of the solvent. However, this leads to two problems: (a) how much solvent is actually left in the flask cannot be accurately estimated, and (b) solvent vapors are discharged into the hood and are not collected for recycling or disposal. We have devised a simple solution to these two problems that uses the Aldrich rotary evaporator antisplash adapter (without return holes, Cat. No. Z17,604-4 to Z20,329-7).

The rotary evaporator antisplash adapter doubles as a solvent trap for the recovery of the crystallization solvent. The compound is placed in a round-bottom flask, and heated while the solvent is gradually added until the compound dissolves completely. The antisplash adapter is then attached to the flask and heating is continued. The solvent that evaporates at this stage condenses and collects in the antisplash adapter. A couple of modifications of this setup are possible. For larger-scale operations, the solutions can be magnetically stirred and heated. Also, for better recoveries of volatile solvents, a reflux condenser can be attached to the top of the antisplash adapter. After the solvent has collected in the adapter, the adapter is disconnected, and the solvent is removed and its volume measured. Besides effecting the desired concentration of the crystallization solution, this procedure allows one to calculate the amount of solvent left in the crystallization flask, and to recycle or properly dispose of the condensed solvent.



We routinely use this setup and find it very convenient. We hope that other researchers will find it equally helpful.

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Department of Chemistry
University of North Dakota
Grand Forks, ND 58202-9024
E-mail: mlakshman@mail.chem.und.nodak.edu

Please turn to page 12 for more Lab Notes.

Aldrich splash-guard adapters

Antisplash, without return holes

Top ₸ joint	Bottom ₸ joint	Cap. (mL)	Cat. No.
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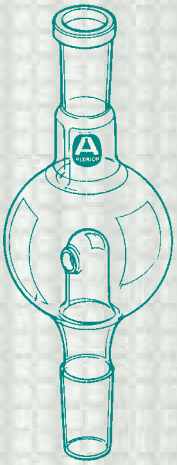
24/40	24/40	250	**Z14,779-6**
24/40	24/40	500	**Z14,781-8**
24/40	14/20	250	**Z14,782-6**
29/32	29/32	100	**Z20,344-0**
29/32	29/32	250	**Z20,327-0**
29/32	29/32	500	**Z20,328-9**
29/32	14.5/23	250	**Z20,329-7**



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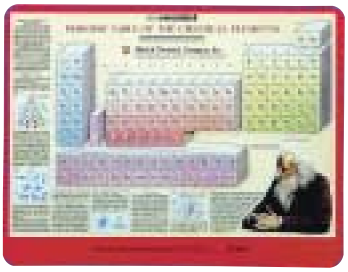

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The Chemical Vapor Deposition of Metal Nitride Films Using Modern Metalorganic Precursors

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Detroit, MI 48202
E-mail: cwinter@sun.science.wayne.edu

Outline

1. Introduction

Metal nitrides of the formula $M_{1.0}N_{1.0}$ (M = Ti, Zr, Hf, V, Nb, Ta) possess a wide range of useful properties, including extreme hardness, good chemical resistance, desirable optical properties, and good electrical conductivity.[1] Application of a thin film of $M_{1.0}N_{1.0}$ to a substrate can confer these characteristics to the surface of the structure. Prominent uses of metal nitride coatings include wear-resistant tool coatings,[2] solar-control coatings for glass,[3] decorative coatings,[4] conductive coatings,[5] and barrier materials in microelectronics.[6,7]

The most urgent application of early transition-metal nitride films is as barrier materials between copper and silicon in microelectronics devices. Copper is replacing aluminum as the interconnection material in sub-0.50 µm ultralarge-scale integrated (ULSI) devices, due to its lower electrical resistivity and fewer electromigration problems.[7,8] However, copper readily diffuses into silicon dioxide layers and silicon substrates under the high temperatures encountered in device fabrication. The interaction of copper with silicon at deposition temperatures leads to the formation of copper silicides as well as copper-doped silicon, both of which degrade the properties of the copper–silicon interface. Therefore, a barrier between copper and silicon is required (**Figure 1**). This barrier must stop the diffusion of copper at deposition temperatures long enough to enable manufacturing of the device, must be unreactive toward both copper and silicon, and should exhibit good adhesion to both copper and silicon. Furthermore, the barrier should be extremely thin (≤10 nm in sub-0.25 µm features[8]) to allow a sufficient amount of copper metal to be placed in the features and to reduce the electrical resistivity of the interconnect structure. Finally, the resistivity of the barrier layer should be <1000 µΩ•cm to maintain excellent electrical conductivity between the copper and silicon features.

A strict requirement of the barrier material is that it must be applied with excellent conformal coverage in high-aspect-ratio features on the substrates (the aspect ratio of a feature is defined as the ratio of its depth to its width). Conformal coverage is the degree to which a film is deposited in shaped formations on the substrate. In excellent conformal coverage, the corners and bottoms of features are coated with the material equally as well as the flat portions of the substrate; in poor conformal coverage, the corners and bottoms of features may be poorly coated or not coated at all. The decreasing size of features and increasing aspect ratios in future generations of microelectronics devices imply that new deposition processes will have to be brought into production to meet the conformal coverage requirements. Of the many film-forming processes that are available, only Chemical Vapor Deposition (CVD) can realistically deliver the conformal coverage that is needed in sub-0.25 µm devices. CVD involves the delivery of molecules to the growing film, as opposed to atoms and small groups of atoms that are involved in physical vapor deposition (PVD) techniques. Under optimum conditions, the molecules involved in CVD are able to adsorb/desorb on the growing film many times before decomposing and promoting film growth. Therefore, extremely uniform film growth can occur under CVD conditions and nearly perfect conformal coverage can ensue. In contrast, the atoms and small groups of atoms involved in PVD processes are highly reactive and adhere strongly to growing film surfaces. As a result, high-aspect-ratio features are poorly coated by PVD techniques, especially on the sides and corners.

This account describes recent advances that have occurred in the chemical vapor deposition of metal nitride films for

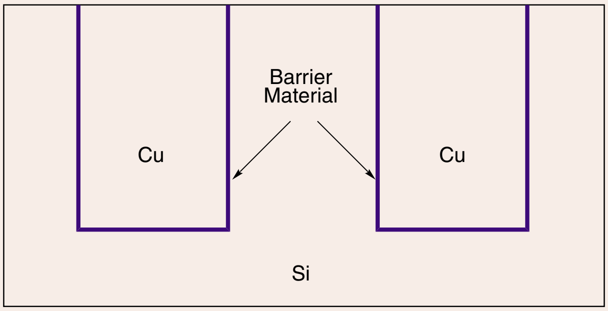


Figure 1. Schematic Representation of a Barrier Layer Between Cu and Si.

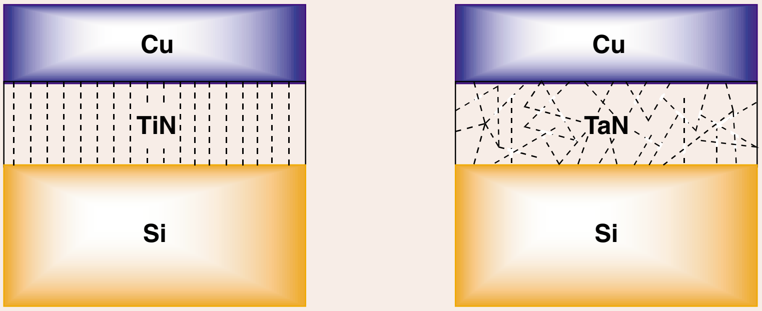


Figure 2. Schematic Representation of Grain Structures in TiN and TaN Films.

application as barrier materials in microelectronics devices. The focus is on new materials, chemical precursors, and chemical questions that address the many materials issues associated with chip manufacturing. Titanium nitride (TiN) is the leading barrier material used between silicon substrates and copper and has been the most studied.[9] Recently, new phases such as tantalum(III) nitride (TaN), amorphous tantalum silicon nitride (Ta–Si–N), and amorphous titanium silicon nitride (Ti–Si–N) have been suggested as barrier materials that are superior to TiN. The status of chemical vapor deposition routes to these materials is described. Additionally, the status of precursors to niobium(III) nitride (NbN) films is discussed, since NbN films should exhibit chemical and physical properties that are similar to those of TaN. Finally, mechanistic studies aimed at understanding the chemical intermediates that are involved in film depositions are presented.

2. Discussion

While many substances have been explored as possible barrier materials, titanium nitride (TiN) has been extensively investigated and is widely regarded as the leading candidate material for a barrier between copper and silicon.[7-9] However, the massive research effort that has been directed toward TiN has identified several shortcomings in its application as a barrier. TiN films are deposited with a characteristic columnar structure, in which the grain boundaries are parallel to each other and approximately perpendicular to the substrate (**Figure 2**). These grain boundaries create fast diffusion paths by which copper atoms can migrate to the silicon layer, leading to device failure.[10] This failure mechanism is particularly acute when thin barrier layers are used. Since future generations of microelectronics devices will require barrier layers that are ≤10 nm thick, new barrier materials will be required to solve the copper migration problem.

2.1. Binary Metal Nitride Films

In view of the potential problems associated with TiN, there has been a considerable research effort devoted to identifying barrier materials that are superior to TiN.[6,7] Recently, tantalum(III) nitride (TaN) films fabricated by PVD techniques were evaluated for their ability to act as a barrier between copper and silicon.[11] In general, TaN films deposited by PVD methods possess preferred (111) crystallographic orientation, exhibit close to 1:1 Ta:N stoichiometry, contain < 5% of elements other than tantalum and nitrogen, and have resistivities of < 600 µΩ•cm. Significantly, a 10-nm-thick TaN film was sufficient to stop diffusion of copper into the silicon substrate after annealing at 700 ºC for 30 min.[11] Moreover, a 25-nm-thick TaN film prevented copper diffusion into silicon after annealing at 800 ºC for 90 min. Based upon these annealing studies, it was claimed that TaN is the best barrier material yet identified for use between copper and silicon. The excellent barrier properties of TaN films were attributed to a disordered grain boundary structure that makes copper atom diffusion through the film inefficient, compared to other barrier materials with more ordered grain structures (**Figure 2**).

Another significant advance was the discovery that M–Si–N (M = Ti, Ta, W) films are excellent barrier materials.[12,13] The enhanced barrier properties of the ternary materials are due to their amorphous nature, which removes low-energy diffusion paths from the barrier. Barrier failure in these materials is associated with crystallization, which provides grain boundaries for rapid copper diffusion. Remarkably, the barrier structure Si/$Ta_{36}Si_{14}N_{50}$ (120 nm)/Cu (500 nm) is stable up to 900 ºC, at which temperature crystallization and concomitant barrier failure ensue.[12b] While many materials and manufacturing issues remain to be resolved, it is clear that TaN based barrier materials are among the best that have been identified to date. However, a detailed evaluation of TaN and Ta–Si–N barrier materials will require that these materials be deposited in high-aspect-ratio features on the substrate with excellent conformal coverage. The conformal coverage issue, in turn, requires a low-temperature CVD process for TaN films.

2.1.1. *Deposition of Tantalum Nitride Films*

Reports of CVD processes to tantalum nitride phases have been limited in number. The common nitride phases of tantalum have stoichiometries of Ta_2N, TaN, and Ta_3N_5.[14] In CVD processes, there is an excess of the nitrogen source, and thus only the nitrogen-rich phases TaN and Ta_3N_5 are generally observed. A difficulty with the deposition of tantalum nitride films is that the reduction of Ta(V) to Ta(III) has a very negative potential.[15] As outlined above, TaN is the phase with the best barrier properties; Ta_3N_5 is an insulator with resistivities of > 10^6 µΩ•cm. Since volatile source compounds are only available in the Ta(V) oxidation state, Ta_3N_5 films are frequently obtained, and it is generally difficult to deposit TaN films at low temperatures. Traditional CVD routes to tantalum nitride phases have involved the CVD reactions of $TaCl_5$ with nitrogen sources at high temperatures. In this way, TaN films have been deposited with a mixture of N_2 and H_2 at ≥ 900 °C (**eq 1**), while the use of ammonia affords Ta_3N_5 films at ≥ 900 °C (**eq 2**).[16,17] However, since semiconductor chip manufacturing has an upper temperature limit of about 400 °C, these two routes are not useful for the fabrication of microelectronics devices.

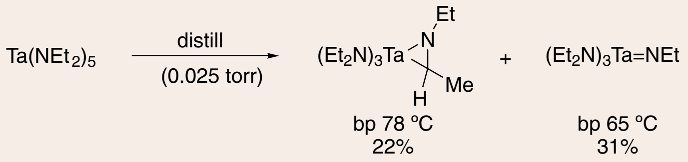
The CVD reaction of $Ti(NMe_2)_4$ or $Ti(NEt_2)_4$ with ammonia at 200–450 °C yields TiN films; this process has been developed into one of the leading routes to TiN films for barrier layer applications.[9] However, the analogous CVD process between $Ta(NMe_2)_5$ and ammonia at 200–400 °C yields Ta_3N_5 films instead (**eq 3**).[18]

$$TaCl_5 + N_2 + H_2 \xrightarrow{>900\ ^\circ C} \text{TaN films} \qquad \textbf{eq 1}$$

$$TaCl_5 + NH_3 \xrightarrow{>900\ ^\circ C} Ta_3N_5 \text{ films} \qquad \textbf{eq 2}$$

$$Ta(NMe_2)_5 + NH_3 \xrightarrow{200\text{–}400\ ^\circ C} Ta_3N_5 \text{ films} \qquad \textbf{eq 3}$$

$$\begin{tikzcd}
TaCl_5 + 5\ LiNR_2 \arrow[r, "\text{solvent}", "-5\ LiCl"'] & Ta(NR_2)_5 \ \ R = Me, Et \arrow[d, "\begin{array}{l}\text{distill}\\ 120\ ^\circ C,\\ 0.1\text{ torr}\\ R = Et\end{array}"] \\
 & Ta(NEt_2)_4 + Ta(NEt_2)_5 + (Et_2N)_3Ta{=}NEt
\end{tikzcd} \qquad \textbf{eq 4}$$



eq 5

$$TaCl_5 + 4\ LiNMe_2 + LiNHBu^t \xrightarrow[40\%]{-5\ LiCl,\ -HNMe_2} (Me_2N)_3Ta{=}NBu^t \qquad \textbf{eq 6}$$

$$Ta(NR)Cl_3py_2 + 3\ LiNEt_2 \xrightarrow{-3\ LiCl} (Et_2N)_3Ta{=}NR \quad R = t\text{-Bu}, i\text{-Pr}, n\text{-Pr} \qquad \textbf{eq 7}$$

$$\text{"}Ta(NEt_2)_5\text{"} \xrightarrow{\text{CVD}} Ta_xN_y \text{ films} \qquad \textbf{eq 8}$$

2.1.2. Synthesis of Tantalum Amide Complexes for Use as CVD Precursors

Lower-temperature approaches to TaN films use dialkylamide-based complexes as single-source precursors. The complex $Ta(NMe_2)_5$ can be prepared in about 30% yield by treatment of $TaCl_5$ with lithium dimethylamide (5 equiv; **eq 4**).[19] $Ta(NMe_2)_5$ is an orange solid that can be sublimed at 90 °C/0.01 torr. While $Ti(NEt_2)_4$ and higher alkyl derivatives are stable up to at least 150 °C, the tantalum(V) analogs decompose at moderate temperatures to several products. The original synthesis of $Ta(NEt_2)_5$ by Bradley and Thomas demonstrated that $Ta(NEt_2)_5$ could be obtained as a pure orange liquid through treatment of $TaCl_5$ with lithium diethylamide.[19] $Ta(NEt_2)_5$ is thermally stable at ambient temperature. However, upon attempted distillation at 120 °C (0.1 torr), mixtures of $Ta(NEt_2)_4$, $Ta(NEt_2)_5$, and the imido complex $(Et_2N)_3Ta{=}NEt$ were obtained (**eq 4**). It was proposed that, upon heating, a diethylamino radical is eliminated from $Ta(NEt_2)_5$ to afford $Ta(NEt_2)_4$, which then reacts with the diethylamino radical to afford $(Et_2N)_3Ta{=}NEt$, diethylamine, and ethylene.

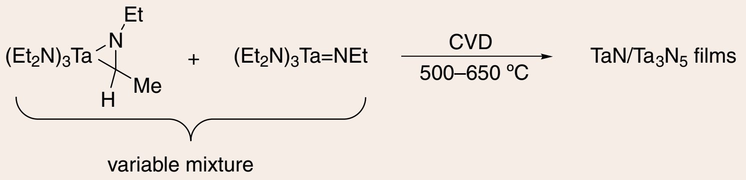
A later study by Sugiyama and coworkers found that distillation of $Ta(NEt_2)_5$ afforded a pale yellow liquid from which $Ta(EtNCHCH_3)(NEt_2)_3$ (bp 78 °C/0.025 torr, 22% yield) and $(Et_2N)_3Ta{=}NEt$ (bp 65 °C/0.025 torr, 31% yield) were isolated as pure materials by fractional distillation (**eq 5**).[20] The imino complex $Ta(EtNCHCH_3)(NEt_2)_3$ was stable below 100 °C, but decomposed to $(Et_2N)_3Ta{=}NEt$ above about 120 °C. Because Sugiyama found no evidence for $Ta(NEt_2)_4$ formation during the synthetic work, the prior claim for the existence of this complex[19a] cannot be regarded as conclusive.[21,22]

Several additional routes to imido complexes of the formula $(R_2N)_3Ta{=}NR$ have been reported. Treatment of $TaCl_5$ with lithium dimethylamide (4 equiv) and lithium *tert*-butylamide (1 equiv) afforded $(Me_2N)_3Ta{=}NBu^t$ in 40% yield as colorless crystals with a melting point of 68–69 °C (**eq 6**).[23] A crystal structure determination demonstrated that the complex was monomeric. The complexes $(Et_2N)_3Ta{=}NR$ (R = *t*-Bu, *i*-Pr, *n*-Pr) were prepared by treatment of $Ta(NR)Cl_3py_2$ with lithium diethylamide (3 equiv; **eq 7**).[24] The diethylamido complexes are liquids with boiling points of about 60 °C (0.1 torr).

2.1.3. Film Depositions Using Tantalum Amide Based Precursors

In an earlier work, Sugiyama reported that "$Ta(NEt_2)_5$" functions as a single-source precursor to tantalum nitride films, although the phase was not identified (**eq 8**).[25] The chemical nature of the precursor was not discussed. Consistent with the work of Bradley[19] and the later report by Sugiyama,[20] the "$Ta(NEt_2)_5$" precursor actually consisted of a mixture of $Ta(EtNCHCH_3)(NEt_2)_3$ and $(Et_2N)_3Ta{=}NEt$.

Recently, it was reported that a mixture of $Ta(EtNCHCH_3)(NEt_2)_3$ and $(Et_2N)_3Ta{=}NEt$ could be used as a precursor to tantalum nitride films.[26,27] Films were deposited with this precursor mixture at low pressure with substrate temperatures of 500–650 °C (**eq 9**). The bubbler containing $Ta(EtNCHCH_3)(NEt_2)_3$ and $(Et_2N)_3Ta{=}NEt$ was heated to 60–100 °C to effect vapor transport with argon carrier gas. Based on Bradley's[19] and Sugiyama's work,[20] it is likely that $(Et_2N)_3Ta{=}NEt$ was the major species that



$$(Et_2N)_3Ta\text{(EtNCHCH}_3\text{)} + (Et_2N)_3Ta{=}NEt \xrightarrow[500\text{–}650\ °C]{CVD} \text{TaN/}Ta_3N_5\text{ films}$$

eq 9

$$(Et_2N)_3Ta{=}NBu^t \xrightarrow[450\text{–}650\ °C]{CVD} \text{TaN films}$$

eq 10

$$\text{"}Ta(NEt_2)_5\text{"} \xrightarrow[< 400\ °C]{CVD} Ta_xC_yN_z\text{ films}$$

eq 11

$$Ta(NMe_2)_5 \xrightarrow[200\text{–}350\ °C]{\substack{CVD\\ H_2\text{ plasma}}} TaN_xC_y\text{ films}$$

At 300 °C:
$x = 1.4$, $y = 0.6$

eq 12

was transported to the deposition chamber. The films thus deposited showed X-ray diffraction patterns consistent with cubic TaN, although some diffraction spectra also revealed weak and broad reflections assignable to tetragonal Ta_3N_5. Analysis of the films by wavelength dispersive spectroscopy revealed that the films were slightly nitrogen-rich (N/Ta 1.1–1.2) and contained a minimum of 15–20% carbon. The carbon content of the films dramatically increased (C/Ta ratios as high as 3) upon raising the deposition temperature from 500 °C to 650 °C, increasing the pressure at which the depositions were carried out, or increasing the temperature at which the precursor mixture was held. The Ta/N ratio did not vary upon changing the deposition parameters; the constant composition was attributed to the fixed Ta/N stoichiometry associated with the strong tantalum–nitrogen imido bond. A subsequent study reported that addition of hydrogen to the carrier gas mixture decreased the carbon content in the films to a constant level of 15–20%, relative to tantalum, under all deposition conditions.[26] It was proposed that the hydrogen in the carrier gas leads to an increase in surface-bound hydride species that can react with surface-bound hydrocarbon fragments to afford volatile neutral hydrocarbons that are swept away from the film-growth environment.

The complex $(Et_2N)_3Ta{=}NBu^t$ has also been evaluated as a precursor to TaN films (**eq 10**).[28-30] The motivation for using $(Et_2N)_3Ta{=}NBu^t$, as opposed to the mixture of $Ta(EtNCHCH_3)(NEt_2)_3$ and $(Et_2N)_3Ta{=}NEt$ described above, was to have a single pure precursor that did not undergo decomposition at temperatures required for vapor transport. Film depositions were carried out at substrate temperatures of 450–650 °C and pressures of about 0.02 torr.[28,29] The bubbler containing $(Et_2N)_3Ta{=}NBu^t$ was heated to 30–50 °C to effect vapor transport. The growth rate of TaN films was constant at about 20 Å/min between 450 and 650 °C. The resistivity of the films was 10^4–10^5 μΩ•cm at 450 °C, but dropped with increasing substrate temperature to about 900 μΩ•cm at 650 °C. The X-ray diffraction patterns of films deposited at 500–650 °C were consistent with the cubic TaN phase, and were made up of randomly oriented crystallites. The film deposited at 500 °C exhibited very broad reflections in the X-ray diffraction spectrum, due to an average grain size of 9.2 nm. Analysis of a film deposited at 600 °C by X-ray photoelectron spectroscopy (XPS) and Rutherford backscattering spectrometry (RBS) revealed a nitrogen-rich composition (N/Ta 1.1–1.3) with about 10% carbon and 5–10% oxygen. The carbon was present as carbide, indicating direct tantalum–carbon bonds. A film deposited at 450 °C had a composition of $Ta_{1.0}N_{1.4}C_{0.7}O_{0.2}$. The conformality of the films was measured in trenches with aspect ratios of 1.75:1 to 2.00:1. At 450 °C, the conformality was 100%, while at 650 °C the values were 25–40%.

A W/CVD-TaN/Si contact structure was fabricated. No tungsten encroachment was found at the bottom of the contact hole, and the structure adhered well as demonstrated by a Scotch™ tape test. An Al/CVD-TaN/Si structure was fabricated as another test for the barrier properties of the TaN layer. The failure temperature of the TaN barrier was found to be 550–600 °C. The barrier-layer performance of CVD-TaN, deposited using $(Et_2N)_3Ta{=}NBu^t$, against copper diffusion was compared with that of PVD-TaN.[30] It was found that the Cu/CVD-TaN/Si structure survived without copper diffusion up to about 550 °C, while the Cu/PVD-TaN/Si structure did not fail until about 600 °C. The increased performance of the PVD-TaN was attributed to its small grain size (20 nm) and preferred (111) crystallographic orientation. In contrast, the CVD-TaN possessed a larger grain size (50–70 nm) and a preferred (200) crystallographic orientation.

Recent work has examined the low-temperature deposition (≤ 400 °C) of tantalum nitride films using a precursor that was claimed to be "$Ta(NEt_2)_5$".[31] Films were deposited with substrate temperatures of 275–400 °C, a reactor pressure of 1 torr, and a vapor transport bubbler temperature of 60 °C (**eq 11**). As noted earlier, 60 °C is a sufficient temperature to cause the conversion of $Ta(NEt_2)_5$ to $Ta(EtNCHCH_3)(NEt_2)_3$ and $(Et_2N)_3Ta{=}NEt$;[19,20] thus, there is some ambiguity as to the nature of the source compound in this work. Films deposited in this study exhibited resistivities of about 6000 μΩ•cm at 400 °C; the resistivities increased with decreasing deposition temperature. A film deposited at 400 °C had a carbon-rich composition of $Ta_{1.0}C_{1.0}N_{0.3}O_{0.1}$, in which the carbon was present predominantly as carbide (XPS analysis). The X-ray diffraction pattern showed a very broad reflection at $2\theta = 35°$ that could be attributed to the (111) plane of TaC or TaN. It was proposed that the film consisted of a Ta(CN) phase, rather than a mixture of TaC and TaN, due to the very high resistivity of the film and the very low resistivities of TaC and TaN. Analysis of a film deposited at 350 °C by transmission electron microscopy revealed an average grain size of about 30 Å.

Han et al. have recently reported the deposition of amorphous films derived from activation of $Ta(NMe_2)_5$ with a remote hydrogen plasma (**eq 12**).[32] Depositions were conducted on silicon substrates at 200–350 °C and ~1 torr. $Ta(NMe_2)_5$ was maintained in a bubbler held at 80 °C and was carried by argon. A film deposited at 300 °C had a stoichiometry of $Ta_{1.0}N_{1.4}C_{0.6}$, demonstrating that the film was both nitrogen- and carbon-rich. XPS indicated that the carbon was present predominantly in carbide form, with the remainder being attributed to hydrocarbons. It was suggested that the hydrocarbon residues originated from incomplete decomposition of the precursor. The films were found to be amorphous by X-ray diffraction and electron microscopy. The lowest film resistivities were 2000 μΩ•cm, and were obtained at a substrate temperature of 350 °C. The step coverage for films deposited in contact holes with an aspect ratio of 3:1 was nearly 100%. The as-deposited films remained amorphous up to 1000 °C, at which temperature crystallization ensued. These films served as effective barriers against the diffusion of platinum into silicon substrates at temperatures of up to 700 °C. A subsequent study found that use of a remote ammonia plasma instead of the remote hydrogen plasma led to a lower nitrogen and carbon content in the films.[33] For example, a film deposited at 300 °C with the remote ammonia plasma had a stoichiometry of $Ta_{1.0}N_{1.1}C_{0.51}$, and an X-ray diffraction spectrum that revealed the presence of cubic TaN with a preferred orientation along the (111) axis. Films deposited with the ammonia plasma showed larger crystallites, an observation that is consistent with the sharp reflections seen in the X-ray diffraction spectrum.

To summarize, amido precursors that have been evaluated as precursors to tantalum nitride films include $Ta(NMe_2)_5$, mixtures of $Ta(EtNCHCH_3)(NEt_2)_3$ and $(Et_2N)_3Ta{=}NEt$, and $(Et_2N)_3Ta{=}NBu^t$. Several groups have claimed to use "$Ta(NEt_2)_5$" as a source compound, but it has been demonstrated that "$Ta(NEt_2)_5$" is unstable at ambient temperature and decomposes to variable mixtures of $Ta(EtNCHCH_3)(NEt_2)_3$ and $(Et_2N)_3Ta{=}NEt$. Use of "$Ta(NEt_2)_5$", mixtures of $Ta(EtNCHCH_3)(NEt_2)_3$ and $(Et_2N)_3Ta{=}NEt$, or $(Et_2N)_3Ta{=}NBu^t$ as precursors yields cubic TaN films, but these films contain a minimum of 15–20% carbon relative to tantalum. Additionally, mixtures of cubic TaN and tetragonal Ta_3N_5 phases have been observed in some depositions using these precursors. The CVD process using $Ta(NMe_2)_5$ and ammonia yields Ta_3N_5 films. Activation of $Ta(NMe_2)_5$ with a remote hydrogen plasma leads to carbon-contaminated Ta_3N_5 films, while use of the same tantalum source with a remote ammonia plasma gives carbon-rich TaN films.

$$\mathrm{NbCl_5 + 5\ LiNMe_2 \xrightarrow{-5\ LiCl} Nb(NMe_2)_5} \qquad \textbf{eq 13}$$

$$\mathrm{NbCl_5 + 5\ LiNR_2 \xrightarrow[76–81\%]{-5\ LiCl} \underset{R\,=\,Et,\ \mathit{n}\text{-}Pr,\ \mathit{n}\text{-}Bu}{Nb(NR_2)_4}} \qquad \textbf{eq 14}$$

$$\mathrm{Nb(NR)Cl_3py_2 + 3\ LiNEt_2 \xrightarrow[30\%]{-3\ LiCl} \underset{R\,=\,\mathit{t}\text{-}Bu,\ \mathit{i}\text{-}Pr,\ \mathit{n}\text{-}Pr}{(Et_2N)_3Nb{=}NR}} \qquad \textbf{eq 15}$$

$$\mathrm{\underset{\substack{R\,=\,Me,\ x\,=\,5\\ R\,=\,Et,\ x\,=\,4}}{Nb(NR_2)_x} + NH_3 \xrightarrow[200–400\ ^\circ C]{CVD} Nb_3N_4\ films} \qquad \textbf{eq 16}$$

$$\mathrm{"Nb(NEt_2)_5" \xrightarrow[>\ 500\ ^\circ C]{CVD} NbN\ or\ Nb_4N_3\ films} \qquad \textbf{eq 17}$$

$$\mathrm{\mathit{n}\text{-}PrN{=}Nb(NEt_2)_3 \xrightarrow[550\ ^\circ C]{CVD} NbN\ films} \qquad \textbf{eq 18}$$

$$\mathrm{TaBr_5 \xrightarrow[\substack{N_2/H_2\ plasma\\ 350–450\ ^\circ C}]{CVD} TaN\ films} \qquad \textbf{eq 19}$$

2.1.4. Precursors and Film-Deposition Processes for Niobium Nitride Films

Although cubic NbN is a metallic nitride that is isostructural with TaN, the low-temperature CVD routes to NbN have been studied less than those to TaN. The chemistry of niobium dialkylamide complexes is different from that observed for tantalum dialkylamides,[34-36] and reflects the greater ease with which Nb(V) is reduced to Nb(IV).[15] Like $Ta(NMe_2)_5$, $Nb(NMe_2)_5$ can be prepared as a brown solid upon treatment of $NbCl_5$ with lithium dimethylamide (**eq 13**).[34] $Nb(NMe_2)_5$ sublimes at 100 °C/0.1 torr, but partial decomposition (30–40%) is observed during the sublimation. Upon treatment of $NbCl_5$ with lithium diethylamide, lithium di-*n*-propylamide, or lithium di-*n*-butylamide, however, complexes of the formula $Nb(NR_2)_4$ (R = Et, *n*-Pr, *n*-Bu) are obtained as dark-red liquids in 76–81% yields after distillation (**eq 14**). There was no evidence for the formation of $Nb(EtNCHCH_3)(NEt_2)_3$ and $(Et_2N)_3Nb{=}NEt$ during the preparation of $Nb(NR_2)_4$. Imido complexes of the formula $(Et_2N)_3Nb{=}NR$ (R = *t*-Bu, *i*-Pr, *n*-Pr) have been prepared in about 30% yields by treatment of $Nb(NR)Cl_3py_2$ (py = pyridine) with lithium diethylamide (**eq 15**).[37] The complexes are yellow liquids that distill at about 60 °C/0.1 torr.

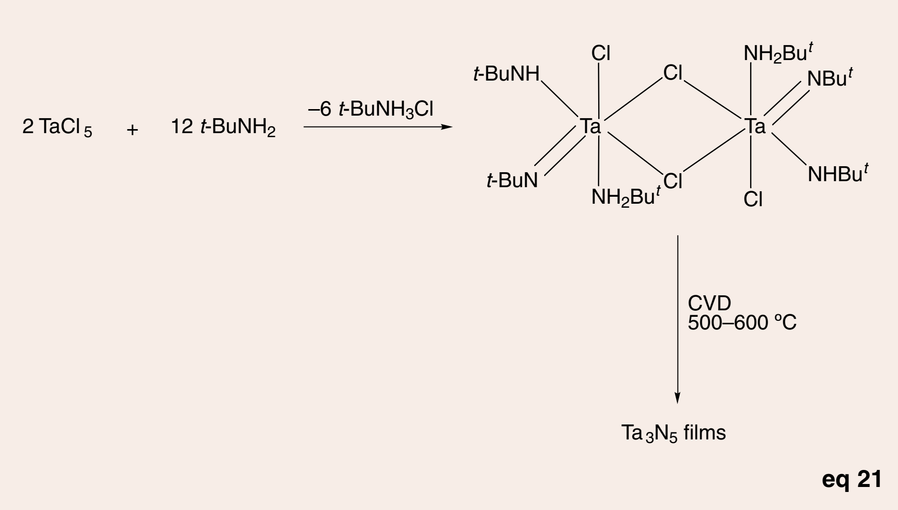
As in the case of TaN, routes to NbN films using $NbCl_5$ as the niobium source proceeded only at high temperatures.[16] The CVD process involving the gas-phase reaction of $Nb(NEt_2)_4$ or $Nb(NMe_2)_5$ with ammonia yielded amorphous niobium(IV) nitride (Nb_3N_4) films, rather than the NbN phase (**eq 16**).[18] Sugiyama and coworkers reported that use of "$Nb(NEt_2)_5$" as a single-source precursor led to the deposition of NbN or Nb_4N_3 films at substrate temperatures of > 500 °C (**eq 17**).[25] However, no further details were given on the properties of the film. As noted previously, "$Nb(NEt_2)_5$" is not a stable complex, and the authors were most likely using $Nb(NEt_2)_4$ as the source compound. The complex $(Et_2N)_3Nb{=}NPr^n$ was also evaluated as a precursor to NbN films (**eq 18**).[37] A film deposited with a substrate temperature of 550 °C and a reactor pressure of 0.01 torr had a stoichiometry of $Nb_{1.0}N_{0.7}C_{0.2}O_{0.2}$. The X-ray diffraction spectrum was consistent with the cubic NbN phase. XPS studies indicated that the carbon and oxygen in the film were present as carbide and oxide, respectively.

2.1.5. Low-Temperature Film Depositions Using Tantalum Pentabromide

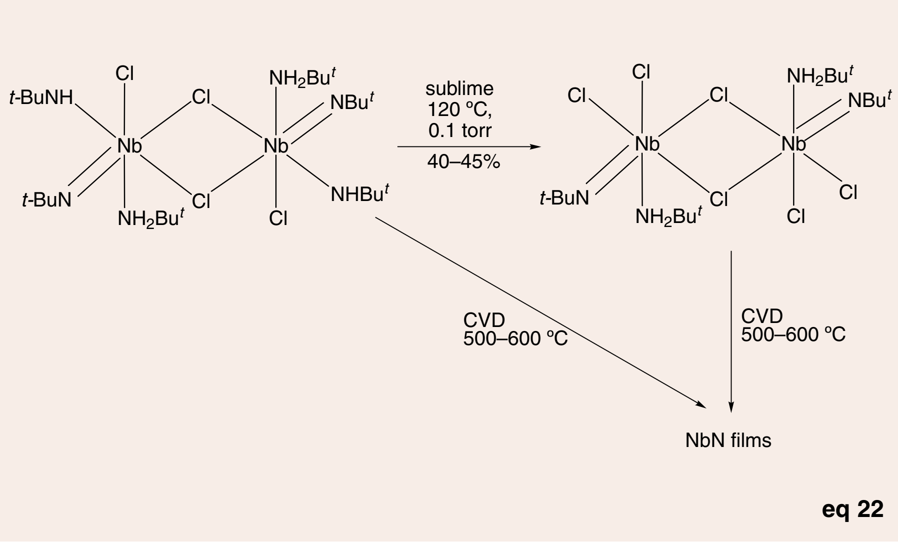
Cubic TaN films have been deposited with $TaBr_5$ as the tantalum source using plasma-assisted CVD (**eq 19**).[38] $TaBr_5$ was chosen as the tantalum source, since it was hypothesized that the weaker tantalum–bromine bonds, as compared to the stronger tantalum–chlorine bonds in $TaCl_5$, would lead to lower-temperature depositions of TaN. Moreover, the larger size of the bromide ion, as compared to the chloride ion, would lead to a very low diffusion constant for bromine in the film, assuring that any residual bromine in the TaN film does not interfere with the properties of the barrier structure. The plasma-assisted CVD was carried out at 350–450 °C and 0.9–1.6 torr using a mixture of nitrogen and

$$\mathrm{TaBr_5} + \mathrm{NH_3} \xrightarrow[\text{CVD}]{\mathrm{H_2},\ 425\ ^\circ\mathrm{C}} \mathrm{Ta_3N_5}\ \text{films (amorphous)}$$

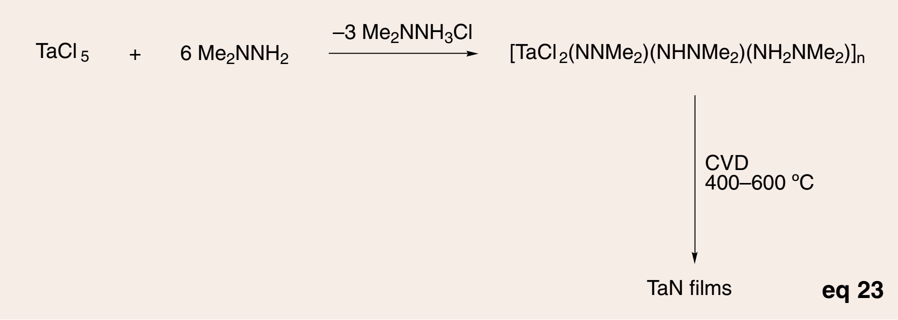
eq 20



eq 21



eq 22



eq 23

hydrogen as the plasma gas. X-ray diffraction spectra indicated that cubic TaN was obtained. The stoichiometry of the films was $Ta_{1.0}N_{1.0}$ with < 3% bromine, as determined by Auger spectroscopy and RBS. The resistivity of the films was as low as 150 μΩ•cm, which is similar to values for high-quality TaN films obtained by PVD methods.[11] The step coverage in a 0.3-μm-diameter trench with an aspect ratio of 4.5:1 was 95%. Accordingly, excellent-quality TaN films are obtained at low substrate temperatures from this process.

The thermal CVD reaction using $TaBr_5$, ammonia, and hydrogen as source compounds has also been reported (**eq 20**).[39,40] Amorphous films with a composition of $Ta_{1.00}N_{1.83}$ were obtained at 425 °C and 0.4 torr. The resistivity of the films was about 2500 μΩ•cm. Upon annealing at 650–700 °C, the films crystallized to the hexagonal Ta_3N_5 phase. Since the stoichiometry of the amorphous film was close to that expected for Ta_3N_5, and this phase crystallizes predominantly upon annealing, it is likely that the amorphous material corresponds predominantly to Ta_3N_5. The amorphous $Ta_{1.00}N_{1.83}$ films were evaluated as barrier materials against copper diffusion into silicon substrates, and were found to fail above 550 °C.

2.1.6. Synthesis and Evaluation of Precursors Derived from Tantalum Pentachloride

Our group has explored the use of compounds derived from the treatment of niobium and tantalum pentachlorides with primary amines and 1,1-dialkylhydrazines as precursors to metal nitride phases.[41,42] As first reported by Nielson and coworkers,[43] treatment of $TaCl_5$ with *tert*-butylamine affords the dimeric, chloride-bridged imido complex $[TaCl_2(NBu^t)(NHBu^t)(NH_2Bu^t)]_2$ (**eq 21**). We found that this complex existed as three major and two minor isomers in chloroform solution, apparently due to the isomerism of the nitrogen ligands about the coordination sphere of the dimeric unit.[41] $[TaCl_2(NBu^t)(NHBu^t)(NH_2Bu^t)]_2$ sublimed at 120 °C/0.1 torr without decomposition, and was evaluated as a precursor to tantalum nitride films.[42] Sublimation of this precursor into a hot-walled CVD reactor held at 500 or 600 °C led to the deposition of yellow-brown films on glass and silicon substrates; these films were identified as Ta_3N_5 by their X-ray powder diffraction patterns. Interestingly, the analogous niobium complex, $[NbCl_2(NBu^t)(NHBu^t)(NH_2Bu^t)]_2$, afforded cubic NbN films in the same reactor at substrate temperatures of ≥ 500 °C (**eq 22**).[42] However, $[NbCl_2(NBu^t)(NHBu^t)(NH_2Bu^t)]_2$ decomposes to $[NbCl_3(NBu^t)(NH_2Bu^t)]_2$ upon sublimation,[41] thus, the basic chemical behaviors of the niobium and tantalum precursors are quite different.

A tantalum complex of the formulation $[TaCl_2(NNMe_2)(NHNMe_2)(NH_2NMe_2)]_n$ was prepared in quantitative yield by treatment of $TaCl_5$ with 1,1-dimethylhydrazine in dichloromethane (**eq 23**).[42,44] This complex sublimed at 150–175 °C/0.1 torr without decomposition. Slow sublimation of this complex into a hot-walled CVD reactor held at 400, 500, or 600 °C resulted in the formation of silver-colored TaN films. The films were smooth and highly adherent, as demonstrated by a Scotch™ tape test.

The X-ray diffraction spectra of the films revealed the cubic TaN phase with preferred orientation along the (200) plane. XPS and RBS measurements gave a stoichiometry of about $Ta_{1.0}N_{1.1}$, with an oxygen content of about 6% and a carbon content below the detection limits of these techniques (< 5%). Electron micrographs showed a smooth surface, with particle sizes between 50–200 Å. The resistivity of a film deposited at 600 °C was 2.1 x 10^5 μΩ•cm.

2.2. Ternary Nitride Films

In recent years, the amorphous ternary nitrides M–Si–N (M = Ti, Ta, Mo, W) have been demonstrated as excellent barrier materials between copper and silicon for use in microelectronics devices.[12,13,45-49] The advantage of these amorphous materials over TiN, TaN, and other crystalline nitrides is the lack of grain boundaries to provide fast diffusion pathways for copper atoms to migrate into the silicon substrate. The failure of M–Si–N barrier materials is associated with crystallization, which supports the idea that copper atoms and other metal atoms migrate along grain boundaries. The first work in this area was reported by Nicolet,[12] who found that amorphous Ta–Si–N films fabricated by sputtering served as barriers between copper and silicon. Most of the work reported to date has used M–Si–N films that are deposited using PVD methods.[45,46] PVD methods are generally "line-of-sight" in nature, and do not afford high conformal coverage of shaped features on substrates. As noted earlier, barrier materials for microelectronics applications must be applied with excellent conformal coverage to silicon substrates to avoid copper diffusion into the silicon substrate and concomitant device failure. Accordingly, there has been significant interest in the development of CVD processes for the deposition of M–Si–N films.

To date, there have been no reports of CVD routes to Ta–Si–N films. This lack of activity reflects in large part the absence of a good low-temperature thermal CVD route to TaN films. Nicolet has found that Ta–Si–N has the highest barrier failure temperature of any ternary nitride that has been studied (900 °C), so there is keen interest in CVD routes to this material.[12,45] The potential importance of Ta–Si–N barrier materials provides a strong impetus for new research in this area.

While Ta–Si–N was found to have the highest barrier failure temperature, Ti–Si–N films have barrier properties that approach those exhibited by Ta–Si–N.[12,45] For example, Nicolet found that a Ti–Si–N structure failed at 850 °C, which is very close to the failure temperature of a Cu/Ta–Si–N/Si structure (900 °C).[12c] Since the CVD reaction of $Ti(NR_2)_4$ with ammonia has been developed as a low-temperature process for TiN films,[9] a basis exists for the exploration of Ti–Si–N films by CVD.

$$Ti(NEt_2)_4 + NH_3 + SiH_4 \xrightarrow[\text{CVD}]{450\ ^\circ\text{C}} Ti_{1.00}N_xSi_y \quad \begin{matrix} x = 1.10\text{–}1.20 \\ y = 0.06 \end{matrix}$$

eq 24

$$TiCl_4 + SiH_4 \xrightarrow[\text{CVD}]{\substack{N_2/H_2\ \text{plasma} \\ 550\text{–}570\ ^\circ\text{C}}} Ti_{1.00}N_xSi_y \quad \begin{matrix} x = 1.0 \\ y = 0.00\text{–}0.26 \end{matrix}$$

eq 25

$$Ti(NEt_2)_4 + NH_3 + SiH_4 \xrightarrow[\text{CVD}]{300\text{–}450\ ^\circ\text{C}} Ti_{1.00}N_xSi_y \quad \begin{matrix} x = \text{ca } 1.1 \\ y = 0.00\text{–}0.25 \end{matrix}$$

eq 26

The first description of a CVD route to Ti–Si–N films was reported by Raaijmakers.[47] The standard CVD process for the low-temperature deposition of conformal TiN—$Ti(NEt_2)_4$ plus ammonia at 450 °C—was modified by the addition of silane (SiH_4). Deposition on silicon substrates at 450 °C led to highly adherent Ti–Si–N films that contained about 6% silicon (**eq 24**). In addition, low carbon (0.5%) and oxygen (1%) levels were observed. The film was amorphous by X-ray diffraction. While TiN films deposited from $Ti(NEt_2)_4$ and ammonia possessed resistivities of about 270 μΩ•cm, the amorphous Ti–Si–N film was found to have a resistivity of 9400 μΩ•cm.

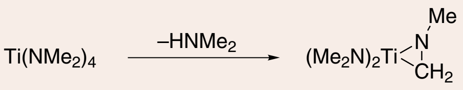
Ti–Si–N films with a silicon content of 16% were fabricated by a plasma-assisted CVD process involving $TiCl_4$, nitrogen, hydrogen, and SiH_4 as the reactants (**eq 25**).[48] The reactants were activated by a dc glow discharge, and the films were deposited on steel substrates that were heated to 500 °C. The films were crystalline by X-ray diffraction, and exhibited preferred growth along the (200) plane. Unlike TiN deposited from $TiCl_4$, nitrogen, and hydrogen by plasma-assisted CVD, the Ti–Si–N film containing 16% silicon did not reveal a detectable columnar structure in cross-section electron micrographs. Additionally, the grain size in the Ti–Si–N films was smaller than that of TiN films deposited by plasma-assisted CVD. Interestingly, the Ti–Si–N films were harder and more resistant to oxidation by the ambient atmosphere than TiN films prepared by plasma-assisted CVD. A recent report has described the thermal CVD of Ti–Si–N films from $TiCl_4$, ammonia, and SiH_2Cl_2 or $TiCl_4$, nitrogen, hydrogen, and SiH_2Cl_2.[49]

Smith and Custer have described the deposition of Ti–Si–N films containing variable amounts of silicon through the thermal CVD reaction between $Ti(NEt_2)_4$, ammonia, and SiH_4 (**eq 26**).[13] Films were grown in a warm-walled reactor with silicon substrate temperatures between 300–450 °C and a working pressure of 20 torr. The films were nitrogen-rich, and contained 0–25% silicon, depending on the amount of SiH_4 added to the reactant stream. The only contaminants observed in the films were carbon (<1.5%) and hydrogen (5–15%). Film resistivity increased exponentially with increasing silicon content. The lowest film resistivities were obtained with a substrate temperature of 350 °C, and ranged between 400 μΩ•cm for pure TiN to 1 Ω•cm for Ti–Si–N containing 25% silicon. It was suggested that the low resistivities observed at 350 °C were due to the nitrogen content in the films being the closest to the idealized value of 1:1 for TiN. Higher-resistivity films deposited at 300, 400, or 450 °C possessed 8–15% excess nitrogen. Transmission electron microscopy demonstrated that the films consisted of about 6-nm nanocrystallites of TiN embedded in an amorphous Ti–Si–N matrix. Deposition of $Ti_{0.46}N_{0.51}Si_{0.03}$ films with resistivities of ≤ 800 μΩ•cm on shaped substrates at 350 °C afforded step coverages of 60% on a 0.2-μm feature with an aspect ratio of 6:1, 75% on a 0.35-μm feature with an aspect ratio of 3:1, and 35–40% on a 0.1-μm feature with an aspect ratio of 10:1. Accordingly, this process provides very good conformal coverage and may provide acceptable films of barrier material in sub-0.18 μm features.

Table 1. Summary of Current CVD Techniques for Depositing Metal Nitride Films

Precursor(s)	Deposition Temp. (°C)	Deposition Pressure (torr)	Film Deposited[a]	Ref.
"$Ta(NEt_2)_5$"	500	not given	unidentified	25
$Ta(EtNCHCH_3)(NEt_2)_3$ + $(NEt_2)_3Ta{=}NEt$	500–650	0.3–1.0	cubic TaN + Ta_3N_5	26,27
$(NEt_2)_3Ta{=}NBu^t$	450–650	0.02	cubic TaN	28–30
"$Ta(NEt_2)_5$"	275–400	1	TaN_xC_y	31
$Ta(NMe_2)_5$ / H_2 or NH_3 plasma	200–350	1	TaN_xC_y	32
$Nb(NEt_2)_4$ or $Nb(NMe_2)_5 + NH_3$	200–450	760	Nb_3N_4	18
"$Nb(NEt_2)_5$"	500	not given	NbN or Nb_4N_3	25
$(NEt_2)_3Nb{=}NPr^i$	550	0.01	cubic NbN	37
$TaBr_5$, N_2/H_2 plasma	350–450	0.9–1.6	cubic TaN	38
$TaBr_5 + NH_3 + H_2$	425	0.4	Ta_3N_5	39,40
$[TaCl_2(NBu^t)(NHBu^t)(NH_2Bu^t)]_2$	500–600	0.1	Ta_3N_5	42
$[NbCl_2(NBu^t)(NHBu^t)(NH_2Bu^t)]_2$	500–600	0.1	cubic NbN	42
$[TaCl_2(NNMe_2)(NHNMe_2)(NH_2NMe_2)]_2$	400–600	0.1	cubic TaN	42,44
$Ti(NEt_2)_4 + NH_3 + SiH_4$	300–450	20	Ti–Si–N	13,47
$TiCl_4 + N_2 + H_2 + SiH_4$ dc glow discharge	850–1100	0.2	Ti–Si–N	48,49

[a] The compositions and properties of the films obtained are critically dependent on the nature of the source compound and the deposition conditions.



eq 27

3. Conclusions and Prospects

This account has summarized the current state of film depositions by CVD techniques for TaN, Ta–Si–N, and related nitride materials that are candidates for advanced barrier layers between copper and silicon in future generations of microelectronics devices (**Table 1**). Precursors that have been used to deposit the cubic TaN phase under thermal CVD conditions include a mixture of imino and imido complexes derived from the decomposition of $Ta(NEt_2)_5$, imido complexes of the formula $(Et_2N)_3Ta{=}NR$, as well as imido complexes derived from treatment of $TaCl_5$ with primary alkylamines. Serious drawbacks of complexes bearing diethylamido ligands include variable selectivity for the cubic TaN phase over the tetragonal Ta_3N_5 phase, incorporation of significant amounts (15–20 atom %) of carbon and oxygen into the film, and film resistivities that are too high for use as barrier layers (generally > 2000 μΩ•cm). The incorporation of carbon into TiN films from $Ti(NR_2)_4$ precursors has been proposed to occur through intramolecular β-hydrogen activation, which leads to a species with a direct titanium–carbon bond (**eq 27**).[50] It is necessary to add a large excess of ammonia to the $Ti(NR_2)_4$ precursor stream to reduce the carbon incorporation in the resultant films to low levels (< 10%).[9] Since a similar process is operant in the formation of $Ta(EtNCHCH_3)(NEt_2)_3$ from $Ta(NEt_2)_5$,[20] it is likely that carbon incorporation in TaN films derived from dialkylamido-based precursors occurs through intermediate species with tantalum–carbon bonds. Intramolecular β-hydrogen activation appears to be a characteristic reaction path for early transition-metal dialkylamido complexes; therefore, it is likely that significant carbon incorporation will be observed when such compounds are used in CVD. Because MN film resistivity increases dramatically with impurity incorporation, TaN films with resistivities below 1000 μΩ•cm may not be accessible from these precursors. Addition of ammonia to precursor streams of tantalum dialkylamido compounds may lower the carbon content, but it is very likely that the high-resistivity Ta_3N_5 phase would result—in analogy with the CVD of Ta_3N_5 films from $Ta(NMe_2)_5$ and ammonia.[18]

While the resistivity of the TaN films deposited from $[TaCl_2(NNMe_2)(NHNMe_2)(NH_2NMe_2)]_n$ is too high for barrier-layer applications, the deposition of high-purity cubic TaN films in a thermal CVD process at temperatures as low as 400 ºC is significant. Additionally, the fact that $[TaCl_2(NNMe_2)(NHNMe_2)(NH_2NMe_2)]_n$ leads to TaN films at substrate temperatures that are up to 600 ºC lower than that observed for $[TaCl_2(NBu^t)(NHBu^t)(NH_2Bu^t)]_2$ argues that hydrazido ligands are powerful reducing agents that greatly facilitate the Ta(V)–Ta(III) reduction.[44] The reducing ability of hydrazine-derived ligands could be used to devise new classes of precursors for the low-temperature CVD of TaN.

The plasma-assisted process involving $TaBr_5$, nitrogen, and hydrogen provides the highest-quality TaN films that are available from any CVD route reported to date.[39] The TaN films are stoichiometric, have resistivities that are comparable to high-quality films obtained by PVD methods,[11] can be deposited with excellent conformal coverage in high-aspect-ratio features, and are deposited at temperatures that are compatible with microelectronics device manufacturing (≤ 400 ºC). Potential drawbacks include the necessity of the plasma processing as well as the presence of small amounts of bromine in the films. Plasma-assisted CVD requires more expensive and elaborate deposition equipment than thermal CVD, and there is potential for damage of the microelectronics device being fabricated due to the highly energetic chemical species that are generated through the plasma activation. The presence of bromine atoms or hydrogen bromide in the films could lead to degradation of the interface between the TaN films and the copper or silicon layers. The use of the plasma is essential to obtaining TaN films, since the thermal CVD process involving $TaBr_5$ and ammonia affords Ta_3N_5 films instead.[40]

The lack of a low-temperature thermal CVD process to high-quality TaN films has so far prevented the development of a CVD process to amorphous Ta–Si–N films. The analogous material Ti–Si–N has been deposited by CVD through modification of two existing processes to TiN films by adding SiH_4 or SiH_2Cl_2 to the precursor streams.[13,47,48] The process using $Ti(NEt_2)_4$, ammonia, and SiH_4 provides low-resistivity, highly conformal Ti–Si–N coatings with properties that appear to be acceptable for barrier-layer applications.[13,47]

The development of new precursors for the deposition of metal nitride films for barrier layer applications presents many challenges for the chemist. To be useful in semiconductor manufacturing, new processes to metal nitride films must afford high-purity, low-resistivity, and highly conformal coatings at deposition temperatures of ≤ 400 ºC. Furthermore, new precursors must be prepared in high yields and high purities by efficient syntheses, and should be liquids at ambient temperature in order to maintain constant surface areas for achieving steady vapor transport from stainless steel bubblers used to contain source compounds. To address these goals, it will be necessary to identify ligands that lead to minimum carbon incorporation in the metal nitride films, and which help to promote reduction to the Ta(III) oxidation state, while still providing high-quality TaN and related thin-film materials. Advances in deposition techniques would also aid in the fabrication of new tantalum-based barrier materials.

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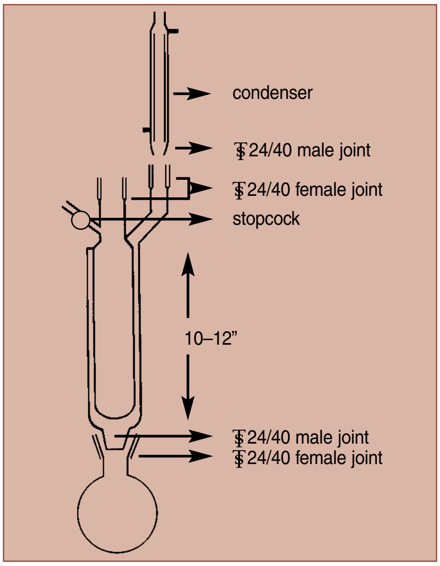
About the Author

Charles H. Winter was born in 1959 in Grand Rapids, Michigan, and grew up in Portage, Michigan, where he attended public schools. He obtained a B.S. degree from Hope College in 1982. While at Hope College, he was introduced to organometallic chemistry through undergraduate research with Professor Michael P. Doyle. He then went on to the University of Minnesota, and obtained his doctoral degree in 1986 under the direction of the late Professor Paul G. Gassman. After an NIH postdoctoral fellowship with Professor John A. Gladysz at the University of Utah, he joined the faculty at Wayne State University in 1988. He is now Professor of Chemistry.

Professor Winter's research interests include synthetic inorganic and organometallic chemistry, as well as chemical vapor deposition. A particular research emphasis in his laboratory is the development of new source compounds for use in CVD processes. Materials systems for which new precursors are being developed include group 4 and 5 nitrides for application as barrier materials in microelectronics devices, lanthanide compounds for application in infrared photonic devices, and magnesium compounds for devices that emit blue and green light. In the area of compound semiconductors, the development of precursors that are designed to decompose under X-ray irradiation is also underway. In addition to research directed toward CVD, Professor Winter maintains significant basic research projects involving the synthesis and properties of metal complexes with new nitrogen-donor ligands, metallocenes and aromatic compounds substituted with unusual main group elements, as well as fundamental chemistry of the group 13 elements. He has been a mentor to 22 doctoral students and is the author of more than 95 publications.

Lab Notes, continued from page 2.

Balki's Modified Abderhalden Drying Apparatus



An innovative and convenient apparatus has been designed, which is especially useful for manipulating air-sensitive compounds.

Because of its horizontal construction, the traditional Abderhalden drying apparatus has certain disadvantages, such as the possibility of sample spillage and the inconvenience of drying liquid samples (that cannot be distilled).

In this modified apparatus, the sample—which is most often stored in a slim, screw-cap vial—is conveniently lowered into the apparatus with the help of long tweezers, forceps (Cat. No. Z22,560-6 or Z22,561-4), or a copper wire that is tied around the neck of the vial.

This modified Abderhalden drying apparatus is very advantageous to use in many applications: It makes it convenient to add or remove solvent or solid materials, and is ideal for carrying out reactions in NMR tubes and for preparing NMR samples after drying the solid samples in the NMR tubes. We have also been successful in growing single crystals of air-sensitive samples using this setup.

I hope that this modification to a widely used apparatus will prove helpful to research scientists all over the world.

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Products for the Deposition of Metal Nitride Films

The following Aldrich products are mentioned in Dr. Winter's review. For more information, please call us at *800-231-8327* (USA) or your local Sigma-Aldrich office, or visit our Web site at *www.sigma-aldrich.com*. Larger quantities are available through Sigma-Aldrich Fine Chemicals. Please call *800-336-9719* (USA) or your local office for availability.

Niobium, Tantalum, and Silicon Compounds

$NbCl_5$ **$TaBr_5$** **$TaCl_5$** **$Ta(NMe_2)_5$** **SiH_2Cl_2** **SiH_4**

51,069-6	**Niobium(V) chloride**, 99.999%, anhydrous, powder
33,660-2	**Niobium(V) chloride**, 99.9+%
21,579-1	**Niobium(V) chloride**, 99%
40,046-7	**Tantalum(V) bromide**, -8 mesh, 98%
51,068-8	**Tantalum(V) chloride**, 99.999%, anhydrous, powder
40,047-5	**Tantalum(V) chloride**, 99.99%
21,863-4	**Tantalum(V) chloride**, 99.8%
49,686-3	**Pentakis(dimethylamino)tantalum**, 99.9% *(packaged in ampules)*
33,339-5	**Dichlorosilane**, 99.99+%
29,522-1	**Dichlorosilane**, 97+%
33,389-1	**Silane**, 99.998+%, electronic grade
29,567-1	**Silane**, 99.9%

Titanium Compounds

$Ti(NMe_2)_4$ **$Ti(NEt_2)_4$** **$TiCl_4$**

46,985-8	**Tetrakis(dimethylamino)titanium**, 99.999%
46,986-6	**Tetrakis(diethylamino)titanium**, 99.999%
25,431-2	**Titanium(IV) chloride**, 99.995+%
20,856-6	**Titanium(IV) chloride**, 99.9%
24,986-6	**Titanium(IV) chloride**, 1.0*M* solution in dichloromethane
34,569-5	**Titanium(IV) chloride**, 1.0*M* solution in toluene
40,498-5	**Titanium(IV) chloride**, *ca.* 0.09*M* solution in 20% hydrochloric acid


Aldrich
Handbook of Fine Chemicals and Laboratory Equipment
2000-2001

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Widely used in organic synthesis and combinatorial applications, here we present all our isocyanates, as well as some popular isothiocyanates. In addition, the brochure highlights our Small Sample Service and several of the polymeric isocyanates in our collection.

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ALDRICH®

Synthetic Applications of Indium Trichloride Catalyzed Reactions

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Central Leather Research Institute
Adyar, Chennai 600 020, India
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Outline

1. Introduction

Lewis acids play a vital role in organic reactions. The Lewis acids most frequently encountered in organic synthesis are $AlCl_3$, BF_3•Et_2O, $ZnCl_2$, $TiCl_4$, and $SnCl_4$. Recently, lanthanide triflates have gained a lot of attention as Lewis acids for organic reactions.[1] Although indium belongs to the same group in the periodic table as boron and aluminum, the utility of indium trichloride as a Lewis acid for organic reactions has not been exploited to a greater extent largely because of its mild Lewis acid character. Recently, it has been proven that indium trichloride is a mild Lewis acid which is stable in an aqueous medium, and that it effectively catalyzes the aldol, Diels–Alder, and Friedel–Crafts reactions. This short review focuses on the effectiveness of indium trichloride as a Lewis acid in organic synthesis, and covers the literature of the past decade. The synthetic applications of indium trichloride prior to 1990 were surveyed by Fedorov and Fedorov[2a] and by Boghosian and Papatheodorou.[2b]

2. Synthetic Applications

2.1. The Diels–Alder Reaction

The Diels–Alder reaction is one of the most powerful methods for the regio- and stereospecific preparation of carbocyclic and heterocyclic ring systems. Lewis acids increase the rate of the reaction and its regio-, endo-, and π-face selectivities by coordination with the dienophile, i.e., with a conjugated C=O or C=N group.

Loh and coworkers[3] have reported that indium trichloride catalyzes the Diels–Alder reaction between cyclopentadiene and acrylates in water (**eq 1**), and have shown that the catalyst can be easily recovered from water and reused after the reaction has been completed.

The imino Diels–Alder reaction is a powerful tool for the synthesis of quinoline and pyridine derivatives. Although Lewis acids often promote the reaction, more than stoichiometric amounts of the acids are required due to the strong coordination of the acids to the nitrogen atoms.[4] In contrast, only a catalytic amount of anhydrous indium trichloride (20 mol %) is needed for the reaction of Schiff bases with cyclopentadiene to afford cyclopentaquinolines (**eq 2**).[5] The use of indium trichloride enhances the rate of the reaction and improves its yield as compared to other Lewis acids (**Table 1**).[6,7] Indium trichloride also catalyzes the Diels–Alder reaction of *N*-benzylidene-1-naphthylamine with cyclopentadiene to afford benzo[*h*]-cyclopenta[*c*]quinoline (**eq 3**).[5]

The pyranoquinoline moiety is present in many alkaloids such as flindersine, oricine and veprisine (**Figure 1**). Pyranoquinoline derivatives possess a wide range of biological activities, such as psychotropic, antiallergic, anti-inflammatory, and estrogenic activities, and are potential pharmaceuticals. Pyranoquinoline derivatives have been synthesized by the BF_3•Et_2O,[8] acetic acid,[9] or ytterbium triflate catalyzed[10] Diels–Alder reaction of *N*-benzylideneaniline with 3,4-dihydro-2*H*-pyran; the yields, however, are low. On the other hand, indium trichloride catalyzes the Diels–Alder reaction of Schiff bases with 3,4-dihydro-2*H*-pyran and affords the corresponding pyranoquinoline derivatives in good-to-moderate yields. Indium trichloride coordinates with the Schiff bases yielding endo/exo products, the ratio of which is determined largely by the electronic effects of the substituents in the Schiff bases (**eq 4**).[11] A comparison of the results obtained with indium trichloride with those obtained with other catalysts is given in **Table 2**. The reaction of 3,4-dihydro-2*H*-pyran with *N*-benzylidene-1-naphthylamine in the presence of 20 mol % indium trichloride provides benzo[*h*]pyrano[3,2-*c*]quinolines (**eq 5**).[11]

Schiff bases react with indene in the presence of indium trichloride affording only the endo isomer of indeno[2,1-*c*]quinolines in moderate yields (**eq 6** and **Table 3**);[11] in the absence of indium trichloride, the reaction does not proceed at all. The endo isomer is obtained as a result of the likely secondary orbital interactions of diene and dienophile. Similarly, *N*-benzylidene-1-naphthylamine reacts with indene to provide benzo[*h*]-indeno[2,1-*c*]quinoline in 50% yield (**eq 7**).[11]

The Diels–Alder reaction of benzo[*b*]-thienylimines with cyclopentadiene and 3,4-dihydro-2*H*-pyran in the presence of anhydrous indium trichloride provides benzo[*b*]thienyl-substituted quinoline derivatives (**Scheme 1**),[12] a class of biologically active agents, in good yields and endo stereoselectivities. The addition is also regioselective with respect to the dihydropyran ring. Similarly, the reaction of imines with enamides leads to the biologically important pyrolloquinolines regioselectively and in moderate yields (**eq 8**).[13]

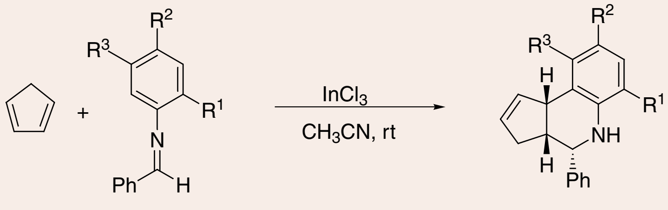
Azabicyclo[2.2.2]octanones have been prepared in moderate yields and regio- and stereoselectivities by the Diels–Alder reaction of either *N*-tosylimines with 2-trialkylsilyloxy-1,3-cyclohexadiene (**eq 9**),[14] or iminocarbamates with 1,3-cyclohexadiene (**eq 10**)[15] in the presence of BF_3•Et_2O. By comparison, the Diels–Alder reaction of Schiff bases with 2-cyclohexenone in the presence of indium trichloride provides a facile route to azabicyclo[2.2.2]octanones (**eq 11** and **Table 4**).[16] Azabicyclononan-8-ones have been similarly prepared in good yields (**eq 12**).[16] Azabicyclooctanones and azabicyclononanones are of interest as precursors of naturally occurring piperidine alkaloids of the prosopis family.[17]

2.2. The Aldol Reaction

The aldol reaction is one of the most important carbon–carbon bond forming reactions for acyclic stereocontrol. Mukaiyama and coworkers[18] have reported that aldehydes smoothly react with trimethylsilyl enol ethers, in the presence of TMSCl and indium trichloride, to produce the corresponding aldol adducts in high yields (**eq 13**).

Catalytic amounts of *tert*-butyldimethylsilyl chloride (TBSCl) and indium trichloride also promote aldol reactions. The conventional Mukaiyama aldol reaction requires strictly anhydrous and nonprotic conditions.[19] Kobayashi has shown that lanthanide triflates are excellent catalysts for the Mukaiyama aldol reaction in aqueous media (THF-H_2O).[20,21] However, efforts to carry out the experiment in water alone afforded only low yields of the products. Loh and coworkers[22] have demonstrated for the first time that indium trichloride catalyzes the Mukaiyama-type reaction of silyl enol ethers and

eq 1

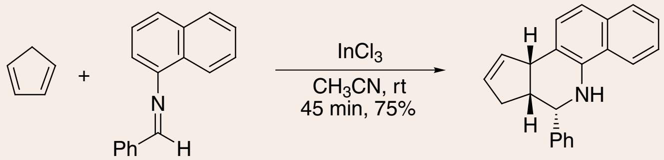


1a–d **2a–d**

eq 2

Table 1. Reaction of Schiff Bases with Cyclopentadiene

Entry	Schiff Base	R¹	R²	R³	Catalyst	Time, h	Product	Yield, %	Ref.
1	**1a**	H	H	H	TFA	2	**2a**	71	6
					$Yb(OTf)_3$	20		85	7
					$InCl_3$	0.5		75	5
2	**1b**	H	NO_2	H	TFA	3	**2b**	98	6
					$InCl_3$	0.5		95	5
3	**1c**	H	OCH_3	H	$Yb(OTf)_3$	20	**2c**	38	7
					$InCl_3$	0.75		58	5
4	**1d**	H	Cl	H	$Yb(OTf)_3$	20	**2d**	85	7
					$InCl_3$	0.5		84	5



eq 3

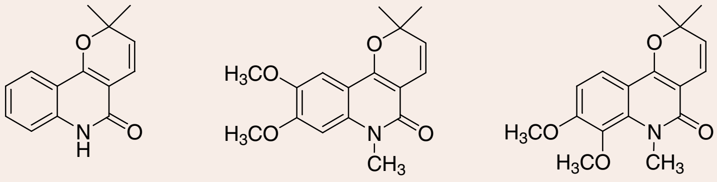
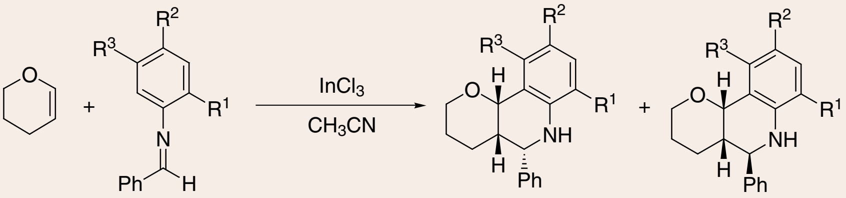


Figure 1

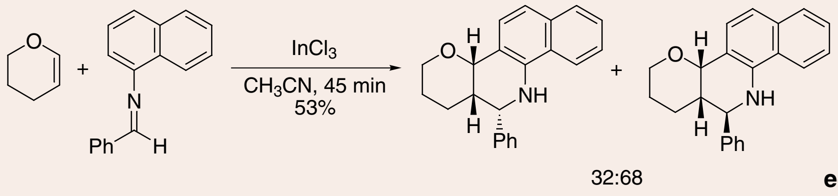


1a, c–e **3a, c–e** **4a,c–e**

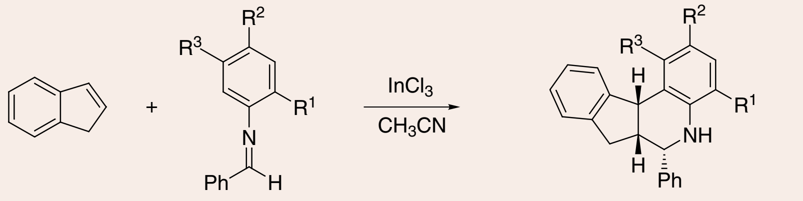
eq 4

Table 2. Reaction of Schiff Bases with 3,4-Dihydro-2*H*-pyran

Entry	Schiff Base	R^1	R^2	R^3	Catalyst	Time, h	Product Ratio 3:4	Overall Yield, %	Ref.
1	**1a**	H	H	H	BF_3•Et_2O $InCl_3$	12 0.5	100:0 41:59	25 80	8 11
2	**1c**	H	OCH_3	H	$Yb(OTf)_3$ $InCl_3$	9 4	37:63 58:42	54 70	10 11
3	**1d**	H	Cl	H	$InCl_3$	0.5	34:66	50	11
4	**1e**	H	CH_3	H	$InCl_3$	2	68:32	70	11



eq 5



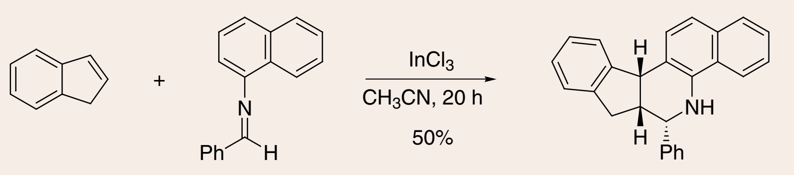
1a, c, d, f, g

5a, c, d, f, g

eq 6

Table 3. Reaction of Schiff Bases with Indene in the Presence of 20 mol % $InCl_3$

Entry	Schiff Base	R^1	R^2	R^3	Time, h	Product	Yield, %
1	**1a**	H	H	H	6	**5a**	40
2	**1c**	H	OCH_3	H	24	**5c**	30
3	**1d**	H	Cl	H	6	**5d**	48
4	**1f**	CH_3	Cl	H	12	**5f**	48
5	**1g**	CH_3	H	CH_3	9, reflux	**5g**	65



eq 7

aldehydes in water (**eq 14**). Recently, Kobayashi[23] has reported that the indium trichloride catalyzed aldol reaction of silyl enol ethers with aldehydes proceeds smoothly in water without using any cosolvents when a small amount of surfactant is present (**eq 15**). Because of its high coordination number and fast coordination–dissociation equilibrium, $InCl_3$ is stable in aqueous media and thereby effectively catalyzes the aqueous aldol reaction.[3] In contrast, other Lewis acids, such as BF_3•Et_2O and $AlCl_3$, react with water to yield the corresponding hydroxide derivatives.

The aldol–Mannich-type reaction is among the most fundamental methods for the synthesis of β-amino ketones and esters. The uncatalyzed synthesis of β-amino ketones and esters by the aldol–Mannich-type reaction gives products in low yields due to severe side reactions such as deamination. Unfortunately, most of the Lewis acids used in aldol–Mannich-type reactions are not stable and decompose or deactivate in the presence of water, which is a by-product of imine formation, or as a result of direct attack by the free amine present. Loh's group[24] has reported that indium trichloride catalyzes the formation of β-amino esters, in better yields, by reaction of an aldehyde, an amine, and an ester-derived silyl enol ether (**eq 16**). The reaction of a ketone-derived silyl enol ether with an aldehyde and an amine affords β-amino ketones in good-to-moderate yields (**eq 17**).[24]

2.3. The Friedel–Crafts Reaction

Indium trichloride catalyzes the acylation of anisole at room temperature, and the yield of the reaction is improved significantly by the addition of silver perchlorate (**eq 18**).[25] The combination of $InCl_3$ and $AgClO_4$ is believed to generate the active catalyst species, $InCl_2(ClO_4)$ or $InCl(ClO_4)_2$, which reacts with the anhydride to form an acyl cation intermediate that is stabilized by the perchlorate anion. This acylium ion intermediate then reacts with aromatics to give the desired ketone. In combination with chlorodimethylsilane, indium trichloride catalyzes the reductive Friedel–Crafts alkylation of aromatics (**eq 19**).[26,27] This transformation is especially valuable in light of the difficulty with which these alkylated aromatics have traditionally been prepared. The tolerance of ester and ether groups, which are frequently used as alkylating reagents, is perhaps due to the weak Lewis acidity of $InCl_3$. In the general systems reported, the alkylations involving esters and ethers give different results that are dependent on the acidity of the catalyst.[28]

2.4. Miscellaneous Reactions

Tetrahydropyrans have been prepared by the indium trichloride mediated Prins-type cyclization in high yields and with high stereoselectivity (**eq 20**).[29] Tetrahydropyrans are useful for the construction of various important carbohydrates and natural products. They have been prepared in the past by the titanium tetrachloride or aluminum trichloride catalyzed reactions of alkoxyallylsilanes with aldehydes, or by the related cross-coupling between homoallyl alcohols and aldehydes.[30]

Sigma-Aldrich Laboratory Equipment

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2000

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Short-Path Distillation Apparatus

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Büchi
Distillation Ovens

KNF Vacuum
Pumps

IKA
Stirrers/Mixers

Eppendorf
Thermomixers

Electronic
Incubators/
Ice Cubes

Easy-Read
Thermometers

IR Thermometer

PLUS:
FREE OFFER
INSIDE

ALDRICH®

Aldrich Kugelrohr
Short-Path Distillation Apparatus

- Distills heat-sensitive compounds
- Distills liquids and low-melting solids from polymers and tars
- Distills with minimal holdup and sample loss
- Removes color and particulates
- Can be used for sublimation/solvent evaporation

Kugelrohr apparatus shown with KNF Laboport vacuum pump (see page 4).

"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 Teflon 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.

Büchi
Distillation Ovens

Model B580 GKR

The small size flasks in this ball-tube oven make it an ideal system for high temperature distillation of small quantities of liquid, for separating solvents from non-volative, oily components in a mixture, or for evaporating quantities of sample that are too small for rotary evaporators. Includes 3 x 20mL ball-tube assembly, ball-tube drive unit, and 60mL rotation drying flask.

Volts	Cat. No.
115	**Z41,222-8**
230	**Z31,916-3**

Accessory ball tubes with vapor ducts

No. Balls x Volume (mL)	Cat. No.
2 x 40	**Z31,920-1**
3 x 20	**Z31,922-8**
4 x 10	**Z31,923-6**

- Variable rotation speed: 0 to 50rpm
- Cooling device cold trap can be cooled down to –80°C
- Ball-tubes with 2, 3, or 4 balls are available
- External ball-tube drive unit for constant rotation
- Linear drying tube holds up to 60mL of solids
- CE compliant

KNF
LABOPORT

Solid Teflon Deep-Vacuum Pumps

Vacuum pump shown with optional baseplate and KNF Precision vacuum controller

"Provides the Deepest Vacuum Available in a Dry Diaphragm Pump"

- ☐ 1.5 torr performance
- ☐ Excellent for use with all solvents
- ☐ Solid Teflon pump heads with Kalrez valves
- ☐ Dry operation, uses no oil and is maintenance-free
- ☐ CE compliant

Specifications:

- Pumping speed: 34L/min
- Max. vacuum: 1.5 torr (29.88in. Hg)
- Max. pressure: 15psig
- Head/valves: Teflon/Kalrez
- Compact cast-alloy case with carrying handle
- Totally-enclosed, fan-cooled, ball-bearing motor
- Hose connections: 3/8in. i.d. barbs
- Dim.: 33 L x 17 W x 22in. H
- Wt: 27lb (12.2kg)

Volts	Cat. No.
115	**Z28,820-9**
230	**Z28,821-7**

Baseplate for units	
	Z28,833-0

See the Equipment Section in the 2000-2001 Aldrich Handbook for more KNF vacuum pumps and accessories.

IKAMAG
Stirring Hot Plates

Low profile, enclosed construction with a connection for the IKATRON electronic thermometer listed separately, below. 90 H x 160 W x 280mm D. Wt = 2.4kg. CE compliant.

- 20L stirring cap.
- Speed range: 0 to 1,100rpm
- Temp. range: ambient to 300°C/572°F
- AlSi plate; diam: 135mm
- Safety circuit fixed at 370°C/698°F

Volts	Cat. No.
115	**Z40,351-2**
230	**Z40,352-0**

Model RCT

Model RCT stirring hot plate shown with optional vertical support rod, boss head clamp, and IKATRON electronic thermometer

IKATRON Electronic Thermometer

Fuzzy logic and 2-point control for optimal control of hot plate temperature. Connects to above hot plates or any unit with a DIN 12878 socket. Includes a 250 L x 3mm diam., PT 1000, SS temperature probe. Dim.: 96 H x 50 W x 35mm D. Wt = 0.2kg.

Z40,353-9

- Digital display
- Measuring range: -10 to 400°C with adjustable safety circuit between 100 and 400°C
- Control precision: ± 0.2°C
- No temperature overshoot

Accessories for Stirring Hot Plates and Electronic Thermometer

Probe extension cable, 2.5m, for the remote connection of IKATRON electronic thermometer to sensor probe.
Z40,355-5

Vertical support rod, SS, threads into top of stirrer base
Z40,356-3

Boss head clamp
Z40,357-1

Adjustable stand support rod, R380
Attaches to side groove of stirring hot plate allowing adjustment to any desired setting along stirrer. Several support rods can be attached to stirrer simultaneously.
Z40,360-1

IKA
Dual-Speed Mixers

Two speed ranges for stirring applications up to 20L (in terms of H_2O) of material. 292 H x 88 W x 188mm D. Wt = 2.9kg. Order stirring shafts separately; see listings in the Aldrich Handbook. CE compliant.

- Two speed ranges:
  - 60 to 500rpm
  - 240 to 2,000rpm
- Viscosity max.: 10,000cps
- Max. torque: 185Ncm
- Adjustable chuck; range: 0.5 to 10mm

	Analog	*w/Digital speed display*
Volts	**Cat. No.**	**Cat. No.**
115	**Z40,395-4**	**Z40,397-0**
230	**Z40,396-2**	**Z40,398-9**

Eppendorf Thermomixers

This new thermomixer combines heating and shaking of 24 x 1.5mL samples at a time to ease user workload. Incubation and mixing may also be performed independently. Autoclavable and freezer-safe rack with 24 numbered positions make processing and transporting samples quick and easy. Short-mix function for quick "vortex" applications.

- Mixing speed: 300 to 1,400rpm
- Mixing stroke: 3mm
- Temp. control range: - 4°C above ambient up to 99°C in 1°C increments
- Temp. accuracy: ± 1°C at 0 to 45°C; ± 2°C above 45°C
- Dim.: 6.5 W x 9.5 D x 5.3in. H
- CE compliant

Volts	Cat. No.
115	**T 1317**
220	**T 1442**

Echotherm Chilling Incubators

Ideal for benchtop use in any laboratory. The unit is designed for standard incubations, culture growth, enzyme reactions, and more. Chill or heat samples with the precise control of 0.1°C selectability. Includes two electropolished steel racks, power cord, and manual. Chamber dim.: 9½ x 9½ x 14in. Overall dim.: 15½ x 16½ x 22½ in. Weight: 45lb.

- Temp. range: 4 to 70°C
- No CFCs; Peltier based cooling
- Digital controls
- Timer with alarm and Auto-off
- UL, CSA, and CE certified

Volts	Cat. No.
115	**Z40,096-3**
230	**Z40,097-1**

Electronic Ice Cubes

Chill samples as low as -10°C on the bench or in the field. Plate surface will go to 0°C in two minutes. Plate dim.: 2⅞ x 4⅜ in. Overall dim.: 3½ x 6½ x 4¾ in. Weight: 6lb.

- Freeze 96-well plates and centrifuge tubes
- No CFCs; Peltier based cooling
- UL, CSA, and CE certified

Volts	Cat. No.
115	**Z40,099-8**
230	**Z40,100-5**

Accessories for Electronic Ice Cubes

Cover for 96-well plates	**Z40,106-4**
Cover for blocks	**Z40,105-6**
Al block for 0.2mL centrifuge tubes	**Z40,101-3**
Al block for 0.5mL centrifuge tubes	**Z40,102-1**
Al block for 1.5mL centrifuge tubes	**Z40,104-8**

Easy-Read Thermometers

Easy-to-read thermometers with black printing on a bright yellow background. Filled with contrasting black, non-hazardous, Enviro-Safe liquid. Calibrated with NIST, DKD standards.

		Immersion level	
	L	*76mm*	*Total*
Range	**(mm)**	**Cat. No.**	**Cat. No.**
-20 to 110°C	200	**Z42,335-1***	**Z42,337-8**
-20 to 150°C	200	**Z42,338-6***	**Z42,339-4**
-20 to 110°C	300	**Z42,341-6**	**Z42,340-8**
-20 to 150°C	300	**Z42,343-2**	**Z42,342-4**
-10 to 225°C	350	–	**Z42,350-5**
-10 to 260°C	350	**Z42,351-3**	–
0 to 230°F	300	**Z42,345-9**	**Z42,344-0**
0 to 300°F	300	**Z42,347-5**	**Z42,346-7**
20 to 435°F	350	–	**Z42,348-3**
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*50mm immersion level

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0 to 220°F	2°F	**Z42,354-8**	**Z42,352-1**

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Z42,281-9

Specifications:

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Accuracy:	±2% of reading or 4°F / 2°C (whichever is greater)
Resolution:	1°C or 1°F
Field of view:	6:1 (at 6in. distance measures 1in. target)
Dim.:	6.7 L x 1.7 W x 1.6in. D (170 x 44 x 40mm)

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Classic	13.5/34	64-80	18-26	5	**Z42,262-2**	**Z34,140-1**
Majestic	17/43	64-76	18-24	7	**Z42,261-4**	**Z34,142-8**
Grande	24/61	62-82	18-27	11	**Z42,260-6**	**Z34,143-6**

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Indium trichloride is also very efficient in effecting the rearrangement of epoxides to the corresponding carbonyl compounds highly regioselectively (**eq 21**).[31]

Mukaiyama et al.[32] have reported that TMSCl and indium trichloride catalyze the reaction of *O*-trimethylsilyl monothioacetals with triethylsilane and silylated carbon nucleophiles to afford the corresponding sulfide derivatives (**eq 22**). These sulfides are of interest because they are not only used as protecting groups, but also as electrophiles in various coupling reactions, especially carbon–carbon bond forming reactions.

Indium trichloride is used as a catalyst for the polymerization of biphenylylchlorophthalide,[33] with *tert*-butylhydroperoxide for vinyl monomers,[34] methyl methacrylates,[35] chlorophthalides[36] and *tert*-butylacetylene.[37] Zhun et al.[38] have reported that treatment of $Me_nPhSiCl_{3-n}$ (n = 0–2) with chlorine in the presence of indium trichloride affords (chlorophenyl)silanes. Indium trichloride also catalyzes the dehydrochlorination of dichloroethane,[39] is used as a promoter for the hydrochlorination of low-molecular-weight polyisobutylenes[40] and the allylation of carbonyl compounds.[41]

Bisindolylmethanes have been prepared in excellent yields by the electrophilic substitution reaction of indole with aldehydes or Schiff bases in the presence of indium trichloride (**Scheme 2**).[42] The reaction is thought to proceed via an electrophilic substitution step of indole with the aromatic aldehydes or Schiff bases. These bisindoles are of current interest as potent CNS depressants.[43]

3. Conclusion

It is evident from the above reports that indium trichloride has emerged as a mild Lewis acid for effecting a variety of chemical transformations in a chemo-, regio-, and stereoselective fashion. Because indium trichloride is catalytically active both in aqueous and organic solvents, it is the mild Lewis acid of choice in a number of synthetic organic reactions.

4. Acknowledgements

We thank all those who have contributed to the chemistry reviewed here and whose names appear in the cited references. We also thank the Council of Scientific and Industrial Research, India, for financial support.

5. References

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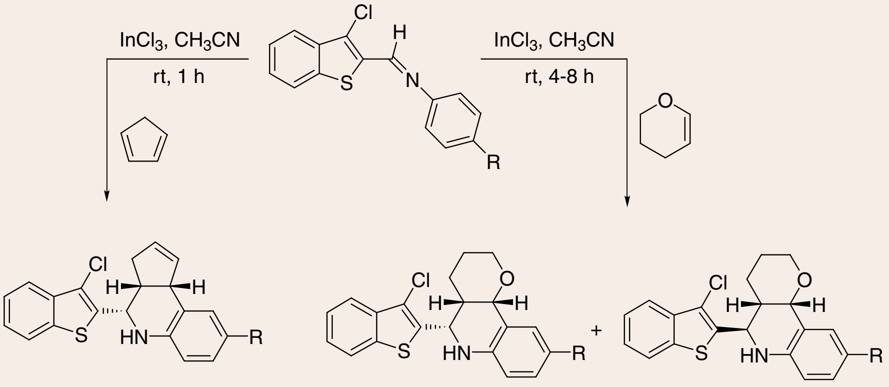
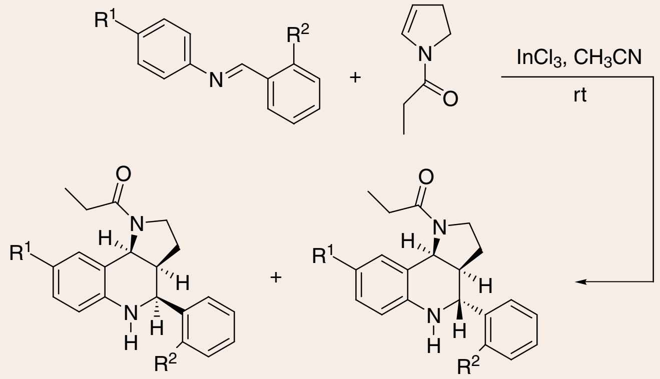


R = H, CH_3, Cl

81–92%
(only endo)

R	Yield	trans/cis
H	55%	46:54
CH_3	57%	68:32

Scheme 1

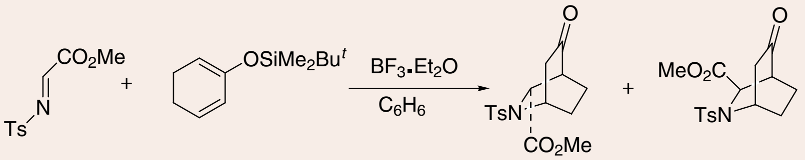


eq 8

R^1 = H, OMe, CO_2Me; R^2 = H, NO_2

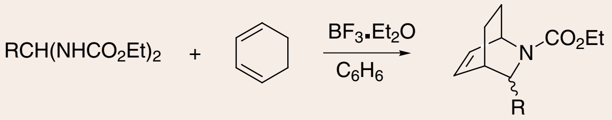
41–50%

exo/endo = 1:1 to 2:1



eq 9

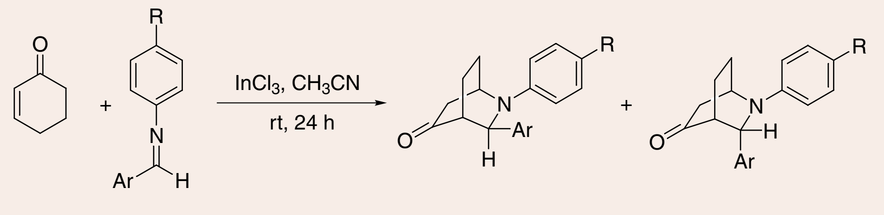
overall yield = 69%
product ratio = 4:3



eq 10

R = H, Ph, $COCH_3$

40–50%

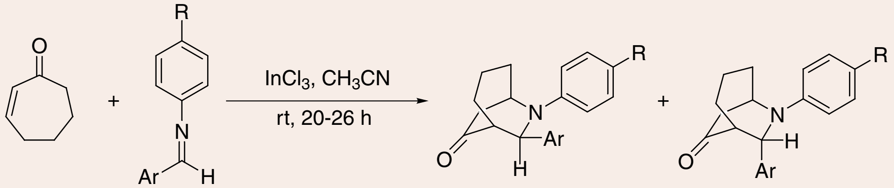


1a–e, h, i **6a–e, h, i** **7a–e, h, i**

eq 11

Table 4. Diels–Alder Reaction of Schiff Bases with 2-Cyclohexenone

Entry	Schiff Base	R	Ar	Product Ratio 6:7	Combined Yield (%)
1	**1a**	H	C_6H_5	69:31	65
2	**1b**	NO_2	C_6H_5	67:33	70
3	**1c**	OCH_3	C_6H_5	68:32	60
4	**1d**	Cl	C_6H_5	73:27	68
5	**1e**	CH_3	C_6H_5	73:27	62
6	**1h**	H	4-Cl-C_6H_4	48:52	65
7	**1i**	Cl	4-Cl-C_6H_4	47:53	74



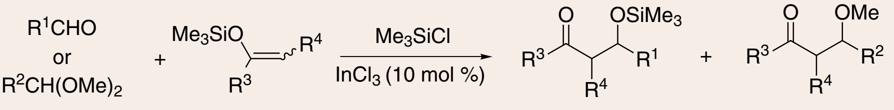
R = H, CH_3, OCH_3, Cl

Ar = C_6H_5, 4-ClC_6H_4

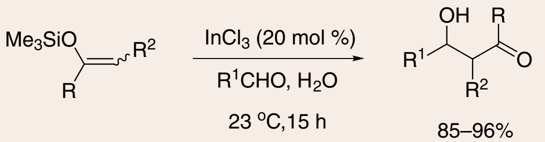
48–78%

exo/endo = 39/61 to 65/35

eq 12

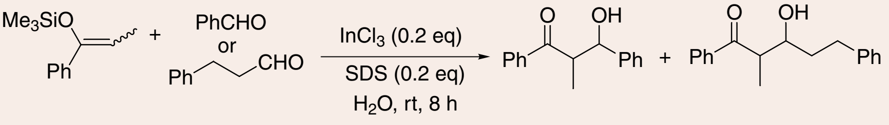


eq 13



85–96%

eq 14



SDS = Sodium dodecylsulfate

75% 54%

eq 15

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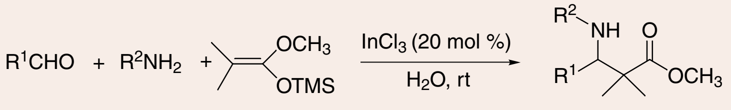
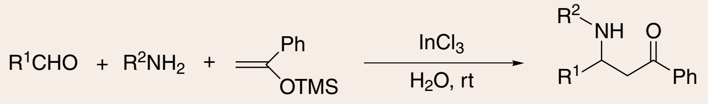


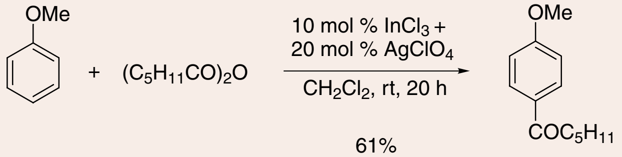
R^1 = H, Ph, 2-Py; R^2 = Ph, 4-ClC_6H_4, 4-$CH_3OC_6H_4$ 21–92%

eq 16

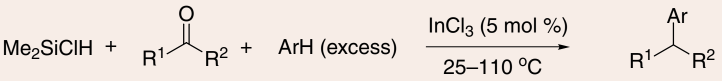


R^1 = H, Ph, 2-Py; R^2 = H, Ph, 4-ClC_6H_4, 4-$CH_3OC_6H_4$ 40–94%

eq 17



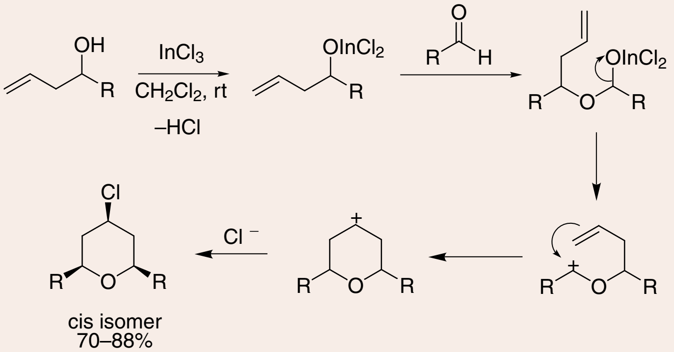
eq 18



R^1 = Ph, 4-ClC_6H_4, 4-CNC_6H_4, 4-$NO_2C_6H_4$, 1-naphthyl,
2-naphthyl, -$(CH_2)_4$-, -$(CH_2)_5$-, Me, n-C_5H_{11} 21–99%

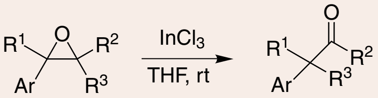
R^2 = H, Me; Ar = Ph, p-tolyl, p-xylyl

eq 19



R = Ph, 4-$CH_3C_6H_4$, 3-$CH_3C_6H_4$, 2-$CH_3C_6H_4$, 4-ClC_6H_4,
4-FC_6H_4, 4-C_2H_5-C_6H_4, n-C_7H_{15}

eq 20

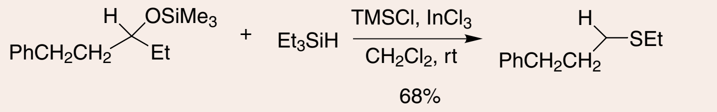


65–91%

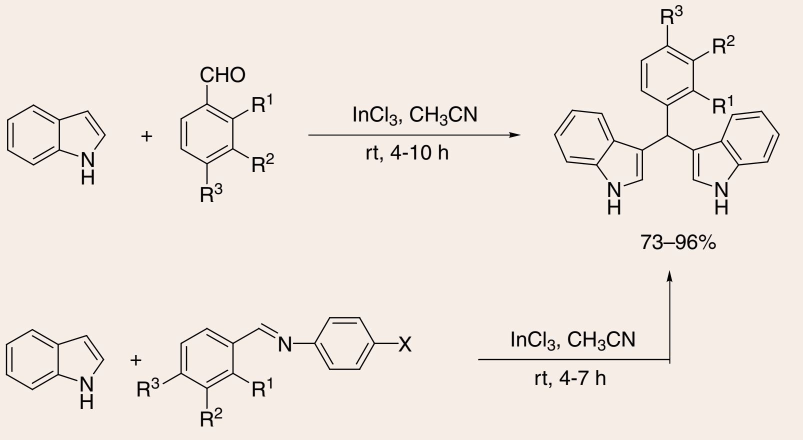
R^1, R^2, R^3 = H, alkyl, Ph

Ar = Ph, 4-$CH_3OC_6H_4$, 3,4-$(CH_3O)_2C_6H_3$, 2-naphthyl

eq 21



eq 22



R^1 = H, CH_3; R^2 = H; R^3 = H, CH_3, OCH_3, Cl

Scheme 2

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About the Authors

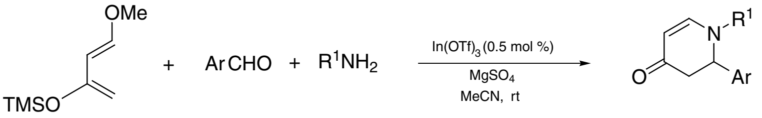
Dr. G. Babu received his M.Sc. degree in Chemistry from Loyola College, University of Madras, and, in August 1993, joined the organic chemistry laboratory of Dr. P.T. Perumal at the Central Leather Research Institute. He was awarded the Ph.D. degree in January 1999 by the University of Madras. His research work involved the synthesis of heterocyclic compounds through Diels–Alder reactions catalyzed by indium trichloride, and the microwave-accelerated synthesis of furfurylidene chalcones. Currently, he is working as a Postdoctral Fellow with Professor A. Wada, Kobe Pharmaceutical University, Japan, on the synthesis of retenoic acid analogs.

Dr. P. T. Perumal obtained his Ph.D. degree in 1981 from the Indian Institute of Science, Bangalore, under the guidance of Prof. M. V. Bhatt. He then worked as a Postdoctoral Research Associate with Prof. H. C. Brown at Purdue University until 1983. After returning to India, he worked briefly as a Scientist at the Indian Institute of Chemical Technology, Hyderabad, and later moved to the Central Leather Research Institute (CLRI), Chennai. He was a Visiting Scientist at the University of Miami in 1989–1990 and the University of Florida in 1990–1991. He has authored more than 60 publications and trained five Ph.D. students. Currently, he is working on natural biocides and the synthesis of heterocyclic compounds and peptidomimetic antimicrobial agents.

Lewis Acids in Organic Synthesis

The preceding review highlights the use of indium(III) chloride as a Lewis Acid. Other Lewis acids also facilitate organic reactions and can often be used in just catalytic amounts. The reactivity and selectivity vary, depending upon reaction conditions and the reagent chosen. Presented here are some examples of the applications in organic synthesis of the triflate (trifluoromethanesulfonate) salts of three popular Lewis acids. A selection of Aldrich products that are mentioned in the review is also included. For additional information, please call our Technical Services Department at **800-231-8327** (USA) or your local Sigma-Aldrich office. Larger quantities are available through Sigma-Aldrich Fine Chemicals. Please call **800-336-9719** (USA) or your local office for availability.

Indium

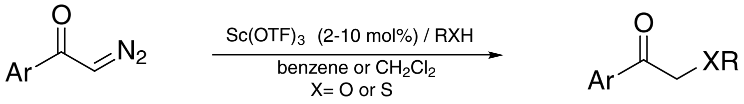


Indium triflate has several applications including catalysis of Friedel–Crafts alkylations[1] and acylations,[2] and is shown here to catalyze the hetero-Diels–Alder reaction. Frost[3] has prepared a series of aryl-substituted tetrahydropyridines, via the imines derived from aryl aldehydes, with a catalyst loading as low as 0.5 mol %.

(1) Miyai, T. et al. *Tetrahedron* **1999**, *55*, 1017. (2) Chauhan, K. K. et al. *Synlett* **1999**, 1743. (3) Ali, T. et al. *Tetrahedron Lett.* **1999**, *40*, 5621.

44,215-1 **Indium(III) trifluoromethanesulfonate** *(Indium triflate)*

Scandium

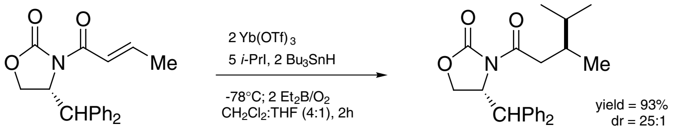


Scandium triflate catalyzes, among other reactions, the intermolecular carbene–heteroatom bond insertion in alcohols and thiols leading to the preparation of α-alkoxy, α-alkylthio, and α-phenylthio aryl ketones.

Pansare, S. V. et al. *Tetrahedron Lett.* **1999**, *40*, 5255. *For a brief review on this catalyst, see* Longbottom, D. *Synlett* **1999**, 2023.

41,821-8 **Scandium trifluoromethanesulfonate**, 99% *(Scandium triflate)*

Ytterbium



Lewis acid assisted diastereoselective free radical conjugate additions compete favorably with their ionic counterparts. In the reaction shown here, Sibi reports that ytterbium triflate gives a 25:1 diastereomeric ratio (dr) using 2 equiv of the Lewis acid and a 20:1 dr at 0.1 equiv. Also, moderate amounts of water seem to have little effect on the outcome of the reaction.

Sibi, M. P. et al. *J. Am. Chem. Soc.* **1999**, *121*, 7517.

43,059-5 **Ytterbium(III) trifluoromethanesulfonate**, 99.99% *(Ytterbium triflate)*
40,532-9 **Ytterbium(III) trifluoromethanesulfonate hydrate**

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38,442-9	*tert*-**Butyldimethylsilyl chloride**, 1.0*M* solution in dichloromethane
44,612-2	**Butyldimethylsilyl chloride**, 98%
47,346-4	*tert*-**Butyldimethylsilyl chloride**, 50 wt. % solution in toluene
14,420-7	**Chlorodimethylsilane**, 98%
38,441-0	**Chlorotrimethylsilane**, 1.0*M* solution in tetrahydrofuran
38,652-9	**Chlorotrimethylsilane**, redistilled, 99+%
C7,285-4	**Chlorotrimethylsilane**, 98%
20,344-0	**Indium(III) chloride**, 99.999%
33,406-5	**Indium(III) chloride**, 98%
33,407-3	**Indium(III) chloride tetrahydrate**, 97%
42,941-4	**Indium(III) chloride**, anhydrous, powder, 99.999+%
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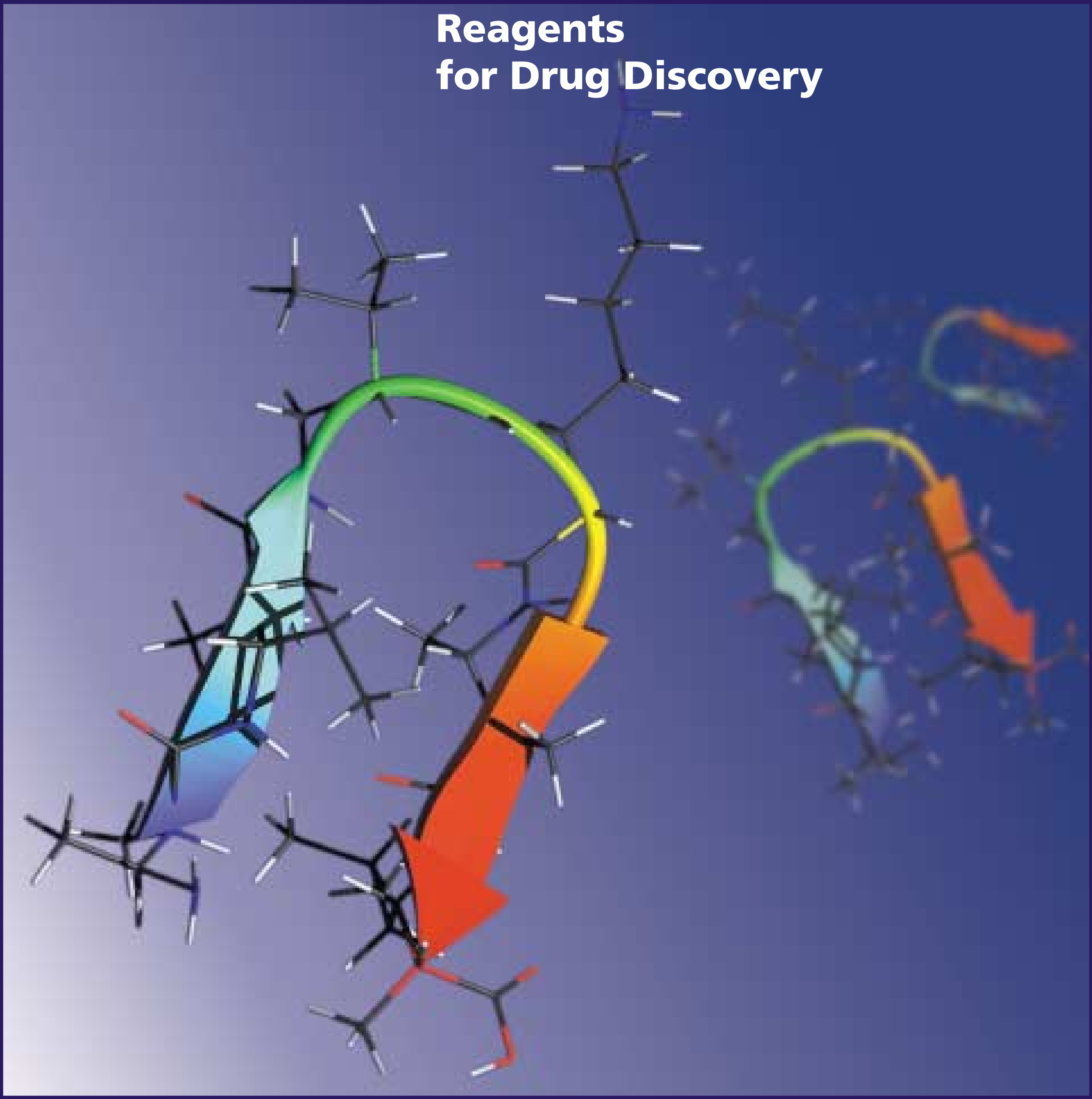

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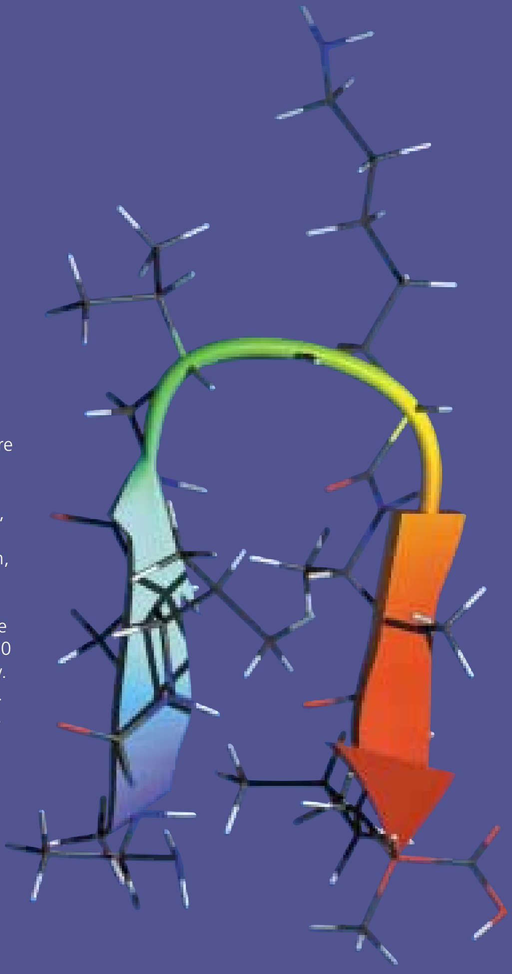

Hairpin structure of a ß-peptide determined by Dieter Seebach, Stefan Abele, Karl Gademann, Bernhard Jaun

Angew. Chemie 1999, 111, 1700 – 1703; Angew. Chemie Int. Ed. Engl. 1999, 38, 1595 – 1597

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Purpald®: A Reagent That Turns Aldehydes Purple!

Harvey B. Hopps
Physical Sciences Department
Amarillo College
Amarillo, TX 79178-0001, USA
E-mail: hbhopps@actx.edu

Introduction

What was described as a new reagent for the qualitative detection of aldehydes has resulted in a host of methods for the quantitative determination of aldehydes. The story began when Dickinson and Jacobsen reported a new, sensitive, and specific test for the detection of aldehydes using 4-amino-3-hydrazino-5-mercapto-1,2,4-triazole (**1**).[1] Because its lengthy name did not give any indication of this important application, Aldrich offered this triazole under the trade name Purpald®, in order to highlight its utility in this respect.

While both aldehydes and ketones readily condense with **1**, only the aminal, **2a**, from an aldehyde can be oxidized to give the conjugated, purple-colored, bicyclic ring system, 6-mercapto-3-substituted-*s*-triazolo-[4,3-*b*]-*s*-tetrazine (**3**).

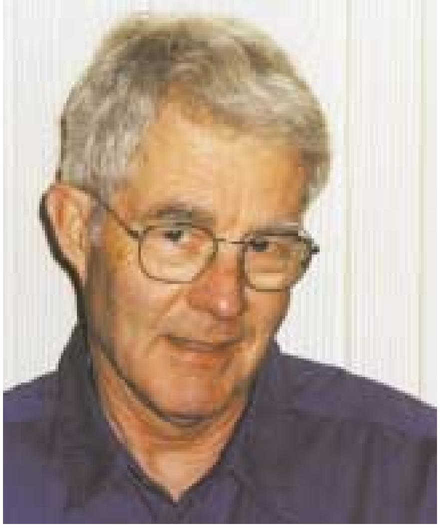
Qualitative Tests

Dickinson and Jacobsen's initial paper described a simple test that uses one drop of the aldehyde and about 150 mg of **1** in 2 mL of 1N NaOH. Aeration of the resulting solution produces an intense color within one minute. This test is both sensitive and specific for aldehydes. The reagent does not give purple condensation products with ketones, esters, amides, hydrazines, hydroxylamines, quinones, aminophenols, uric acid, or formic acid, which are known to interfere with the usual test reagents such as Fehling's solution, and Tollens' and Schiff's reagents. The test is sensitive to aldehydes at a concentration of 1 x 10^{-4} M. The authors examined the purple-colored solutions obtained from a variety of aldehydes and reported an absorption band in the visible region at 520–555 nm. Very hindered aldehydes may require longer reaction times. **Table 1** lists some representative aldehydes and reaction times necessary for color changes.[2]

Dickinson and Jacobsen mentioned in a footnote that acetic acid, known to contain 0.05% acetaldehyde, gave a positive test with **1**.[1] Recently, a student obtained a positive test with a sample of 95% 3-pentanone, which clearly indicated the presence of a low concentration of an aldehyde.[3] Therefore, care must be taken, if one is relying on the test, when dealing with samples of unknown purity. Other misleading results can be obtained when certain substances are oxidized to aldehydes under the test conditions. Durst and Gokel[4] reported that the use of ethylene glycol, known to be readily oxidized, as the solvent might give spurious results. They described the use of a phase-transfer catalyst to improve the test for lipophilic aldehydes, which have low solubilities in aqueous media. The oxidation of aminal **2** to **3** was also carried out using hydrogen peroxide[5] or periodate ion.[6,7] Rahn and Schlenk[8] observed a positive test from ozonides. Purpald® has been used to prepare filter paper test strips,[9] in TLC spray reagents,[8] and as a reagent for the post-column derivatization in high-pressure liquid chromatography.[5,10] The sensitivity limit of this reagent (a distinct purple solution is produced) is under 1 mg of Purpald® in 0.6 mL of dilute NaOH with 37% fomaldehyde solution.[3] At this level, the cost of Purpald® is less than that of the silver nitrate used in the Tollens' aldehyde test.

Quantitative Tests

Following their initial report, Jacobsen and Dickinson described the use of **1** in spectrophotometric quantitative assays of aldehydes.[11] They found that Beer's law was followed for 0.5–5 ppm formaldehyde within the limit of ± 3%. Also, the same ± 3% limit pertained to 5–20 ppm formaldehyde after suitable dilution. The colored product, **3**, from a group of aldehydes displayed a λ_{max} absorption between 532 and 549 nm. Nakano has described the detrimental effects of copper (II) and cobalt ions in the course of formaldehyde determinations.[12] The addition of EDTA markedly inhibited the interference of Cu(II) ion.



Applications

The spectrophotometric quantitative assays have led to a wide range of applications for Purpald®, including the detection of aldehydes in gases, liquids, and on solid surfaces. The detection of formaldehyde vapor has been extensively studied.[13-18] Quesenberry and Lee[6] described a rapid formaldehyde assay using Purpald® under periodation conditions, and attained the sensitivity level of as little as 1 nmol formaldehyde. Lambert et al.[16] described a solid reagent of Purpald®–acetone aminal on sodium bicarbonate, which responded to formaldehyde in the sub-ppm concentration range. Spreitzer and Jaeger[19] have reported a method for the determination of ppb amounts of formaldehyde in aqueous solution with Purpald®. Fujiwara et al.[20] reviewed the microscale determination of formaldehyde in vaccines with **1**. Mimura et al.[7] have compared the Purpald® method with the acetylacetone method for the detection of formaldehyde. The presence of formaldehyde on the surface of natural wood[21] and boards bonded with urea–formaldehyde resin[22] has been detected using Purpald®.

Other aldehydes that have been detected by using **1** include: aldehydes in disinfectant

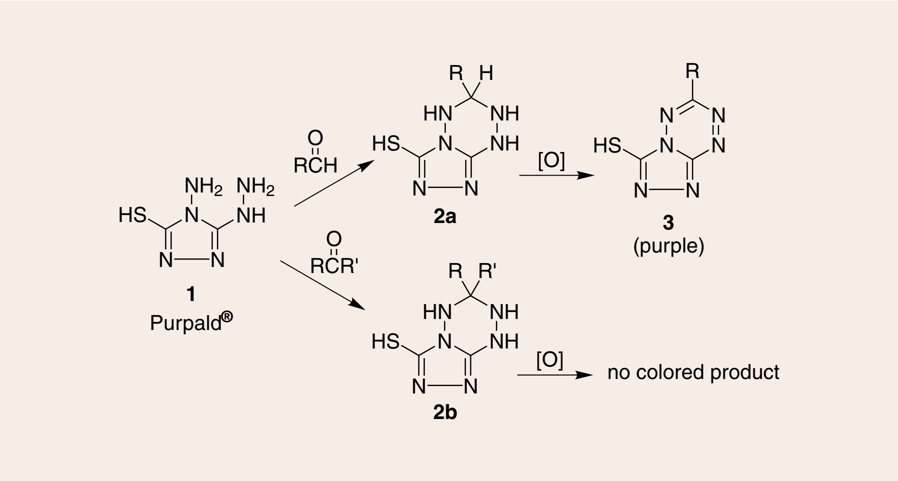


Table 1. Reactions of Representative Aldehydes with 1[2]

Aldehyde	Color	Time
5-Hydroxypentanal	purple	<30 sec
Crotonaldehyde	purple	—
trans-Cinnamaldehyde	purple	<5 min
α-Methylcinnamaldehyde	purple	<10 min
β-Phenylcinnamaldehyde	purple	—
Benzaldehyde	purple	<1 min
2-Nitrobenzaldehyde	purple-brown	<30 sec
4-Acetamidobenzaldehyde	purple-brown	<5 min
2-Chloro-6-nitrobenzaldehyde	purple	<5 min
10-Methylanthracene-9-carboxaldehyde	purple	very slow

solutions,[23] acetaldehyde on the surface of fruit,[24] semialdehydes,[25] invert sugars,[26,27] and lipid aldehydes.[8] A number of reports have also described analytical procedures, which utilize the formation of an aldehyde and its subsequent quantitative spectrophotometric measurement using Purpald®. For example, Sugano and co-workers[28] analyzed hydrogen peroxide in serum by adding methanol and the enzyme necessary to catalyze the peroxide oxidation of methanol to formaldehyde. Formaldehyde concentrations were then determined with Purpald®. Additional examples of substances analyzed in this way include: methanol,[29,30] sugars and glycols,[31] serum triglycerides,[32] diprophylline which contains a glycol moiety,[33] glafenine,[34] clindamycin,[35] uric acid,[36] and methylenebisthiocyanate.[37] Multistep processes, which ultimately produce an aldehyde, include the assay of acyl-CoA synthetase,[38] catalase activity in tissue,[39] and D-amino acid oxidase.[40]

Conclusion

This interesting reagent came to light shortly after it was mentioned for the qualitative detection of aldehydes in "Brownstein's Closet" section of *CHEMTECH*.[41] Naturally, it was prepared and offered by Aldrich. The anticipated use as a quantitative reagent has not been forthcoming; however, it has been widely employed as a quantitative spectrophotometric reagent. Recently, Brandl[42] has suggested that Purpald® will replace the Tollens' test for aldehydes in the student laboratory. Purpald® is both sensitive and specific for aldehydes. The test is fast and easy to perform, and avoids the potentially explosive silver salts associated with the Tollens' test. The toxicity of Purpald® has not been determined.

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Purpald is a registered trademark of Sigma-Aldrich Co.

About the Author

Harvey B. Hopps received a B.A. degree from Occidental College in 1956, an M.S. degree from the University of Arizona in 1958, and a Ph.D. degree from Purdue University in 1962. After spending one year as postdoctoral scientist at New York University with Professor Kurt Mislow, he joined Aldrich as a group leader in research. He became Technical Services Manager in 1969, and Aldrich–Boranes Manager in 1972. He moved to Fumico, Inc. in 1981, and served as Head of Chemistry until he joined Amarillo College in 1996 as Instructor in the Physical Sciences Department, where he teaches organic and general chemistry. His interests include the local helium industry, fishing, and teaching fly-tying.

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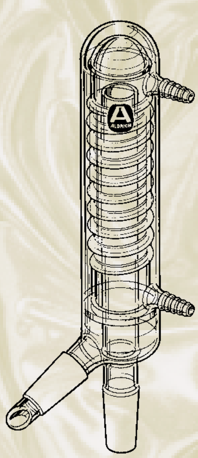

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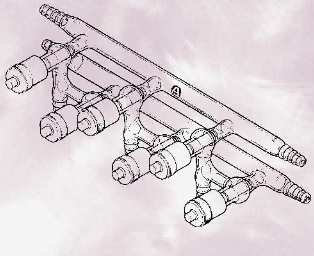

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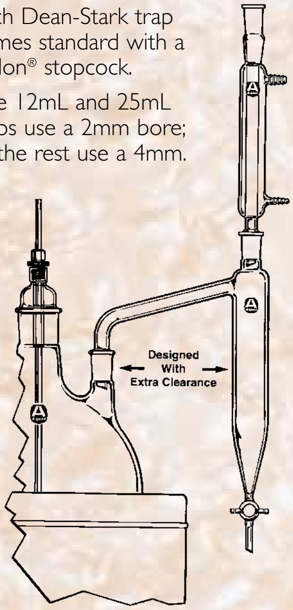

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25	280	80	50mL – 5L	24/40	**Z42,302-5**
100	350	100	5L – 12L	24/40	**Z42,303-3**
300	440	170	22L – 50L	24/40	**Z42,304-1**
500	455	170	22L – 50L	24/40	**Z42,306-8**

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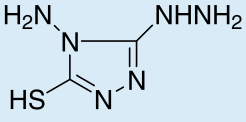
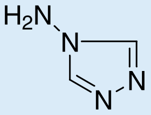
AMINOTRIAZOLES

Purpald®, an aminotriazole, was discussed in the previous article as a valuable agent for the colorimetric analysis of aldehydes. This product and other aminotriazoles also find utility in organic synthesis, especially for pharmaceuticals. See below for a few examples, and don't hesitate to call our Technical Services Department at **800-231-8327** (USA) or your local Sigma-Aldrich office for more information or to suggest new products. Larger quantities are available through Sigma-Aldrich Fine Chemicals. Please call **800-336-9719** (USA) or your local office for availability.



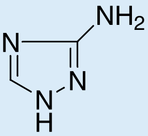
Purpald® continues to be useful as a complexation reagent for the spectrophotometric determination of aldehydes, e.g., in drug concentration analyses and in determining airborne formaldehyde. It was also used to prepare a series of antimicrobials.[1]

16,289-2 **Purpald®**, 99+% *(4-Amino-3-hydrazino-5-mercapto-1,2,4-triazole)*



This 4-aminotriazole was used in a study of anti-inflammatory COX-2 inhibitors[2] and in the preparation of fluconazole,[3] an antifungal.

A8,180-3 **4-Amino-1,2,4-triazole**, 99%



Several patents describe the use of 3-aminotriazole in the preparation of fungicides and herbicides. It was also used in the structure-activity analysis of angiotensin II receptor antagonists.[4]

A8,160-9 **3-Amino-1,2,4-triazole,** 95%

OTHER AMINOTRIAZOLE LISTINGS:

14,026-0	**3-Amino-5-mercapto-1,2,4-triazole**, 95%
19,068-3	**3-Amino-5-methylthio-1*H*-1,2,4-triazole**, 98%
28,207-3	**3-Amino-1,2,4-triazole-5-carboxylic acid hydrate**, 98%
34,152-5	**4-Amino-3,5-di-2-pyridyl-4*H*-1,2,4-triazole**, 97%
43,854-5	**4-Amino-5-(4-pyridyl)-4*H*-1,2,4-triazole-3-thiol**, 97%
43,855-3	**4-Amino-5-phenyl-4*H*-1,2,4-triazole-3-thiol**, 97%
D2,620-2	**3,5-Diamino-1,2,4-triazole**, 98%

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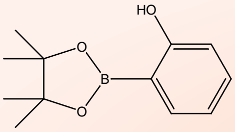
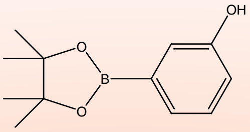
ARYLBORONIC ACID-PINACOL ESTERS

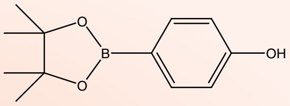
The synthesis of biaryl compounds via the Suzuki coupling reaction has become more commonplace now that many arylboronic acids are readily available. Several years ago, Miyaura demonstrated the utility of cyclic pinacol esters of arylboronic acids in Suzuki coupling reactions.[1,2] Aldrich offers the following arylboronic acid-pinacol esters[3] as part of a growing line of products used in the Suzuki coupling reaction and other synthetic and combinatorial methodologies. For a complete listing of Aldrich products, please request your **FREE** copy of the *2000–2001 Aldrich Handbook of Fine Chemicals and Laboratory Equipment* at **800-231-8327** (USA) or your local Sigma-Aldrich office, or visit us on the Web at **www.sigma-aldrich.com**.



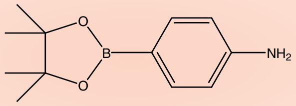
52,255-4



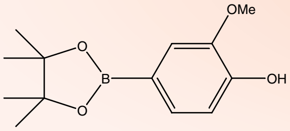
52,256-2



52,257-0



51,875-1



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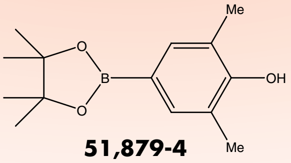
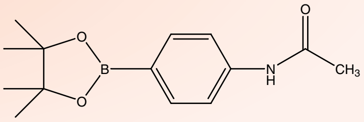


51,879-4



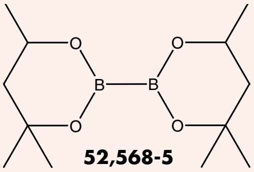
51,877-8

52,255-4	**2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenol** *(2-Hydroxyphenylboronic acid, pinacol cyclic ester)*
52,256-2	**3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenol** *(3-Hydroxyphenylboronic acid, pinacol cyclic ester)*
52,257-0	**4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenol**, 97% *(4-Hydroxyphenylboronic acid, pinacol cyclic ester)*
51,875-1	**4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)aniline**, 97% *4-Aminophenylboronic acid, pinacol cyclic ester)*
51,878-6	**2-Methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol**, 98% *(4-Hydroxy-3-methoxyphenylboronic acid, pinacol cyclic ester)*
51,879-4	**2,6-Dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol**, 97% *(4-Hydroxy-3,5-dimethylphenylboronic acid, pinacol cyclic ester)*
51,877-8	**4′-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)acetanilide**, 97% . . . . *(4-Acetamidophenylboronic acid, pinacol cyclic ester)*

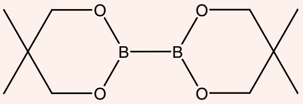
DIBORON ESTERS

NEW!

Aldrich is pleased to offer two new diboron esters to help develop the chemistry surrounding the Suzuki coupling reaction.[3] These new diboron esters exhibit different solubility and reactivity characteristics than the analogous bis(pinacolato)diboron and bis(catecholato)diboron, also available from Aldrich.



52,568-5



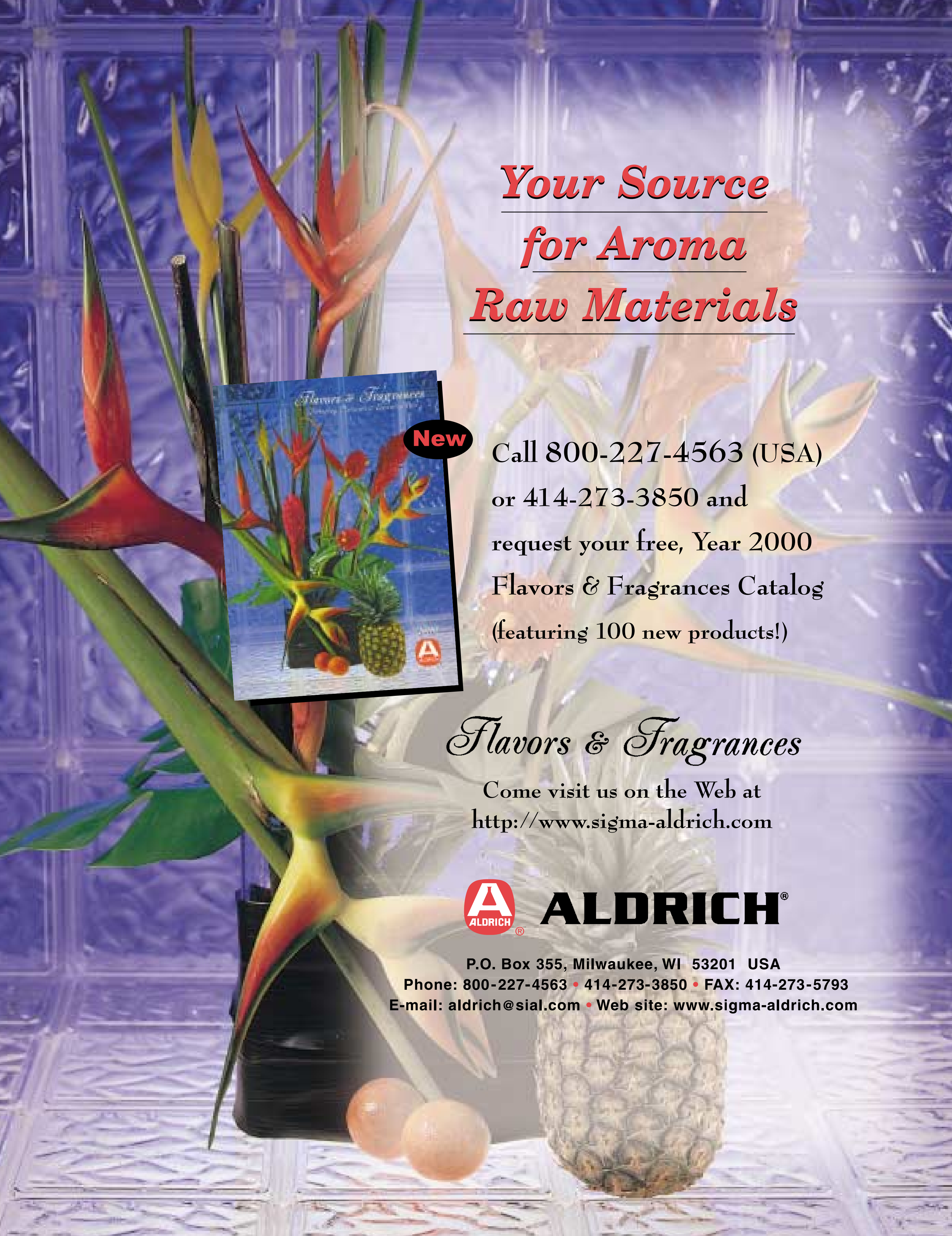
51,880-8

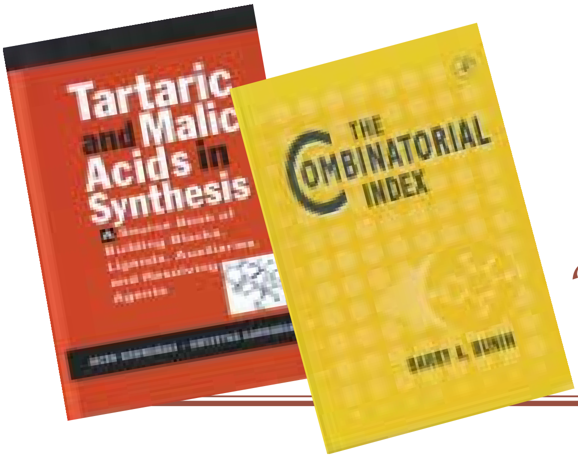
52,568-5	**Bis(hexylene glycolato)diboron**, 96%
51,880-8	**Bis(neopentyl glycolato)diboron**, 97%

Also Available:

47,328-6	**Bis(catecholato)diboron**, 97%
47,329-4	**Bis(pinacolato)diboron**, 98%

References: (1) Ishiyama, T. et al. *Tetrahedron Lett.* **1997**, *38*, 3447. (2) Ishiyama, T. et al. *J. Org. Chem.* **1995**, *60*, 7508. (3) Patents pending, including WO/98/45265.





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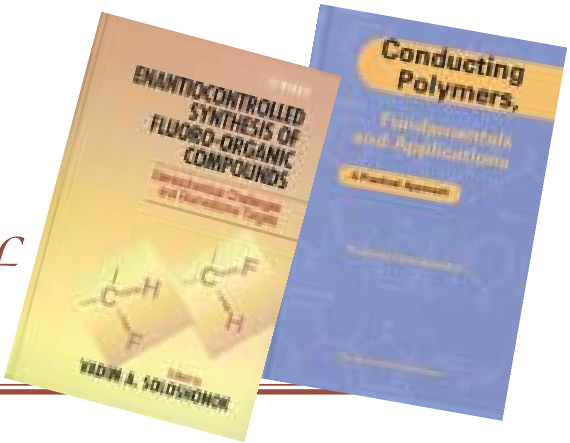


Tartaric and Malic Acids in Synthesis: A Source Book of Building Blocks, Ligands, Auxiliaries, and Resolving Agents

J. Gawronski and K. Gawronska, John Wiley & Sons, New York, NY, 1999, 591pp. Hardcover. Provides chemists with a concise, yet comprehensive, review of the chemical properties and synthetic applications of derivatives of tartaric and malic acids. Includes hundreds of reaction schemes and figures, more than 70 tables of data and references for 2,000 compounds, and over 2,500 references to primary, secondary, and patent literature sources.

Z42,244-4

Enantiocontrolled Synthesis of Fluoro-Organic Compounds: Stereochemical Challenges and Biomedical Targets

V. A. Soloshonok, Ed., John Wiley & Sons, Chichester, England, 1999, 690pp. Hardcover. Selective insertion of fluorine substituents in strategic positions of bioactive molecules is a powerful and versatile tool for the design of new drugs, diagnostic agents, agrochemicals, and biomedical probes. This is the first book to give a comprehensive overview of the preparative methods for enantiocontrolled synthesis of fluorine-containing compounds of biomedical importance.

Z42,243-6

Conducting Polymers, Fundamentals and Applications: A Practical Approach

P. Chandrasekhar, Kluwer Academic Publishers, Boston, MA, 1999, 760pp. Hardcover. Deals with the practical fundamentals and applications of conducting polymers. This book may be used as a basis for further work, as a reference, or as a text supplementing advanced undergraduate- or graduate-level courses.

Z42,253-3

Sax's Dangerous Properties of Industrial Materials

10th ed., R. J. Lewis, Sr., John Wiley & Sons, New York, NY, 1999, 4,000pp. Hardcover. Three-volume set outlines the hazards of more than 23,500 industrial and laboratory chemicals. Individual listings include DPIM number, physical properties, synonyms, CAS No., toxicity data, DOT hazard code, hazard rating, OSHA, ACGIH, and MAK exposure limits, as well as NIOSH REL limits, DOT classification, and safety profiles, including both carcinogenic and reproductive effects data.

3-volume set
Z42,239-8

Concise Polymeric Materials Encyclopedia

J. C. Salamone, CRC Press, Boca Raton, FL, 1998, 1760pp. Hardcover. Contains more than 1,100 articles providing a synopsis of the topics described. Featuring contributions from more than 1,800 scientists from all over the world, the book discusses a vast array of subjects related to the synthesis, properties, and applications of polymeric materials, development of modern catalysts in preparing new or modified polymers, modification of existing polymers by chemical and physical processes, and biologically oriented polymers.

Z42,237-1

The Combinatorial Index

B. A. Bunin, Academic Press, New York, NY, 1998, 322pp. Hardcover. This compendium of methods from the primary literature provides quick and convenient access to reliable synthetic transformations as well as information on linkers and analytical methods. Each synthetic procedure is preceded by a section entitled "Points of Interest", which highlights the strengths and weaknesses of the various studies. The index covers the use of solution-based synthesis for the generation of molecular diversity, and includes a structural appendix showing functional group transformations.

Z42,250-9

Lewis Acid Reagents: A Practical Approach

H. Yamamoto, Ed., Oxford University Press, New York, NY, 1999, 288pp. Hardcover. A laboratory manual providing step-by-step protocols for using Lewis acid reagents to catalyze organic synthesis processes. Discusses a variety of new selective organic syntheses that are now available using modified/designed reagents.

Z42,248-7

Combinatorial Chemistry

N.K. Terrett, Oxford University Press, New York, NY, 1998, 200pp. Softbound. Provides a concise and comprehensive overview of combinatorial techniques for academic and industrial researchers and students. Includes extensive reference sections for further reading.

Z41,256-2

Asymmetric Fluoroorganic Chemistry: Synthesis, Applications, and Future Directions

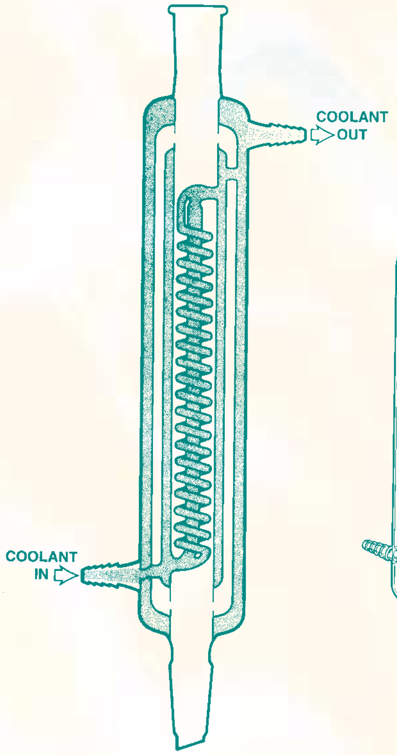
P. V. Ramachandran, Oxford University Press, New York, NY, 1999, 320pp. Hardcover. This book collects current work on the synthesis of fluoroorganic compounds beginning with a review of fluorine-containing chiral compounds of biomedical interest. Subsequent chapters address reagent- and substrate-controlled asymmetric synthesis, the synthesis of fluorine-containing target molecules, bio-organic synthesis, and asymmetric fluoroorganic compounds in materials chemistry and agrochemistry.

Z42,249-5

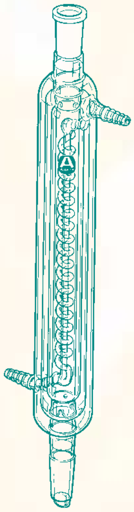
Reagent Chemicals

9th ed., American Chemical Society, Washington, DC, 1999, 768pp. Hardcover. Provides test procedures and other valuable information required to ensure that chemicals meet the latest ACS reagent specifications.

Z42,183-9



Cross-section of
cooling surface area



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Large	610	90	**Z42,232-0**
Cold Traps			
500mL bulb	460	50	**Z10,690-9**
1000mL bulb	475	50	**Z28,452-1**
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Potassium hydroxide, pellets, 85+% A.C.S. reagent			**22,147-3**

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Cold traps

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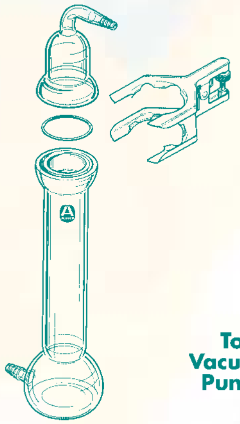

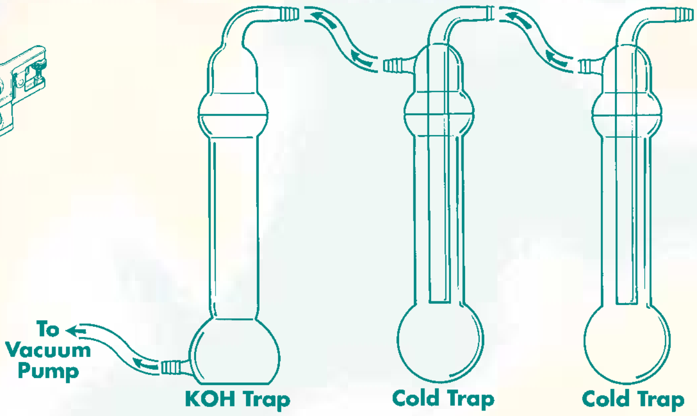

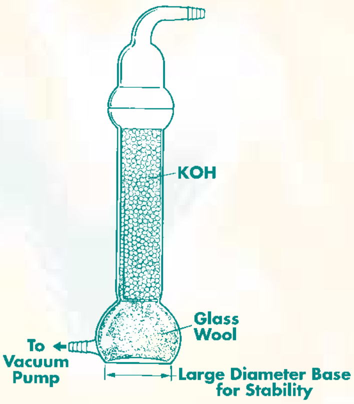

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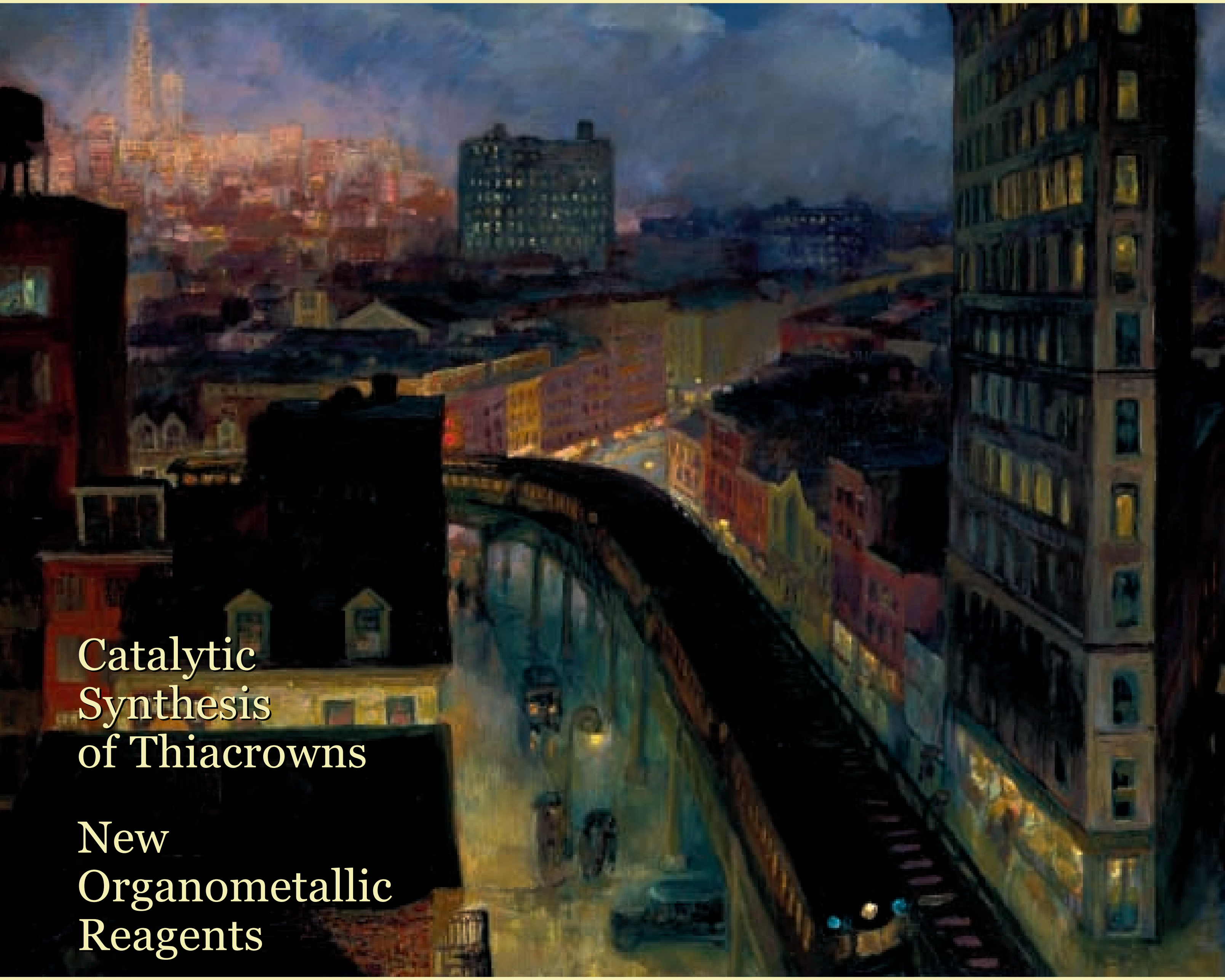
AN EXCLUSIVE REVIEW BY DR. REUBEN D. RIEKE

Aldrichimica ACTA

VOL. 33, NO. 2 • 2000



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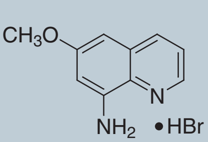
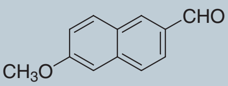


Quinoline building block.[1] Used as an amino component in a novel series of bladder-selective diaminocyclobutenedione potassium channel openers.[2]

(1) Armer, R.E. et al. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2430. (2) Butera. J.A. *J. Med. Chem.* **2000**, *43*, 1187.

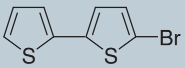
52,809-9 8-Amino-6-methoxyquinoline hydrobromide, 97%



Employed in the synthesis of biologically active naphthalenes.[1] The aldehyde moiety has been elaborated into an oxetane in a photocyclization[2] and to a butanone in the preparation of the NSAID nabumetone.[3]

(1) Bosca, F. et al. *Photochem. Photobiol.* **2000**, *71*, 173. (2) Abe, M. et al. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3261. (3) Prabhakar, C. et al. *Org. Process Res. Dev.* **1999**, *3*, 121.

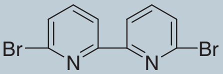
53,308-4 6-Methoxy-2-naphthaldehyde, 98%



Used recently in the synthesis of oligothiophenes [1,2] and oligothienylferrocene complexes.[3]

(1) Jiang, B. et al. *J. Am. Chem. Soc.* **1999**, *121*, 9744. (2) Ibrahim, M. A. et al. *Synth. Met.* **1999**, *105*, 35. (3) Zhu, Y.; Wolf, M. O. *Chem. Mater.* **1999**, *11*, 2995.

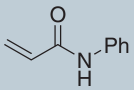
52,285-6 5-Bromo-2,2′-bithiophene, 96%



Direct copper catalyzed substitution of the bromines with nitrogen led to chiral bipyridine ligands based on camphor sultam or a prolinol ether.[1] The bis(3-pyrazolyl) derivative was studied as a tetradentate chelating ligand.[2]

(1) Kandzia, C. et al. *Tetrahedron: Asymmetry* **1993**, *4*, 39. (2) Couchman, S. M. et al. *Polyhedron* **1999**, *18*, 2633.

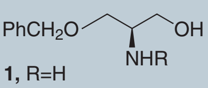
51,388-1 6,6'-Dibromo-2,2'-dipyridyl, 90%



The BPO initiated graft polymerizations of this N-substituted acrylamide and *N*-isopropylacrylamide (41,532-4) onto ethylene-propylene-diene terpolymer were conducted. Thermal and mechanical properties were studied along with changes in morphology upon irradiation.

Park, K-G et al. *J. Appl. Polym. Sci.* **1999**, *74*, 3259.

53,004-2 *N*-Phenylacrylamide, 99%



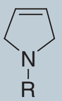
1, R=H
2, R=BOC

Used for preparing the enantiopode of Garner's aldehyde,[1] peptide nucleic acid (PNA) analogs,[2] and chiral gadolinium complexes that are employed as MRI contrasting agents.[3]

(1) Avenoza, A. et al. *Synthesis* **1997**, 1146. (2) Ramasamy, K. S.; Seifert, W. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1799. (3) Sajiki, H. et al. *Synth. Commun.* **1996**, *26*, 2511.

47,375-8 (*R*)-(+)-2-Amino-3-benzyloxy-1-propanol, 97% (99% ee/GLC) **(1)**

47,376-6 (*R*)-(+)-3-Benzyloxy-2-(*tert*-butoxycarbonylamino)-1-propanol, 98% **(2)**



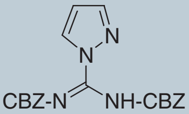
1, R=CBZ
2, R=BOC

Used to prepare fluoro-substituted pyrrolidinyl-2-pyridinones as antibacterial agents[1] and in the study of Protein Kinase C (PKC) inhibitors.[2,3]

(1) Li, Q. et al. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1953. (2) Jagdmann, G.E. et al. *ibid.* **1995**, *5*, 2015. (3) Lai, Y. et al. *ibid.* **1995**, *5*, 2151.

49,412-7 Benzyl 3-pyrroline-1-carboxylate, 90% **(1)**

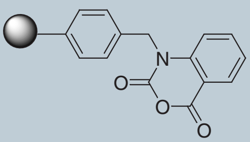
47,751-6 *tert*-Butyl 2,5-dihydro-1*H*-pyrrole-1-carboxylate, 97% **(2)**



Bis-protected guanylating agent used in the preparation of guanidinonaphthyl amino acid esters, "inverse" substrates for trypsin and trypsin-like enzymes.[1,2]

(1) Tanizawa, K. et al. *Chem. Pharm. Bull.* **1999**, *47*, 104. (2) Sekizaki, H. et al. *Tetrahedron Lett.* **1997**, *38*, 1777.

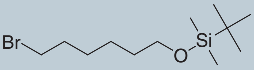
43,942-8 *N*,*N'*-Bis(benzyloxycarbonyl)-1*H*-pyrazole-1-carboxamidine, 97%



The highly reactive anhydride moiety makes this a commonly used scavenger resin to remove primary and secondary aliphatic amines from solution-phase reactions.

Coppola, G.M. *Tetrahedron Lett.* **1998**, *39*, 8233.

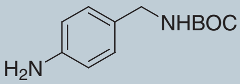
51,437-3 Isatoic anhydride, polymer-bound, 2.0-2.5 mmol N/g



A pheromone intermediate was prepared by displacement of the bromide with an acetylene followed by selective deprotection of the silyl group with neutral alumina in the presence of a THP ether.

Capdevila, A. et al. *Org. Lett.* **1999**, *1*, 845.

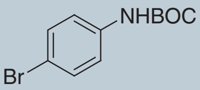
51,314-8 (6-Bromohexyloxy)-*tert*-butyldimethylsilane, 99%



Pharma building block used in the preparation of topomerase inhibitors,[1] neuroprotective agents,[2] and novel antagonists for vascular $5HT_{1B}$-like receptors.[3]

(1) Dudouit, F. et al. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 553. (2) Di Fabio, R. et al. *J. Med. Chem.* **1999**, *42*, 3486. (3) Moloney, G.P. et al. *ibid.* **1999**, *42*, 2504.

52,562-6 4-[(*N*-BOC)aminomethyl]aniline, 97%



BOC protection makes this aniline a good substrate for Suzuki coupling. Two examples are the biaryls from reaction with pyridine[1] or 3-benzaldehyde[2] boronic acids.

(1) Lamothe, M. et al. *J. Med. Chem.* **1997**, *40*, 3542. (2) Coutts, I.G.C. et al. *Tetrahedron Lett.* **1997**, *38*, 5563.

52,724-6 *N*-(*tert*-Butoxycarbonyl)-4-bromoaniline, 97%

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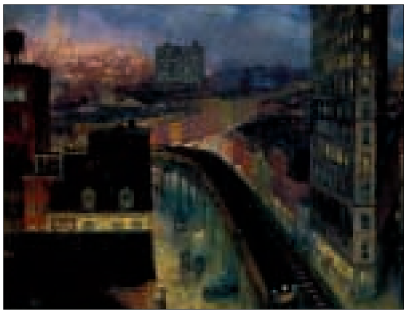

The City from Greenwich Village (oil on canvas, 26 in. x 33¾ in.) was painted in 1922 by the American artist John Sloan, one of a number of artists who came to be called the "Ash Can School" because of their use of busy city streets, tenements, and back alleys as subjects. Sloan, who was born in 1871 in Lock Haven, Pennsylvania, worked during the 1890s as a newspaper illustrator in Philadelphia, where he came in contact with the artist Robert Henri. Henri had returned from several years' study in Paris determined to lead a revolt against academic art and with a strong belief that works of art should reflect the reality of contemporary life.

After 1904, Sloan settled permanently in New York, and though he continued to work as an illustrator, he devoted himself increasingly to the pursuit of subjects of human interest and the depiction of scenes of everyday life among ordinary people in the city. He was one of the original members of a group of artists called The Eight, who were not united by a common style but by a rejection of academic aestheticism. This group came into being in 1907, when the National Academy of Design rejected the work of Sloan, George Luks, and William Glackens, and Henri withdrew his own paintings in protest from the Academy's annual exhibition.

The City from Greenwich Village shows the view from the artist's Washington Place studio out over the street on a rainy winter evening. Automobiles and figures bearing umbrellas make their way under the elevated trains, which ran then along Sixth Avenue. Electric lights reflect from the rainy streets and cast a glow between the buildings, and the lights of the skyscrapers at the far left are like a celestial vision in the distance. A much more romantic image than is commonly found in Sloan's earlier works, it is a celebration of the energy and excitement of a great modern city.

This painting is a gift of Helen Farr Sloan to the National Gallery of Art, Washington, D.C.

Table of Contents

Lab Notes

Analysis of Volatile Compounds in Resins by GC/MS

A convenient and simple way to analyze volatile compounds in resins used in polymerization processes is by GC/MS. The power of GC/MS as an analytical tool is well developed and most laboratories are now equipped with bench-top GC/MS units. Therefore, it is quite convenient to use GC/MS to analyze the amount of monomers present in a resin, the volatile products from polymerization (condensation), or the impurities in a resin. The difficulty in analyzing a resin arises from the fact that it is usually a thick and viscous liquid. The normal procedure of using a solvent to dissolve the resin is tedious and difficult and requires the judicious choice of solvent. In addition, the solvent peak in GC/MS often obscures the small amount of volatile compounds to be analyzed. The use of fixed-volume micro syringes allows simple, direct analysis of the sample without contamination. The micro syringe (Dynatech Mini-injector, from 0.01 to 0.10 microliters, Aldrich Cat. No. Z17,096-8 and Z17,099-2) is dipped directly into the resin sample. Normal injection is made into a GC/MS. The injection port is kept at the appropriate temperature, and the needle is left in the injection port for sufficient time to allow the vaporization of volatile compounds from the needle (about one minute). The needle can be cleaned with appropriate solvents and any residue burned off using a burner. We have used this method successfully to analyze the amount of allyl alcohol (a potent irritant) in a Vibrin resin.

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E-mail: aleong@ehc.edu

Preventing Cross-Contamination in Solvent Stills Connected in Series to the Same Inert Gas Manifold

We have always had the problem of solvents getting contaminated with other solvents, when several stills were connected to a common inert gas source. The flow of the inert gas was designed to entrain the solvent vapors by entering the still with the low-vapor-pressure solvent and ending in a bubbler next to the high-vapor-pressure solvent. But, often, solvents were contaminating each other during the distillation due to changes in the rate of inert gas flow, water flow cutoff, or power failure.

To minimize this contamination, we have designed a new piece of glassware called a Protecting Head, as shown in **Figure 1**. Since the solvent vapors are carried deep inside the side arm, they condense, allowing only the inert gas to escape. In a typical setup, each still is fitted with a protecting head and connected to the common inert gas manifold through T-connectors. Any contaminated solvent accumulated in the side arm is periodically removed through the bottom stopcock, making sure that the accumulated solvent does not reach the bottom of the inner tube.

We have successfully used this setup in the distillation of such solvents as diethyl ether, dichloromethane, hexane, toluene, acetonitrile, and THF. We hope that chemists the world over will find it equally useful.

Maravanji S. Balakrishna, Assistant Professor
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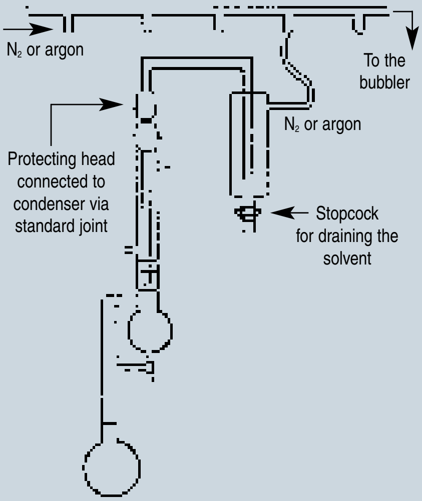
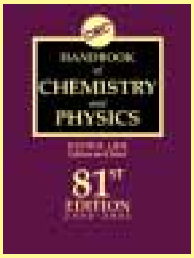


Figure 1
Solvent Still with a Still Protecting Head.



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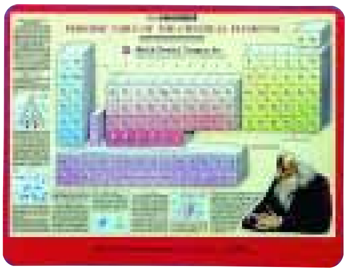

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The Catalytic Synthesis of Thiacrowns from Thietanes and Thiiranes by Metal Carbonyl Complexes

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E-mail: adams@mail.chem.sc.edu

Outline

1. Introduction
2. Metal-Promoted Ring Opening of Thietanes
3. The Catalytic Macrocyclization of Thietanes
4. Metal-Catalyzed Transformations of Thiiranes
5. Acknowledgments
6. References

1. Introduction

Polythioether macrocycles or thiacrowns, as they are more commonly called, are an extensive family of large-ring heterocycles that contain sulfur.[1] 1,4,7,10,13,16-Hexathiacyclooctadecane, **A**, is a typical example. This compound will be identified by the symbol 18S6, where the 18 indicates the number of atoms in the ring and the 6 the number of sulfur atoms in the ring without specifying their locations. Other compounds in this review will be identified similarly. Thioether sulfur atoms can bind effectively to transition-metal ions.[2] Because of their potential for polydentate coordination and the increased stabilization that this produces, much attention has been focused on the ligand properties of the thiacrowns, **B**.

We have recently developed the first procedures for synthesizing thiacrowns catalytically from thietane and thiirane reagents (**eq 1**,[3-4] **2**[5]).

Thietane **I**[6] and thiirane **II**[7] are the parent members of two families of strained-ring thioethers. Both compounds contain about 80 kJ/mol (19 kcal/mol) of strain energy,[8] and are readily polymerized by Lewis acid (**eq 3**, **4**) and Lewis base catalysts (**eq 5**, **6**).[9,10] Thietanes are readily desulfurized on a clean molybdenum surface.[11] Thiiranes are desulfurized more easily than thietanes, because the olefin remnant is an excellent leaving group.[12] Thiiranes are readily desulfurized by many metal complexes. In fact, thiiranes have been used as reagents for the synthesis of metal sulfide complexes.[13]

Historically, thiacrowns have been made through the reaction of organic thiols with organic halides in the presence of base.[1a] The yields are typically low and the products are difficult to isolate (**eq 7**), although the recent development of the cesium salt method has provided significantly better yields in a number of cases.

2. Metal-Promoted Ring Opening of Thietanes

Our efforts to prepare thiacrowns catalytically began in earnest in the early 90s when we discovered that bridging thietane ligands in metal complexes engaged in facile ring-opening reactions with nucleophiles.

These reactions resulted in the cleavage of one of the carbon–sulfur bonds with nucleophiles as simple as the halide ions. The reaction of $Os_3(CO)_{10}(\mu\text{-}\overline{SCH_2CMe_2CH_2})$ (**1**), which contains a bridging 3,3-dimethylthietane ligand, with halides yielded anionic ring-opened γ-halothiolate complexes **2**, that we typically neutralized by proton addition (**eq 8**).[14] The reaction caused cleavage of one of the carbon–sulfur bonds and produced an inversion of configuration at the carbon atom where the nucleophile was added. This is consistent with the backside addition mechanism.

Activation of the thietane toward nucleophilic addition occurs as a result of the donation of electron density from the sulfur atom to the metal atoms. This produces a partial positive charge on the sulfur and a smaller, but still significant, increase in positive charge on the adjacent carbon atoms (see **3**). This effect is apparently sufficient to permit the ring-opening addition of the halide ions.

The first major step toward macrocycle synthesis was the discovery that **1** produced a

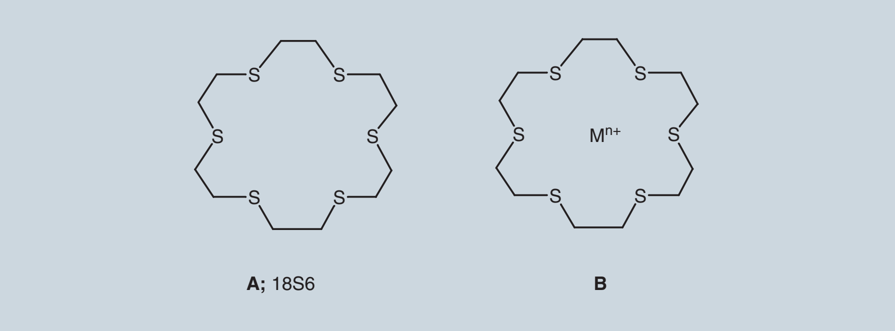
ring-opening trimerization of 3,3-dimethylthietane (3,3-DMT) upon addition of two more equivalents of 3,3-DMT to yield $Os_3(CO)_{10}(SCH_2CMe_2CH_2)_3$ (**4**). It is proposed that **4** is formed through the series of nucleophilic ring-opening additions that begins with a process analogous to that shown in equation 8, traverses a series of zwitterionic thietanium—thiolate intermediates, and finishes with a ring-opening oxidative addition of the last thietanium ring to the cluster. The last step also opens the ring and the cluster, and the reaction terminates (**Scheme 1**).[15] Thermal decarbonylation of **4** results in closure of the cluster, while its treatment with CO at elevated temperatures leads only to the addition and insertion of one CO group at the carbon terminus of the hydrocarbon chain.[15] We were unable to obtain any thiacrowns from compound **4**.

The first successful construction of the thiacrown grouping from a thietane was achieved in the reaction of the trirhenium complex $Re_3(CO)_{10}(\mu\text{-}\overline{SCH_2CH_2CH_2})(\mu\text{-}H)_3$ (**5**) with thietane (**Scheme 2**).[16] Compound **5** contains a bridging thietane ligand similar to that found in **1**. Complex **5** gives rise to $Re_3(CO)_{10}(\mu\text{-}SCH_2CH_2CH_2\text{-}12S3)(\mu\text{-}H)_3$ (**6**) by the addition of three equivalents of thietane in a series of ring-opening steps, also believed to involve zwitterionic intermediates, that terminate with a recyclization. Compound **6** was characterized crystallographically by preparing its PMe_2Ph derivative (**Figure 1**), and was found to contain a 12S3 thiacrown grouping linked to the cluster via a $SCH_2CH_2CH_2$ chain. This linkage results in the formation of a positive charge on that sulfur atom in the 12S3 ring. The thiolato sulfur atom that is coordinated to the cluster formally has a negative charge, and thus **6** is also a zwitterion. It was subsequently found that the 12S3 thiacrown could be cleaved from the linkage to the cluster by treatment with bases.

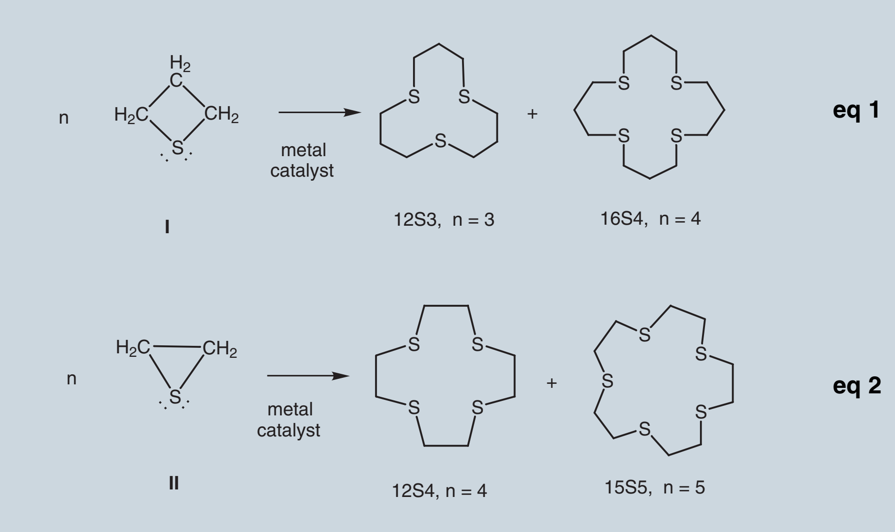
3. The Catalytic Macrocyclization of Thietanes

The first catalytic process for synthesizing 12S3 was developed by using compound **6**. It was found that thietane itself is sufficiently basic to cleave the macrocycle from the chain, when it is allowed to react with **6** in the absence of solvent at its boiling point (94 °C). This cleavage leads to the regeneration of the intermediate, **C**, and closes the catalytic cycle (**Scheme 2**).[3] The reaction also yields small amounts (1%) of the thiacrown 16S4, but the principal products are polymers that significantly exceed the yield of 12S3 by a factor of four on a per weight basis. Nevertheless, the reaction can provide useful quantities of 12S3 with a catalytic turnover frequency (TOF = number of moles of product/mole of catalyst-day) of 46. The reaction is successful largely because of the involvement of the zwitterionic intermediates that increase the probability for the recyclization step relative to simple polymerization.

Next, we discovered that certain third-row transition-metal complexes containing *terminally* coordinated thietane ligands were even more effective catalysts for producing 12S3 from thietane. The most efficient catalyst is $Re_2(CO)_9(\overline{SCH_2CH_2CH_2})$ (**7**), which produces 12S3 at a rate of 146 turnovers/day and with a chemoselectivity of up to 85%.[4] The conversion is not complete and the yield based on the amount of thietane consumed is only about 40%, but the unreacted thietane can be recovered and recycled. It was also found that $Os_4(CO)_{11}(\overline{SCH_2CH_2CH_2})(\mu\text{-}H)_4$,[17] and $W(CO)_5(\overline{SCH_2CH_2CH_2})$ yield 12S3 at rates of 110 and 26 turnovers/day, respectively. The tungsten catalyst exhibits a lower selectivity (about 50%),[18] but is still an attractive catalyst, because it is easily

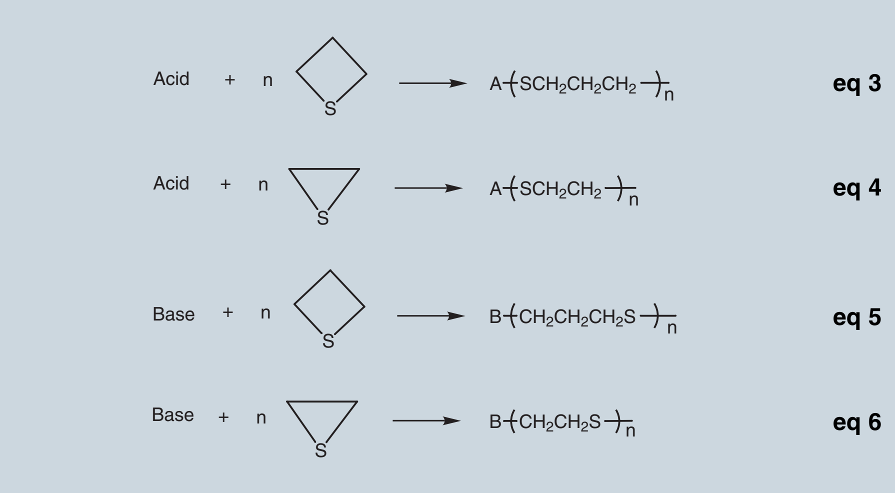


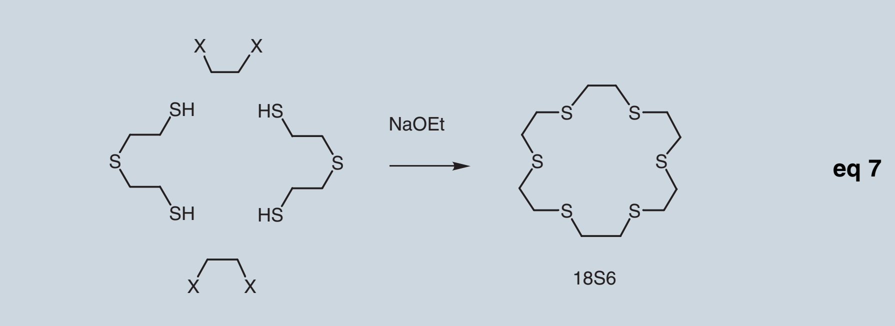
A; 18S6 **B**

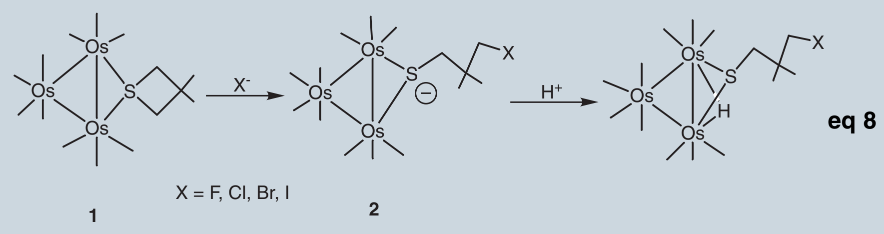


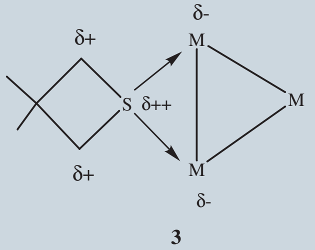
I

II

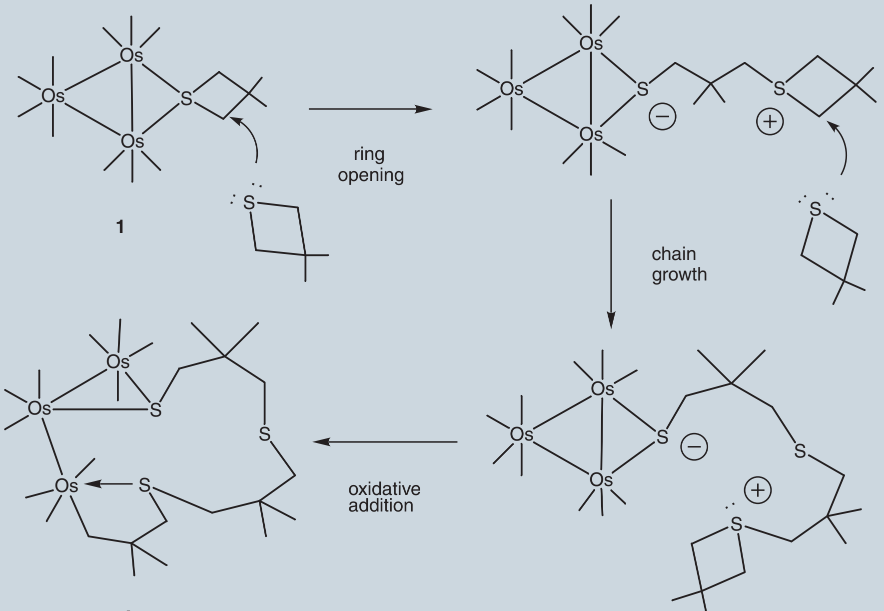








3



Scheme 1

prepared from the reaction of $W(CO)_5(NCMe)$ with thietane. In fact, $W(CO)_5(NCMe)$ can be used as the catalyst precursor with similar results. The ruthenium homolog, $Ru_4(CO)_{11}(SCH_2CH_2CH_2)(\mu\text{-}H)_4$, is significantly less active and less selective than its osmium counterpart. Likewise, the chromium complex $Cr(CO)_5(SCH_2CH_2CH_2)$ is significantly less effective than the tungsten analog. The reason for this is not clear, but it is possible that the metal–sulfur bonds in the thietane complexes are weaker for the first-row metals and, therefore, do not provide as much activation of the thietane ligand as they do in the cases of the third-row metal complexes.[19]

The proposed mechanism for the formation of 12S3 by **7** is shown in **Scheme 3**.[4] The rate of the reaction is first-order in dirhenium, but all transformations are proposed to occur at a single metal site. As with **6**, it is believed that the zwitterionic character of the intermediates promotes the formation of the macrocycle. This reaction is more efficient than that of **6**, because the recyclization occurs at the terminally coordinated thiolate sulfur atom. This thiolate sulfur is more exposed than the bridging thiolate in **6** and more basic than the thioether sulfur in **6**, which is the actual site of recyclization in the trirhenium system. Recyclization at the thiolate sulfur atom (see Scheme 3) can explain the higher selectivity for 12S3 formation. This recyclization produces the 12S3 as a sulfur-bound ligand in the complex **8**. Compound **8** was isolated and characterized crystallographically. It was observed spectroscopically in significant amounts in catalyst solutions, and it exhibits exactly the same activity as **7**, as it must if it is a member of the same catalytic cycle. Importantly, the catalytic cycle is completed simply by substitution of the 12S3 ligand by thietane, a process that is easier than cleaving 12S3 from the $SCH_2CH_2CH_2$ tether in **6**. This can explain the higher activity of catalyst **7**.

Next, our efforts were directed toward expanding the scope of the reaction to try to prepare new polythioether macrocycles. By adding methyl substituents to the thietane ring, we were able to prepare 3,7,11-Me_3-1,5,9-12S3, which exists as a mixture of cis and trans isomers.[20] We were also able to prepare 3,3,7,7,11,11-Me_6-1,5,9-12S3 from 3,3-DMT,[21] and, by using enantiomerically enriched (*R*)-2-methylthietane, the macrocycle (2*R*,6*R*,10*R*)-2,6,10-Me_3-1,5,9-12S3, which has three stereogenic centers all of the same configuration.[22] A summary of the results that were obtained with the $Re_2(CO)_9$ catalysts is shown in **Table 1**.

It was found that the rate of formation of the 12S3 products decreases as the level of substitution on the thietane ring increases. This is probably due to simple steric inhibitions. In addition, the selectivity for the 12S3 ring also declines. The yield of the $Me_6$12S3 from 3,3-DMT is only about 10%. Significant quantities of 3,3,7,7,11,11,15,15-Me_8-1,5,9,13-16S4 and 3,3,7,7,11,11,15,15,19,19-Me_{10}-1,5,9,13,17-20S5 are also obtained, but polymers are the principal products. This is because the methyl substituents retard not only the opening of the thietane ring, but also the recyclization step.

We were even able to prepare polyselenaether macrocycles by replacing the sulfur atom in the thietane ring with a selenium atom. From the reaction of 3,3-dimethylselenetane we have obtained good yields of the new compound 3,3,7,7,11,11-Me_6-1,5,9-12Se3, together with smaller amounts of the new heterocycles 3,3,7,7-Me_4-1,5-8Se2 and 3,3,7,7,11,11,15,15-Me_8-1,5,9,13-16Se4, which contain two and four selenium atoms, respectively.[23]

Interestingly, we were even able to obtain some members of a new family of polythiolactones catalytically from β-propiothiolactone (**9**) (**eq 9**).[24] These reactions proceed readily at room temperature. The principal products are polymers. Indeed, it is only when the reaction is diluted with inert solvents, such as methylene chloride, that the macrocycles are obtained. Since it was not possible to isolate a metal complex of **9**, catalyst precursors such as $Re_2(CO)_9(NCMe)$ were used. Surprisingly, the first-row metal carbonyl $Mn_2(CO)_9(NCMe)$ was just as effective a catalyst as the third-row rhenium complex for these β-propiothiolactone reactions. Even more surprising, it was found that $Mn_2(CO)_{10}$ was as effective a catalyst as $Mn_2(CO)_9(NCMe)$. It was subsequently observed that these reactions were light-dependent and did not take place at all in the absence of room light. Inhibition by radicals and other evidence point strongly to a radical-based mechanism for these reactions (**Scheme 4**)^{24}. Additional studies showed that only metal-based radicals were sufficiently active to initiate these reactions. Organic radicals, such as TEMPO, were completely ineffective. The reasons for this are not clear at this time.

The conformations of these macrocycles differ significantly from those of the classical thiacrowns. For example, the π-conjugation effects between the sulfur atom and the carbonyl group induce an s-trans conformation at the C–C bond between the carbonyl group and its neighboring methylene group. This, in turn, forces the sulfur atoms to turn toward the interior of the ring as shown in the structure of **10** (**Figure 2**). The 24-membered ring in **11** contains such a large cavity that it occludes a molecule of solvent when it crystallizes from solution (**Figure 3**).

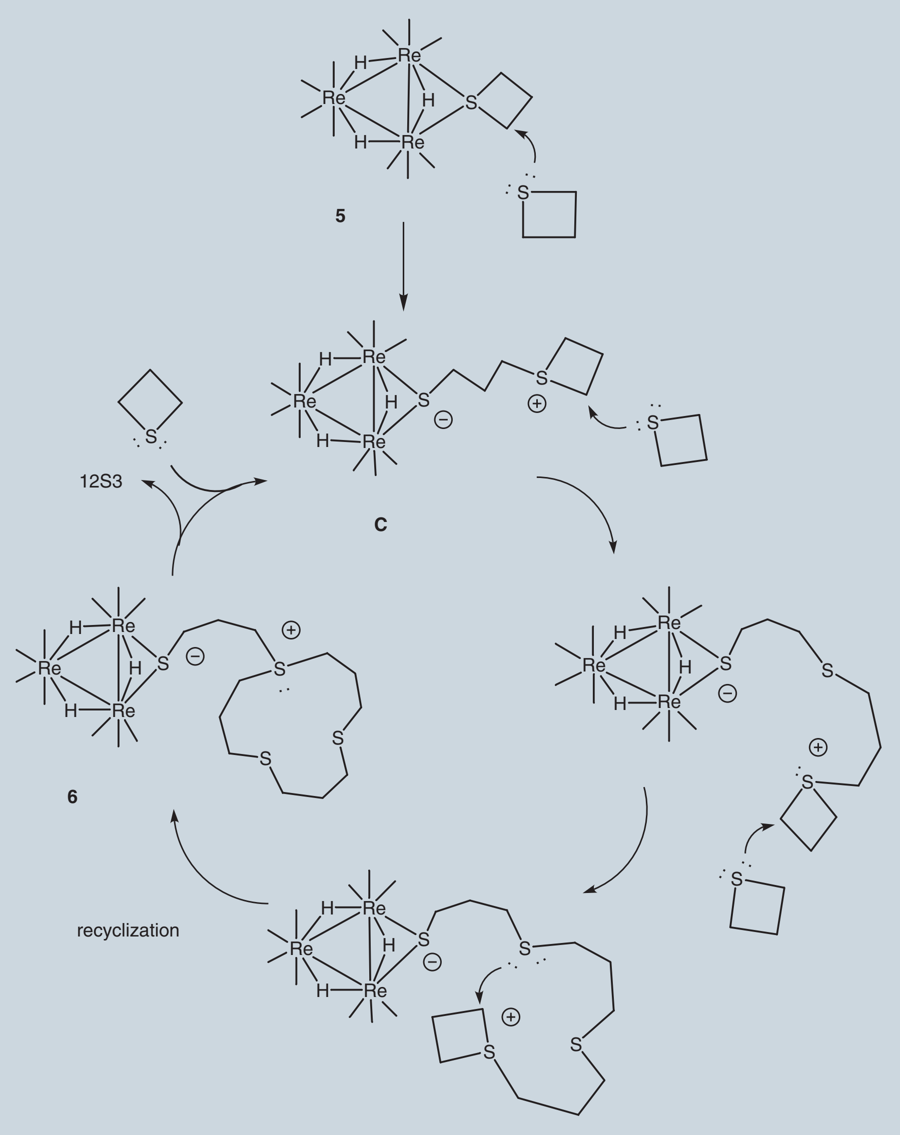
Compound **11** is one of those rare examples of a molecule that possesses S_6 symmetry. These thiacrowns are slowly degraded by hydrolysis at the sulfur–carbonyl bond when left in the open air. We have not yet been able to prepare metal complexes of these thiacrowns. It may be that the donor ability of the sulfur atom is diminished sufficiently by its conjugation to the carbonyl group that complexation with metal ions may no longer be possible.

4. Metal-Catalyzed Transformations of Thiiranes

There are very few examples of stable metal–thiirane complexes: Abel et al. have reported some complexes of *cis*-1,4-cyclohexadienebisepisulfide to the group VI metals, and have structurally characterized the chromium complex $Cr(CO)_4$(*cis*-1,4-cyclohexadienebisepisulfide).^{25} Amarasekera et al. have prepared the thiirane–ruthenium complex $[Cp(PPh_3)_2Ru(\overline{SCH_2CH_2})][O_3SCF_3]$.^{26}

We have prepared a series of (thiirane)$W(CO)_5$ complexes that are similar to Abel's compounds by the reaction of $W(CO)_5(NCMe)$ with the corresponding thiirane: $W(CO)_5(\overline{SCH_2CH_2})$ (**12**), $W(CO)_5$(*cis*-$\overline{SCHMeCHMe}$) (**13**), and $W(CO)_5$(*trans*-$\overline{SCHMeCHMe}$) (**14**).^{5} Compound **13** was characterized crystallographically, and a diagram of its molecular structure is shown in **Figure 4**. The thiirane is coordinated to the tungsten through one of the two lone pairs of electrons on the sulfur atom. In solution, however, the compound exists as a mixture of two isomers that differ by the coordination of the two inequivalent lone pairs of electrons on the sulfur atom.

The thiirane complex **12** readily reacts with thiirane to yield a series of cyclic disulfides, **15**–**17**, including a small amount of



Scheme 2

the pentadisulfide, as the principal products (**eq 10**). Small amounts of the polythioethers 12S4, 15S5 and 18S6 are obtained (see below), and there is also some minor competing desulfurization to yield elemental sulfur.^{25} Interestingly, one equivalent of ethylene is produced for each disulfide group that is formed. The current evidence is consistent with a mechanism of backside ring-opening addition of a free molecule of thiirane to one of the methylene groups of the thiirane ligand (**Scheme 5**).

The zwitterion **D** eliminates ethylene to yield an intermediate containing a SCH_2CH_2S or "dithietane" grouping, as shown in **E**. 1,2-Dithietane is an unstable molecule and has not yet been isolated. It is proposed that the dithietane groupings simply condense to yield the various cyclic disulfides, dimer **15**, trimer **16**, etc., which are then released from the tungsten to regenerate the catalyst. Evidence for the existence of a dithietane intermediate was obtained by trapping it with dimethyl acetylenedicarboxylate (DMAD). When the reaction was performed in the presence of DMAD, dithiacyclohexene **18** was formed catalytically at a rate of 1.5 turnovers/h. Compound **18** was not obtained from mixtures of the cyclic disulfide products with DMAD in the presence of $W(CO)_5(NCMe)$.

Interestingly, in the presence of DMAD, the formation of the cyclic disulfides **15**–**17** is greatly suppressed, and the polythioethers 12S4 and 15S5 become the principal products. Evidently, the alkyne somehow slows the elimination of ethylene from the intermediate, **D**, but allows further thiirane ring-opening additions, which are then terminated with a macrocyclization (**Scheme 6**).

When compound **13** was allowed to react with *cis*-$\overline{SCHMeCHMe}$ in the presence of DMAD, cyclic disulfides were formed.

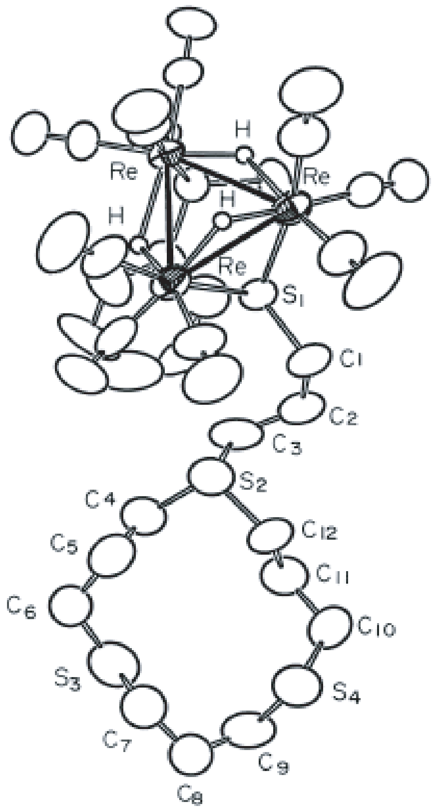
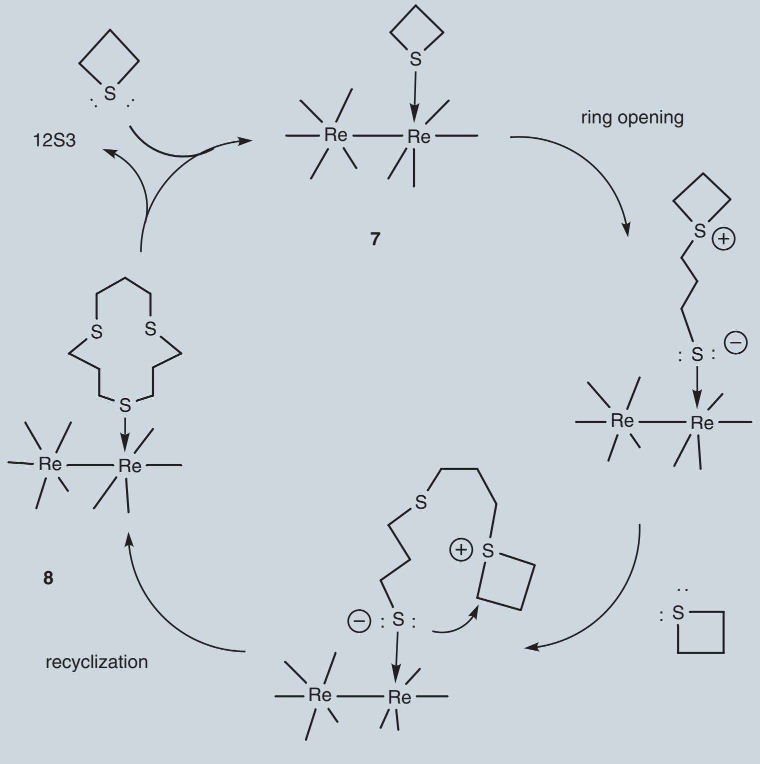


Figure 1. An ORTEP diagram of the molecular structure of the PMe_2Ph derivative of trirhenium cluster complex **6** containing the dangling 1,5,9-trithiacyclododecane macrocycle.



Scheme 3

Structural characterization of these disulfides showed that all adjacent carbon atoms always had the same stereochemistry, as observed in the structure of (3*S*,4*S*,7*R*,8*R*,11*S*,12*S*)-hexamethyl-1,2,5,6,9,10-hexathiacyclododecane.[5]

We have also found that vinylthiiranes **19–23** can be effectively transformed into 3,6-dihydro-1,2-dithiins **24–27** by tungsten carbonyl compounds such as $W(CO)_5(NCMe)$ (**eq 11**).[27]

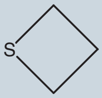
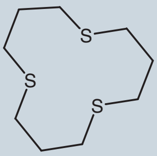
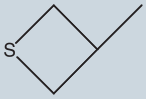
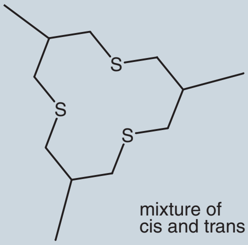
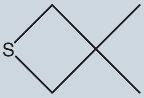
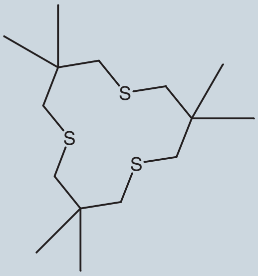
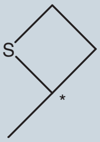
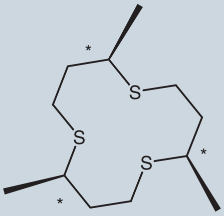
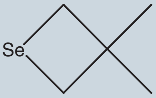
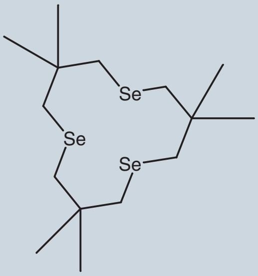
These reactions are accompanied by the formation of equivalent amounts of the corresponding butadienes and proceed to essentially 100% conversion, when they are performed at 25 °C. Interestingly, the reaction is inhibited by methyl groups on the thiirane ring, but is accelerated when methyl groups are placed on the vinyl group. Turnover frequencies (TOFs) range from a low of 2 h^{-1} to a high of 29 h^{-1} for these compounds (**Table 2**).

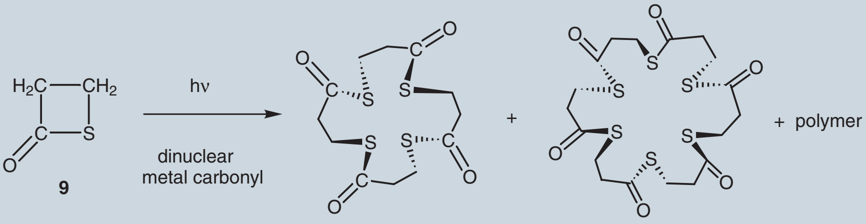
The tungsten complex $W(CO)_5(\overline{SSCH_2CH{=}CHCH_2})$ (**28**) was isolated from the vinylthiirane reaction and was structurally characterized (**Figure 5**).[27a] This compound contains a dihydrodithiin ligand coordinated to the tungsten through one of the sulfur atoms. The W–S and S–S bond distances are 2.549(2) Å and 2.062(2) Å, respectively.

Compound **28** has been observed as a component in the catalytic cycle (**Scheme 7**). $W(CO)_5(NCMe)$ is a good catalyst precursor, but is not a component in the catalytic cycle. ^{13}C NMR studies of catalytically active solutions have shown that $W(CO)_5(NCMe)$ and **28** are converted to vinylthiirane-containing tungsten complexes **29** (two isomers that differ as a result of which of the two lone pairs of electrons on the sulfur atom is coordinated) during the catalysis. Unlike the reactions of the simple thiiranes, it has been proposed that the thiirane ring opening occurs spontaneously (step a) to give an allylium–thiolate intermediate, **F**.[27] This could explain the enhancement of the reaction rate by methyl substituents on the vinyl group. Intermediate **F** then rapidly adds a second equivalent of vinylthiirane (step b) to yield a thiiranium–thiolate species, **G**, which eliminates butadiene (step c) to yield the stable dihydrodithiin complex **28**. Another equivalent of vinylthiirane then displaces the dihydrodithiin ligand to release the product, **24**, and complete the catalytic cycle (step d).

Interestingly, the catalysis is significantly increased when a phosphine ligand is substituted for CO on the tungsten atom. For example, the turnover frequency for the catalytic formation of **24** from **19** by $W(CO)_4(PPh_3)(NCMe)$ is 47 h^{-1}, nearly three times that by $W(CO)_5(NCMe)$. The rate increase can be attributed to steric crowding

Table 1. Derivatives of 12S3 Obtained by Using $Re_2(CO)_9$(thietane) as Catalysts

Thietane		12S3 Product	Turnover Freq./h
	→		6.1
	→	 mixture of cis and trans	2.0
	→		0.03
 (*R*) isomer	→	 (*R*,*R*,*R*) isomer	0.2
	→		1.5



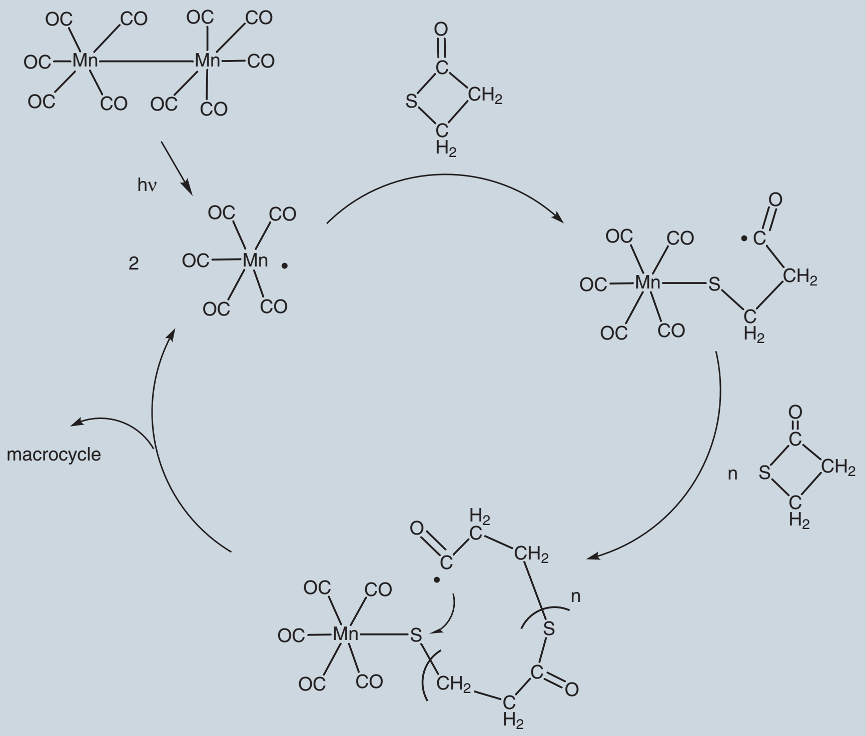
9

10, 22%

11, 2%

55%

eq 9



Scheme 4

effects that promote the spontaneous ring-opening step of **19**.

Dihydrodithiins belong to the family of allyl disulfide compounds that are found naturally in allylium plant species, including onions and garlic, and exhibit a range of antiviral, antifungal, and antibiotic properties.[28]

We have now prepared and characterized the first generation of catalysts for the formation of thiacrowns both from thietanes and from thiiranes. Some of these catalysts are very efficient and could be used for the large-scale synthesis of certain thiacrowns; for example the dirhenium complex **7** has been used to prepare 12S3 on a gram scale.[29] The potential for preparing chiral thiacrowns catalytically is evident, although this cannot be done efficiently at this time. Moreover, at present, we have little control of the size of the macrocyclic ring that is obtained. The use of moderating agents or cocatalysts may be of value in achieving these goals.

5. Acknowledgments

I would like to thank the many students who have contributed to these studies over the last few years. Their names are given in the citations listed below. These studies were supported by the Division of Chemical

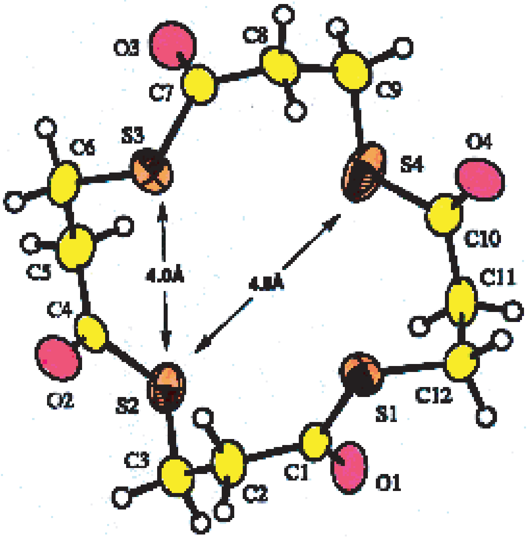


Figure 2. An ORTEP diagram of the molecular structure of 1,5,9,13-tetrathiacyclohexadecane-2,6,10,14-tetrone (**10**).

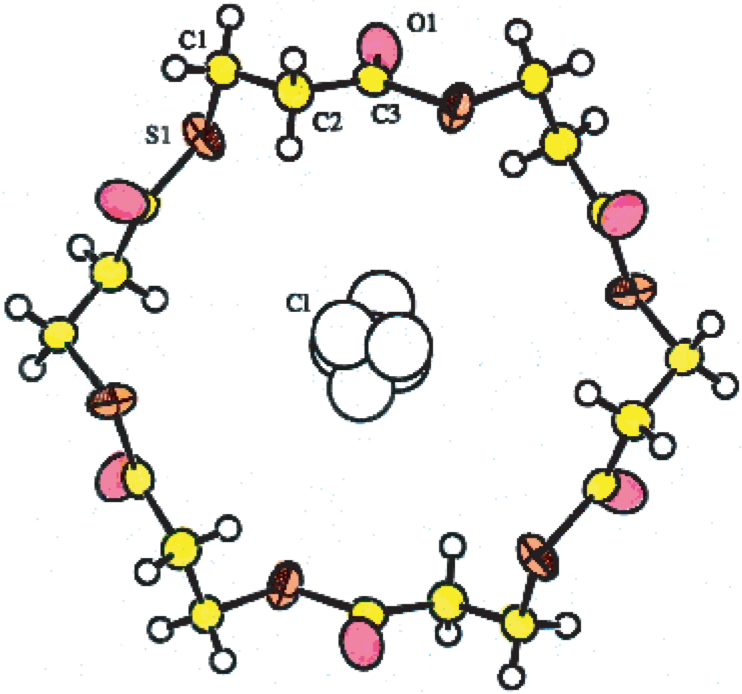


Figure 3. An ORTEP diagram of the molecular structure of 1,5,9,13,17,21-hexathiacyclotetracosane-2,6,10,14,18,22-hexone (**11**). A CH_2Cl_2 molecule with a threefold disorder cocrystallized from the crystallization solvent and is located in the center of the cyclic thiolactone.

Sciences of the Office of Basic Energy Sciences of the U.S. Department of Energy and by the National Science Foundation.

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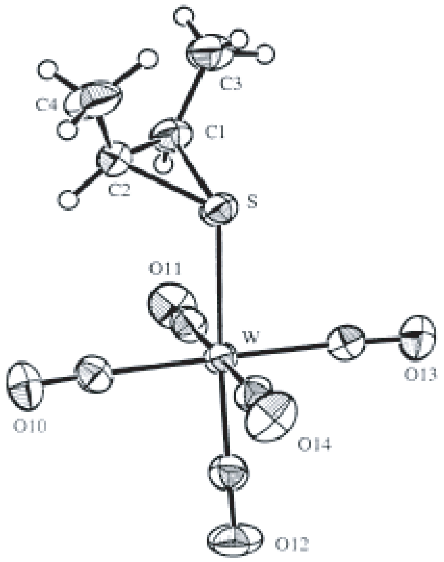
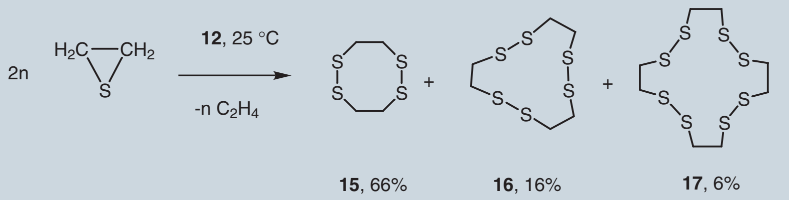
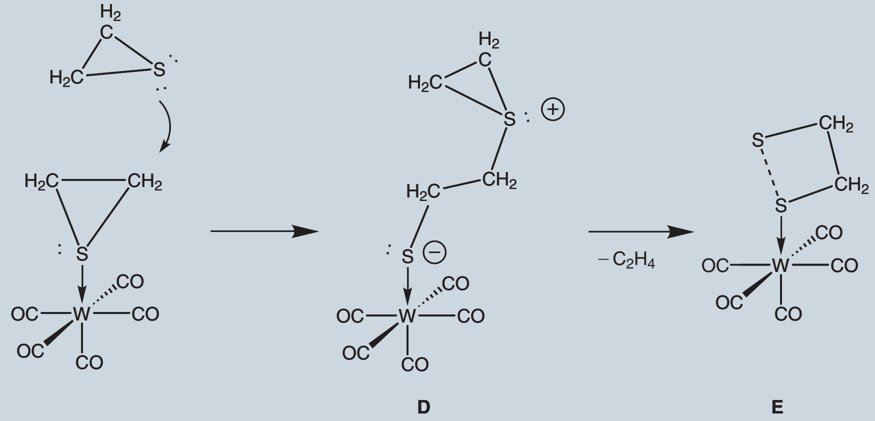


Figure 4. An ORTEP diagram of the molecular structure of the thiirane–tungsten complex W(CO)₅(*cis*-SCHMeCHMe) (**13**).



eq 10



Scheme 5

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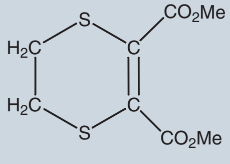

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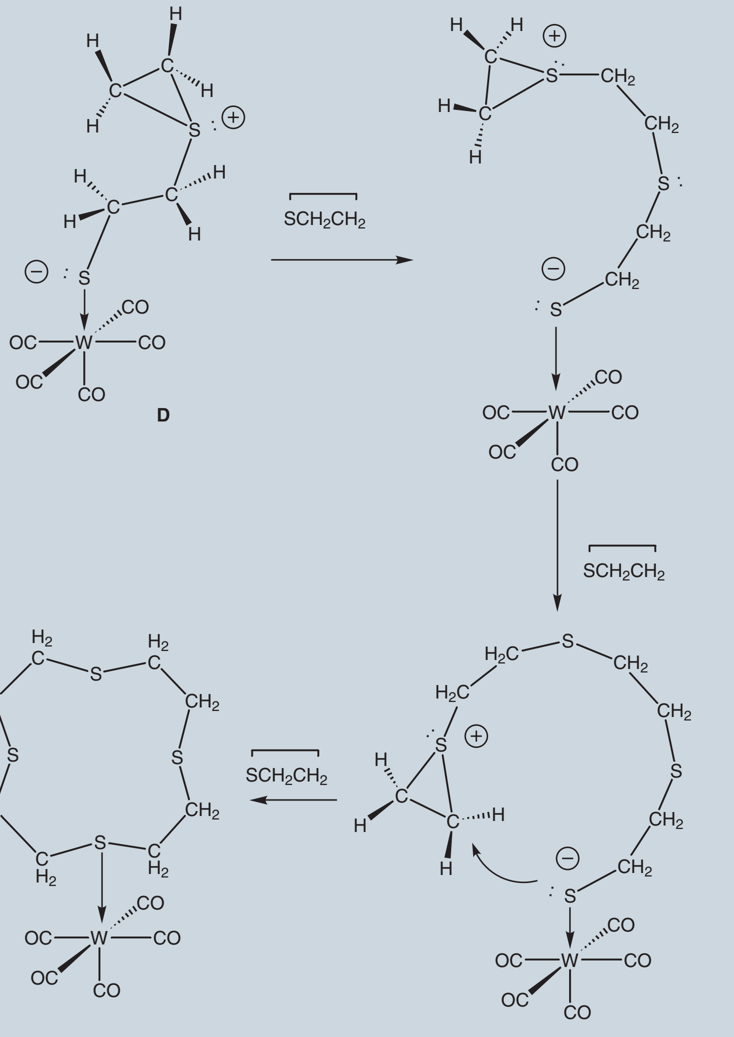
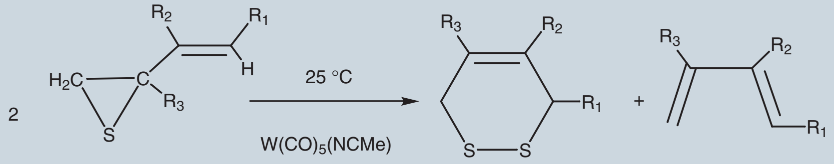


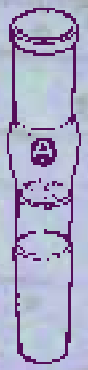
Scheme 6



eq 11

19; R_1=R_2=R_3=H
20; R_1=R_3=H, R_2=Me
21; R_1=Me, R_2=R_3=H
22; R_1=R_2=Me, R_3=H
23; R_1=R_2=H, R_3=Me

24; R_1=R_2=R_3=H
25; R_1=R_3=H, R_2=Me
26; R_1=Me, R_2=R_3=H
27; R_1=R_2=Me, R_3=H
25; R_1=R_2=H, R_3=Me



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About the Author

Richard D. Adams received a B.S. degree in 1969 from the Pennsylvania State University and a Ph.D. in chemistry in 1973 from the Massachusetts Institute of Technology for research performed under the direction of F. A. Cotton. He was an Assistant Professor of Chemistry at SUNY Buffalo, 1973–75, and Assistant and Associate Professor at Yale, 1975–84. In 1984, he moved to the University of South Carolina as Professor of Chemistry, and, in 1995, was appointed as the Arthur S. Williams Professor of Chemistry.

In 1999, he was the recipient of the American Chemical Society Award in Inorganic Chemistry, the Charles H. Herty Medal of the Georgia section of the American Chemical Society, and the Charles H. Stone Award of the Carolina-Piedmont section of the American Chemical Society. He has received a Senior Scientist award from the Alexander von Humboldt Foundation, and was selected as a Visiting Professor at the Institut Universitaire de France, 1999–2000. He is the American Regional Editor for the Journal of Organometallic Chemistry and a coeditor of the Journal of Cluster Science.

His research interests lie in the synthesis, structures, and catalytic properties of metal carbonyl cluster complexes. He is the author of over 400 research publications.

Table 2. Results of the Catalytic Transformations of Vinylthiiranes to Dihydrodithiins by $W(CO)_5(NCMe)$

Reactant	Product	% Yield[a]	TOF (h^{-1})[b]
19	**24**	86	15
20	**25**	84	29
21	**26**	86	24
22	**27**	80	19
23	**25**	34	2

[a] Isolated yields after 24 h. [b] Measured at the end of a 4-h period.

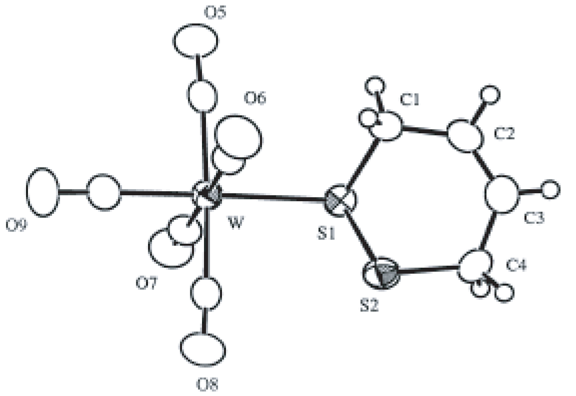
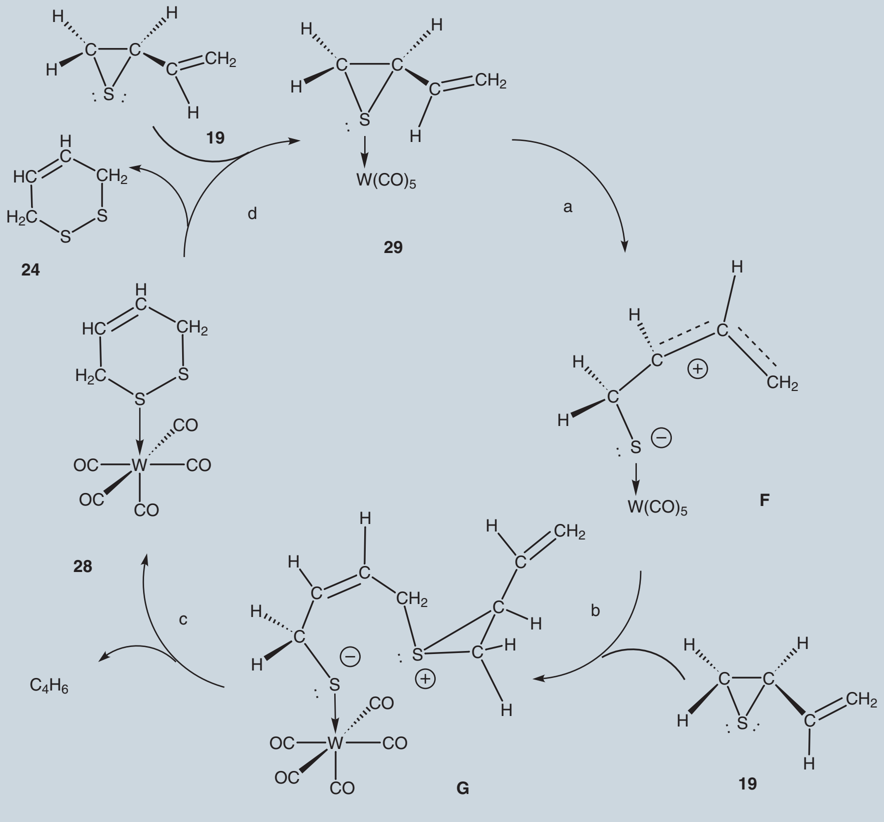


Figure 5. An ORTEP diagram of the molecular structure of $W(CO)_5(SSCH_2CH{=}CHCH_2)$ (**28**).



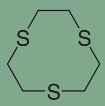
Scheme 7

Thiacrown Ethers

The chemistry of thiacrown ethers centers on their ability to coordinate with a variety of metal ions to form chelates as well as bridges. Numerous attempts have been made toward the synthesis of these useful yet somewhat elusive structures; the preceding review highlights some new advances in this area. Several of these marcrocycles are available through Aldrich and are listed below. For additional information, please call our Technical Services department at **800-231-8327** (USA) or your local Sigma-Aldrich office. Larger quantities are available through Sigma-Aldrich Fine Chemicals. Please call **800-336-9719** (USA) for availability.

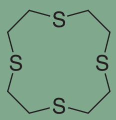
Thiacrowns

30,080-2



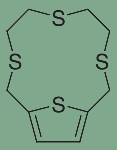
100mg
500mg

28,136-0



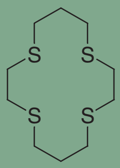
100mg
250mg

36,140-2



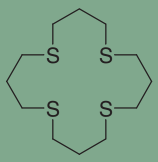
500mg

25,072-4



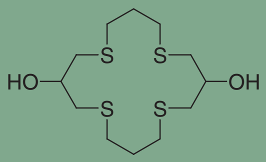
100mg
500mg

28,129-8



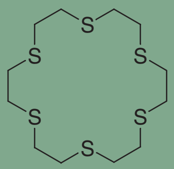
100mg

25,823-7



250mg
1g

28,127-1



50mg
250mg

Thietane and Thiiranes

18,894-8

5g
25g

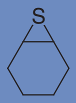
12,825-2

25g
100mg

P5,320-9

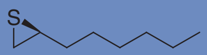
5g
25g

C10,260-1



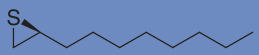
5g
10g

47,731-1



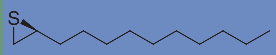
100mg

47,733-8



100mg

47,734-6



100mg

The following products are also mentioned in Professor Adams's review:

24,526-7	**Dimanganese decacarbonyl**, 98%
21,400-0	**TEMPO**, free radical, 98%
D13,840-1	**Dimethyl acetylenedicarboxylate**, 99% (DMAD)

References: (1) Pluta, K. *Heterocycles* **1999**, *51*, 2861. (2) Itoh, T. et al. *J. Mol. Catal. B: Enzym* **1997**, *3*, 259. (3) Sato, M.; Akabori, S. *Trends Org. Chem.* **1990**, *1*, 213. (4) Kellogg, R.M. *Crown Compd.* **1992**, 261. (5) Cooper, S.R. *Acc. Chem. Res.* **1998**, *21*, 141.

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The Preparation of Highly Reactive Metals and the Development of Novel Organometallic Reagents†

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Rieke Metals, Inc.
1001 Kingbird Road
Lincoln, NE 68521

Outline

1. Introduction

In the last three decades, considerable effort has been extended to generate ever more reactive metals with an eye to preparing novel organometallic reagents. Success in these studies has rapidly increased the array of novel organometallic reagents for the synthetic community. In 1972, we reported a general approach for preparing highly reactive metal powders by reducing metal salts in ethereal or hydrocarbon solvents using alkali metals as reducing agents.[1] Several basic approaches are possible and each has its own particular advantages. For some metals, all approaches lead to metal powders of identical reactivity. However, for other metals one method can lead to a far superior reactivity. High reactivity, for the most part, refers to oxidative addition reactions. Since our initial report, several other reduction methods have been reported including metal–graphite compounds, a magnesium anthracene complex, and dissolved alkalides.[2]

Although our initial entry into this area of study involved the reduction of $MgCl_2$ with potassium biphenylide, our early work concentrated on reductions without the use of electron carriers. In this approach, reductions are conveniently carried out with an alkali metal and a solvent whose boiling point exceeds the melting point of the alkali metal. The metal salt to be reduced must also be partially soluble in the solvent, and the reductions are carried out under an argon atmosphere (**eq 1**).

The reductions are exothermic and are generally completed within a few hours. In addition to the metal powder, one or more moles of alkali salt are generated. Convenient systems of reducing agents and solvents include potassium and THF, sodium and 1,2-dimethoxyethane (DME), and sodium or potassium with benzene or toluene. For many metal salts, solubility considerations restrict reductions to ethereal solvents. Also, for some metal salts, reductive cleavage of the ethereal solvents requires reductions in hydrocarbon solvents such as benzene or toluene. This is the case for Al, In, and Cr. When reductions are carried out in hydrocarbon solvents, solubility of the metal salts may become a serious problem. In the case of Cr, this was solved by using $CrCl_3$•3THF.[3]

A second general approach is to use an alkali metal in conjunction with an electron carrier such as naphthalene. The electron carrier is normally used in less than stoichiometric proportions, generally 5 to 10 mol %, based on the metal salt being reduced. This procedure allows reductions to be carried out at ambient temperature, or at least at lower temperatures as compared with the preceding approach, which requires refluxing. A convenient reducing metal is lithium. Not only is the procedure much safer when lithium is used rather than sodium or potassium, but in many cases the reactivities of the metal powders produced are greater.

A third approach is to use a stoichiometric amount of preformed lithium naphthalenide. This approach allows for the very rapid generation of the metal powders, since the reductions are diffusion controlled. Very low to ambient temperatures can be used for the reduction. In some cases, the reductions are slower at low temperatures because of the low solubility of the metal salts. This approach frequently generates the most active metals, as the relatively short reduction times at low temperatures restrict the sintering (or growth) of the metal particles.

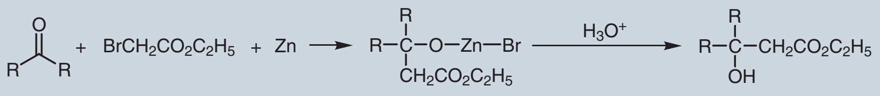
This article will concentrate on two metals prepared by these approaches: zinc and magnesium.

2. Rieke® Zinc

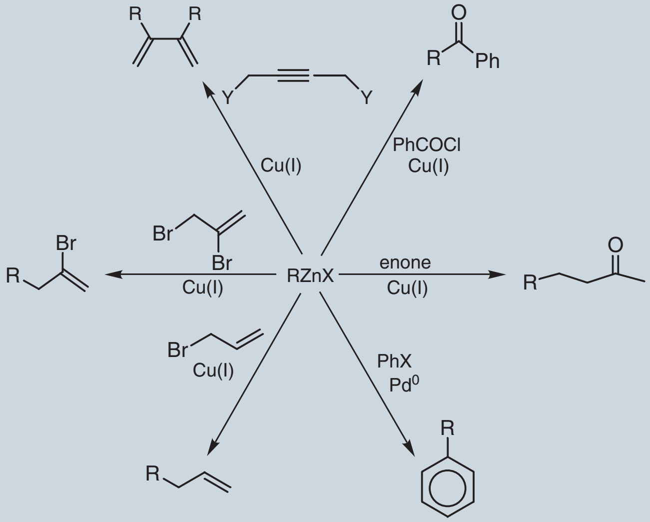
2.1. Direct Oxidative Addition to Functionalized Alkyl and Aryl Halides

Prior to the discovery of Rieke® zinc, it was not possible to react alkyl, aryl, and vinyl bromides or chlorides directly with zinc. The one exception was the Reformatsky reaction, which is used to produce β-hydroxy esters (**eq 2**). The reaction was typically done in refluxing solvent and gave only modest yields. However, using Rieke® zinc, it became possible to react ethyl α-bromoacetate at -5 °C in THF or diethyl ether. Ethyl α-chloroacetate also reacts, but at a slightly higher temperature (10 °C). Diethyl ether is the best solvent for these reactions. The activated zinc is prepared

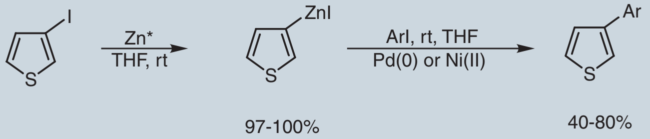
$$MX_n + n\,K \longrightarrow M^* + n\,KX$$ **eq 1**



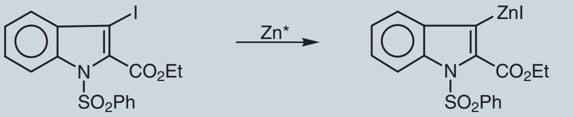
eq 2



Scheme 1. Some General Reactions of Functionalized Organozinc Reagents with Electrophiles.



eq 3



eq 4

as usual in THF, which is then stripped off and replaced with dry diethyl ether. A one-to-one mixture of aldehyde or ketone and α-bromo ester is then added at -5 °C. After stirring for one hour at room temperature, the reaction is followed by the normal workup procedure.[4]

The preparation of organozincs from alkyl, aryl, and vinyl bromides or chlorides was formerly possible only by a metathesis reaction of a zinc halide salt with a preformed organolithium or Grignard reagent. Unfortunately, the organolithium and Grignard reagents have a limited utility, since they are not compatible with many types of functionality. Rieke® zinc, on the other hand, will react directly with the bromides or chlorides, and will tolerate a wide variety of functional groups such as chlorides, nitriles, esters, amides, ethers, sulfides, and ketones. Also of significance, is that aryl halides show no scrambling of position when *ortho*-, *meta*-, or *para*-substituted substrates are used.

The active zinc reacts extremely rapidly with alkyl iodides at room temperature. The reaction times with alkyl bromides at room temperature range from minutes up to several hours. Most aryl iodides react at room temperature, while aryl bromides generally require one or more hours of heating at reflux temperatures. Most alkyl chlorides do not react unless they have an electron-withdrawing group relatively close to the carbon–halogen bond. Aryl chlorides also generally do not react with the active zinc.

The reactions of organozinc reagents with various electrophiles was well developed prior to our work. Now, this chemistry can be extended to functionalized organozinc reagents. **Scheme 1** shows some of the general reactions possible. Negishi and King had developed the use of palladium catalysts to cross-couple organozinc reagents,[5] and Knochel and co-workers had developed the use of CuCN•2LiBr for a number of cross-coupling reactions.[6] We recently demonstrated that CuI•2LiBr is generally just as effective as copper cyanide.[7]

Organozinc reagents can also be generated from heterocyclic iodides and bromides. The first example, 3-thienylzinc iodide, was prepared by the room temperature oxidative addition of Rieke® zinc to 3-iodothiophene to form a thermally stable species (**eq 3**).[8] This same procedure was used to prepare 3-indolylzinc iodide reagents (**eq 4**), which could not be synthesized by metathesis of organolithium reagents.[9] Many other types of heterocyclic organozinc reagents are also possible.[10,11]

Remarkably, Rieke® zinc reacts rapidly with secondary and tertiary alkyl iodides and bromides. The resulting organozinc halides can be readily used in all of the standard cross-coupling reactions mentioned above.[1] Several examples of reactions with benzoyl chloride are shown in **Tables 1–3**.[1d]

The intermolecular 1,4-addition of alkyl- and arylzinc reagents can be readily carried out with CuCN•2LiBr or CuI•2LiBr in moderate to excellent yields. Recently, we reported that secondary and tertiary alkylzinc bromides can, in fact, undergo 1,4-addition without the presence of a copper catalyst.[1] Moreover, the reaction conditions will tolerate a wide range of functional groups. The reaction is performed in a THF/pentane (1:9) solvent with BF_3•Et_2O and TMSCl (**eq 5**). A few typical examples are shown in **Table 4**.[1d]

Recently, we reported the first electrophilic amination of organozinc halides.[12] This reaction proceeds well with functionalized primary, secondary, and tertiary organozinc bromides. Also, functionalized benzylic zinc bromides, arylzinc halides, and heterocyclic zinc halides work equally well. The reaction (**eq 6**) involves the addition of the organozinc halide to di-*tert*-butyl azodicarboxylate (DTBAD) (**Table 5**). Depending on the mode of deprotection, the adducts can be converted into hydrazine derivatives or amines.

The active zinc may also lend itself toward the possibility of forming configurationally stable organometallics. For example, *cis*-4-*tert*-butylcyclohexyl iodide inserted zinc and was quenched with D_2O at low temperature to give the trans monodeuterated product (**eq 7**).[13]

Active zinc is an effective mediator in intramolecular conjugate additions. For example, a spirodecanone was formed from the 1,4-addition of the organozinc reagent, which was readily available from the primary iodide (**eq 8**).[14] Other types of ring closures also occur (**eq 9, 10**), and are thought to proceed by a mechanism that does not involve a free radical pathway.

The direct insertion of active zinc into the carbon–iodine bond of 6-iodo-3-functionalized-1-hexenes forms the corresponding primary alkylzinc iodides, which then undergo an intramolecular insertion of the olefinic π-bond into the zinc–carbon bond to form methyl cyclopentanes (**eq 11, 12**).[15] When R is methyl, the product diastereomeric ratio is high. This is a significant finding in that this step is a regiospecific 5-*Exo-Trig* cyclization, which can occur in the presence of functional groups. The cyclization produces an intermediate that can be elaborated further with various electrophiles. This methodology has been extended to ω-alkenyl-*sec*-alkylzinc reagents (**Scheme 2**).[16]

The reaction of aryl- and alkylzinc halides with allylic halides in the presence of CuI•2LiBr proceeds cleanly by SN2’ substitution. The yields are generally in the neighborhood of 90%. The SN2’/SN2 ratio is generally 95:5 or higher.[17-19] Following Negishi’s procedure,[5] the cross-coupling of aryl- and alkylzinc halides with aryl or vinyl iodides or bromides using a palladium catalyst proceeds in excellent yields (**Table 6**).[19]

2.2. Structure–Reactivity of Rieke® Zinc

The reaction of organic halides with magnesium or lithium in the zerovalent state is the most direct and commonly used method to prepare organometallic compounds containing these metals. However, these reactions do not show much structure selectivity, and have been referred to as “among the least selective of organic reactions”. We have recently demonstrated that competitive kinetic studies can be accurately carried out with Rieke® zinc.[20,21] Surprisingly, the highly reactive zinc shows remarkable selectivity. For example, a tertiary alkyl bromide is almost thirty times more reactive than a primary alkyl bromide. The relative reactivities of alkyl, aryl, vinyl, benzylic, and allylic bromides represent a range of over six powers of ten. Accordingly, one can accurately predict which bromide will react selectively in di- or polybrominated compounds. A simple example is shown in **Scheme 3**.[21]

Table 1. Tertiary Alkylzinc Bromides

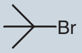
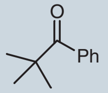
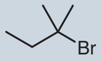
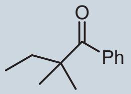
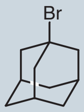
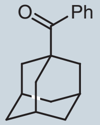
Bromide	PhCOCl (equiv)	Product	Yield (%)
	0.7		75
	0.7		86
	0.7		72

Table 2. Secondary Alkylzinc Bromides

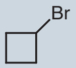
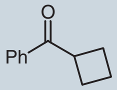
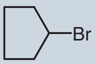
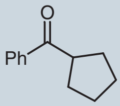
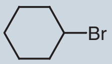
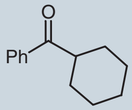
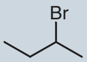
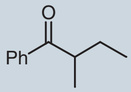
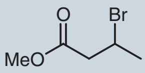
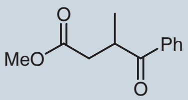
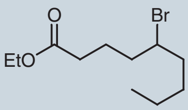
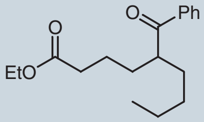
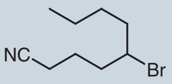
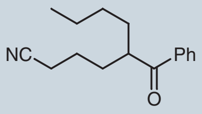
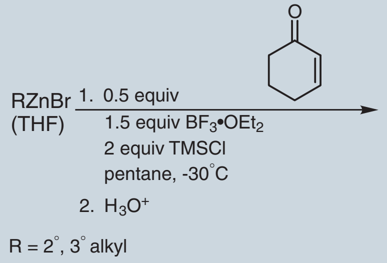
Bromide	PhCOCl (equiv)	Product	Yield (%)
	0.7		75
	0.9		84
	0.7		99
	1.0		95

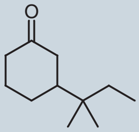
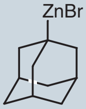
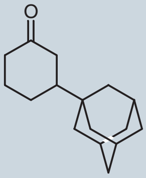
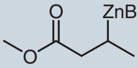
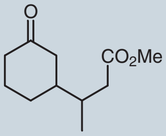
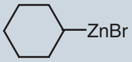
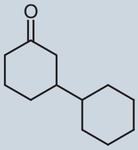
Table 3. Functionalized Secondary Alkylzinc Bromides

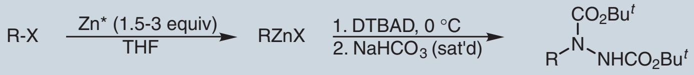
Bromide	PhCOCl (equiv)	Product	Yield (%)
	0.7		75
	0.7		54
	0.7		60



eq 5

Table 4. 1,4-Addition of Secondary and Tertiary Alkylzinc Bromides to Cyclohexenone without a Copper Catalyst

RZnBr	Product	Yield (%)
		74
		54
		51
		73



1a-k **2a-k**

1a-i,k, X = Br; **1j,** X = I

eq 6

3. Synthesis of Specialized Polymers and New Materials via Rieke® Metals

3.1. Formation of Polyarylenes Mediated by Rieke® Zinc

Polyarylenes, such as poly(*para*-phenylenes) (PPP) and polythiophenes (PTh), are a class of conjugated polymers with electrical conductivity and other interesting physical properties.[22] The synthetic methodology for the formation of polyarylenes includes electrochemical polymerization of aromatic compounds, oxidative polymerization of benzene or thiophene with an oxidant such as FeCl$_3$, and catalytic cross-coupling polymerization of Grignard reagents. A facile synthesis of polyarylenes was recently achieved in our laboratories by utilizing Rieke® zinc (Zn*).[23] Rieke® zinc was found to react chemoselectively with dihaloarenes to yield monoorganozinc arenes quantitatively (**Scheme 4**). Significantly, no bis(halozincio)arene was formed. The organozinc intermediate was polymerized by addition of a catalytic amount of Pd(PPh$_3$)$_4$ (0.2 mol %) to give a quantitative yield of the polyarylene (PPP or PTh). The method has been extended to synthesize a series of polymeric 3-substituted thiophenes such as poly(3-methylthiophene), poly(3-phenylthiophene), and poly(3-cyclopentylthiophene) (**Scheme 5**). The advantages of this method for the synthesis of polyarylenes include the quantitative selectivity of Zn* for dihaloarenes, the use of only a very small amount of catalyst (which makes the separation of the polymer easier), mild reaction conditions, and high yields of the resulting polymers.

3.2. Regiocontrolled Synthesis of Poly(3-alkylthiophenes) and Related Polymers Mediated by Rieke® Zinc

Regioregular head-to-tail (HT) poly(3-alkylthiophenes) (P3ATs) are one of the most highly conducting groups of polymers, and have recently been synthesized in our laboratories[24] and elsewhere.[25] Our synthesis involves a catalytic cross-coupling polymerization of a 2-bromo-5-(bromozincio)-3-alkylthiophene (**4**), which is generated by the regioselective oxidative addition of Zn* to 2,5-dibromo-3-alkylthiophene (**3**) (**Scheme 6**). The synthesis has been extended to a fully regiocontrolled synthesis, mediated by Rieke® zinc, of a series of poly(3-alkylthiophenes) with different percentages of head-to-tail linkages in the polymer chain.[26] The organozinc intermediate **4** is polymerized, either by Ni(DPPE)Cl$_2$ to afford a completely regioregular HT P3AT (**5**), or by Pd(PPh$_3$)$_4$ to afford a totally regiorandom HT-HH P3AT (**6**). The regioregular HT P3AT has a longer electronic absorption wavelength,[27] a smaller band gap (1.7 eV), and a much higher iodine-doped film electrical conductivity (~10^3 S•cm^{-1}) than those of the regiorandom P3AT (band gap: 2.1 eV, iodine-doped film conductivity: ~5 S•cm^{-1}). The cast film of regioregular P3AT is a flexible, crystalline, self-ordered, bronze-colored film with a metallic luster, whereas that of the regiorandom polymer is an amorphous, orange, transparent film.

Scheme 7 depicts a novel, regiocontrolled synthesis of poly(3-alkylthio-thiophenes) using Rieke® zinc.[26] This synthesis is one of very few examples of a regiospecific synthesis for this class of polymers.

4. Rieke® Magnesium

Perhaps the most widely known and used organometallic reagent is the Grignard reagent. Although commonly thought to be completely general, there are many organic halides that do not form Grignard reagents with ordinary magnesium turnings. The use of Rieke® magnesium dramatically increases the range of Grignard reagents that are possible.[28-30] Also, in many cases, it allows Grignard formation to occur at a lower temperature, thus avoiding decomposition or unwanted additions.[31] The high reactivity of Rieke® magnesium is demonstrated by its reaction with bromobenzene in a few minutes at -78 °C.[32] Chlorobenzene reacts even at 0 °C. Most dramatic is the ability to generate the Grignard reagent from fluorobenzene. Rieke® magnesium can be used successfully with other halides, which fail to react or give poor yields with standard turnings, including aryl halides containing ether groups and many types of heterocyclic halides. The advantages of low-temperature Grignard preparation include many benzylic systems, which tend to yield homocoupled products at room temperature or above. Another simple example involves 1-bromo-3-phenoxypropane. Although the Grignard reagent is easy to generate at room temperature, it eliminates the phenoxy group by an S$_N$2 reaction to generate cyclopropane. This reaction is, in fact, a standard way to prepare cyclopropane as the cyclization cannot be stopped. However, by using the highly reactive magnesium, the Grignard can be prepared at -78 °C, where it does not cyclize and can be reacted with a wide range of electrophiles.

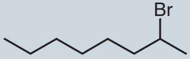
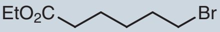
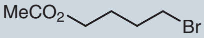
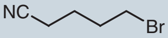
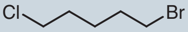
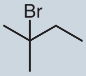
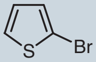
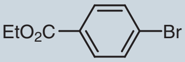
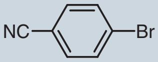
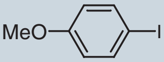
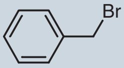
The highly reactive magnesium can be used to prepare di-Grignard reagents from dihalides. As with zinc, the reactive magnesium demonstrates unusual selectivity and can be used to cleanly prepare mono-Grignard reagents from dihalides under the proper conditions. This is in sharp contrast to ordinary turnings, which, for most dihalides, give a mixture of mono-Grignard, di-Grignard, and unreacted dihalide.[30,33]

Recent studies have demonstrated that Rieke® magnesium will readily form substituted (2-butene-1,4-diyl)magnesium complexes from a wide range of substituted 1,3-butadienes.[34] These complexes,[35-39] as well as the corresponding calcium, barium, and strontium complexes,[40,41] react with a wide range of electrophiles to produce complex acyclic, cyclic, and spirohydrocarbons in high yields. The mode of addition depends on whether the electrophile is soft or hard, as illustrated in **Schemes 8** and **9**.

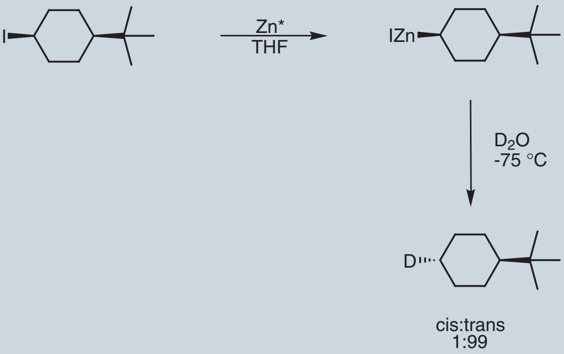
5. Summary

With the advent of highly reactive zinc and magnesium, a number of novel organometallic reagents have been prepared. These reagents allow the facile construction of complex and highly functionalized molecules. The convenient availability of these metals and many organometallic reagents sets the stage

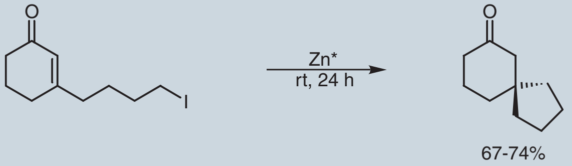
Table 5. The Amination of Organozinc Halides[a,b]

	Starting Halide	Zn*:**1**	Product NMR/Isolated Yield
1a		2:1	**2a**, 94/94
1b		2:1	**2b**, 95/90
1c		2:1	**2c**, 90/90
1d		2:1	**2d**, 94/90
1e		2:1	**2e**, 90/81
1f		2:1	**2f**, 73/75
1g		1.5:1	**2g**, 80/80
1h		3:1	**2h**, -/40
1i		3:1	**2i**, 65/66
1j		3:1	**2j**, 55/-
1k		1.5:1	**2k**, 90/90

[a] Reaction temperature: 25 °C (**1a-g,j,k**); 70 °C (**1h,i**).
[b] Reaction time: 3 h (**1a-c,e,f,h-j**); 1 h (**1d**); 0.5 h (**1g,k**)

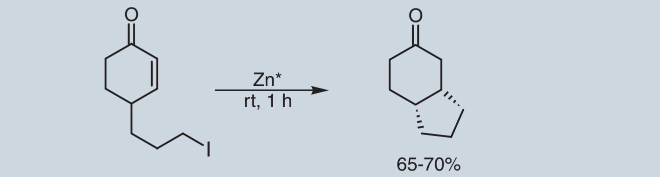


eq 7

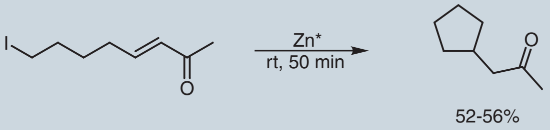


eq 8

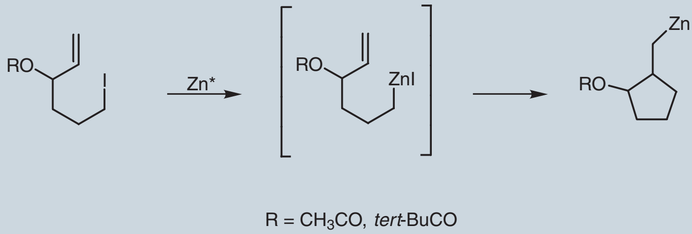
for further advances in both zinc and magnesium chemistry.



eq 9



eq 10



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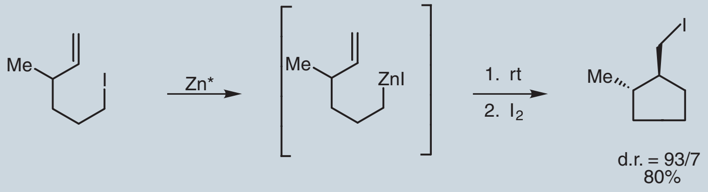

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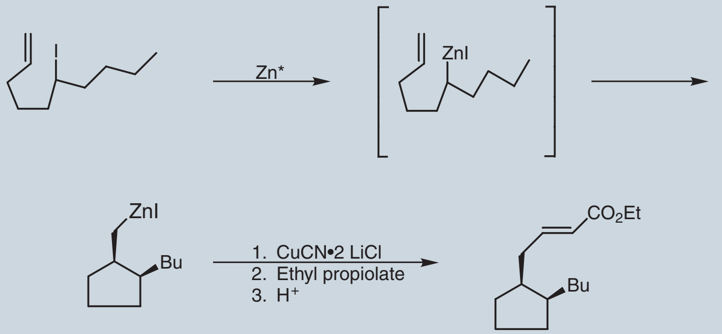
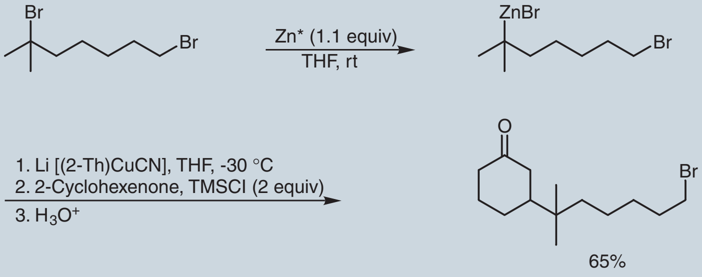


Scheme 2. Olefinic π-Bond Insertion into the Carbon–Zinc Bond.



Scheme 3. Selectivity in the Reaction of Zn* with Dibromoalkanes.

6. References and Notes

(†) This account is based partially on the review cited in reference 1(d).

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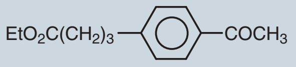
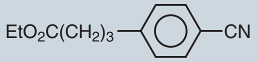
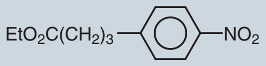
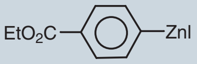
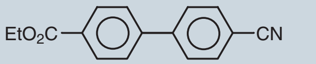
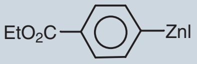
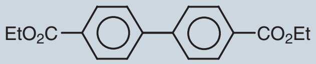
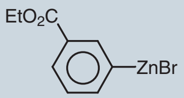
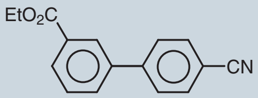
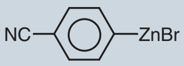
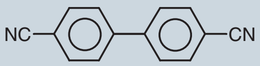
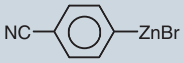
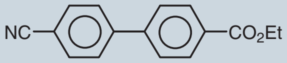
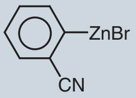
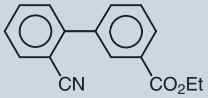
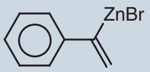
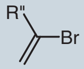
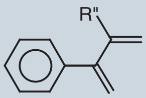
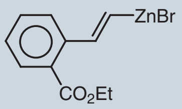
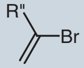
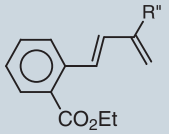
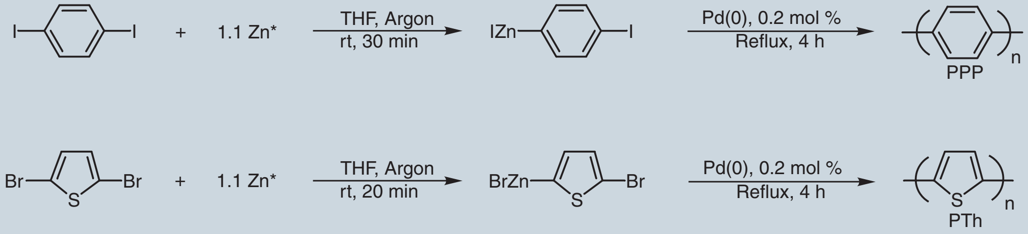
Table 6. Coupling Reactions of RZnX with Aryl and Vinyl Halides Catalyzed by $Pd(PPh_3)_4$

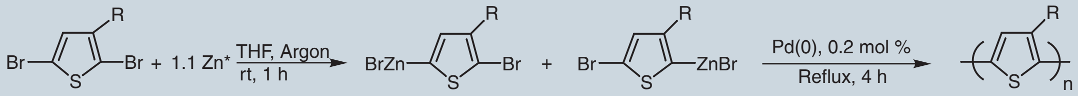
$$\mathrm{RZnX} + \mathrm{R'Y} \xrightarrow[\mathrm{THF}]{5\ \mathrm{mol}\ \%\ \mathrm{Pd(PPh_3)_4}} \mathrm{RR'}$$

Entry	RZnX	R'Y	Product	Yield (%)[a]
1	$EtO_2C(CH_2)_3ZnBr$	*p*-$BrC_6H_4COCH_3$		86
2	$EtO_2C(CH_2)_3ZnBr$	*p*-BrC_6H_4CN		93
3	$EtO_2C(CH_2)_3ZnBr$	*p*-$BrC_6H_4NO_2$		90
4		*p*-BrC_6H_4CN		80
5		*p*-$IC_6H_4CO_2Et$		94
6		*p*-BrC_6H_4CN		82
7		*p*-BrC_6H_4CN		95
8		*p*-$IC_6H_4CO_2Et$		82
9		*m*-$BrC_6H_4CO_2Et$		93
10 11				R" = H, 85 R" = CH_3, 86
12 13				R" = H, 95 R" = CH_3, 93

[a] Isolated yields.

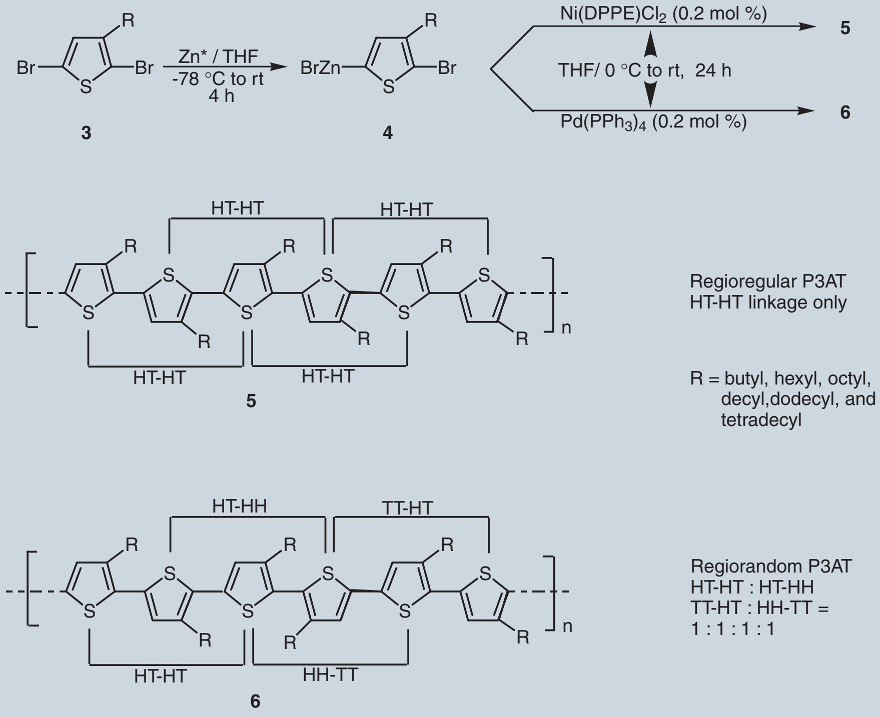


Scheme 4. Rieke® Zinc Mediated Synthesis of Polyarylenes.

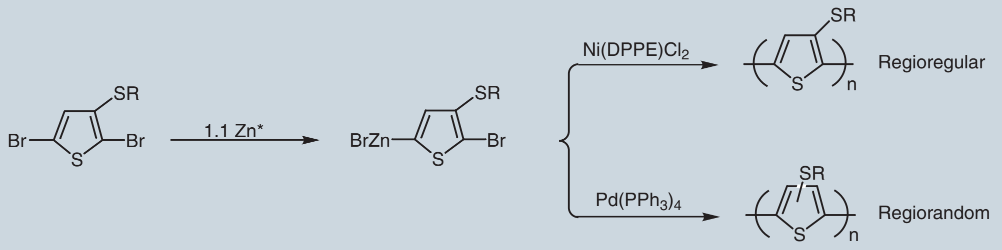


R	Regioselectivity (%)		Yield (%)
CH_3	80	20	98
Cyclopentyl	71	29	96
Phenyl	66	34	98

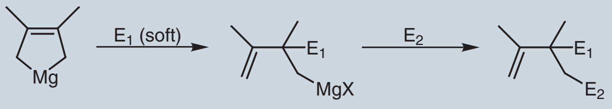
Scheme 5. Synthesis of Poly(3-substituted thiophenes) Mediated by Rieke® Zinc.



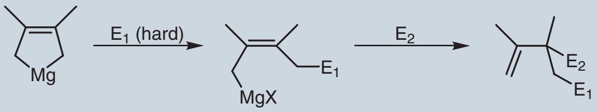
Scheme 6. Regiocontrolled Synthesis of Poly(3-alkylthiophenes) Mediated by Rieke® Zinc.



Scheme 7. Regiocontrolled Synthesis of Poly(3-alkylthio-thiophenes) Mediated by Zn*.



Scheme 8. Reaction of a Soft Electrophile with (2,3-Dimethyl-2-butene-1,4-diyl)magnesium.



Scheme 9. Reaction of a Hard Electrophile with (2,3-Dimethyl-2-butene-1,4-diyl)magnesium.

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About the Author

Reuben D. Rieke grew up in Fairfax, Minnesota. He received a Bachelor of Chemistry degree from the University of Minnesota–Minneapolis, doing undergraduate research with Professor Wayland E. Noland. He received a Ph.D. from the University of Wisconsin–Madison in 1966 under the direction of Professor Howard E. Zimmerman. He then did postgraduate work with Professor Saul Winstein at UCLA. He taught at the University of North Carolina at Chapel Hill from 1966 to 1976, and at North Dakota State University in Fargo from 1976 to 1977. He is currently Howard S. Wilson Professor of Chemistry at the University of Nebraska–Lincoln. His present research interests include the development and utilization of novel organometallic reagents derived from highly reactive metals. He is also interested in the synthesis of novel polymers using highly reactive metals. In 1991, Dr. Rieke and his wife, Loretta, founded Rieke Metals, Inc.

Sigma-Aldrich Laboratory Equipment

Summer 2000 Spotlight

Corning® System 45
Peptide Vessels

Pharmaceutical Chemistry Equipment

Peptide Synthesis Vessels

Aldrich Flask Throne

Table-Top Buchner Funnels

Electronic Chilling/Heating Plates

Coated Multiwell Plates

Glove Boxes and Accessories

Aldrich Custom Glassware

ALDRICH

About Corning® System 45 Glassware

- ◆ Eliminates grease, ground glass, and frozen joints
- ◆ Requires only a simple twist to make a perfect, gas-tight seal
- ◆ Wide standard openings permit easy access to funnel contents

PEPTIDE SYNTHESIS PRODUCTS

Peptide Synthesis Vessels with removable fritted disc

Cylindrical style vessel has a 2mm PTFE valve at the top. The 32mm threaded bottom valve assembly incorporates System 45 technology. The coarse fritted disc is easily removed from the PTFE adapter for cleaning and/or replacement. PTFE top and bottom valves require ¼ turn to open or close.

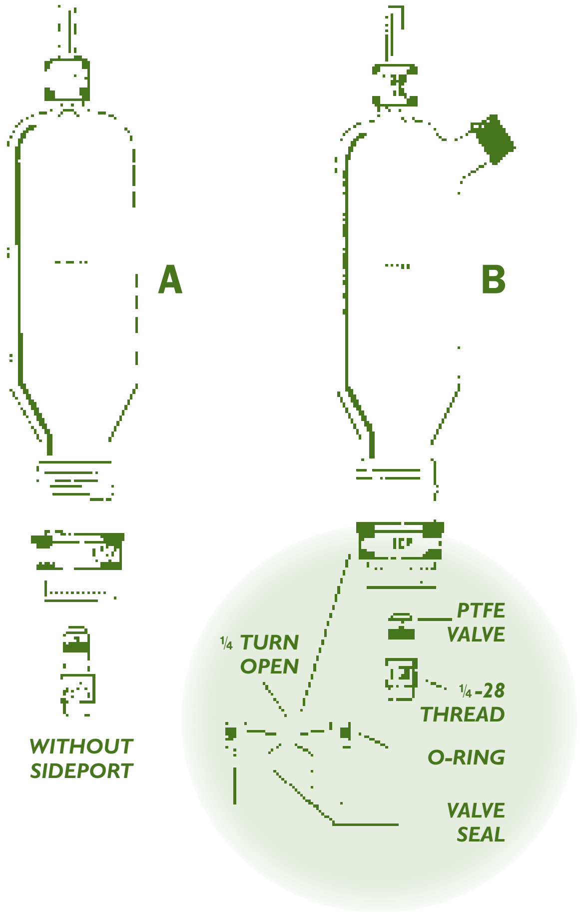
Valve stems have a ¼-28 internal thread in the stem which allows a variety of adapters to be used. For male ¼-28 and male Luer adapters, see Cat. Nos. Z41,741-6 and Z41,742-4 below. (Corning 46806)

A. Without sideport

Approx. cap. (mL)	L x diam. (mm)	Cat. No.
20	50 x 28	**Z41,899-4**
60	100 x 32	**Z41,900-1**
125	105 x 45	**Z41,902-8**
250	155 x 51	**Z41,903-6**
500	220 x 70	**Z41,904-4**

B. With GL-18 threaded sideport

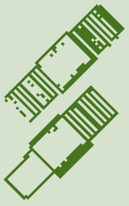
Approx. cap. (mL)	L x diam. (mm)	Cat. No.
20	50 x 28	**Z41,856-0**
60	100 x 32	**Z41,885-4**
125	105 x 45	**Z41,886-2**
250	155 x 51	**Z41,887-0**
500	220 x 70	**Z41,888-9**



Threaded vessel adapters

Teflon PTFE. (Corning 42290)

¼-28 Male to ¼-28 male	**Z41,741-6**
¼-28 Male to male Luer	**Z41,742-4**



Vessels with sideport and removable fritted disc

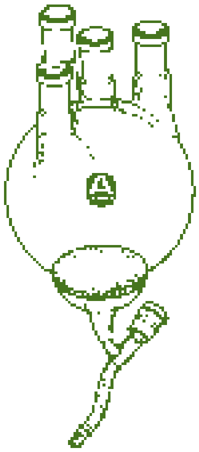
Cylindrical style vessel has a 2mm PTFE valve at the top, with a ₸14/20 outer joint sideport. The 32mm threaded bottom valve assembly incorporates System 45 technology.

The coarse fritted disc is easily removed from the PTFE adapter for cleaning and/or replacement. PTFE bottom valve requires ¼ turn to open or close. Valve stems have a ¼-28 internal thread in the stem which allows a variety of adapters to be screwed into place. For male ¼-28 and male Luer adapters, see Cat. No. Z41,741-6 and Z41,742-4 on previous page. (Corning 46808)

Cap. (mL)	Approx. L x diam. (mm)	Cat. No.
20	50 x 28	**Z41,910-9**
60	100 x 32	**Z41,911-7**
125	105 x 45	**Z41,912-5**
250	155 x 51	**Z41,913-3**
500	220 x 70	**Z41,914-1**

Aldrich solid-phase peptide synthesis flasks

Has three ₸24/40 side joints and a center joint that varies in size according to the capacity of the flask. Coarse frit (25 to 50µm) and PTFE Rotaflo stopcock permit rapid filtration and resin washing.



Cap. (L)	Center ₸ joint	Cat. No.
1	24/40	**Z16,229-9**
5	34/45	**Z16,230-2**
12.1	45/50	**Z16,228-0**

Aldrich Flask Throne

Provides safe, hands-free support for round-bottom flasks sizes 10 to 22L.

Designed by Aldrich chemists to prevent the costly breakage of large round-bottom flasks during washing and cleaning operations or when transferring product from the flask.

A slotted hole provides secure support while tipping flask joint downward to dump contents. 19 L x 19 W x 10in. H. (Flask, tray, and spatula not included).

- Prevents flask breakage, loss of product, and chemical exposure
- For benchtop use or inside fume hoods to transfer product from flask to bottles or trays
- Pays for itself with the cost of just one broken flask
- Chemically-resistant LDPE

Z41,156-6

POLYETHYLENE BUCHNER FUNNELS

Porous Filter Plate Funnels

Large capacity, PE funnels are a one piece design with a choice of fixed or removable Fritware porous filter plates supported by a multiple ring grid.

- Filter plates are made of HDPE 6.4mm ($\frac{3}{8}$in.) thick
- A non-porous ring at the periphery of the plate which seals filter paper when used
- Vacuum connector accepts 12.7mm ($\frac{3}{8}$in.) i.d. tubing
- Available with medium or coarse porous filter plates
- Use below 52°C (125°F).

Perforated Filter Plate Funnels

These funnels are also available with fixed or removable perforated filter plates.

- Filter plates are made of HDPE 4.8mm ($\frac{3}{16}$in.) thick with 4.8mm perforations on 11mm ($\frac{7}{16}$in.) centers
- The fixed version is for coarse filtration or use with cloth or paper filter
- The removable filter plate can be used in precious metals recovery
- Use below 52°C (125°F).

Filter Paper Discs

Fit table top Buchner funnels for fast filtering. Paper has a rough crepe surface with thickness: 0.25mm, weight: 70g/m^2, flow rate: 235mL/min, retention: 24µm, and wet strength: 25cm of H_2O.

10.25in. i.d. Buchner Funnels

Overall H: 178mm (7in.), rim to plate: 127mm (5in.).

Porosity	Plate	Cat. No.
Coarse	Fixed	**Z10,439-6**
Medium	Fixed	**Z42,026-3**
Coarse	Removable	**Z42,027-1**
Medium	Removable	**Z42,029-8**
Perforated	Fixed	**Z11,621-1**
Perforated	Removable	**Z42,030-1**
Filter paper discs		**Z17,757-1**

18in. i.d. Buchner Funnels

Overall H: 292mm (11.5in.), Rim to plate: 229mm (9in.).

Porosity	Plate	Cat. No.
Coarse	Fixed	**Z10,441-8**
Medium	Fixed	**Z42,035-2**
Coarse	Removable	**Z42,036-0**
Medium	Removable	**Z42,037-9**
Perforated	Fixed	**Z11,623-8**
Perforated	Removable	**Z42,038-7**
Filter paper discs		**Z17,759-8**

24in. i.d. Buchner Funnels

Overall H: 330mm (13in.), Rim to plate: 267mm (10.25in.).

Porosity	Plate	Cat. No.
Coarse	Fixed	**Z10,442-6**
Medium	Fixed	**Z42,042-5**
Coarse	Removable	**Z42,043-3**
Medium	Removable	**Z42,044-1**
Perforated	Fixed	**Z11,624-6**
Perforated	Removable	**Z42,046-8**
Filter paper discs		**Z17,760-1**

36in. i.d. Buchner Funnels

Overall H: 375mm (14.75in.), Rim to plate: 375mm (12in.).

Porosity	Plate	Cat. No.
Coarse	Fixed	**Z42,050-6**
Medium	Fixed	**Z42,051-4**
Coarse	Removable	**Z42,052-2**
Medium	Removable	**Z42,053-0**
Perforated	Fixed	**Z42,054-9**
Perforated	Removable	**Z42,055-7**
Filter paper discs		**Z42,060-3**

TABLE-TOP BUCHNER FUNNELS

316L Stainless Steel Buchner Funnels

For Pharmaceutical, High Purity, and GMP Applications And With Solvents That Degrade Polypropylene Funnels

- Heavy gauge, electropolished stainless steel
- Easy to remove perforated plate for thorough cleaning
- Welded seams, ½ in. o.d. hose connector
- Autoclavable

Funnel o.d. (cm)	Ht. plate to top (cm)	Cat. No.
25	12.7	**Z24,557-7**
50	25.4	**Z24,558-5**

Whatman Filter Paper Circles

Grade 3.

Diam. (cm)	Cat. No.
24	**Z24,048-6**
50	**Z24,562-3**

HEATING & COOLING EQUIPMENT

Echotherm Digital Electronic Chilling/Heating Plate

Chill and heat samples from -10 to 90.0°C with precise control in your lab or in the field. The plate surface will reach below 0°C in under two minutes and will heat to 37°C in less time. Small, compact size uses very little bench space. Overall dim.: 6.5 W x 8.75 D x 3.5in. H. Plate dim.: 2.875 x 4.375in.

- Chill and heat 96-well plates and centrifuge tubes
- No CFCs, Peltier based cooling
- Digital control to 1°C from -10 to 90°C
- RS232 I/O port for control and data collection
- Count down timer (up to 30 days) with alarm and user settable Auto-Off
- Universal power supply: 100, 115, or 230 VAC, 50/60 Hz.
- UL, CSA, and CE approved

Plug type	Cat. No.
US	**Z42,440-4**
UK	**Z42,441-2**
Euro	**Z42,442-0**

Echotherm Covers

For 96-well plates
Z40,106-4

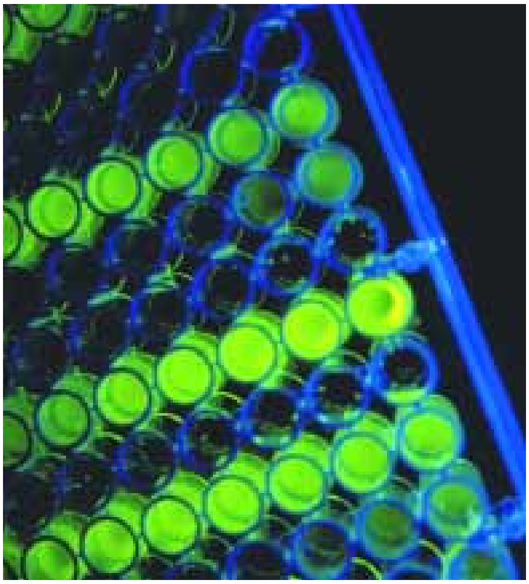
For blocks
Z40,105-6

Aluminum Blocks for Centrifuge Tubes

Fits 0.2mL tube
Z40,101-3

Fits 0.5mL tube
Z40,102-1

Fits 1.5mL tube
Z40,104-8



Coated Multiwell Plates for High Throughput Screening

Using proprietary coupling technologies, SIGMA has developed streptavidin coated microplates configured expressly for high throughput screening applications. These 96-well, flat-bottom polystyrene plates are coated on the bottom and wall up to a working volume of 100µL.

- Low well-to-well and plate-to-plate variability
- Binding capacity: 20–25pmoles biotin/well
- Blocked to prevent non-specific binding up to 200µL volume

Color	Cat. No.
Clear	**Z38,246-9**
White	**Z38,247-7**
Black	**Z38,248-5**

PRODUCTS FOR **CRITICAL ENVIRONMENTS**

PLAS-LABS Basic Glove Boxes

Single station. These economical units are lightweight and portable, and are engineered to fit general isolation applications in chemical, pharmaceutical, bio-tech, and waste management laboratories of universities and industry. Dim.: inside—41 W x 28 D x 26in. H; outside—55 W x 35 D x 27in. H. Dimensions include transfer chamber. Wt = 150lb.

- Clear, one piece, acrylic top with molded white base
- Double layered, closed cellular neoprene gaskets for airtight seal between top and base
- Adjustable SS clamps compensate for wear
- Ambidextrous Hypalon gloves with SS O-rings
- Transparent transfer chamber (12L x 11in. i.d.) with adjustable vacuum gauge
- Three-tier, suspended (sliding) shelves are spaced 7in. apart and hold 330 culture plates 18H x 18W x 10in D overall. Shelves are made of 0.375in. clear acrylic
- Four purge valves—two on transfer chamber, two on main chamber
- Multiple electrical outlet strip—UL, CSA, CE approved

Plug type	Cat. No.
US	**Z26,987-5**
UK	**Z34,104-5**
Euro	**Z34,108-8**

PLAS-LABS Nitrogen Dry Boxes

Single station. Designed for working in Nitrogen, Argon, and Plasma type atmospheres. Dim.: inside—41 W x 28 D x 26in. H; outside—55 W x 35 D x 38in. H. Dimensions include transfer chamber. Wt = 250lb. Similar to the basic glove box, with additional features.

- Gas-drying train with DesiSphere desiccating canisters. Self-sealing quick-disconnects enable change of drying train without disturbing internal atmosphere
- Two vacuum/pressure pumps—one for transfer chamber, one for drying train to speed purging
- Fluorescent light system with illuminated controls

Plug type	Cat. No.
US	**Z26,992-1**
UK	**Z34,109-6**
Euro	**Z34,111-8**

Plas-Labs Glove Box Accessories & Supplies

Anti-Static Work Station Ionizer

Effectively eliminates all static charges within 36 inches of the unit. Dim.: 4.25 W x 2.5 D x 5.0in. H. Input voltage: 110/220 VAC; 50–60 Hz, CE compliant.

Plug type	Cat. No.
US	**Z42,443-9**
UK	**Z42,444-7**
Euro	**Z42,445-5**

Catalyst Heater Unit *(not shown)*

For use with Nitrogen dry box to remove trace amounts of oxygen and to maintain incubation temperature levels of 35° to 37°C. CE compliant.

Plug type	Volts	Cat. No.
US	120	**Z27,311-2**
UK	230	**Z34,114-2**
Euro	230	**Z34,115-0**

Digital Humidity Indicator

Measures internal glove box humidity. Includes: programmable logic controller, humidity sensor with 24 inch cable, two adjustable alarm relays (one audible alarm), on/off switch, and pilot light. Dim.: Outside—6.9 W x 9.0 D x 4.5in. H. CE compliant.

- Input Voltage: 115/230 VAC; 50–60 Hz
- Humidity range: 0–100%
- Accuracy: 2% RH (0–90% RH)
  3% RH (90–100% RH)
- Operating temperature: 23–131°F (-5–55°C)

Plug type	Cat. No.
US	**Z42,450-1**
UK	**Z42,452-8**
Euro	**Z42,453-6**

Digital Pressure Indicator

Measures internal glove box pressure. Includes: programmable logic controller with large, display, differential pressure sensor, adjustable audible alarm, on/off switch, pilot light, and 24in. of ⅛in. i.d. PVC tubing. Dim.: Outside—6.9 W x 9.0 D x 4.5in. H. CE compliant.

- Input Voltage: 115/230 VAC; 50–60 Hz
- Range: ±2in. water column
- Accuracy: 1% of full scale
- Operating temperature: 32–125°F (0–52°C)
- Barbed hose connections

Plug type	Cat. No.
US	**Z42,446-3**
UK	**Z42,447-1**
Euro	**Z42,449-8**

Controlled Purge System

Maintains a slight positive pressure in any Plas-Labs glove box. Controls nitrogen (inert) gas consumption by regulating flow rate, while an integral humidity sensor continually monitors internal humidity level.

Includes: programmable logic controller, humidity sensor, black metal housing, two manually adjustable high and low gas flow knobs, audible alarm, timer, solenoid valve, and stainless steel compression fittings for gas line hook-up. A pressure relief valve (Z42,459-5) is required for this system. Dim.: 8.25 W x 9.00 D x 7.50in. H. CE compliant.

- Input Voltage: 115/230 VAC; 50–60 Hz
- Humidity range: 0–100%
- Accuracy: 0.5% for full scale
- Gas connections: ⅛ NPT stainless steel compression fittings
- Gas inlet pressure: 4 psi

Plug type	Cat. No.
US	**Z42,454-4**
UK	**Z42,455-2**
Euro	**Z42,456-0**

Pressure Relief Valve

Z42,459-5

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Sigma-Aldrich Fine Chemicals is the development and manufacturing division of Sigma-Aldrich, Inc

Rieke® Organozinc Reagents

Available Exclusively from Aldrich!

Organozinc compounds, first prepared by Frankland in 1848,[1] are used extensively in organic synthesis today. Interestingly, the choice of preparative route to organozinc reagents of the type RZnX (R=alkyl, aryl; X=halide)[2-5] does play an important role in the reactivity and stability of these compounds. Aldrich now offers a comprehensive line of Rieke® Organozinc Reagents that are stable as solutions in tetrahydrofuran. These reagents have different reactivity and selectivity properties than the analogous Grignard Reagents, and are employed in cross-coupling reactions,[6-8] Michael additions, and electrophilic amination reactions.[9] If you do not see the compound you need, please let us know. Your new product suggestions are always welcome!

References: (1) Frankland, E. *Liebigs Ann. Chem.* **1848**, *71*, 171. (2) Erdik, E. *Organozinc Reagents in Organic Synthesis*; CRC Press, Inc.: Boca Raton, FL, 1996; Aldrich Catalog Number Z28,012-7. (3) Rieke, R. D.; Hanson, M. V. *Tetrahedron* **1997**, *53*, 1925. (4) Hanson, M. V. et al. *Tetrahedron Lett.* **1994**, *35*, 7205. (5) Cintas, P. *Activated Metals in Organic Synthesis*; CRC Press, Inc.: Boca Raton, FL, 1993; Aldrich Catalog Number Z24,607-7. (6) Miller, J. A.; Farrell, R. P. *Tetrahedron Lett.* **1998**, *39*, 7275. (7) Zhu, L. et al. *J. Org. Chem.* **1991**, *56*, 1445. (8) Negishi, E. et al. *ibid.* **1977**, *42*, 1821. (9) Velarde-Ortiz, R. et al. *Tetrahedron Lett.* **1998**, *39*, 9157.

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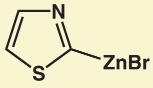
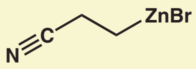
49,940-4
$C_3H_2BrNSZn$



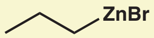
50mL

49,790-8
C_3H_4BrNZn



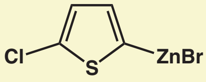
50mL

49,937-4
C_3H_7BrZn



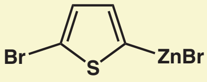
50mL

49,784-3
$C_4H_2BrClSZn$



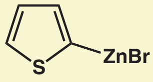
50mL

49,766-5
$C_4H_2Br_2SZn$



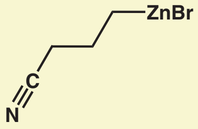
50mL

49,941-2
C_4H_3BrSZn



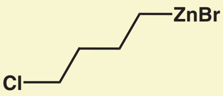
50mL

49,796-7
C_4H_6BrNZn



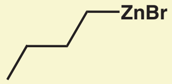
50mL

49,777-0
$C_4H_8BrClZn$



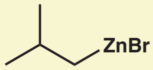
50mL

49,774-6
C_4H_9BrZn



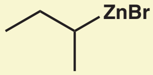
50mL

49,896-3
C_4H_9BrZn



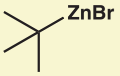
50mL

49,773-8
C_4H_9BrZn



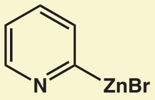
50mL

49,775-4
C_4H_9BrZn



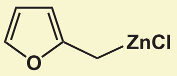
50mL

49,938-2
C_5H_4BrNZn



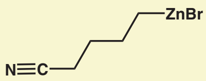
50mL

53,526-5 New!
C_5H_5ClOZn



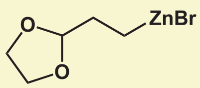
50mL

49,789-4
C_5H_8BrNZn



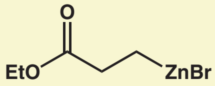
50mL

53,368-8 New!
$C_5H_9BrO_2Zn$



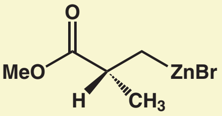
50mL

49,852-1
$C_5H_9BrO_2Zn$



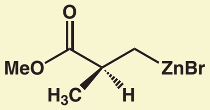
50mL

49,949-8
$C_5H_9BrO_2Zn$



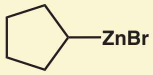
50mL

49,881-5
$C_5H_9BrO_2Zn$



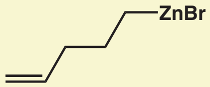
50mL

49,804-1
C_5H_9BrZn



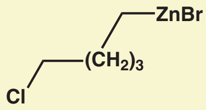
50mL

49,907-2
C_5H_9BrZn



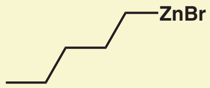
50mL

49,781-9
$C_5H_{10}BrClZn$



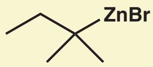
50mL

49,928-5
$C_5H_{11}BrZn$



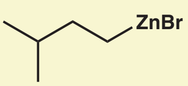
50mL

49,890-4
$C_5H_{11}BrZn$



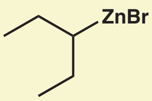
50mL

49,889-0
$C_5H_{11}BrZn$



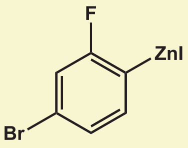
50mL

49,927-7
$C_5H_{11}BrZn$



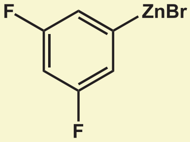
50mL

53,524-9 New!
$C_6H_3BrFIZn$



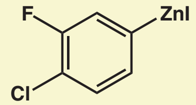
50mL

53,372-6 New!
$C_6H_3BrF_2Zn$



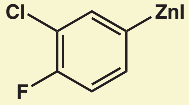
50mL

52,450-6
$C_6H_3ClFIZn$



50mL

49,778-9
$C_6H_3ClFIZn$



50mL

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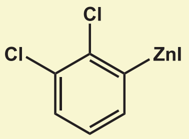
53,521-4 New!

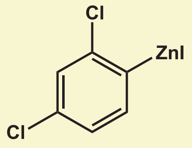
$C_6H_3Cl_2IZn$



50mL

53,522-2 New!

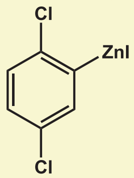
$C_6H_3Cl_2IZn$



50mL

53,523-0 New!

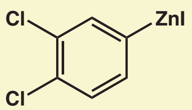
$C_6H_3Cl_2IZn$



50mL

49,806-8

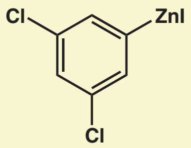
$C_6H_3Cl_2IZn$



50mL

49,807-6

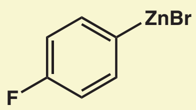
$C_6H_3Cl_2IZn$



50mL

49,864-5

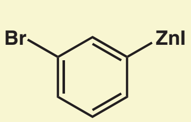
C_6H_4BrFZn



50mL

49,764-9

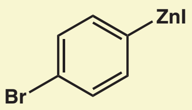
C_6H_4BrIZn



50mL

49,765-7

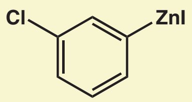
C_6H_4BrIZn



50mL

49,782-7

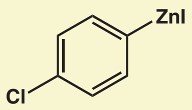
C_6H_4ClIZn



50mL

49,783-5

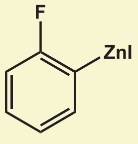
C_6H_4ClIZn



50mL

53,351-3 New!

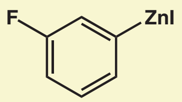
C_6H_4FIZn



50mL

52,048-9

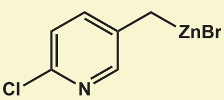
C_6H_4FIZn



50mL

53,347-5 New!

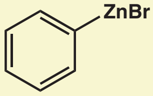
$C_6H_5BrClNZn$



50mL

52,471-9

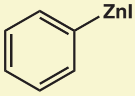
C_6H_5BrZn



50mL

49,933-1

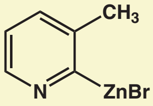
C_6H_5IZn



50mL

49,897-1

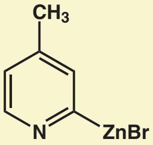
C_6H_6BrNZn



50mL

49,899-8

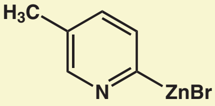
C_6H_6BrNZn



50mL

49,900-5

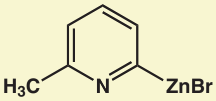
C_6H_6BrNZn



50mL

49,901-3

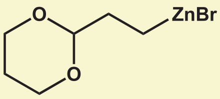
C_6H_6BrNZn



50mL

53,355-6 New!

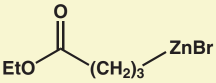
$C_6H_{11}BrO_2Zn$



50mL

49,849-1

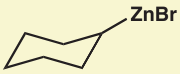
$C_6H_{11}BrO_2Zn$



50mL

49,803-3

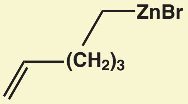
$C_6H_{11}BrZn$



50mL

49,873-4

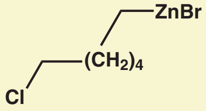
$C_6H_{11}BrZn$



50mL

49,779-7

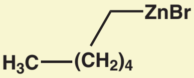
$C_6H_{12}BrClZn$



50mL

49,876-9

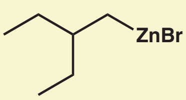
$C_6H_{13}BrZn$



50mL

49,854-8

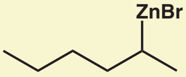
$C_6H_{13}BrZn$



50mL

49,874-2

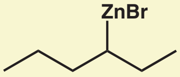
$C_6H_{13}BrZn$



50mL

49,875-0

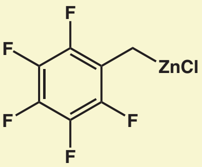
$C_6H_{13}BrZn$



50mL

49,906-4

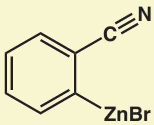
$C_7H_2ClF_5Zn$



50mL

52,023-3

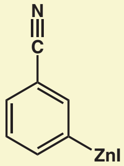
C_7H_4BrNZn



50mL

49,794-0

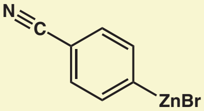
C_7H_4INZn



50mL

52,029-2

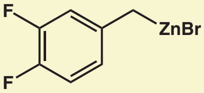
C_7H_4BrNZn



50mL

52,169-8

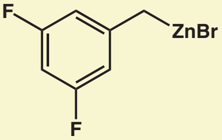
$C_7H_5BrF_2Zn$



50mL

49,947-1

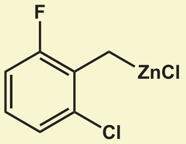
$C_7H_5BrF_2Zn$



50mL

53,525-7 New!

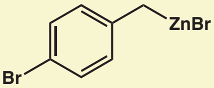
$C_7H_5Cl_2FZn$



50mL

49,946-3

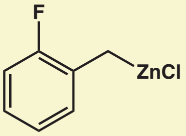
$C_7H_6Br_2Zn$



50mL

49,858-0

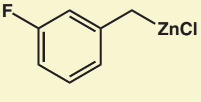
C_7H_6ClFZn



50mL

49,859-9

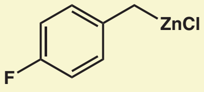
C_7H_6ClFZn



50mL

49,860-2

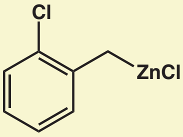
C_7H_6ClFZn



50mL

49,756-8

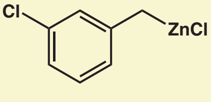
$C_7H_6Cl_2Zn$



50mL

49,757-6

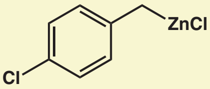
$C_7H_6Cl_2Zn$



50mL

49,776-2

$C_7H_6Cl_2Zn$



50mL

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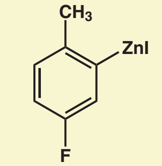
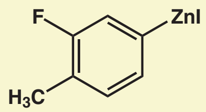
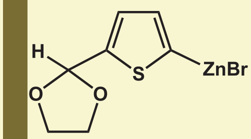
49,862-9
C_7H_6FIZn


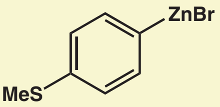
50mL

49,861-0
C_7H_6FIZn


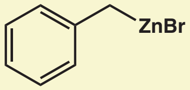
50mL

53,369-6 New!
$C_7H_7BrO_2SZn$


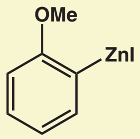
50mL

52,022-5
C_7H_7BrSZn


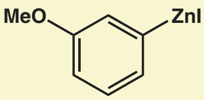
50mL

49,751-7
C_7H_7BrZn


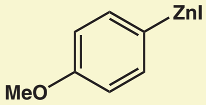
50mL

49,882-3
C_7H_7IOZn


50mL

49,883-1
C_7H_7IOZn


50mL

49,885-8
C_7H_7IOZn


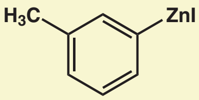
50mL

49,942-0
C_7H_7ISZn

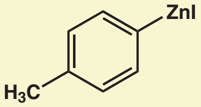

50mL

49,893-9
C_7H_7IZn

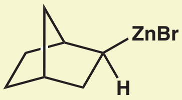

50mL

49,894-7
C_7H_7IZn


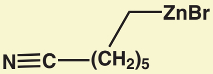
50mL

49,895-5
C_7H_7IZn


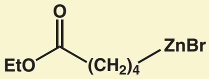
50mL

49,905-6
$C_7H_{11}BrZn$


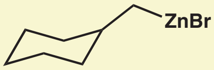
50mL

49,792-4
$C_7H_{12}BrNZn$


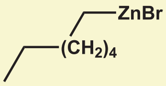
50mL

49,851-3
$C_7H_{13}BrO_2Zn$


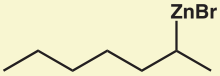
50mL

49,802-5
$C_7H_{13}BrZn$


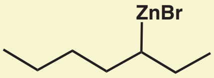
50mL

53,327-0 New!
$C_7H_{15}BrZn$


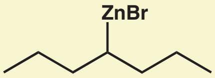
50mL

49,869-6
$C_7H_{15}BrZn$


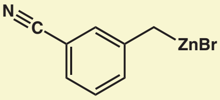
50mL

49,871-8
$C_7H_{15}BrZn$


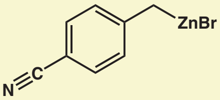
50mL

49,872-6
$C_7H_{15}BrZn$


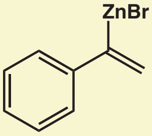
50mL

51,737-2
C_8H_6BrNZn


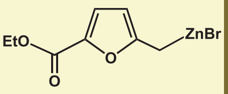
50mL

51,738-0
C_8H_6BrNZn


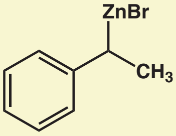
50mL

49,939-0
C_8H_7BrZn


50mL

53,352-1 New!
$C_8H_9BrO_3Zn$


50mL

49,877-7
C_8H_9BrZn


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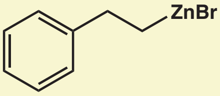
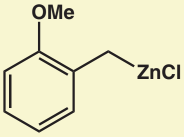
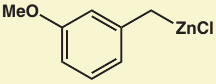
49,930-7
C_8H_9BrZn


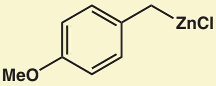
50mL

49,878-5
C_8H_9ClOZn


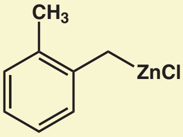
50mL

49,879-3
C_8H_9ClOZn


50mL

49,880-7
C_8H_9ClOZn


50mL

49,886-6
C_8H_9ClZn


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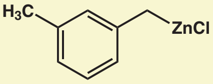
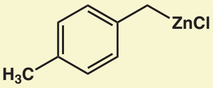
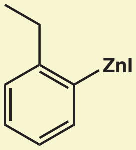
49,887-4
C_8H_9ClZn


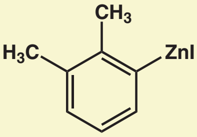
50mL

49,888-2
C_8H_9ClZn


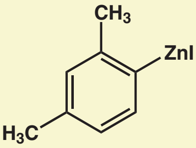
50mL

49,856-4
C_8H_9IZn


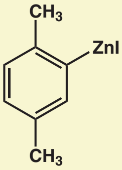
50mL

49,837-8
C_8H_9IZn


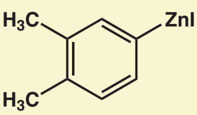
50mL

49,838-6
C_8H_9IZn


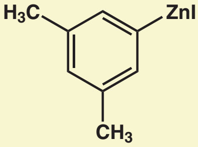
50mL

49,839-4
C_8H_9IZn


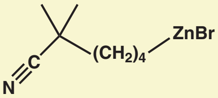
50mL

49,841-6
C_8H_9IZn


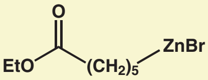
50mL

49,842-4
C_8H_9IZn


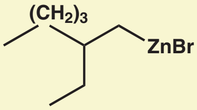
50mL

49,892-0
$C_8H_{14}BrNZn$


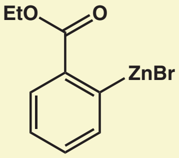
50mL

49,850-5
$C_8H_{15}BrO_2Zn$


50mL

49,855-6
$C_8H_{17}BrZn$


50mL

52,047-0
$C_9H_9BrO_2Zn$


50mL

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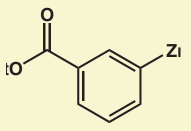
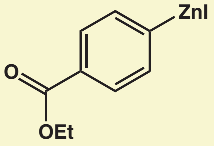
49,846-7
$C_9H_9IO_2Zn$



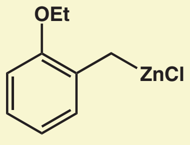
50mL

49,847-5
$C_9H_9IO_2Zn$



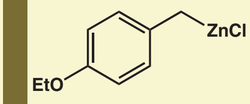
50mL

49,944-7
$C_9H_{11}ClOZn$



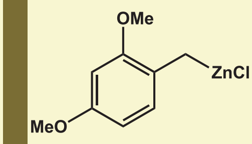
50mL

49,945-5
$C_9H_{11}ClOZn$



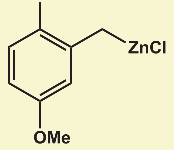
50mL

53,330-0 New!
$C_9H_{11}ClO_2Zn$



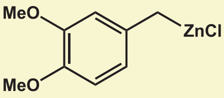
50mL

53,331-9 New!
$C_9H_{11}ClO_2Zn$



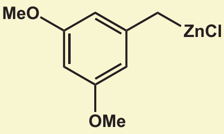
50mL

53,332-7 New!
$C_9H_{11}ClO_2Zn$



50mL

53,333-5 New!
$C_9H_{11}ClO_2Zn$

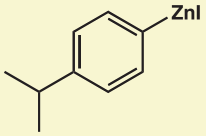


50mL

49,935-8
$C_9H_{11}IZn$

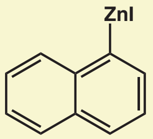
50mL

49,936-6
$C_9H_{11}IZn$



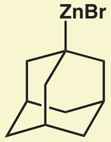
50mL

49,904-8
$C_{10}H_7IZn$



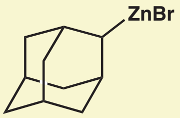
50mL

49,760-6
$C_{10}H_{15}BrZn$



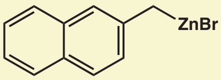
50mL

49,761-4
$C_{10}H_{15}BrZn$



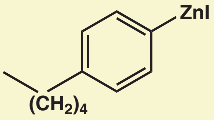
50mL

49,902-1
$C_{11}H_9BrZn$



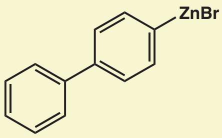
50mL

49,908-0
$C_{11}H_{15}IZn$



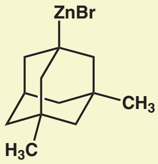
50mL

52,472-7
$C_{12}H_9BrZn$



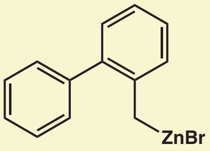
50mL

49,843-2
$C_{12}H_{19}BrZn$



50mL

49,762-2
$C_{13}H_{11}BrZn$



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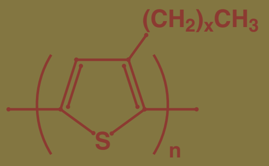

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X=7	44,571-1	Poly(3-octylthiophene-2,5-diyl)
X=9	49,534-4	Poly(3-decylthiophene-2,5-diyl)
X=11	45,065-0	Poly(3-dodecylthiophene-2,5-diyl)

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X=5	51,082-3	Poly(3-hexylthiophene-2,5-diyl)
X=7	51,083-1	Poly(3-octylthiophene-2,5-diyl)
X=9	51,085-8	Poly(3-decylthiophene-2,5-diyl)
X=11	51,086-6	Poly(3-dodecylthiophene-2,5-diyl)

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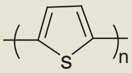
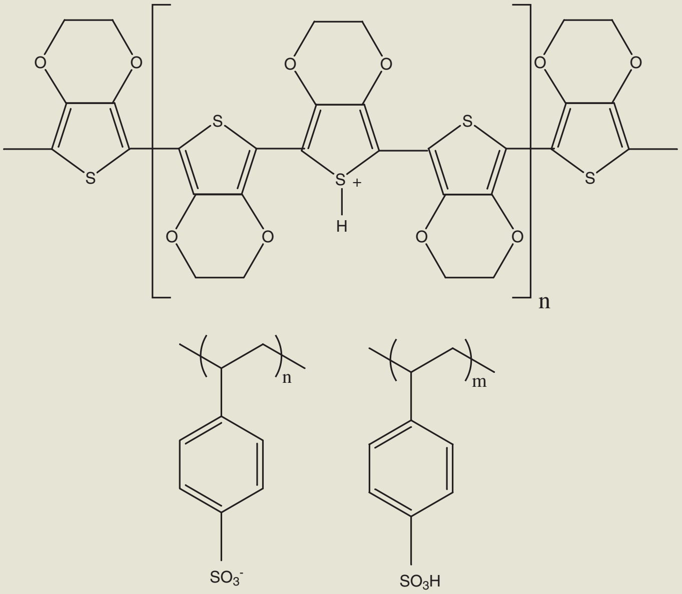
New! Conducting Polymers

52,593-6 **Poly(thiophene-2,5-diyl)**, Br terminated
Undoped form





48,309-5 **Poly(styrenesulfonate)/poly(2,3-dihydro-thieno-[3,4-*b*]-1,4-dioxin)**, 1.3 wt. % dispersion in water
[or Poly(3,4-oxyethyleneoxythiophene)/poly(styrene sulfonate); PEDOT/PSS]
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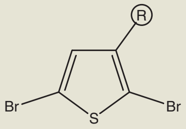
References (1) Berggren, M. et al. *Nature* **1994**, *372*, 444. (2) Bao, Z.; Lovinger, A.J. *Chem. Mater.* **1999**, *11*, 2607. (3) Sapp. S.A. et al. *ibid.* **1998**, *10*, 2101. (4) Heywang, G.; Jonas, F. *Adv. Mater.* **1992**, *4*, 116. (5) McCullough, R.D. et al. *J. Org. Chem.* **1993**, *58*, 904. (6) Chen, T.-A. et al. *J. Am. Chem. Soc.* **1995**, *117*, 233. (7) Blohm, M.L. et al. *Macromolecules* **1993**, *26*, 2704.

New! Precursors



52,549-9 **2,5-Dibromo-3-butylthiophene**, 96%
R = $-CH_2(CH_2)_2CH_3$

45,637-3 **2,5-Dibromo-3-hexylthiophene**, 97%
R = $-CH_2(CH_2)_4CH_3$

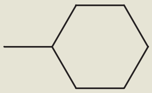
52,548-0 **2,5-Dibromo-3-octylthiophene**, 96%
R = $-CH_2(CH_2)_6CH_3$

45,638-1 **2,5-Dibromo-3-decylthiophene**, 97%
R = $-CH_2(CH_2)_8CH_3$

45,640-3 **2,5-Dibromo-3-dodecylthiophene**, 97%
R = $-CH_2(CH_2)_{10}CH_3$

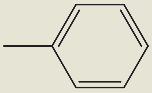
52,551-0 **2,5-Dibromo-3-cyclohexylthiophene**, 97%

R =

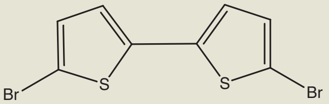


52,550-2 **2,5-Dibromo-3-phenylthiophene**, 97%

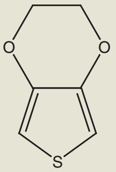
R =



51,549-3 **5,5'-Dibromo-2,2'-bithiophene**, 99%



48,302-8 **2,3-Dihydrothieno[3,4-*b*]-1,4-dioxin**
(or 3,4-Ethylenedioxythiophene)



Add a Little Tellurium to Your Synthetic Plans!

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Instituto de Química, Universidade de São Paulo
Av. Prof. Lineu Prestes, 748
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Outline

1. Introduction

The preparation of the first organotellurium compound, the volatile and malodorous diethyl telluride, was described by Wöhler in 1840.[1] About this compound Wöhler wrote: "and because its highly obnoxious and persistent smell is connected to unpleasantness, which one wouldn't like to endure a second time".[2] Heeren also stated: "the smell is so persistent, that one has to avoid social life for several months in order not to molest other people".[3] These statements were probably responsible for the long hibernation of the organic chemistry of tellurium. It was only about a century later that the first comprehensive account of the organic chemistry of this element appeared in the literature as part of a chapter in *Houben-Weyl*.[4] Rheinboldt's group showed that several classes of organic tellurium compounds were solid, and most of them were almost odorless, especially the aromatic ones. Petragnani, Rheinboldt´s last student, undertook extensive studies of the reactivity of inorganic and organic tellurium compounds towards several organic functional groups. This work, performed in the 1950s and 1960s, formed the basis for the development of the organic chemistry of tellurium.

The increasing number of publications dealing with organic tellurium compounds reflects the rising interest in this field of chemistry. Whereas only about 50 papers were published between 1910 and 1950, an average of about one hundred papers per year on the organic chemistry of tellurium appeared between 1950 and 1990. In 1990, a second, 1000-page volume of *Houben-Weyl* was devoted exclusively to organotellurium chemistry![5]

Research on the synthetic applications of tellurium reagents experienced a considerable impetus following the explosive growth of organoselenium chemistry that began with the discovery in the early 70s of the selenoxide syn elimination. However, chemists soon realized that exploitation of the similarities between selenium and tellurium was of less interest than exploiting the differences between the two, and some laboratories began to take advantage of the unique features of organotellurium compounds.

This account reviews the preparations and some synthetically useful transformations of organic tellurium compounds, and the transformations promoted in organic substrates by electrophilic or nucleophilic tellurium species. It is intended for the nonspecialist and focuses on the contributions from our laboratory. It is not an exhaustive review; the interested reader is directed to several extensive reviews and books that were written about the subject in the last decades.[5,6]

2. Main Classes of Tellurium Compounds

Several types of compounds containing tellurium are known.[5] However, only the classes that are most often used will be discussed in this review (**Figure 1**).

The aliphatic diorgano tellurides **1** are very bad smelling yellow oils, which must be handled in a hood. Disposable gloves must be used to manipulate them, and all the glassware used for their preparation must be immersed into a solution of sodium hypochlorite immediately after use. The diaryl or aryl alkyl tellurides are dense yellow oils or crystalline solids, which are easier to handle. Some of the

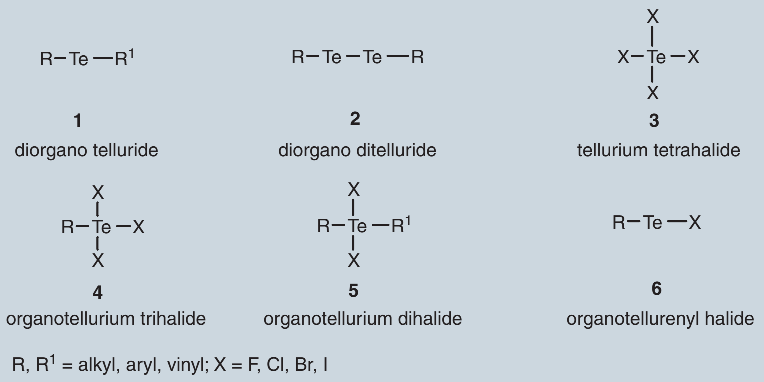


Figure 1. Most Often Used Classes of Tellurium Compounds.

diaryl derivatives are almost odorless solids. The same comments are valid for the diorgano ditellurides **2**, which are dark-red oils (aliphatic derivatives) and dark-red crystalline solids (aromatic ditellurides). It is recommended that solutions of tellurides or ditellurides not be kept in contact with air, since an amorphous white solid will form after some time. Evaporation of the solvent, however, minimizes the air oxidation. In contrast, the pure liquids or solids can be handled in air with no need for special precautions, but prolonged exposure to the air and to ambient light should be avoided.

Tellurium tetrachloride (**3**, X = Cl) is the most commonly used tellurium tetrahalide. It is a very hygroscopic white solid, which decomposes immediately upon contact with metallic spatulas. Thus, porcelain spatulas must be used to manipulate this reagent.

Aromatic tellurium trichlorides (**4**; R = Aryl, X = Cl) are very stable crystalline solids, usually yellow and almost odorless. Contact with metallic spatulas, with moist solvents, or prolonged exposure to light must be avoided. Organotellurium tribromides (**4**, X = Br) are yellow crystalline solids, and the triiodides (**4**, X = I) are dark-red solids. The bromo and iodo derivatives are not widely used for preparative purposes in contrast to the aryltellurium trichlorides, which are frequently used in several synthetic transformations. The aliphatic organotellurium trihalides are much less stable—depositing tellurium when in contact with light—and are not extensively used.

Diorganotellurium dichlorides (**5**, X = Cl) are odorless viscous oils or colorless crystalline solids. These compounds are more stable than the corresponding diorgano tellurides **1** and are not moisture- or air-sensitive. Diorganotellurium dibromides and diiodides are less common than the diorgano dichlorides.

For synthetic purposes, organotellurenyl halides **6** are generated in situ by reaction of the appropriate diorgano ditelluride **2** with the corresponding halogen in an inert solvent. These compounds are not stable, and only those possessing electron-donating groups suitably positioned to coordinate with tellurium can be isolated.

Organotellurols (RTeH), the tellurium analogs of alcohols, constitute another class of tellurium compounds and are generated in situ, in view of their high susceptibility to oxidation.

The classes of organotellurium compounds mentioned above can be prepared by interaction of nucleophilic or electrophilic tellurium species with different classes of organic compounds. Such species can be generated from elemental tellurium or from diorgano ditellurides as discussed in the following sections.

3. Preparation and Reactivity of Nucleophilic Tellurium Species

3.1. Preparation

Figure 2 and **Scheme 1** show the most important nucleophilic species of tellurium. Hydrogen telluride (**7**) is prepared by hydrolysis of Al_2Te_3.[7] Alkali tellurides **8** and **9**, and ditellurides **10** are prepared from elemental tellurium and reducing agents.[8] These species are generated in situ in an inert atmosphere, since they react rapidly with oxygen.

Organotellurolates **12** can be prepared either by reaction of a diorgano ditelluride **2** with a reducing agent, usually sodium borohydride,[9] or by reaction of elemental tellurium with Grignard[10a] or organolithium reagents (**Scheme 1**).[10b] The success of this reaction is highly dependent on the granule size of the tellurium used. Usually, tellurium powder of 200–300 mesh is appropriate. Alkali organotellurolates **12** are easily oxidized by air to the corresponding diorgano ditelluride **2**, or can be alkylated with R'X to give diorgano tellurides **1**.

3.2. Alkylation Reactions

The interaction of nucleophilic tellurium species with organic substrates can give access to other classes of organotellurium compounds or can reduce several functional groups. Alkali tellurides **8** and **9**, or ditellurides **10**, are potent nucleophiles and react rapidly with alkyl halides.[6t,u,11] **Table 1** summarizes some representative examples of such reactions leading to dialkyl tellurides **1**[12,8k,i] and dialkyl ditellurides **2**.[8i] Alkali organotellurolates **12** are also potent nucleophiles and are used to prepare symmetrical and unsymmetrical tellurides (**Table 2**).[13-15]

3.3. Hydrotelluration of Alkynes

One of the most synthetically useful reactions of nucleophilic tellurium species involves the addition of organotellurolate anions to alkynes.[6s-v,14,16] The products of the reaction are *Z* vinylic tellurides **13**, which are precursors of *Z* vinylic organometallic reagents (see Section 5). The *Z* isomers are formed exclusively and are stereochemically stable. No isomerization to the *E* olefin has been reported to date. The hydrotelluration of alkynes is performed in ethanol, and the tellurolate anion is generated by reduction of the corresponding diorgano ditelluride **2** with sodium borohydride. The reduction of the diorgano ditelluride is evidenced by the change of the dark-red color of the ditelluride to the pale-yellow color of the organotellurolate solution. Care must be taken to exclude oxygen from the reaction medium to avoid oxidation of the tellurolate anion **12** back to the diorgano ditelluride **2**. The vinylic tellurides **13** are pale-yellow oils or solids. Only the low-molecular-weight compounds are bad smelling; the examples shown in **Table 3** are almost odorless and stable enough to be purified by column chromatography, which allows their use in synthesis.

Alkyl tellurolate anions **12** react with alkynes more rapidly than their aryl-substituted counterparts (Entries 1 and 2, Table 3).[14,16] Conjugated dialkynes react even faster (Entry 3, Table 3),[17] and alkynes conjugated to unsaturated systems exhibit high regioselectivities.[16] In these reactions, only the 1-substituted vinylic telluride is formed (Entries 1-4, Table 3). However, simple alkynes containing electron-withdrawing groups at C-3 exhibit a reduced regioselectivity (Entry 5, Table 3).[18]

A remarkable improvement in the hydrotelluration reaction was recently achieved in our group. The tellurolate anion

12 was generated by reacting elemental tellurium with alkyllithium, followed by addition of deoxygenated ethanol and then the alkyne. Under these conditions, the manipulation of the bad-smelling dibutyl ditelluride was avoided.[19]

Reaction of disodium telluride (**8**) with alkynes gives bisvinylic tellurides analogous to **14**. The reaction times, however, are longer than those of the hydrotelluration with organotellurolates (**eq 1**).[18]

A noteworthy fact in the hydrotelluration of alkynes is its anti addition, leading to the *Z* isomer. In contrast, all other hydrometallation reactions previously reported are syn and yield the *E* isomer. We and others explored this fact using *Z* vinylic tellurides as sources of reactive *Z* vinylic organometallics (see Section 5).

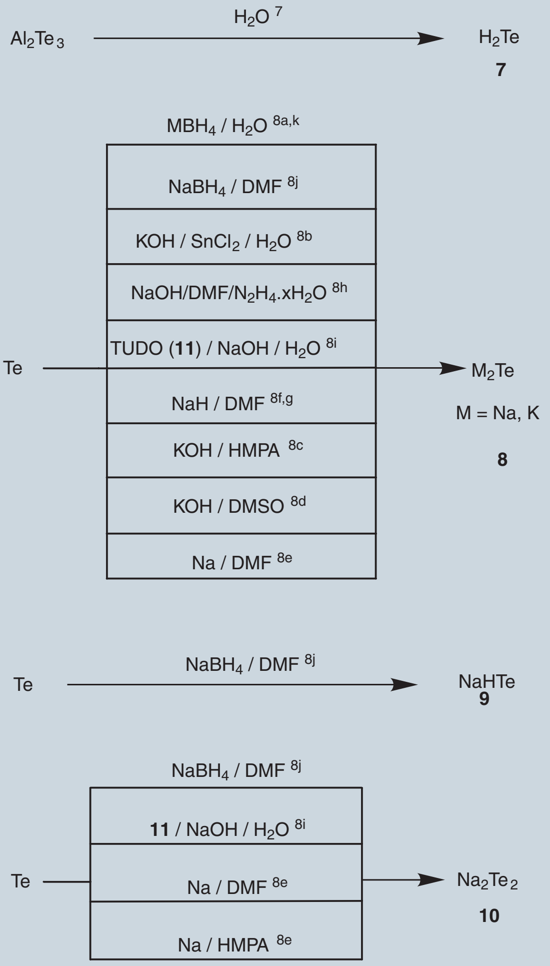
3.4. Vinylic Substitution

The vinylic substitution by tellurolate anions has not been extensively investigated. It is, however, an efficient method for synthesizing vinylic tellurides of defined stereochemistry. (*E*)-β-Bromostyrene reacts with organotellurolate anions to give *E* vinylic tellurides **15** (**eq 2**).[14,20] Reaction of β-haloenones **16a** and **16b** with organotellurolates **12** gives the corresponding vinylic tellurides (*Z*)-**17a** and **17b** (**Scheme 2**).[21b,c] The preparation of the β-haloenones starting materials sometimes requires drastic reaction conditions. In view of the synthetic potential of the vinylic substitution by tellurolate anions, we used enolphosphates instead as starting materials for the preparation of vinylic tellurides, since the enolphosphates can be prepared under very mild conditions. We utilized two methods for this purpose: (a) deprotonation of β-dicarbonyl compounds with sodium hydride followed by capture of the enolate with diethylphosphorochloridate, or (b) conjugate addition of a cuprate to an enone and O-functionalization to the enolphosphate **18b**.[22]

The reaction of enolphosphates **18a** and **18b** with lithium butyltellurolate (**12c**), generated by reaction of *n*-butyllithium with elemental tellurium, occurs rapidly to give the corresponding vinylic tellurides **17c** and **17d** in good yields (**Scheme 3**). Mixtures of *Z* and *E* enolphosphates afford the *Z* vinylic telluride. The substitution reaction probably occurs via an addition–elimination mechanism with the intermediate formation of an enolate. A through-space interaction of the carbonyl oxygen with the tellurium atom[21a] should favor rotamer **19**, which eliminates X^- to give only the *Z* isomer (**Scheme 4**).[21d]

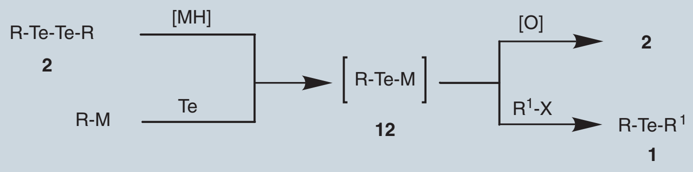
3.5. Reduction Reactions

From a synthetic point of view, the preceding three types of reactions of nucleophilic tellurium are the most promising ones. In the remainder of this section, we will discuss the reactions of nucleophilic tellurium, which do not lead to the incorporation of tellurium in the organic substrate.



TUDO = Thioureadioxide [HN=C(NH_2)S(O)OH,**11**]

Figure 2. Generation Methods of the Most Important Nucleophilic Species of Tellurium.



M = Li, MgX, Na; [MH] = Na/NH_3, Li/THF, $NaBH_4$, $LiAlH_4$, Al(*i*-Bu)$_2$H, **11**/NaOH
R, R^1 = alkyl, vinyl, aryl, alkynyl

Scheme 1

The first such transformation, reported by Petragnani in 1960, consisted of the debromination of *vic*-dihalides **20** by diaryl tellurides **22** and led to olefins **21**.[23a] Later on, this reaction was transformed into a catalytic process, in which the diaryl telluride was constantly regenerated (**Scheme 5**).[23b,c] Recently, the mechanism of this reaction was explored.[23d] Following the discovery of this reaction, several other synthetic transformations, which employed nucleophilic tellurium to remove halogen as well as other heteroatoms from organic substrates, were

Table 1. Alkylations of Nucleophilic Tellurium Species

$$\mathrm{Te}\ \xrightarrow[\text{2) R-X}]{\text{1) [H]}}\ \underset{\mathbf{1}}{\text{R-Te-R}}\ \text{ or }\ \underset{\mathbf{2}}{\text{R-Te-Te-R}}$$

[H]	R-X (Conditions)	Product	Yield (%)	Ref.
Na, NH_3 liq.	*i*-PrBr	$(i\text{-Pr})_2Te$	80	12
KBH_4, NaOH, Ar, reflux, 2h	*n*-OctBr, MeOH, reflux, 1 h	$(n\text{-Oct})_2Te$	78	8k
11, NaOH, H_2O THF, CTAB	*n*-OctBr, THF, N_2, CTAB, reflux, 2 h	$(n\text{-Oct})_2Te$	85	8i
CTAB, THF, DMSO, **11**, NaOH, reflux, 1 h	*n*-OctBr, rt, 1 h	$(n\text{-OctTe})_2$	98	8i

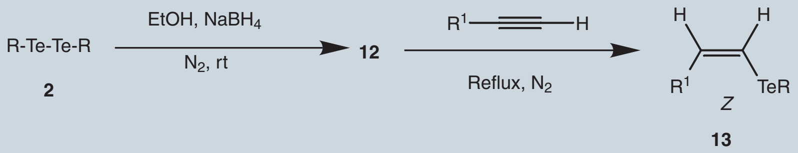
CTAB = Cetyltrimethylammonium bromide

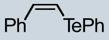
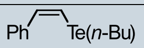
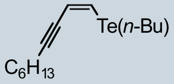
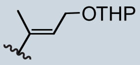
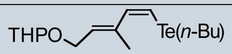
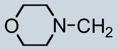
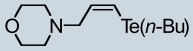
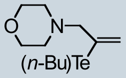
Table 2. Reactions of Organotellurolates as Nucleophiles

$$\underset{\mathbf{12}}{\text{R-Te-M}}\ \xrightarrow{\text{R}^1\text{-X}}\ \underset{\mathbf{1}}{\text{R-Te-R}^1}$$

[R-Te-M] (Generation Method)	R^1-X (Conditions)	Product	Yield (%)	Ref.
$(PhTe)_2/NaBH_4$ EtOH, N_2	$n\text{-}C_{12}H_{25}Br$, reflux, 3.5 h	$PhTe(n\text{-}C_{12}H_{25})$	76	13
Te/(*E*)-PhCH=CHMgBr, THF, reflux	$n\text{-}C_4H_9Br$, rt, 0.5 h	$(E)\text{-}PhCH{=}CHTe(n\text{-}C_4H_9)$	79	14
$(p\text{-}CH_3OC_6H_4Te)_2$/**11**, NaOH, THF, CTAB	$n\text{-}C_{12}H_{25}Br$ reflux, 6.0 h	$p\text{-}CH_3OC_6H_4Te(n\text{-}C_{12}H_{25})$	96	15

Table 3. Hydrotellurations of Alkynes



Entry	R	R^1	Reaction Time (h)	Product	Yield (%)	Ref.
1	Ph	Ph	20	 **13a**	93	16
2	*n*-Bu	Ph	1.7	 **13b**	93	14
3	*n*-Bu	$C_6H_{13}{-}C{\equiv}C$	0.25	 **13c**	89	17
4	*n*-Bu		5	 **13d**	83	16
5	*n*-Bu		5	 **13e** +  **13f** **13e**:**13f** (9:1)	80	18

described.[6p,q,t,u] Some representative examples are shown in **Schemes 6**[24] and **7**.[25]

Nucleophilic tellurium can act as a mild and selective reducing agent. Among the most interesting of such transformations, the reduction of double bonds conjugated to carbonyl groups should be mentioned (**Scheme 8**).[26] Probably due to some resistance to using tellurium reagents, synthetic organic chemists have not taken full advantage of this mild and selective transformation. Several other reducing agents and experimental conditions can be used, and other functionalities can be reduced.[6p,t]

4. Preparation and Reactivity of Electrophilic Tellurium Species

4.1. Preparation

Tellurium tetrachloride (**3**, X = Cl) is prepared by passing a stream of chlorine over elemental tellurium in an appropriate glass apparatus.[6t] The reaction is exothermic and requires only initial heating. After completion of the reaction, the product is distilled with the aid of a Bunsen burner into glass ampoules, which are sealed after **3** crystallizes. Using the procedure described in *Inorganic Synthesis*,[27] 1–2-mol batches are easily prepared in a few hours.

Tellurium tetrachloride (**3**, X = Cl) reacts with several functional groups giving organotellurium trichlorides (**4**, X = Cl). The most useful transformations are the reactions with activated aromatics and alkynes, e.g., **23**[28] and **24**[29] (**Scheme 9**). Organotellurium trichlorides **25** and **26** can be reduced to diorgano ditellurides **27**, when the reaction is performed in the presence of air. Several reducing agents can be used in this reaction step.[5,6t,u] Alternatively, if the reaction is performed under inert atmosphere in the presence of an alkyl halide, the intermediate organotellurolate can be alkylated to give diorgano tellurides **28** and **29** (**Scheme 9**).[29d]

Organotellurium tribromides and triiodides (**4**, X = Br, I) are obtained by halogenolysis of the tellurium–tellurium bond of diorgano ditellurides **2** (**Scheme 10**). These tribromides and triiodides are less explored than the organotellurium trichlorides.[5,6t,30]

As mentioned before, only a few classes of organotellurenyl halides **6** are stable. Those used for synthetic purposes are generated in situ by reaction of the corresponding diorgano ditellurides (e.g., **30**) with halogens (see Scheme 10) and captured, immediately, by a Grignard or organolithium reagent to give a diorgano telluride (e.g., **31**) (**eq 3**).[5,14,31]

Tellurium tetrachloride, aryltellurium trichlorides, and organotellurenyl halides react with a number of organic functional groups. In this review, we shall comment on only a few examples, which present some synthetic potential.

4.2. Reaction with Alkynes

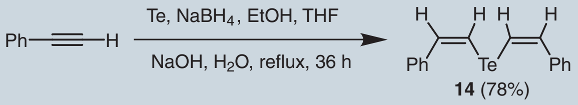
The reaction of aryltellurium trichlorides (e.g., **25**) with alkynes (e.g., **32**) leads to (*Z*)-1-telluro-2-chloroalkenes (**33**), when R is an aryl group.[29c] On the other hand, when propargyl alcohols **34** and **35** are used, different products, **36** and **37**, are formed, depending on the nature of the substituents on C–1 (**Scheme 11**).[29e]

4.3. Tellurocyclization of Alkenes

The first synthetic transformation using electrophilic tellurium was reported by Petragnani over forty years ago. γ,δ-Unsaturated carboxylic acids were reacted with tellurium tetrachloride, aryltellurium trichlorides, or naphthyltellurium iodide to give the corresponding tellurolactones.[32a] This paper has a special significance, since it also reported, for the first time, the cyclization of an unsaturated substrate by arylselenenyl halides. This fact is very often omitted in texts dedicated to organoselenium chemistry, which report the discovery of this reaction as occurring about fifteen years later. In view of the synthetic importance of the selenocyclization of unsaturated substrates, the corresponding tellurocyclization was also explored. γ,δ-Unsaturated carboxylic acids (e.g., **38**)[32a] are transformed into lactones by reaction with electrophilic tellurium species (e.g., **25**). The diorganotellurium dichlorides (e.g., **39**) formed are reduced to the corresponding tellurides (e.g., **40**) by reaction with a suitable reducing agent. The detellurated lactone (e.g., **41** or **43**) is obtained by reaction of **39** or **40** with tri-*n*-butyltin hydride in toluene. The intermediate free radical can be captured by a suitable radical trapping agent (e.g., **42**) to give the chain-elongation product **43**.[32c] These transformations are illustrated in **Scheme 12**. Substrates containing other functional groups have also been used in cyclofunctionalization reactions.[6p,q,t]

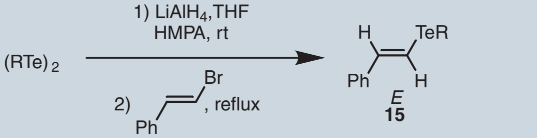
5. Transmetalation Reactions of Organic Tellurides

The most promising synthetic transformation of tellurium compounds is their conversion into reactive organometallic compounds by reaction with commercially available alkyllithiums or with other easily prepared organometallic species. The tellurium–lithium exchange is one of the fastest lithium–metalloid exchange reactions.[33]



14 (78%)

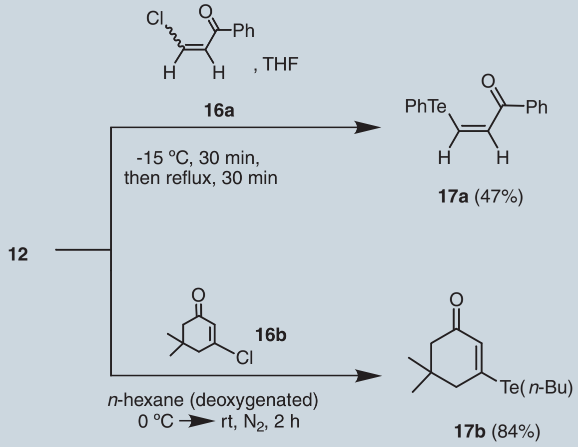
eq 1



15

15a; R = n-C_4H_9, 15 min (83%)
15b; R = p-$CH_3OC_6H_4$, 3 h (86%)

eq 2



17a (47%)

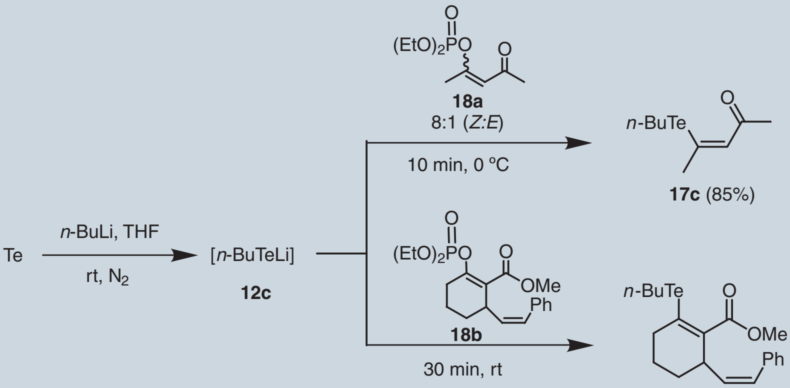
ref. 21b

17b (84%)

ref. 21c

12a = PhTeLi (generated by reaction of PhLi with Te)
12b = (n-Bu)TeAl(i-Bu)$_2$ (generated by reduction of (n-BuTe)$_2$ with DIBAL-H)

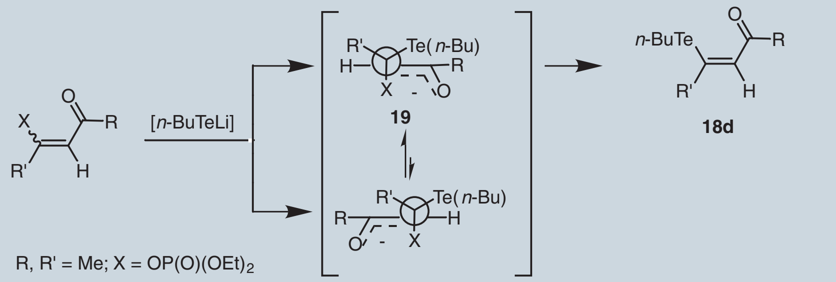
Scheme 2



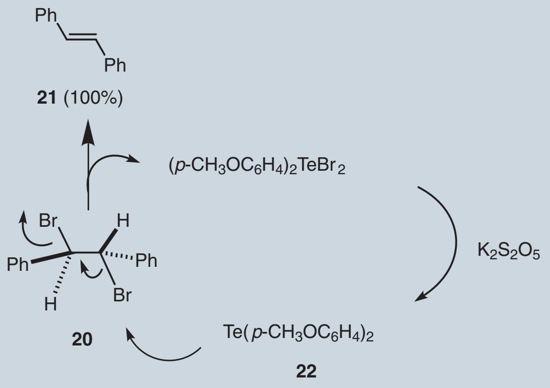
17c (85%)

17d (80%)

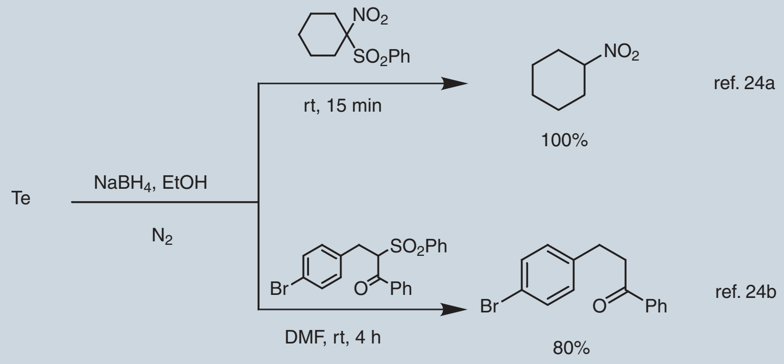
Scheme 3



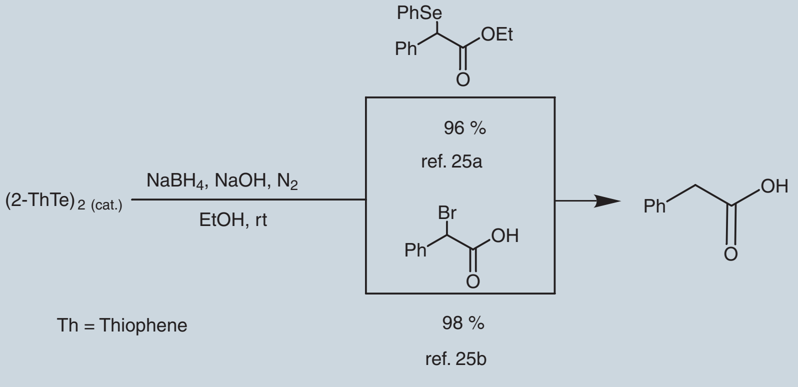
Scheme 4



Scheme 5



Scheme 6



Scheme 7

As mentioned in the preceding sections, the preparation of organic tellurium compounds is nowadays a routine practice, and compounds with defined stereochemistry can be easily obtained. Their transformation into reactive organometallics is a powerful synthetic tool that allows for the formation of new carbon–carbon bonds in a stereoselective way.

Several years ago, we showed that tellurium is preferentially transmetalated when phenylseleno(phenyltelluro)methane (**44**) is treated with *n*-butyllithium in THF at –78°C (Entry 1, **Table 4**).[34a] Later on, a number of alkyllithiums were prepared by the transmetalation of tellurides. Alkyl, aryl, ethynyl, allyl, benzyl, and vinyl tellurides are also transmetalated. Table 4 shows representative examples of such transformations; the transmetalation of vinylic tellurides will be discussed later in more detail in view of the synthetic potential of the resulting organometallics. In some cases, the telluride is generated in situ and transmetalated in a one-pot process (Entries 8, 9, and 10, Table 4).[34b-d]

Acyllithiums can be obtained by treating telluro esters **45** with alkyllithiums at low temperature (**Scheme 13**). The telluro esters are obtained by reaction of acyl chlorides with organotellurolate anions.[35]

Kauffmann reported the first transmetalation of a vinylic telluride with organolithium compounds.[36] Phenyl vinyl telluride (**47**) was deprotonated by LDCA in THF, and the resulting vinyl anion, **48**, was reacted with chlorotrimethylsilane to give telluride **49**. Vinyl silane **49** was then transmetalated with phenyllithium to give the corresponding vinyllithium, which was captured with chlorotrimethylsilane to give the bi-silylated ethene **50** (**Scheme 14**).

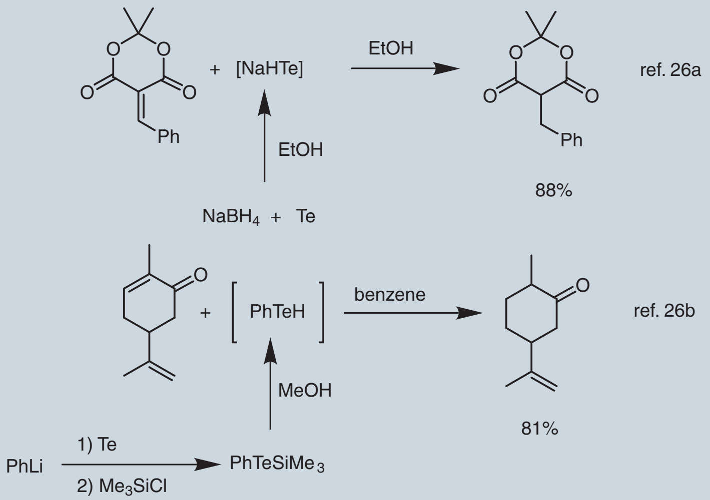
This sequence of reactions showed that phenyl vinyl telluride (**47**) could be considered a synthetic equivalent of 1,1-dilithioethene (**51**). This conclusion drew our attention to the synthetic potential of vinylic tellurides. At that time, very little was known about the preparation of vinylic tellurides, and, before exploring the transmetalation reaction synthetically, we developed a number of methods to prepare vinylic tellurides of defined stereochemistry.[14,16,18,37,38a] The most promising method has already been discussed in Section 3, and consists of the hydrotelluration of alkynes. Recently, the methods of preparing vinylic tellurides were reviewed by us.[6v]

In 1987, Sonoda and coworkers reported that the transmetalation reaction of 1-(phenyltelluro)-2-phenylethene with *n*-butyllithium, followed by capture with benzaldehyde, gives the corresponding allylic alcohol with retention of the double bond configuration.[34b] We observed that, depending on the length of time the reaction mixture of the aryl vinyl telluride and *n*-butyllithium is allowed to equilibrate prior to addition of the electrophile, complex mixtures of products can be formed (**Scheme 15**).[38a] This problem was overcome by using butyl vinyl tellurides instead of aryl vinyl tellurides. At the time we initiated the study of the transmetalation reactions of vinylic tellurides,[37,38a] the use of alkyl groups linked to tellurium had not been considered by the tellurium chemists, in view of comments in the older literature about the low stability of the aliphatic tellurium compounds. However, as commented on at the beginning of this review, these compounds are quite stable and can be handled without any need for special precautions. The transmetalation using butyl vinyl tellurides **13** or bisvinyl tellurides **14** occurs rapidly in THF at -78°C, and the vinyl anion is captured with a number of electrophiles, such as aldehydes, ketones, alkyl halides, carbon dioxide, and so on.[38] Representative examples of these reactions are shown in **Table 5**. The reaction is stereospecific: starting from the *Z* vinylic telluride **13** or **14**, only the *Z* olefin **52** is obtained. More recently, it has been shown that the transmetalation of the *E* vinylic tellurides also presents a general character.[38c,d]

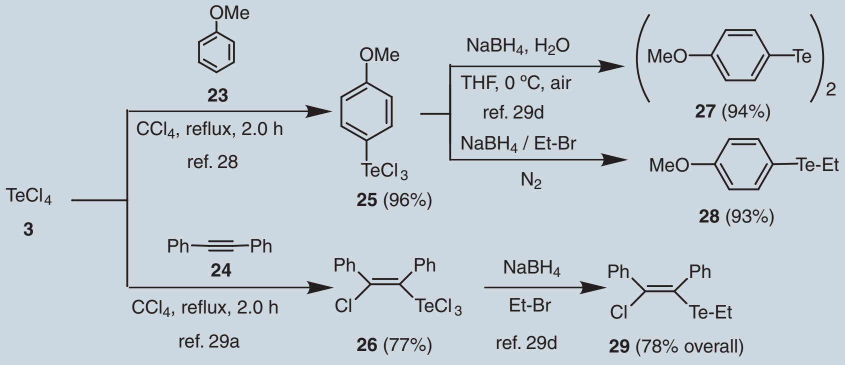
The transmetalation of vinylic tellurides occurs also with other organometallic reagents, namely organosodium,[39a] potassium,[39a] calcium,[39a] magnesium,[39a] aluminum,[39b] and zinc.[39c,d]

The transmetalation with higher-order lithium cyanocuprates **53** is the most versatile and promising transmetalation reaction of vinylic tellurides **13**.[40] Different non-transferable ligands have been used (**Table 6**).[16] The reaction occurs with retention of the double bond geometry, and the *Z* vinyl cyanocuprates react with unhindered enones (e.g., **55a**) in the usual way. Hindered enones (e.g., **55b**) fail to react when the *Z* vinyl cyanocuprate is generated in THF.[41a] However, the reaction is successful when boron trifluoride is added to the reaction mixture (Entries 3 and 4, Table 6).[41b] A similar result is obtained by using diethyl ether as solvent, even in the absence of boron trifluoride. A useful variation of the transmetalation reaction involves the use of vinyl thienyl tellurides. Treatment of **13j** with dilithium dibutyl cyanocuprate **53d** generates in one step the vinyl cyanocuprate with the nontransferable 2-thienyl ligand, **54d** (Entry 4, Table 6).[16,41]

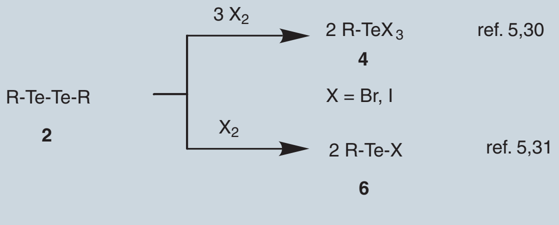
Enolate **57**, resulting from the 1,4 addition of *Z* vinyl cyanocuprates **54** to enones (e.g., **55a**), can be captured by electrophiles, giving access to useful synthetic intermediates. Among the most interesting, we mention



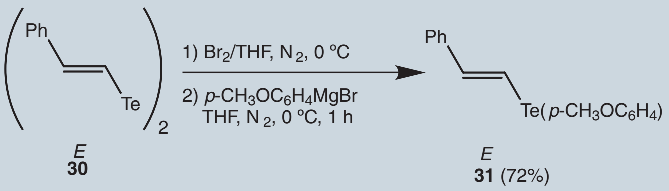
Scheme 8



Scheme 9



Scheme 10



eq 3

enolphosphates **58**[22] and enol triflates **59**.[42] As stated before (Section 3), enolphosphates are valuable starting materials for tri- and tetrasubstituted *Z* vinylic tellurides.[21d] Enol triflate **59a** gives access to highly unsaturated systems **60** and **62** by palladium-catalyzed reaction with alkynes or *Z* vinylzinc chlorides (e.g., **61**) (**Scheme 16**).[42]

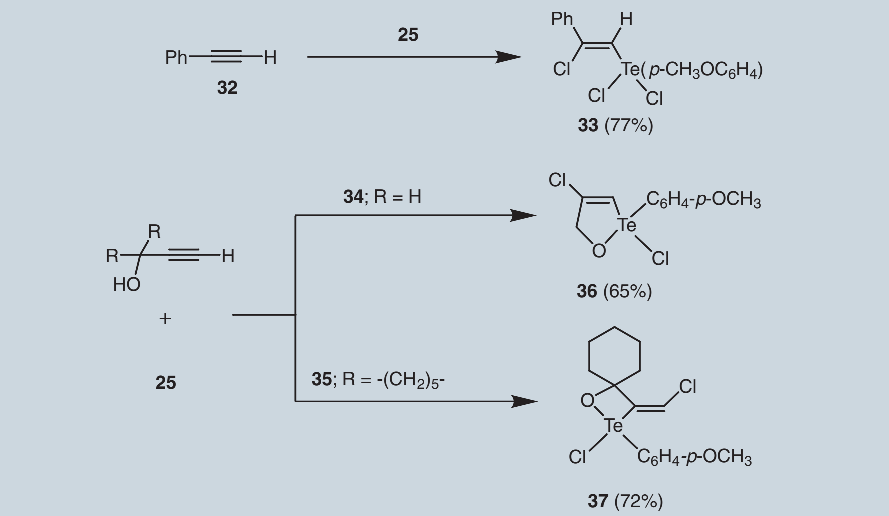
The *Z* vinylic cyanocuprates also react with epoxide **63**, giving the *Z* homoallylic alcohol **64**.[16,43] The reaction is stereospecific and offers the possibility of its application in enantioselective synthesis (**eq 4**).

Keeping in mind the easy access to vinylic tellurides (see Section 3), and their fast transmetalation to widely used reactive organometallics, we can consider this reaction sequence a valid alternative to the known methods of generating vinyllithiums and, especially, vinylcuprates. In addition, the trans hydrotelluration of alkynes is unique among the known, synthetically useful hydrometalations, since it allows for the direct preparation of reactive *Z* organometallics via transmetalation reactions. This is not possible with the known processes, which give rise to the *E* isomers (**Scheme 17**).[44]

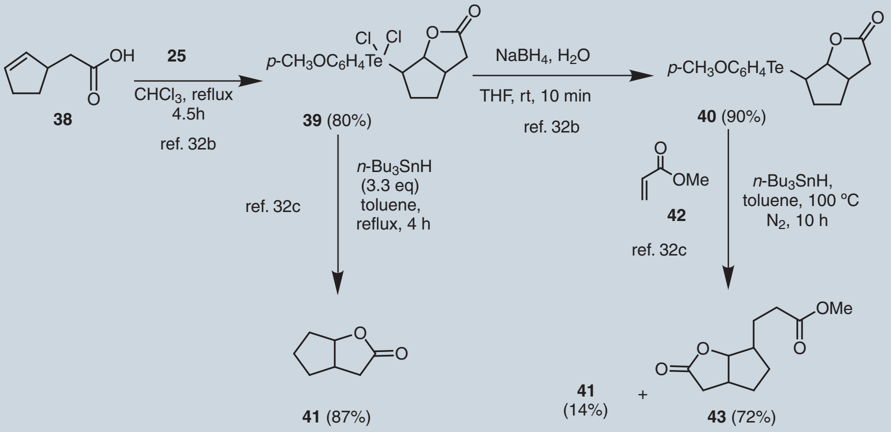
6. Coupling Reactions of Vinylic Tellurides

The nature of the counterion of the higher-order cyanocuprates plays a crucial role in the course of their reaction with vinylic tellurides. We found that, when one or both metal cations in the cuprate are Mg (**65** and **66**), the transmetalation is not observed. A coupling between the alkyl group of the cuprate and the vinylic telluride occurred instead (**Scheme 18**). The reaction is stereospecific, with retention of the *Z* geometry of the double bond.[45a] With lower-order cyanocuprates **67** and **68**, the coupling reaction occurs even when the counter ion is lithium.[21c, 45b] When the double bond is conjugated to a carbonyl or carboxyl group, the stereochemistry of the double bond of the coupling product, **69**, depends on the reaction conditions.[21c] Gilman cuprates also couple efficiently with vinylic tellurides.[45c] Treatment of the preformed *Z* vinyl cyanocuprate with $ZnCl_2$ and subsequent reaction with bromoalkynes allows the synthesis of *Z* enynes **70** and *Z* enediynes **71** (**Scheme 19**).[46]

Recently, we have developed a catalytic coupling process of vinylic tellurides with alkynes. The reaction is performed by adding the vinylic telluride to a mixture of $PdCl_2$ and CuI in dry methanol. The alkyne and triethylamine are then added to this mixture. This coupling process gives *Z* enyne **72** and *Z* enetriyne **73** in good yields (**Scheme 20**).[47]



Scheme 11



Scheme 12

Table 4. Transmetalation Reactions of Organic Tellurides

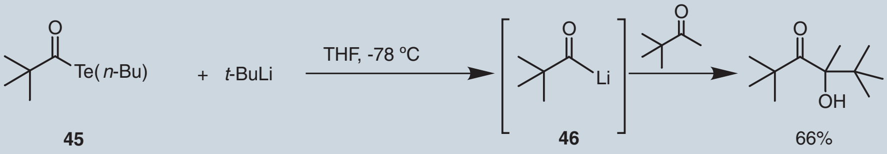
$$R{-}Te{-}R^1 \xrightarrow[\text{2) } E^+]{\text{1) } n\text{-BuLi}} R{-}E \quad + \quad R^1{-}Te{-}(n\text{-Bu})$$

Entry	R	R¹	E⁺	Product	Yield (%)	Ref.
1	$PhSeCH_2$ (**44**)	Ph	H_3O^+	$PhSeCH_3$	90	34a
2	$PhCH_2OCH_2$	*n*-Bu	PhCHO	$PhCH_2OCH_2CH(OH)Ph$	66	34c
3	Me_2NCH_2	*n*-Bu	PhCHO	$Me_2NCH_2CH(OH)Ph$	73	34c
4	Me_3SiCH_2	*n*-Bu	PhCHO	$Me_3SiCH_2CH(OH)Ph$	89	34c
5	$n\text{-BuTeCH}_2$	*n*-Bu	PhCHO	$BuTeCH_2CH(OH)Ph$	81	34c
6	$PhC{\equiv}C$	Ph	PhCHO	$PhC{\equiv}CCH(OH)Ph$	89	34b
7	Ph	Ph	PhCHO	$Ph_2CH(OH)$	80	34b
8	$CH_2{=}CH{-}CH_2$ [a]	Ph	PhCHO	$CH_2{=}CH{-}CH_2CH(OH)Ph$	96	34b
9	$CH_3CH_2CH_2$ [a]	*s*-Bu	PhCHO	$CH_3CH_2CH_2CH(OH)Ph$	84	34b
10	$PhCH_2$ [a]	*n*-Bu	PhCHO	$PhCH_2CH(OH)Ph$	89	34d

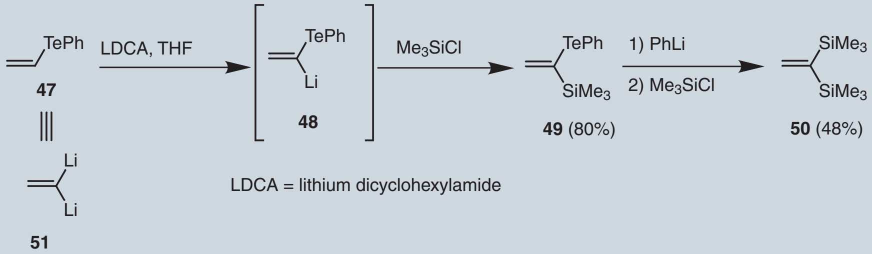
[a] The tellurides were generated in situ by reaction of allyl bromide, *n*-propyl iodide, or benzyl chloride with PhTeLi, *s*-BuTeLi, or *n*-BuLi, respectively. This was followed by reaction with *n*-BuLi (Entry 8 and 10) or *s*-BuLi (Entry 9) and benzaldehyde.

7. Concluding Remarks

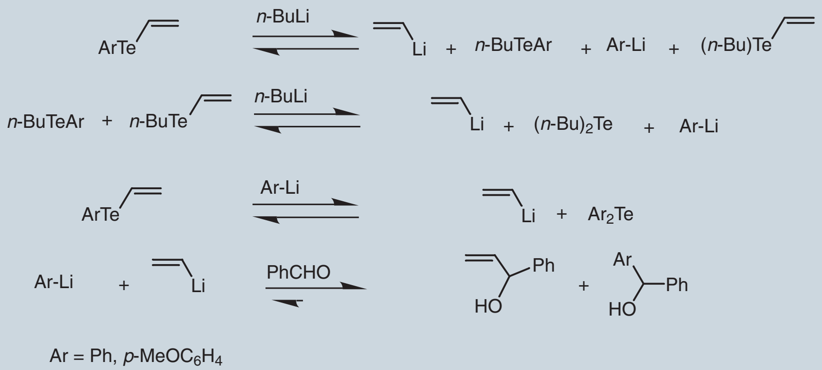
In the past few years, tellurium chemists have transformed this branch of organic chemistry into an attractive research field, and have developed safe methods to synthesize and handle tellurium compounds. This has led to the avoidance of volatile and malodorous reagents of the element, which had been a serious drawback to the practical application of tellurium compounds in the past. In addition, highly selective transformations of organic substrates are currently performed with tellurium reagents, and very mild conditions are used to remove the tellurium atom from these substrates. In some cases, this tellurium removal gives access to extremely useful synthetic intermediates such as *Z* vinyllithiums and *Z* vinylcuprates. The recently disclosed versatility of the organic chemistry of tellurium allows the assembly of highly unsaturated systems of defined stereochemistry, and opens the way to the use of *Z* vinylic tellurides in the synthesis of natural products that contain conjugated dienes, *Z* enynes, or *Z* enediynes.[48] The success of these transformations shows that tellurium reagents have a promising future in the synthesis of complex molecules, and we believe that the recent progress in the chemistry of this element will prompt synthetic organic chemists to include tellurium reagents in their synthetic plans.



Scheme 13



Scheme 14



Scheme 15

8. Acknowledgments

J. V. Comasseto wants to thank his students, who have worked in this field, and whose names appear in the references cited. R. E. Barrientos-Astigarraga thanks FAPESP for a Ph.D. fellowship. FAPESP and CNPq are acknowledged for continued support of our work. The authors thank Prof. Helena M. C. Ferraz and Prof. Liliana Marzorati for their valuable comments.

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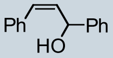
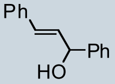
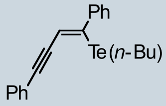
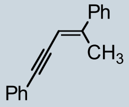
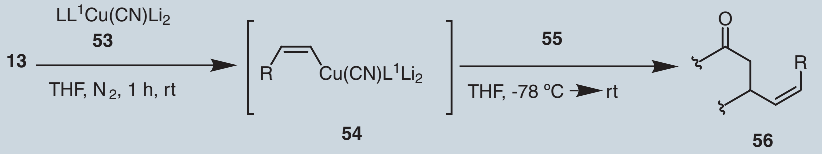
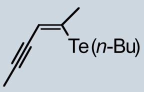
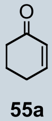
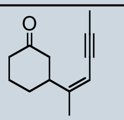
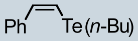
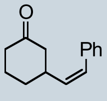
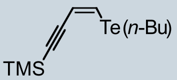
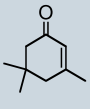
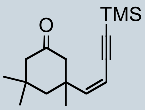
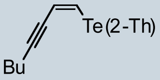
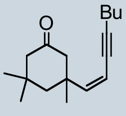
Table 5. Stereospecific Transmetalation of Vinylic Tellurides[a]

Vinylic Telluride	E$^+$	Product	Yield (%)	Ref.
13b	PhCHO	 **52a**	85	38a
14	PhCHO	**52a**	80	38a
15a	PhCHO	 **52b**	79	38a
 **13g**	Me_2SO_4	 **52c**	93	38b

[a] Reaction conditions: (i) n-BuLi, THF, N_2, –78 ˚C; (ii) E$^+$.

Table 6. Transmetalation of Vinylic Tellurides with Lithium Cyanocuprates



Entry	Vinylic Telluride	LL^1	L^1	Enone	Product (Yield, %)	Ref.
1	 **13f**	(Me, Me) **53a**	Me **54a**	 **55a**	 **56a** (63)	16
2	 **13b**	(n-Bu, Imid) **53b**	Imid **54b**	**55a**	 **56b** (88)	16
3	 **13i**	(n-Bu, 2-Th) **53c**	2-Th **54c**	 **55b** (BF_3•Et_2O)	 **56c** (81)	41b
4	 **13j**	(n-Bu, n-Bu) **53d**	2-Th **54d**	**55b** (BF_3•Et_2O)	 **56d** (70)	41b

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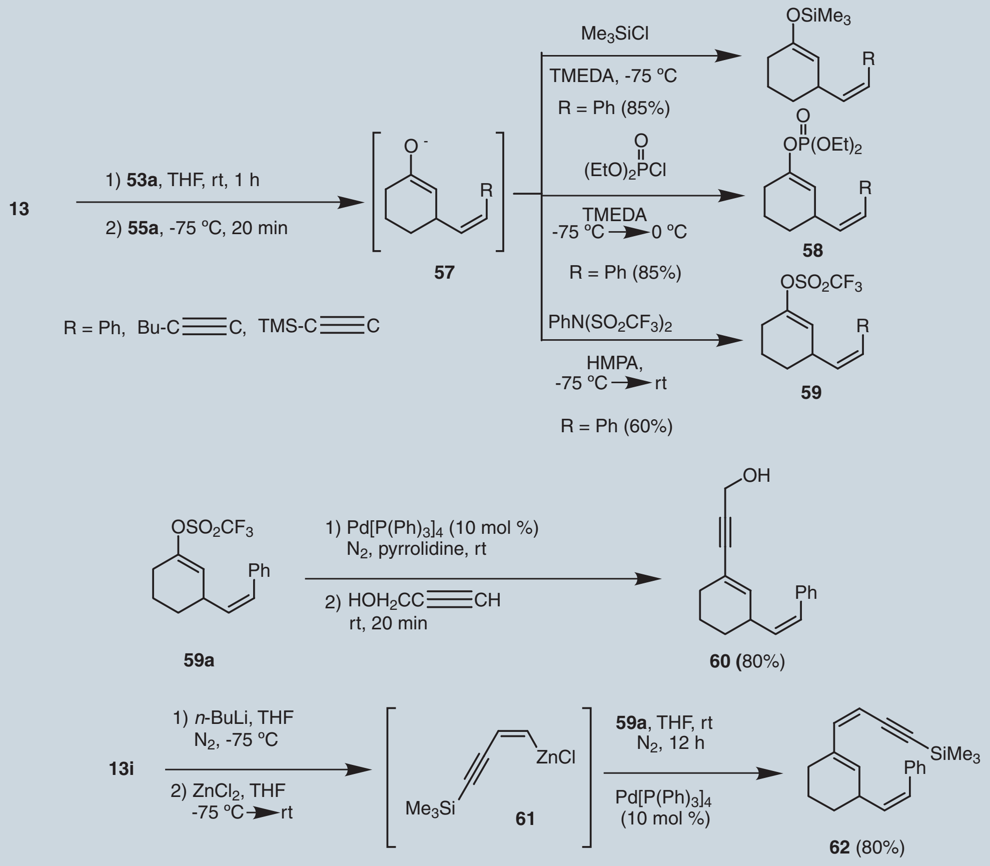
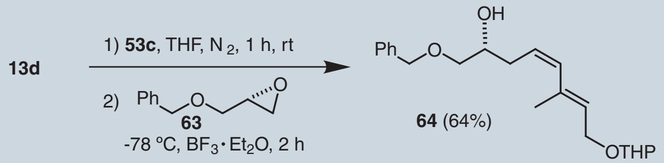
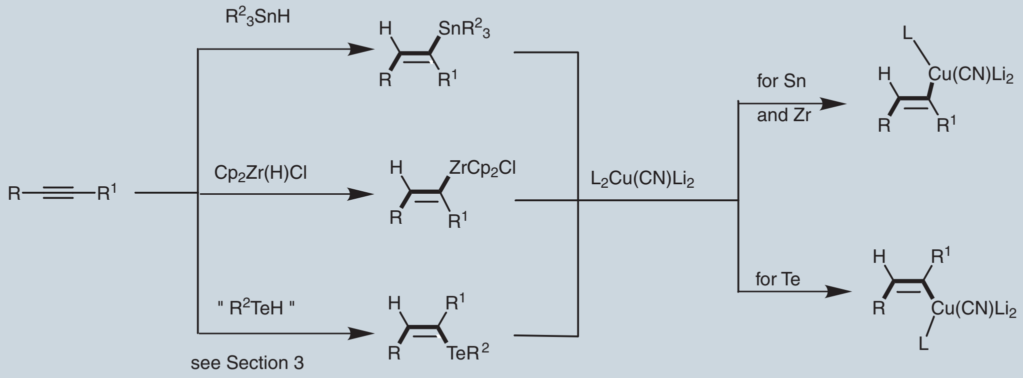


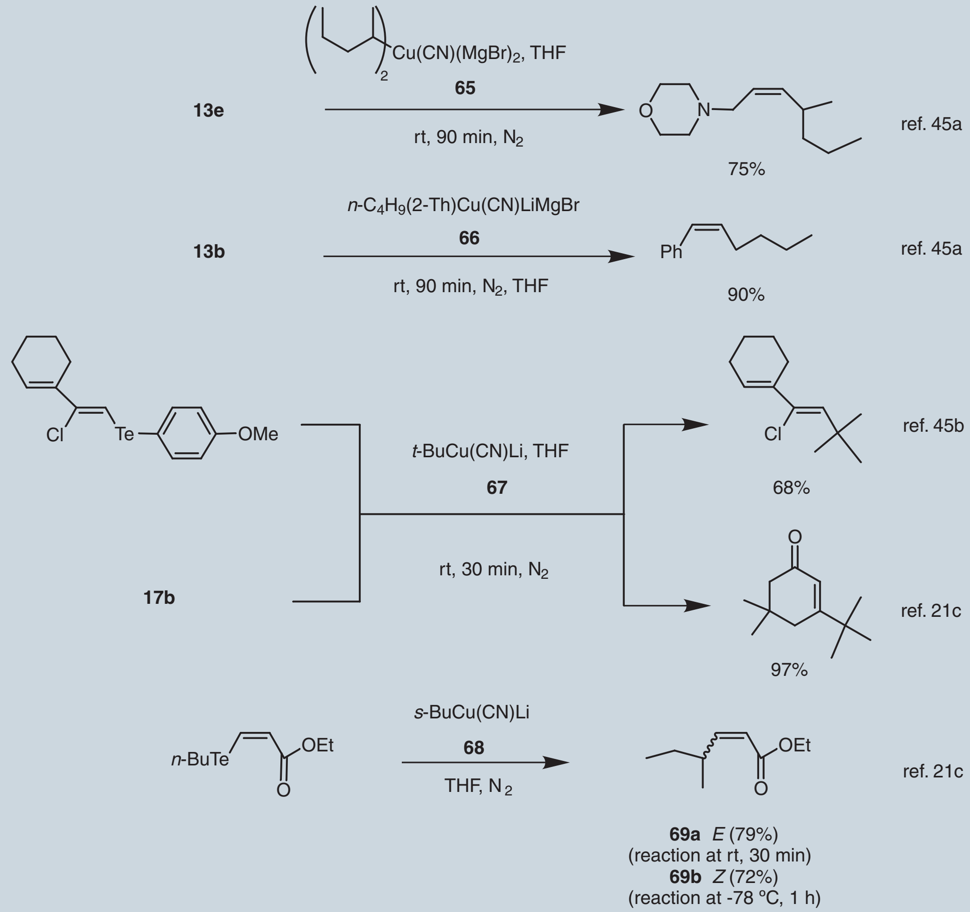
Scheme 16



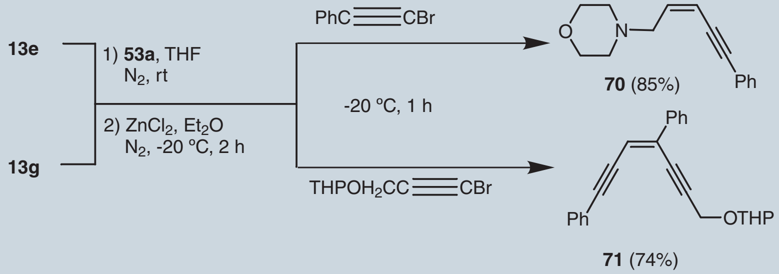
eq 4



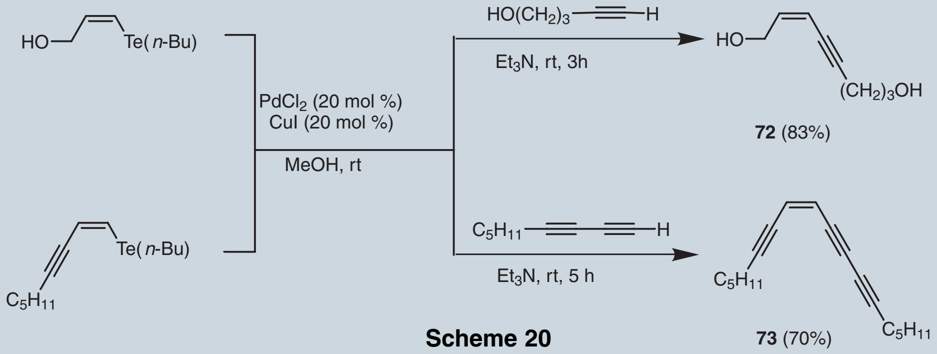
Scheme 17



Scheme 18



Scheme 19



Scheme 20

J.V. *Synth. Commun.* **1994**, *24*, 575. (b) Engman, L.; Cava, M.P. *J. Org. Chem.* **1982**, *47*, 3946.

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About the Authors

João Valdir Comasseto was born in 1949 in Santa Maria - RS, South Brazil. He received his B.Sc. in 1972 from the University of Santa Maria. In 1973, he moved to the University of São Paulo to pursue graduate studies in selenium chemistry under the supervision of Prof. Nicola Petragnani, and was awarded his Ph.D. degree in 1978. He spent one year as an Alexander von Humboldt fellow at the University of Cologne, Germany, working with Prof. E. Vogel. After his return to Brazil, he worked for two years at the University of São Carlos (São Paulo State) before moving to the University of São Paulo, where he has been a full Professor of Chemistry since 1992. His main research interest is the development of new synthetic reagents based on selenium and tellurium compounds.

Rafael Eliseo Barrientos-Astigarraga was born in Asunción, Paraguay, in 1974. In 1993, he moved to Brazil where he studied chemistry at the University of São Paulo and received his B.Sc. in 1996. Currently, he is enrolled in the Ph.D. program and is working on the development of organotellurium compounds as new synthetic reagents under Prof. J. V. Comasseto's supervision.

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40,068-8	**Sodium tellurite**, -100 mesh, 99%
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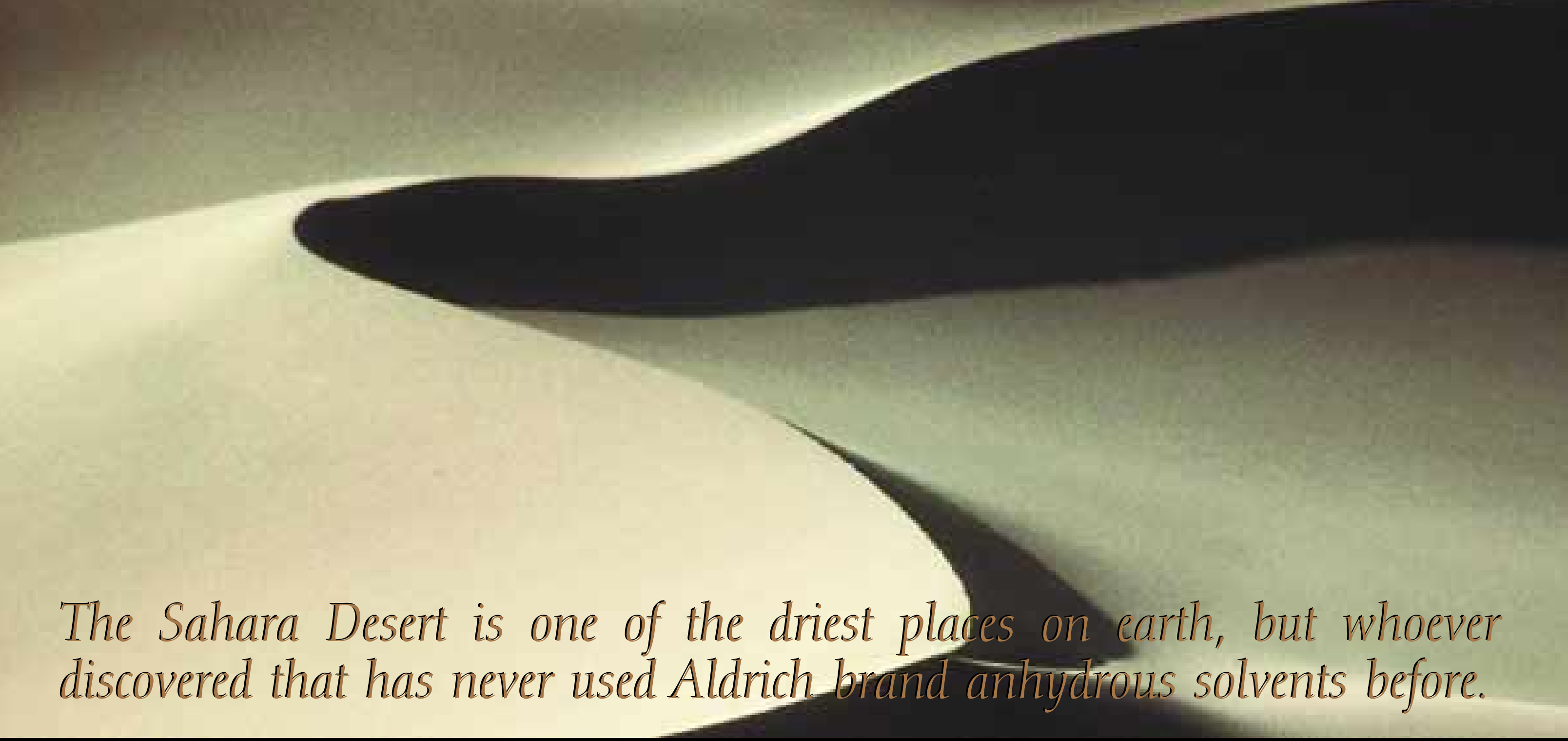

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To inquire about products, quotes, or to receive a copy of the latest Aldrich Solvents Catalog, contact Brian Case at **1-800-771-6737** (USA) or fax your requests to **(414) 298-6327**. Larger quantities are available through Sigma-Aldrich Fine Chemicals. Please call 1-800-336-9719 (USA) for availability. Requests for quotes on equipping stockrooms are always welcome.

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Cat. No.	Product Name	Water Content
27,100-4	**Acetonitrile**, 99.8%	10ppm
* 29,629-5	**Anisole**, 99.7%	20ppm
* 40,176-5	**Benzene**, 99.8%	10ppm
29,409-8	**Benzonitrile**, 99+%	30ppm
30,519-7	**Benzyl alcohol**, 99.8%	30ppm
* 30,944-3	**1,3-Butanediol**, 99+%	30ppm
28,154-9	**1-Butanol**, 99.8%	50ppm
29,481-0	**2-Butanol**, 99.5%	50ppm
28,772-5	**Butyl acetate**, 99+%	50ppm
27,145-4	**Butyl ether**, 99.3%	30ppm

More Anhydrous Solvents

	Cat. No.	Product Name	Water Content
	30,697-5	*tert*-**Butyl methyl ether**, 99.8%	30ppm
	33,526-6	**Carbon disulfide**, 99+%	50ppm
	28,911-6	**Carbon tetrachloride**, 99.5+%	20ppm
	28,451-3	**Chlorobenzene**, 99.8%	50ppm
*	41,425-5	**1-Chlorobutane**, 99.5%	20ppm
	37,297-8	**Chloroform**, 99+% (stabilized with amylenes)	10ppm
	28,830-6	**Chloroform**, 99+% (stabilized with .5-1% ethanol)	10ppm
*	29,477-2	**Decahydronaphthalene**, 99+%, mixture of cis and trans	20ppm
	45,711-6	**Decane**, 99+%	50ppm
*	24,066-4	**1,2-Dichlorobenzene**, 99%	30ppm
	27,099-7	**Dichloromethane**, 99.8%	10ppm
	51,713-5	**Diethyl carbonate**, 99+%	20ppm
	51,712-7	**Dimethyl carbonate,** 99+%	20ppm
	27,101-2	*N,N*-**Dimethylacetamide**, 99.8%	50ppm
	22,705-6	*N,N*-**Dimethylformamide**, 99.8%	50ppm
	29,630-9	**1,4-Dioxane**, 99.8%	30ppm
*	27,102-0	**1,3-Dioxolane,** 99.8% (stabilized with 75ppm BHT)	30ppm
	29,787-9	**Dodecane**, 99+%	30ppm
*	29,608-2	**Ether**, 99.8%	30ppm
	27,098-9	**Ethyl acetate**, 99.8%	50ppm
	45,983-6	**Ethyl alcohol**, 200 proof, 99.5+%	50ppm
	27,764-9	**Ethyl alcohol**, denatured	30ppm
*	29,684-8	**Ethylbenzene**, 99.8%	20ppm
	25,952-7	**Ethylene glycol dimethyl ether**, 99.5%	30ppm
	32,455-8	**Ethylene glycol**, 99.8%	30ppm
	24,665-4	**Heptane**, 99%	10ppm
*	29,631-7	**Hexadecane**, 99+%	30ppm
*	29,609-0	**Hexane**, 95+%	10ppm
*	22,706-4	**Hexanes**	10ppm
	47,140-2	**Hexyl alcohol**, 99+%	50ppm
	30,696-7	**Isoamyl acetate**, 99+%	50ppm
*	29,685-6	**Isopropyl ether**, 99%	20ppm
	28,446-7	**2-Methoxyethanol,** 99.8	50ppm
	28,166-2	**2-Methoxyethyl ether**, 99.5%	50ppm
	29,699-6	**Methyl acetate**, 99.5%	30ppm
	32,241-5	**Methyl alcohol**, 99.8%	20ppm
*	27,725-8	**2-Methylbutane**, 99+%	10ppm
	30,943-5	**3-Methyl-1-butanol**, 99+%	30ppm
	29,105-6	**Methyl formate**, 99%	50ppm
*	29,482-9	**2-Methyl-1-propanol**, 99.5%	30ppm
	47,171-2	**2-Methyl-2-propanol**, 99.5+%	50ppm
	32,863-4	**1-Methyl-2-pyrrolidinone**, 99.5%	50ppm
	27,438-0	**Methyl sulfide,** 99+%	30ppm
	27,685-5	**Methyl sulfoxide**, 99.8%	50ppm
*	30,030-6	**Methylcyclohexane**, 99+%	20ppm
	41,424-7	**2-Methyltetrahydrofuran**, 99+%	20ppm
	29,682-1	**Nonane**, 99+%	50ppm
*	29,698-8	**Octane**, 99+%	20ppm
	29,788-7	**1-Octanol**, 99+%	30ppm
	23,670-5	**Pentane**, 99+%	10ppm
*	30,031-4	**Petroleum ether**	10ppm
	27,954-4	**1-Propanol**, 99.7%	50ppm
	27,847-5	**2-Propanol,** 99.5%	30ppm
*	31,032-8	**Propylene carbonate,** 99.7%	20ppm
	27,097-0	**Pyridine**, 99.8%	30ppm
*	37,169-6	**Tetrachloroethylene**, 99+%	20ppm
	40,175-7	**Tetrahydrofuran**, 99.9% (inhibitor-free)	30ppm
*	18,656-2	**Tetrahydrofuran**, 99.9% (inhibited with 0.025% BHT)	20ppm
	52,265-1	**1,2,3,4-Tetrahydronaphthalene**, 99%	50ppm
*	29,310-5	**Tetrahydropyran**, 99%	30ppm
*	24,451-1	**Toluene**, 99.8%	10ppm
	52,264-3	**Tributylamine**	50ppm
	29,610-4	**1,2,4-Trichlorobenzene**, 99+%	20ppm
	29,899-9	**1,1,1-Trichloroethane**, 99.5%	50ppm
	37,214-5	**Trichloroethylene**, 99+%	20ppm
	24,050-8	**1,1,2-Trichlorotrifluoroethane**, 99.8%	20ppm
*	30,405-0	**Triethyl orthoformate**, 98%	30ppm
	30,547-2	**Trimethyl orthoformate**, 99.8%	20ppm
*	36,006-6	**2,2,4-Trimethylpentane**, 99.8%	30ppm
*	29,632-5	*m*-**Xylene**, 99+%	20ppm
*	29,633-3	*p*-**Xylene,** 99+%	20ppm
*	29,478-0	*o*-**Xylene**, 97%	30ppm

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CAT. NO.	PRODUCT NAME
49,444-5	**Acetonitrile**, 99.93+%
49,618-9	**Chloroform**, 99.9+%
49,445-3	**Dichloromethane**, 99.9%
49,448-8	*N,N*-**Dimethylformamide**, 99.9+%
49,451-8	**Ethyl acetate**, 99.8+%
49,452-6	**Heptane**, 99+%
49,449-6	**1-Methyl-2-pyrrolidinone**, 99.5+%
49,443-7	**Methyl alcohol**, 99.93%
49,442-9	**Methyl sulfoxide**, 99.8%
49,441-0	**Pyridine**, 99.9+%
49,446-1	**Tetrahydrofuran**, 99.9+%
49,616-2	**Butyl acetate**, 99.7%
49,617-0	**1-Chlorobutane**, 99.5+%
49,621-9	*N,N*-**Diisopropylethylamine**, 99.5%
E 7023	**Ethanol**, absolute, 200 proof
E 7148	**Ethanol**, 190 proof

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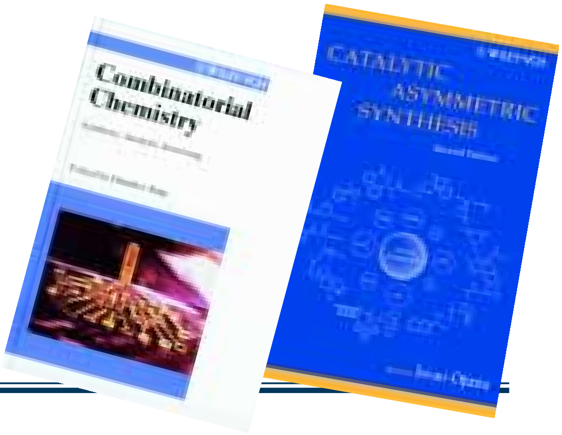
from the aldrich bookshelf



Catalytic Asymmetric Synthesis

2nd ed., I.Ojima, Ed., John Wiley & Sons, New York, NY, 2000, 880pp. Hardcover. The field of catalytic asymmetric synthesis has grown immensely, spawning effective new methods for obtaining enantiomerically pure compounds on a large scale, and stimulating new applications in diverse fields—from medicine to materials science. The second edition addresses these rapid changes through new or substantially revised contributions from world leaders in the field. It provides many excellent references and an appendix that displays and cross-references all the catalysts described in the book.

Z42,461-7

Principles of Process Research and Chemical Development in the Pharmaceutical Industry

O. Repic, John Wiley & Sons, New York, NY, 1997, 213pp. Hardcover. Explains the goals and basic principles of chemical development. Explores crucial aspects of a new process that must be considered when scaling up a research synthesis to industrial levels. Key topics include: qualities of an ideal process, techniques for minimizing impurities, criteria for cost-effective synthesis of enantiopure compounds by resolutions, asymmetric synthesis and the "chiral pool" strategy, synthesis for labeling substances with isotopes, and new drug registration requirements.

Z42,301-7

Annual Reports in Organic Synthesis

Academic Press, Orlando, FL. Softbound. Abstracts the latest synthetic reactions from the major chemistry journals.

Yr.	Pp.	Cat. No.
1996	470	**Z28,180-8**
1997	435	**Z40,257-5**
1998	544	**Z42,256-8**
1999	403	**Z42,257-6**

Fmoc Solid Phase Peptide Synthesis: A Practical Approach

W.C. Chan, Ed., Oxford University Press, New York, NY, 2000, 376pp. Hardcover. Covers the essential procedures for the production of linear peptides as well as more advanced techniques for preparing cyclic, side-chain modified, phospho- and glycopeptides. Other topics include convergent peptide synthesis, peptide-protein conjugation, chemoselective ligation, and chemoselective purification.

Z42,426-9

Combinatorial Chemistry: Synthesis, Analysis, Screening

G. Jung, Ed., John Wiley & Sons, New York, NY, 2000, 634pp. Hardcover. This book is one of the most comprehensive and up-to-date sources on the latest developments in the field of combinatorial chemistry. The book places special emphasis on organic chemistry and biochemistry.

Z42,427-7

Silicon in Organic, Organometallic, and Polymer Chemistry

M. A. Brook, John Wiley & Sons, New York, NY, 1999, 680pp. Hardcover. A well-organized, practical overview that covers all aspects of organosilicon chemistry, including fundamentals of silicon reactivity, formation and cleavage of non-carbon bonds to silicon, and formation and cleavage of Si–C bonds. Contains an extensive, graphical index for easy access to functional group transformations.

Z42,242-8

Biotransformations in Organic Chemistry: A Textbook

4th ed., K. Faber, Springer-Verlag, New York, NY, 2000, 453pp. Softbound. Provides a basic introduction to the use of biocatalysts for modern preparative organic chemistry. Includes new chapters on peroxidase reactions and the handling of biocatalysts.

Z42,331-9

Handbook of Derivatization Reactions for HPLC

G. Lunn and L. C. Hellwig, John Wiley & Sons, New York, NY, 1998. Hardcover and CD-ROM. This print and electronic database represents a tremendous time-saver for analytical chemists working in the popular area of HPLC. By abstracting and evaluating the most important derivatization procedures, chemists can avoid lengthy information searches to consult the primary literature. Both the print and fully searchable CD-ROM databases offer everything an analytical chemist needs to conduct derivatizations.

Z42,423-4

Drugs: Synonyms & Properties

G.W.A. Milne, Ed., Ashgate Publishing Co., Burlington, VT, 2000, 1,400pp. Hardcover. Provides comprehensive coverage of the 10,000 drugs currently in use worldwide. Includes an index of 60,000 drug synonyms and trade names with a cross-reference to their main entry. For each main entry, the following information is provided: chemical name and a list of trade names and synonyms, CAS Registry number, EINECS number, Merck Index number, physical properties, and the known biological activity and indicated applications.

Z42,365-3

Solid-Phase Organic Synthesis

K. Burgess, John Wiley & Sons, New York, NY, 1999, 250pp. Hardcover. Presents key developments in the use of solid-phase synthesis in combinatorial chemistry. Conveys the crucial role solid-phase synthesis plays in combinatorial chemistry. Highlights solid-phase synthesis of natural product derivations, synthesis of guanidine, palladium catalyzed C–C bond forming reactions, resin-supported capture agents, and more.

Z42,173-1

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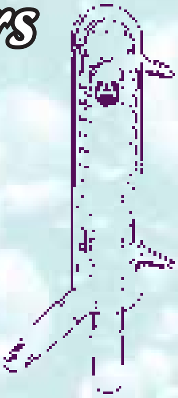
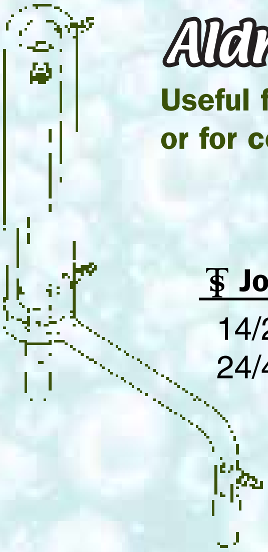


Vapors rise up the inner tube and condense on the highly efficient spiral path. Replaces traditional 3-piece distillation setup.

$ Joint	Overall H (mm)	Cat. No.
14/20	255	**Z42,229-0**
24/40	275	**Z42,230-4**



Aldrich Water-Cooled Distilling Heads

Useful for removal of solvents from reaction mixtures or for concentrating solutions prior to crystallization.

$ Joint	Overall H (mm)	Side-Arm Clearance (mm)	Cat. No.
14/20	210	175	**Z41,548-0**
24/40	400	330	**Z41,549-9**

Aldrich Multi-Purpose Distillation Heads

With vacuum take-off and antisplash design. Useful as concentrators, condensers, reflux heads, or addition funnels. 4mm Teflon® stopcock.

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$ Joint	Overall H (mm)	Cat. No.
24/40	430	**Z22,332-8**
29/32	415	**Z22,333-6**

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The 12mL and 25mL traps use a 2mm bore; all the rest use a 4mm.

Cap. (mL)	Overall H (mm)	Side-Arm Clearance (mm)	Suggested Flask Size	$ Joint	Cat. No.
12	205	80	50mL – 5L	14/20	**Z20,254-1**
25	255	80	50mL – 5L	14/20	**Z42,307-6**
25	280	80	50mL – 5L	24/40	**Z42,302-5**
100	350	100	5L – 12L	24/40	**Z42,303-3**
300	440	170	22L – 50L	24/40	**Z42,304-1**
500	455	170	22L – 50L	24/40	**Z42,306-8**

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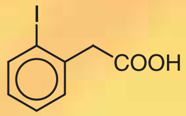
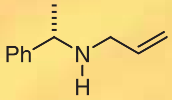


Used in the synthesis of nitrogen-containing heterocycles via vinylogous Pummerer reactions of amido sulfoxides.

Padwa, A.; Kuethe, J.T. *J. Org. Chem.* **1998**, *63*, 4256.

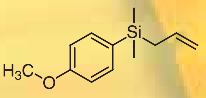
53,147-2 **2-Iodophenylacetic acid**, 97%



Nitrogen-containing heterocycles have recently been prepared from this chiral amine in a tandem aminocarbonylation/Pauson–Khand reaction.

Balsells, J. et al. *Org. Lett.* **1999**, *1*, 1981.

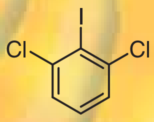
52,554-5 **(*S*)-*N*-Allyl-α-methylbenzylamine,** 97%



This silane is a key intermediate in the synthesis of a silicon linker, useful for the traceless synthesis of pyridine-based tricyclics.

Woolard, F.X. et al. *J. Org. Chem.* **1997**, *62*, 6102.

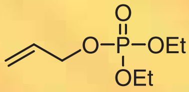
51,104-8 **Allyl(4-methoxyphenyl)dimethylsilane,** 98%



Useful for the synthesis of *m*-terphenyls, and, subsequently, novel cyclophanes.[1,2]

(1) Rajakumar, P.; Srisailas, M. *Tetrahedron Lett.* **1997**, *38*, 5323. (2) Kannan, A. et al. *J. Org. Chem.* **1996**, *61*, 5090.

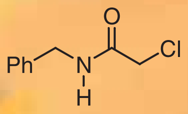
51,045-9 **1,3-Dichloro-2-iodobenzene,** 98%



A simple, one-step reaction employing this reagent leads to the direct regioselective dehydrogenation of aldehydes and cyclic ketones.

Shvo, Y.; Arisha, A.H.I. *J. Org. Chem.* **1998**, *63*, 5640.

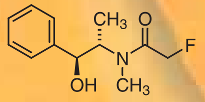
52,585-5 **Diethyl allyl phosphate,** 98%



Employed in the synthesis of novel tetrazoles via tetrazolylbenzyl radicals.

Biadatti, T. et al. *Tetrahedron Lett.* **1998**, *39*, 19.

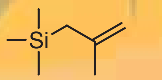
53,199-5 **2-Chloro-*N*-benzylacetamide,** 97%



This chiral auxiliary provides practical access to a wide range of α-fluorocarboxylic acids in high enantiomeric excess.

Myers, A.G. et al. *Tetrahedron Lett.* **1998**, *39*, 1335.

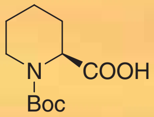
52,561-8 **(1*S*,2*S*)-Pseudoephedrine α-fluoroacetamide,** 98%

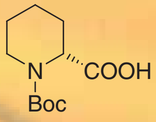


Utilized in the catalytic synthesis of optically active allyl α-amino acids.

Fang, X. et al. *J. Org. Chem.* **1999**, *64*, 4844.

51,026-2 **Methallyltrimethylsilane,** 97%





Synthons for the synthesis of the immunosuppressive agent FK506[1] and the thrombin inhibitor inogatran,[2] and for preparing new cyclosporin derivatives.[3]

(1) Baker, R.K. et al. *Tetrahedron Lett.* **1998**, *39*, 229. (2) Preville, P. et al. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1563. (3) Eberle, M.K. et al. *J. Med. Chem.* **1995**, *38*, 1853.

51,636-8 **(*S*)-(–)-1-(*tert*-Butoxycarbonyl)-2-piperidinecarboxylic acid,** 98% (98% ee/GLC)

51,634-1 **(*R*)-(+)-1-(*tert*-Butoxycarbonyl)-2-piperidinecarboxylic acid,** 98% (98% ee/GLC)

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VOL. 33, NO. 3 • 2000

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About Our Cover

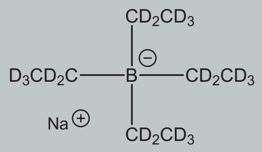
Street in Venice (oil on wood panel, 17¾ in. x 21¼ in.) was painted by the American artist John Singer Sargent. Sargent was born in Florence in 1856 to affluent expatriate American parents and spent most of his life in Europe. He lived mainly in Paris until 1884, and then in London, where he died in 1925. His formal instruction in art was in Rome, Florence, and Paris, and, from 1877, he exhibited at the official salons in the French capital. Sargent traveled extensively, copying Velázquez at the Prado in Madrid and Frans Hals in Belgium and Holland, and developing a style that combines close observation with a fluent and painterly technique derived at least partly from these earlier masters. In 1881, he met James McNeill Whistler in Venice, where he painted this picture, probably in the fall of 1882. By the end of the nineteenth century, he had become the most celebrated international society portrait painter of his time, with a wealthy, aristocratic, and fashionable clientele; but he sought every chance he could to escape the constraints of formal portraiture for genre subjects.

Sargent does not paint the colorful, idealized views of scenes like the Piazza San Marco or the Grand Canal, commonly portrayed by many of his contemporaries, but captures a casual moment in one of the back streets of a working class district of Venice. Observed by two men standing near a doorway, a young woman hurries along, her expression preoccupied and aloof, her shawl drawn about her against the chill. The limited range of color, the deep perspective view of the narrow street, and the dark silhouettes of the men, one of whom glances at the woman, create a mood that is almost sinister, and certainly ambiguous. Who is this young woman? Who are the two men? Do they know her? We cannot be sure, but this mystery is one reason that Sargent's painting is so compelling and so memorable.

This painting is a gift of the Avalon Foundation to the National Gallery of Art, Washington, D.C.

"Please Bother Us."

Clint Lane, President



$$D_3CD_2C-\overset{CD_2CD_3}{\underset{CD_2CD_3}{B^{\ominus}}}-CD_2CD_3 \quad Na^{\oplus}$$

Professor Janusz Pawliszyn of the University of Waterloo, Waterloo, Canada, kindly suggested that we make sodium tetraethylborate-d_{20}, which is used as a derivatization reagent for the determination of alkyllead and inorganic lead in aqueous samples. Dr. Pawliszyn's method can be adapted for field measurements, and has the potential of becoming a general method for the speciation of inorganic and organometallic compounds.

Yu, X.; Pawliszyn, J. *Anal. Chem.* **2000**, *72*, 1788.

49,504-2
Sodium tetraethylborate-d_{20},
98 atom % D

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.

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Lab Notes

Effective Cooling System in Bulb-to-Bulb Distillation

Bulb-to-bulb distillation is a useful laboratory technique for the small-scale purification of liquid substances. In this microscale, short-path technique, a small quantity of material is redistilled using several glass bulbs connected in line. In some Kugelrohr models, heating is carried out by a built-in oven, and control of both temperature and stirring speed is performed by an integrated electronic controller. The flask containing the product to be distilled and the collecting bulbs are connected to a rotary device (**Figure 1**).

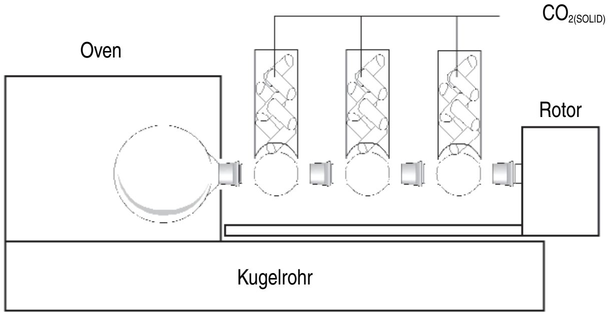

Figure 1: Bulb-to-bulb distillation apparatus with a cooling system of open cylinders filled with dry ice.

Traditionally, cooling of the collecting bulbs has been carried out with dry ice in acetone (-78˚C), especially when working with low-boiling substances or when distilling under vacuum. This cooling technique has several drawbacks:

a) Acetone is usually applied by a piece of cotton held with tweezers and may accidentally drip on the Kugelrohr apparatus and attack the plastic cover. It may also drip inside the housing, through the control buttons, and damage the electronic circuit boards. Acetone can also dissolve the plastic parts of the front panel and lead to the fusion of the buttons to the housing.

b) Acetone, because of its low flash point (-18 ˚C), could ignite if it contacts the electrical system since the rotor can generate sparks.

c) From an operational point of view, the ground joints, which connect the glass bulbs, usually are not lubricated with vacuum grease to avoid contaminating the final distillate during its recovery. As a result, and even though the bulb-to-bulb seal is usually good, a reabsorption of acetone through the joints could happen principally when the distillation is carried out under vacuum. In this case, contamination of the distillate with acetone could become a problem, especially when dealing with low-boiling substances.

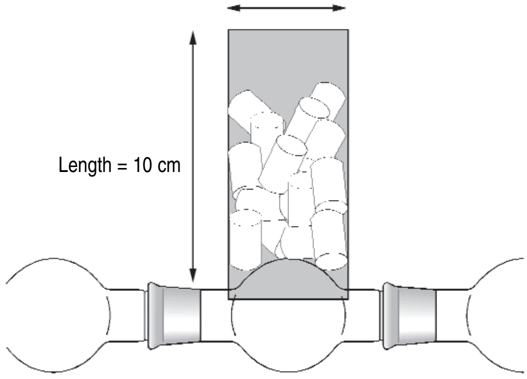

Figure 2(a): Detail of the cylindrical dry-ice container of the cooling system.

To avoid these problems, we have designed and used extensively a new, safe, and simple cooling system. In this system, the distillation bulbs are cooled with dry ice without the use of acetone. As containers of solid dry ice (coolers), we use cheap and readily available plastic or cardboard cylindrical tubs of 4 to 5 cm in diameter and 10 cm in length (**Figure 2a**).

To adapt the cylindrical container to the shape of the cooling bulb and to increase the cooling surface, it is recommended that two circular cuts be made on opposite sides of the bottom of the cylinder (**Figure 2b**).

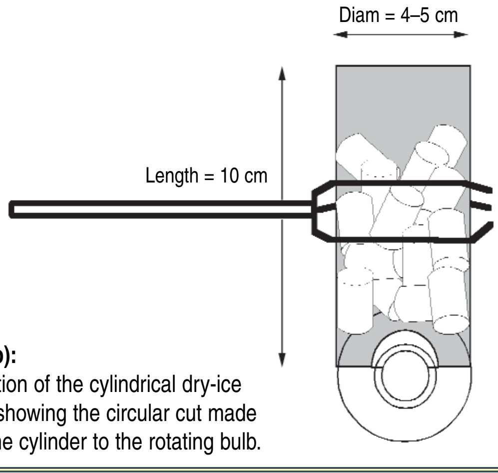

Figure 2(b):
Cross section of the cylindrical dry-ice container showing the circular cut made to adapt the cylinder to the rotating bulb.

Ángel M. Montaña, Ph.D., and **Pedro M. Grima**
Departamento de Química Orgánica, Universidad de Barcelona
Martí i Franquès 1-11, 08028-Barcelona, Spain
E-mail: ammontana@qo.ub.es

Do you have an innovative shortcut or unique laboratory hint you'd like to share with your fellow chemists? See the inside back cover for details.

Tailoring Polystyrene Solid-Phase Synthesis Resins: Incorporation of Flexible Cross-Linkers

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The Scripps Research Institute
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Outline

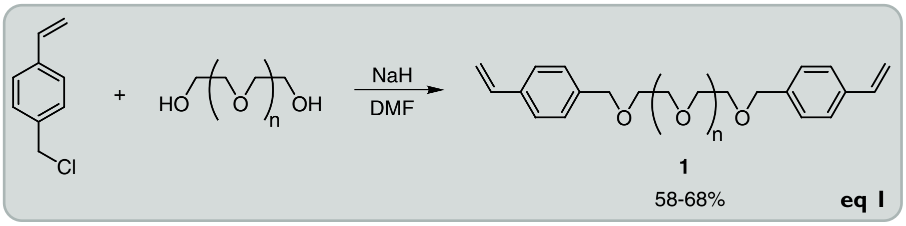
Pictured above, left to right: *Pat Toy*, *Kim Janda*, and *Tom Reger*

1. Introduction

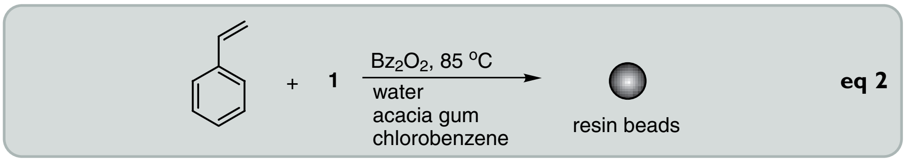
Combinatorial and parallel synthesis techniques have become commonplace in modern organic chemistry.[1] These techniques often employ polymeric supports to immobilize either the substrate or the reagent in order to simplify compound manipulation and purification. Insoluble polymer resins are most commonly used for such applications,[2] but soluble polymers have also proven useful.[3] Until recently, the insoluble polymer resin of choice has been the one originally introduced by Merrifield,[4] divinylbenzene-cross-linked polystyrene (DVB-PS), and this resin is commercially available derivatized with a wide variety of functional groups for substrate attachment.

While much research has been directed toward the optimization of linker groups for substrate and reagent attachment to the resin,[5] the field of resin development has been relatively neglected.[6] The bulk of research along this line has thus far focused on optimizing the polymeric supports for the specific requirements of oligomeric biomolecule synthesis.[7] Considering that the science of small-organic-molecule synthesis is much more widely practiced and more applicable to the process of drug discovery than the fields of polypeptide and polynucleotide synthesis, it seems odd that little has been done to develop solid-phase synthesis supports specifically designed for use in organic synthesis. This is especially true if "solid-phase synthesis supports are like solvents".[8] The reactions used in oligomeric biomolecule synthesis often require highly polar or aqueous solvents and reaction conditions, whereas small-organic-molecule synthesis often requires relatively nonpolar solvents or anhydrous reaction conditions. If one of the functions of the support is to solvate the substrate, it would seem logical that fundamentally different polymeric matrices would be required for optimal performance in these substantially different applications.

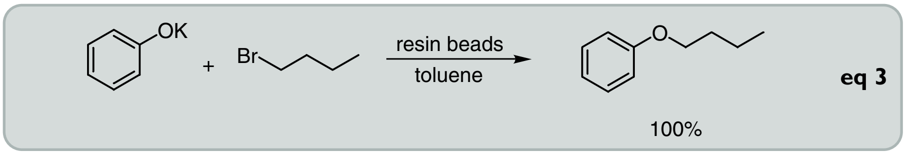
Strategies to identify polymeric supports that are more suitable for solid-phase *organic* synthesis (SPOS) have included the reformatting of DVB-PS;[9] the addition of either poly(ethylene glycol) (PEG),[10] polystyrene,[11] or hydrocarbon[12] grafts to DVB-PS resins; the use of macroporous polystyrene-[13] or PEG-based[14] matrices; and the grafting of polystyrene onto polypropylene[15] or Teflon® surfaces.[16] A different approach that has recently emerged involves the replacement of divinylbenzene as the cross-linker in polystyrene resins with relatively more flexible molecules. The preparation and utility of these polymers is the focus of the current review. The new cross-linkers have been designed both to increase the flexibility of the polymer backbone to allow for better diffusion through the matrix and also to impart a variety of solvent-like properties to the resins. While chiral *cross-linkers* have also been used, they are not discussed here, since the resins prepared with them were designed to induce the asymmetric catalysis of specific reactions rather than to serve as general supports for solid-phase synthesis.[17] The current review will only cover resins that are of general utility in the solid-phase synthesis of both peptides and small organic molecules.



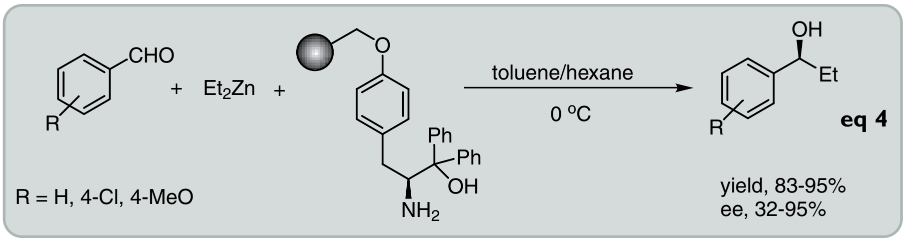
eq 1



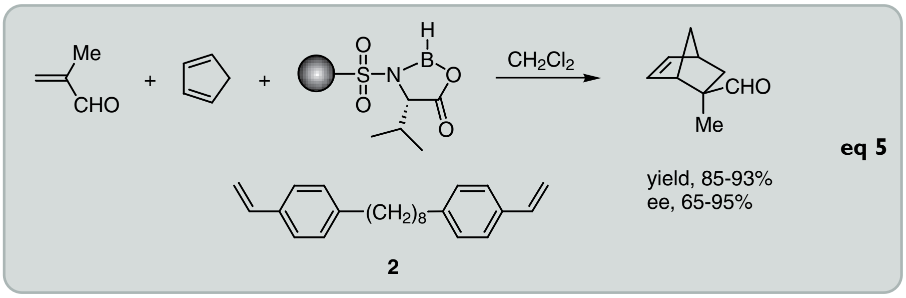
eq 2



eq 3



eq 4



eq 5

2. Poly(ethylene glycol) Cross-Linked Resins

The strategy of using flexible cross-linkers to prepare polystyrene resins was first introduced by Itsuno et al.[18] In this work, PEG molecules of various molecular weights were capped by two styrene moieties (**eq 1**) and these bifunctional molecules (**1**) were used to cross-link polystyrene resins. The resins were prepared by suspension polymerization (**eq 2**).[19] In this process, a stirred suspension of monomer solution droplets in an aqueous phase is heated to initiate radical polymerization, which converts each droplet into an individual resin bead.

2.1. Physical Properties

Kurth and co-workers have studied the physical properties of resins cross-linked by **1** (n = 1, 2, 4, and 6).[20] Polystyrene resins prepared with **1** (n = 1, 2, 4, and 6) were found to swell to a much greater extent than resins cross-linked with a comparable amount of DVB in solvents in which swelling was observed (toluene and dimethoxyethane). In fact, they found that a resin cross-linked with 20% **1** (n = 6) swelled nearly as much as 2% DVB-PS. This is significant since it is commonly observed that increased cross-linking leads to a dramatic decrease in resin swelling. It should be noted that only at such higher levels of cross-linking did resin swelling increase with PEG chain length. At lower levels of cross-linking, all resins exhibited similar swelling, regardless of cross-linker length.

The diffusive properties and mass transport through these PEG cross-linked resin beads were examined by measuring the kinetics of triethyloxonium tetrafluoroborate fluorescence quenching of dansyl groups covalently incorporated into the beads.[20] Unfortunately, the results of these studies were equivocal. The quenching, and therefore diffusion, was fastest in toluene, the solvent in which the resins exhibited the most swelling. This observation lends credibility to the common assumption that increased resin swelling is important to the overall success of solid-phase synthesis. However, the PEG cross-linked beads exhibited faster fluorescence quenching than 2% DVB-PS beads only in low-swelling solvents and slower quenching than 2% DVB-PS beads in high-swelling solvents. Since all of the PEG cross-linked beads swell to a greater extent than do DVB-PS beads, an unidentified phenomenon is clearly playing a role. Furthermore, it is interesting to note that the length of the cross-linker again appeared to have no effect on diffusion, since all PEG cross-linked resins of equal cross-linking exhibited similar rates of fluorescence quenching.

2.2. Phase-Transfer Catalysis

Itsuno et al. were the first to report the preparation (**eq 1**) and use of resins containing flexible cross-linkers **1**.[18] The basis for the design of these cross-linkers was to take advantage of the propensity of PEG to adopt helical crown ether-like conformations in order to prepare resins that would bind alkali cations, and thus would serve as phase-transfer catalysts in the Williamson ether synthesis. They prepared a variety of resins containing **1** and styrene and tested them as catalysts in the reaction of 1-bromobutane with potassium phenoxide (**eq 3**). It was observed that, when PEG with a molecular weight of ≥ 400 D (**1**, n > 7.7) was used to prepare the cross-linker, the resins did serve as effective phase-transfer catalysts. This is presumably due to the ability of the longer PEG chains to form the desired crown ether-like environments that bind potassium cations.

2.3. Catalysis of the Asymmetric Addition of Diethylzinc to Aldehydes

After establishing that beads of PEG cross-linked polystyrene resin were viable as phase-transfer catalysts, Itsuno et al. examined the attachment of a chiral auxiliary to such a resin and the ability of this auxiliary to induce asymmetric catalysis.[21] In this study, **1** (n = 3) was used as the cross-linking agent of the resin, and the reaction studied was the asymmetric ethylation of aromatic aldehydes (**eq 4**). It was observed that, when the chiral auxiliary was incorporated during the polymerization reaction in the form of a chiral monomer, resins cross-linked with **1** (n = 3) afforded higher enantioselectivities than did resins cross-linked with DVB. Apparently, the observed increased swelling of the resin incorporating **1** in the reaction medium results in better solvation and stabilization of the reaction complex, which lead to the enhanced enantioselectivity.

Another potentially important observation was that these resins appeared to be more mechanically stable than DVB-PS resins cross-linked at equal molar percentages. After 4 days of magnetic stirring in toluene, resin beads 20% cross-linked by **1** (n = 3) did not show any loss of shape, whereas 20% DVB-PS beads did.[21] The development of resins with increased mechanical stability would eliminate the need for the specialized reaction agitation methods and glassware commonly used in solid-phase synthesis. Standard glassware and magnetic stirring could be used, since stirring would not grind the resin and make it difficult to filter.

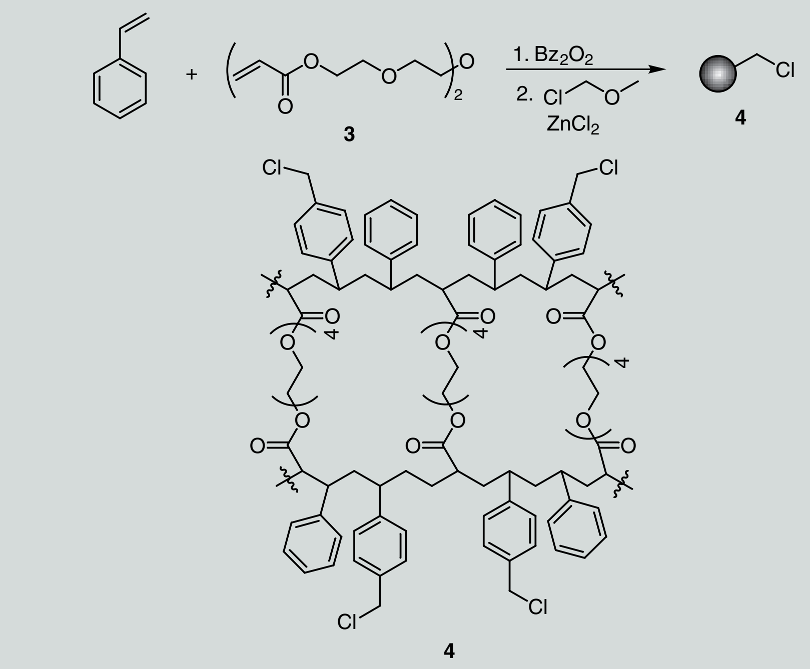
2.4. Catalysis of the Asymmetric Diels–Alder Reaction

The solid-phase, asymmetric Diels–Alder reaction of methacrolein with cyclopentadiene has also been examined using flexibly cross-linked resins (**eq 5**).[22] Results from resins cross-linked with DVB, **1** (n = 0, 3, and 7.7), and **2** were compared. The resin cross-linked with DVB afforded the lowest enantioselectivity, while resins containing **1** (n = 0, 3, and 7.7) afforded the highest. Interestingly, using cross-linker **2**, a hydrocarbon analog of **1**, resulted in intermediate enantioselectivity. This indicates that not only is the flexibility of **1** important, but that its polarity also plays a role in enhancing the asymmetric induction.

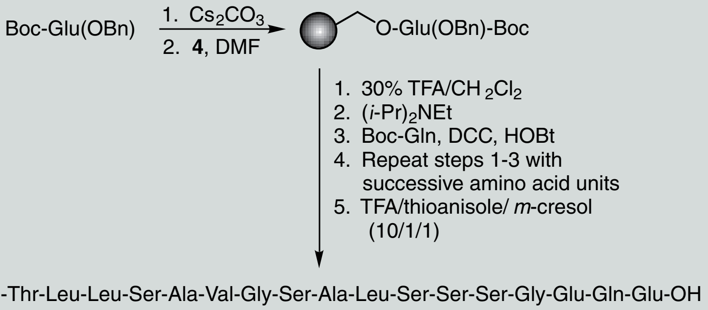
2.5. Polypeptide Synthesis

Pillai and co-workers have pioneered the use of PEG cross-linked polystyrene resins in polypeptide synthesis.[23] They prepared tetraethylene glycol diacrylate (**3**) and used it to prepare cross-linked resin **4**, in which the chloromethyl functional groups were introduced after polymerization (**eq 6**). Again, the tetraethylene glycol was incorporated with the intention of increasing the polarity of **4**, and thus making it more amenable for use in polypeptide synthesis. To demonstrate the utility of **4**, it was employed in the synthesis of the 18-residue, C-terminal region of Pardaxin using a standard Boc protecting group strategy to afford the pure polypeptide in 68% overall yield (**Scheme 1**).[23a] Pillai's group has also incorporated 4-chloromethyl-3-nitro, aminomethyl, α-bromopropionyl, α-aminopropionyl, 4-bromomethyl-3-nitrobenzamido, and 4-aminomethyl-3-nitrobenzamido linker groups into **4**. These linkers allow for peptide cleavage, in high yield and purity, by photolysis, trifluoroacetic acid treatment, transesterification, and ammonolysis.[23b] It was also found that **4**, containing 4 mole percent of **3**, was synthetically useful for the preparation of C-terminal peptide-*N*-alkylamides.[23c] While **4** has shown great utility in the synthesis of polypeptides, it should be noted that the ester linkages of **3** could make it less useful for the syntheses of small organic molecules, which require strongly basic or reductive reaction conditions.

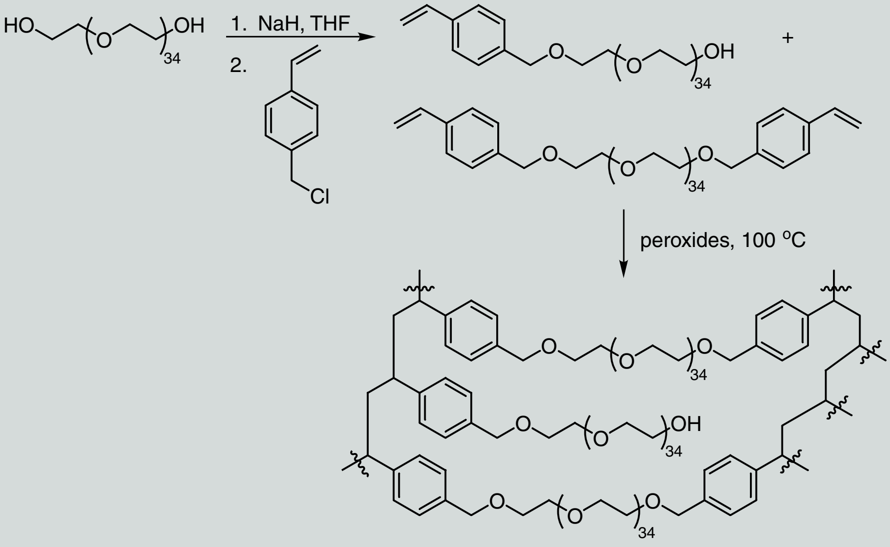
While the polymers studied by Pillai and Kurth contained little PEG relative to polystyrene, Meldal and co-workers have examined PEG-PS hybrid polymers, which



eq 6



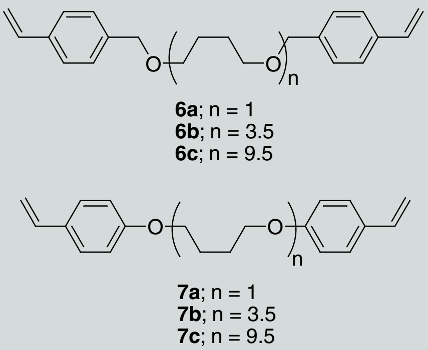
Scheme 1



5

Scheme 2

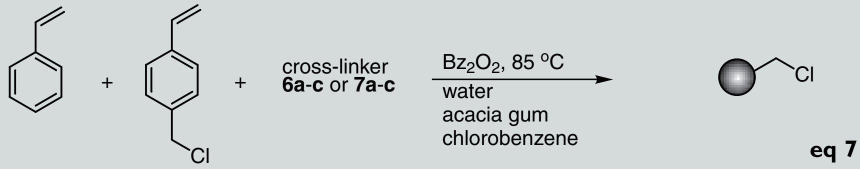
contain much higher proportions of PEG.[24] They randomly derivatized PEG (molecular weight 1500) with 4-vinylbenzyl chloride and polymerized the styrene functional groups of this product mixture to afford polymer **5** (**Scheme 2**). A pentapeptide was prepared with **5** using standard Fmoc-pentafluorophenyl ester methodology. In order to overcome the chemical lability of the benzyl ether linkages in **5**, they used 4-(3-chloropropyl)styrene for PEG alkylation in their second-generation resin.



6a; n = 1
6b; n = 3.5
6c; n = 9.5

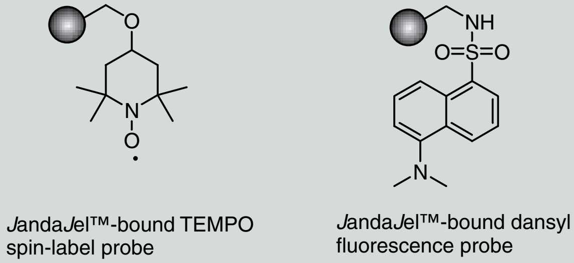
7a; n = 1
7b; n = 3.5
7c; n = 9.5

Figure 1. Polytetrahydrofuran Cross-Linkers.



eq 7

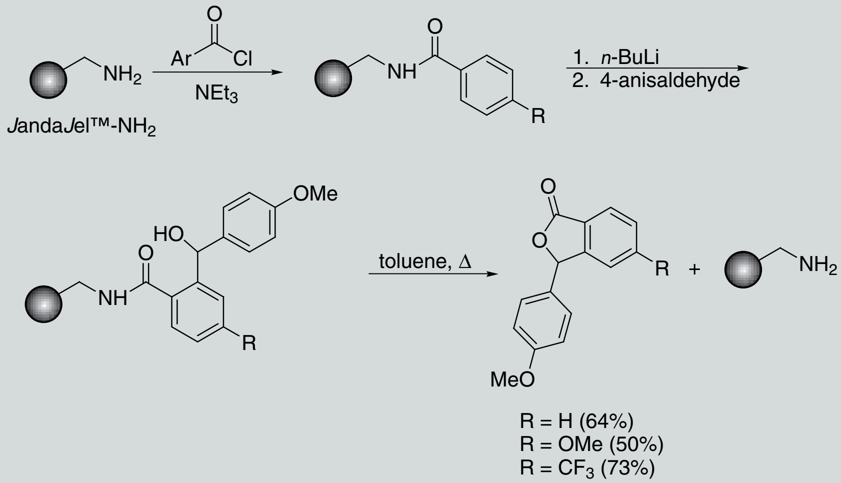
(When cross-linked with 2 mol % **7a**, the product resin is known by the trade name *J*anda*J*el™.)



*J*anda*J*el™-bound TEMPO spin-label probe

*J*anda*J*el™-bound dansyl fluorescence probe

Figure 2



Scheme 3

3. Polytetrahydrofuran Cross-Linked Resins

Recently, we introduced a class of resins designed specifically for SPOS. Unlike the PEG-based cross-linkers of Itsuno, Pillai, and Meldal, these resins incorporate cross-linkers **6** and **7**[25] that are derived from polytetrahydrofuran (PTHF) (**Figure 1**).[26,27] Since one of the functions of the resin is to solvate attached substrates, we thought it might be beneficial to use cross-linkers that closely resemble solvents used in traditional solution-phase synthesis. In this regard, tetrahydrofuran and diethyl ether (which architecturally resembles PTHF) are much more commonly used than ethylene glycol (which resembles PEG).

3.1. Physical Properties

The resin beads were prepared using the same suspension polymerization technique reported by Kurth[20] (**eq 7**), and were observed to exhibit remarkable swelling in solvents regularly used in organic synthesis (THF, dichloromethane, dimethylformamide, benzene, dioxane) as compared to standard DVB-PS resins.[26] It appears that the inherent flexibility and polarity of **6** and **7** allow for increased interaction between solvent and resin. This interaction is expected to enhance the performance in SPOS of resins incorporating **6** and **7**, since it is commonly believed that resin swelling is important for the success of SPOS.[28] Since the length of the cross-linker did not appear to be important in terms of increased swelling, **7a** was chosen for use in all subsequent studies. **7a** is the simplest and most economical to prepare, and the phenyl ether linkages are compatible with a broader range of reaction conditions than the benzylic linkages of **6a**. Resins containing 2 mole percent of **7a** are known as *J*anda*J*el™ resins.[27]

To analyze *J*anda*J*el™ on a molecular level and compare it to a standard DVB-PS Merrifield resin, EPR and fluorescence spectroscopy were employed.[29] The EPR study involved the incorporation of a TEMPO spin-label probe to determine the internal viscosity of the swollen resins (**Figure 2**). The fluorescence study involved the measurement of the fluorescence maxima of a dansyl probe incorporated into the resin (**Figure 2**).

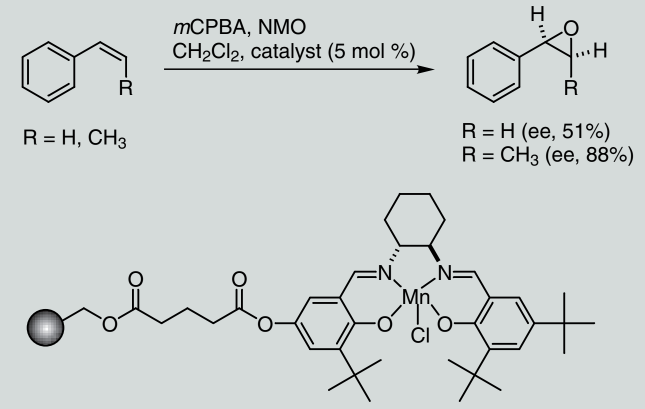
The results of these studies were equivocal, since the EPR data indicated that the viscosity of swollen *J*anda*J*el™ is greater than that of the Merrifield resin, but the fluorescence results showed that there is in fact a good correlation between swelling, solvation, and, perhaps, diffusion in the interior of the resin beads. Taken together, these results indicate that the relationship between resin swelling, solvation, and diffusion is complex and that more research is required in order to better understand the processes involved.

3.2. Directed Ortho Lithiation and Phthalide Library Synthesis

To demonstrate the synthetic utility of the new resins, we prepared a combinatorial library of phthalide compounds using directed ortho-lithiation reactions (**Scheme 3**).[30] The use of this type of directed ortho-metallation reaction in solid-phase synthesis had previously had only limited success. We showed that, under mild reaction conditions, an array of both metallation substrates and electrophiles could be used to afford the desired products in good yields. Importantly, it was found that the PTHF resins afforded higher yields than did the DVB-PS resin. Another noteworthy aspect of the synthetic scheme is that cleavage of the product is an intramolecular process, and, therefore, only the desired molecules are released from the resin upon heating, leading to essentially pure products.

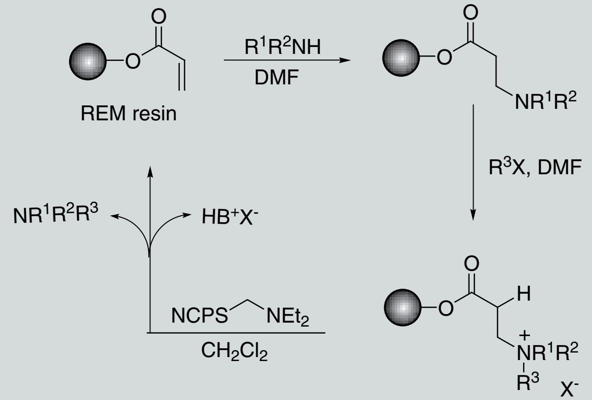
3.3. Catalysis of the Jacobsen Asymmetric Epoxidation

In an effort to develop a reuseable catalyst for the asymmetric epoxidation of unfunctionalized olefins, we have attached a chiral (salen)Mn complex to *J*anda*J*el™.[31] The complex is linked to hydroxymethyl-functionalized resin through a glutarate spacer. This places the catalyst sufficiently away from the polymer backbone to allow unimpeded access of the olefinic substrate to the active metal center. As substrates for the supported catalyst, we examined styrene and *cis*-β-methylstyrene, which, upon reaction with *m*CPBA/NMO, provided the desired epoxides with enantiomeric excesses that were nearly equivalent to those achieved using the commercial, homogeneous Jacobsen catalyst (**eq 8**). The catalyst was used for three cycles before a significant decline in enantioselectivity or yield was observed. This system offers an improvement over earlier attempts to immobilize this expensive catalyst system on an insoluble support, since the previous systems generally suffered from the inability of reuse and/or lower enantioselectivities. The superior swelling of *J*anda*J*el™ may result in better solvation of the reaction complex thus minimizing any loss of enantioselectivity resulting from heterogenization of the catalyst.



JandaJel™-supported Jacobsen catalyst

eq 8



Scheme 4

3.4. Multipolymer System for the Synthesis of Tertiary Amines

In another example of the utility of *J*anda*J*el™, we have combined the use of soluble polystyrene with the insoluble cross-linked resin. An acrylate linker was attached to the hydroxymethyl resin to afford a REM resin,[32] which was used to prepare tertiary amines (**Scheme 4**).[33] In the original work with REM resin, a tertiary amine base was used to effect the elimination of the product from the resin and the product salts had to be removed by either extraction or chromatography.[32] We eliminated the need for final purification by attaching the tertiary amine base to soluble, non-cross-linked polystyrene (NCPS). NCPS was found to effectively cleave the products from the resin. Removal of the reusable resin by filtration was followed by concentration of the reaction solution, which contained both the desired product and the NCPS byproducts. The resulting mixture was washed with methanol to dissolve the product but not the NCPS; concentration of the methanol solution afforded the pure products. This work is important because it is the first example of the use of soluble polymer-bound reagents to cleave products from SPOS resins. This concept could be exploited to increase the array of available cleavage reactions, which do not generate byproducts that necessitate product purification; in turn, this would dramatically increase the SPOS universe in terms of types of reactions used and classes of compounds prepared.

3.5. Shape-Encoded Urea Library Synthesis

In developing a new encoding system for the deconvolution of split-mix combinatorial compound libraries, we have used monolithic polystyrene forms cross-linked with **7a** (**Figure 3**).[34] In a seminal publication, Sherrington and co-workers reported that monolithic polystyrene discs could function as supports for solid-phase synthesis.[9a] These discs were prepared simply by polymerizing styrene and divinylbenzene in test tubes and slicing the thus formed polymeric rods into discs of the desired thickness. This observation inspired us to prepare a series of monoliths of different shapes in which the shape itself served as an encoding element. Using this methodology, 24 out of a theoretical 25-member library of urea compounds were prepared using only 11 reactions (**Scheme 5**).

4. Miscellaneous Resins

In work similar to that of Janda and co-workers, Pillai's group introduced a series

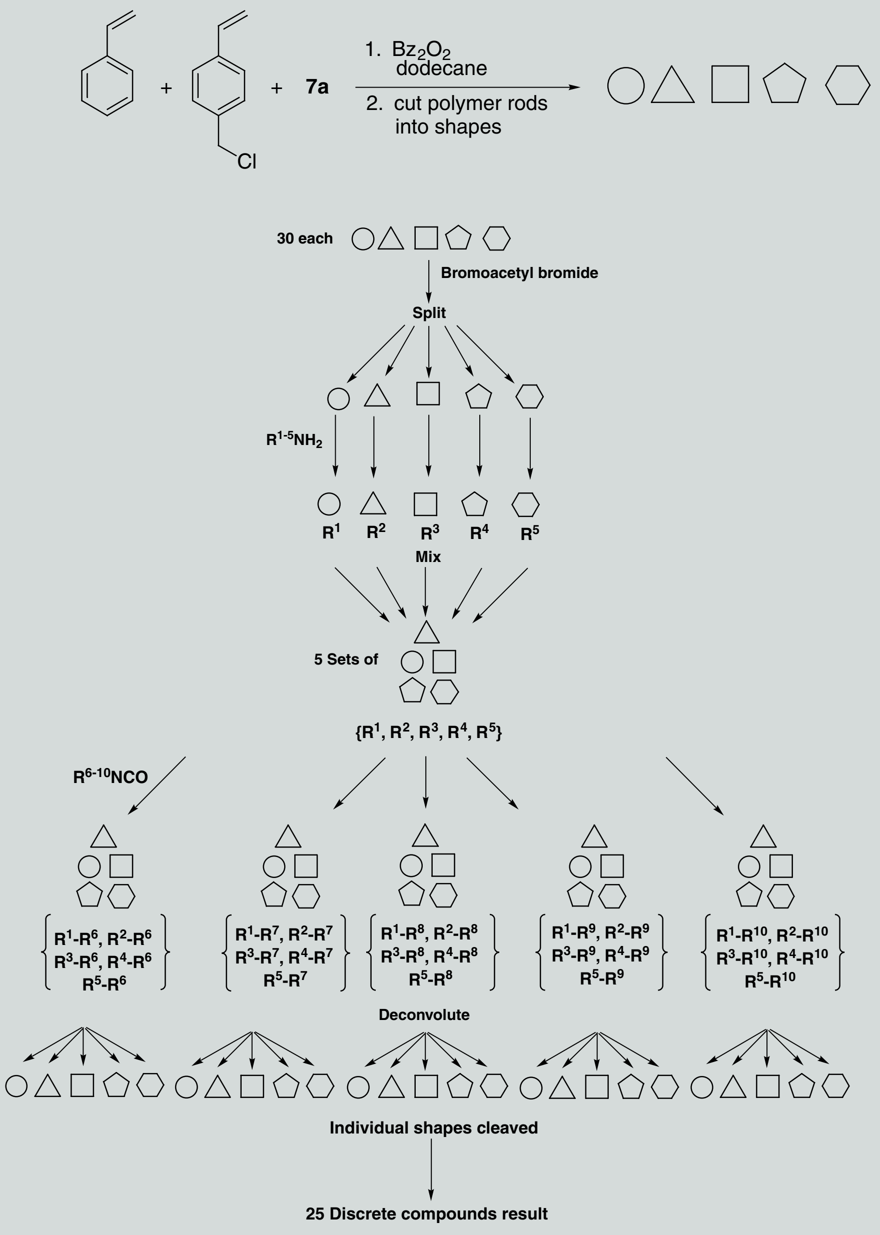
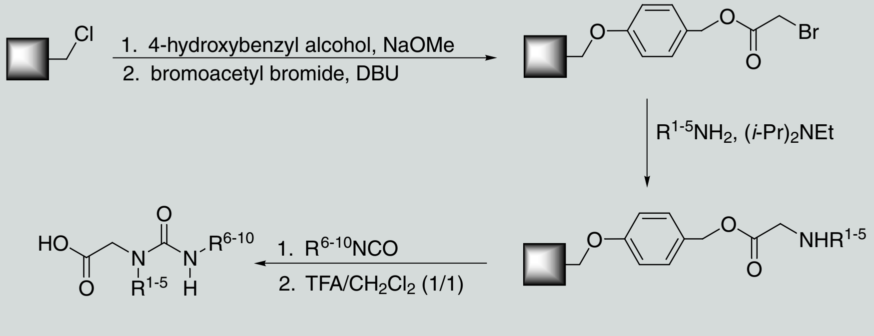


Figure 3



Scheme 5

of resins for the solid-phase synthesis of nonpolar polypeptide sequences, and attempted to modulate and optimize the polarity of the resins by incorporating 1,4-butanediol diacrylate (**8**) and 1,6-hexanediol diacrylate (**9**) (**eq 9**).[35] They chose these cross-linkers as replacements for **3**, because they were less polar in nature.

4.1. Polypeptide Synthesis

Polystyrene resins **8**-PS and **9**-PS were prepared from **8** and **9**, respectively, and were used for the synthesis of a variety of polypeptides. The first report of the utility of **9**-PS was the synthesis of partial-sequence fragments of thioredoxin using standard coupling procedures.[35a,b] Resin **8**-PS was employed as the support for the synthesis of several model polypeptides.[35c] Importantly, it was found that **9**-PS afforded better coupling yields and higher product purities than DVB-PS in the synthesis of identical sequences, thus validating the researchers' hypothesis.[35d]

5. Concluding Remarks

The emergence of combinatorial chemistry has spurred renewed interest in polymer-assisted synthesis. As more elaborate solid-phase syntheses are undertaken and more demanding reaction conditions are used, polymers with different physical and chemical properties will become necessary. Polystyrene resins have served admirably as supports for a variety of reactions and as the basis for the research described in this account. The modification and fine tuning of the structure and polarity of the polystyrene cross-linker has resulted in polymers with unique and improved properties. It is expected that future research in this field will further advance the science of solid-phase synthesis.

6. Acknowledgements

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7. References and Notes

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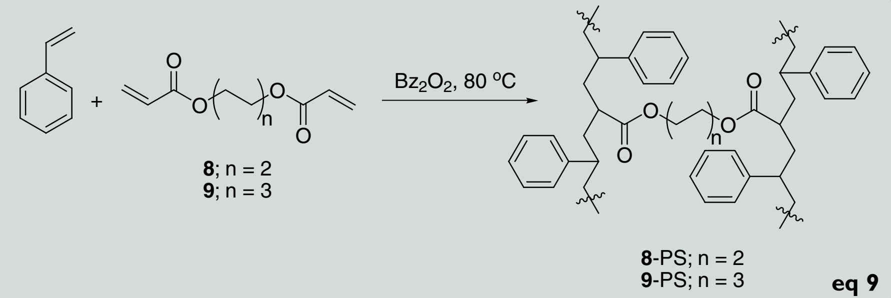

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(27) Resins containing 2 mole percent **7a** are known as *J*anda*J*els™ and are available—with aminomethyl, chloromethyl, hydroxymethyl, and Wang linker functional groups—from Aldrich Chemical Co. See page 94 of this issue for more details.

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Patrick H. Toy received a B.S. degree in chemistry from The Ohio State University (1990). He began his graduate studies in organic chemistry at The University of Minnesota with the late Professor Paul G. Gassman. He finished his Ph.D. studies with Professor Martin Newcomb at Wayne State University, where he studied the mechanisms of enzyme-catalyzed hydroxylation reactions (1998). As a postdoctoral research associate at The Scripps Research Institute with Professor Kim D. Janda, he invented the *J*anda*J*el™ solid-phase organic synthesis resins. He is currently learning the intricacies of combinatorial synthesis from the drug discovery perspective at Wyeth-Ayerst Research.

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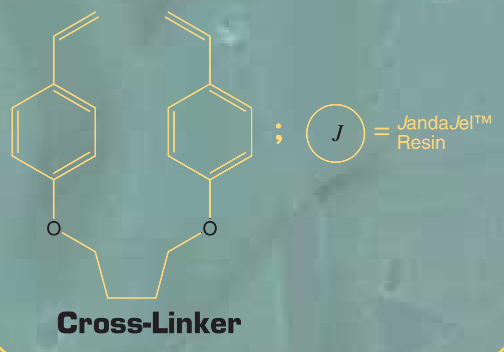

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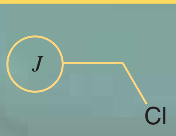
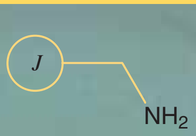


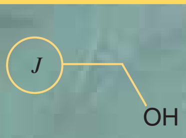
52,453-0 50-100 mesh
52,454-9 100-200 mesh
52,455-7 200-400 mesh

*J*anda*J*el™ -NH_2



52,460-3 50-100 mesh
52,461-1 100-200 mesh

*J*anda*J*el™ -OH



52,456-5 50-100 mesh
52,457-3 100-200 mesh

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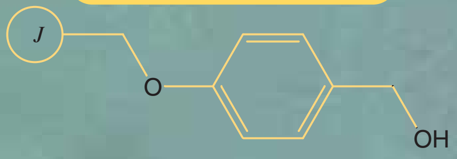

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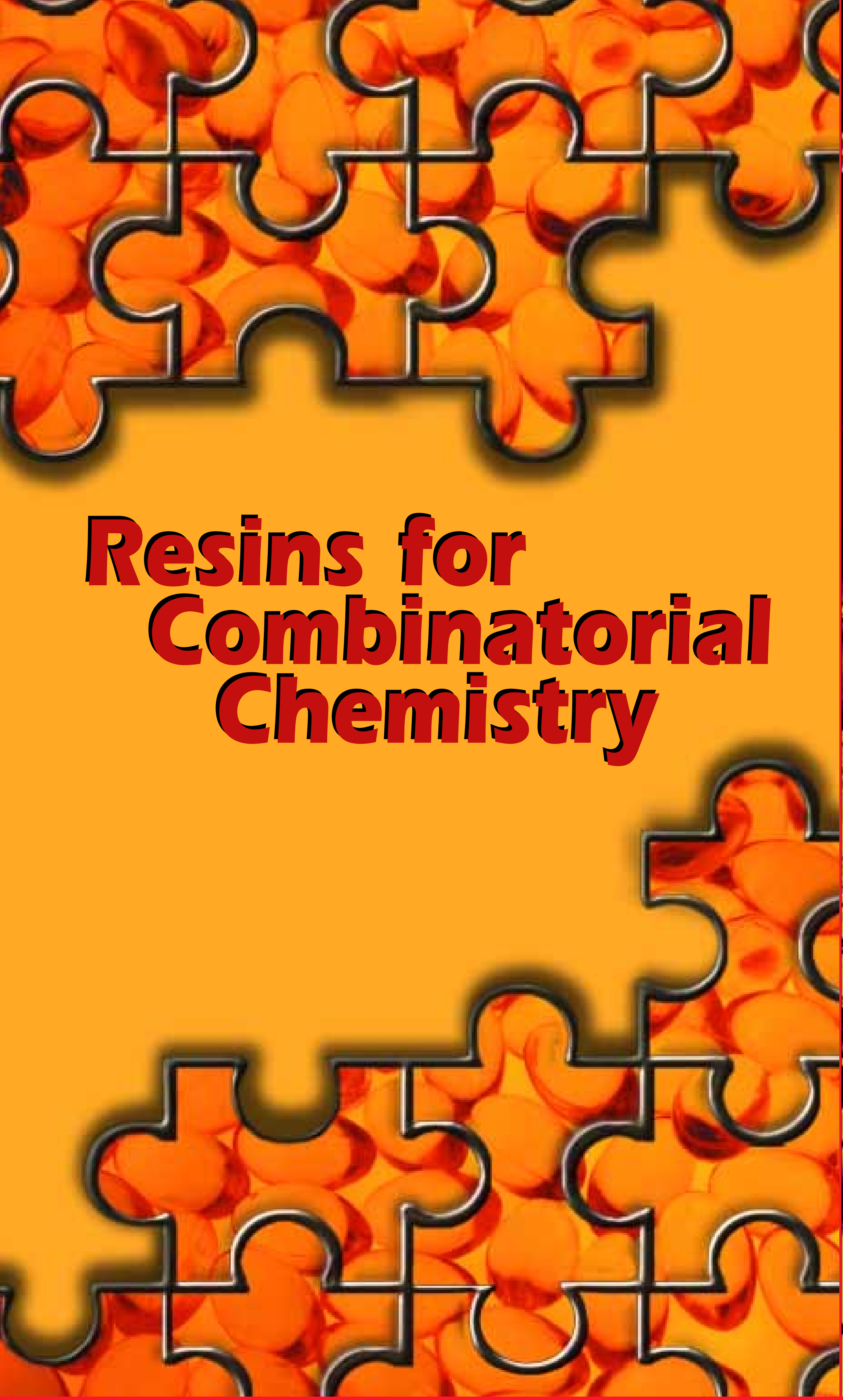

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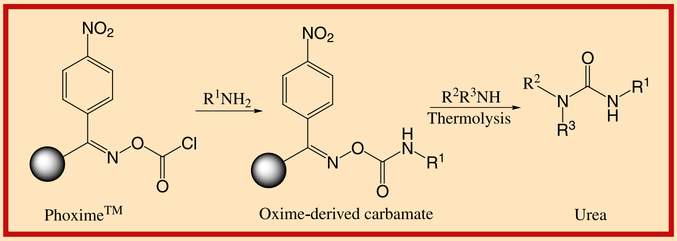

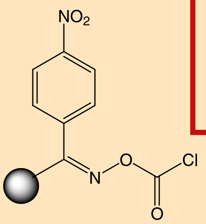

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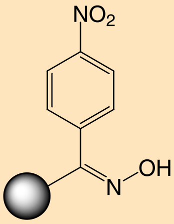

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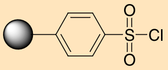
New Scavenger Resins

Sulfonyl chloride, polymer-bound

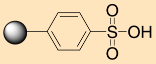


Reacts with alcohols and amines.[2,3]

51,623-6, 100-200 mesh, 1.5-2.0 mmol/g,

51,622-8, macroporous, 70-90 mesh, 2.5-3.5 mmol/g

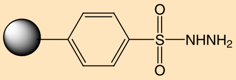
p-Toluenesulfonic acid, polymer-bound



Reacts with alcohols and amines.[4]

53,231-2, macroporous, 30-60 mesh, 2.0-3.0 mmol/g

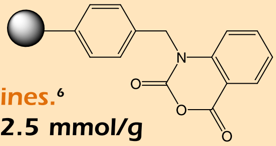
p-Toluenesulfonyl hydrazide, polymer-bound



Reacts with aldehydes and ketones.[5]

53,233-9, 100-200 mesh, *ca.* 1.5 mmol/g

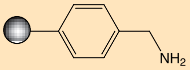
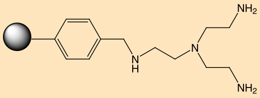
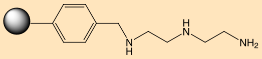
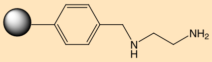
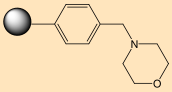
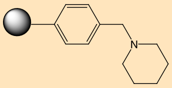
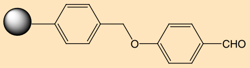
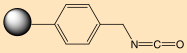
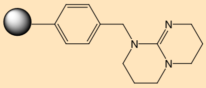
Isatoic anhydride, polymer-bound



Reacts with amines and hydrazines.[6]

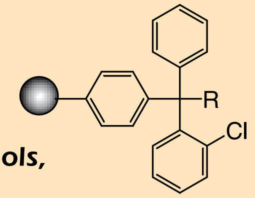
51,437-3, 200-400 mesh, 2.0-2.5 mmol/g

Other Scavengers

Resin Name	Structure	Reacts with
Poly(styrene-*co*-divinylbenzene), aminomethylated **51,563-9, 70-90 mesh, 1.5-2.0 mmol N/g** **47,366-9, 200-400 mesh, *ca.* 2 mmol N/g** **47,367-7, 200-400 mesh, *ca.* 4 mmol N/g**		**RCOCl, RSO_2Cl,** **RNCO, RNCS, H^+**
Tris(2-aminoethyl)amine, polymer-bound **47,210-7, 4.0-5.0 mmol N/g**		**RCOCl, RSO_2Cl,** **RNCO, RNCS, H^+**
Diethylenetriamine, polymer-bound **47,978-0, 200-400 mesh, 2.5-3.0 mmol N/g**		**RCOCl, RSO_2Cl,** **RNCO, RNCS, H^+,** **RCHO, Anhydrides**
Ethylenediamine, polymer-bound **47,209-3, 200-400 mesh, 2.5-3.0 mmol N/g**		**RCOCl, RSO_2Cl,** **RNCO, RNCS, H^+,** **RCHO**
Morpholine, polymer-bound **49,381-3, 200-400 mesh, 2.5-4.0 mmol N/g**		**H^+**
Piperidine, polymer-bound **49,461-5, 200-400 mesh, 3.0-4.0 mmol N/g**		**H^+**
4-Benzyloxybenzaldehyde, polymer-bound **47,208-5, 200-400 mesh, 2.5-3.0 mmol CHO/g**		**RNH_2, $RNHNH_2$, NH_2OR,** **1,2-Aminothiols**
Isocyanate, polymer-bound **47,368-5, 200-400 mesh, 1.75-2.25 mmol N/g**		**RNH_2, $RNHNH_2$, RO^-**
1,3,4,6,7,8-Hexahydro-2*H*-pyrimido[1,2-*a*]-pyrimidine, polymer-bound* **35,875-4, 8.0-8.5 mmol N/g**		**Ar-OH, ROOR**

***7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD), polymer-bound**

2-Chlorotrityl Resins



2-Chlorotrityl resins[7-9] were developed for the attachment of carboxylic acids, alcohols, phenols, and amines under very mild conditions.

2-Chlorotrityl chloride, polymer-bound

R= Cl

53,230-4 100-200 mesh, 1% DVB, 1.0-1.5 mmol/g
53,229-0 200-400 mesh, 1% DVB, 1.0-1.5 mmol/g
53,228-2 200-400 mesh, 2% DVB, 0.3-0.8 mmol/g

An acid-labile resin that was first utilized for the attachment of carboxylic acids for SPPS. More recently, this versatile support has been used for the immobilization of alcohols,[10] phenols,[11] amines,[12] and hydroxylamines.[13]

2-Chlorotrityl alcohol, polymer-bound

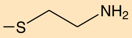
R= OH

52,938-9 200-400 mesh, 1% DVB, 0.4-0.6 mmol/g

An acid-labile resin that can be used for the immobilization of hydrazines and thiols.

2-Chlorotrityl cysteamine, polymer-bound

R=



53,010-7 200-400 mesh, 1% DVB, 0.4-0.6 mmol/g

An acid-labile resin that possesses a free amine, which allows this resin to be used in the preparation of cysteamines.

2-Chlorotrityl glycinol, polymer-bound

R= $O(CH_2)_2NH_2$

53,029-8 200-400 mesh, 1% DVB, 0.4-1.0 mmol/g

An acid-labile resin that can be used in the formation of ß-amino alcohols.

2-Chlorotrityl hydrazine, polymer-bound

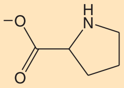
R= $HNNH_2$

53,094-8 200-400 mesh, 1% DVB, 0.4-0.6 mmol/g

2-Chlorotrityl hydrazine resin has been utilized in the preparation of hydrazides and hydrazones.[14]

2-Chlorotrityl proline, polymer-bound

R=

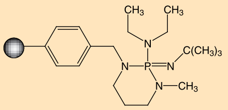


52,939-7 200-400 mesh, 1% DVB, 0.4-1.0 mmol/g

An acid-labile resin for the preparation of prolines.

Other New Linkers

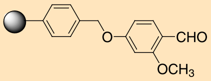
2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine, polymer-bound (BEMP resin)



53,649-0 100-200 mesh, 1% DVB, 2.0-2.5 mmol/g

A polymer-supported base used for the N-alkylation reactions of weakly acidic heterocycles.[15] Utilized in the synthesis of unnatural peptides.[16]

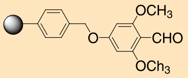
AMEBA resin (FMP resin; Sasrin Aldehyde resin)



51,644-9 100-200 mesh, 1% DVB, 1.0-1.5 mmol/g

*AMEBA (**A**cid-sensitive **ME**thoxy**B**enz**A**ldehyde) resin is an acid-labile resin utilized in the synthesis of secondary sulfonamides, amides, ureas, and carbamates.[17-20]*

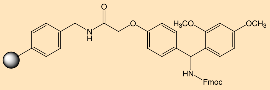
4-Hydroxy-2,6-dimethoxybenzaldehyde, polymer-bound



53,821-3 100-200 mesh, 1% DVB, 1.0-1.5 mmol/g

An acid-sensitive linker employed in the synthesis of sulfonamides and carboxamides.

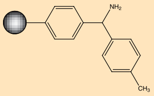
Knorr Linker amide resin (Rink Amide AM resin)



52,429-8 100-200 mesh, 1% DVB, 0.4-0.6 mmol/g

Utilized in the synthesis of carboxamides.[21,22]

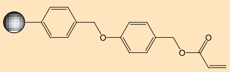
4-Methylbenzhydrylamine hydrochloride, polymer-bound (MBHA)



51,322-9 100-200 mesh, 1% DVB, 0.5-1.0 mmol/g

Used to attach carboxylic acids or amines in the synthesis of peptides.

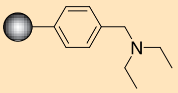
REM resin on Wang



53,738-1 70-90 mesh, 1% DVB, *ca.* 0.5 mmol/g

REM supported on Wang resin is utilized in the synthesis of 5,6-dihydropyrimidine-2,4-diones[23] and N-substituted ß-aminopropionic acid oligomers.[24]

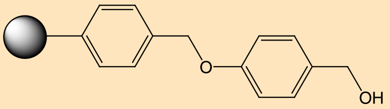
Diethylamine, polymer-bound



53,733-0 100-200 mesh, 1% DVB, 1.0-1.5 mmol/g

Diethylamine resin is a versatile base support for SPOS.[25]

Benzyloxybenzyl alcohol, polymer-bound (Wang Resins)



For many years, Wang resin has been utilized as a linker for peptide synthesis. Recently, Wang resin was found to be very useful in SPOS as an immobilization resin for acids and phenols.[26]

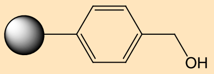
New Wang Resins

51,564-7	**70-90 mesh, 1% DVB, 0.5-1.0 mmol/g**
51,565-5	**70-90 mesh, 1% DVB, 1.0-1.5 mmol/g**
51,033-5	**70-90 mesh, 1% DVB, 1.5-2.0 mmol/g**
51,475-6	**200-400 mesh, 1% DVB, 0.5-1.0 mmol/g**
52,052-7	**200-400 mesh, 1% DVB, 1.5-2.0 mmol/g**

Additional Wang Resins

47,063-5	**100-200 mesh, 1% DVB, 0.5-1.0 mmol/g**
52,277-5	**100-200 mesh, 1% DVB, 0.7-1.0 mmol/g**
52,060-8	**100-200 mesh, 1% DVB, 1.0-1.5 mmol/g**
51,474-8	**100-200 mesh, 1% DVB, 1.5-2.0 mmol/g**
47,703-6	**200-400 mesh, 1% DVB, 1.0-1.5 mmol/g**

Benzyl alcohol, polymer-bound

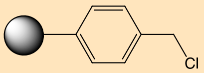


Benzyl alcohol, polymer-bound, also called hydroxymethylpolystyrene, is similar to Merrifield resin in that its utility lies with the immobilization of carboxylic acids. Further, this resin can be modified for the attachment of amines.[27]

New Hydroxymethylpolystyrenes

51,566-3	**70-90 mesh, 1% DVB, 0.5-1.0 mmol/g**
51,567-1	**70-90 mesh, 1% DVB, 1.0-1.5 mmol/g**
49,922-6	**70-90 mesh, 1% DVB, 2.0-3.0 mmol/g**
51,476-4	**100-200 mesh, 1% DVB, 0.5-1.0 mmol/g**
48,512-8	**100-200 mesh, 1% DVB, 1.0-2.0 mmol/g**

Merrifield Resins

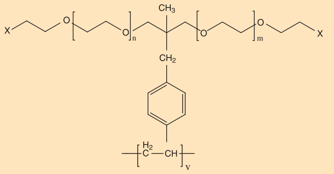


Historically, this resin has been used as a solid support for peptide synthesis. Recent applications include its use as a support for carboxylic acids in SPOS.

49,919-6	**70-90 mesh, 1% DVB, 1.0-1.5 mmol/g**
49,918-8	**70-90 mesh, 1% DVB, 1.5-2.0 mmol/g**
51,607-4	**100-200 mesh, 1% DVB, 0.5-1.0 mmol/g**
51,595-7	**100-200 mesh, 1% DVB, 1.0-1.5 mmol/g**
49,704-5	**100-200 mesh, 1% DVB, 1.5-2.0 mmol/g**
49,705-3	**100-200 mesh, 1% DVB, 2.0-3.0 mmol/g**
49,706-1	**100-200 mesh, 1% DVB, 3.5-4.5 mmol/g**
22,148-1	**200-400 mesh, 1% DVB, 1.0-1.5 mmol/g**
43,795-6	**200-400 mesh, 1% DVB, 1.5-2.0 mmol/g**
45,696-9	**200-400 mesh, 1% DVB, 3.0-3.5 mmol/g**
47,451-7	**200-400 mesh, 1% DVB, 3.5-4.5 mmol/g**
22,150-3	**200-400 mesh, 2% DVB, 1.0-1.5 mmol/g**
44,911-3	**200-400 mesh, 2% DVB, 2.0-2.5 mmol/g**

References: (1) Scialdone, M.A. *J. Org. Chem.* **1998**, *63*, 4802. (2) Zhong, H.E. et al. *ibid.* **1997**, *62*, 9326. (3) Rueter, J.K. et al. *Tetrahedron Lett.* **1998**, *39*, 975. (4) Flynn, D.L. et al. *J. Am. Chem. Soc.* **1997**, *119*, 4874. (5) Emerson, D.W. et al. *J. Org. Chem.* **1979**, *44*, 4634. (6) Coppola, G.M. *Tetrahedron Lett.* **1998**, *39*, 8233. (7) Akaji, K.; Kiso, Y. *ibid.* **1997**, *38*, 5185. (8) Marti, R.E. et al. *ibid.* **1997**, *38*, 6145. (9) McNally, J.J. et al. *ibid.* **1998**, *39*, 967. (10) Wenschuh, H. et al. *J. Org. Chem.* **1995**, *60*, 405. (11) Shankar, B.B. et al. *Tetrahedron Lett.* **1998**, *39*, 2447. (12) Hoekstra, W.J. et al. *ibid.* **1997**, *38*, 2629. (13) Mellor, S.L. et al. *ibid.* **1997**, *38*, 3311. (14) Stravropoulos, G. et al. *Lett. Pept. Sci.* **1995**, *2*, 315. (15) Wei, X. et al. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1089. (16) O'Donnell, M.J. et al. *J. Am. Chem. Soc.* **1996**, *118*, 6070. (17) Wilson, T.M. et. al. *Tetrahedron Lett.* **1997**, *38*, 7151. (18) Sarantakis, D.; Bickster, J.J. *ibid.* **1997**, *38*, 7325. (19) Kearney, P.C. et al. *J. Org. Chem.* **1998**, *63*, 196. (20) Bilodeau, M.T.; Cunningham, A.M. *ibid.* **1998**, *63*, 2800. (21) Rink, H. *Tetrahedron Lett.* **1987**, *28*, 3787. (22) Albericio, F. et al. *J. Org. Chem.* **1990** *55*, 3730. (23) Kolodziej, S.A.; Hamper, B.C. *Tetrahedron Lett.* **1996**, *37*, 5277. (24) Hamper, B.C. et al. *J. Org. Chem.* **1998**, *63*, 708. (25) Berteina, S.; De Maesmaeker, A. *ibid.* **1998**, *39*, 5759. (26) Wang, Y; Wilson, S.R. *Tetrahedron Lett.* **1997**, *38*, 4021. (27) Burdick, D.J. et al. *ibid.* **1993**, *34*, 2589.

ArgoGel® Resins



ArgoGel® resins offer several advantages over standard polystyrene resins, including (1) a solution-like environment for bound molecules that facilitates the transition of synthesis conditions between the solid and solution phases, and (2) excellent gel-phase NMR capabilities.

48,247-1	**ArgoGel® - Cl**	**mean bead size 170 µm, 0.4-0.5 mmol/g**
48,270-6	**ArgoGel® - Wang-Cl**	**mean bead size 170 µm, 0.35-0.45 mmol/g**
48,236-6	**ArgoGel® - OH**	**mean bead size 170 µm, 0.4-0.5 mmol/g**
49,567-0	**ArgoGel® - MB-OH**	**mean bead size 170 µm, 0.35-0.40 mmol/g**
48,245-5	**ArgoGel® - Wang**	**mean bead size 170 µm, 0.35-0.45 mmol/g**
48,243-9	**ArgoGel® - NH_2**	**mean bead size 170 µm, 0.4-0.5 mmol/g**
48,244-7	**ArgoGel® - AS-SO_2NH_2**	**mean bead size 170 µm, 0.35-0.41 mmol/g**
48,268-4	**ArgoGel® - MB-CHO**	**mean bead size 170 µm, 0.35-0.45 mmol/g**
48,267-6	**ArgoGel® - Rink**	**mean bead size 170 µm, 0.3-0.4 mmol/g**

ArgoPore® Resins

ArgoPore® macroporous resin beads are characterized by high internal surface areas and cross-linking levels. Advantages include: (1) compatibility with a greater range of solvents, (2) low predictable swelling in all solvents, and (3) ideally suited to automation.

48,250-1	**ArgoPore® - Cl**	**60-140 mesh, 0.6-1.1 mmol/g**
49,565-4	**ArgoPore® - OH**	**60-140 mesh, 0.6-1.1 mmol/g**
48,252-8	**ArgoPore® - Wang**	**60-140 mesh, 0.5-1.0 mmol/g**
49,564-6	**ArgoPore® - NH_2 LL (Low Loading)**	**60-140 mesh, 0.2-0.6 mmol/g**
48,249-8	**ArgoPore® - NH_2**	**60-140 mesh, 0.6-1.1 mmol/g**
49,563-8	**ArgoPore® - NH_2 HL (High Loading)**	**60-140 mesh, 1.1-1.6 mmol/g**
48,253-6	**ArgoPore® - AS-SO_2-NH_2**	**60-140 mesh, 0.5-1.0 mmol/g**
49,566-2	**ArgoPore® - MB-CHO**	**60-140 mesh, 0.5-0.9 mmol/g**
48,272-2	**ArgoPore® - Rink**	**60-140 mesh, 1.0-2.0 mmol/g**

TentaGel™ Resins

TentaGel™ resins exhibit high-pressure stability and excellent swelling properties in aqueous media and in many organic solvents.

86331F	**TentaGel™ HL-Br**	**mean bead size 110 µm, *ca.* 0.48 mmol/g**
86332F	**TentaGel™ HL-$CH(OEt)_2$**	**mean bead size 110 µm, *ca.* 0.40 mmol/g**
86333F	**TentaGel™ HL-COOH**	**mean bead size 110 µm, *ca.* 0.40 mmol/g**
86334F	**TentaGel™ HL-NH_2**	**mean bead size 110 µm, *ca.* 0.40 mmol/g**
86337F	**TentaGel™ HL-OH**	**mean bead size 110 µm, *ca.* 0.40 mmol/g**
86341F	**TentaGel™ HL-PHB**	**mean bead size 75 µm, *ca.* 0.35 mmol/g**
86342F	**TentaGel™ HL-RAM**	**mean bead size 75 µm, *ca.* 0.35 mmol/g**
86343F	**TentaGel™ HL-S-Trityl**	**mean bead size 110 µm, *ca.* 0.40 mmol/g**
86353F	**TentaGel™ MB-Br**	**mean bead size 140-170- µm, *ca.* 0.40 mmol/g**
86354F	**TentaGel™ MB-$CH(OEt)_2$**	**mean bead size 140-170 µm, *ca.* 0.40 mmol/g**
86355F	**TentaGel™ MB-COOH**	**mean bead size 140-170 µm, *ca.* 0.40 mmol/g**
86356F	**TentaGel™ MB-NH_2**	**mean bead size 140-170 µm, *ca.* 0.40 mmol/g**
86371F	**TentaGel™ MB-OH**	**mean bead size 140-170 µm, *ca.* 0.40 mmol/g**
86373F	**TentaGel™ MB-PHB**	**mean bead size 140-170 µm, *ca.* 0.40 mmol/g**
86374F	**TentaGel™ MB-RAM**	**mean bead size 140-170 µm, *ca.* 0.35 mmol/g**
86376F	**TentaGel™ MB-S-Trityl**	**mean bead size 140-170 µm, *ca.* 0.35 mmol/g**
86363F	**TentaGel™ S-Br**	**mean bead size 90 µm, *ca.* 0.26 mmol Br/g**
86357F	**TentaGel™ S-Br**	**mean bead size *ca.* 130 µm, *ca.* 0.25 mmol Br/g**
86336F	**TentaGel™ S-COOH**	**mean bead size 90 µm, *ca.* 0.25 mmol/g**
86358F	**TentaGel™ S-COOH**	**mean bead size 150-200 µm, *ca.* 0.25 mmol/g**
86364F	**TentaGel™ S-NH_2**	**mean bead size 90 µm, *ca.* 0.26 mmol/g**
86359F	**TentaGel™ S-NH_2**	**mean bead size 150-200 µm, *ca.* 0.45 mmol/g**
86365F	**TentaGel™ S-OH**	**mean bead size 90 µm, *ca.* 0.26 mmol/g**
86361F	**TentaGel™ S-OH**	**mean bead size 100-200 µm, *ca.* 0.26 mmol/g**
86366F	**TentaGel™ S-PHB**	**mean bead size 90 µm, *ca.* 0.24 mmol/g**
86407F	**TentaGel™ S-RAM**	**mean bead size 90 µm, *ca.* 0.24 mmol/g**
86387F	**TentaGel™ S-S-Trityl**	**mean bead size 90 µm, *ca.* 0.25 mmol/g**

Sigma-Aldrich Laboratory Equipment

winter 2000

Ceramus® Bottle-Top Dispensers

Solvents & Liquid Handling

Ceramus®
Bottle-Top
Dispensers

AldraSORB™
Trapping
Packets and
Solvents

NMR Solvent
Special

NMR Tubes
and
Accessories

Syringes
and Filters

PerformaTherm®
Thermometers

ALDRICH®

CERAMUS® Bottle-Top Dispensers

New!

"Precision dispensers for organic and aqueous solvents"

- *Chemically inert—ceramic dispenser piston in a borosilicate glass barrel*
- *Microstep volume adjustment—ensures reproducibility*
- *Rotates on the bottle—for convenience*
- *Recirculation system—for fast priming without loss of reagent*
- *Lifetime calibration—supplied with individual serial number and test certificate*
- *Fixed- and adjustable-volume models*

CERAMUS® bottle-top dispensers have a unique ceramic piston in a borosilicate glass barrel which guarantees the highest degree of chemical resistance, without abrasion or swelling due to solvent effects. Dispensers fit bottles with A 45 threads and include threaded adapters A 32, A 38, and S 40.

Specifications:

Piston—99.7% pure aluminum oxide
Barrel—Duran® borosilicate glass
Valve block and housing—ECTFE
Valves—borosilicate glass ball and seat (HF: ceramic); Hastelloy® discharge valve spring
Suction and discharge tubes—FEP
Sterilization—Steam sterilizable at 121°C/2 bar, complete unit without disassembly
Luer-lock connection—for filters and drying tubes

Adjustable-volume dispensers

Range (mL)	Increment (mL)	Reproducibility (CV%)	Cat. No.
0.2 – 1.0	0.05	0.2	**Z34,146-0**
0.4 – 2.0	0.05	0.1	**Z34,147-9**
1.0 – 5.0	0.1	0.1	**Z34,148-7**
2.0 – 10.0	0.25	0.1	**Z34,149-5**
5.0 – 30.0	0.5	0.1	**Z34,150-9**
10.0 – 60.0	1.0	0.1	**Z34,151-7**
HF adjustable-volume dispenser			
2.0 – 10.0	0.25	0.1	**Z34,159-2**

Fixed-volume dispensers

Cap. (mL)	Precision (R%)	Reproducibility (CV%)	Cat. No.
1	0.5	0.2	**Z34,152-5**
2	0.5	0.1	**Z34,153-3**
5	0.5	0.1	**Z34,154-1**
10	0.5	0.1	**Z34,156-8**
25	0.5	0.1	**Z34,157-6**
50	0.5	0.1	**Z34,158-4**

AldraSORB™ Trapping Packets and Solvents

"Keep water levels under control"

- Maintains low levels of water impurities for up to 3 months
- Functionally used and tested for use in automated instrumentation
- Ideal for solid phase and solution phase peptide synthesis
- Individual and bulk sizes available

WATER impurities in solvents can lead to inconsistent results, especially for peptide, DNA, and "super anhydrous" applications.

THE AldraSORB™ trapping packet is a revolutionary product that keeps water levels under control. Each is made from an ultra-high molecular weight, electronic grade, hydrophobic polyethylene membrane containing pharmaceutical grade molecular sieves. The full filtration capability of the molecular particulates is maintained and the surrounding solvent is not compromised. AldraSORB™ trapping packets will effectively dry solvents below 50ppm. Low levels of water impurities are maintained for up to three months of continuous use depending on the solvent being "trapped" and the amount of air exposure the solvent experiences. The packet is non-hazardous. Not recommended for solvents having more than 0.05% or 500ppm of water.* Any packet that comes into contact with a solvent should be treated as hazardous waste and disposed of accordingly.

* Risk of excessive heat generation is possible for solvents with a water content of 500ppm or more.

Size	Recommended solvent volume (mL)	Cat. No.
Small (¾ x 1¾ in.)	25–200	**Z50,900-0**
Medium (1 x 4in.)	200–1,000	**Z50,901-9**
Large (1¼ x 4¾ in.)	1,000–4,000	**Z50,902-7**

AldraSORB™ Solvents are now available

This new line of specialty solvents incorporates the AldraSORB™ trapping packets to maintain low water impurity levels. Solvents are available in a 1L size.

Name	Cat. No.
Acetonitrile	**53,947-3**
N,N-Dimethylacetamide	**53,954-6**
N,N-Dimethylformamide	**53,946-5**
1,4-Dioxane	**53,953-8**
Methyl alcohol	**53,945-7**
Methyl sulfoxide	**53,950-3**

For more information on these AldraSORB™ trapping packets or solvents please call 800-231-8327 (USA) or contact us on the Web at www.sigma-aldrich.com.

For a Limited Time Only,

SAVE

on Aldrich Deuterated Solvents

Don't Miss Out on This Special Offer. Order Today!

ALDRICH brand deuterated solvents are used everyday by companies worldwide for NMR spectroscopy applications. Our name has been synonomous with high-quality NMR products at competitive prices for over 20 years. We have an unsurpassed selection of deuterated solvents in various isotopic purities and packaging schemes in stock and ready to be sent to you. Now until **January 31, 2001**, you can enjoy significant savings on most deuterated solvents listed in Aldrich's *Deuterated Solvents for NMR* brochure. To receive the discounted price, mention promotional code ***AD-500*** when placing your order.

SAVE 20% on **100 atom % D** deuterated solvents and ampule packs. Below are a few examples of products available at this special discount.

15,185-8	Chloroform-*d*, 100.0 atom % D
17,586-2	Acetone-d_6, 100.0 atom % D
15,619-4	(Methyl Sulfoxide)-d_6, 100.0 atom % D
23,699-3	Pyridine-d_5, 100.0 atom % D
45,335-8	Deuterium Oxide, 100.00 atom % D

Ampule packs

26,978-6	Deuterium Oxide, 100.0 atom % D (10 x 0.5mL)
23,691-8	Chloroform-*d*, 100.0 atom % D (10 x 0.5mL)
42,578-8	Toluene-d_8, 100.0 atom % D (10 x 1mL)

SAVE 35% on **non-100 atom % D** deuterated solvents and ampule packs. Below are a few examples of products available at this special discount.

15,180-7	Acetonitrile-d_3, 99.6 atom % D
15,194-7	Methyl-d_3 alcohol-*d*, 99.8+ atom % D
15,200-5	Trifluoroacetic acid-*d*, 99.5 atom % D
15,183-1	Chloroform-*d*, 99.8 atom % D (contains 1% v/v TMS)
18,596-5	(Methyl Sulfoxide)-d_6, 99.9 atom % D (contains 1% v/v TMS)

Ampule packs

23,688-8	Benzene-d_6, 99.6 atom % D (10 x 1mL)
23,700-0	Acetic-d_3 acid-*d*, 99.9 atom % D (10 x 0.5mL)
26,984-0	Tetrahydrofuran-d_8, 99.5 atom % D (10 x 1mL)

The above listings are only a sample of the products you can purchase at significant savings. *For a complete list of products and unit sizes available, visit our award winning Web site at* ***www.sigma-aldrich.com****. To place an order, please contact our ordering department at* ***1-800-558-9160*** (USA). *To receive your copy of the* Deuterated Solvents for NMR *brochure, please contact Brian Case at* ***bcase@sial.com****.*

NMR Tubes & Accessories

Wilmad® 5mm NMR tubes for Protein and Peptide Analysis

New!

These premium tubes offer:

- Highest resolution possible
- The most reproducible spectra
- Use with 800MHz spectrometers

Length (in.)	Concentricity/ camber (μm)	Wilmad No.	Cat. No.
7	3.8/3.8	541-PP-7	**Z41,200-7**
8	3.8/3.8	541-PP-8	**Z41,201-5**
7	2.5/3.8	542-PP-7	**Z41,202-3**
8	2.5/3.8	542-PP-8	**Z41,203-1**

THESE NMR tubes are especially suited for biotechnology, 2D and 3D studies, and/or high field strength spectrometers.

THIS unbreakable NMR tube carrier fits into a lab coat pocket like a pen. Provides protection for sample and lab personnel when transporting samples. Has a snap-on cap and a shirt clip that secures carrier in pocket. Holds one 5mm diam. x 7in. L NMR tube.

Aldrich pocket NMR tube carriers

Color	Cat. No.
Red	**Z28,609-5**
White	**Z28,605-2**
Blue	**Z28,610-9**

Color assortment pack

One of each color carrier; red, white, and blue.

Cat. No.
Z28,619-2

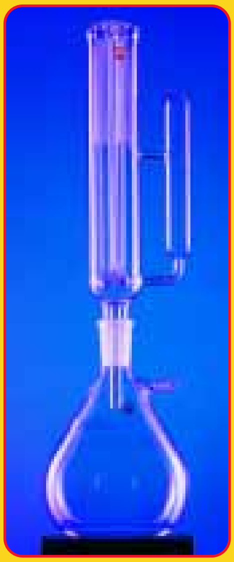
Aldrich dual-action NMR tube cleaners

- Washes tubes inside and out simultaneously
- Specially designed to prevent accidental breakage of tubes
- Highly efficient solvent jets improve cleaning and reduce solvent usage
- For 7 or 8in. L, 5mm NMR tubes
- Optional 1,000mL reservoir flasks

No. positions	₸ 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 flasks

₸ Joint	Cat. No.
24/40	**Z41,418-2**
29/32	**Z42,161-8**



For a full line of NMR tubes and accessories please see the Spectroscopy section of the Aldrich 2000-2001 Handbook.

PRODUCTS for Liquid Handling

All polypropylene Luer lock syringes

NON-CONTAMINATING, sterile, disposable syringe has PP barrel and plunger with a safety stop to prevent plunger separation. Luer lock centered on barrel. Individually peel-packed. Order needles or syringe filters separately.

Cap. (mL)	Grad. int. (mL)	Cat. No.
3	–	**Z24,800-2**
5	0.2	**Z24,801-0**
10	0.5	**Z24,802-9**
20	1.0	**Z24,803-7**

Perfektum® glass syringes

Cap. (cc)	Grad. int. (cc)	Tip style	Cat. No.
1	0.05	needle-lock Luer	**Z18,130-7**
2	0.1	needle-lock Luer	**Z18,131-5**
		metal Luer	**Z18,132-3**
		glass Luer	**Z18,133-1**
5	0.2	needle-lock Luer	**Z18,135-8**
		metal Luer	**Z18,136-6**
		glass Luer	**Z18,137-4**
10	0.2	needle-lock Luer	**Z18,138-2**
		metal Luer	**Z18,139-0**
		glass Luer	**Z18,140-4**
20	1.0	needle-lock Luer	**Z18,141-2**
		metal Luer	**Z18,142-0**
		glass Luer	**Z18,143-9**
30	1.0	needle-lock Luer	**Z18,144-7**
		glass/metal Luer	**Z18,145-5***
50	2.0	needle-lock Luer	**Z18,146-3**
		glass/metal Luer	**Z18,147-1***
100	4.0	needle-lock Luer	**Z15,037-1**
		glass/metal Luer	**Z18,037-8***

*Has glass tip with removable metal Luer adapter

ALL are made from borosilicate glass. Metal parts are chrome-plated brass. Syringes have male Luer fittings.

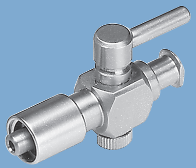
- Matched serial numbers on barrels and plungers for critical applications, not interchangeable
- Frosted, individually lapped barrels and plungers withstand somewhat higher pressures
- Conform fully to U.S. Government specifications GG-S-921 Band GG-S-935
- Individually boxed

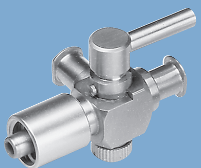
Stainless steel stopcocks

New!

MADE from corrosion-resistant 303 stainless steel, with male-to-female Luer connections.

1-way	**Z50,655-9**
3-way	**Z50,656-7**





Please see the 2000-2001 Aldrich Handbook for a full line of syringes, filters, and fittings.

OSMONICS® Cameo Syringe Filters

Applications:

- HPLC or GC sample preparation
- Ion chromatography
- Sample detection levels <230nm

CAMEO 17 and 30mm syringe filters offer 20% greater effective surface area over smaller 13 and 25mm sizes for improved performance. The improved flow channel design and reduced spacing between supports are designed to speed up and increase sample volume throughput with minimum hold-up volume and reduced back pressure. All filters have female Luer lock inlets.

Cat. No.	Diameter (mm)	Filter material	Sample volume (mL)	Pore size (μm)
S-6062	17	Polypropylene	12	0.22
S-6187	17	Polypropylene	12	0.45
S-6312	30	Polypropylene	120	0.22
S-6437	30	Polypropylene	120	0.45
S-6562	17	Polypropylene with glass prefilter*	12	0.22
S-6687	17	Polypropylene with glass prefilter*	12	0.45
S-6812	30	Polypropylene with glass prefilter*	120	0.22
S-6937	30	Polypropylene with glass prefilter*	120	0.45
S-7062	17	PTFE	12	0.22
S-7187	17	PTFE	12	0.45
S-7312	30	PTFE	120	0.22
S-7437	30	PTFE	120	0.45
S-7562	17	PTFE with glass prefilter*	12	0.22
S-7687	17	PTFE with glass prefilter*	12	0.45
S-7812	30	PTFE with glass prefilter*	120	0.22
S-7937	30	PTFE with glass prefilter*	120	0.45
S-8062	17	Nylon	12	0.22
S-8187	17	Nylon	12	0.45
S-8312	30	Nylon	120	0.10
S-8437	30	Nylon	120	0.22
S-8562	30	Nylon	120	0.45
S-8687	30	Nylon	120	1.2
S-8812	30	Nylon	120	5.0
S-8937	17	Nylon with glass prefilter*	12	0.22
S-9062	17	Nylon with glass prefilter*	12	0.45
S-9187	30	Nylon with glass prefilter*	120	0.22
S-9312	30	Nylon with glass prefilter*	120	0.45

*Built-in glass prefilters are designed to dramatically improve sample volume throughputs

Please see the 2000-2001 Aldrich Handbook for a full line of syringes, filters, and fittings.

To order (USA), call 1-800-558-9160 or visit our Web site at www.sigma-aldrich.com.

ORDERING Information

Call:

800-558-9160

Outside USA and Canada:

414-273-3850

Fax:

800-962-4979

Outside USA and Canada:

414-273-4979

Laboratory Equipment mailing address:

P.O. Box 2060
Milwaukee, WI
53201 USA

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www.sigma-aldrich.com

PerformaTherm™ Non-Mercury Thermometers

New!

"The first non-mercury thermometer with the performance of mercury"

FINALLY a thermometer that combines the safety aspects of a spirit filled thermometer with the accuracy and response time of a mercury filled thermometer. Contains an easy-to-read dark blue liquid fill that is biodegradable, nontoxic, and nonhazardous. Thermometers are supplied in a protective leatherette case with a calibration report, including NIST traceability. Meets all ASTM standards for accuracy, tolerance, and uncertainty.

Range	Calibration points	Divisions	Cat. No.
-38 to 2°C	-37, -30, -20, -10, 0°C	0.1°C	**Z51,049-1**
-8 to 2°C	-7, 0, 10, 20, 30°C	0.1°C	**Z51,050-5**
25 to 55°C	0, 25, 35, 45, 55°C	0.1°C	**Z51,051-3**
50 to 80°C	0, 50, 60, 70, 80°C	0.1°C	**Z51,052-1**
75 to 105°C	0, 75, 85, 95, 105°C	0.1°C	**Z51,054-8**
-36 to 35°F	-35, -15, 0, 15, 32°F	0.2°F	**Z51,056-4**
18 to 89°F	20, 32, 50, 70, 88°F	0.2°F	**Z51,057-2**
77 to 131°F	32, 80, 95, 115, 130°F	0.2°F	**Z51,058-0**
122 to 176°F	32, 125, 145, 160, 175°F	0.2°F	**Z51,059-9**
167 to 221°F	32, 168, 185, 200, 220°F	0.2°F	**Z51,060-2**
Set of 5 thermometers (°C)			**Z51,055-6**
Set of 5 thermometers (°F)			**Z51,061-0**

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Sigma-Aldrich Fine Chemicals is the development and manufacturing division of Sigma-Aldrich, Inc

Year 2001 ACS Award Recipients

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

ACS Award for Creative Work in Synthetic Organic Chemistry: Professor *Eric N. Jacobsen*, Harvard University

One of the fastest-rising stars in chemistry, Professor Jacobsen has had a profound impact on the field of organic chemistry in a relatively short period of time. He has contributed to such diverse areas as asymmetric catalysis (e.g., Jacobsen epoxidation, HKR), synthetic methodology, synthesis of complex molecules (e.g, diltiazem, muconin, taurospongin, LTA_4 methyl ester), combinatorial chemistry, and physical organic chemistry. Professor Jacobsen has also been highly successful in making several of his synthetic methods general, practical, and readily scalable. In addition to these stellar accomplishments in research, Professor Jacobsen has consistently been recognized as an outstanding and talented teacher.

ACS Award in Inorganic Chemistry: Professor *Edward I. Solomon*, Stanford University

Widely regarded as a leading international authority in physical inorganic and bioinorganic chemistry, Professor Solomon has also made significant contributions in the areas of catalysis and surface science. One of the best inorganic spectroscopist in the world, Dr. Solomon's profound knowledge of the theory and practice of inorganic spectroscopy is nowhere more evident than in his outstanding contributions to our understanding of the electronic structure and function of metalloproteins, "blue copper" proteins in particular. Examples of his seminal contributions in this area include his studies of hemocyanin, tyrosinase, plastocyanin, and rubredoxin, as well as the processes of electron transfer and dioxygen binding and activation.

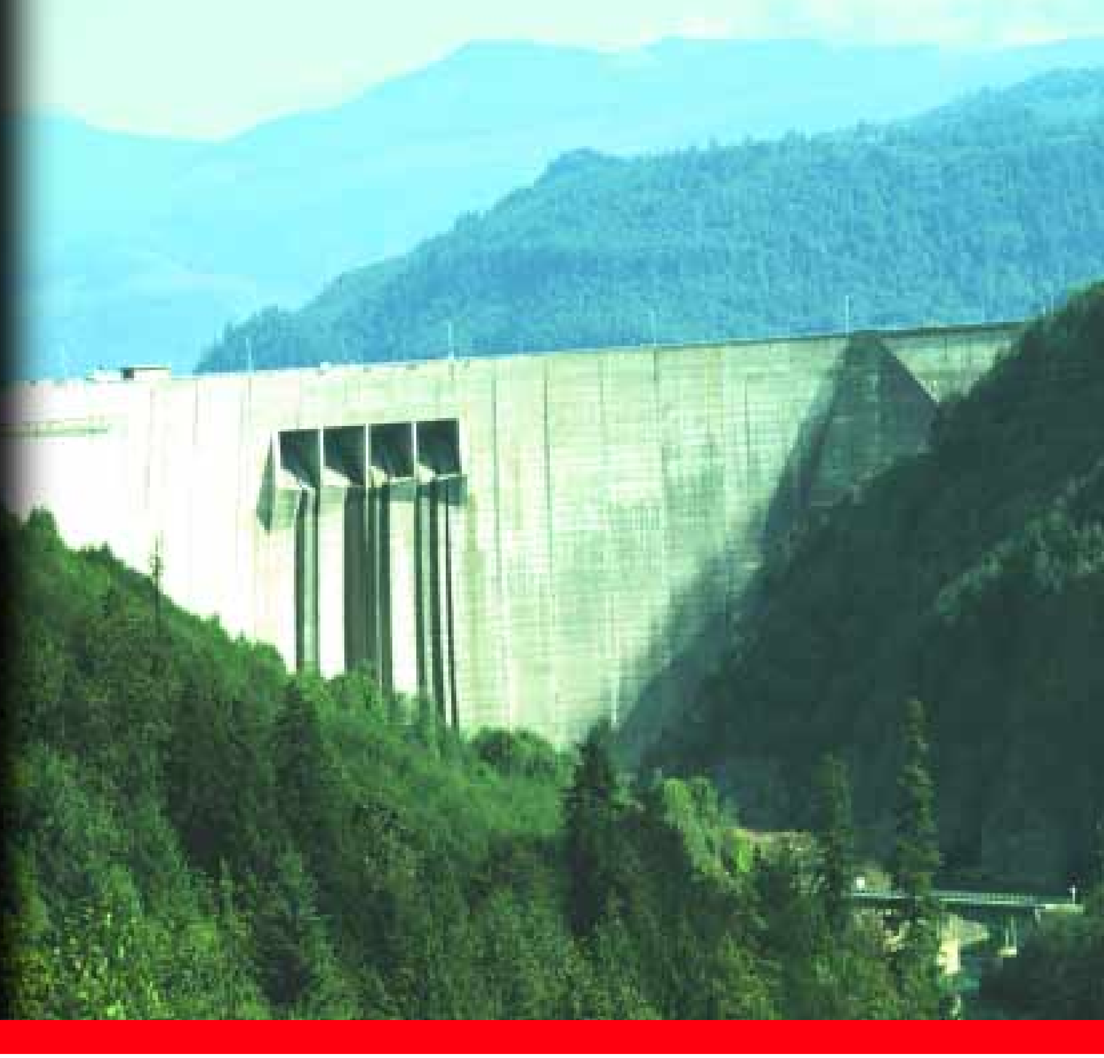
Herbert C. Brown Award for Creative Research in Synthetic Methods:
Professor *Robert H. Grubbs*, The California Institute of Technology (Caltech)

A leading and very productive investigator in the areas of organometallic and catalytic chemistry (with about 25 patents and over 300 refereed publications), Professor Grubbs has significantly enhanced our fundamental understanding of olefin polymerization (e.g., Ziegler, ROMP) and metathesis reactions (e.g., RCM). His readily available and well-defined ruthenium carbene complexes have contributed significantly to the widespread use of olefin metathesis in polymer and synthetic chemistry. In recognition of his outstanding contributions in these areas, Professor Grubbs has received several other prestigious awards, including the ACS Award in Organometallic Chemistry (1988), the ACS Award in Polymer Chemistry (1995), and the Arthur C. Cope Scholar Award (1990).

Aldrich would also like to congratulate Professor **Peter G. Schultz** of The Scripps Research Institute and The Genomics Institute for being selected to receive the year 2001 ***Alfred Bader Award in Bioinorganic or Bioorganic Chemistry***. Professor Schultz has distinguished himself as a first-class scientist, educator, and industry pioneer. As scientist, he has carried out vigorous research that bridges several scientific fields, including chemistry, biology, and materials science. Catalytic antibodies, methodology for incorporating unnatural amino acids in proteins, and the application of combinatorial approaches to materials science are just a few of the scientific areas in which he has been a trendsetter. As a founding scientist of The Affymax Research Institute and the founder and director of Symyx Technologies, he has pioneered the application of combinatorial techniques to the development of new pharmaceuticals and materials with novel properties.

Congratulations to each and all!

NEW ALDRASORB™ SOLVENTS



KEEP WATER LEVELS UNDER CONTROL

Aldrich is proud to add a new line of specialty anhydrous solvents to its already comprehensive list of products. We have incorporated a new advanced molecular packet system in the solvents listed below, that effectively maintains low water impurity levels longer than ever before. The amount of water picked up by solvents from opening and closing of the bottle can be significant. AldraSORB™ solvents stay dry through repeated use. The secret behind its effectiveness is the molecular packet inserted into the solvent just before packaging. This packet is made from a pharmaceutical quality, hydrophobic membrane material that has been tested safe for long-term exposure to the solvent. The membrane maintains full filtration of its molecular sieve particulates, thus the integrity of the solvent is not compromised and your automated equipment is safe. The packet maintains low water levels (<50 ppm) for up to 3 months, depending upon the solvent and length of time it is exposed to the atmosphere.

ALDRICH NOW OFFERS THE FOLLOWING AldraSORB™ SOLVENTS IN THE 1L SIZE.

CAT. NO.	PRODUCT NAME
53,947-3	**Acetonitrile**, 99.8%
53,954-6	*N,N*-**Dimethylacetamide**, 99.8%
53,946-5	*N,N*-**Dimethylformamide** (DMF), 99.8%
53,953-8	**1,4-Dioxane**, 99.8%
53,945-7	**Methyl alcohol**, 99.8%
53,950-3	**Methyl sulfoxide**, 99.8%

For more information on these solvents or the AldraSORB™ packets themselves, please call 800-558-9160 ext. 5223 or contact us on the Web at www.sigma-aldrich.com.

AldraSORB is a trademark of Sigma-Aldrich Co.

www.sigma-aldrich.com

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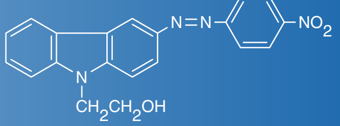
NetworkWorld E-COMM INNOVATOR OF THE YEAR 2000

Intermediates for NLO Polymers

The last decade has seen a rising trend towards the use of organic polymers as photonic components because of their ease of processing and fabrication; compatibility with metals, ceramics, semiconductors, and glasses; good mechanical strength; and flexibility to tailor nonlinear optical properties.[1] A primary requirement for a material to exhibit nonlinear optical (NLO) activity is that it should be noncentrosymmetric. In polymer-based NLO materials, the chromophore can be incorporated into a polymer matrix in a number of ways. Early efforts focused on guest–host systems. More recently, the chromophores were covalently attached to the polymer backbone as side chains, or made part of the polymer backbone itself, markedly improving long–term stability, and permitting their use in practical devices.[1,2]

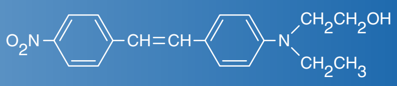
Aldrich offers a wide selection of **intermediates for NLO polymers**; a sampling of these, including some of our recent additions, are highlighted below with application information. This is followed by some of the better-characterized **NLO chromophores**.[3] For a comprehensive list, request your **FREE copy of the Aldrich Stains & Dyes Catalog**; for recent additions, visit our award-winning Web site, **www.sigma-aldrich.com**, and search our product database in eight different ways including by substructure! If you are interested in special grades, e.g., low–metal dyes, please contact us at aldrich@sial.com. To obtain quotes on larger quantities, please contact Sigma-Aldrich Fine Chemicals on the Web at **www.sigma-aldrich.com/safc** or by phone at **800-336-9719 (USA)**, or contact your local office.

Intermediates for NLO Polymers & Chromophores



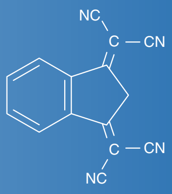
NEW! **51,489-6 3-[(4-Nitrophenyl)azo]-9*H*-carbazole-9-ethanol**

Used in the synthesis of a photorefractive homopolymer with pendant azocarbazole moieties so that all of the necessary elements of photorefractivity have been incorporated into a single monomer.[4]



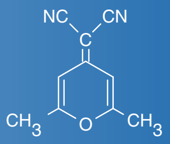
NEW! **51,856-5 2-[Ethyl[4-[2-(4-nitrophenyl)ethenyl]phenyl]amino]ethanol**, 98%

Employed in the synthesis of a second–order chromophore covalently attached to a photorefractive terpolymer.[5]



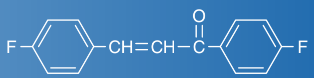
NEW! **46,461-9 (Indan-1,3-diylidene)dimalononitrile**, 97%

Intermediate for the strong electron-withdrawing acceptor moiety in the synthesis of a novel push-pull chromophore.[6]



NEW! **51,688-0 (2,6-Dimethyl-4*H*-pyran-4-ylidene)malononitrile**, 99%

Dye intermediate used in the synthesis of an electrooptical chromophore.[7]



47,212-3 *trans*-4,4'-Difluorochalcone, 98%

Utilized in the synthesis of a quasi-two-dimensional charge–transfer chromophore containing main–chain polymers. This enhances mechanical and thermal properties, while retaining optical transparency and NLO effects, when compared to single–crystal chalcone chromophores.[8]

NLO Chromophores

86,099-9 Crystal Violet, certified (C.I. 42555)
22,928-8 Crystal Violet, A.C.S. reagent
36,482-7 Disperse Red 13 (C.I. 11115)
36,483-5 Disperse Yellow 7 (C.I. 26090)
37,006-1 3-Methyl-4-nitropyridine *N*-oxide, 98%

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Highlights from Two Decades of Synthetic Radical Chemistry

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Outline

1. Introduction

There are often exciting, yet unexploited opportunities at the interface between two disciplines or subdisciplines. In the early 1970s, organic synthesis was a thriving and rapidly growing field that was already having an impact on other fields of science. Likewise, organic radical chemistry was a well-established, if smaller, discipline. Seminal work on the structure and reactivity of radicals had followed from the importance of organic radicals in polymer chemistry, auto-oxidation, and in other processes. Yet, the two fields had little overlap. Synthetic chemists knew that radicals were highly reactive, and deduced from this that radicals were unselective and therefore uncontrollable. No doubt the usefulness of radicals in polymer chemistry contributed to a simplistic notion that polymers would form whenever radicals were generated in the presence of alkenes. Organic radical chemists knew that radical reactions could be controlled in highly selective ways, and leaders like Walling, Beckwith, and Ingold, among others, postulated that radicals could be used in synthesis. But, by and large, organic radical chemists did not know the topical problems in synthesis. In short, no one knew both the problems and the solutions.

Fortunately for me, this disjoint persisted throughout the decade of the 1970s. Only in the 1980s, as I started my independent career, did a small but visible group of researchers begin to recognize and exploit the potential of synthetic radical chemistry. Early researchers like Barton, Stork, and Hart, among others, came from the synthesis side, but immersed themselves in the reactions and chemistry of radicals. Others, like Giese, Beckwith, Porter, and Newcomb, for example, took on the challenge of identifying interesting problems in synthesis and developing solutions for them by using radical chemistry. New people soon joined the field. Barriers tumbled, and a lively, open exchange of results and ideas between synthetic chemists and radical chemists created a dynamic that was ideal for rapid progress. That dynamic exists even today.

This review highlights contributions to synthetic radical chemistry from our research group at the University of Pittsburgh. The organization is more thematic than chronological, and the approach is personal and selective, not historical or comprehensive. By using these highlights, I intend to show how radical reactions have grown from an interesting curiosity to a mainstream tool in organic synthesis. Much work from other groups could be highlighted to augment and supplement these examples, and the omission of this work in no way minimizes its importance. Indeed, we were frequently influenced by the results and thinking of others, as I hope they were at times influenced by us.

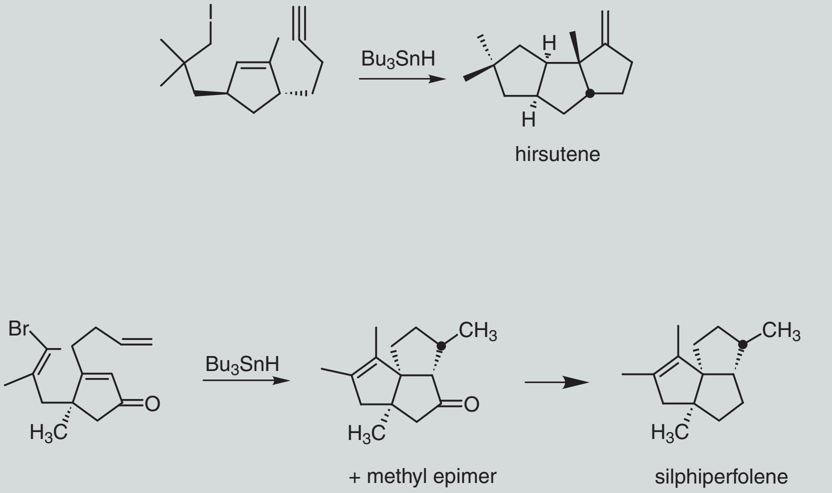
2. Tandem Radical Reactions

Given my training with Andrew Kende and Barry Trost, I entered the open middle ground squarely from the synthesis side. Professor William Saunders taught a Physical Organic Chemistry course at the University of Rochester. Among many other things, he drilled us in the kinetics of radical polymerizations. This served me well later on, because a sound knowledge of radical kinetics is an indispensable tool for a synthetically inclined radical chemist. As a postdoctoral fellow in Barry Trost's group, I was first exposed to radical chemistry in a group meeting, when some of Bernd Giese's additions of organic mercury hydrides to electron-poor alkenes were discussed.[1] At the time, these reactions (now called Giese reactions and usually done with tin or silicon hydrides) looked like a recipe for polymerization, but Giese's clear kinetic analysis explained why what looked like a minor miracle was an easily understandable outcome based on rates and selectivities.

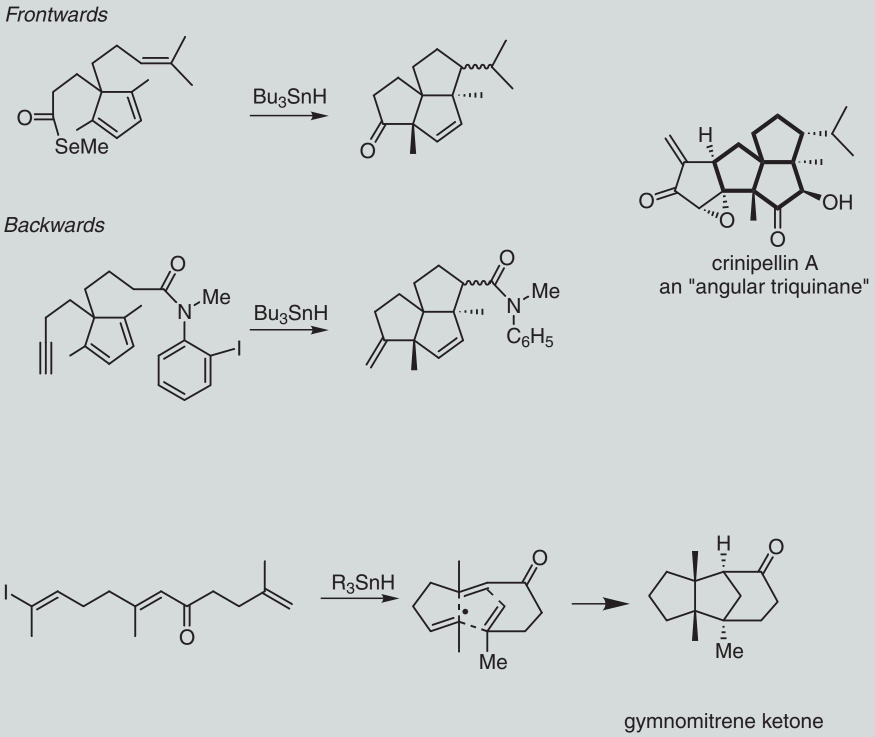
Professor Dennis P. Curran (left) receiving the *2000 ACS Award for Creative Work in Synthetic Organic Chemistry* from Dr. Chris D. Hewitt, V.P., Marketing and R&D, Aldrich Chemical Company.

Giese's work impressed me, and, in seeking to learn more about radical reactions, I read a raft of papers, including Beckwith and Ingold's review on "Free Radical Rearrangements".[2] This was a treasure-trove of unexploited synthetic reactions (almost 800 references!) with kinetic information on how to use them. My interest in the synthesis of polyquinanes,[3] coupled with my new knowledge of the hexenyl radical cyclization, led to my group's first radical chemistry project on "tandem radical cyclizations". Model studies were done in early 1982, and a synthesis of hirsutene was completed in 1984 by Donna Rakiewicz (**Scheme 1**).[4] Simple by today's standards, it nicely illustrates the power of radical reactions: two rings are formed in a single step with complete stereocontrol of the ring fusion. This success led to a synthesis of isomers of hirsutene like capnellene[5] (see Scheme 4 below) and silphiperfolene[6] (also shown in Scheme 1) and, more generally, to a comprehensive strategy to make molecules of this class based on the formation of vicinal bonds.[7]

Over the course of this project, we began to realize that radical reactions were ideal for sequencing—for a very fundamental reason: the product of every radical reaction is a radical. This natural generation of the precursor for the trailing reaction in sequence from the leading reaction, coupled with the mildness and selectivity of radical reactions, prompted us to start designing and implementing new sequences of radical reactions that included the formation of non-vicinal carbon–carbon bonds.[8] **Scheme 2** shows a synthesis of a portion of crinipellin in which a diene is used to make bonds in a 1,4 fashion. We also used this exercise to point out that tandem radical reactions such as this one have a directionality and can be run from "front to back" or "back to front" (which depends only on your perspective). A very recent synthesis of gymnomitrene ketone,[9] also shown in Scheme 2, provides an example of a kind of round-trip radical reaction, where the last radical cyclization occurs at the same site as the initial radical reaction. This results in geminal (1,1) bond formation. All of these routes are unusually direct.



Scheme 1. Tandem Radical Cyclizations Forming Vicinal Bonds.

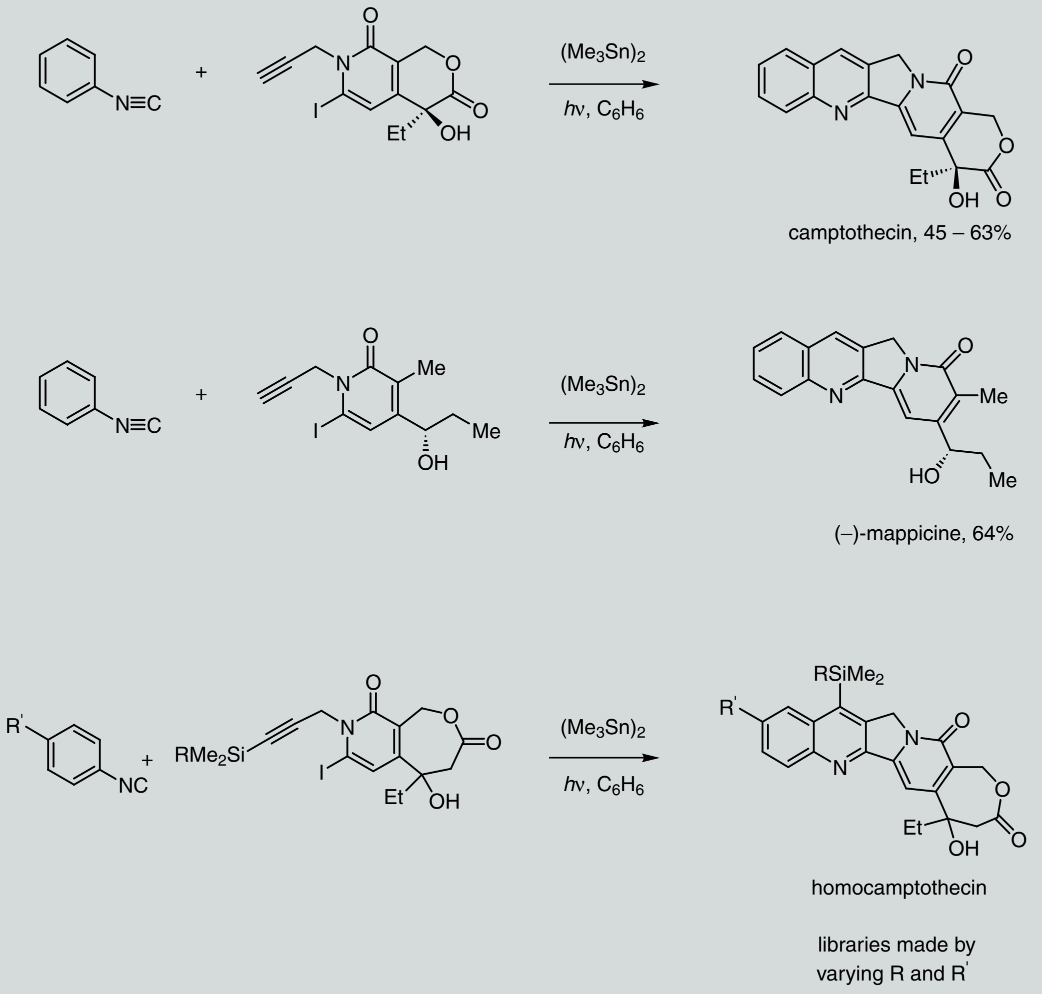


Scheme 2. Tandem Cyclizations Forming Non-Vicinal Bonds.

Isonitriles can also be used to form vicinal carbon–carbon bonds, and this has been an enduring theme in our lab over the 1990s, as illustrated by the syntheses of mappicine and camptothecin (**Scheme 3**).[10] These syntheses emerged from the basic research program on radical annulations, and have now advanced to the point where both have been conducted in parallel in our Combinatorial Chemistry Center.[11] The goals of the project have evolved from developing and illustrating new radical reactions—through illustrations in total synthesis—to using these reactions as tools in medicinal chemistry. For example, we have made over 100 analogs of homocamptothecin by the route shown in the lower part of Scheme 3.[12] The generality of this reaction is most impressive; we have conducted over 400 isonitrile annulations over the years (about three-fourths of these recently in a parallel setting), and we still have no example of a failure. Functional groups that have been present include free alcohols, amines, esters, chlorides, terminal alkenes, and many more. Few reactions have such a scope. One of the analogs of camptothecin that we made several years ago, 7-*tert*-butyldimethylsilyl-10-hydroxycamptothecin (DB-67), is currently a preclinical candidate for cancer chemotherapy.[13]

3. Atom-Transfer Reactions

An important branch point in our work occurred in 1984, when Ming-Hsin Chen made an interesting observation. Expecting to make capnellene (**3**), he reduced iodide **1**, and eventually made **3** after several hours, but this was not the primary product of the reaction (**Scheme 4**).[14] The starting material, **1**, was quickly consumed to give vinyl iodide **2**, which was then reduced in a slower reaction by tin hydride. As the results imply, one can simply isomerize **1** to **2** by heating or photolyzing without the tin hydride. Although the specific reaction was new, the basic principles of the so-called "atom transfer radical cyclization" (ATRC) had been laid out by Kharasch many years ago. These principles were rapidly expanded and applied to develop a number of valuable new reactions, including the atom-transfer radical addition and annulation, examples of which are shown in Scheme 4.[15] More recently, transfers of groups such as phenylselenyl[16] and xanthyl[17] have been developed into useful methods, and even the classical Kharasch reaction itself has seen a major rebirth in synthesis and in polymer chemistry.[18]



Scheme 3. Synthesis of Camptothecin and Mappicine Analogs by Cascade Isonitrile Annulation.

4. Radical Translocations

In some synthetic plans, the most difficult part is the synthesis of the radical precursor and not the radical reaction itself. To address problems like this, we introduced "radical translocation" reactions.[19] A number of methods are now available to first generate a radical in a protecting group, translocate this radical to the desired site, and then have it undergo a reaction.[20] This allows one to indirectly use a C–H bond as a radical precursor and to form a bond adjacent to a protected functionality without even removing the protecting group. A related development is the introduction of "self-oxidizing protecting groups", as illustrated in **Scheme 5**.[21] A limitation of some of these reactions is that the hydrogen transfer step is not completely regioselective.[22]

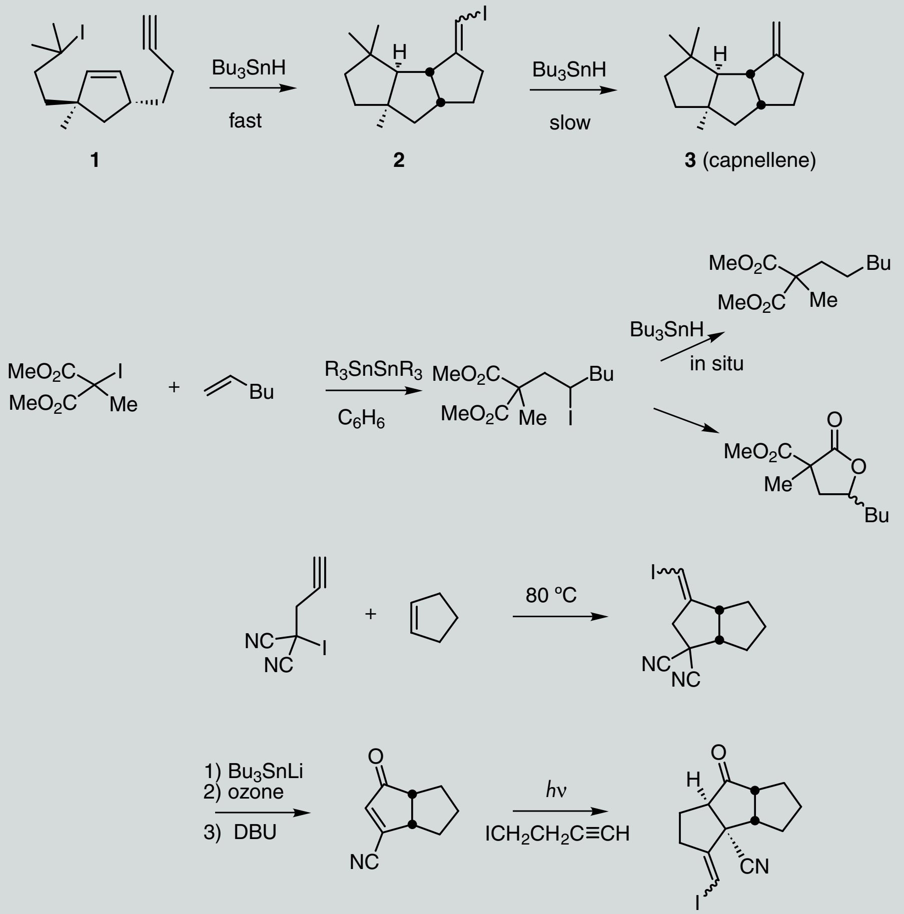
5. Unimolecular Chain-Transfer (UMCT) Reactions

Competing bimolecular reactions often cause problems in radical chemistry, but these can be minimized if the key chain-transfer reaction is intramolecular. Based on this simple notion, we introduced the use of silicon hydrides to control selectivity in unimolecular chain-transfer reactions (**Scheme 6**).[23] Unfortunately, the wide applicability of this valuable concept has been limited, because the silicon hydrides studied so far have only marginally acceptable rate constants for the 1,5-hydrogen transfer reactions. However, modification of the silicon substituents might give more useful reagents, and other methods such as homolytic substitution at Si–Sn bonds can also be used.[24]

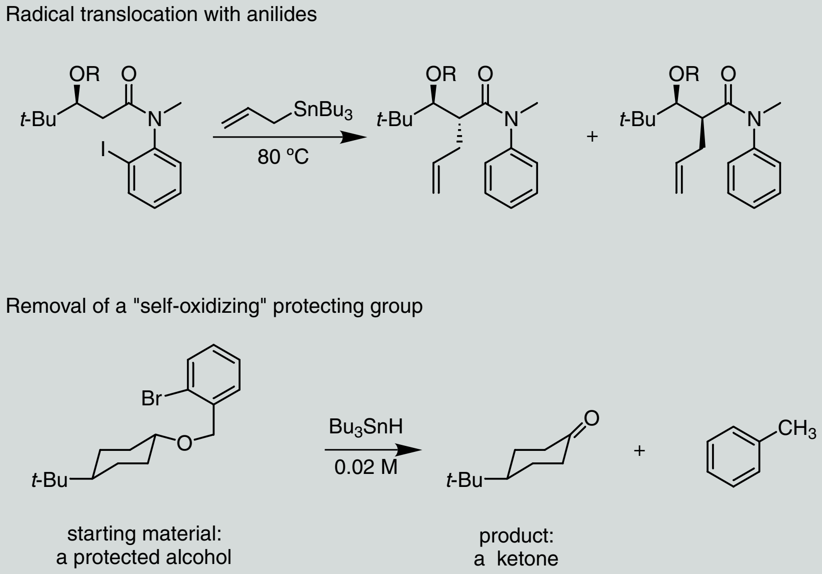
6. Stereochemistry

As synthetic applications of radical reactions became more and more sophisticated, the study of their stereochemistry followed naturally. Much work on stereoselective radical cyclizations followed from Beckwith's model for substituted hexenyl radical cyclizations.[25] The purposeful study of acyclic stereoselection came later, and we, Giese, and Porter systematically applied the principles of conformational analysis and radical chemistry to predict which kinds of existing chiral auxiliaries would be useful in radical chemistry.[26] An example of our own work with Oppolzer's sultam is shown in **equation 1**.[27] This work then led to the design and introduction of a number of new chiral auxiliaries, and, more recently, chiral Lewis acids,[28] especially tailored to the needs of radical reactions.

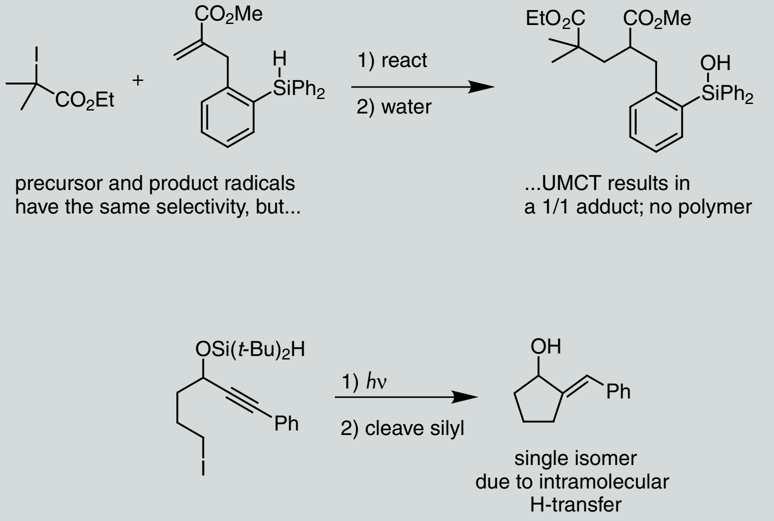
More recently, we have been developing stereoselective reactions that capitalize on features that are unique to radicals. For example, "stereoselection at the steady state" is a conceptually new way to control stereoselection that does not use traditional competing reactions with diastereomeric transition states, but instead a difference in the steady-state population of isomeric intermediates, to control stereoselection.[29] The principles are not unique to radical chemistry, but so far there are no examples outside of this realm. Chirality-transfer reactions also offer interesting possibilities



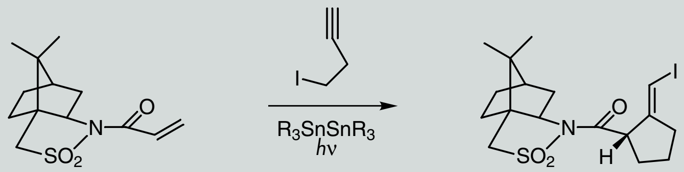
Scheme 4. Atom-Transfer Cyclization, Addition, and Annulation.



Scheme 5. Examples of Radical Translocation Reactions.



Scheme 6. Unimolecular Chain-Transfer Reactions.



eq 1

because radical reactions are so fast; that is, radicals are so short-lived. Low-energy bond rotations that would normally interconvert intermediates may be slow on the radical time scale. For example, cyclization of axially chiral amide **4** appears to go through a racemic radical intermediate, **5**, but this is not the case because the cyclization of **5** is fast (**Figure 1**).[30] There is faithful transfer of the axial chirality in **5** to the stereocenter in **6**.

7. Fluorous Tin Reagents

Finally, in efforts to make organotin chemistry more practical and user friendly, we have developed a number of fluorous reagents; some representative fluorous tin hydrides are shown in **Figure 2**.[31] These mimic tributyltin hydride quite well as radical chain-propagating reagents, but they are very easy to remove and recover by liquid–liquid extraction with a solvent like perfluorohexane, or by solid–liquid extraction over silica gel with a fluorocarbon bonded phase. The liquid–liquid extraction procedure is especially convenient for larger-scale reactions, since the tin reagent is readily recovered and reused, while the solid–liquid extraction is especially convenient for small-scale (parallel) synthesis.

8. Conclusions

The fluorous reagents described in Figure 2 bring us full circle to the introduction. Organic radical chemistry now thrives both as an independent discipline and as an important component of the field of organic synthesis. But there are now exciting and unexplored opportunities at the interface between traditional organic synthesis and organofluorine (fluorous) chemistry. These opportunities have existed for some time, yet only recently has a small but growing group of chemists begun to recognize and exploit them. There will be rewards for those who take the time to learn about both areas and to bring that knowledge together to solve problems in synthesis.

9. Acknowledgements

Over the past two decades, our accomplishments in radical chemistry have been a collaborative effort in every respect: First and foremost, collaborative with the graduate students, postdoctoral fellows, and visiting professors, who provided not only the results and some crucial observations, but also injected their own interpretations and ideas. Second, collaborative with many colleagues, who helped us with experiments, ideas, and frequently even encouragement. The names of many of these colleagues and coworkers are listed in the references. Finally, I am grateful to the University of Pittsburgh for providing the environment and facilities for conducting this research, and to the funding agencies (NIH, NSF, PRF) and companies (Bayer, among others) that have supported this work.

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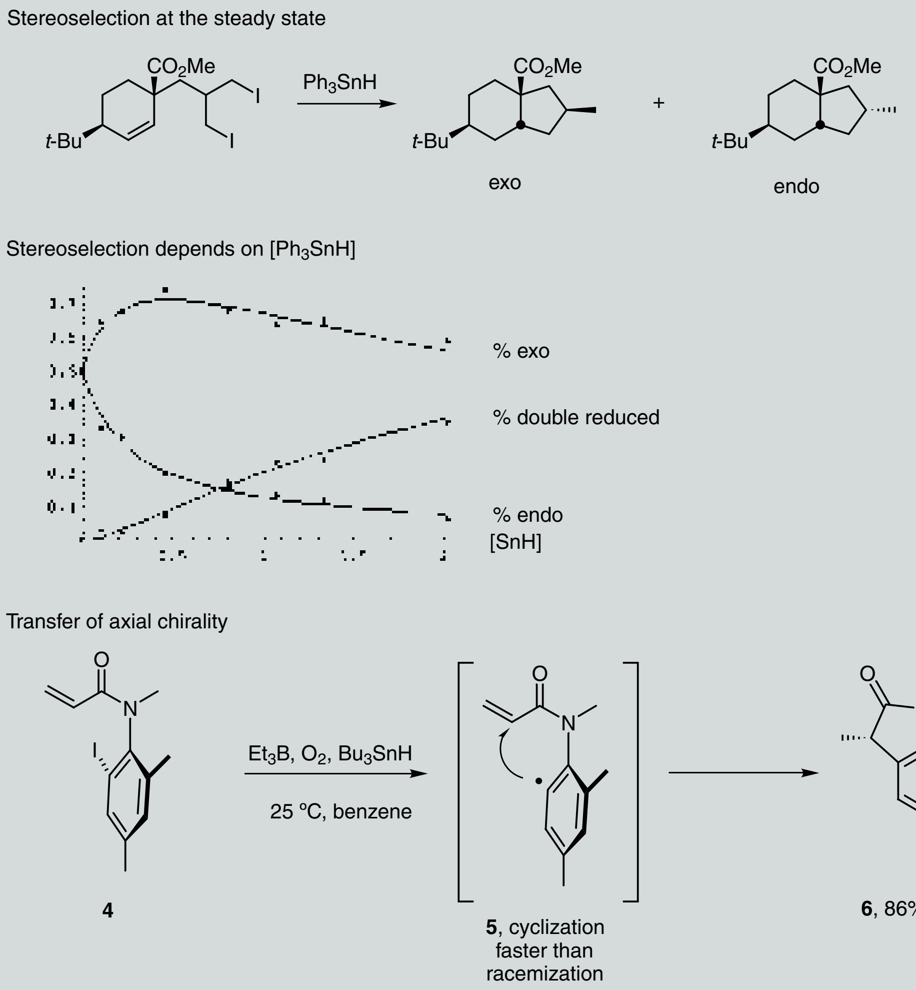

Stereoselection at the steady state

Stereoselection depends on [Ph$_3$SnH]

Transfer of axial chirality

4

5, cyclization faster than racemization

6, 86% ee

Figure 1. New Methods of Stereocontrol with Radicals.

$(C_6F_{13}CH_2CH_2)_3SnH$

$(C_4F_9CH_2CH_2)_3SnH$

$(C_6F_{13}CH_2CH_2CH_2)_3SnH$

$(C_4F_9CH_2CH_2CH_2)_3SnH$

$C_{10}F_{21}CH_2CH_2SnMe_2H$

$C_8F_{17}CH_2CH_2SnMe_2H$

$C_6F_{13}CH_2CH_2SnMe_2H$

Figure 2. A Family of Fluorous Tin Hydrides.

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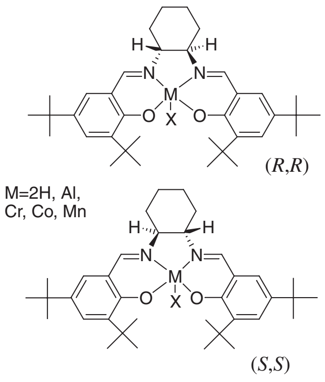
About the Author

Dennis P. Curran received his B.S. degree in 1975 from Boston College and his Ph.D. in 1979 from the University of Rochester, where he worked under Professor Andrew S. Kende. After a two-year postdoctoral stay with Professor Barry M. Trost at the University of Wisconsin, Dr. Curran joined the faculty of the Chemistry Department at the University of Pittsburgh in 1981. He now holds the ranks of Distinguished Service Professor and Bayer Professor of Chemistry, and is the American Editor of *Tetrahedron: Asymmetry* and *Tetrahedron Letters*. Among other awards, Dr. Curran has received the American Chemical Society Award for Creativity in Organic Synthesis (2000), the Cope Scholar Award (1988), and the Janssen Prize for Creativity in Organic Synthesis (1998). He is currently the Chairman of the ACS Division of Organic Chemistry and an Alexander von Humboldt Research Fellow. Dr. Curran has authored over 200 papers, six patents, and one book, and is well known for his work at the interface of radical chemistry and organic synthesis. More recently, he has made significant contributions to the emerging discipline of fluorous chemistry. This has recently led to the founding of a new company, Fluorous Technologies, Inc., in Pittsburgh, PA. Additional information can be found at http://radical.chem.pitt.edu.

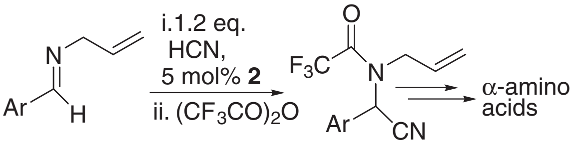
Versatile Chiral Salen Catalysts

Professor Eric N. Jacobsen and co-workers have developed various metal chiral salen catalysts and demonstrated their utility in the preparation of chiral building blocks. These catalysts are used in the Strecker reaction;[1] the asymmetric ring opening[2] of meso epoxides[3] with TMS-N_3 and of terminal epoxides with water;[4,5] the hetero-Diels–Alder reactions,[6] as shown below; and in the epoxidation of unfunctionalized olefins.[7] In addition to the Co and Mn chiral salen catalysts, Aldrich now offers the new Al and Cr counterparts.



(*R*,*R*)				**(*S*,*S*)**			
M	**X**	**Cat. No.**		**M**	**X**	**Cat. No.**	
1, 2H	–	40,441-1		1, 2H	–	40,443-8	
2, Al	Cl	53,196-0 NEW!		2, Al	Cl	53,197-9 NEW!	
3, Cr	Cl	53,194-4 NEW!		3, Cr	Cl	53,195-2 NEW!	
4, Co	Cl	47,459-2		4, Co	Cl	47,460-6	
5, Mn	Cl	40,444-6		5, Mn	Cl	40,445-4	

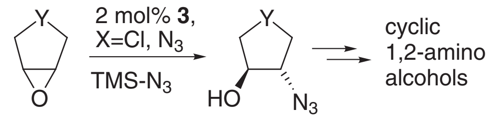
Strecker Reaction[1]



Ar=Ph, 4-MeO-C_6H_5, 1-Naphthyl, 2-Naphthyl

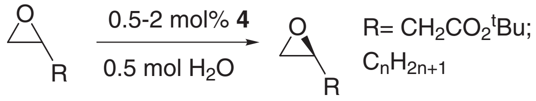
ee >91%, yield >90%

Asymmetric Ring Opening[2,3]



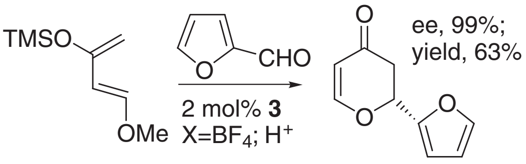
Y	ee%	yield%	Y	ee%	yield%
CH_2	94	97	O	97	96
$(CH_2)_2$	85	96	$NCOCF_3$	95	87

Hydrolytic Kinetic Resolution[4,5]



ee >95%; yield >90%

Diels–Alder Reaction[6]



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References: (1) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 5315. (2) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421. (3) Schaus, S. E. et al. *J. Org. Chem.* **1997**, *62*, 4197. (4) Liu, P.; Panek, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 1235. (5) Savle, P. S. et al. *Tetrahedron: Asymmetry* **1998**, *9*, 1843. (6) Schaus, S. E. et al. *J. Org. Chem.* **1998**, *63*, 403. (7) Bell, D. et al. *Tetrahedron Lett.* **1996**, *37*, 3895.

d-Metal Complex Salts

Coordination chemists have long been studying the relationship between chemical structure and the physical properties of the bulk material. This research has unearthed a wide assortment of applications for metal complex salts ranging from catalysis[1,2] and deposition,[3,4] to magnetism[5] and photochemical studies.[6] Other complex metal salts have found uses in biological studies as precursors to potential antitumor agents[7] or as specific chelators for the removal of copper.[8]

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NEW!	**52,964-8**	**Dipotassium tetraiodomercurate(II)**, 99.99%
	22,430-8	**Lithium tetrachlorocuprate(II)**, 0.1*M* solution in tetrahydrofuran
NEW!	**52,971-0**	**Potassium hexabromopalladate(IV)**, 99.99+%
	20,606-7	**Potassium hexachloroplatinate(IV)**, 98%
	47,344-8	**Potassium hexacyanochromate(III)**, 99.99%
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	20,581-8	**Sodium tetrachloropalladate(II)**, 98%

References:

(1) Berkowitz, W.F.; Wu, Y. *Tetrahedron Lett.* **1997**, *38*, 3171. (2) Grushin, V.V. *J. Am. Chem. Soc.* **1999**, *121*, 5831. (3) Gorostiza, P. et al. *J. Electroanal. Chem.* **1999**, *469*, 48. (4) Koumoto, K. et al. *Chem. Mater.* **1999**, *11*, 2305. (5) Dujardin, E. et al. *J. Am. Chem. Soc.* **1998**, *120*, 11347. (6) Mansour, M. A. et al. *Inorg. Chem.* **1998**, *37*, 4625. (7) Ali Khan, S.R.S.R. et al. *Bioorg. Med. Chem.* **2000**, *8*, 515. (8) Ogra, Y. et al. *J. Inorg. Biochem.* **1999**, *75*, 199.

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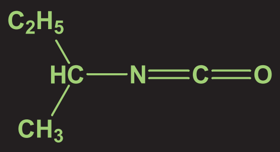
B9,573-6
Butyl isocyanate, 98%
bp 115°C
available to 100 kg

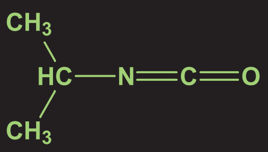


$(C_2H_5)(CH_3)HC—N{=}C{=}O$

51,177-3
sec-**Butyl isocyanate**, 98%
bp 101°C
available to 100 kg

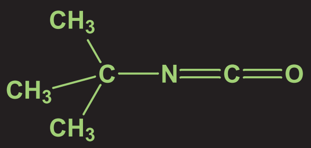
$ClCH_2CH_2—N{=}C{=}O$

24,164-4
2-Chloroethyl isocyanate, 95%
bp 135°C
available to 100 kg



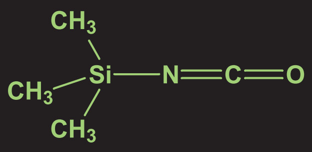
$(CH_3)_2HC—N{=}C{=}O$

14,107-0
Isopropyl isocyanate, 98+%
bp 74-75°C
available to 100 kg



$(CH_3)_3C—N{=}C{=}O$

14,445-2
tert-**Butyl isocyanate**, 97%
bp 85-86°C
available >100 kg



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4th ed., F. A. Carey and R. J. Sundberg, Kluwer Academic Publishers, Boston, MA, 2000, 818pp. Hardcover. The fourth edition provides updated material, but continues the essential elements of the previous edition. The material in Part A is organized on the basis of fundamental structural topics such as structure, stereochemistry, conformation, aromaticity, and basic mechanistic types, including nucleophilic substitution, addition reactions, carbonyl chemistry, aromatic substitution, and free radical reactions. As in the earlier editions, the text contains extensive references to both the primary and review literature and provides examples of data and reactions.

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Solid-Phase Synthesis and Combinatorial Technologies

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Thin-Layer Chromatography

4th ed., B. Fried and J. Sherma, Marcel Dekker Press, New York, NY, 1999, 512pp. Hardcover. Emphasizes the general practices and instrumentation involving TLC and HPTLC, as well as their applications based on compound types. Provides a sound understanding of the underlying theory necessary for optimizing these techniques. Includes over 1,150 up-to-date references, new drawings of chromatograms, a glossary of important terms, and a list of supply and equipment sources.

Z50,000-3

Bretherick's Handbook of Reactive Chemical Hazards

6th ed., P. Urben, Ed., Butterworth Publishers, Stoneham, MA, 1999, 2,576pp. Hardcover. Contains specific information on the stability of listed compounds, reactivity of mixtures, and associated chemical hazards. Covers over 5,000 elements and compounds. Each compound is identified by its IUPAC-based name, CAS registry number, empirical formula, and structure.

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Catalysis from A to Z: A Concise Encyclopedia

B. Cornils, W. A. Herrmann, R. Schlögl, and C.-H. Wong, Eds., John Wiley & Sons, New York, NY, 2000, 658pp. Hardcover. Provides a concise reference to keywords and concepts for all aspects of catalysis. Includes coverage of homogeneous and heterogeneous catalysis and biocatalysis. Contains relevant references, abbreviations, trade names, important catalytic processes, named reactions, and more.

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Organic Synthesis on Solid Phase: Supports, Linkers, Reactions

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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Practical Problem Solving in HPLC

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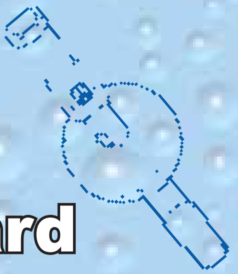
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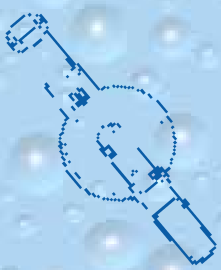
C. Antisplash with return hole

Top ₷ Joint	Bottom ₷ Joint	Cap. (mL)	Cat. No.	Cat. No.	Cat. No.
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24/40	14/20	250	Z16,615-4	Z14,782-6	Z16,616-2
24/40	14/20	500	Z54,900-2	Z54,912-6	Z54,920-7
24/40	24/40	100	Z54,901-0	Z17,604-4	Z54,921-5
24/40	24/40	250	Z16,405-4	Z14,779-6	Z16,406-2
24/40	24/40	500	Z16,613-8	Z14,781-8	Z16,614-6
29/32	14/20	100	Z54,902-9	Z54,913-4	Z54,922-3
29/32	14/20	250	Z54,903-7	Z54,914-2	Z54,923-1
29/32	14/20	500	Z54,904-5	Z54,915-0	Z54,925-8
29/32	24/40	100	Z54,905-3	Z54,916-9	Z54,926-6
29/32	24/40	250	Z54,906-1	Z54,917-7	Z54,927-4
29/32	24/40	500	Z54,908-8	Z54,918-5	Z54,928-2
29/32	29/32	100	Z54,909-6	Z20,344-0	Z54,929-0
29/32	29/32	250	Z20,324-6	Z20,327-0	Z20,330-0
29/32	29/32	500	Z20,325-4	Z20,328-9	Z20,331-9

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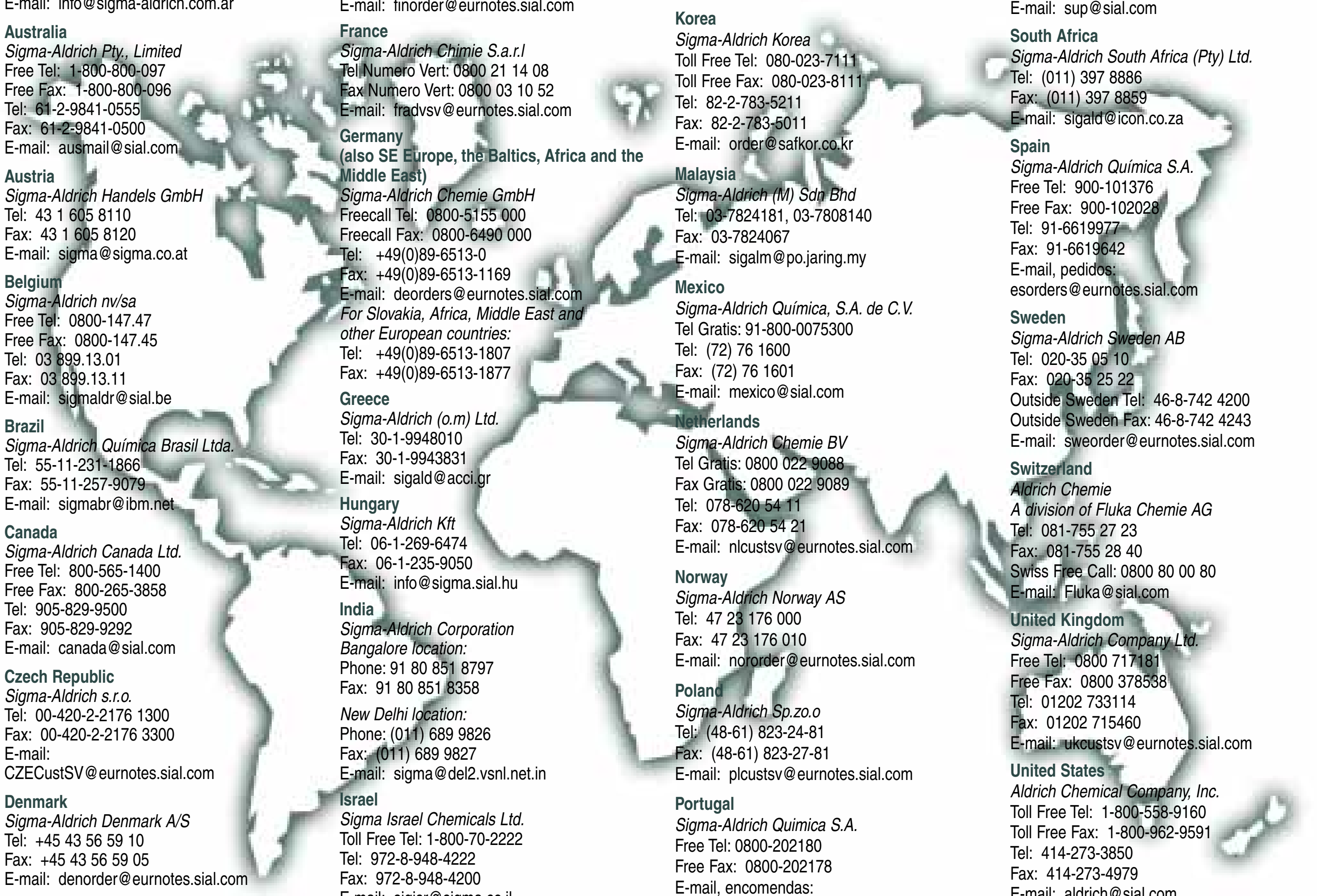

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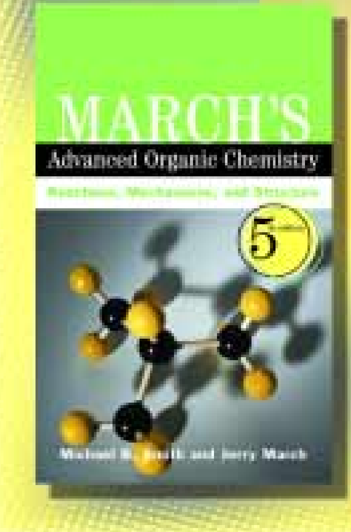

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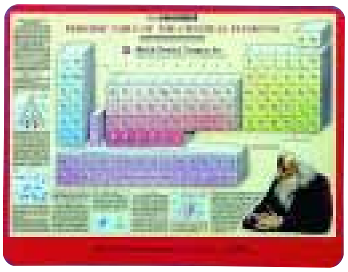

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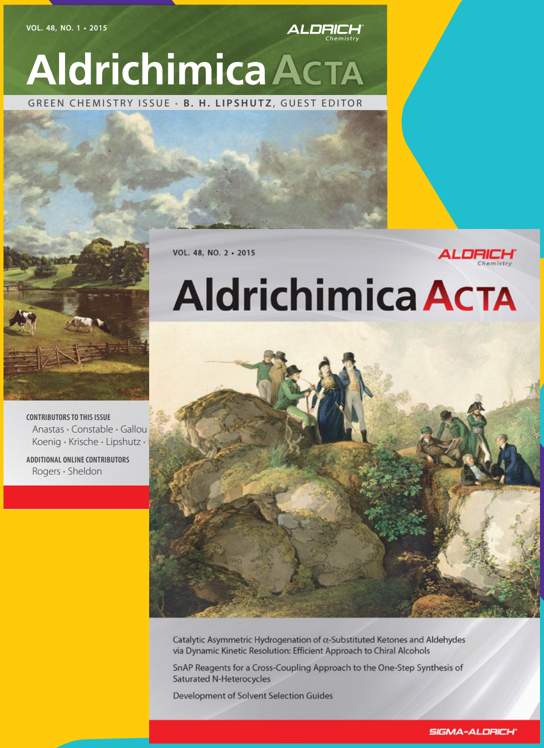

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