Aldrichimica Acta

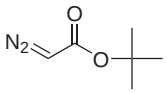
Volume 31, Number 1, 1998

Applications of cis-1-Amino-2-indanol in Asymmetric Synthesis

Synthetic Applications of Zinc Borohydride

New Products

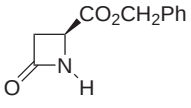
tert-Butyl diazoacetate is widely utilized for cyclopropane synthesis. High enantioselectivities have been achieved by utilizing chiral catalysts such as Co(III)-salen complexes or bisoxazolines.[1,2]

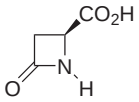


(1) Fukuda, T.; Katsuki, T. *Tetrahedron* **1997**, *53*, 7201. (2) Bedekar, A.V. et al. *J. Org. Chem.* **1997**, *62*, 2518.

48,075-4 *tert*-Butyl diazoacetate

Building blocks for γ-keto-α-amino acids,[1] and lactendiynes.[2]



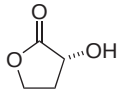


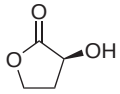
(1) Baldwin, J. E. et al. *Tetrahedron* **1995**, *51*, 4733. (2) Banfi, L. et al. *ibid.* **1997**, *53*, 3249.

46,897-5 Benzyl (*S*)-(–)-4-oxo-2-azetidinecarboxylate, 97%

47,327-8 (*S*)-(–)-4-Oxo-2-azetidinecarboxylic acid, 98%

The polyether antibiotic monensin,[1] an A-ring synthon for vitamin D_3 analogs,[2] and pesticides have been prepared from these hydroxybutyrolactones.[3]





(1) Collum, D.B. et al. *J. Am. Chem. Soc.* **1980**, *102*, 2118. (2) Dauben, W.G.; Lewis, T.A. *Synlett* **1995**, 857. (3) Buser, H.P. et al. *Tetrahedron* **1991**, *47*, 5709.

44,423-5 (*S*)-(–)-α-Hydroxy-γ-butyrolactone, 97% (98% ee/GLC)

44,428-6 (*R*)-(+)-α-Hydroxy-γ-butyrolactone, 97% (98% ee/GLC)

Compound **1** is often used as an ethylene oxide equivalent.[1,2] Compound **2** also undergoes ring opening through nucleophilic attack at carbon. These compounds have been utilized in the preparation of 3-(2'-hydroxyethyl)azetidin-2-ones[3] and glycol sulfonate surfactants.[4]

1

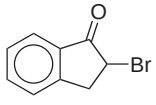
2

(1) Lohray, B.B. *Synthesis* **1992**, 1035. (2) Angelaud, R. et al. *Tetrahedron Lett.* **1995**, *36*, 3861. (3) Baldwin, J.E. et al. *Tetrahedron* **1995**, *51*, 5169. (4) Gautun, O.R. *Acta Chem. Scand.* **1996**, *50*, 170.

47,169-0 1,3,2-Dioxathiolane 2,2-dioxide, 98%

46,416-3 1,3-Propanediol cyclic sulfate, 98%

A number of compounds with potential pharmacological activity have been prepared from this indanone. Examples include antioxidants containing indoline chromophores,[1] and antiulcer agents derived from indeno[1,2-*d*]thiazoles.[2]



(1) Brown, D.W. et al. *Tetrahedron* **1991**, *47*, 4383. (2) Inoue, H. et al. *Yakugaku Zasshi* **1994**, *114*, 523.

46,350-7 2-Bromo-1-indanone, 90%

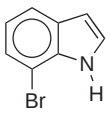
This aza-Wittig reagent has been used to prepare *N*-Cbz-protected β-sulfinylenamines,[1] cyanine dyes,[2] and phosphorane iminato complexes of a variety of elements including sulfur, aluminum, boron, and titanium.[3-6]

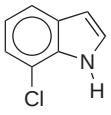
$Ph_3P=NTMS$

(1) Arnone, A. et al. *J. Org. Chem.* **1996**, *61*, 3375. (2) Mazieres, M.R. et al. *Tetrahedron* **1995**, *51*, 1405. (3) Folkerts, H. et al. *Z. Anorg. Allg. Chem.* **1994**, *620*, 1986. (4) Heshmatpour, F. et al. *ibid.* **1995**, *621*, 443. (5) Moehlen, M. et al. *ibid.* **1996**, *622*, 1692. (6) Ruebenstahl, T. et al. *ibid.* **1995**, *621*, 953.

47,225-5 1,1,1-Trimethyl-*N*-(triphenylphosphoranylidene)-silanamine, 97%

7-Substituted indoles[1,2] and indole alkaloids[2,3] are prepared from these heterocycles via palladium coupling or via the dianion.



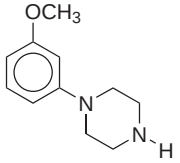


(1) Dobson, D. R. et al. *Synlett* **1992**, 79.
(2) Hutchings, R.H.; Meyers, A.I. *J. Org. Chem.* **1996**, *61*, 1004. (3) Banwell, M.G. et al. *J. Chem. Soc., Chem. Commun.* **1995**, 2551.

47,372-3 7-Bromoindole, 97%

47,373-1 7-Chloroindole, 97%

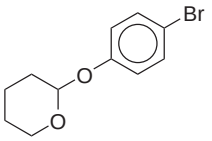
Potential high-affinity serotonin 5-HT_{1A} receptor ligands,[1] antibacterials,[2] and inhibitors of phosphodiesterases[3] have been prepared from this piperazine.



(1) Kuipers, W. et al. *J. Med. Chem.* **1995**, *38*, 1942. (2) Gadre, J. N. et al. *Indian J. Heterocycl. Chem.* **1994**, *3*, 289. (3) Monge, A. et al. *Arch. Pharm. (Weinheim, Ger.)* **1993**, *326*, 879.

47,168-2 1-(3-Methoxyphenyl)piperazine, 95%

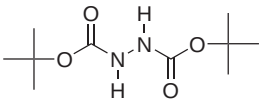
This protected bromophenol has been used to prepare *p*-ethynylphenol via a palladium coupling reaction.[1] A number of other *p*-substituted phenols have been synthesized using the Grignard reagent prepared from this compound.[2]



(1) Mery, S.J. et al. *Macromolecules* **1995**, *28*, 5440. (2) Ruenitz, P.C. et al. *J. Med. Chem.* **1996**, *39*, 4853.

47,781-8 2-(4-Bromophenoxy)tetrahydro-2*H*-pyran, 98%

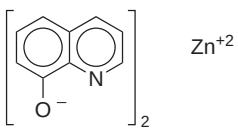
Valuable reagent for the preparation of symmetrical disubstituted hydrazines, pyrazolidines, and phthalazines.[1,2]



(1) Meissner, R. et al. *J. Am. Chem. Soc.* **1997**, *119*, 77. (2) Narukawa, Y. et al. *Tetrahedron* **1997**, *53*, 539.

14,046-5 Di-*tert*-butyl hydrazodiformate, 97%

Organic thin-film electroluminescent materials have been prepared from zinc quinolate.[1-3]



(1) Hopkins, T.A. et al. *Chem. Mater.* **1996**, *8*, 344. (2) Wang, G.M. et al. G*aodeng Xuexiao Huaxue Xuebao* **1995**, *16*, 230; *Chem. Abstr.* **1996**, *124*, 215861w. (3) Huang, Z. et al. *Gongneng Cailiao* **1995**, *26*, 362; *Chem. Abstr.* **1996**, *124*, 40857v.

47,175-5 8-Hydroxyquinoline, zinc salt, 99%

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Volume 31, Number 1, 1998

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About our Cover

The Dancing Couple (oil on canvas, 40-3/8 x 56-1/8 in.), by the Dutch artist Jan Steen (1625/26 – 1679), appears to represent a group of merrymakers. Under a vine-covered arbor outside a tavern they converse, drink, smoke, and watch a country bumpkin try to get a shy young woman to dance. Trying to play the dandy, the young peasant wears a jaunty cap adorned with cock feathers and an oversized white collar which is inappropriate for the rest of his costume. The crowds by the tents in the distance indicate that we are at a village fair or *kermis*. Steen's great empathy for the variety of characters of different ages and social classes who appear in his paintings is obvious, and extends to including himself in the picture. He is the man seated at the table stroking his companion affectionately under the chin.

More subtle meanings would have been recognized in the painting by the artist's contemporaries. The pair of figures which includes the artist himself, the old couple at the end of the table, and the loving mother holding her child in her lap all show an enduring love which contrasts with the transitory misalliance of the pair at the center of the picture. The broken eggs, the cut flowers spilled on the ground, and the boy blowing bubbles are all symbols of the transience of life and life's pleasures which would have been well understood in seventeenth century Holland.

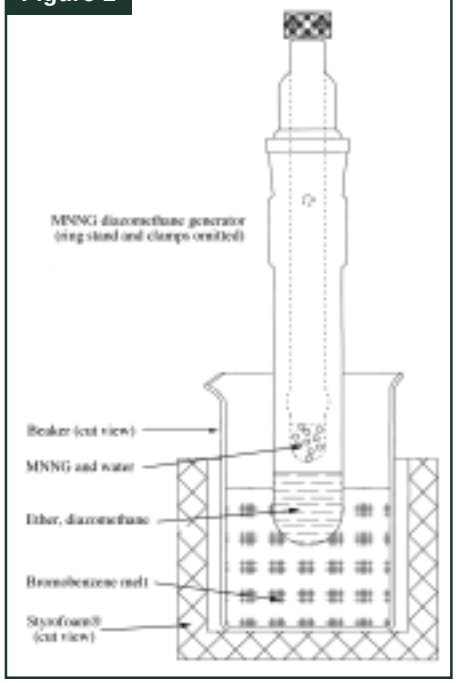
This painting is part of the Widener Collection at the National Gallery of Art.

Lab Notes

Improving the Production of Diazomethane by Generating It below Its Boiling Point

Although reactions with diazomethane are very rugged,[1] its preparation from MNNG has literally been quite volatile until we used cooling, as shown in **Figure 1**. We used the polished clear-seal-joint glass generator (Aldrich Cat. No. **Z10,159-1**) exclusively to rule out any contamination by the O-ring (Aldrich Cat. No. **Z10,100-1**). However, by using this apparatus, the chance of getting a usable diazomethane-ether solution was only slightly better than 50:50 because the gas was lost mainly through the glass joint. In contrast, a much more strongly colored ether solution is obtained when the following method is used.

Figure 1



The inner tube of the generator is charged with 1g MNNG and 1mL of water as recommended,[2] closed with two septa (the upper septum used in a previous run), placed into the outer vessel which contains about 6mL of ether (the ether should not touch the inner tube so as not to facilitate freezing of the aqueous solution in the inner tube), and the apparatus is held together with the clamp provided. The assembled generator is attached to a ring stand with an appropriate clamp and lowered into the bromobenzene melt (-31 °C), *the depth of insertion being adjusted to give an optimum between preventing the reagents from freezing (which would stop the generation of diazomethane) and having a large condensing (cold) area.* The melt is produced by pouring liquid nitrogen into bromobenzene until most (not all) of it solidifies. Here it is done in a beaker insulated with Styrofoam®; a small Dewar would probably be advantageous. After a few minutes of cooling, 1.5mL of 5 M NaOH is added over 1-2 min[2] (much faster addition than without this cooling). The buildup of pressure can be felt and monitored via the plunger of the syringe containing the NaOH solution. The reaction is allowed to continue for 30 min with occasional slight shaking of the generator, and liquid N_2 is added if needed to maintain the melt. The generator (still assembled) is then removed from the melt to allow it to warm up. Just before reaching room temperature the ether-diazomethane solution can be pipetted (positive displacement pipettes) as needed. For example, 100µL of an aqueous oxalic acid solution (can be an HPLC fraction; mobile phase: aqueous TFA; here usually below 30 mg/L oxalic), in a 5mL vial with a threaded Teflon® inlay cap, is titrated by shaking with the diazomethane solution in 100-500µL portions until the yellow color persists. After discarding the aqueous layer and evaporating the larger part of the ether layer with a micro refluxer,[3] which retains the diester, conventional MS can be used to obtain excellent mass spectra of the oxalic acid dimethyl ester. *We have used this generator hundreds of times without cooling and about twenty times with the cooling described here without ever experiencing a safety-related incident.*

References: (1) Diazomethane as a Highly Selective Fatty Acid Methylating Reagent for Use in Gas Chromatographic Analysis: Mueller, H.W. *J. Chromatogr., B* **1996**, *679*, 208. (2) The Preparation and Reactions of Diazomethane: Black, T.H. *Aldrichimica Acta* **1983**, *16*, 3. (3) Microliter Techniques in the Formation of New Derivatives for Gas Chromatographic Analysis: Dünges, W. *Anal. Chem.* **1973**, *45*, 963.

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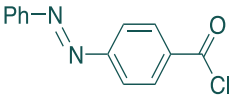
***Editor's Note*:** The reader should evaluate the suitability of a given experimental procedure for his/her purposes, and should exercise due caution in using any such procedure, especially for the first time. Anyone working with diazomethane must wear the proper protective attire and conduct all manipulations in a well-ventilated hood equipped with a safety shield. In addition to the references cited above, the reader is urged to consult other writeups and safety warnings about diazomethane generation and properties such as Moore, J.A.; Reed, D.E. *Org. Synth.* **1973**, *Coll. Col. V*, 351; or the *Aldrich Catalog Handbook of Fine Chemicals*, 1996-1997 ed., pp T218-220.

"Please Bother Us."

by Jai Nagarkatti

Jai Nagarkatti, President

Professor David Morris of the University of Glasgow kindly suggested that we offer 4-(phenylazo)-benzoyl chloride. This compound has been used to prepare reversible photoregulatable enzyme inhibitors[1] and photoresponsive peptides.[2]



(1) Westmark, P.R. et al. *J. Am. Chem. Soc.* **1993**, *115*, 3416. (2) Yamamoto, H. et al. *Int. J. Biol. Macromol.* **1990**, *12*, 257

17,345-2 4-(Phenylazo)benzoyl chloride, 97%

Naturally, we made this useful compound. It was no bother at all, just a pleasure to be able to help.

Do you have an innovative shortcut or unique laboratory hint you'd like to share with your fellow chemists? If so, please send it to Aldrich (attn: Lab Notes, *Aldrichimica Acta*). For submitting your idea, you will receive a complimentary, laminated periodic table poster (Cat. No. **Z15,000-2**). If we publish your *Lab Note*, you will also receive an Aldrich periodic table turbo mouse pad (Cat. No. **Z24,409-0**). It is Teflon®-coated, 8½ x 11in., with a full-color periodic table on the front. We reserve the right to retain all entries for future consideration.

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Applications of *cis*-1-Amino-2-indanol in Asymmetric Synthesis

This Review Is Dedicated to Professor Carl R. Johnson on the Occasion of His 60th Birthday

Chris H. Senanayake
Director of Chemical Process Research
Chemical Research and Development
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Outline

1. Introduction

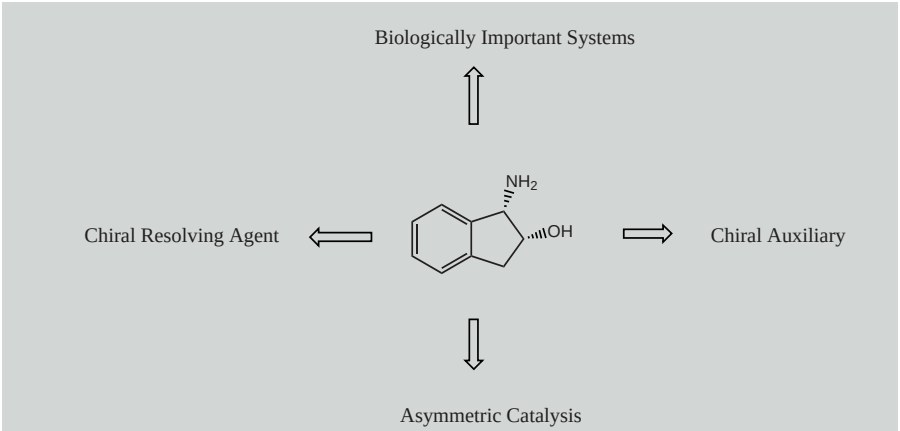
The world has realized, and scientists have documented, that, in general, enantiomers are recognized differently by enzymes, receptors, and other binding sites in biological systems. Many studies have shown that two enantiomers of a chiral drug usually display different biological activities, and one enantiomer is sometimes detrimental. In the past ten years, the chemical community has realized that the preparation of enantiopure materials is critically important to mankind, and many research groups have devoted a considerable amount of time to the development of new asymmetric synthesis methods. However, finding generally useful chiral building blocks for asymmetric synthesis is still a significant challenge.[1] In many cases, it has been recognized that chiral amino alcohols are versatile reagents for the generation of enantiopure materials.[2] The rigid benzocycloalk-1-ene-derived vicinal cis amino alcohols represent a chemically and biologically appealing subclass of these amino alcohols. It has been revealed in the literature that the constrained aminoindanol platform plays a crucial role in biological systems and in the field of asymmetric synthesis (**Scheme 1**). This review focuses on the importance and general applicability of *cis*-1-amino-2-indanol as a chiral template in organic synthesis.

2. The Importance of *cis*-1-Amino-2-indanol in Biological Systems

The significance of HIV protease inhibitors in the treatment of the acquired immunodeficiency syndrome (AIDS) is now well documented.[3] In the early 1990s, the Merck group developed a series of novel HIV-PR transition-state isosteres that contained the constrained *cis*-1-amino-2-indanol unit.[4] After several structural modifications, Merck's orally active HIV protease inhibitor, Crixivan® (Indinavir sulfate), was developed and is one of the leading drugs for the treatment of AIDS to date.[5] The single enantiomeric Crixivan® has five stereogenic centers, and, interestingly, four stereocenters are controlled by the indane backbone.[6] Since the discovery of *cis*-1-amino-2-indanol as an important subunit in drug design, the emphasis on this chiral motif has increased not only in drug design but also in the asymmetric synthesis of several biologically active molecules (**Figure 1**).[7]

3. Synthesis of Chiral *cis*-1-Amino-2-indanol

While a great deal of emphasis has been placed on the synthesis of rigid benzocycloalk-1-ene-derived *cis*-1-amino-2-alcohols,[8] strikingly practical syntheses have remained



Scheme 1. The importance of *cis*-1-amino-2-indanol.

elusive until recently.[9] Chiral 1,2-epoxides and 1,2-diols derived from benzocycloalkanes have become available by either asymmetric epoxidation (AE) or asymmetric dihydroxylation (AD) of the corresponding prochiral olefins **1**.[10] These oxygenated adducts have served as excellent precursors of *cis*-amino alcohols **2** in appropriately chosen selective amination reactions (**Scheme 2**).[8,9,11]

The recent literature has revealed that the Merck[9a,c] and Sepracor groups[9d] have independently developed two practical processes for the preparation of (1*S*)-amino-(2*R*)-indanol. These two groups have demonstrated the power of Jacobsen's epoxidation by using the complementary Mn-(salen) catalysts (MnLCl, **7**)[10a,b,i,12] for indene epoxidation, followed by either a C-1 or C-2 chiral transfer process of the C-O bond of indene oxides **4** resulting in enantiopure (1*S*)-amino-(2*R*)-indanol (**Scheme 3**).

As illustrated in **Scheme 3**, the Sepracor group demonstrated that (1*R*, 2*S*)-indene oxide could be prepared in 83% yield and 84% enantiomeric excess from readily available indene in the presence of 1.5 mol% of (*R*,*R*)-MnLCl and 13% NaOCl in dichloromethane. The optically active indene oxide was then subjected to nucleophilic opening with ammonia to provide *trans*-aminoindanol, which was transformed without isolation into its benzamide in 84% ee by using the Schotten-Baumann conditions; following crystallization the benzamide was isolated in >99.5% ee. The optically pure *trans*-benzamidoindane was then converted to the optically pure benzoxazoline **5** simply by exposing it to 80%

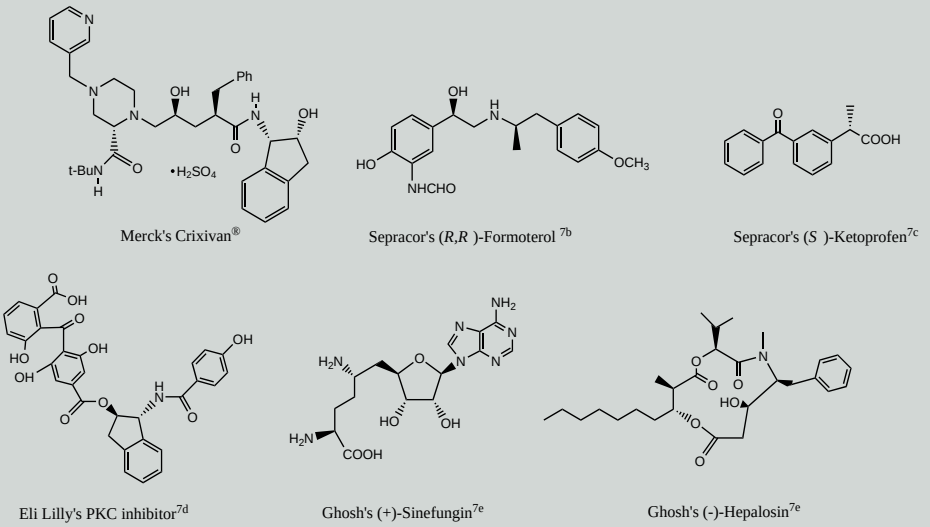
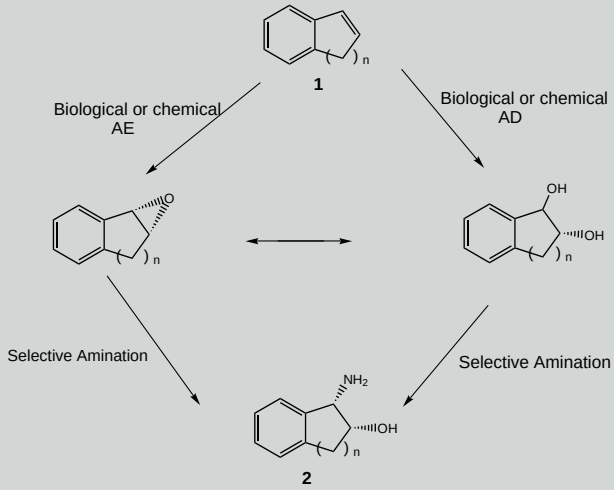
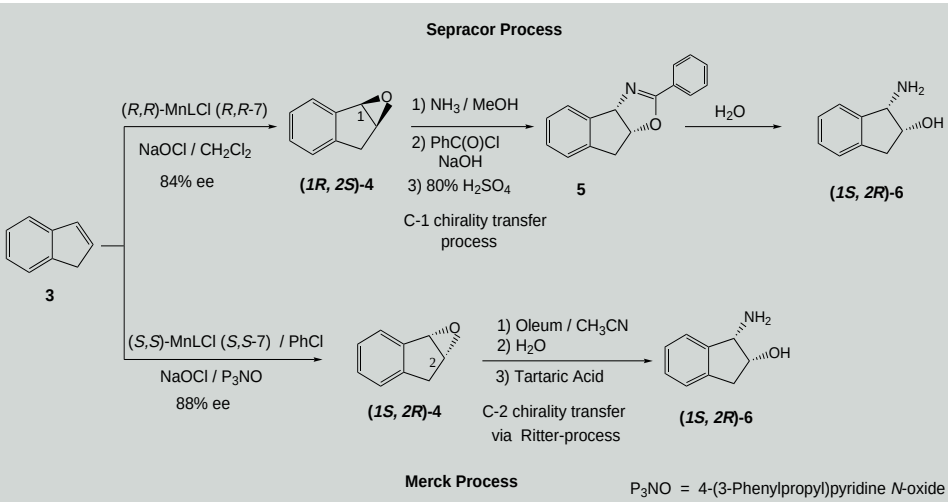


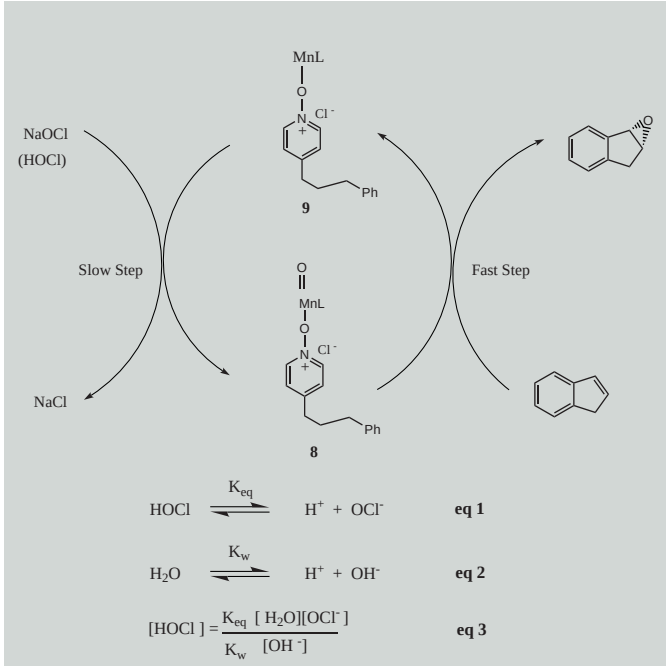
Figure 1. Relevance of *cis*-1-amino-2-indanol to bioactive molecules.



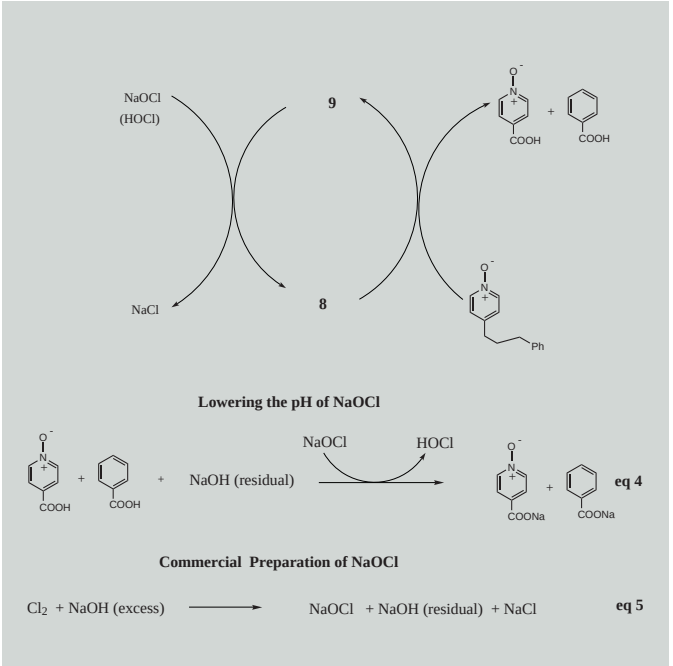
Scheme 2. Synthetic approaches to *cis*-1-amino-2-indanol.



Scheme 3: Practical preparations of (1*S*)-amino-(2*R*)-indanol via Jacobsen's epoxidation.



Scheme 4. Mechanism of indene epoxidation.

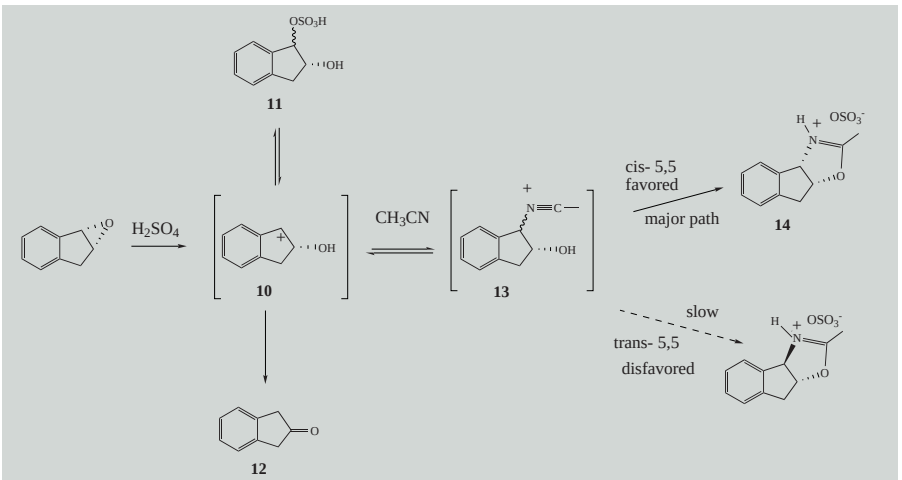


Scheme 5. Secondary oxidation-hypochlorite decomposition phenomena.

H_2SO_4; addition of water resulted in *cis*-1-amino-2-indanol (*1S,2R*)-**6**.[9d] The overall yield of optically pure (*1S,2R*)-**6** from indene is 40%, and the preparation has been carried out on a multikilogram scale.

A complementary approach to the synthesis of (*1S,2R*)-**6** has been developed by Senanayake et al. by utilizing (*S,S*)-MnLCl as catalyst in a hypochlorite medium to provide (*1S,2R*)-indene oxide. Without isolation, the oxide is converted to *cis*-aminoindanol stereo- and regioselectively using the Ritter technology (**Scheme 3**).

Several key issues have been addressed and resolved in both Jacobsen's AE[9c] and the Ritter technologies[9a] in the process of developing a reproducible and practical synthesis of chiral *cis*-aminoindanol.



Scheme 6. Thermodynamically driven equilibration process for *cis*-oxazoline **14**.

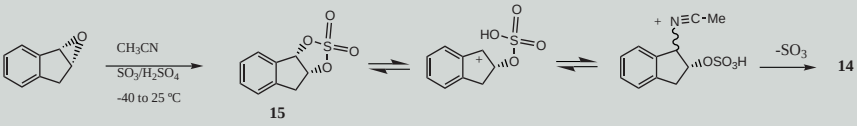
3.1. Jacobsen's Asymmetric Epoxidation of Indene

Jacobsen[10b,g] and Katsuki[10n] have shown the importance of chiral manganese-salen complexes in the catalytic asymmetric epoxidation of unfunctionalized olefins. In these salen systems, the addition of appropriate *N*-oxides activates and stabilizes the catalyst systems.[13] Recently, Senanayake and coworkers illustrated this point with the addition of an axial ligand, 4-(3-phenylpropyl)-pyridine *N*-oxide (P_3NO),[12a] to the Jacobsen (*S,S*)-MnLCl-NaOCl-PhCl system. A highly activated and stabilized catalyst for indene epoxidation resulted.[9c] Furthermore, the catalyst loading was reduced to <0.4 mol%. Several kinetic studies indicated that the active catalyst was Mn^{V}-oxo species **8**,[9c] and hypochlorous acid (HOCl) was the true oxidant.[14] In addition, the Merck group indicated that the slow step in the epoxidation process was the oxidation of Mn^{III} species **9** to Mn^{V}-oxo **8** (**Scheme 4**).[14] During the development of the epoxidation of indene, the Merck team observed that NaOCl decomposed throughout the course of the reaction, giving rise to problems with reagent stability and stoichiometry. They also observed a secondary oxidation process, which provided isonicotinic acid and benzoic acid via benzylic oxidation of P_3NO (**Scheme 5**).[9c] The decomposition was due to an insufficient amount of hydroxide in the hypochlorite. They demonstrated that, based on the equilibrium equations for the dissociation of HOCl and water and by evaluating several kinetic studies, HOCl was involved in the rate-determining step of the epoxidation and its concentration was inversely proportional to the hydroxide ion concentration (**eq 3**).[14] Furthermore, the

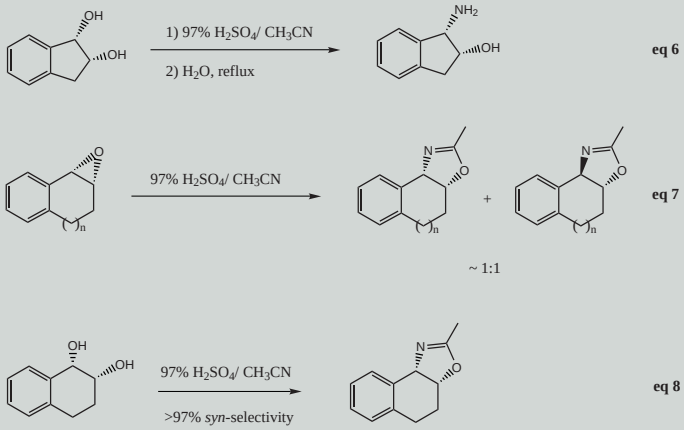
hydroxide ion concentration was lowered in the NaOCl by the carboxylic acid generated from the secondary oxidation of P_3NO (**eq 4** and **5**). This, in turn, increased the HOCl concentration in the organic layer and led to its decomposition in the presence of the manganese catalyst. With proper adjustment of the hydroxide ion concentration of commercial 2 M NaOCl from 0.03-0.18 to 0.3 M, the hypochlorite can be stabilized and the secondary oxidation minimized (**eq 5**). This reagent mixture has been utilized on a multikilogram scale to prepare (1*S*,2*R*)-indene oxide in 89% yield and 88% ee.[9c]

3.2. Ritter-Type Technology for *cis*-1-Amino-2-indanol Synthesis

Styrene oxide gave poor yields of regioisomeric oxazolines when exposed to the conditions of the Ritter reaction.[15] Recently, Senanayake et al. demonstrated that when indene oxide was subjected to the Ritter reaction conditions (acetonitrile/97% H_2SO_4), methyl oxazoline **14** was formed as the major product in moderate yield.[9a] Several factors were pointed out by a low-temperature NMR study of this Ritter process. As depicted in **Scheme 6**, the epoxide formed a 1:1 mixture of methyloxazoline and sulfate **11** at -40 °C. While warming the reaction to 22 °C, the sulfate ester was simply converted to the corresponding oxazoline sulfate. The proposed mechanism for syn-selective oxazoline formation is an acid-induced ring opening of indene oxide to produce carbonium ion **10**, which is converted to nitrilium species **13** on the way to the *cis*-5,5-ring-derived oxazoline. In this fascinating Ritter process, two roadblocks for product formation were identified: (a) polymerization via the carbonium ion, and (b) hydrogen shift from the initial carbonium ion to form 2-indanone (>12%). Senanayake et al. demonstrated that the byproduct-forming processes were suppressed by stabilizing the carbonium ion with a catalytic amount of sulfur trioxide added to the Ritter mixture. As depicted in **Scheme 7**, sulfur trioxide captured the epoxide to form sulfate intermediate **15**, which eventually led to product **14**. In addition, the chirality of the epoxide was effectively transferred from the C-2 to the C-1 position of the amino alcohol. By utilizing the Ritter acid as an oleum (21% SO_3-H_2SO_4), a highly practical and cost-effective process was developed for the conversion of chiral indene oxide to chiral *cis*-1-amino-2-indanol (>80% yield).[9a,6]

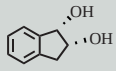
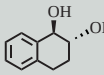
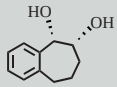
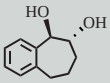


Scheme 7. Sulfur trioxide catalyzed Ritter process.

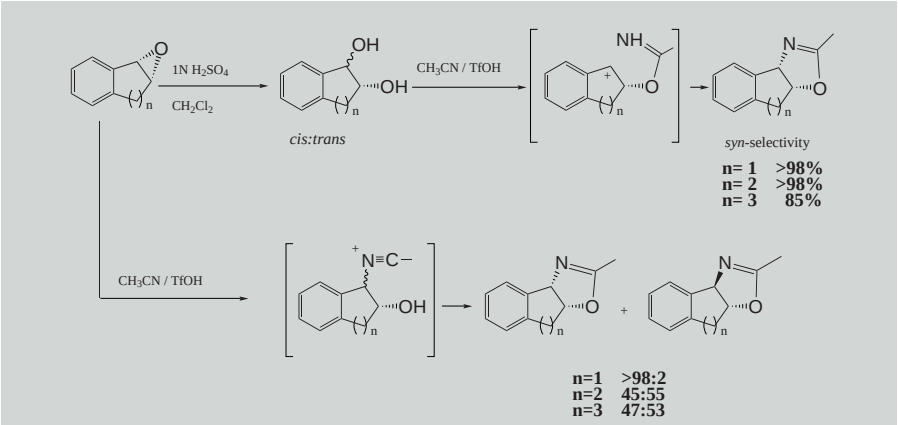


Scheme 8. Ritter process applied to *cis*-1,2-diols.

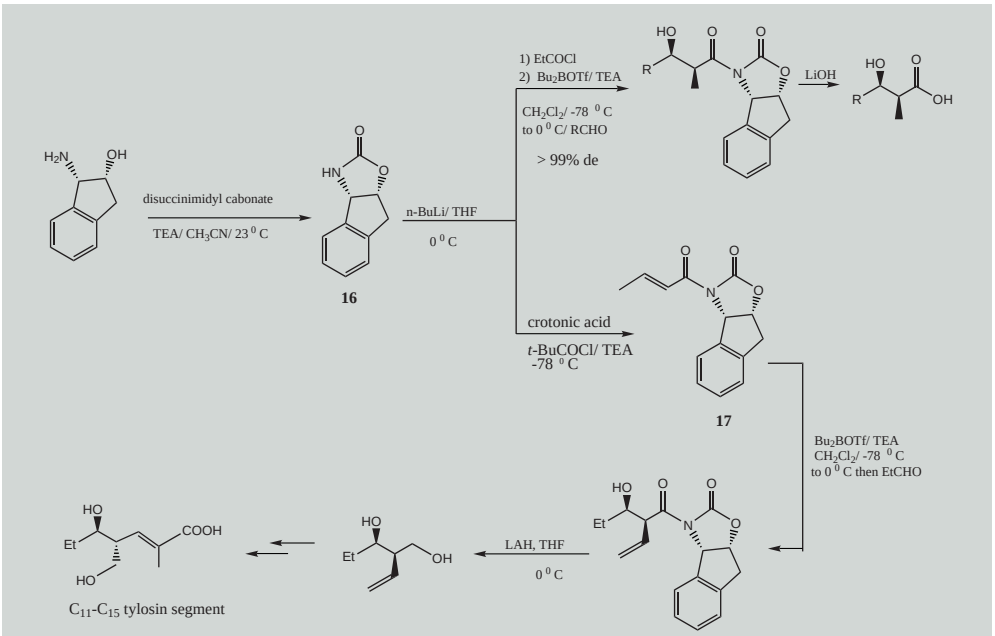
Table 1. *syn*-Selective amination process for diols.

Diol (% ee)	Acid	cis/trans Amino Alcohol	% ee (yield %) of cis Amino Alcohol
 (>99)	TfOH	>98:2	>99(87)
	97% H_2SO_4	>97:3	>99(81)
 (85)	TfOH	98:2	85(78)
 (>99)	TfOH	99:1	>99(80)
	97% H_2SO_4	98:2	>99(75)
 (99)	TfOH	97:3	99(71)
	TfOH	86:14	--(63)
 (90)	TfOH	85:15	90(62)

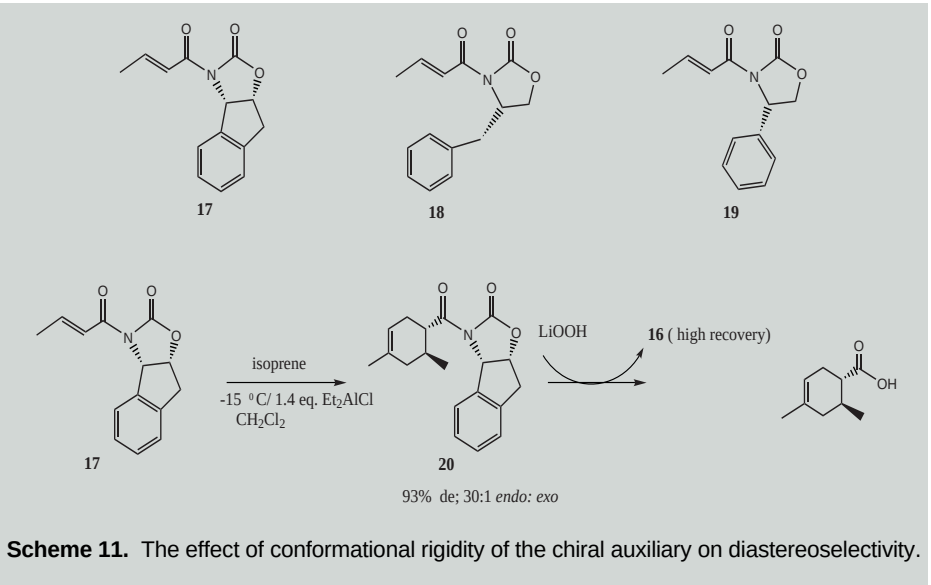
Senanayake and co-workers have shown that chiral indan-1,2-diols[9a,b,11] also undergo Ritter-type reactions leading to *cis*-1-amino-2-indanol; however, SO_3 is not necessary to obtain high yields (**Scheme 8, eq 6**).[9b] The issues associated with diols are quite different from those of epoxides and can be explained simply by examining larger-ring analogs of indane, such as tetralin and subarane. When the Ritter methodology was applied to larger-ring analogs, such as tetralin oxide or subarane oxide, poor oxazoline regio- and stereoselectivity resulted (**eq 7**). However, diols of tetralin provided extremely interesting results (**eq 8**). As illustrated in **Table 1**, *cis*- or *trans*-tetralin-1,2-diol provided the



Scheme 9. Proposed mechanism for amination of diols and epoxides.



Scheme 10. Highly selective syn-aldol approach to the C_{11}-C_{15} segment of tylosin.



Scheme 11. The effect of conformational rigidity of the chiral auxiliary on diastereoselectivity.

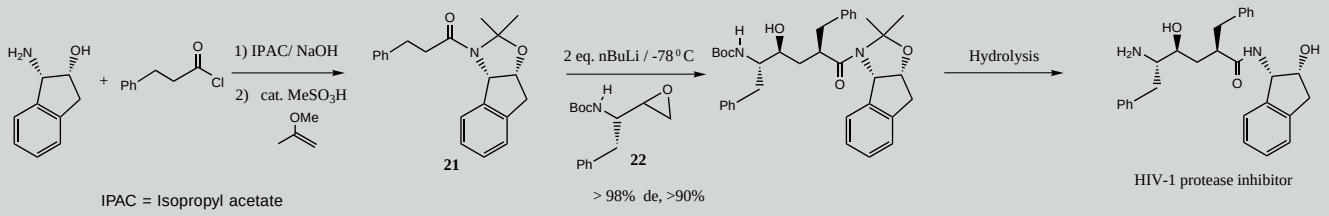
corresponding oxazoline in high yield and ≥97% syn-selectivity. Since the stereochemistry at the C-1 position of the diols is irrelevant to the resultant stereochemistry of the amino alcohol, the chiral epoxide was converted under acidic conditions to a mixture of cis and trans diols, which were then subjected to Ritter-type conditions (TfOH-CH_3CN) to provide > 97% syn-selectivity (**Scheme 9**).[9b] These valuable findings have allowed the preparation of constrained, larger-ring cis amino alcohols that are chemically and biologically important.

4. Applications of *cis*-1-Amino-2-indanol as a Chiral Auxiliary

Rigid *cis*-aminoindanol and its derivatives have become useful and effective chiral auxiliaries in several asymmetric synthetic processes because of their availability, ease of recovery, and the high degree of asymmetric induction that results. It is important to note that both enantiomers of *cis*-aminoindanol are readily available from commercial suppliers.[12] This section focuses on the utility of aminoindanol as a chiral auxiliary in asymmetric synthesis.

4.1. Oxazolidinones Derived from cis-1-Amino-2-indanol

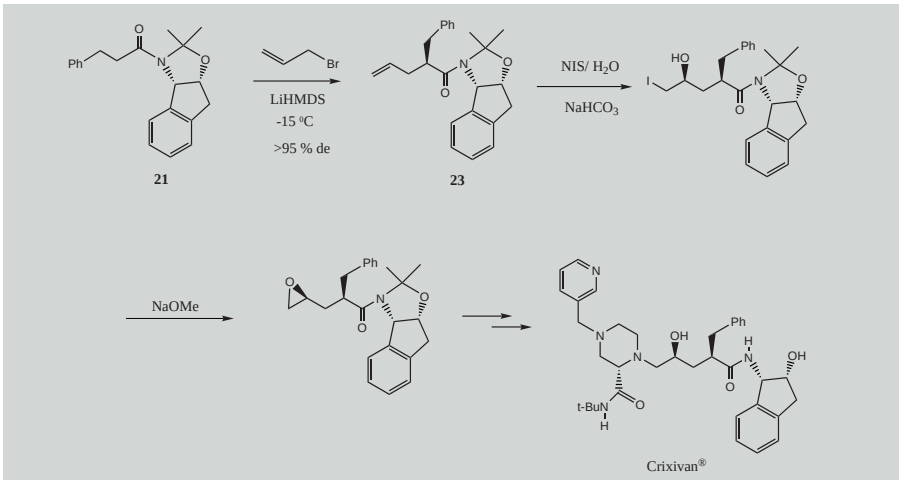
Optically pure oxazolidinones are an extremely important and extensively studied class of chiral auxiliaries.[16] Evans and others have demonstrated the value of the asymmetric aldol reaction by applying it to the synthesis of complex natural products and biologically important targets.[1a] Many chiral amino alcohols have served as backbones of oxazolidinones; however, conformationally constrained oxazolidinones are still needed. In 1992, Ghosh and co-workers provided the first example of the utility of rigid, *cis*-1-amino-2-indanol-derived, oxazolidinone **16** as a chiral auxiliary in the asymmetric syn-aldol reaction.[7e,f,17] As illustrated in **Scheme 10**, the boron enolate of constrained *N*-acyl oxazolidinone underwent essentially complete diastereofacial selectivity in the aldol condensation with various aldehydes. The removal of the auxiliary with LiOH was mild and highly effective, and led to a good recovery of the chiral auxiliary. An aldol condensation of oxazolidinone **17** has been utilized in the synthesis of the



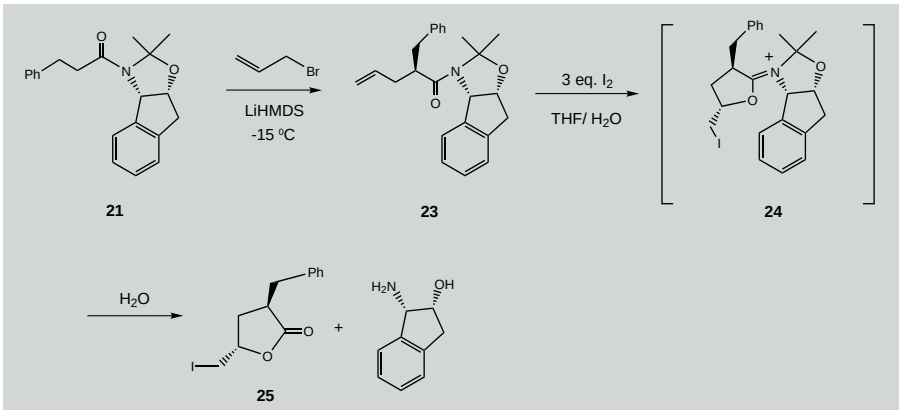
Scheme 12a. Aminoindanol acetonide as a chiral auxiliary in the diastereoselective synthesis of HIV-1 protease inhibitor.

C_{11}-C_{15} segment of the macrolide antibiotic tylosin.[17]

Recently, the Merck group has demonstrated the viability of the chiral auxiliary **16** as a phenylglycinol equivalent in the metal-mediated asymmetric Diels-Alder reaction.[18] Evans has shown that, by using oxazolidinone **18,** very high levels of diastereofacial selectivity are accessible in the Diels-Alder reaction of isoprene (88% de). In contrast, much lower levels of selectivity are obtained with phenylglycinol derivative **19** (35% de).[19] The Merck group has postulated that the low level of selectivity in the case of **19** is due to the rotationally labile phenyl moiety that can be less sterically demanding in some of its conformations. Owing to the conformational rigidity of the tricyclic core of the aminoindanol auxiliary, high levels of asymmetric induction had been expected in the Diels-Alder reaction. Indeed, this turned out to be the case: the rationally designed tricyclic auxiliary provided 93% de in the case of isoprene (**Scheme 11**).[18]



Scheme 12b. Diastereoselective allylation—epoxide formation process for Crixivan®.



Scheme 13. Asymmetric synthesis of *anti*-2,4-disubstituted-γ-butyrolactones.

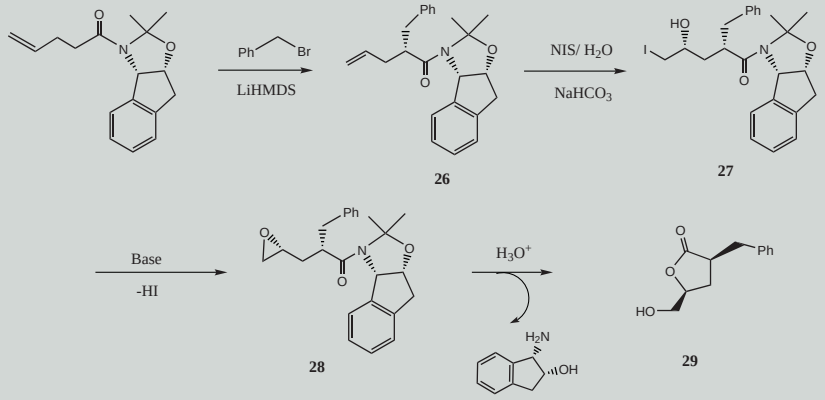
4.2. Aminoindanol Acetonide as a Chiral Auxiliary

Askin and co-workers have demonstrated that the rigid tricyclic aminoindanol acetonide can be utilized as a chiral platform for the diastereoselective alkylation of the *Z* lithium enolate of amide **21** with amino epoxide **22** to give a >98% de during the synthesis of HIV-1 protease inhibitor (**Scheme 12a**).[20] This alkylation strategy has been utilized in the highly diastereoselective (>95% de) synthesis of the orally active HIV protease inhibitor Crixivan®, which belongs to one of the important classes of new drugs for the treatment of AIDS (**Scheme 12b**).[6,21] Askin's technology has set the stage for the identification of a new aminoindanol acetonide, which has become a very important chiral auxiliary in many asymmetric syntheses.

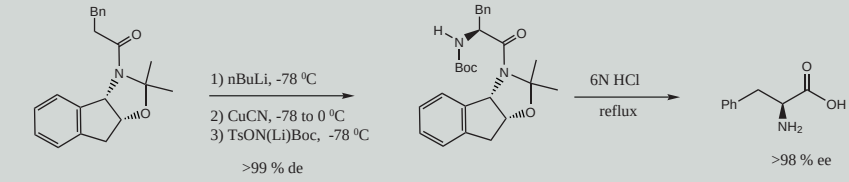
The Askin methodology was extended to the asymmetric synthesis of *syn*- and *anti*-2,4-disubstituted-γ-butyrolactones (**Schemes 13 and 14**).[21b] Amide **21** was allylated in excellent yield and with a high degree of diastereoselectivity (97:3) by reacting it with lithium hexamethyldisilazide/ allyl bromide at -30 °C. Olefin **23** was then subjected to Yoshida's conditions (I_2/THF/ H_2O) providing anti lactone **25** in a >95% selectivity.[22] Presumably, **25** was generated from cyclic iodoimidate **24** upon hydrolysis. Interestingly, pro-(2*S*) diastereomer **26** was prepared in high yield and excellent diastereoselectivity by reversal of the order of introduction of the benzyl and allyl groups. Exposure to the buffered iodohydrin conditions resulted in formation of the 2,4-*syn*- adduct **27** with high selectivity (97% de). In basic medium, **27** led to epoxide **28**. *syn*-2,4-Disubsitituted-γ-butyrolactone **29** was then obtained via acid-mediated lactonization of **28**.[21b]

In a conceptually related system, Armstrong and co-workers indicated that the electrophilic amination of lithium amide enolates with lithium *t*-butyl-*N*-tosyloxy-carbamate [TsON(Li)Boc] does not take place as expected; however, the corresponding amide cuprate proved to be an excellent chiral amination unit in the synthesis of chiral amino acids (**Scheme 15**).[23]

In contrast to Armstrong's work, Kress and co-workers achieved a nice entry into



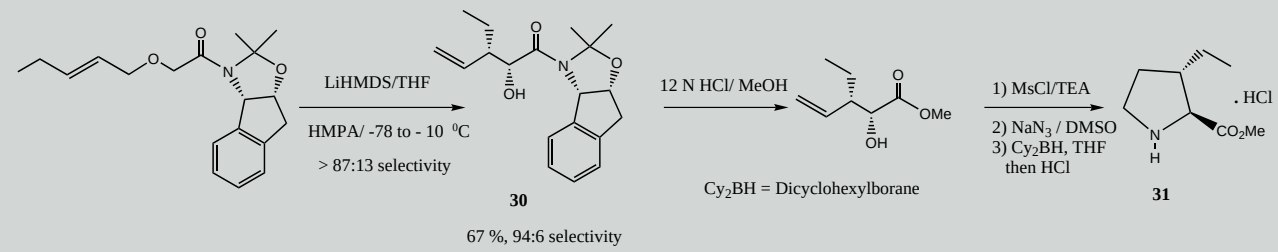
Scheme 14. Stereocontrolled synthesis of *syn*-2,4-disubstituted-γ-butyrolactones.



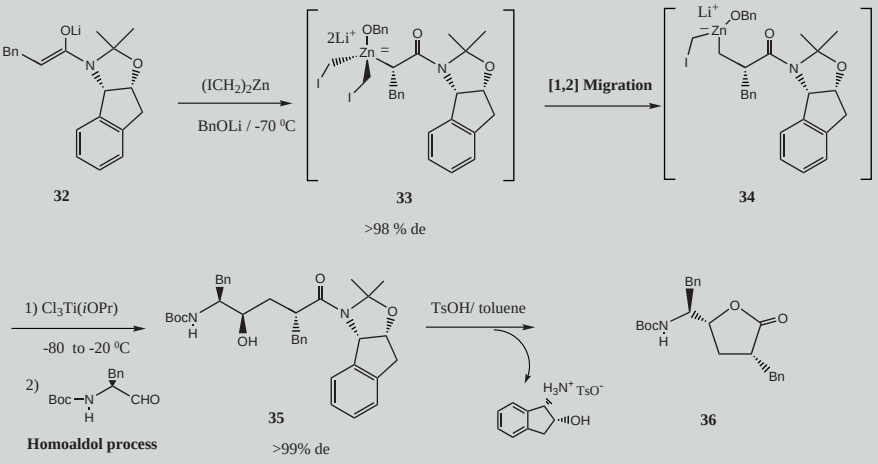
Scheme 15. Electrophilic amination of amide cuprates for the synthesis of amino acids.

cyclic and acyclic amino acids using the [2,3] Wittig rearrangement of aminoindanol-derived lithium amide enolates. They demonstrated that high levels of stereocontrol can be achieved in the Wittig rearrangement via a rigid tricyclic aminoindanol platform.[24] The scope of this methodology was established using a variety of *trans*-disubstituted olefins that underwent the sigmatropic rearrangement to produce excellent syn selectivity in the adducts. *syn*-Adduct **30** was converted to the anti-configured chiral proline derivative **31** using routine manipulations (**Scheme 16**).

Recently, the Merck group has elaborated on this methodology by using the conformationally constrained amide enolate **32** in a homoaldol process.[25] Their approach to the synthesis of highly functionalized chiral *syn*-2,4-disubstituted-γ-butyrolactones is unique and elegant and involves a tandem [1,2] migration/homoaldol protocol. As illustrated in **Scheme 17**, enolate **32** is reacted first with bis(iodomethyl)zinc, followed by exposure to lithium phenylmethoxide. The resulting intermediate undergoes a [1,2] migration to alkoxy zincate **34**. The stereoselectivity of



Scheme 16. [2,3] Wittig rearrangement of aminoindanol-derived lithium amide enolates.



Scheme 17. Tandem [1,2] migration/homoaldol protocol for the synthesis of optically pure γ-lactones.

the [1,2] migration is outstanding, producing a >98% de. Zinc homoenolate **34** is then transmetalated with (*i*PrO)$TiCl_3$ and reacted with *N*-(*tert*-butoxycarbonyl)phenylalaninal to provide the homoaldol adduct **35** in 59% yield and a >99% de. Treatment of γ-hydroxyamide **35** with *p*-toluenesulfonic acid generated lactone **36** in good yield. It is important to note that pure (*1S, 2R*)-*cis*-aminoindanol crystallizes out of the reaction mixture as the *p*-toluenesulfonate salt and is recovered by filtration.

4.3. cis-1-p-Tolylsulfonamido-2-indanol as a Chiral Auxiliary

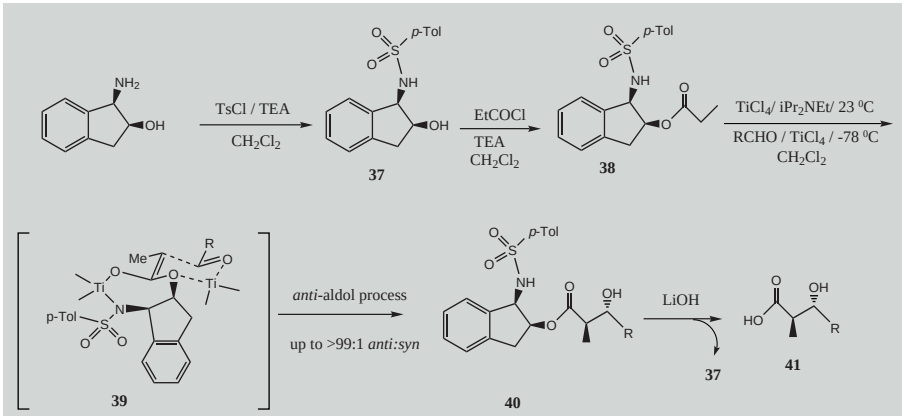
Interestingly, all the examples discussed thus far took advantage of the C-1 amine moiety of aminoindanol as a handle in a wide variety of known reactions to produce important chiral intermediates. It is known that

amide-derived chiral auxiliaries sometimes require harsh conditions in order to remove them, and have a limited synthetic applicability. On the other hand, ester-derived chiral auxiliaries can be removed under much milder conditions and have proved to be very useful chiral auxiliaries in certain asymmetric syntheses.

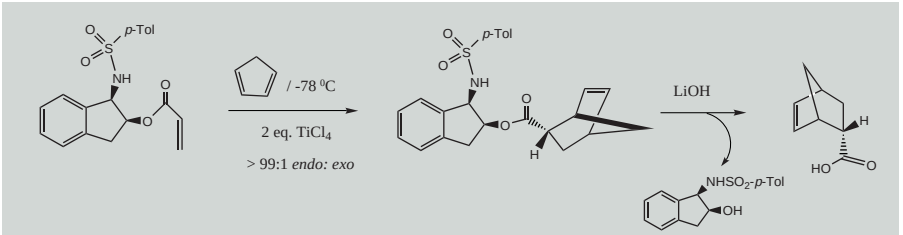
Very recently, Ghosh and co-workers have brilliantly demonstrated that, not only the C-1 amine, but also the C-2 hydroxyl moiety of the aminoindanol, can be effectively utilized in several asymmetric synthetic processes *because the rigid aminoindanol backbone has a highly defined chiral environment*. For example, enantiomerically pure *cis*-1-*p*-tolylsulfonamido-2-indanol (**37**) is converted to ester **38** in high yield. Ester **38** is then conveniently transformed into the titanium enolate with $TiCl_4$–*i*Pr_2NEt. The titanium enolate reacts with aldehydes, precomplexed with $TiCl_4$, and leads to *anti*-aldol esters **40** in excellent diastereoselectivities. Hydrolysis of **40** affords *anti*-aldol acid **41** in high enantiomeric purities (**Scheme 18**).[26] This result is in contrast to that obtained with the boron enolate derived from amide **17,** as shown in **Scheme 10**.[17]

With the development of the new chiral auxiliary, *cis*-1-*p*-tolylsulfonamido-2-indanol, Ghosh found that it can be used highly diastereoselectively in the titanium-promoted Diels-Alder reaction leading to complete endo adducts (**Scheme 19**).[27]

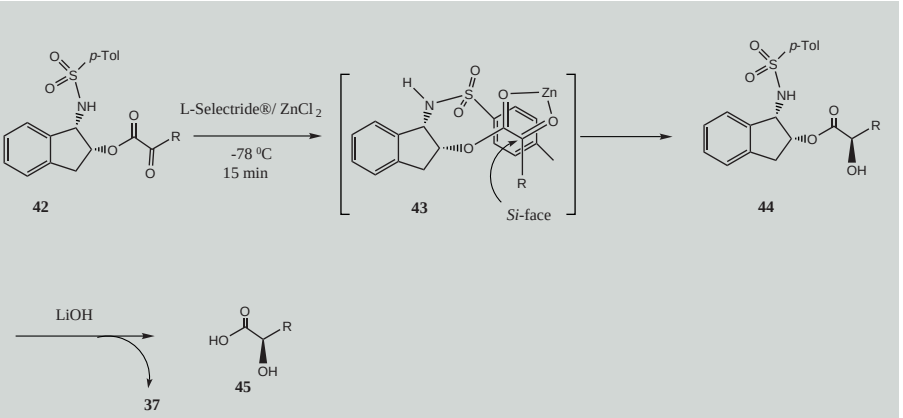
In addition, the chelation-controlled Selectride® reduction of α-keto esters **42** afforded α-hydroxy esters **44** in high yields and excellent diastereoselectivities.[28] It is important to note that α-keto ester reduction by L-Selectride® most likely proceeds through the locked s-*cis* conformation **43** due to metal chelation. Mild hydrolysis of **44** provided essentially optically pure α-hydroxy acids **45**. In this process, the recovery of the auxiliary is quantitative (**Scheme 20**).



Scheme 18. Highly diastereoselective approach to anti aldol esters.



Scheme 19. Chiral auxiliary in the titanium-promoted Diels-Alder reaction.



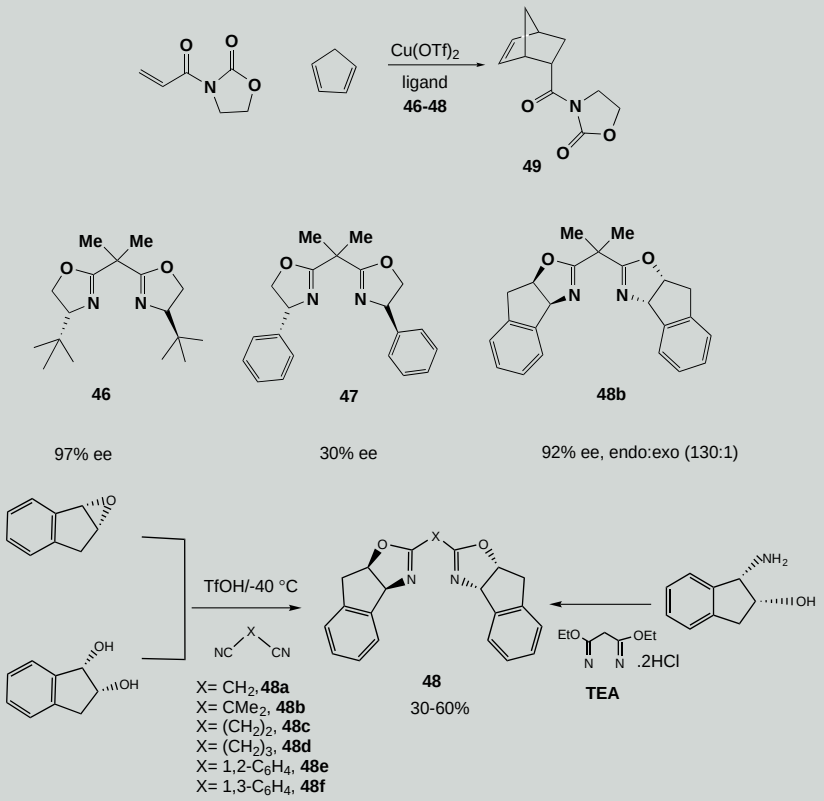
Scheme 20. Synthesis of enantiopure α-hydroxy acids.

5. *cis*-1-Amino-2-indanol in Asymmetric Catalysis

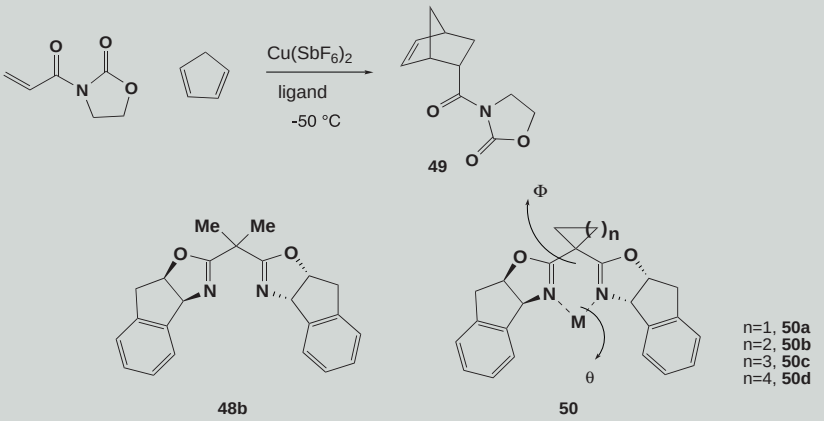
One of the most economical ways of generating single enantiomers is by utilizing asymmetric catalysis. Recently, much emphasis has been placed on the design and development of cost-effective chiral catalysts that display a high degree of reactivity and enantioselectivity.[29] Of the various enantioselective catalytic reactions, the Diels-Alder, aldol, cyclopropanation, reduction and oxidation reactions have generated the most interest and still represent a challenge to academic and industrial chemists alike.[1,30] In particular, many groups have recently indicated that conformationally constrained ligands derived from *cis*-1-amino-2-indanol derivatives play an important role in many asymmetric catalytic processes, such as reduction,[31] Diels-Alder,[32] cyclopropanation[33] and radical conjugate addition reactions.[34]

5.1. Catalytic Asymmetric Diels-Alder Reaction of Constrained Phenylglycinol Surrogates

Recently, Evans and co-workers have documented that the C_2-symmetric *tert*-leucinol-derived bis(oxazoline)Cu(II) complexes **46**-**48** are effective catalysts in the asymmetric Diels-Alder reaction and provide high levels of induction (up to 96% de; 97% ee).[35] Interestingly, the two-point-binding Diels-Alder reactions involving the phenylglycinol-bis(oxazoline)Cu(II) catalyst derived from **47** result in a dramatic decrease in selectivity (30% ee).[32a] Encouraged by the outstanding stereocontrolled outcome in the Diels-Alder reaction of indane-derived chiral auxiliaries, the Merck group and Ghosh independently extended the *constrained phenylglycinol concept* to the indane-bis(oxazoline) family in the catalytic sense.[32] The indane-derived bis(oxazoline) ligands **48**



Scheme 21. The role of the conformation of indanebis(oxazoline)Cu(II) catalysts in the Diels-Alder Reaction.



Ligand	ϕ °	% ee *endo* (*S*)	*endo:exo*
50a, n=1	110.6	96.3	44:1
50b, n=2	108.0	92.0	38:1
50c, n=3	105.8	89.0	37:1
50d, n=4	103.7	83.0	26:1
48b	104.1	82.5	49:1

Scheme 22. The increased enantioselectivity with spirobis(oxazoline)Cu(II) catalysts.

are accessible from a unique Ritter-type process using 1,2-dioxygen derivatives of indane.[36] Alternatively, these constrained ligands are also obtained from the bisimidate condensation of *cis*-1-amino-2-indanol, followed by alkylation of **48a**[12a] with the appropriate alkylating agents (**Scheme 21**).[32b,c]

Several interesting observations were made by the Merck group when they subjected a series of indanebis(oxazoline) derivatives to the Evans copper triflate-catalyzed Diels-Alder conditions. In contrast to phenylglycinol ligand **47**, rigid indane-derived ligand **48b** afforded 92% ee of the endo Diels-Alder product with an endo:exo selectivity of 130:1 at -65 °C.[32a] It is important to note that 1,2-benzo ligand **48e** provided moderate selectivity with a sense of induction opposite to that observed with ligands **46** and **47**. Larger-bite-size ligands displayed a low level of induction (**48c**, **48d**, and **48f**).[32a]

The Merck group has also shown that the bite angle of the six-membered metal-containing ring greatly influences the enantioselectivity of the catalytic Diels-Alder reaction. In their study of spiro ligands **50a-d** they have shown that, by increasing the bite angle of the metal core ($\phi = \theta$), a higher enantioselectivity is observed at -50 °C. The cyclopropyl-derived spiro ligand **50a** displays the highest selectivity (**Scheme 22**).[32c] Recently, Sibi has demonstrated that **50a** is an excellent spiro ligand in enantioselective conjugate radical addition reactions (up to 98% ee).[34]

Ghosh's work was based predominantly on **48a**, which proved to be an effective ligand for metal-mediated catalytic Diels-Alder reactions (excellent endo/exo selectivity and up to 99% ee of endo enantioselectivity).[32b] He also demonstrated that ligand **48a** could be utilized in the synthesis of the C_3-C_{14} segment of laulimalide via a catalytic hetero Diels-Alder reaction (**Scheme 23**).[32d] As shown in **Table 2**, the hetero Diels-Alder reaction involving rigid indane-derived ligands provided higher levels of induction. Surprisingly, Evans' ligand **46** gave poor selectivity and, as expected, phenylglycinol ligand **47** resulted in low induction.[32d]

5.2. Asymmetric Reduction Catalyzed by Oxazaborolidines

Oxazaborolidines are an extremely important class of enantioselective reducing agents which have been utilized in the reduction of several functional groups, such as ketones and imines, to produce high levels of enantiomeric excesses. Since the extraordinary discoveries by Itsuno[37] and Corey,[38] an enormous number of chiral β-amino alcohols have served as backbones

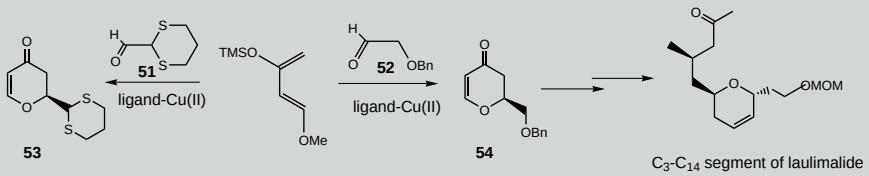
of oxazaborolidines.[39] Most of the enantiopure β-amino alcohols have been synthesized from natural sources (example, amino acids); however, extensive synthetic manipulations were required for the synthesis of unnatural antipodes. Therefore, the development of highly selective oxazaborolidine catalysts from β-amino alcohols (readily accessible from practical technologies such as asymmetric dihydroxylations (AD),[40] asymmetric aminohydroxylations (AA),[41] asymmetric epoxidations (AE),[10a,b] asymmetric ring opening (ARO),[42] and simple Ritter-type chemistry[9a,b,11]) will provide practical catalytic reducing agents for carbonyl groups.

In 1991, Didier and co-workers first observed that stoichiometric amounts of *cis*-1-amino-2-indanol could be used in the borane reduction of acetophenone. However, they also noted that "no systems were found to be efficient with catalytic amounts of ligands".[31a] Recently, the Sepracor group has shown that optically pure *cis*-1-amino-2-indanol is an extremely effective enantioselective catalyst for the borane reduction of several important α-halo ketones.[31b,c,43] In this study, several important observations were made about the borane-reduction with indanyl systems. One such observation was that the B-Me catalyst **55b** was active at a lower temperature and provided a higher induction than the B-H catalyst **55a**. For example, in the enantioselective reduction of α-chloroacetophenone, catalyst **55b** gave 96% ee at -20 °C, while catalyst **55a** resulted in 91.7 % ee at 23 °C (**Scheme 24**).

Currently, the Sepracor group is utilizing the indane catalyst in the synthesis of optically pure formoterol.[7b,44] Formoterol is a fast- and long-acting as well as extremely potent β_2-adrenergic receptor agonist. It is used as a bronchodilator in the therapy of asthma and chronic bronchitis.[45] The (*R,R*) enantiomer of formoterol is 1000 times more potent than the (*S,S*) enantiomer.[46] During the development of an asymmetric synthesis of (*R,R*)-formoterol, there was a need for a reliable and practical reducing agent that could be used in the large-scale preparation of chiral bromohydrin **57** from bromoketone **56** (**Scheme 25**).

In the early attempts to effect the chiral reduction of **56**, 20 mol % of *B*-methyloxazaborolidine **55b** was used as the catalyst and BH_3·THF (0.7 equiv) as the reducing agent.[7b] This particular catalyst had been prepared by reacting (*1R,2S*)-1-amino-2-indanol with trimethylboroxine, followed by azeotropic distillation with toluene. The high cost of these reagents and the additional handling prompted the study of the reduction with in situ-generated B-H oxazaborolidine **55a** as a catalyst. Selected results from this study are summarized in **Table 3**.[47]

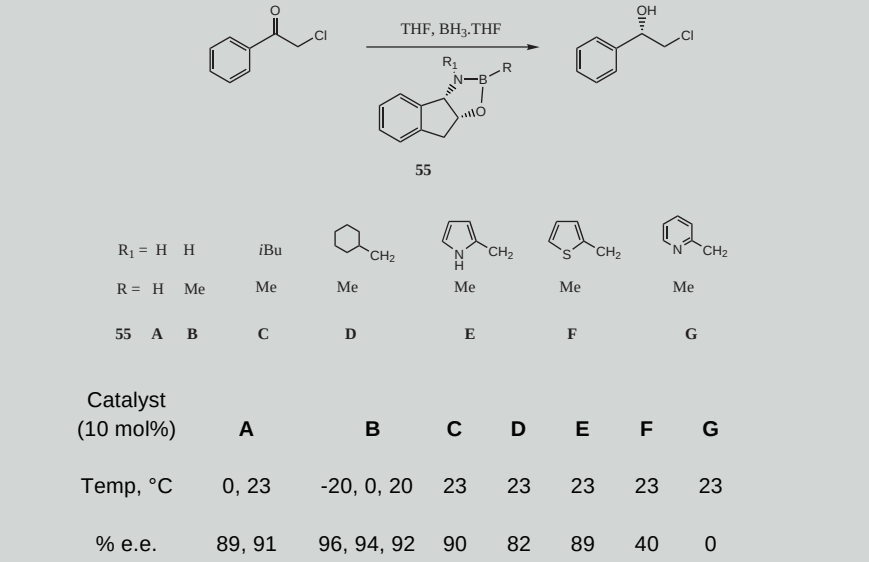
While the highest selectivities were achieved by using catalyst **55a** at -10 °C, the ee's were lower (i.e., 93% vs. 96%) when in situ-prepared **55b** was used (entries 9 and 2). As illustrated in **Table 3**, the boron source did not have a profound effect on the enantioselectivity of catalyst **55a** (entries 1 and 2). On the other hand, the B-Me catalyst **55b** exhibited a higher selectivity with BH_3·THF than with BH_3·Me_2S (entries 9 and



Scheme 23. Indanebis(oxazoline)Cu(II) catalyzed hetero Diels-Alder reaction.

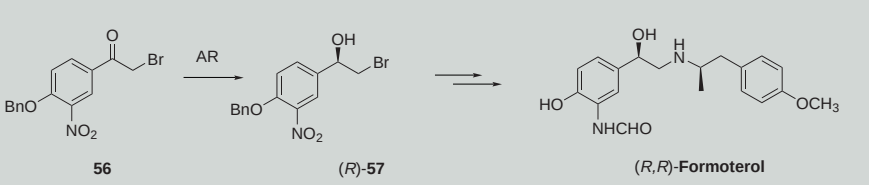
Table 2. Bis(oxazoline)Cu(II) catalyzed hetero Diels-Alder reaction at -78 °C

Entry	Aldehyde	Ligand	Product	% Yield	% ee
1	**51**	**48a**	**53**	46	81
2	**51**	**47**	**53**	20	59
3	**52**	**47**	**54**	76	51
4	**52**	**48a**	**54**	72	85
5	**52**	**46**	**54**	76	38



Catalyst (10 mol%)	A	B	C	D	E	F	G
Temp, °C	0, 23	-20, 0, 20	23	23	23	23	23
% e.e.	89, 91	96, 94, 92	90	82	89	40	0

Scheme 24. Asymmetric reduction of ketones with oxazaborilidine catalysts derived from *cis*-1-amino-2-indanol.



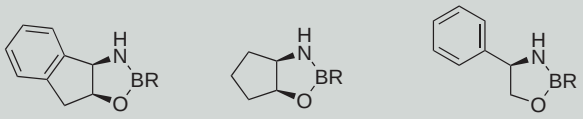
Scheme 25. Approach to the asymmetric synthesis of (*R,R*)-formoterol.

Table 3. Enantioselectivity of the asymmetric reduction of bromoketone **56**.

Entry	Catalyst	Mol	Boron Source	Temperature	ee (*R*)
1	**55a**	10 %	BH_3· THF	-10°C	95 %
2	**55a**	10 %	BMS	-10°C	96 %
3	**55a**	10 %	BMS	0 °C	90 %
4	**55a**	10 %	BMS	25°C	90 %
5	**55b**	10 %	BMS	-10°C	32 %
6	**55b**	10 %	BMS	0 °C	82 %
7	**55b**	10 %	BMS	25°C	90 %
8	**55b**	10 %	BH_3· THF	-10°C	87 %
9	**55b**	10 %	BH_3· THF	0 °C	93 %
10	**55b**	10 %	BH_3· THF	25°C	89 %
11	**55b**	5 %	BH_3· THF	0 °C	93 %
12	**55b**	1 %	BH_3· THF	0 °C	91 %

All reactions were run at a total concentration of 0.3 M in THF. The ketone was added to the mixture of catalyst and borane over a 2-h period. The reaction yields are >98%.

Table 4. Asymmetric borane reduction of **56** using catalysts **55**, **58**, and **59**.[a]



55 **58** **59**

a (R=H)

Catalyst	Product	% ee
55	(*R*)-**57**	93
58	(*R*)-**57**	87
59	(*R*)-**57**	65[b]

b (R=Me)

55	(*R*)-**57**	95
58	(*R*)-**57**	20
59	(*R*)-**57**	75

[a]All reactions were carried out at 0°C using BH_3•THF. [b]Optimal conditions (using catalyst **59a** with BH_3•SMe_2 at 25 °C) gave 91% ee.

6). The optimum temperature for B-H catalyst **55a** was -10 °C in the presence of either boron source. In contrast, the optimal temperature for the B-Me catalyst **55b** was dependent on the boron source: 25 °C in the case of BH_3·Me_2S and 0 °C in the case of BH_3· THF.

In addition, the rate of ketone addition to the catalyst system did not severely affect the enantioselectivity. It became clear that each catalyst had its own optimal conditions with respect to temperature, boron source, and additives.

Recently, Senanayake and co-workers have studied the conformational role of the phenyl moiety and the cyclopentane ring of catalyst **55** in the reduction of ketone **56**.[47] To clarify the conformational issues, catalysts **58** and **59** were also evaluated. As shown in **Table 4**, the results indicate that removal of the fused benzene ring from the aminoindanol platform decreases the enantioselectivity. Detaching the methylene link in the catalyst gives rise to some interesting results: B-H system **59a** results in lower selectivity as compared to catalyst **55**; whereas B-Me system **59b** displays only moderate enantioselectivity. This is in agreement with recent results reported by Wills and co-workers in their asymmetric reduction of ketones utilizing asymmetric transfer hydrogenation reactions.[48] They indicated that (*1R,2S*)-aminoindanol was an excellent chiral ligand for ruthenium-catalyzed transfer hydrogenations (KOH/2-propanol) of ketones (up to 98% ee). On the other hand, phenylglycinol displayed a dramatic decrease in enantioselectivity in the reduction process (23% ee).[48] Direct comparison studies of the effects of catalysts **55**, **58,** and **59** on the enantioselectivity in the reduction of ketone **56** indicated that the constrained indane platform displayed a higher degree of selectivity.

After understanding the critical parameters of catalyst **55**, catalyst **55a** was chosen for the Sepracor process because it was easier to handle, the preparation was less time consuming, and no expensive reagents were involved. More importantly, bromohydrin **57** was isolated by crystallization and thus enriched in its enantiopurity. For the overall process, these conditions presented the most cost-effective and efficient preparation of **57**. This reduction process has been validated on a multikilogram scale whereby bromohydrin **57** is obtained in 85% yield and 99% ee. From a practical point of view, B-H catalyst systems are always much more preferred over the B-alkyl counterparts.

6. *cis*-1-Amino-2-indanol as a Chiral Resolving Agent

During the past few decades, chemists have spent an enormous amount of time on the development of efficient and practical syntheses of chiral α-arylpropanoic acids, which are used as anti-inflammatory medicaments. One of the key approaches to preparing optically pure forms of the isomers of α-arylpropanoic acids is by resolution of a racemate. A number of chiral amines are known for their resolution of chiral acids on a commercial scale. Notable examples include brucine, quinidine, cinchonidine, morphine, ephedrine, and 1-(1-naphthyl)ethylamine. Some of these chiral amines are expensive and are often difficult to recover. For example, ketoprofen has been resolved using (–) cinchonidine; however, this method has several practical limitations.[49]

Recently, the Sepracor group has demonstrated that enantiopure *cis*-1-amino-2-indanol is highly effective in the diastereomeric resolution of racemic ketoprofen.[7c] They discovered that water plays a crucial role in the resolution process and catalytic amounts of water (<3.8 wt%) are required in acetonitrile to obtain high yields of the preferred diastereomer. In addition, they have demonstrated that the unwanted isomer can be recycled, and enantiopure *cis*-1-amino-2-indanol can be easily recovered. The *cis*-1-amino-2-indanol-mediated resolution process is Sepracor's current manufacturing process for either enantiomer of ketoprofen, which is extremely productive and cost-effective.[7c]

7. Conclusion

By examining the examples discussed in this review, it becomes clear that the *cis*-1-amino-2-indanol nucleus has played a powerful role in asymmetric synthesis and the biological manifold.

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About the Author

Dr. Chris H. Senanayake was born in Sri Lanka. He received a B.S. degree (First Class) in Chemistry in 1982 from the University of Sri Jayawardanepura in Sri Lanka. After coming to the United States, he completed his M.S. degree at Bowling Green State University in 1983 with Professor Thomas Kinstle in synthetic chemistry. He obtained his Ph.D. in 1987 under the guidance of Professor James H. Rigby at Wayne State University where he worked on the total synthesis of complex natural products such as ophiobolanes, and completed the first total synthesis of grosshemin in the guaianolide family. He then undertook a postdoctoral fellowship with Professor Carl R. Johnson and worked on the total synthesis of polyol systems such as amphotericin B and compactin analogs, and the synthesis of C-nucleoside precursors. In 1989, he joined Dow Chemical Co. as a Senior Research Chemist in the Department of Process and Development. After a brief stay at Dow Chemical, he joined the Merck Process Research Group in 1990 as a Senior Research Chemist. After a series of accomplishments in synthetic organic chemistry and obtaining a prestigious Merck Management Award in chemistry, he was promoted to Research Fellow in 1993. In 1996, he joined Sepracor, Inc. as Director of Chemical Process Research. He is responsible for the design and development of chemical processes for the commercialization of pharmaceutical drugs.

Dr. Senanayake's current research interests focus on the development of new asymmetric methods for the synthesis of bioactive molecules and heterocycles, and on catalytic, enzymatic, and mechanistic studies. He is the author of approximately 50 papers and patents in several areas of synthetic organic chemistry.

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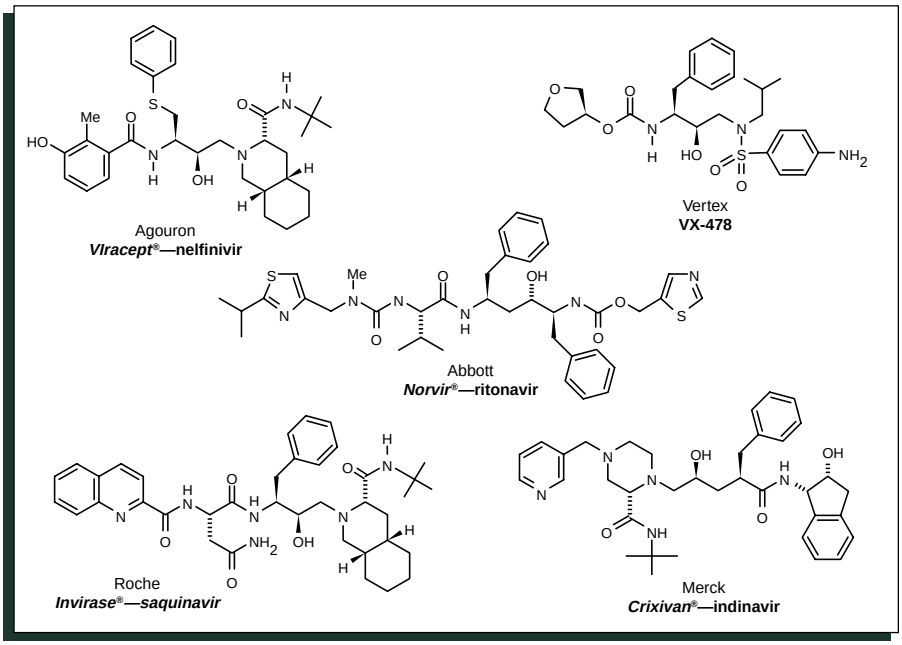
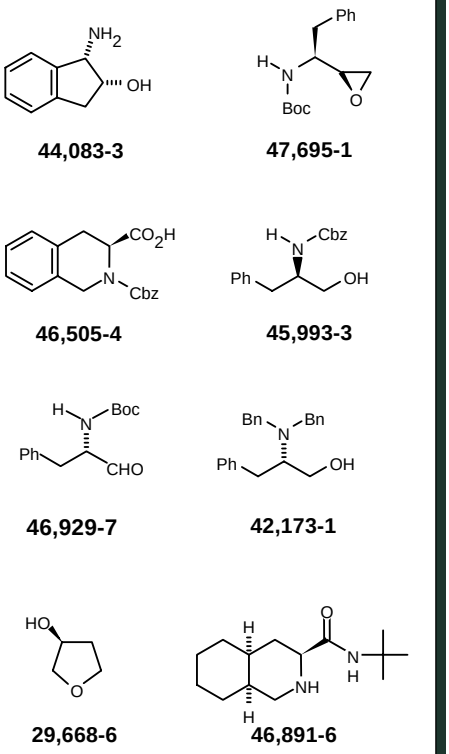
Building Blocks for HIV Protease Inhibitors

Protease inhibitors are an important new class of totally synthetic drugs for the treatment of AIDS. They are "peptoids" or "peptido-mimetics" (similar to peptides) that bind and block the active site of the proteinase enzyme necessary for HIV replication, thus stopping the virus from developing. The complexity of protease inhibitors (see figure) has generated much effort toward the efficient synthesis of intermediates used in their preparation. Several of these key intermediates are listed below. Please inquire about larger quantities of any of these products.





Products

44,083-3	**(1*S*,2*R*)-(–)-*cis*-1-Amino-2-indanol,** 99%
44,084-1	**(1*R*,2*S*)-(+)-*cis*-1-Amino-2-indanol,** 99%
46,505-4 NEW!	**(*S*)-(+)-2-(Benzyloxycarbonyl)-1,2,3,4-tetrahydro-3-isoquinoline-carboxylic acid,** 97%
46,929-7 NEW!	**(*S*)-(–)-2-(*tert*-Butoxycarbonylamino)-3-phenylpropanal,** 97%
46,928-9 NEW!	**(*R*)-(+)-2-(*tert*-Butoxycarbonylamino)-3-phenylpropanal,** 97%
46,891-6 NEW!	**[3*S*(3α,4aβ,8aβ)]-*N*-*tert*-Butyldecahydro-3-isoquinoline-carboxamide,** 98%
47,695-1 NEW!	***tert*-Butyl [*S*-(*R**,*R**)]-(–)-(1-oxiranyl-2-phenylethyl)carbamate,** 99%
45,993-3 NEW!	**(*R*)-(+)-2-(Carbobenzyloxyamino)-3-phenyl-1-propanol,** 97%
42,173-1	**(*S*)-(+)-2-(Dibenzylamino)-3-phenyl-1-propanol,** 99%
29,668-6	**(*S*)-(+)-3-Hydroxytetrahydrofuran,** 99%
30,975-3	**(*R*)-(–)-3-Hydroxytetrahydrofuran,** 98%

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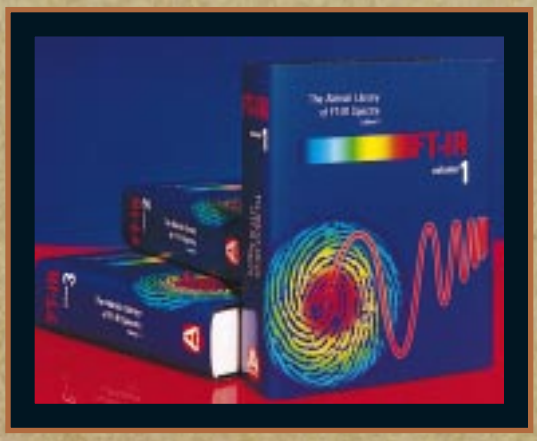
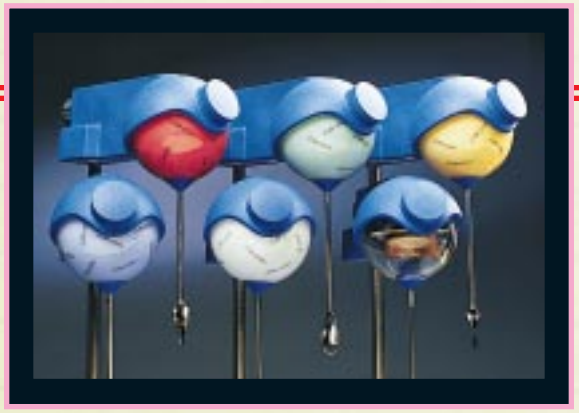


TOOLS FOR RESEARCH

EQUIPMENT ■ SOFTWARE ■ BOOKS

ALDRICH®

IKA



IKA "LAB EGG" STIRRERS

Ideal for stirring small quantities (up to 2L). Borosilicate glass bottom is available in six colors. Supplied with a vane stirrer. 89 H x 86 W x 175mm D. Wt = 0.4kg.

- Speed range: 0 to 2,000rpm
- Viscosity range: 0 to 100mPas
- Universal voltage range: 100 to 240V

To brighten up the Lab

Color	Cat. No.	Each
Transparent	Z40,470-5	
Off white	Z40,471-3	
Apricot	Z40,472-1	
Sea green	Z40,474-8	
Creamy blue	Z40,475-6	
Salmon pink	Z40,476-4	
Lab egg accessories		
Stand	Z40,477-2	
Propeller agitator	Z40,478-0	

IKA DUAL-SPEED MIXERS

Two speed ranges for stirring applications up to 20L (in terms of H_2O) of material. Wt= 2.9 kg. Order stirring shafts separately, below.

- 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.	Each	Cat. No.	Each
115	Z40,395-4		Z40,397-0	
230	Z40,396-2		Z40,398-9	

Propellers	
4-blade, 50mm stirrer diam., 8 diam. x 350mm L shaft	Z40,430-6
4-blade, 100mm stirrer diam., 8 diam. x 350mm L shaft	Z40,394-6
Mixer stand	Z40,391-1
Boss head clamp, fits rods 8 to 17mm diam.	Z40,393-8
Strap clamp, 220 L x 13mm diam.	Z40,362-8

IKA Model A10 ANALYTICAL MILL

Grinds dry, hard, brittle substances to a uniform grain size typically for analytical evaluation. Built-in safety switch prevents mill from being operated without cap. Motor stops in case of overload and high temperatures. Complete unit includes mill, grinding chamber reducer, SS cutter, and lid.

- 304 stainless steel, double-walled grinding chamber and cutter
- Sample volume: 50mL
- 5 minute timer
- Optional cooling connection

Volts	Cat. No.	Each
115	Z40,463-2	
230	Z40,464-0	

IKA Mill Accessories	
Hard metal cutter, tungsten carbide	Z40,465-9
Star-shaped cutter, 304 SS	Z40,467-5

(Not for use with coffee beans)

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

IKAMAG Model RCT basic stirring hot plate

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.

- 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.	Each
115	Z40,351-2	
230	Z40,352-0	

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.

- Digital display
- Measuring range: -10 to 400°C with adjustable safety circuit between 100 and 400°C
- Control precision: ± 0.2°C **Z40,353-9**

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**

Holding rod, SS **Z40,359-8**

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

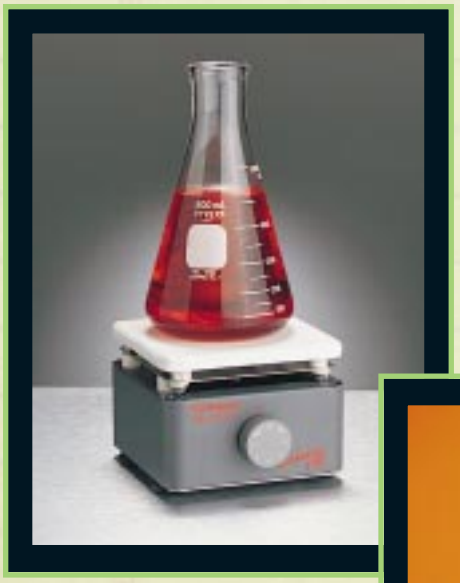
IKA heating baths

Cylindrical design with two transport handles for secure carrying. May be used as oil or water baths. Digital models display the "target", "set", and selected "safety" temperatures. 230V models are supplied with a Schuko plug.

Specifications (all models):
Effective volume: 4L
Heating power: 1,000W
Inside diam.: 200mm
Dim.: 340 diam. x 250mm H

Model	Temp. Range (°C)	Wt (kg)	*115V* Cat. No.	*230V* Cat. No.	Each
HB 4 basic bath	RT to 225	3.9	Z40,486-1	Z40,488-8	
HB 4 digital bath	RT to 200	3.9	Z40,489-6	Z40,491-8	
HBR 4 digital bath, w/magnetic stirring	RT to 200	4.4	Z40,492-6	Z40,493-4	

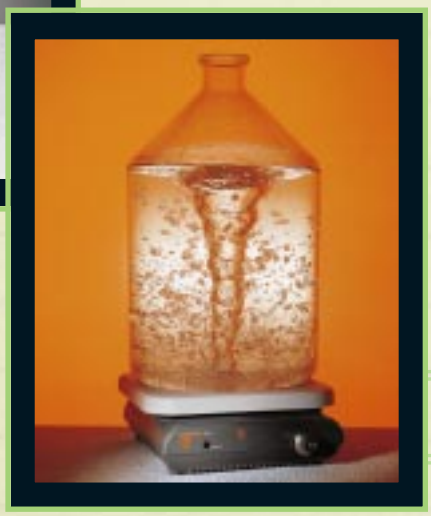
CORNING



Corning Scholar 170 hot plate

Economical hot plate has a white enameled steel top plate that provides adjustable heat up to 400°C. Dual heat shields dissipate heat and keep the case cool. Compact 5 x 5in. size. UL/CUL approved. 120V.

Z40,234-6



Corning model 611 high volume stirrer

Newly designed to stir high volumes of liquid (up to 5 gallons) with ease.

- One year warranty
- 120 volt; 100 to 1,100rpm stir range
- Rugged ABS top, 11 x 11in.
- Weight: 11lb (5kg); dimensions: 4.8 H x 12.0 W x 14.4in. D

To really stir things up

Z40,721-6

2-in-1

Corning Model 443i bench ISFET/pH meter kits

- Uses ISFET or pH probes
- Automatic Temperature Compensation (ATC)
- Auto-end point, three point calibration
- RS232 output, data logging
- GLP functions
- Two year meter warranty; one year sensor warranty
- UL/CSA/CE approved

The Corning bench top model 443i meter was designed to offer greater measurement flexibility. Kit includes pH electrode, buffer sachets, electrode arm, and electrode storage bottle. Order ISFET probe separately (see Z40,724-0 below)

Feature	Range	Resolution	Accuracy
pH	-1.99 to 16.00	0.01	0.01
mV	-1999 to 1999	1	1
Temp. °C	-5.0 to 105.0	0.1	0.5 or 1%
ISFET	-0.0 to 60.0		

120V	**Z40,722-4**
220V	**Z40,723-2**

ISFET probe for use with Corning model 443i meter
Z40,724-0

Corning Scholar 425 pH Meter

Economical meter that provides pH and temperature on a large display. Includes 3-in-1 electrode and buffers for initial calibration of unit. AC/DC adapter or 9V battery.

- Easy to use, only three buttons, one button "cal"
- Automatic Temperature Compensation (ATC)
- Auto read feature and % slope readout

Specifications:	pH	Temperature
Range	0.00 to 14.00pH	0 to 100°C
Resolution	.01 pH	1°C
Accuracy	±.01 pH	±1°C

Volts	Cat. No.	Each
120V	Z40,727-5	
220V	Z40,728-3	

Corning pH/ISE/mV/T meters

- LCD display, % slope readout
- Automatic Temperature Compensation (ATC)
- Auto-Buffer recognition and automatic calibration
- Two year warranty
- CE mark of conformity

Offers microcomputer technology for automatic operation and user friendly calibration. New design offers splash resistant housing with improved software capabilities. Includes meter, electrode arm, electrode, ATC probe, and starter kit. BNC connector.

Model	430 *Student*	440 *Easy-to-use*	445 *General*	450 *Research*	455 *ISE*
Functions	pH/mV/T	pH/mV/T	pH/mV/T	ISE/pH/mV/T	ISE/pH/mV/T
pH resolution	0.01	Select to 0.01	Select to 0.01	Select to 0.001	Select to 0.001
accuracy	±0.01	±0.01	±0.01	±0.001	±0.001
mV range	±1999*	±1999	±1999.9	±1999.9	±1999.9
Res./accuracy	1/±1	1/±1	0.1/±0.2	0.1/±0.2	0.1/±0.2
ISE conc.	–	–	–	$10^{\pm 4}$	$10^{\pm 9}$
Res./accuracy	–	–	–	1 ISD/±0.5%	1 ISD/±0.5%
T range (°C)	0-100	-5-105	-5-105	-30-130	-30-130
Res./accuracy	1/±1	0.1/±0.5	0.1/±0.5	0.1/±0.5	0.1/±0.5
Electrode input	Single BNC	Single BNC	Single BNC	Dual BNC	Dual BNC
Electrode	3 in 1	3 in 1	3 in 1	high performance	high performance
ATC	in triode	in triode	in triode	temp. probe	temp. probe
RS232C	–	yes	yes	yes	yes
120V Cat. No.	Z28,302-9	Z28,304-5	Z28,306-1	Z28,309-6	Z28,312-6
Each					
230V Cat. No.	Z28,303-7	Z28,305-3	Z28,308-8	Z28,311-8	Z28,313-4
Each					

**The student model has only absolute mV, all other models have both absolute and relative mV functions.*

BÜCHI SafetyVAP Rotary Evaporators

*Büchi SafetyVAP rotary evaporators have unique safety and performance features that make them ideal for use in chemical, pharmaceutical, and R&D laboratories. Available with either **analog controls** for economy, or **digital controls** for reproducibility and methods validation.*

SafetyVAP Model R-114 with analog controls

- Ideal for routine laboratory distillations
- Analog control of bath temperature and rotation speed

SafetyVAP Model R-124 with digital controls

- Ideal for application reproducibility and methods validation
- Digital control of bath temperature and rotation speed
- Sealed control panel with bright LED display
- Optional vapor-temperature sensor

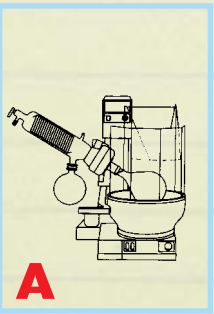
Brand new brand

Features for all models:

- Process sample volumes of 1 to 3L
- PLASTIC+GLAS plastic-coated glassware
- Sparkless, brushless drive motor, speed range: 5 to 240rpm
- Water bath temp. range: ambient to 100°C; control accuracy: ±2°C
- Combi-Clip secures evaporator flask during operation
- Servo-Jack raises and lowers evaporator safely
- Over-temperature safety shutoff if bath liquid level falls too low
- Safety shield option that surrounds the hot bath
- Rugged Teflon-coated stationary vacuum seal

Select from three condenser assembly configurations to suit the application

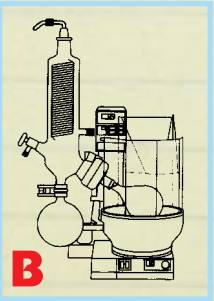
All Büchi SafetyVAP models are supplied with a ₮24/40 joint on the evaporator flask and a BJ 35/20 joint on the receiving flask. Glass component parts can be interchanged from one condenser assembly to another using the same evaporator.



A Diagonal condenser assembly

For simple distillation of solvents and general use. Tap-water-cooled. Inlet feed tube for continuous feed of volumes exceeding flask capacity. Optional vapor-temperature sensor (for Model R-124A only).

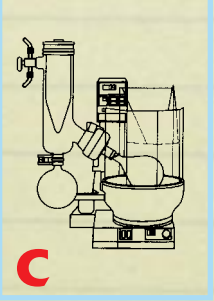
Display/Model	115V Cat. No.	Each	230V Cat. No.	Each
Analog/R-114A	Z40,260-5		Z40,264-8	
Digital/R-124A	Z40,267-2		Z40,270-2	
Vapor-temperature sensor for Digital Model R-124A			Z40,273-7	



B Vertical condenser assembly

For distilling high boiling solvents (>100°C). Tap-water-cooled. Continuous feed can be used simultaneously with optional vapor-temperature sensor (for Model R-124V only).

Display/Model	115V Cat. No.	Each	230V Cat. No.	Each
Analog/R-114V	Z40,261-3		Z40,265-6	
Digital/R-124V	Z40,268-0		Z40,271-0	
Vapor-temperature sensor for Digital Model R-124V			Z40,273-7	



C Cold-trap condenser assembly

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

Display/Model	115V Cat. No.	Each	230V Cat. No.	Each
Analog/R-114C	Z40,262-1		Z40,266-4	
Digital/R-124C	Z40,269-9		Z40,272-9	

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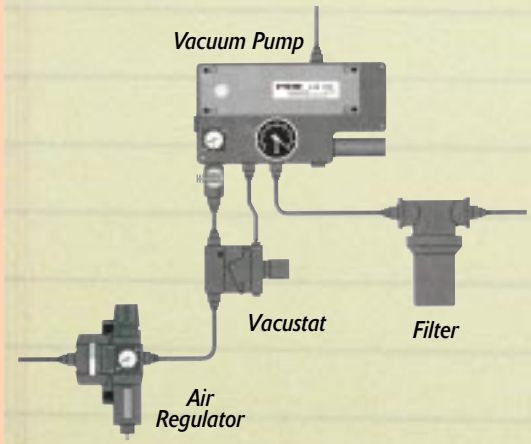
Complete system with pump w/EPDM gaskets and flap valves
Z40,543-4

Complete system with pump w/Viton gaskets and flap valves
Z40,544-2



LAB VAC Vacuum Pump System

PUMP SPECIFICATIONS:

Pumping speed: 170Lpm
Max. vacuum: 11mm Hg (abs)
Optimal air pressure: 78psi, 87psi max.
Temp. range: -20 to 80°C
Dim.: 4.92 H x 9.06 W x 2.52in. D
Wt: 2.98lb (1.35kg)

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COMPATIBILITY TABLE

The pump's gaskets and flap valves are vital for proper operation. Select EPDM or Viton pump components based on the compatibility data in the table below. Avoid drawing particulates, vapors, or liquids into the pump by installing a vacuum filter and/or trap.

E = Excellent, insignificant effect, recommended
G = Good, minor chemical attack
P = Poor, moderate chemical attack, limited service
U = Unsuitable, severe attack, not recommended

Material	Recommended gasket material	
	EPDM	*Viton*
Acetic acid	E	G
Acetone	E	U
Ammonia	E	U
Amyl alcohol	E	G
Benzene	U	E
Butanol	G	E
Carbon tetrachloride	U	E
Chlorobenzene	U	E
Chloroform	U	E
Cyclohexane	U	E
Dioxane	G	-
Ethanol	E	E
Ethyl acetate	G	E
Ethyl ether	P	U
Hexane	U	E
Hydrochloric acid	E	E
Methanol	E	E
Methylene chloride	G	E
Methyl ethyl ketone	E	U
Nitric acid	G	E
Petrol	U	E
Propanol	E	E
Sodium hydroxide	E	G
Sulfuric acid	G	E
Tetrachloroethylene	U	E
Tetrahydrofuran	G	U
Trichloroethane	U	E
Toluene	U	E
Xylene	U	E

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The Pro Version is an enhanced NMR reference and search program. It allows sub-structure and sub-spectra search and the ability to search imported experimental spectra and compare them on-screen. The program also permits advanced data field searching, including physical properties such as boiling point, melting point, density, and refractive index. Multi-level searching capability allows hit lists to be further refined and saved. Spectral report editor allows customization of printouts or exports with user data.

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Z40,704-6

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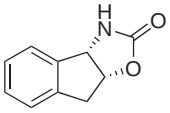


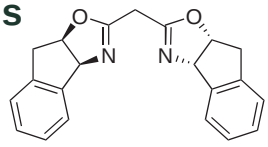
• Chiral auxiliaries for highly diastereoselective Diels-Alder reactions[1] and highly enantioselective aldol reactions.[2]

(1) Davies, I.W. et al. *Tetrahedron Lett.* **1995**, *36*, 7619. (2) Ghosh, A.K. et al. *J. Chem. Soc., Chem. Commun.* **1992**, 1673.

46,396-5 **(3a*R*-*cis*)-(+)-3,3a,8,8a-Tetrahydro-2*H*-indeno-[1,2-*d*]oxazol-2-one,** 98%

46,397-3 **(3a*S*-*cis*)-(–)-3,3a,8,8a-Tetrahydro-2*H*-indeno-[1,2-*d*]oxazol-2-one,** 98%

Bis(oxazoline) Ligands



• C_2 symmetric ligands for enantioselective catalysis.

• Easily form bidentate coordination complexes due to the strong affinity of the oxazoline nitrogen for various metals.

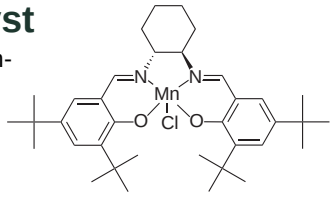
• High enantioselectivities are obtained in various reactions.

Reviews: Gant, T.G.; Meyers, A.I. *Tetrahedron* **1994**, *50*, 2297. Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339.

46,415-5 **[3a*R*-[2-(3'a*R**,8'a*S**),3'aβ,8'aβ]]-(+)-2,2'-Methylenebis(3a,8a-dihydro-8*H*-indeno[1,2-*d*]oxazole),** 98%

46,707-3 **[3a*S*-[2-(3'a*R**,8'a*S**),3'aα,8'aα]]-(–)-2,2'-Methylenebis(3a,8a-dihydro-8*H*-indeno[1,2-*d*]oxazole),** 98%

Jacobsen's Catalyst



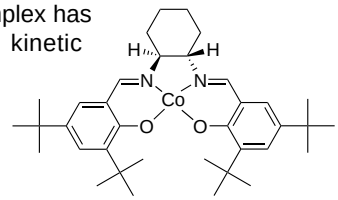
• Chiral catalyst for the asymmetric epoxidation of unfunctionalized olefins.

• High enantioselectivities and yields are obtained for a variety of substrates.

Zhang, W. et al. *J. Am. Chem. Soc.* **1990**, *112*, 2801. Zhang, W.; Jacobsen, E.N. *J. Org. Chem.* **1991**, *56*, 2296. Jacobsen, E.N. et al. *J. Am. Chem. Soc.* **1991**, *113*, 7063. Lee, N.H.; Jacobsen, E.N. *Tetrahedron Lett.* **1991**, *32*, 6533. Deng, L.; Jacobsen, E.N. *J.Org.Chem.* **1992**, *57*, 4320. Palucki, M. et al. *Tetrahedron Lett.* **1995**, *36*, 5457.

40,445-4 **(*S*,*S*)-(+)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride**

40,444-6 **(*R*,*R*)-(–)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride,** 98%



This chiral Co(II) salen complex has been used for the hydrolytic kinetic resolution (HKR) of terminal epoxides[1] and for the enantioselective catalytic ring opening of meso epoxides.[2]

(1) Tokunaga, M. et al. *Science* **1997**, *277*, 936. (2) Jacobsen, E.N. et al. *Tetrahedron Lett.* **1997**, *38*, 773.

(*S*,*S*)

47,460-6 **(*S*,*S*)-(+)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II)**

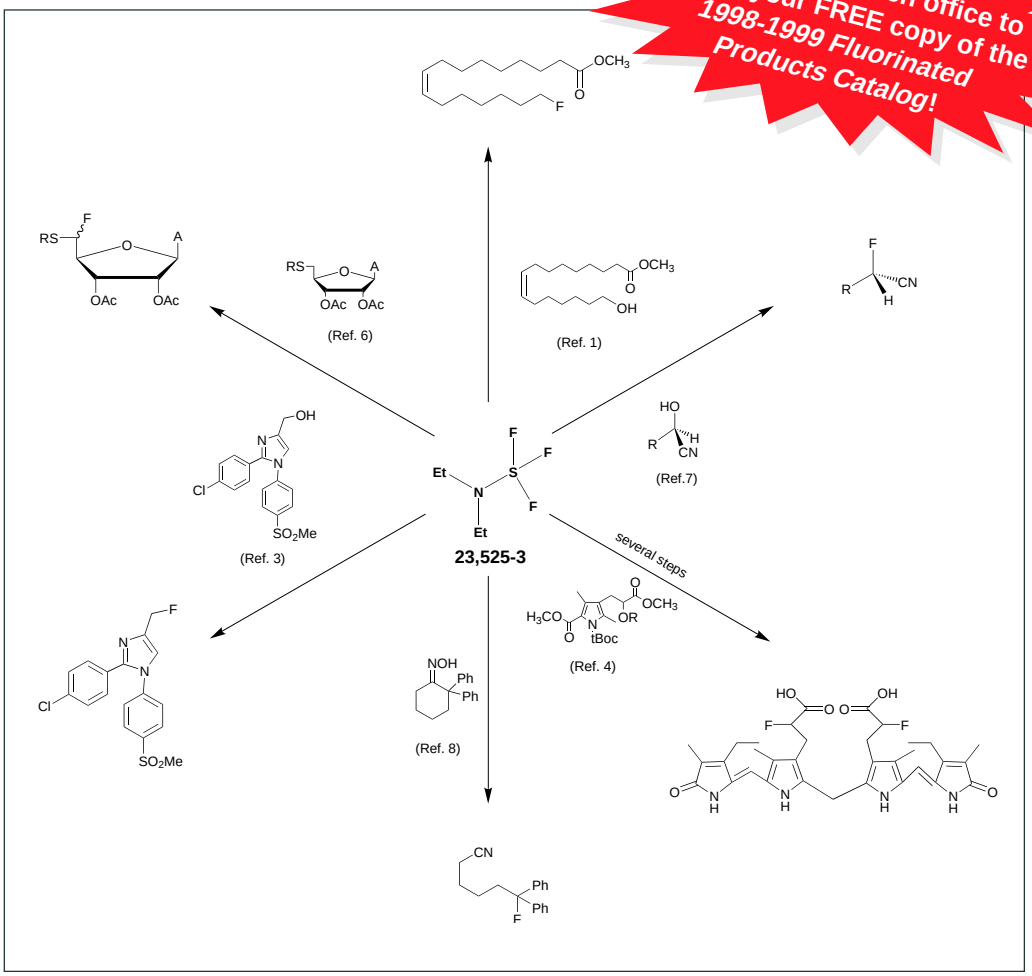
47,459-2 **(*R*,*R*)-(–)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II)**

Fluorinating Agents

Dialkylaminosulfur Trifluorides

Selective introduction of fluorine into organic molecules is of increasing importance, especially for the preparation of potential new drugs.

Key to this development is the commercial availability of suitable fluorinating agents. One class of such compounds, the dialkylaminotrifluorosulfuranes, are useful and versatile fluorinating agents. **Carbolabs**, a recent addition to the **Sigma-Aldrich** family, has over 15 years of experience in the manufacture of this class of fluorinating agents.



The three most important dialkylaminotrifluorosulfuranes are (diethylamino)sulfur trifluoride (DAST), (dimethylamino)-sulfur trifluoride (Methyl-DAST), and morpholinosulfur trifluoride (Morph-DAST). They mimic sulfur tetrafluoride—a highly toxic and difficult-to-handle gas—in reactions with alcohols and carbonyl groups. Recent applications of DAST include the preparation of fluorinated fatty acids,[1] carboxylic acid fluoride polymers,[2] novel, potentially orally active anti-inflammatory agents,[3] and the first fluorinated Bilirubin.[4] Illustrative examples of DAST chemistry are shown in the scheme. For a more extensive introduction, see reference 5.

23,525-3 (Diethylamino)sulfur trifluoride

24,821-5 (Dimethylamino)sulfur trifluoride

33,891-5 Morpholinosulfur trifluoride

References: (1) Buist, P.H. et al. *J. Chem. Soc., Perkin Trans. 1* **1997,** 2617. (2) Hagaman, E.W. et al. *Anal. Chem.* **1997,** *69,* 3950. (3) Khanna, I.K. et al. *J. Med. Chem.* **1997,** *40,* 1634. (4) Boiadjiev, S.E.; Lightner, D.A. *J. Org. Chem.* **1997,** *62,* 339. (5) Dmowski, W. In *Chemistry of Organic Fluorine Compounds: A Critical Review;* Hudlicky, M; Pavlath, A.E., Eds.; ACS Monograph 187; American Chemical Society: Washington, DC, **1995**; pp199-262. (Aldrich Cat No. **Z25,649-8**). (6) Robins, M.J.; Wnuk, S.F. *J. Org. Chem.* **1993,** *58,* 3800. (7) Stelzer, U.; Effenberger, F. *Tetrahedron: Asymmetry* **1993,** *4,* 161. (8) Kirihara, M. et al. *J. Chem. Soc., Chem. Commun.* **1997,** 599.

Synthetic Applications of Zinc Borohydride

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Outline

1. Introduction

Although numerous literature references are available on the synthetic applications of various metal borohydrides,[1] only sodium borohydride has gained commercial status, in spite of its poor solubility in organic solvents and lesser reactivity. Moreover, the reagent is inevitably used in excess quantities. To overcome these drawbacks, soluble metal borohydrides such as lithium borohydride,[2] calcium borohydride,[2] and zinc borohydride have been developed. Among these reagents zinc borohydride is unique because: (i) Zn^{2+} is a soft Lewis acid as compared to Ca^{2+}, Li^+, and Na^+ which are hard acids, and (ii) Zn^{2+} has a better coordinating ability and is thus expected to impart selectivity in hydride transfer reactions. Indeed, literature reports on $Zn(BH_4)_2$ indicate that the chemoselective reduction of β-keto esters to the corresponding β-hydroxy esters can be easily achieved with better isomeric control because of the better coordinating ability of zinc with the carbonyl group of the ester.[3] This reaction has been utilized in the synthesis of certain natural products and in prostaglandin synthesis. Ranu[4] has reported $Zn(BH_4)_2$ to be a mild reducing agent capable of reducing aldehydes in the presence of ketones,[5] and ketones in the presence of enones.[6] Under these conditions, $Zn(BH_4)_2$ does not reduce carboxylic acids or esters. However, in the presence of trifluoroacetic anhydride, $Zn(BH_4)_2$ reduces carboxylic acids but not esters.[7] The reduction of esters by $Zn(BH_4)_2$ requires longer reaction times (24 h) and the influence of ultrasonic irradiation. Understandably, aromatic esters and benzyl esters are not at all reduced under these conditions thus allowing selectivity in the reduction of esters.[8] Furthermore, $Zn(BH_4)_2$–silica reduces enones to the corresponding allylic alcohols[9] and epoxides to alcohols.[10]

It would appear from the preceding reports that $Zn(BH_4)_2$ is a mild reagent with only a limited scope. However, the unique properties of $Zn(BH_4)_2$ come to light when subjected to tandem reduction-hydroboration, discovered by Brown and Narasimhan.[11,12] In this reaction, when an unsaturated ester is treated with a metal borohydride, the ester group is reduced much faster than that of a saturated ester, and the double bond also gets hydroborated. However, this depends on the extent of polarization of the borohydride ion by the counter ion. The feasibility of the tandem reduction-hydroboration reaction can be inferred from the reaction of the borohydride reagent with methyl 10-undecenoate which would be rapidly converted to 1,11-undecanediol. Exploring this reaction with $Zn(BH_4)_2$ has enhanced the potential of this reagent in synthetic applications.

2. Preparation of $Zn(BH_4)_2$[13,14]

In a typical procedure, a 500-mL round-bottom flask, equipped with a magnetic pellet and fitted with a reflux condenser carrying a take-off adapter, is flame-dried while a stream of nitrogen is passed through the system. The assembly is allowed to cool to room temperature while the flow of nitrogen is maintained. Freshly fused $ZnCl_2$ (18g;125mmol) is added followed by $NaBH_4$ (11g ; 291mmol). 250 mL of dry THF is then added through a double-ended needle and the contents are stirred at room temperature for

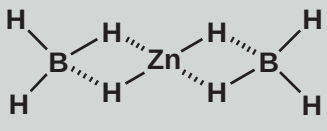


Chart 1

72 hours. The clear supernatant layer is used as such for reactions after estimating its hydride strength (4.4 M in H^-). The absence of chloride is confirmed as reported earlier.[15] Atomic absorption measurements indicate the presence of Na^+, in addition to zinc and boron, and confirm the analogous results reported in the literature.[15] $Zn(BH_4)_2$ can be thought of as a complex having the structure shown in **Chart 1**.

Interestingly, the ^{11}B NMR spectrum shows a quintet at $\delta = -45$ corresponding to the BH_4^- ion when $BF_3 \cdot Et_2O$ is used as the external standard. The reagent is stable over a period of 6 months when stored under nitrogen at room temperature.

3. Synthetic Applications

3.1. Tandem Reduction–Hydroboration of Esters

Earlier reports have indicated that the reduction of aliphatic esters by $Zn(BH_4)_2$ in DME is very slow. However, under vigorous conditions, it is possible to reduce aliphatic esters in the presence of aromatic esters. In addition, $Zn(BH_4)_2$ in THF reduces esters in the following order: unsaturated ester >> aliphatic ester >> aromatic ester (**Table 1**).[16] These rate differences have been exploited in the facile reduction of a number of aliphatic esters in the presence of aromatic esters under simple reaction conditions and without employing ultrasonic irradiation (**Table 2**). The intermediate borate esters can also be oxidized to the corresponding aldehydes (entries 8 and 9).[17]

Interestingly, the rapid reduction of the unsaturated ester methyl 10-undecenoate indicated autocatalysis; this meant that the addition of olefin might catalyze the reduction of esters. When this idea was applied to the reduction of methyl benzoate, a remarkable rate enhancement was observed (**Table 3**).[18] The ^{11}B NMR spectrum of the reaction mixture indicated that hydroboration of the olefin occurred prior to reduction of the ester; i.e., the propensity of $Zn(BH_4)_2$ to hydroborate the alkene was greater than its propensity to reduce the ester. The peak at $\delta = 56$ indicated that the hydroboration of cyclohexene led to a dialkylboron species which could catalyze the reduction of the ester as depicted in **Scheme 1**.

Consequently, several aromatic esters were reduced in good yields and the reduction was tolerant of other reducible groups such as chloro, bromo, nitro, etc. (**Table 4**).[16] The organoboron intermediates can also be oxidized with dichromate solution to the corresponding aldehydes providing a one-pot conversion of esters to aldehydes. This

Table 1. Reduction of esters by $Zn(BH_4)_2$ in THF.

		% reaction[a]					
Entry	Methyl Ester	0.25 h	0.5 h	1 h	2 h	4 h	5 h
1	Myristate	1.5	4.5	15	61	94	98
2	Benzoate	-	-	-	4	9	
3	Pivalate	4	8	27	46	71	93[b]
4	10-Undecenoate	-	gel	98			

[a]Percent reaction is the number of mmoles of ester that were reduced divided by the number of mmoles of ester used. It was determined by analysis of residual hydride in the reaction mixture and by assuming an uptake of two hydrides per ester reduced. [b]after 8 h.

Table 2. Facile reduction of aliphatic esters by $Zn(BH_4)_2$.

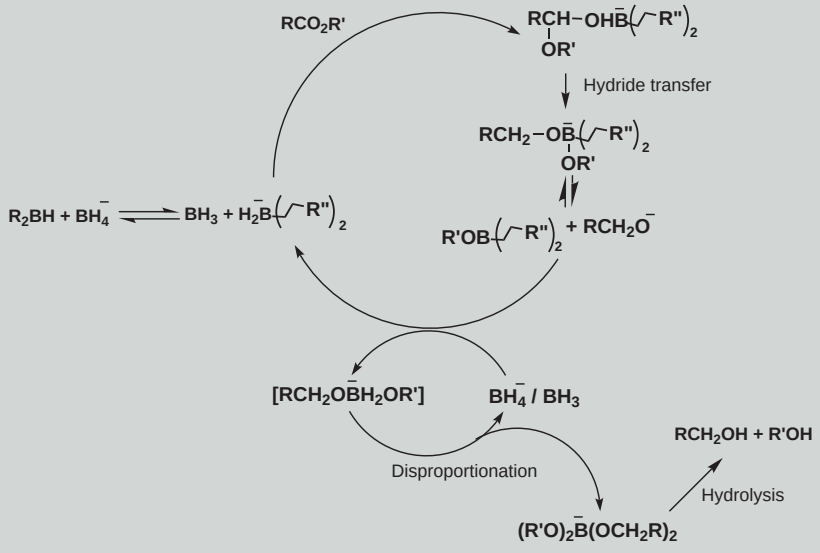
Entry	Ester[a]	Time, h	Product	% Yield
1	Methyl 10-undecenoate	1	1,11-Undecanediol	90
2	Dimethyl brassylate[b]	6	1,13-Tridecanediol	74
3	Methyl nonanoate	5	1-Nonanol	75
4	Methyl myristate	5	1-Tetradecanol	85
5	Methyl pivalate	6	2,2-Dimethyl-1-propanol	75
6	Methyl 3-bromopropionate	2	3-Bromo-1-propanol	79
7	Methyl phenylacetate	5	Phenethyl alcohol	75
8	Methyl myristate	6	1-Tetradecanal	80
9	Methyl phenylacetate	6	Phenylacetaldehyde	76

[a][ester]:[H^-]=1:2. [b][ester]:[H^-]=1:4

Table 3. Alkene-catalyzed reduction of esters with $Zn(BH_4)_2$.

			% reaction[a]					
Entry	Ester	Alkene[b]	0.25 h	0.5 h	1 h	2 h	4 h	5 h
1	Methyl myristate	-	1.5	4.5	15	61	94	98
2	Methyl myristate	Cyclohexene	36	64	84	104[c]		
3	Methyl benzoate	-				4	9	
4	Methyl benzoate	Cyclohexene	9	16	34	60	87	101[c]
5	Methyl 2-chlorobenzoate	-			16	23	38	46
6	Methyl 2-chlorobenzoate	Cyclohexene			34	46	71	82
7	Methyl 2-chlorobenzoate	1-Decene			38	47	77	89
8	Methyl 2-chlorobenzoate	1,5-Cyclooctadiene			36	44	73	87

[a]Percent reaction is defined as in Table 1. [b]10 mol%. [c]These results include the hydride consumption for cyclohexene.



Scheme 1. Mechanism of alkene-catalyzed reduction of esters.

Table 4. Reduction of methyl esters, RCO_2Me, by $Zn(BH_4)_2$ in refluxing THF catalyzed by cyclohexene.

Entry	R	Time, h	Product, R	% Yield
1	C_6H_5	5	C_6H_5	72
2	2-ClC_6H_4	4	2-ClC_6H_4	83
3	3-$NO_2C_6H_4$	3	3-$NO_2C_6H_4$	80
4	4-$NO_2C_6H_4$	3	4-$NO_2C_6H_4$	75
5	4-HOC_6H_4	4	4-HOC_6H_4	72
6	2-HO-C_6H_4	4	2-HO-C_6H_4	70
7	4-$MeO_2CC_6H_4$	2	4-$HOCH_2C_6H_4$	70
8	$C_6H_5CH_2$	2	$C_6H_5CH_2$	75
9	$CH_3(CH_2)_{12}$	2	$CH_3(CH_2)_{12}$	76
10	$MeO_2C(CH_2)_{11}$	4	$HOCH_2(CH_2)_{11}$	76
11	CH_2=$CH(CH_2)_8$[a]	2	$HO(CH_2)_{10}$	80

[a] Cyclohexene was not used; [ester]:[H^-]=1:2

Table 5. Reactivity of $Zn(BH_4)_2$ towards various functional groups.

		% reaction					
Entry	Substrate	0.25 h	0.5 h	1 h	2 h	4 h	5 h
1	Methyl myristate	1.5	4.5	15	61	94	98
2	Methyl benzoate				4	9	
3	Palmitic acid	35	65	74	84	92	94
4	Benzoic acid	46	51	56	61	85	92
5	1-Dodecene		72	80	96	98	99

Table 6. Competitive studies of the reduction of various substrates with zinc borohydride.

Entry	Substrate Pair	k_1/k_2[a]
1	Methyl myristate/Methyl benzoate	100
2	Methyl myristate/Methyl benzoate[b]	12
3	Palmitic acid/Benzoic acid	13
4	Palmitic acid/Methyl myristate	100
5	1-Dodecene/Methyl myristate	2.7
6	1-Dodecene/Palmitic acid	1.7

[a] k_1 and k_2 are calculated using the Ingold-Shaw equation. [b] The reduction was carried out in the presence of 10 mol % of cyclohexene as catalyst.

Table 7. Relative reactivity of functional groups towards $Zn(BH_4)_2$.

Entry	Functional Group	Relative Reactivity
1	Methyl benzoate	1
2	Methyl myristate	12
3	Benzoic acid	96
4	Palmitic acid	1200
5	1-Dodecene	2040

tendency of $Zn(BH_4)_2$ to hydroborate unsaturated systems in preference to reduction of carbonyl groups is in contrast to the behavior of other metal borohydrides. Indeed a study of the relative reactivity of $Zn(BH_4)_2$ towards various functional groups represented by methyl myristate, methyl benzoate, palmitic acid, benzoic acid and 1-dodecene indicated that hydroboration of the olefin is much faster than reduction (**Table 5**).[19]

To elucidate the spectrum of reactivity of $Zn(BH_4)_2$, competitive experiments were performed. In a typical procedure, to an equimolar mixture of methyl myristate and methyl benzoate was added just enough hydride to react with only one of the substrates. The products were analyzed by GLC and the relative reactivity obtained by using the Ingold-Shaw equation (**Table 6**).[20] The results indicated that the aliphatic ester was reduced much faster than the aromatic ester. Similarly, the aliphatic acid, palmitic acid, was reduced more rapidly than benzoic acid. This allowed us to determine the order of reactivity of the other substrates relative to that of methyl benzoate (**Table 7**): olefin > aliphatic CO_2H > aromatic CO_2H > aliphatic ester > aromatic ester. This spectrum of reactivity of $Zn(BH_4)_2$ indicates that it prefers to attack a nucleophilic carbon rather than an electrophilic one. This is contrary to the reactivity pattern of other metal borohydrides, which are nucleophilic species and prefer to attack an electrophilic carbon and seldom hydroborate olefins. This boranelike characteristic of $Zn(BH_4)_2$ offers an alternative to borane–methyl sulfide (BMS) in organic synthesis.

3.2. Reductions

3.2.1. Reduction of Carboxylic Acids

A number of carboxylic acids were reduced to the corresponding alcohols in good yields and using only stoichiometric quantities of zinc borohydride (**Table 8**).[21] These facile reductions are thought to take place as shown in **Scheme 2**.

3.2.2. Reduction Of Amino Acids

Chiral amino alcohols are useful in, among others, asymmetric synthesis,[22] peptide and pharmaceutical chemistry,[23] and the synthesis of insecticidal compounds.[24] Earlier preparative methods used reduction of esters of amino acids by sodium in ethanol.[25] Subsequently, $LiAlH_4$[26] and $NaBH_4$[27] were used for the reduction of esters. Moreover, reduction of amino acids directly to the amino alcohols was accomplished using $LiAlH_4$[28] or BMS in the presence of $BF_3 \cdot Et_2O$.[29] Metal borohydrides do not reduce amino acids; however, $LiBH_4$ with Me_3SiCl reduces amino acids to the corresponding alcohols.[30,31] Similarly, $NaBH_4$ in the presence of $BF_3 \cdot Et_2O$ also reduces amino acids.[32] The reduction in these cases is by borane which is generated in situ. Recently, $NaBH_4$–H_2SO_4 and $NaBH_4$–I_2 were used for the reduction of amino acids and derivatives.[33,34] Reductions of 1kg-scale quantities are effected with either BMS or $LiAlH_4$. However, the methods suffer from high cost, inflammability of the reagents used, and laborious isolation procedures. In the case of amino acids, it is necessary to use an excess of 1 molar equivalent of borane to compensate for complexation of the reducing agent with the amino group (**eq 1**).

Since $Zn(BH_4)_2$ had been shown to reduce carboxylic acids to the corresponding alcohols in excellent yields,[21] and in view of its basic nature, it was reasoned that such amine-borane complexation was not likely to occur and hence excess reagent might not be required. Thus, the reduction of amino acids to amino alcohols utilizing only stoichiometric quantities of zinc borohydride proceeded to completion (**Table 9**).[35] With excess hydride, no significant change in the reaction time or yield of the product was observed. Moreover, the excess hydride was liberated instantaneously during hydrolysis. These observations led to the conclusion that there was no strong coordination between boron and nitrogen, as is observed in the case of trivalent borane reagents. The intermediate obtained is presumably oxazaborolidine, which is highly useful in the enantioselective reduction of prochiral ketones.

The intermediate boroxazoles from chiral amino acids are optically active and are useful in asymmetric synthesis. The amino alcohols are obtained by simple hydrolysis of the boroxazoles. The method offers a simple and rapid conversion of amino acids to amino alcohols in excellent yields.

3.2.3. Reduction of Amides

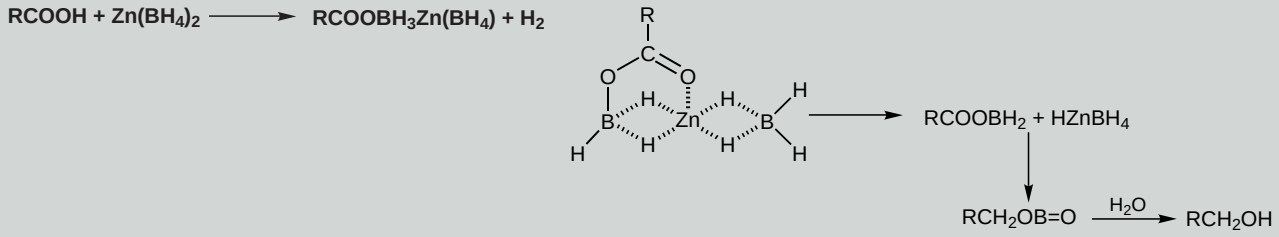
Reduction of carboxylic acid amides can lead to the formation of aldehydes or alcohols by cleavage of the C-N bond, or amines by cleavage of the C-O bond. All three product types have been observed when boron reagents were employed as reducing agents (**Table 10**).

Metal borohydrides do not reduce amides. However, the combination of metal borohydride and an electrophile has been used to effect this transformation. Thus, $NaBH_4$ reduces amides in the presence of carboxylic acids,[36] sulfonic acids,[37] and Lewis acids.[38] The mechanism of the reaction is believed to involve coordination of the metal with oxygen, rather than in situ generation of borane. Interestingly, $Zn(BH_4)_2$ can be used to reduce amides without the use of excess reagent. Thus, reduction of acetanilides by $Zn(BH_4)_2$ results in the evolution of one equivalent of hydrogen. Further reaction results in complete reduction to afford the amine.[39] A series of amides were reduced to yield the corresponding *N*-ethylanilines (**Table 11**). The products were isolated by simple hydrolysis of the reaction mixture (**eq 2**).

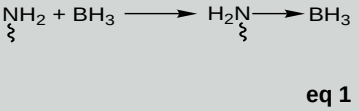
Table 8. Reduction of carboxylic acids with $Zn(BH_4)_2$.[a]

Entry	Substrate[b]	Time, h	Product	% Yield[c]
1	Benzoic acid	6	Benzyl alcohol	90
2	Palmitic acid	6	Cetyl alcohol	95
3	Palmitic acid[d]	6	Hexadecanal	90
4	Valeric acid	3	Amyl alcohol	95
5	2-Chlorobenzoic acid	6	2-Chlorobenzyl alcohol	90
6	4-Nitrobenzoic acid	4	4-Nitrobenzyl alcohol	90
7	3-Nitrobenzoic acid	4	3-Nitrobenzyl alcohol	90
8	3-Bromopropionic acid	6	3-Bromo-1-propanol	75
9	3,4,5-Trimethoxybenzoic acid	5	3,4,5-Trimethoxybenzyl alcohol	70
10	Pivalic acid	2	Neopentyl alcohol	70
11	Phenylacetic acid	3	Phenethyl alcohol	95
12	Phenylacetic acid	3	Phenylacetaldehyde	90
13	Cinnamic acid[e]	5	3-Phenylpropanediol[f]	90
14	2-Hydroxybenzoic acid[e]	4	no reaction	
15	Acetylsalicylic acid	3	2-Hydroxybenzyl alcohol	85
16	10-Undecenoic acid[e]	1	1,11-Undecanediol	90
17	Brassylic acid[g]	4	1,13-Tridecanediol	70
18	Terephthalic acid[g]	5	1,4-Benzenedimethanol	70

[a]All reactions were carried out at reflux in THF; no catalyst was used. [b][acid]:[H^-]=5:16.5. [c]Isolated crude product. [d]Oxidized using aqueous acidic sodium dichromate solution in $CHCl_3$. [e][acid]:[H^-]=5:22. [f]Mixture of 1,2-diol and 1,3-diol (3:2) by ^1H NMR. [g][acid]:[H^-]=5:33.



Scheme 2. Mechanism of the reduction of acids with zinc borohydride.



eq 1

Table 9. Reduction of amino acids by $Zn(BH_4)_2$.[a]

Entry	Substrate	Time (h)	Product	% Yield	Rotation of Amino Alcohol
1	Glycine	7	2-Aminoethanol	70	
2	L-Phenylalanine	5	L-Phenylalaninol	87	-21.7° (c = 1.7, EtOH)
3	L-Leucine	4	L-Leucinol[b]	85	+4.2° (c = 0.9, EtOH)
4	L-Isoleucine	3	L-Isoleucinol[b]	85	+6.7° (c = 1.0, EtOH)
5	L-Valine	4	L-Valinol	85	+8.7° (c = 1.1, EtOH)
6	L-Proline	3	L-Prolinol	85	+37.0° (c = 1.0, EtOH)

[a][substrate]:[H^-] = 1:3 ; in refluxing THF; no catalyst was used. [b]The reported values are: L-leucinol [+4° (c = 9, EtOH)] and L-isoleucinol[+5.4° (c = 1.6, EtOH)] . The *Aldrich Catalog/Handbook of Fine Chemicals*, 1996-1997 ed.; Aldrich Chemical Co.: Milwaukee, WI; pp 895 and 872.

Table 10. Reduction of carboxylic acid amides with various boron reagents.[a]

Entry	Substrate	Reagent	Product
1	$RCONH_2$	Borane-THF, BMS	RCH_2NH_2
2	RCONHR	Borane-THF, BMS	RCH_2NHR
3	$RCONR_2$	Borane-THF, BMS	RCH_2NR_2
4	$RCONR_2$	Sia_2BH[b]	RCHO
5	$RCONH_2$	Sia_2BH[b]	-
6	$RCONR_2$	9-BBN	RCH_2OH
7	$RCONH_2$	9-BBN	stops at deprotonation stage

[a]For a review, see Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*; Academic Press: London, UK, 1988; pp 138-140. [b]Sia_2BH is disiamylborane.

3.3. Hydroborations

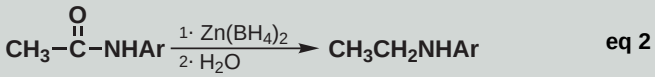
The electrophilic nature of the reagent shows potential for use in hydroboration reactions. The important features to be considered in hydroboration reactions are stoichiometry and regio- and stereoselectivity. Thus, while three equivalents of olefin are hydroborated by one molar equivalent of borane, controlled hydroboration to dialkyl or

monoalkyl species can be achieved with hindered alkenes. In the case of $LiBH_4$/ether[40] and $Ca(BH_4)_2$/THF in the presence of ethyl acetate,[41] tandem reduction-hydroboration results in the formation of dialkylborinate species indicating two equivalents of alkene uptake per BH_4^- ion. Such controlled hydroboration products are very useful as synthetic intermediates. Hence it is important to determine the number of alkenes that can be hydroborated with one molar equivalent of BH_4^- ion.

Table 11. Reduction of anilides by $Zn(BH_4)_2$.

Entry	Substrate	Time, h	Product	% Yield
1	Acetanilide	5	*N*-Ethylaniline	90
2	3'-Chloroacetanilide	4	*N*-Ethyl-3-chloroaniline	85
3	4'-Chloroacetanilide	4	*N*-Ethyl-4-chloroaniline	85
4	4'-Bromoacetanilide	4	*N*-Ethyl-4-bromoaniline	85
5	4'-Methoxyacetanilide	6	*N*-Ethyl-4-methoxyaniline	70
6	2'-Nitroacetanilide	8	*N*-Ethyl-2-nitroaniline	30[a]
7	3',4'-Dichloroacetanilide	5	*N*-Ethyl-3,4-dichloroaniline	80
8	4'-Bromo-3'-chloroacetanilide	5	*N*-Ethyl-4-bromo-3-chloroaniline	75
9	Benzanilide	7	*N*-Benzylaniline	70
10	2'-(Carbomethoxy)acetanilide	4	2-(Ethylamino)benzyl alcohol	80

[a]70% of unreacted anilide was recovered. [anilide]:[H^-]=5:11

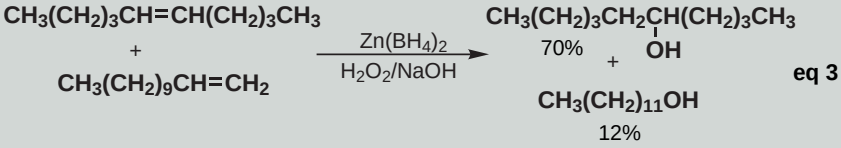


eq 2

Table 12. Hydroboration of alkenes: species and stoichiometry.[a]

Entry	Alkene/BH_4^- Ratio	^{11}B NMR δ(ppm)[b]	Alkene Consumed/BH_4^-
1	1	32 & 55	1
2	2	33 & 54	1.8
3	3	54 & 80	2.4
4	4	54 & 86	3.0

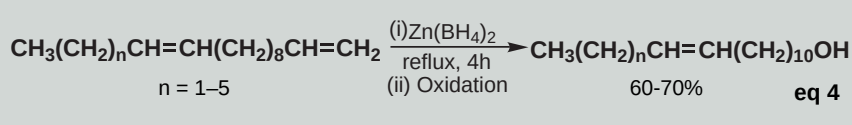
[a]Based on GC analysis, on a 2-m 3% OV-17 column, after 4 h of reflux. [b]With reference to BF_3•OEt_2.



eq 3

Table 13. Comparison of the relative reactivities of terminal and internal alkenes (k_t/k_i) towards hydroboration with various boron reagents.

Entry	Boron Reagent / Alkene	9-BBN	ThxBHCl .SMe_2	$HBBr_2$ .SMe_2	BMS	$Zn(BH_4)_2$	$Ca(BH_4)_2^-$ EtOAc
1	$CH_3(CH_2)_7$ ═	180	9.1	5.0	2.8	6.5	9.0
2	H, H; C=C; Bu^n, Bu^n	1.0	1.0	1.0	1.0	1.0	1.0



eq 4

3.3.1. Hydroboration of Simple Olefins

It is well-known that hydroboration of simple, linear, terminal alkenes using borane leads to the formation of trialkylboron species. However, it should be noted that mono- and dialkylboranes would also be present in the reaction mixture depending on the structure of the alkene and its concentration. The nature of the organoborane species formed and hence the stoichiometry of the reaction can be determined by ^{11}B NMR and hydride analysis studies. The results are presented in **Table 12**.

$Zn(BH_4)_2$ is able to hydroborate a terminal olefin leading to the formation of a trialkylboron species (which is evident from the peak at δ = 83) with excess alkene. This reduction may be utilized for the conversion of alkenes to alcohols whereby maximum use is made of the reagent. Interestingly, dialkylborinate is the major product when a starting ratio of two equivalents of alkene per borohydride ion is used. The dialkylborinate species is very valuable in the preparation of symmetrical ketones.

3.3.2. Hydroboration of Dienes

Regioselectivity is one of the major interests in hydroboration reactions. While a number of reagents are known to be more selective towards the terminal carbon atom, it was felt that if $Zn(BH_4)_2$ were to exhibit even marginal regioselectivity it might be very useful synthetically in view of the simplicity of its workup procedure. Accordingly, to elucidate the regioselectivity of the reagent, a competitive experiment was performed between a terminal olefin, 1-dodecene, and an internal olefin, 5-decene, with just enough hydride to hydroborate one of them (**eq 3**). From the Ingold-Shaw equation, the relative reactivity of the terminal versus internal double bond towards hydroboration was calculated as $k_t/k_i = 5.9$. This result indicates that $Zn(BH_4)_2$ exhibits a selectivity comparable to that of dibromoborane (**Table 13**).[41] This improved selectivity, as compared with that of BH_3•THF or BMS, can be taken advantage of in the hydroboration of dienes containing both terminal and internal double bonds.

An immediate synthetic application of this result was realized in the regioselective hydroboration of 1,11-dienes to produce (*Z*)-11-alken-1-ols, which are pheromone components for many species (**eq 4**).[42] The results are comparable to those of other hydroboration methods. Although 9-BBN, a dialkylborane species, shows excellent terminal carbon selectivity, its use yields only 68% of the required alkenol and suffers from contamination by cyclooctanediol. On the other hand,

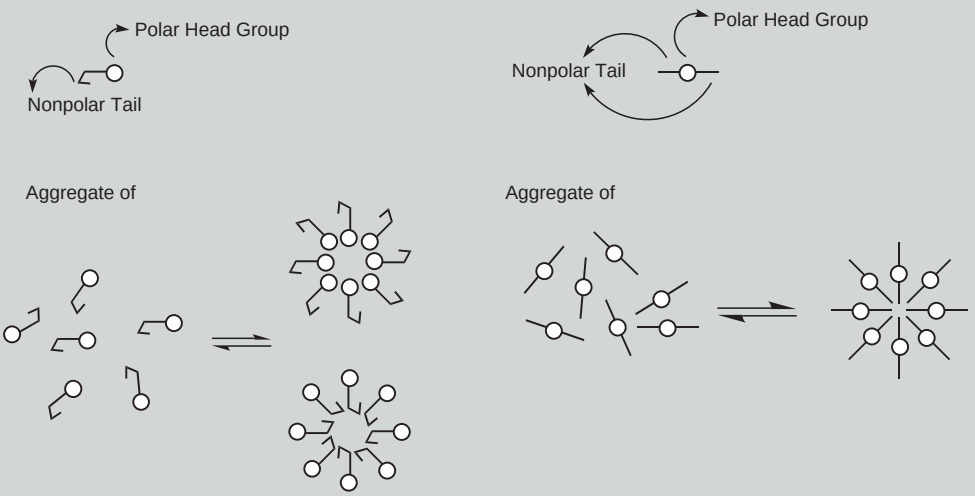
use of $Zn(BH_4)_2$ produces the terminal alcohol in good yield without the complication of side products. Interestingly, the organoboron intermediate was oxidized with sodium dichromate directly to (*Z*)-11-hexadecenal (**eq 5**). 9-BBN and the other selective reagents produce additional side products.

$$CH_3(CH_2)_3CH{=}CH(CH_2)_8CH{=}CH_2 \xrightarrow[\text{reflux, 4h}]{\text{(i) } Zn(BH_4)_2 \quad \text{(ii) } Na_2Cr_2O_7} CH_3(CH_2)_3CH{=}CH(CH_2)_9CHO$$

60%

eq 5

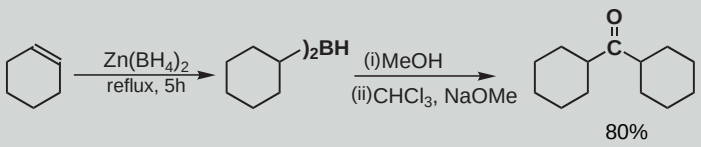
As indicated earlier, in order to derive the maximum utility from the reagent, two equivalents of diene were reacted with 1 equivalent of BH_4^-. Interestingly, ^{11}B NMR analysis of the quenched reaction mixture indicated the formation of monoalkyl boronates in major quantities. A possible in situ micellization of the intermediate could explain this observation. When hydroborated, a simple hydrocarbon diene would become bipolar in nature and hence result in aggregation of monomers (**Scheme 3**). Consequently, the rate of further hydroboration by the monohydroborated species would be very much reduced.



Scheme 3. In situ micellization during the hydroboration of long-chain dienes.

3.3.3. Hydroboration of Cyclic Olefins

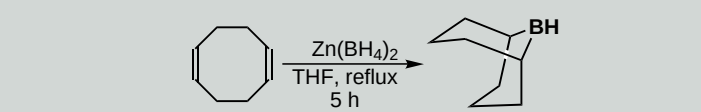
Cyclic olefins such as cyclohexene possess an internal double bond. Thus, hydroboration of these systems should stop at the dialkylboron stage due to steric hindrance. Indeed, hydroboration of cyclohexene by $Zn(BH_4)_2$ stops at the dialkylboron stage ($\delta = 53$, using $BF_3{\bullet}Et_2O$ as external standard). This dialkylboron intermediate can be converted to symmetrical ketones by treatment with $CHCl_3$ and NaOMe (**eq 6**).[43]



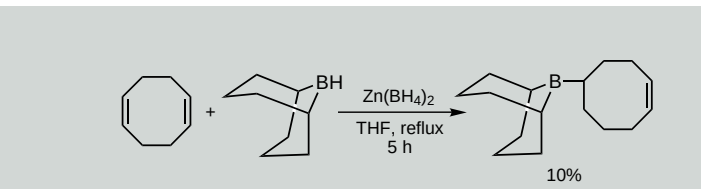
80%

eq 6

Hydroboration of 1,5-cyclooctadiene by simple borane reagents leads to the formation 9-borabicyclo[3.3.1]nonane (9-BBN), a highly selective hydroborating and reducing agent. Under the present reaction conditions, 1,5-cyclooctadiene is hydroborated intramolecularly and isomerizes to the stable 9-borabicyclo[3.3.1]nonane product (**eq 7**). This should be quite useful in the in situ generation of 9-BBN. A considerable amount of trialkylboron species is also observed by ^{11}B NMR, indicating further hydroboration of the cyclooctadiene by 9-BBN (**eq 8**).[44]



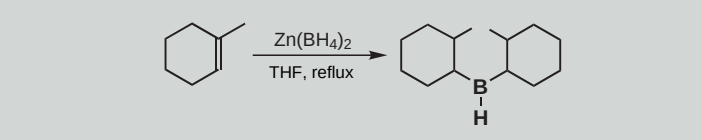
eq 7



10%

eq 8

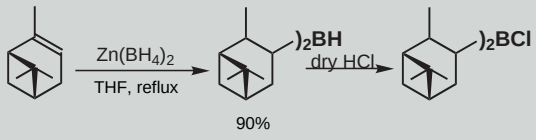
Substituted cyclic olefins such as 1-methylcyclohexene and α-pinene are easily hydroborated to the corresponding dialkylborinate species (**eq 9**).



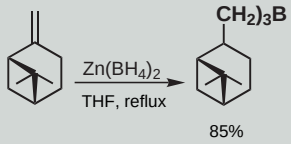
90%

eq 9

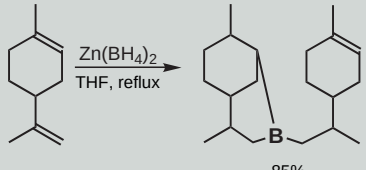
It should be pointed out that, in the case of α-pinene, the dialkylborinate intermediates can react with prochiral substrates such as



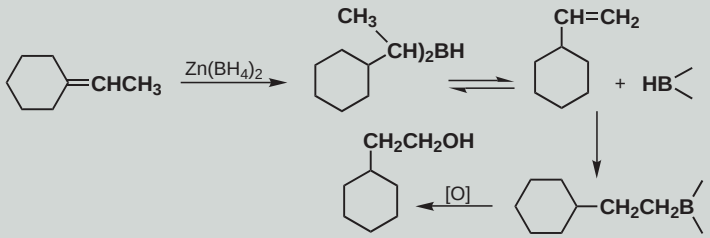
eq 10



eq 11



eq 12

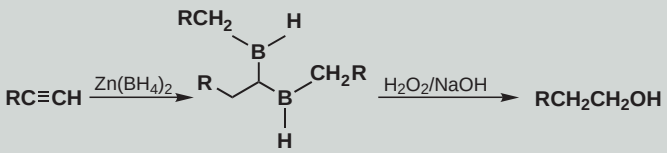


Scheme 4

Table 14. Alcohols obtained by hydroboration of olefins with $Zn(BH_4)_2$.

Entry	Substrate[a]	Time, h	Product	% Yield[b]
1	1-Dodecene	3	1-Dodecanol	90
2	1-Decene	3	1-Decanol	92
3	5-Decene	4	5-Decanol	85
4	Cyclohexene	4	Cyclohexanol	90
5	1,5-Cyclooctadiene	4	1,5-Cyclooctanediol 4-Cycloocten-1-ol (90:10)	85[c]
6	1,7-Octadiene	3	1,8-Octanediol	90
7	Ethylidenecyclohexane	4	1-Cyclohexylethanol 2-Cyclohexylethanol (90:10)	85[c]
8	1-Methylcyclohexene	4	2-Methylcyclohexanol cis:trans=85:15	90[c]
9	α-Pinene	4	Isopinocampheol	90
10	β-Pinene	4	Myrtanol	85
11	Limonene	4	Limonene-2,9-diol	85

[a][alkene]:[H^-]=1:2; in refluxing THF. The oxidations were carried out with H_2O_2/NaOH. [b]Isolated yield based on reacted olefin. [c]Yield of the mixture.



eq 13

activated ketones to produce optically active reduction products as reported in the literature using diisopinocampheylborane[45] or diisopinocampheylchloroborane (DIP-Chloride™)[46] (**eq 10**). Thus, this approach can offer a one-pot process for asymmetric synthesis.

Recently, *B*-hydroxydiisopinocampheylborane (Ipc_2BOH), prepared by the hydrolysis of the hydrido compound, has been employed as a chemoselective reducing agent for aldehydes over ketones.[47] Oxidation of the organoboron afforded isopinocampheol in excellent yield. Curiously, β-pinene produces a triorganoborane with $Zn(BH_4)_2$ as indicated by the ^{11}B NMR spectra of the reaction mixture (**eq 11**). Oxidation of the triorganoborane intermediate affords myrtanol.

Hydroboration of limonene also produced a significant amount of the corresponding trialkylborane. Presumably, the cyclic dihydroboration took place first resulting in a R_2BH species, which then hydroborated one more equivalent of limonene selectively at the terminal position (**eq 12**). On oxidation, the intermediate trialkylborane yields limonene-2,9-diol and minor amounts of *p*-menth-1-en-9-ol.

Interestingly, ethylidenecyclohexane, a sterically hindered substrate, also produced a significant amount of the trialkylboron intermediate. Upon oxidation, a small amount (10%) of the rearranged alcohol, 2-cyclohexylethanol, was also observed spectroscopically. It is likely that the initial organoboron intermediate underwent partial isomerization to the terminal position and yielded the isomerized trialkylborane as a minor product (**Scheme 4**). At high temperature such isomerism—to the terminal position thereby relieving the steric strain—has been observed with disiamylborane. These intermediates can be utilized in several synthetic transformations following the methods given in the literature. The simple application of the present method is summarized in **Table 14**.

3.3.4. Hydroboration of Alkynes

Alkynes undergo dihydroboration with $Zn(BH_4)_2$ giving rise to dibora adducts. Oxidation with alkaline hydrogen peroxide produces the corresponding alcohols in 40-90% yields (**eq 13** & **Table 15**).[19]

Generally, in the presence of excess alkyne, monohydroboration results. Unlike other metal borohydrides, and although $Zn(BH_4)_2$ is a basic reagent, it is still able to hydroborate without the addition of any Lewis acid or ester. Presumably, the soft Lewis acid nature of Zn^{2+} ion polarizes the borohydride ion and generates an electrophilic species which then reacts with the double bond.

Table 15. Hydroboration of alkynes with $Zn(BH_4)_2$.[a]

Entry	Alkyne	Time (h)	Product	Yield[b] (%)
1	1-Hexyne	3	1-Hexanol	80
2	1-Octyne	3	1-Octanol	80
3	1-Hexadecyne	4	1-Hexadecanol	90
4	1-Octadecyne	4	1-Octadecanol	90
5	3-Hexyne	4	3-Hexanone	75
6	1-Octyne[c]	3	1-Octanol	40
			Octanal	60

[a][alkyne]:[H^-]=1:2; refluxing THF. [b]Isolated yield. [c][alkyne]:[H^-]=10:1

4. Conclusion

In conclusion, $Zn(BH_4)_2$ can be used for the selective reduction of functional groups under various conditions. The reagent also offers an alternative to BMS in hydroboration reactions. Its remarkable regioselectivity, coupled with a simple workup procedure, makes it more advantageous to use than other selective reagents such as 9-BBN in the synthesis of several pheromones.

5. Acknowledgments

It is a pleasure to thank Professor T.R. Govindachari, our advisor, and earlier coworkers—Drs. K. Ganeshwar Prasad and S. Madhavan and Mr. Prem Palmer. We also thank all those who have contributed to the chemistry reviewed here and whose names appear in the cited references.

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About the Authors

Dr. S. Narasimhan received his Ph.D. degree in 1978 from Madras University under the guidance of Prof. N. Venkatasubramanian. From 1979 to 1982, he worked as a Postdoctoral Research Associate with Prof. H.C. Brown at Purdue University. He then returned to India and accepted the position of Scientist at IDL Nitro Nobel Basic Research Institute in Bangalore. He joined the Centre for Agrochemical Research in 1988 and was promoted recently to Deputy Director and Head of the laboratory. His research interests are focused on developing pheromone technology and new synthetic methods using organoboron chemistry. He has developed a number of commercial plant-protection formulations based on natural product extracts and has received a Technology Transfer Award from SPIC. He has authored more than 60 publications and trained 5 Ph.D.'s. He is currently developing novel chiral oxazaborolidines and doing pioneering work in the application of pheromone technology to control serious crop pests in India.

Mr. R. Balakumar received his M.Sc. and M.Phil. in Chemistry from Madras Christian College. He joined Dr. S. Narasimhan's group in February 1995 and is currently working towards his Ph.D. His research project involves the synthesis of oxazaborolidines using novel synthetic routes and studying their utility as chiral reagents in imparting enantioselectivity in reductions, Diels-Alder, and other reactions. Another project involves the study of zinc and zirconium borohydride as potential reducing agents.

METAL BOROHYDRIDES
and anhydrous halides

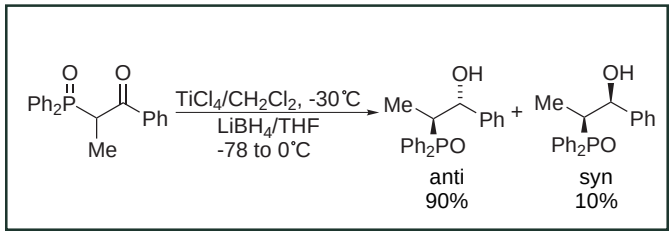
As Dr. Narasimhan has described in the preceding review, zinc borohydride has unique properties. Unfortunately, it is also not stable long enough to be offered commercially; hence, it must be prepared in situ.[1] Aldrich is pleased to offer the highest quality zinc borohydride precursors available anywhere. Zinc chloride is offered in powder or bead form, with total oxygen and water content less than 100 ppm, for use in the preparation of $Zn(BH_4)_2$ without further purification or drying. Some of the many recent applications of metal borohydrides are illustrated here.

$Ca(BH_4)_2$

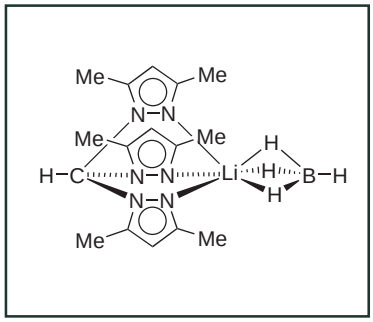
Prepared from very dry $CaCl_2$ and $NaBH_4$, $Ca(BH_4)_2$ reduces lysergic acid esters to the corresponding alcohols in 81-85% yield.[2] It has also been used by Narasimhan in the reduction of aliphatic and aromatic esters to alcohols,[3] and in the regioselective hydroboration of terminal alkenes.[4]

$LiBH_4$

In the presence of $TiCl_4$, $LiBH_4$ reduced α-alkyl-β-ketophosphine oxides to the corresponding β-hydroxyphosphine oxides in good yields and high anti diastereoselectivity.[5]



Parkin and coworkers employed $LiBH_4$ in the synthesis of bis- and tris(pyrazolyl)hydroborato ligands with bulky triptycyl substituents. These ligands inhibit formation of 6-coordinate sandwich complexes and allow freer access to the metal center in the thallium complexes prepared.[6] Cotton and other researchers reported a potpourri of novel products in the reduction of $TaCl_5$ with $LiBH_4$ in the presence of lithium diphenylformamidinate.[7] Novel pyrazolyl or bipyridyl complexes with lithium borohydride have potential applications in fuel cells with controlled and safe delivery of hydrogen.[8]



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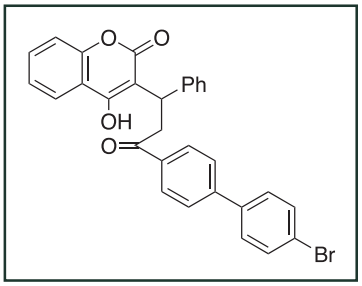
$NaBH_4$

Used so extensively it has become a standard laboratory reagent! References to applications of $NaBH_4$ abound in the literature; here are only three recent ones:

Surprisingly high (~90%) de is achieved in the reduction of the ketone shown here to the corresponding alcohol.[9]



A $[HFe_3(CO)_{11}]^-$ species was generated in situ using $NaBH_4$ and $Fe(CO)_5$ in trifluoroacetic acid. When reacted with alkynes, this species led to the production of cyclobutenediones.[10] α,β-Unsaturated nitriles were reduced chemoselectively to the corresponding saturated nitriles with $BiCl_3/NaBH_4$.[11]

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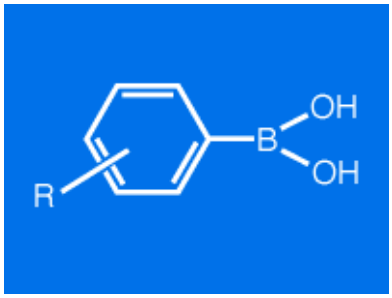

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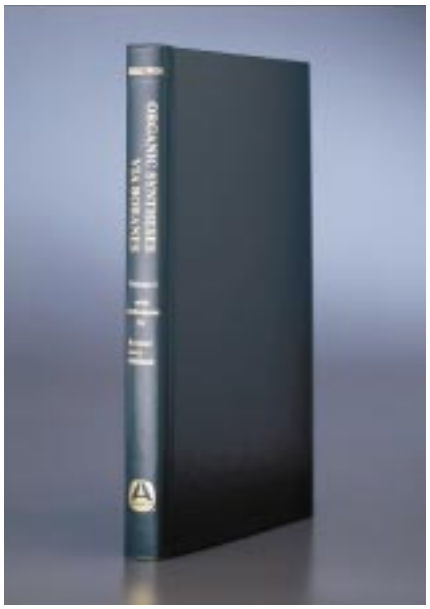

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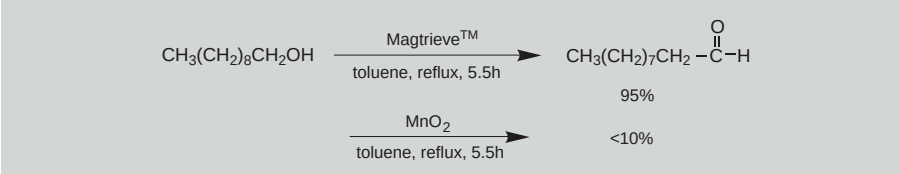

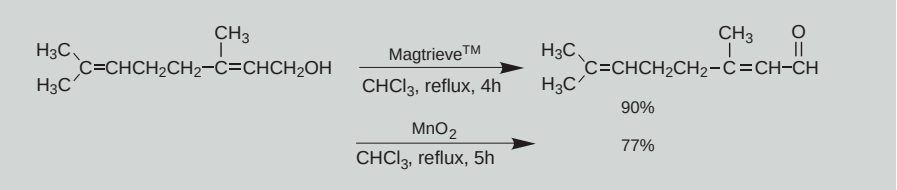

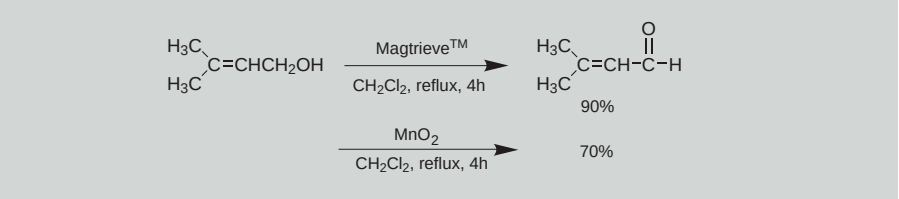

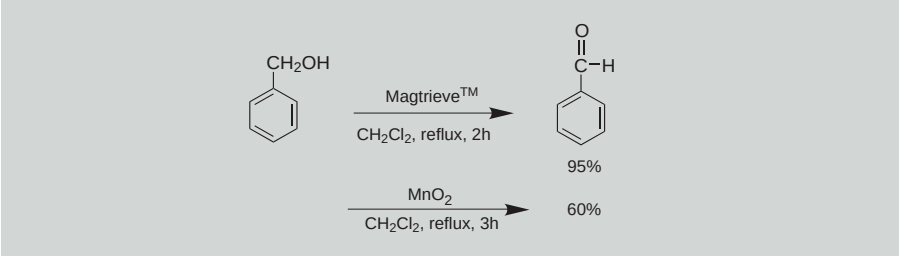

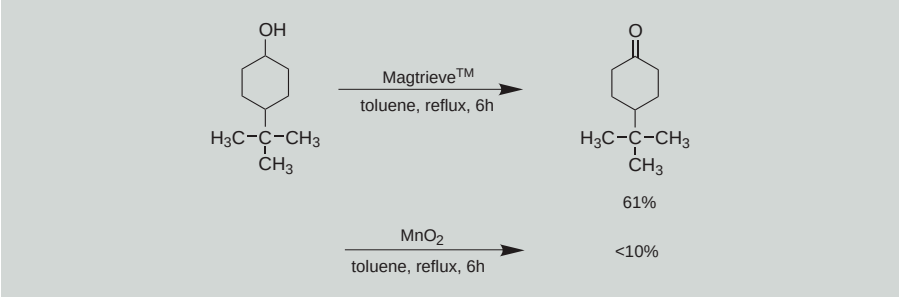

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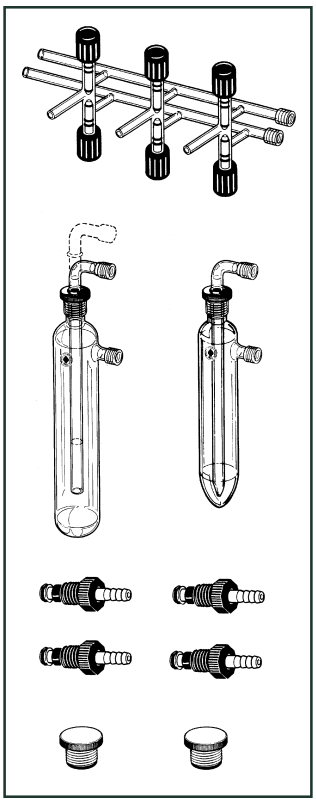

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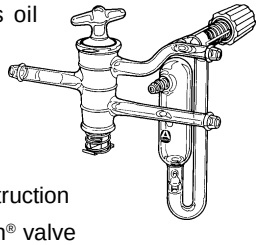


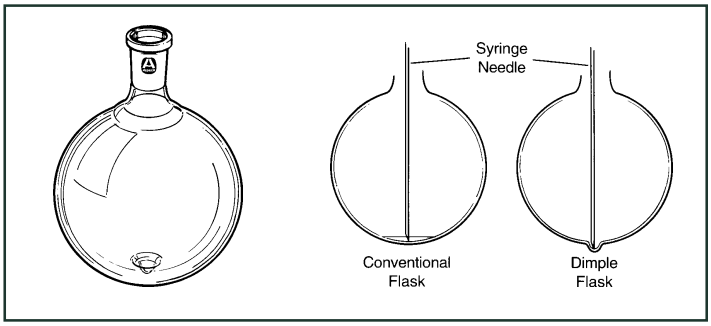
- Built-in check valve prevents oil and air from being pulled into system
- Rear hose connector vents toxic gases from bubbler to fume hood
- Sturdy, high-performance construction

With manually adjustable Teflon® valve
Z22,532-0

With spring-loaded automatic valve
Z22,533-9

Aldrich Dimple Flasks

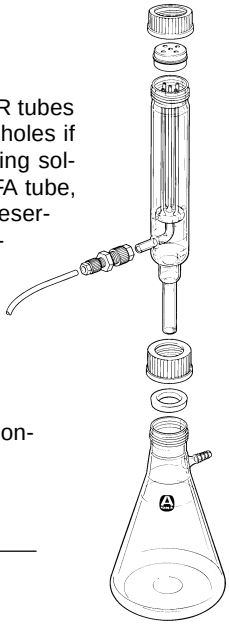
These flasks are designed to permit complete removal of liquids using non-coring type syringe needles, gauges 12 to 20, that are used for piercing rubber septa. A small indentation or "dimple" at the bottom



of the flask acts as a reservoir to collect liquids which may then be drawn off via syringe. The dimple is small enough that it does not interfere with the use of egg-shaped magnetic stirring bars.

Cap. (mL)	14/20 joint Cat. No.	24/40 joint Cat No.
25	**Z40,632-5**	--
50	**Z40,633-3**	--
100	**Z40,634-1**	**Z40,636-8**
250	--	**Z40,637-6**
500	--	**Z40,638-4**
1,000	--	**Z40,639-2**

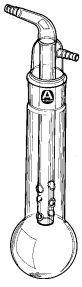
Aldrich 5-Position NMR Tube Cleaner System



Washes up to five 5-mm (o.d.) x 7-in. (l) NMR tubes at once. NMR tube caps can be used to plug holes if less than five tubes are to be cleaned. Cleaning solvent is pulled from an external container via PFA tube, eliminating repetitious filling of side-mounted reservoirs. *Note: Bottle for cleaning solvent is not supplied.*

- Totally inert—cleaning solvents contact only borosilicate glass, PTFE, and PFA.
- Top PTFE tube holder provides a vacuum-tight seal.
- No ground glass joints to freeze; no grease contamination.
- Modular components are easy to replace.

Description	Cat. No.
NMR tube cleaner system, complete	**Z28,838-1**



Aldrich Cold Traps

Large-capacity traps with removable cold fingers and choice of 55/50 joint or 50-mm O-ring joint. Traps with O-ring joint include pinch clamp.

A. Traps with 55/50 joint

Bulb Cap. (mL)	*Complete* Cat. No.
500	**Z10,310-1**
1,000	**Z28,450-5**

B. Traps with 50-mm O-ring joint

Bulb Cap. (mL)	*Complete* Cat. No.
500	**Z10,690-9**
1,000	**Z28,452-1**

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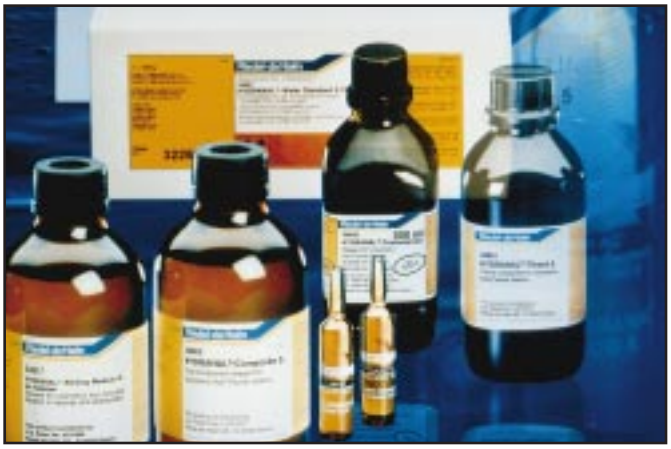
HYDRANAL® Reagents



The HYDRANAL® line of reagents and water standards for Karl Fischer moisture determinations is now available directly from Riedel-de Haën through Aldrich. Free of pyridine, carbon tetrachloride, and 2-methoxyethanol, HYDRANAL®-KF reagents and water standards provide fast, accurate results without compromising laboratory safety.

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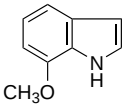
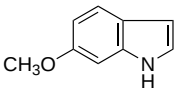
Aldrichimica Acta
Volume 31, Number 2, 1998

Benzotriazole-Based Intermediates: Reagents for Efficient Organic Synthesis

Manganese-Based Organic and Bioinorganic Transformations

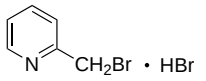
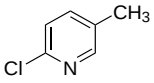
New Products

Important synthons which have been used to prepare a number of biologically active compounds. Examples include the preparation of apoyohimbines,[1] 3-(tetrahydropyridinyl)-indoles,[2] and platelet activating factor antagonists.[3]

(1) Leonard, J. et al. *Tetrahedron Lett.* **1997**, *38*, 3071. (2) Gharagozloo, P. et al. *Tetrahedron* **1996**, *52*, 10185. (3) Sheppard, G.S. et al. *J. Med. Chem.* **1994**, *37*, 2011.

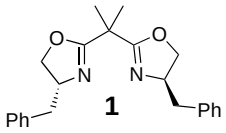
11,398-0 **7-Methoxyindole**, 97%
13,985-8 **6-Methoxyindole**, 98%

A number of biologically active heterocycles have been prepared from these pyridines. Examples include tachykinin NK_2 receptor antagonists and endothelin receptor antagonists.[1-3]

(1) Smith, P. W. et al. *J. Med. Chem.* **1995**, *38*, 3772. (2) Huang, L. J. et al. *Chem. Pharm. Bull.* **1992**, *40*, 2547. (3) Neidhart, W. et al. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2223.

49,104-7 **2-(Bromomethyl)pyridine hydrobromide**, 98%
49,532-8 **6-Chloro-3-picoline**, 98%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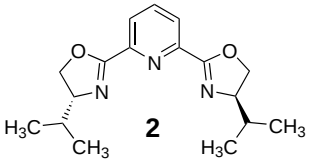
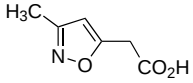

2

Bisoxazoline **1** has been used to prepare a catalyst used for the hetero- and carboannulation of allenes.[1] It has also been used to prepare a catalyst for highly stereoselective iron-mediated enediene carbocyclizations.[2] A catalyst for highly enantioselective hydrosilylation of ketones and for C-H insertion reactions has been prepared from ligand **2**.[3]

(1) Larock, R.C.; Zenner, J.M. *J. Org. Chem.* **1995**, *60*, 482. (2) Takacs, J.M. et al. *J. Org. Chem.* **1995**, *60*, 3473. (3) Nishiyama, H. et al. *Organometallics* **1991**, *2*, 500.

49,530-1 **[*R*(*R**, *R**)]-(+)-2,2'-Isopropylidenebis(4-benzyl-2-oxazoline),** 95%

47,749-4 **2,6-Bis-[(4*R*)-(+)-isopropyl-2-oxazolin-2-yl]pyridine**, 99%

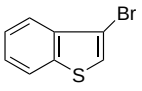


Cyclooxygenase and 5-lipoxygenase inhibitors have been prepared from this isoxazole.

Flynn, D.L. et al. *J. Med. Chem.* **1991**, *34*, 518.

48,968-9 **3-Methyl-5-isoxazoleacetic acid**, 98%

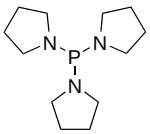
A variety of 3-substituted benzothiophenes have been prepared via lithiation of this compound. Examples include the trifluoromethyl ketone and the boronic acid.[1,2]



(1) Kerdesky, F.A.J.; Basha, A. *Tetrahedron Lett.* **1991**, *32*, 2003. (2) Thompson, W.J. et al. *J. Org. Chem.* **1988**, *53*, 2052.

49,497-6 **3-Bromothianaphthene**, 95%

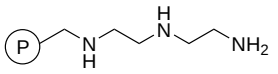
This pyrrolidinyl phosphine has been used in the multigram synthesis of phosphorodithioate DNA.



Wiesler, W.T.; Caruthers, M.H. *J. Org. Chem.* **1996**, *61*, 4272.

49,392-9 **Tris(1-pyrrolidinyl)phosphine**, 97%

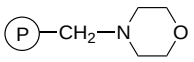
Used in the purification of chemical libraries by complementary molecular reactivity and molecular recognition (CMR/R) strategies.[1] Immobilizes RCHO, RCO_2H, RCOCl, and anhydrides.[2] Simple filtration and evaporation yields highly pure (95+%) products.[3] Now available in two different loadings.



(1) Flynn, D.L. et al. *J. Am. Chem. Soc.* **1997**, *119*, 4874. (2) Parlow, J.J. et al. *J. Org. Chem.* **1997**, *62*, 5908. (3) Parlow, J.J. et al. *Tetrahedron Lett.* **1997**, *38*, 7959.

47,978-0 **Diethylenetriamine**, **polymer-bound**, 2.5-3.0 mmol N/g
49,438-0 **Diethylenetriamine**, **polymer-bound**, 4.0-5.0 mmol N/g

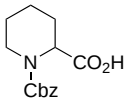
Employed as a high-capacity acid scavenger in parallel purification of reaction solutions. Often used in conjunction with other polymeric scavengers such as polymer-bound isocyanates to yield highly pure products.



Booth, R.J.; Hodges, J.C. *J. Am. Chem. Soc.* **1997**, *119*, 4882.

49,381-3 **Morpholine**, **polymer-bound**, 2.75-3.25 mmol N/g, 1 % cross-linked, 200-400 mesh

This protected pipecolinic acid has been used to prepare β-turn mimics and the natural product (±)-δ-coniceine.[1,2]



(1) Genin, M.J. et al. *J. Org. Chem.* **1993**, *58*, 860. (2) Martin-Lopez, M.J.; Bermejo-Gonzalez, F. *Tetrahedron Lett.* **1994**, *35*, 4235.

49,502-6 **1-(Carbobenzyloxy)-2-piperidinecarboxylic acid**, 97%

Aldrichimica Acta

Volume 31, Number 2, 1998

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About Our Cover

Saint Cecilia and an Angel (oil on canvas, 34 5/8 x 42 1/2 in.) depicts Cecilia, a third-century Roman Christian. According to legend, she, her husband, Valerian, and his brother suffered martyrdom for their faith. It was said that Cecilia was so close to Heaven that she could hear the singing of the angels, and that her soul was so filled with Heavenly music that she invented the organ in order to express it. Consequently, she came to be regarded as the patron saint of music.

Although *Saint Cecilia and an Angel* traditionally has been attributed to Orazio Gentileschi (1563-1639), inconsistencies in the handling of the paint in various parts of the picture suggest that it was executed by not one, but two artists. As early as 1662 the name of Giovanni Lanfranco (1582-1647) was linked to the picture, and recent stylistic analysis and a rereading of the records documenting its provenance confirm that much of the painting was executed by Gentileschi before its completion by Lanfranco.

Study of X-radiographs, pigment analyses, and X-ray fluorescence also support this conclusion, but differences can be detected even with the naked eye. The fluid brushwork of the sleeves and boneless rubbery hands are both characteristic of Lanfranco's style, in contrast to the more literal representation of Gentileschi. The picture also shows the influence of Caravaggio, who used ordinary people rather than idealized types as models and showed them at close range emerging from a neutral space into a strong light, heightening both the realism and the expressiveness of the subject.

This painting is part of the Samuel H. Kress Collection at the National Gallery of Art.

Lab Notes

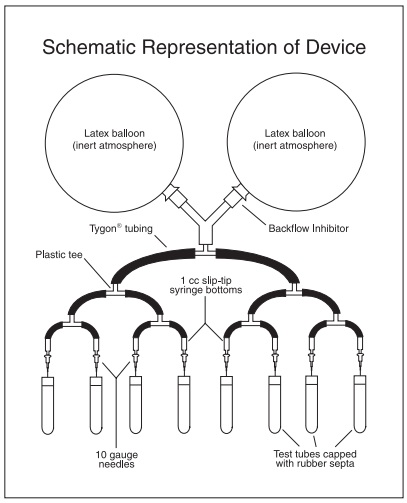
A Useful Technique for Creating and Maintaining Inert Atmospheres Simultaneously Within a Large Number of Reaction Vessels

Here is an interesting and effective method for providing respite from the cumbersome process of purging a large number of reaction vessels with an inert gas (i.e., N_2, Ar, etc.), and maintaining a positive (inert gas) pressure in all of them throughout the reaction process. In our laboratory, we carry out a large number of assays on the oxidative abilities of novel peptide ligand systems complexed with a number of different metal atoms. In order to assess each ligand's oxidative potential properly, all possible combinations of metal, ligand, oxidizing agent, and substrate must be examined in detail (as well as the necessary control environments). Needless to say, it is not unusual to be running 10-20 concurrent tests on any given day. The need to create and maintain an oxygen-free environment in each of these vessels is crucial in the determination of the effectiveness of each possible combination of components (in order to be assured that the oxygen atom was donated by the oxidizing agent). The purging process required to prepare and maintain this large number of separate inert atmospheres leads to a waste of valuable time, and can be shortened considerably through the use of the following apparatus.

The design of this apparatus is based essentially on the premise that a single source of positive pressure can be used to create and maintain inert environments in each of the reaction vessels (either from a balloon or directly from a tanked source). In prior reaction preparations and procedures, we have had to purge each reaction vessel separately, with each requiring its own source of positive pressure. Also, during the course of a reaction sequence in which separate balloons are used for individual reaction vessels, the chance that one of the balloons will pop (thereby violating the integrity of the enclosed inert atmosphere) is much greater than if only one source consisting of two balloons were used for all the vessels.

The apparatus consists of a single source of inert gas, comprised of two latex balloons equipped with backflow inhibitors. This arrangement insures the preservation of atmospheric integrity should one of the balloons pop—in which case it prevents gas loss through the hole created in the system—and maintains a positive pressure inside the reaction vessels. This gas introduction system is connected to a series of continuously branching tubes (through the use of 3-way plastic tees), each terminating in the "bottom" of a 1-mL slip-tip syringe which is fitted with a 10-gauge needle. The needle is then inserted into the septum at the top of the reaction vessel (usually a 16 x 125 mm test tube).

There are many other reasons for utilizing this apparatus besides its obvious, timesaving benefits. The use of balloons as the providers of positive inert pressure during extended-time reactions considerably reduces the amount of gas used as compared with the amount that would be needed if the "constant flow" method is employed.



Steve Flemer, Jr., Graduate Student
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P.O. Box 5752
Burlington, VT 05402

Please turn to page 65 for another Lab Note selection entitled "Separating DMF from Alkylated Nucleosides by Silica Gel Column Chromatography".

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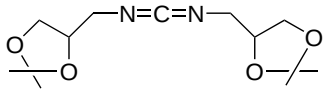
"Please Bother Us."

by Jai Nagarkatti

Jai Nagarkatti, President



Dr. Henry Rapoport of the University of California, Berkeley kindly suggested that we make this carbodiimide (BDDC). It is an attractive alternative to dicyclohexylcarbodiimide (DCC) or diisopropylcarbodiimide (DIC) for peptide coupling reactions or O-acylations. An important advantage of BDDC versus DCC or DIC is that the urea byproduct formed during the coupling reaction is easily removed using a mild acid wash, alleviating the need for chromatographic purification of the product.

Gibson, F.S.; Park, M.S.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 7503.

48,212-9 **1,3-Bis(2,2-dimethyl-1,3-dioxolan-4-ylmethyl)carbodiimide,** 95%

Naturally, we made this useful reagent. It was no bother at all, just a pleasure to be able to help.

Do you have an innovative shortcut or unique laboratory hint you'd like to share with your fellow chemists? If so, please send it to Aldrich (attn: Lab Notes, *Aldrichimica Acta*). For submitting your idea, you will receive a complimentary, laminated periodic table poster (Cat. No. **Z15,000-2**). If we publish your *Lab Note*, you will also receive an Aldrich periodic table turbo mouse pad (Cat. No. **Z24,409-0**). It is Teflon®-coated, 8½ x 11in., with a full-color periodic table on the front. We reserve the right to retain all entries for future consideration.

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Benzotriazole-Based Intermediates: Reagents for Efficient Organic Synthesis

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University of Florida
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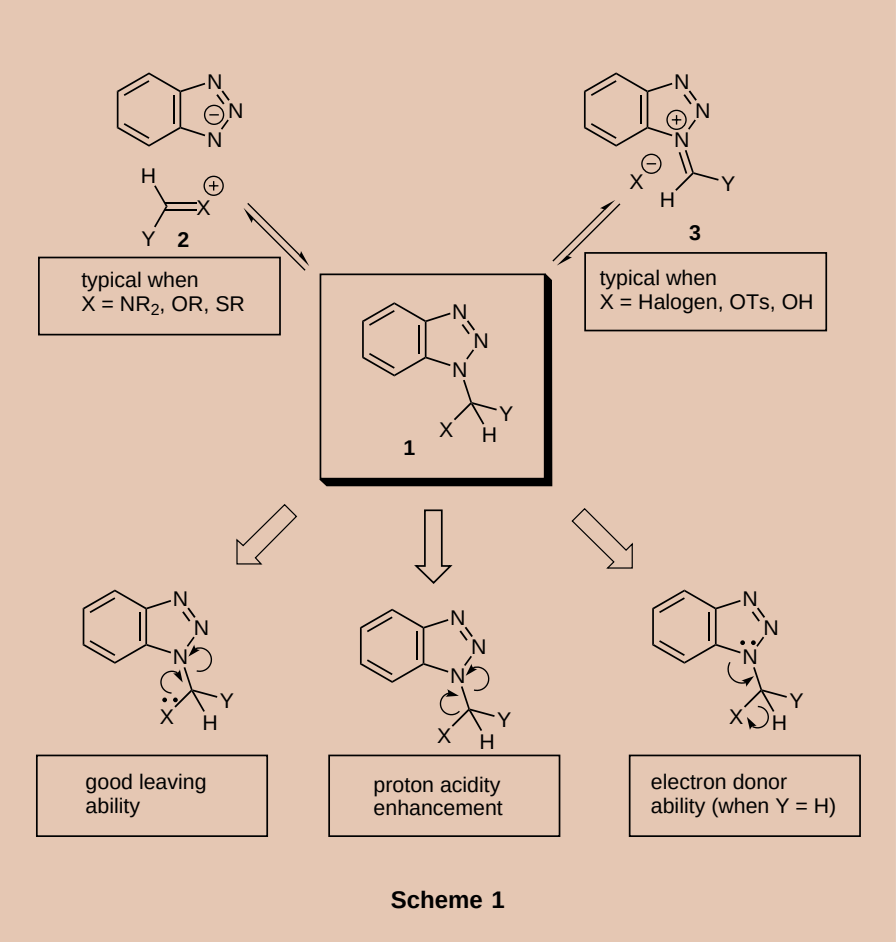
Outline

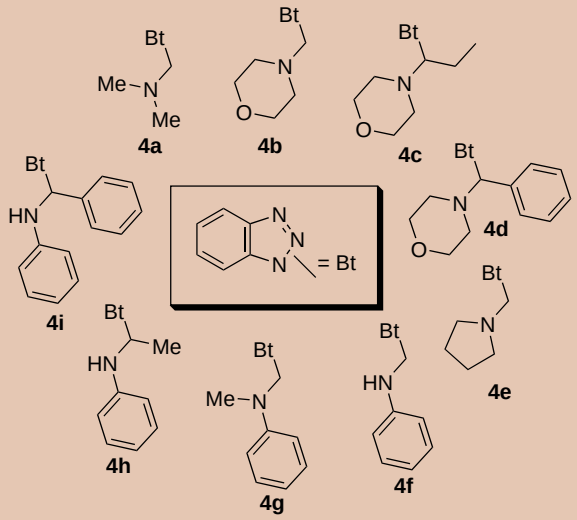
1. Introduction

During the last decade benzotriazole-mediated synthetic methodology has developed rapidly and has now become an important synthetic tool for many chemical processes, including multistep preparations of drugs, biologically active compounds, and synthetic analogs of natural products. The multifaceted nature of benzotriazole intermediates **1** is embedded in their versatile electronic character: in many cases the benzotriazole heteroring can act as an electron-donating or electron-withdrawing moiety, depending on the type of substituent that is attached to nitrogen **(Scheme 1)**. Many applications of benzotriazoles depend both on the good leaving ability of the benzotriazole moiety upon displacement with nucleophiles, and on the α-proton acidity enhancement in **1**.

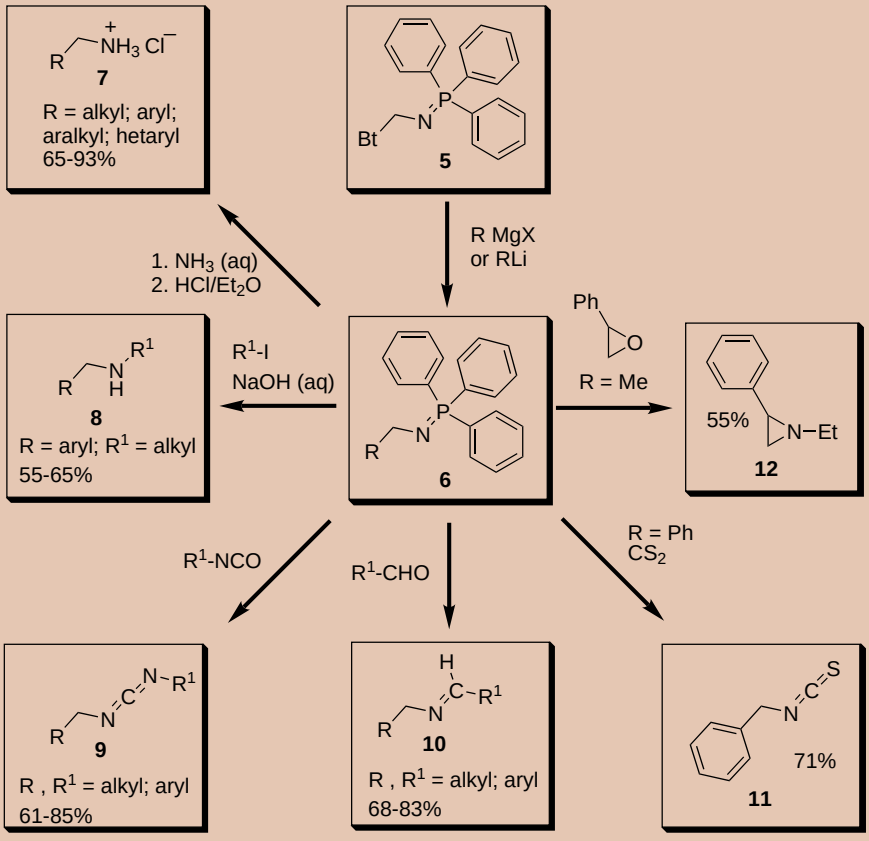
This review aims to highlight a few of the numerous benzotriazole-based reactions which can be carried out with commercially



Scheme 1



Scheme 2



Scheme 3

available benzotriazole derivatives, and which enable the efficient preparation of many key classes of organic compounds. It thus supplements our recent comprehensive review on benzotriazole chemistry.[1] The present review is organized into sections outlining the scope of the reactions used in the preparation of particular series of compounds.

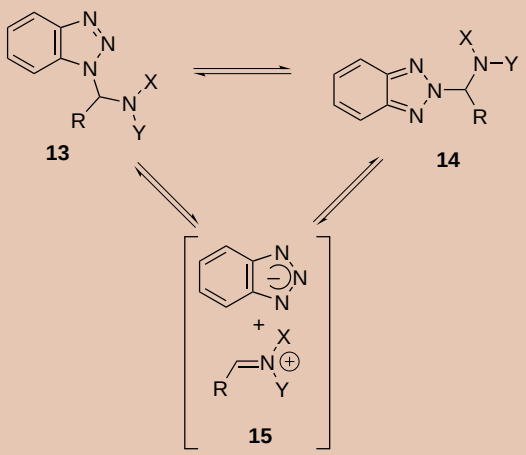
2. Synthesis of Amines and Amine Derivatives

The preparation of amines using the benzotriazole methodology is particularly well-studied, and numerous routes involving benzotriazole as a leaving group in carbon-carbon bond-forming reactions are known. Primary, secondary, and tertiary amines can all be prepared successfully in high yields. Structures of some commercially available benzotriazole-aldehyde-amine adducts are given below **(Scheme 2)**.

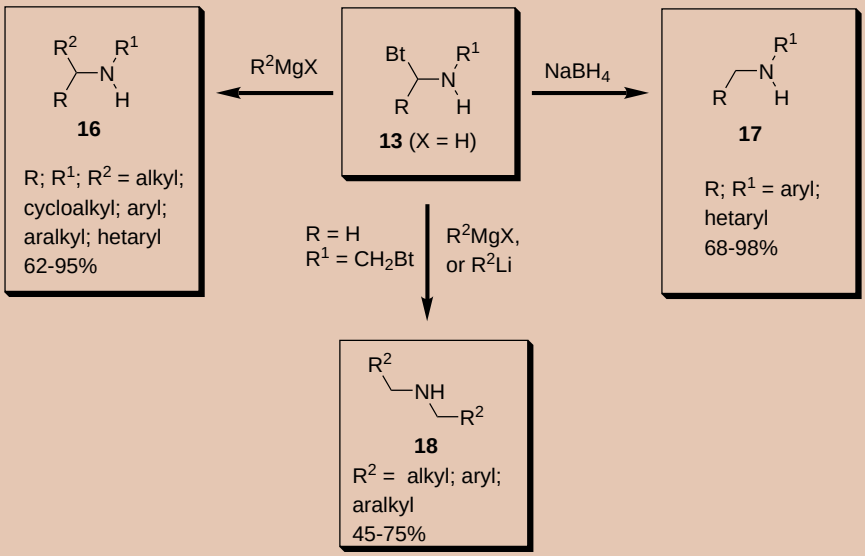
Primary amines of type **7** can be obtained starting with the reactions of Betmip, 1-(triphenylphosphoroylideneaminomethyl)-benzotriazole **(5)**, with a variety of Grignard or organolithium reagents **(Scheme 3)**. The resulting phosphazenes **6** are hydrolyzed directly to primary amines **7** in a one-pot reaction.[2-4] Various amine derivatives—carbodiimides **9**, Schiff bases **10**, isothiocyanate **11**, aziridine **12**—are also readily available via Betmip **(Scheme 3)**.[3,4]

Secondary amines can be synthesized efficiently starting from the adducts of benzotriazole, an aldehyde (aliphatic, aromatic, or heteroaromatic) or sometimes a ketone, and a primary amine (aliphatic or aromatic). In general, successful replacement of the benzotriazole moiety in systems of type Bt-C-N in reactions with a wide variety of nucleophiles, including unstabilized carbanions (organometallics) and sodium borohydride, depends on the existence of an equilibrium between benzotriazole adducts **13** (and their 2-isomers **14**) and the ion pairs **15** **(Scheme 4)**. The immonium cations are formed most easily in polar solvents; otherwise, the equilibrium may be shifted by heating in nonpolar media. Treatment of adducts **13** (X = H) with Grignards or with sodium borohydride affords numerous aliphatic, aromatic, or heteroaromatic secondary amines in good to excellent yields **(Scheme 5)**.[5-8] Secondary amines **8** can also be made by treating the intermediate phosphazenes **6** with alkyl iodides followed by hydrolysis with aqueous sodium hydroxide **(Scheme 3)**.[3,4]

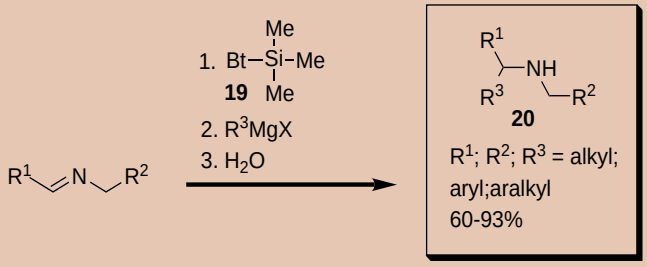
Benzotriazole derivative **13** (**Scheme 5,** $R = H$, $R^1 = CH_2Bt$) is a valuable intermediate for the preparation of symmetrical secondary amines **18**.[9] On the other hand, unsymmetrical secondary amines can be prepared starting



Scheme 4



Scheme 5



Scheme 6

with the reaction of imines with 1-trimethylsilylbenzotriazole **(19) (Scheme 6)**: the intermediate *N*-silylated benzotriazole adducts are treated in situ with Grignard reagents and then hydrolyzed to form secondary amines **20** in good yields.[10]

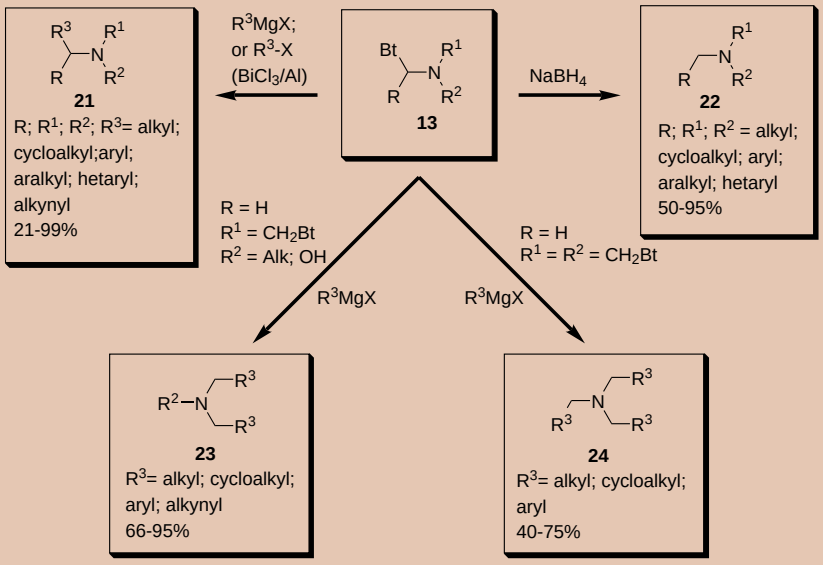
A large variety of symmetrical, partly symmetrical, and nonsymmetrical tertiary amines is particularly easily available from adducts **13** by displacement of the benzotriazole moiety with carbanions (Grignard, organolithium, organozinc reagents) or with sodium borohydride **(Scheme 7)**.[9,11-16] The use of a water-tolerant catalyst system ($BiCl_3$/Al) allows alkyl halides to be employed for the preparation of tertiary amines in aqueous media **(Scheme 7)**.[17,18]

Symmetrical tertiary amines can also be prepared in high yields using benzotriazole derivatives of type $RN(CH_2Bt)_2$ or $N(CH_2Bt)_3$ **(Scheme 7)**. Reactions of the adducts, derived from benzotriazole, formaldehyde and a primary amine or hydroxylamine, with Grignard reagents lead to tertiary amines with two identical substituents **23**. Similarly, $N(CH_2Bt)_3$ affords tertiary amines with three identical substituents **24**.[9]

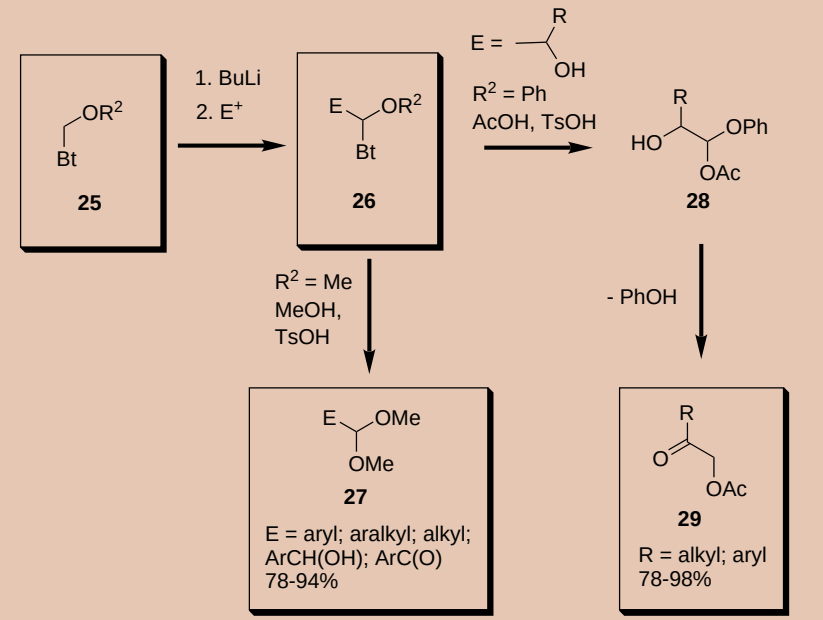
3. Benzotriazoles as Formyl and Acyl Anion Equivalents

Although many formyl and acyl anion equivalents are extensively documented, the use, in this regard, of benzotriazole derivatives of types **25 (Scheme 8)** and **30 (Scheme 9)** offers a number of advantages: convenient availability of starting materials, adequate reactivity towards electrophiles, and mild hydrolysis conditions. (Benzotriazol-1-yl)-methoxymethane **(25)** (**Scheme 8,** R^2 = Me) is a versatile formyl anion synthon: it can be efficiently converted into benzotriazolyl-containing ethers of type **26**. Upon treatment with methanol in the presence of *p*-toluenesulfonic acid, substituted 1-(α-methoxyalkyl)benzotriazoles **26** (R^2 = Me) smoothly give the corresponding dimethyl acetals **27** in good yields.[19] 1-(α-Phenoxyalkyl)benzotriazoles **(26)** (R^2 = Ph) produce the intermediate acetates **28**, which are directly converted into the appropriate acetoxymethyl ketones **29** after elimination of phenol.[20]

In general, (benzotriazol-1-yl)phenoxymethane **(25)** (R^2 = Ph) can be considered an acyl anion equivalent.[21] Two lithiation reactions, each followed by reaction with a different electrophile, produce the intermediates **30** and **31**, respectively. In turn, ethers **31** may be hydrolyzed directly to ketone derivatives **32-34 (Scheme 9)**.[21-23] The pathways of **Scheme 9** allow the efficient conversion of aldehydes to functionalized ketones; the corresponding simple ketones,



Scheme 7



Scheme 8

α-hydroxy ketones, α-amino ketones, and acylsilanes can be prepared similarly. Moreover, acylsilanes are more easily accessible by this approach[23] than by previous methods.[24,25]

When intermediate **30** contains a vinyl moiety (e.g., **35, Scheme 10**) it can be similarly converted into the substituted derivatives **36**. Treatment of **36** with Grignard reagents affords vinyl ethers **37**, which are hydrolyzed without isolation to form a series of substituted ketones **38**.[26] (Benzotriazol-1-yl)vinylethoxymethane **(35)** is an acrolein anion equivalent which allows the preparation of α,β-unsaturated ketones with additional functionality, including α-hydroxy ketones **(39)**, 1,4-diketones **(40)**, or γ-alkoxycarbonyl ketones **(41) (Scheme 10)**.[27,28]

Another formyl anion equivalent, 9-(α-benzotriazolylmethyl)carbazole **(42, Scheme 11)**, can be considered as a formaldehyde *N,N*-aminal. Lithiation at the methylene carbon of **42**, followed by treatment with various electrophiles, affords intermediates **43** smoothly. Hydrolytic removal of both heterocyclic groups leads to a convenient preparation of α-functionalized aldehydes **44**.[29-32]

The intermediates **43** also serve as acyl anion synthons in the facile preparation of α-hydroxy ketones **46**, α-keto amides **48**, and simple ketones **50** by the sequences depicted in **Scheme 11**.[31,32] The elaboration of this approach to the synthesis of β-amino ketones **54** is shown in **Scheme 12**: reaction of commercially available *N*-morpholinyl- or *N*-pyrrolidinyl-benzotriazolylmethanes **51** with 9-vinylcarbazole gave a series of addition products **52**. Introduction of an electrophile followed by hydrolysis affords amino ketones **54**.

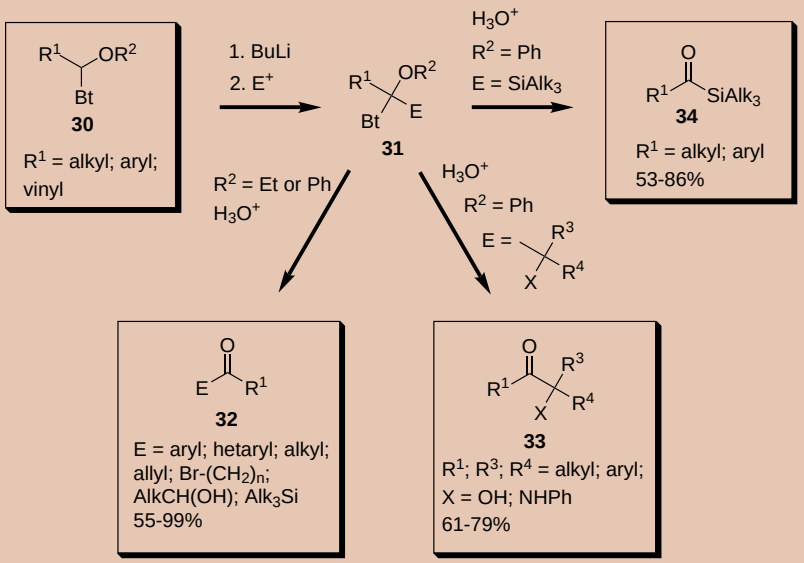
4. Benzotriazole Derivatives as Sulfonylating and Acylating Agents: Preparation of Benzenesulfonamides, Benzenesulfonates, and Various Amides

The preparation of benzenesulfonamides **56** and benzenesulfonates **57** was achieved in good yields[33] by the ready displacement of the benzotriazole moiety in 1-(benzenesulfonyl)-benzotriazole **(55, Scheme 13)**. Amination of **55** with aliphatic amines does not require the use of an extra equivalent of base, which is advantageous when compared to the analogous reaction of benzenesulfonyl chloride. The lower reactivity makes **55** more selective towards primary as compared to secondary amines, or aliphatic as compared to aromatic amines.

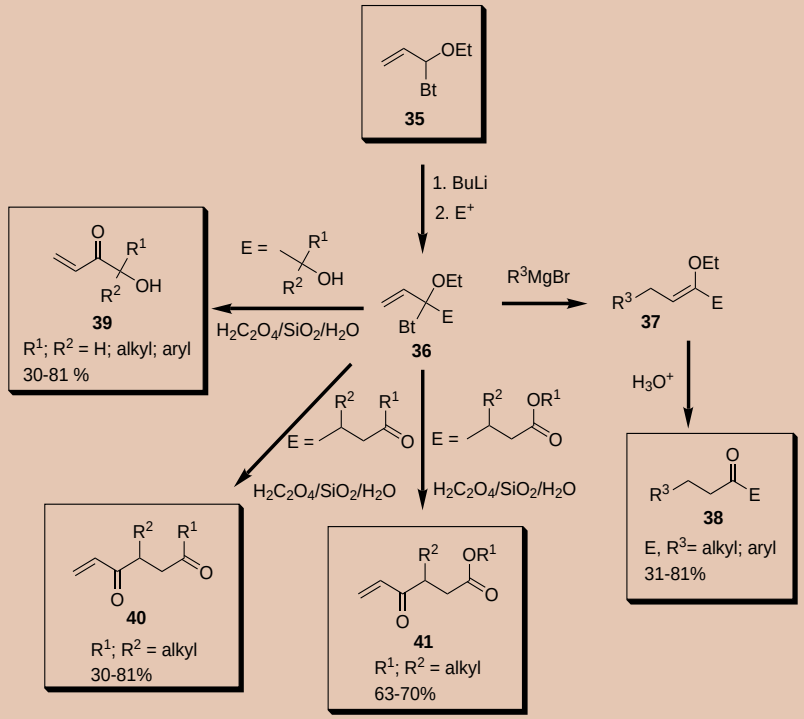
1-(*tert*-Butoxycarbonyl)benzotriazole **(58a)** and 1-(4-methoxybenzyloxycarbonyl)-benzotriazole **(58b)** are effective for the protection of amino groups in amino acids.[34] The enhanced sensitivity of these protective groups towards acids suggests the use of **58** in peptide synthesis.

5. Heterocyclization and Related Reactions Involving Benzotriazole Derivatives

Commercially available benzotriazole derivatives can be used in many transformations to form heterocycles, as illustrated by the following representative examples.



Scheme 9



Scheme 10

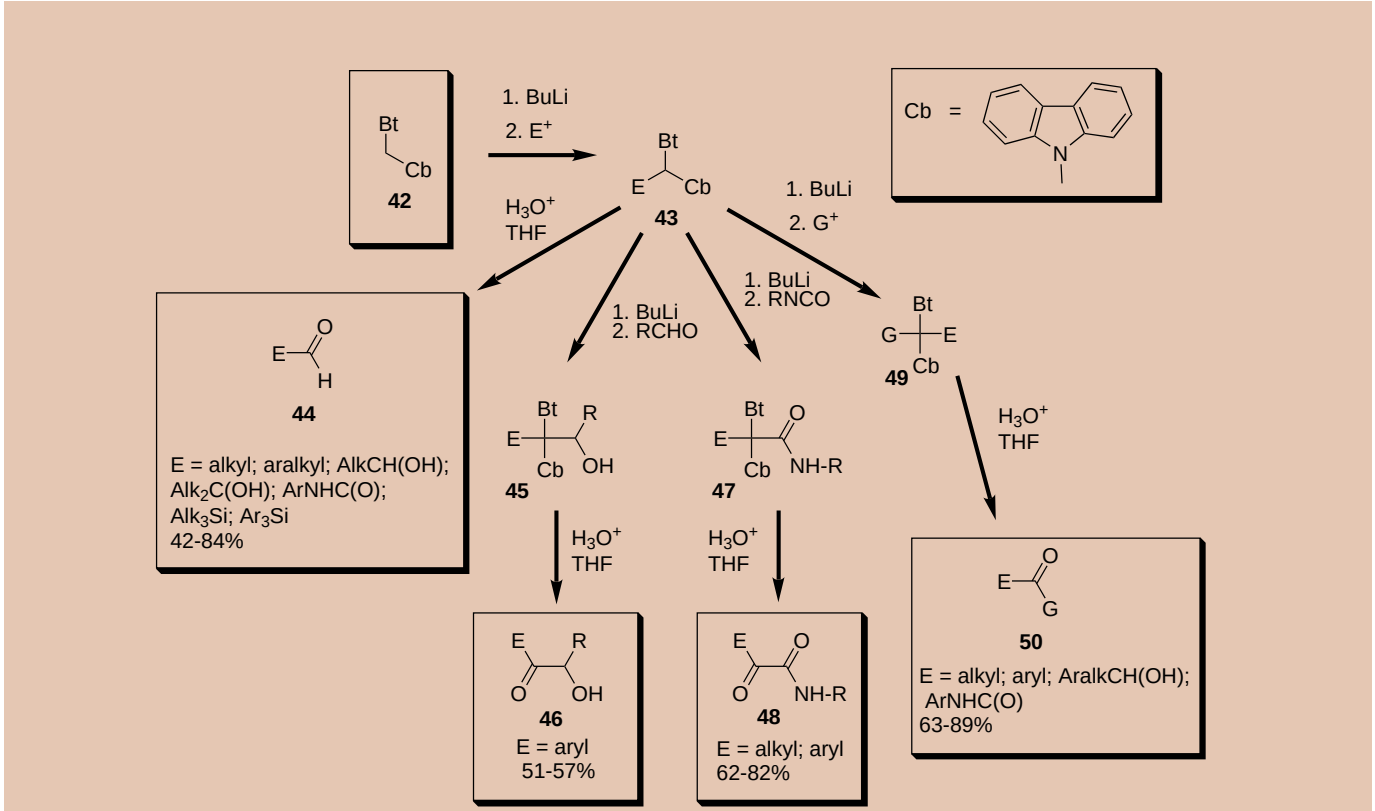
5.1. Tetrahydroquinolines

Benzotriazoles of type **61**, some of which are now available commercially (R = Me, Ph), allow *N*-phenylimmonium cations to be generated under mild conditions (*cf*. **Scheme 4**). Subsequent addition to olefins in accordance with Markovnikov's rule in regiospecific reactions leads to the preparation of several types of 2-*unsubstituted* 1,2,3,4-tetrahydroquinolines **(Schemes 14-17)**.

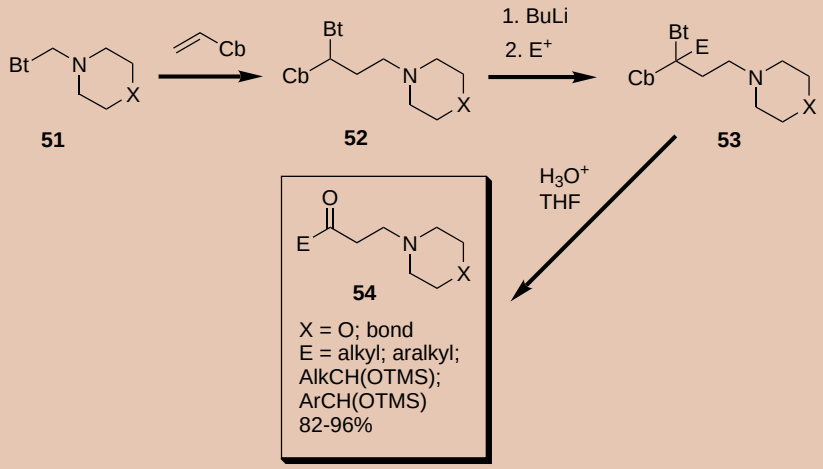
N-Methylaniline derivative **61** (R = Me) reacts with ethyl vinyl ether to form intermediate **62**. Compound **62** reacts with benzotriazole (generated as a side product in the preceding cyclization step) to form the stable intermediate **63**, which reacts with Grignard reagents to yield 4-substituted *N*-methyl-1,2,3,4-tetrahydroquinolines **64**.[35] In a similar fashion, styrene gives **64** (R = R^1 = Ph) in moderate yield in a one-pot reaction.[36] *N*-Methyl- and *N*-ethyl-1,2,3,4-tetrahydroquinolines **64** were prepared when **61** (R = Me, Et) was reacted with acetaldehyde. In contrast to the case of ethyl vinyl ether, intermediate **65** is not isolable, as the hydroxyl group is rapidly displaced by benzotriazole to give intermediates **63** (R=Me, Et). The synthetic utility of such intermediates is demonstrated through their conversion into 4-alkyl/aryl-substituted tetrahydroquinolines **64** and through the nucleophilic displacement of benzotriazole by alkoxide anion to form alkoxy derivatives **66** in good yields **(Scheme 14)**.[37]

With cyclic analogs of vinyl ethers (2,3-dihydrofuran and 2,3-dihydropyran), adducts **61** usually give a mixture of products **67** and **68 (Scheme 15)**. However, this mixture, when treated with lithium aluminum hydride in refluxing anisole, yields the sole product **69**, which contains a remote hydroxyl functionality.[35] Reaction of **61** with higher aliphatic aldehydes leads to mixtures of diastereomers **70**, which, upon treatment with lithium aluminum hydride, afford single product **71** in excellent yield **(Scheme 16)**. Moreover, the reaction of **70** with Grignard reagents is the preferred route to 3-substituted 1,2,3,4-tetrahydroquinolines **72**: The bulky phenyl group is introduced in the trans position only, whereas the methyl Grignard leads to a mixture of cis and trans products.[37] Finally, 4-amino-1,2,3,4-tetrahydroquinolines **74** can be conveniently prepared from adducts **61** and enamines: the intermediate cyclic amides **73** are reduced by lithium aluminum hydride to give **74** in 70-95% yields **(Scheme 17)**.[38]

The scope of the methods for the preparation of variously substituted



Scheme 11



Scheme 12

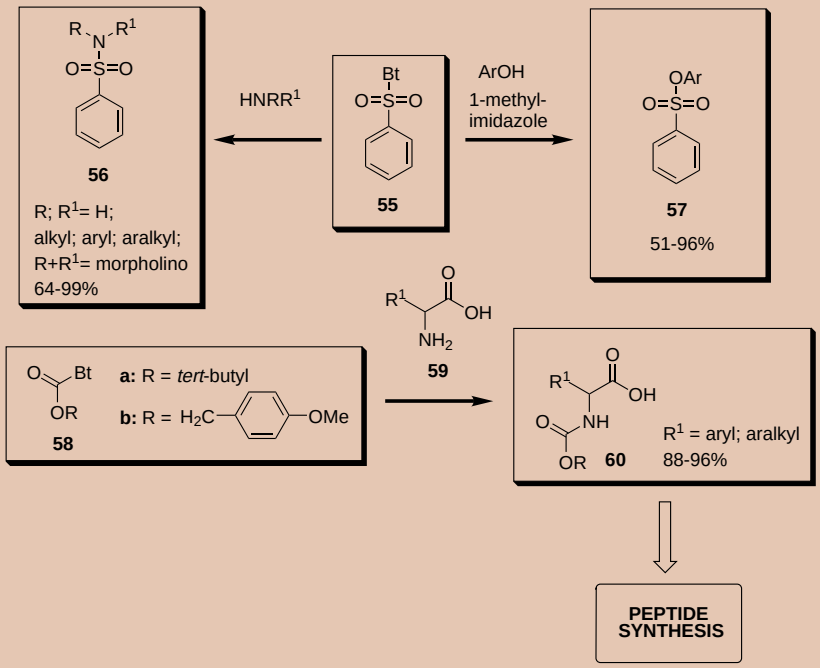
1,2,3,4-tetrahydroquinolines using the benzotriazole methodology has been outlined in a recent review.[39]

5.2. Stable Free Radicals from Benzotriazole-Containing Precursors

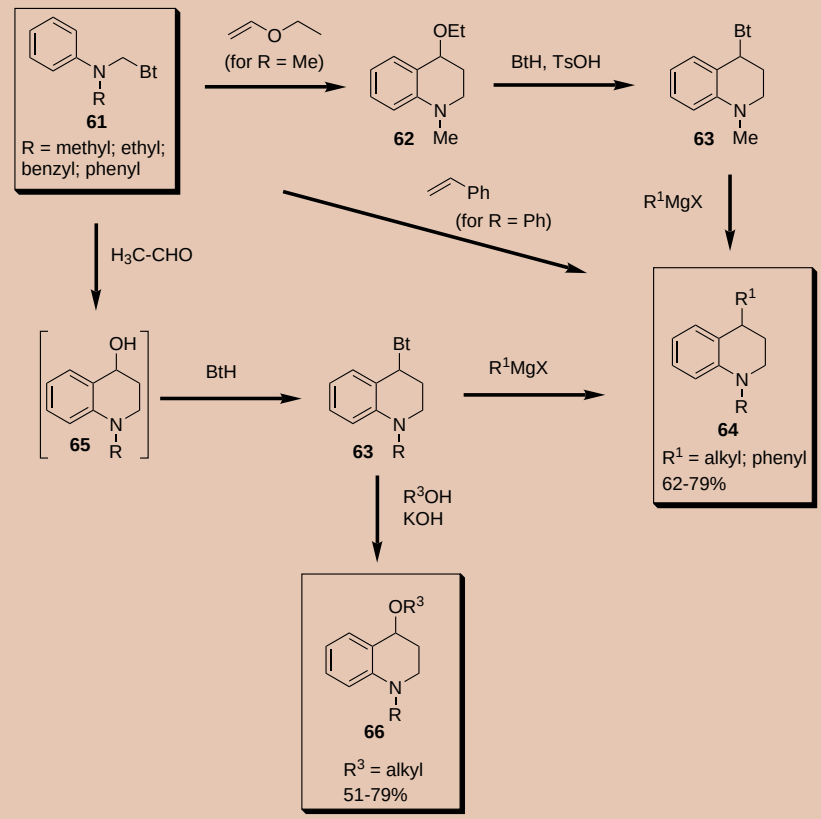
The adducts of benzotriazole, formaldehyde, and secondary amines **76** were successfully used in the preparation of 3-substituted 2,4,6-triphenylverdazyl free radicals **77** containing various di(cyclo)alkylamino moieties at the C-3 position **(Scheme 18)**.[40] The first bisverdazyl radical *N*,*N*-bonded in the C-3 positions, **77a**, was prepared from the corresponding piperazine adduct **76a**.

5.3. Betmip in the Preparation of Various Heterocycles

Displacement of benzotriazole in **5** by primary amines, followed by treatment with diaryl α-diketones, affords a series of substituted imidazoles **78**, including several phenanthro[9,10-*d*]imidazoles **(Scheme 19)**.[41] Treatment of Betmip with methylidenetriphenylphosphorane gives an intermediate **79**, which, when treated with α-dicarbonyl compounds in situ, enables the convenient



Scheme 13



Scheme 14

preparation of substituted pyrroles **80** and benzazepine **81** in good yields.[42] Phosphonate **(82)**, prepared in situ from Betmip and the lithium salt of diethyl phosphite, reacts with *o,o*-dicarbonyl compounds yielding isoquinolines **83**.[43] The majority of the heterocyclization reactions discussed can be conducted in a facile one-pot manner.

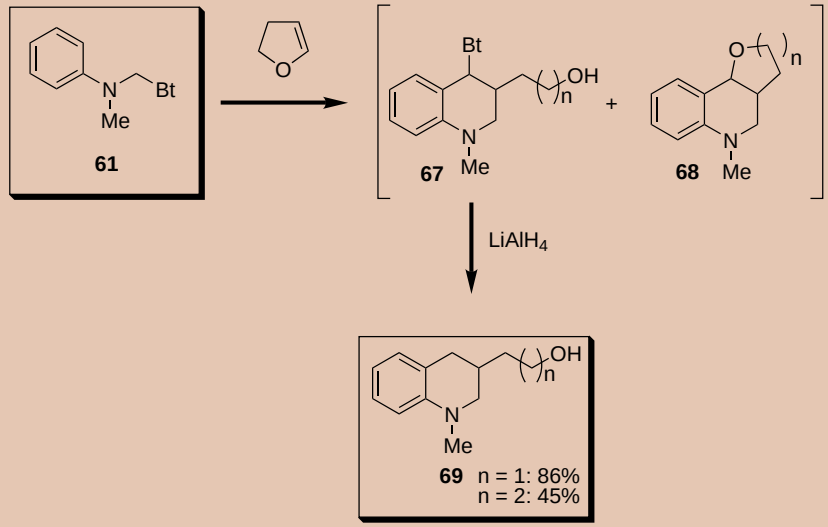
5.4. Syntheses of Nitrogen-Containing Heterocycles Involving 1-(Cyanomethyl) benzotriazole[44-46]

1,3-Cycloaddition of sodium azide and **84** affords tetrazole **85** bearing a benzotriazolylmethyl functionality. The latter is subsequently alkylated and treated with Grignard reagents to afford 2-aryl-2-(tetrazol-5-yl)propanes **87** in moderate yields **(Scheme 20)**.[45]

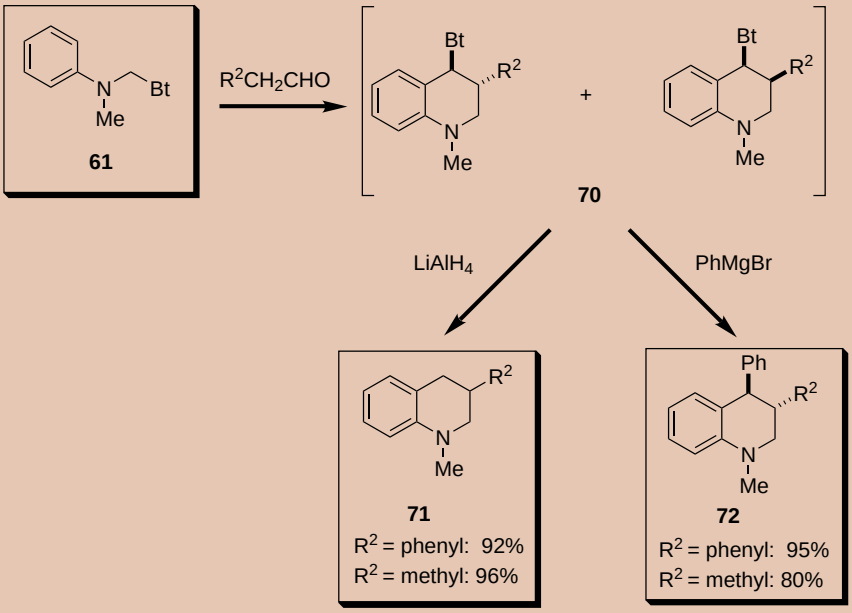
Conversion of nitrile **84** into amide **88** was achieved by treatment with hydrogen peroxide; however, this amide can be prepared in a more convenient way[46] and will soon be available commercially. Its conversion into thioamide **(89)**, followed by condensation with bromoacetophenone (Hantzsch thiazole synthesis) affords the corresponding 2-(benzotriazol-1-ylmethyl)thiazoles **90**. These were successfully used in the preparations of 2-[(trisubstituted)methyl]-thiazoles **92**, and furan- and thiophene-derivatized thiazoles **93** in good yields.[44] While reaction of (cyanomethyl)benzotriazole with chalcones under basic conditions (secondary amines) affords a series of 2-disubstituted-amino-4,6-diarylpyridines **94**, the use of a stronger base (NaOH) leads to 4,6-diarylpyrid-2-ones **95** in moderate yields. This reaction gave much better results when amide **88** was employed as the reagent: pyridones **95** were obtained in moderate to excellent yields.[46] This new method allows the preparation of 3-*unsubstituted* pyrid-2-ones in a simple and efficient fashion.

6. Conclusion

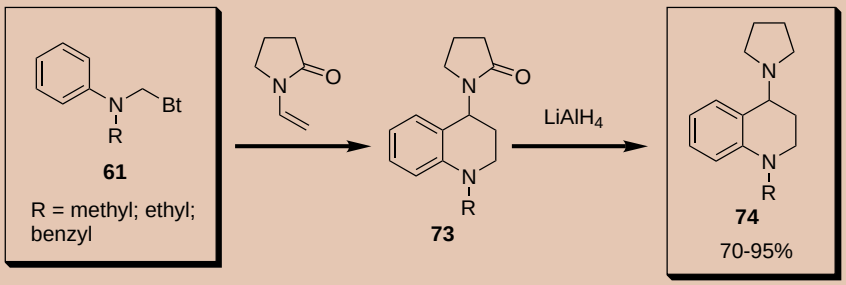
Most of the benzotriazole derivatives discussed in this review are either already available or will be available in the near future from Aldrich Chemical Co. Their selection for inclusion in this review was based primarily on their versatile character which allows the preparation of a large variety of organic compounds. The present review was not designed to be comprehensive, but rather to summarize some of the major recent trends in the rapidly developing field of benzotriazole-based synthetic methodology.



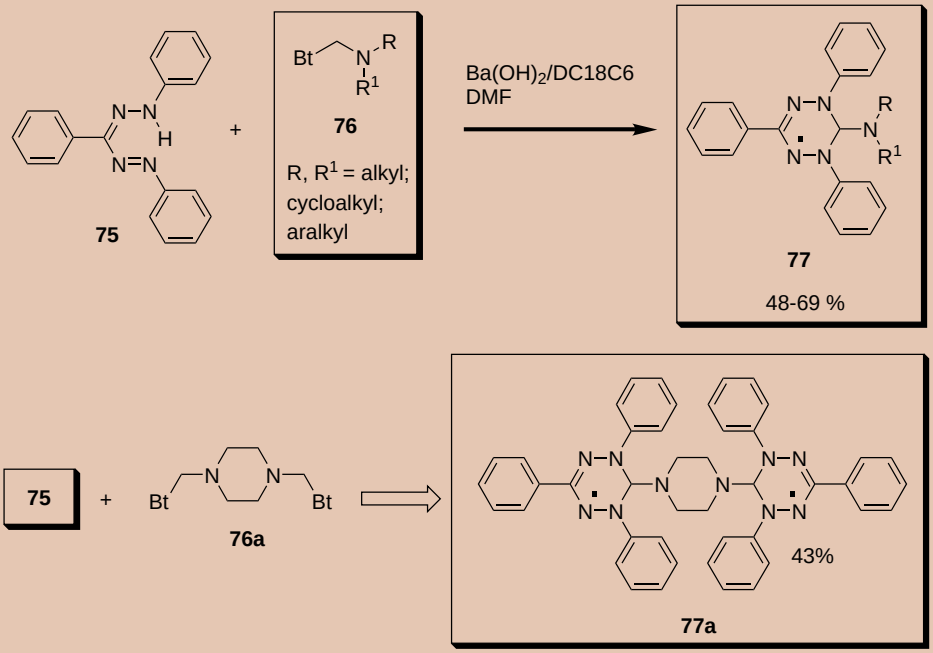
Scheme 15



Scheme 16

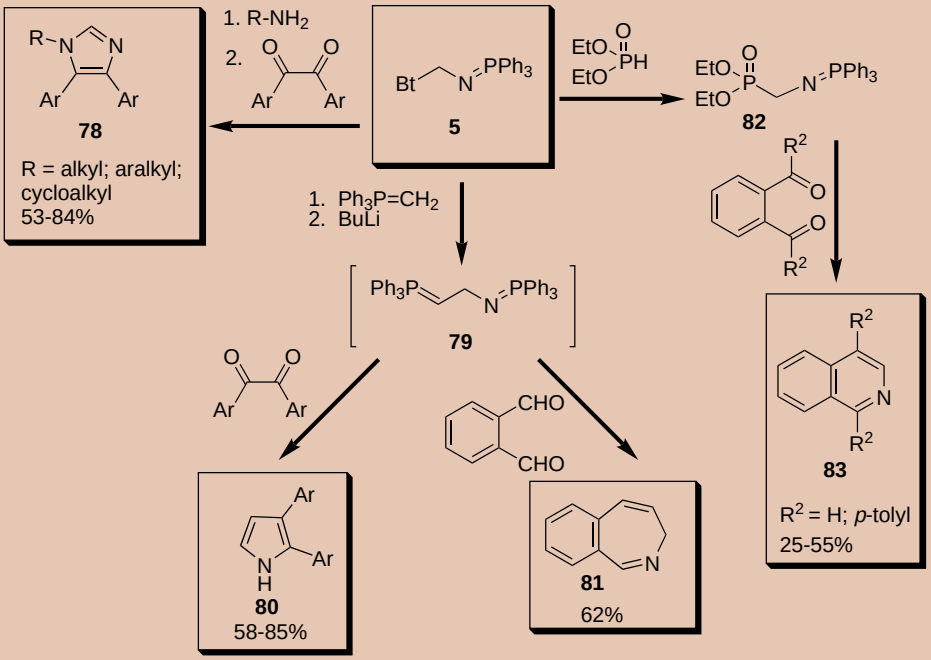


Scheme 17

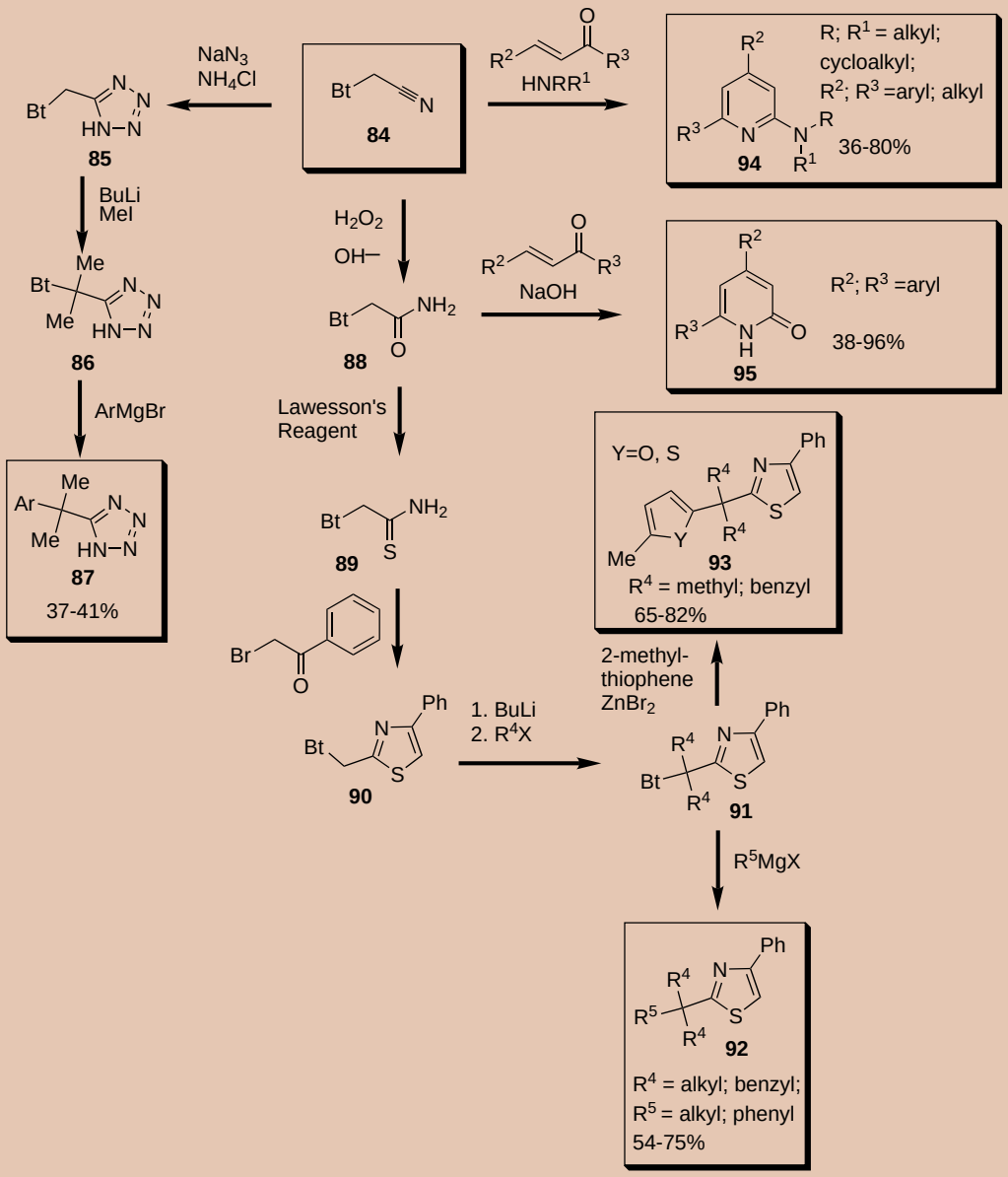


DC18C6 = *cis*-Dicyclohexano-18-crown-6

Scheme 18



Scheme 19



Scheme 20

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About the Authors

Alan Katritzky was born in England and educated at Oxford. He was a lecturer at Cambridge University before moving to Norwich in 1962 as Founder-Dean of the School of Chemical Sciences at the new University of East Anglia. Since 1980 he has been Kenan Professor and Director of the Center for Heterocyclic Compounds at the University of Florida. His research interests encompass much of heterocyclic chemistry together with synthetic methods, physical organic chemistry, and quantitative structure–property relationships. He has traveled widely and published extensively. Further details of his current activities and news of his group and ex-group members may be found at his home page, http://ufark12.chem.ufl.edu/.

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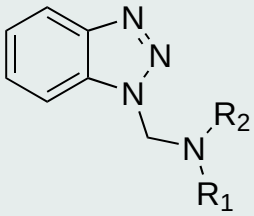
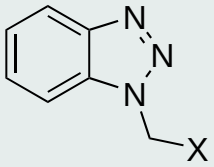
(Aminomethyl)benzotriazoles



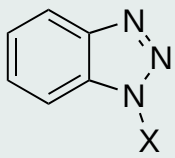
R_1 = H; R_2 = Ph	**46,561-5**	***N*-Phenylbenzotriazolemethanamine**, mixture of Bt1 and Bt2 isomers
R_1,R_2 = $(CH_2)_2O(CH_2)_2$	**46,750-2**	**(4-Morpholinylmethyl)benzotriazole**, 97%, mixture of Bt1 and Bt2 isomers
R_1 = R_2 = Me	**46,560-7**	***N*,*N*-Dimethylbenzotriazolemethanamine**, mixture of Bt1 and Bt2 isomers

Other Methyl Benzotriazoles



X = OH	**41,023-3**	**1*H*-Benzotriazole-1-methanol**, 98%
X = OMe	**43,802-2**	**1-(Methoxymethyl)-1*H*-benzotriazole**, 99%
X = OPh	**46,572-0**	**1-(Phenoxymethyl)-1*H*-benzotriazole**, 97%
X = Cl	**44,005-1**	**1-(Chloromethyl)-1*H*-benzotriazole**, 98%

Other Benzotriazoles

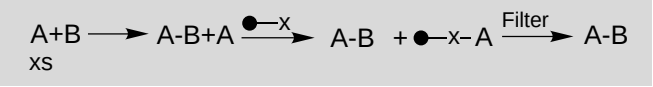


X = H	**B1140-0**	**Benzotriazole**, 99%
X = SO_2Ph	**46,573-9**	**1-(Phenylsulfonyl)-1*H*-benzotriazole**, 97%
X = CH_2NC	**36,799-0**	**1*H*-Benzotriazol-1-ylmethyl isocyanide**, 96%
X = CHO	**44,691-2**	**1*H*-Benzotriazole-1-carboxaldehyde**, 90%
X = $SiMe_3$	**42,509-5**	**1-(Trimethylsilyl)-1*H*-benzotriazole**, 98%

Scavenger Resins in Combinatorial Chemistry

Combinatorial chemistry has become an increasingly valuable tool for drug discovery.[1] The majority of the work in this area has concentrated on solid-phase reactions.[1] Although there have been instances of solution-phase libraries,[2] their widespread use has been limited by the ease of purification of the reaction mixtures at each step.

Within the last few years, the use of scavenger or quench reagents for solution-phase synthesis has been reported.[3] The theory behind this use is that the scavenger/quench resins contain active groups that mimic the limiting reagent(s) in the reaction. Upon completion of the reaction, the resin is added to the reaction mixture to bind any of the unreacted second reagent. Filtration of the resulting resin-bound material yields a relatively pure product.

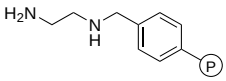
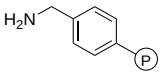
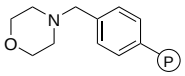
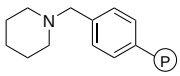
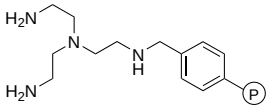
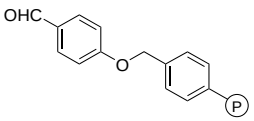
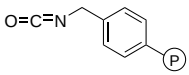
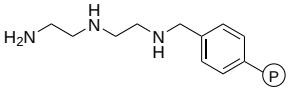


There are many advantages to using scavenger reagents. Since the reactions are run in solution, there is no need to invest time and effort in transferring and optimizing the reactions for use in the solid phase. Also, more than one scavenger resin can be used concurrently to remove multiple reagents and/or reaction byproducts, thus significantly easing reaction workup. By choosing the appropriate scavenger resin, one can eliminate the potential need for large excesses of expensive reagents. Most scavenger resins can be synthesized from commercially available materials; however, a good number of them are now commercially available. (Please see the Aldrich catalog listings provided in the table below.)

The choice of scavenger resin strongly depends on the type of reagent or byproduct that needs to be removed from the reaction mixture. Listed in the table below are some of the more common resins and the functional groups they react with.

Some of the compound libraries synthesized by the scavenger/quench resin method are ureas,[3a,3b] thioureas,[3a] amides,[3b,3d] sulfonamides,[3a,3b,3d] carbamates,[3b] benzoxazinones,[4] and dihydropyridones.[5]

For additional information, including unit sizes and prices, please contact your local Sigma-Aldrich office.

Polystyrene Resin	Structure	Reacts With...
47,209-3 **Ethylenediamine, polymer-bound**		RCOCl, RSO_2Cl, RNCS, RNCO, H^+
47,366-9, 2 mmol N/g **47,367-7,** 4 mmol N/g **Poly(styrene-*co*-divinylbenzene), aminomethylated**[3a]		RCOCl, RSO_2Cl, RNCS, RNCO, H^+
49,381-3 **Morpholine, polymer-bound**[5]		H^+
49,461-5 **Piperidine, polymer-bound**		H^+
47,210-7 **Tris(2-aminoethyl)amine, polymer-bound**[3a,5]		RCOCl, RSO_2Cl, RNCS, RNCO, H^+
47,208-5 **4-Benzyloxybenzaldehyde, polymer-bound**[5]		$RNHNH_2$, NH_2OR, RNH_2
47,368-5 **Isocyanate, polymer-bound**[3a,3b]		RNH_2
47,978-0 **Diethylenetriamine, polymer-bound**[3c,3d]		RCHO, RCO_2H, RCOCl, $(RCO)_2O$

References: (1) Review articles: (a) Hermkens, P.H.H. et al. *Tetrahedron* **1996**, *52*, 4527. (b) Idem *ibid.* **1997**, *53*, 5643. (c) Balkenhohl, F. et al. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288. (d) Thompson, L.A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555. (e) Terrett, N.K. et al. *Tetrahedron* **1995**, *51*, 8135. (2) See the solution-phase selections in refs. 1c, 1d, & 1e. (3) (a) Booth, R. J.; Hodges, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 4882. (b) Kaldor, S.W. et al. *Tetrahedron Lett.* **1996**, *37*, 7193. (c) Parlow, J.J. et al. *J. Org. Chem.* **1997**, *62*, 5908. (d) Flynn, D.L. et al. *J. Am. Chem. Soc.* **1997**, *119*, 4874. (4) Parlow, J.J.; Flynn, D.L. *Tetrahedron* **1998,** *54*, 4013. (5) Cresswell, M.W. et al. *ibid.* **1998**, *54*, 3983.

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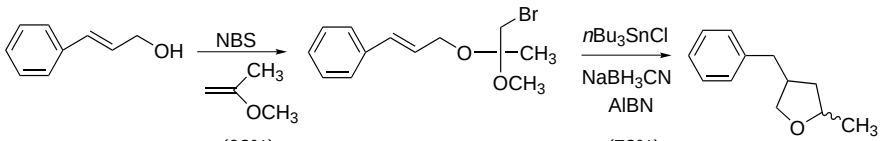
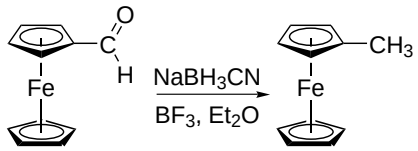
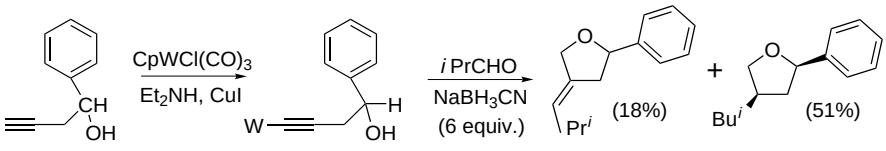
Alcohols are converted to cyclic ethers via bromoketals.
Srikrishna, A. et al. *Tetrahedron* **1997**, *53*, 10479.



Alkyl halides such as 1-iodoadamantane are converted to the corresponding alcohols by a sonochemical, aerobic process.[1] Sodium cyanoborohydride can potentially be used in the large-scale preparation of functionalized alkylferrocenes from acylferrocenes.[2]
(1) Sawamura, M. et al. *Chem. Lett.* **1997**, *8*, 705. (2) Bhattacharyya, S. *J. Chem. Soc., Dalton Trans.* **1996**, *24*, 4617.



Construction of furan and pyran derivatives via tungsten-carbene complexes.
Liang, K-W. et al. *J. Am. Chem. Soc.* **1997**, *119*, 4404.



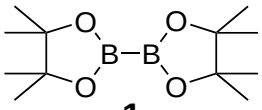
Biotin labelling of oligogalacturonides.
Ridley, B.L. et al. *Anal. Biochem.* **1997**, *249*, 10.

Stabilization of fluorescent-labelled DNA and RNA.
Proudnikov, D.; Mirzabelkov, A. *Nucleic Acids Res.* **1996**, *24*, 4535.

15,615-9 **Sodium cyanoborohydride,** 95%
29,681-3 **Sodium cyanoborohydride,** 1.0*M* solution in tetrahydrofuran
29,694-5 **Sodium cyanoborohydride,** 5.0*M* solution in aqueous ~1*M* sodium hydroxide

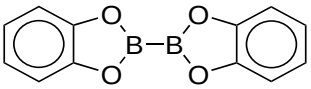
Diboron Esters

The cross-coupling of aryl electrophiles and arylboronic acids or esters to give biaryl compounds, commonly referred to as Suzuki coupling, has become a valuable tool for the organic chemist.[1-4] The popularity of the Suzuki coupling reaction has created a need for a variety of substituted arylboronic acids and esters. The classical route to arylboronic acids involves the low-temperature reaction of trialkyl borates, $B(OR)_3$, with Grignard or aryllithium reagents.[5] However, one drawback of this route is that the highly basic conditions present in the reaction mixture severely limit the choice of substituents on the phenyl ring.



1

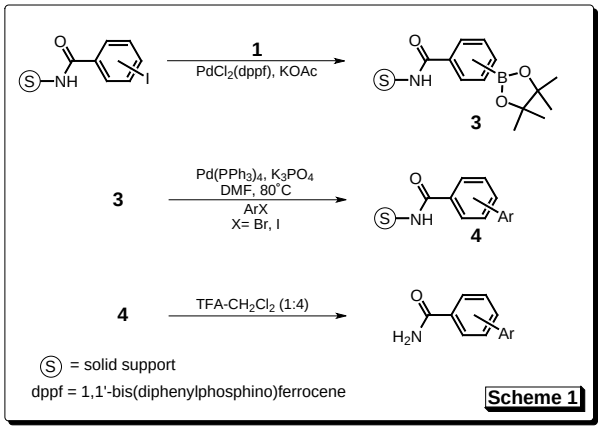
Miyaura has shown that the diboron ester bis(pinacolato)diboron **(1)** reacts with aryl halides in the presence of palladium catalysts to give arylboronic esters, which are readily converted to arylboronic acids.[6] The mild reaction conditions present for this route and the subsequent Suzuki coupling reaction allow for a wide choice of functionality on the aryl rings. Shown here are some applications for the reagents bis(pinacolato)diboron **(1)** and bis(catecholato)diboron **(2)**. For a list of arylboronic acids available from Aldrich, please visit Aldrich Organometallics on the Web at **www.sial.com/aldrich/organometallics/**.



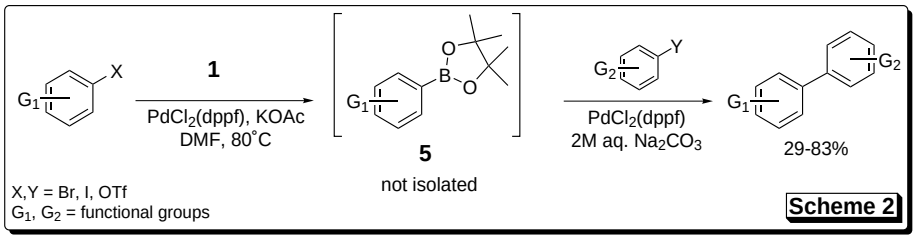
2

Synthesis of Arylboronic Acids and Esters

Reagents **1** and **2** react with a variety of substituted aryl halides[6] and triflates[7] to give arylboronic acids and esters that contain functional groups such as cyano, ester, carbonyl, and nitro groups. The wide variety of arylboronic acids available via **1** and **2** makes this class of compounds suitable for solid-phase combinatorial studies (Scheme 1).[8,9] Arylboronic acids also show biological activity[10-13] and possess molecular recognition properties.[14-18]



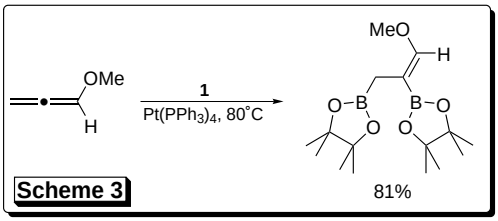
Scheme 1



Scheme 2

Recent uses of **1** have focused on the *in situ* generation of unsymmetrical biaryls via arylboronic ester intermediate **5** which need not be isolated (Scheme 2).[19]

Diboration of Unsaturated Compounds



Scheme 3

Alkenes,[20,21] alkynes,[22] and allenes[23] (Scheme 3) undergo diboration reactions with reagent **1** in the presence of transition-metal catalysts. Reagent **2** undergoes similar reactions with olefins,[24] and is used extensively in mechanistic studies that have shown that the B-B bond undergoes oxidative addition to give bis(boryl) metal complexes.[25]

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

References: (1) Stanforth, S.P. *Tetrahedron* **1998**, *54*, 263. (2) Saito, S. et al. *Tetrahedron Lett.* **1996**, *37*, 2993. (3) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (4) Watanabe, T. et al. *Synlett* **1992**, 207. (5) Brown, H. C. *Organic Syntheses via Boranes*; Wiley-Interscience: New York, NY, 1975; Vol. 1 (Aldrich Catalog No. **Z40,094-7**). (6) Ishiyama, T. et al. *J. Org. Chem.* **1995**, *60*, 7508. (7) Ishiyama, T. et al. *Tetrahedron Lett.* **1997**, *38*, 3447. (8) Piettre, S.R.; Baltzer, S. *ibid.* **1997**, *38*, 1197. (9) Brown, S. D.; Armstrong, R.W. *J. Am. Chem. Soc.* **1996**, *118*, 6331. (10) Reetz, M.T. et al. *ibid.* **1994**, *116*, 11588. (11) Paugam, M-F. et al. *ibid.* **1994**, *116*, 11203. (12) Groziak, M.P. et al. *ibid.* **1994**, *116*, 7597. (13) Hamachi, I. et al. *ibid.* **1994**, *116*, 7437. (14) James, T.D. et al. *Chem. Commun.* **1996**, 281. (15) London, R.E.; Gabel, S.A. *J. Am. Chem. Soc.* **1994**, *116*, 2562. (16) Idem *ibid.* **1994**, *116*, 2570. (17) Sandanayake, K.R.A.S. et al. *J. Chem. Soc., Chem. Commun.* **1994**, 1621. (18) Sandanayake, K.R.A.S.; Shinkai, S. *ibid.* **1994**, 1083. (19) Giroux, A. et al. *Tetrahedron Lett.* **1997**, *38*, 3841. (20) Ishiyama, T. et al. *Chem. Commun.* **1996**, 2073. (21) Idem *ibid.* **1997**, 689. (22) Ishiyama, T. et al. *Organometallics* **1996**, *15*, 713. (23) Ishiyama, T. et al. *Tetrahedron Lett.* **1998**, *39*, 2357. (24) Iverson, C.N.; Smith, M.R., III *Organometallics* **1997**, *16*, 2757. (25) For rhodium, see: Marder, T.B. et al. *Chem. Commun.* **1997**, 53.

Manganese-Based Organic and Bioinorganic Transformations

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Northridge, CA 91330-8262

Outline

1. Introduction

Two major reasons prompted me to write this review, which highlights the important aspects of manganese-based organic and bioinorganic reactions. The first reason is the necessity to bring together and analyze the major achievements in the research field blossoming at the interface of organic, inorganic, organometallic, coordination, and biological chemistry. Surveys of manganese(III)-mediated radical organic reactions have appeared in the past seven years;[1-4] however, none of these presents the broader perspective of the subject while emphasizing the significance and stature of this transition metal in modern chemistry and biology. Major breakthroughs have occurred in the areas of selective radical C-C bond formation, asymmetric epoxidation of double bonds, catalytic oxidation of alkanes, design and synthesis of artificial assemblies possessing enzymatic activities, as well as in the total synthesis of natural products. In addition, the central role played by manganese species in biological redox processes[5,6] further underscores the potential of this subject to attract an ever-increasing number of investigators as evidenced by about 500 research publications a year in chemical periodicals alone!

The second reason is the strong feeling that I have—after working in this field for two decades[2,4]—that, despite its remarkable contribution to organic synthesis, manganese chemistry has been generally overlooked by industry. One of the reasons for this neglect may have been the need for stoichiometric quantities of manganese complexes in most of the reactions, which would have produced large amounts of chemical waste. While *"manganophobia"* has some reasons to exist, developments that have occurred in this field in the last decade have made the use of manganese compounds much more environmentally benign. In particular, low-valent manganese compounds may be oxidized by standard means to regenerate the active species; moreover, the catalytic versions of some key transformations have been successfully elaborated.[7,8]

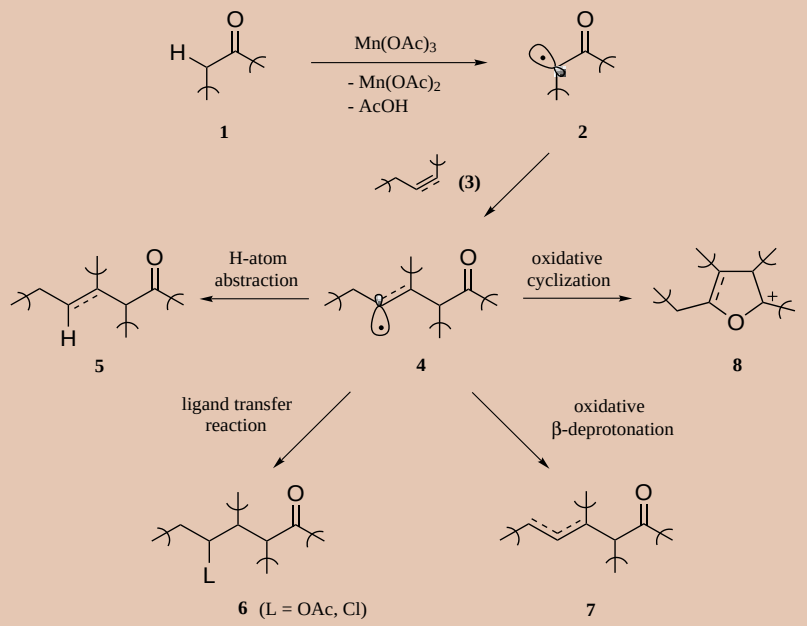
Thus, one of the major goals of this review is to attract the attention of our colleagues from industry to this field by illustrating the maturity of manganese chemistry, its viability, and its remarkable accomplishments. The review covers the pertinent literature through February 1998. Since its primary goal is demonstrating the breadth of manganese chemistry and pointing out some of its most notable features, the literature sources are selectively covered.

2. Manganese(III)-Mediated Radical Carbon-Carbon Bond Formation

2.1 Mechanistic Aspect

A one-electron oxidation of carbonyl compounds constitutes an initial step in manganese(III)-mediated radical reactions.[4] Its rate is directly proportional to both enolizability and acidity,[9,10] with reactions reaching completion in 1 minute to several days at 0°–140 °C. The essential molecular moieties in proradical **1** are an activating carbonyl or carbonyl-like group and an α-disposed C-H bond (**Scheme 1**). Although a direct ESR observation of radicals **2** is still lacking, their transiency is well substantiated by several lines of evidence. Among these, the most unambiguous ones include the isolation

of the corresponding C-C[11-15] and C-O[13] dimers, the stereomutation of cis double bonds,[16] and the trapping of intermediate radicals with molecular oxygen.[17] The radical addition across multiple bonds is governed by steric and electronic effects, and, at this stage of development, can be comfortably predicted in most of the cases. Since α-oxo- and α,α-dioxoalkyl radicals are ambiphilic and electrophilic,[18] respectively, the typical "matching" substrates are those with electron-rich unsaturated moieties. Not only electronic, but also steric requirements are involved since the ability of substrate **3** to "enter" the transition metal's ligand sphere is vital for the initiation step. It is well documented that introducing unsaturated compounds increases the rate of oxidation substantially, thus accelerating the overall process.[13,19,20] It remains a dream of "manganese chemists" to isolate and structurally characterize a reactive intermediate with both carbonyl and unsaturated molecules bound to the metal. Derived from the addition step, adduct radicals **4** are the central species whose relative stabilities, conformational and configurational rigidities, and transformation pathways determine the selectivity and synthetic outcome of the reaction. While H-atom abstraction from carbonyl compounds



Scheme 1. Generic Representation of the Interaction of Carbonyl Compounds with Unsaturated Substrates.

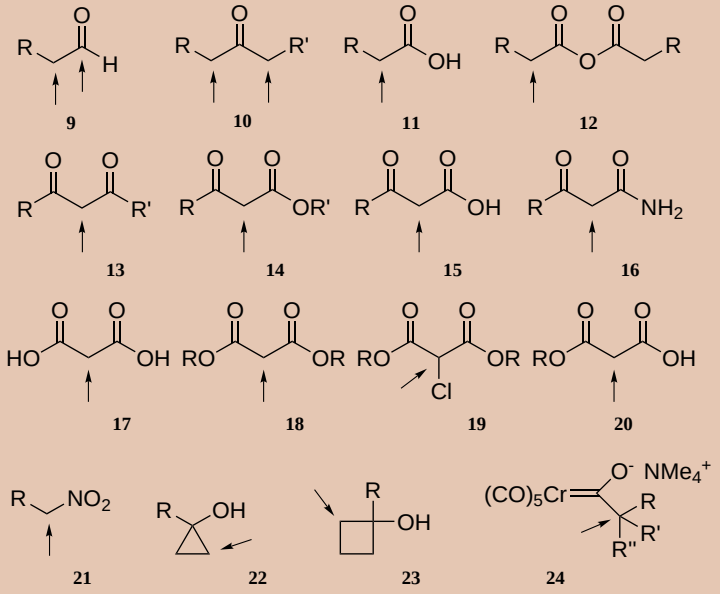


Chart 1. The Regioselectivity of Radical Generation (arrows indicate the locations of unpaired electrons in educt radicals).

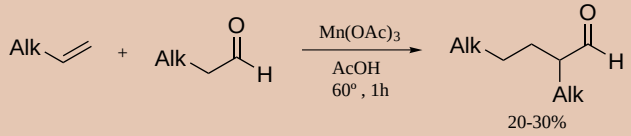
or solvents is reminiscent of classical radical reactions,[21] introducing a transition metal in a higher oxidation state alters the purely "radical nature" of the process. In particular, oxidation of adduct radicals **4** gives rise to the corresponding cations and cationoid species and, subsequently, to the "ionic" transformation paths, such as ligand transfer reactions, β-deprotonations, and cyclizations upon the carbonyl group. Thus, "reduced" species **5** along with "oxidized" species **6-8** represent the typical spectrum of generally isolable organic products. For a given reaction, the chemoselectivity can be improved[4] by using cupric acetate, a powerful oxidizer of alkyl radicals,[22] as a co-oxidant. Scheme 1 represents a simplified model for manganese(III)-mediated radical reactions. While the focus of this review does not allow for an in-depth discussion of the intimate mechanistic details, it should be mentioned that the mechanism is far from being fully understood and multiple "white spots" are still awaiting clarification.

The selectivity in manganese chemistry is a multifaceted issue dealing with various intermediate steps of the reaction. Some of these facets are: (a) regioselectivity of the initiation step that generates radicals **2**; (b) regio- and chemoselectivities of the addition step as determined by the stereoelectronic characteristics of radical species **2** and unsaturated recipients **3**; and (c) chemo-, regio-, and stereoselectivities of the transformations of adduct radicals **4** to end products. The first aspect, regioselectivity of the initiation step, depends upon the number of unequivalent C-H bonds located alpha to the activating groups and upon the experimental conditions used. The diversity of organic molecules that can act as proradicals is exhibited in **Chart 1**; the arrows indicate the positions of the unpaired electrons in the corresponding radicals. The scope of the reaction has been expanded and its synthetic power maximized by using not only aldehydes **9**, ketones **10**, monocarboxylic acids **11** and their anhydrides **12**, but also β-dicarbonyl compounds, such as β-diketones **13**, β-keto esters **14**, β-keto carboxylic acids **15** and amides **16**, and malonic acid and its derivatives **17-20**[4]. Nitroalkylation with proradicals **21** represents an isolated case with a carbonyl-like activating group.[20,23] Chronologically, the most recent types of proradicals are cycloalkanols **22**[24] and **23**,[25] and chromium carbene complexes **24**.[26]

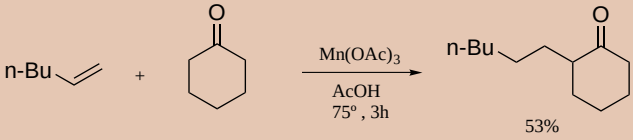
2.2 Intermolecular Reactions

Since 1968, manganese(III)-mediated intermolecular reactions have been extensively developed and currently constitute a powerful asset for modern organic synthesis.[12,27] A variety of classes of unsaturated organic compounds has been used as substrates in radical addition, substitution, conjugate addition, tandem cyclization and polycyclization reactions. The regio- and chemoselectivity of the addition step (**Scheme 1**) are determined by steric and electronic parameters of the educt radical **2** and unsaturated component **3**, and by the relative stabilities of the isomeric adduct radicals **4**. In the vast majority of experimental protocols, manganese(III) acetate has been used in glacial acetic acid as a solvent.[4] Although ethanol,[25,28,29] dimethylformamide,[24,26,30] and benzene[31] are well suited for some types of reactions, their utilization remains rather limited. Recently discovered manganese(III) tris(2-pyridinecarboxylate) has become an important addition to a family of radical initiators capable of oxidizing the *noncarbonyl*

α-Alkylation of Aldehydes and Ketones

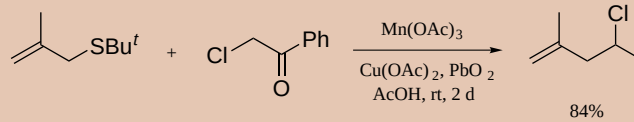


eq 1[32]

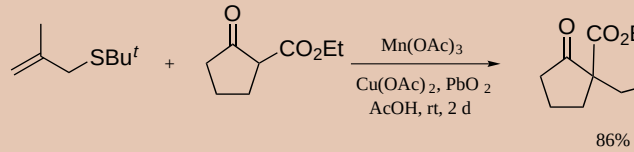


eq 2[32]

Radical Allylation of Mono- and Dicarbonyl Compounds

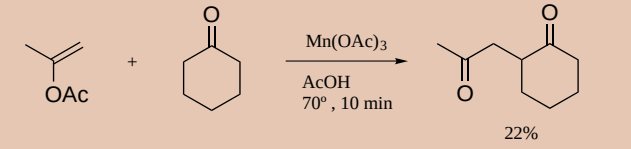


eq 3[33]



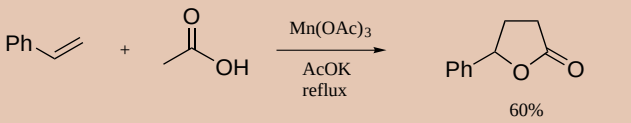
eq 4[33]

Radical Acetonylation—Synthesis of 1,4-Diketones

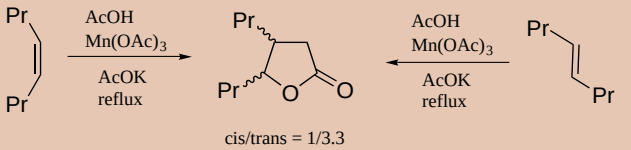


eq 5[34a]

Lactonization of Alkenes—Synthesis of Butyrolactones



eq 6[27]



eq 7[10]

types of proradicals, such as cyclopropanols,[24,30] cyclobutanols,[25] and chromium(0) complexes.[26] The following intermolecular reactions have been selected for discussion on the basis of their chemo-, regio-, and stereoselectivity; feasibility; predictability; and the ease of isolation of the products.

Alkylation of aldehydes and ketones with alkenes generally lacks selectivity at the initiation step (acyl and α-formyl alkyl radicals are formed) and during the conversion of the corresponding adduct radicals to end products.[4] The optimization of experimental conditions (concentration of metal oxidant, temperature) has led to α-alkylated aldehydes and ketones chemoselectively and in low to moderate yields (**eq 1**, **2**).[32] An attractive extension of the parent reaction is the allylation of ketones and β-dicarbonyl compounds with allyl sulfides (**eq 3**, **4**).[33] While the exact role of co-oxidants cupric acetate and lead(IV) oxide is not fully understood, the reaction proceeds readily affording α-allyl derivatives in moderate to good yields (43-86%). 1,4-Diketones, an important class of organic compounds with many practical applications, have become more accessible by the direct radical addition of ketones to enol acetates.[34] Although yields are relatively low (20-30%), the reaction works well both for acyclic and cyclic ketones, and, if fully optimized, it may become a viable synthetic method (**eq 5**).

The lactone-forming reaction of alkenes with carboxylic acids has been widely recognized outside the "manganese community". First discovered in 1968,[27] the reaction has been thoroughly studied to resolve major mechanistic issues,[10,35] expand its scope, and demonstrate its applicability for the construction of biologically relevant organic molecules (vide infra). In particular, the interaction of acetic acid with mono- and disubstituted alkenes produces the corresponding butyrolactones with a yield of 16-74% (**eq 6**).[27,36] In the case of acyclic alkenes, the stereoselectivity is compromised by internal rotation taking place in the adduct radicals.[10,37] Thus, *cis*- and *trans*-4-octenes give rise to the same cis/trans ratio of the corresponding annulation products—with the trans butyrolactone being favored **(eq 7)**.[10] This behavior is also observed with dimethyl maleate and dimethyl fumarate.[37] Cycloalkenes give varying stereochemical results that are dependent on ring size: while the cis-fused bicyclic lactone is preferentially formed in the case of cyclohexene (cis/trans 5.4:1), the opposite is true for cyclooctene (cis/trans 1:2.4).[10] The lactone annulation of 1,3-alkadienes has become a key step in the large-scale synthesis of sorbic acid, a food preservative,[38] and in the preparation of pyrethroids, environmentally benign agents

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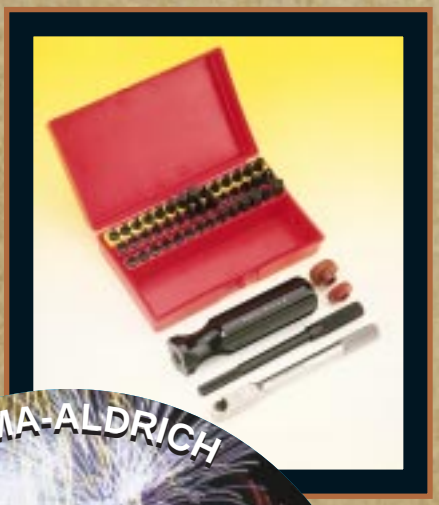

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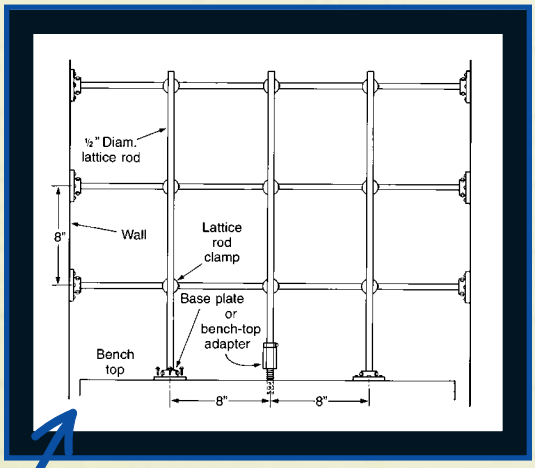

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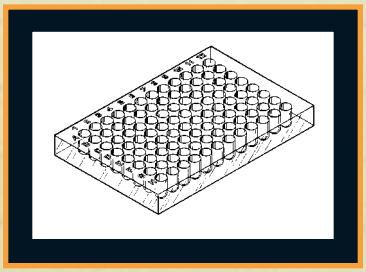

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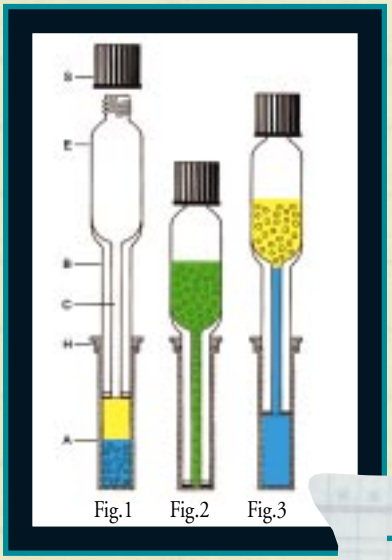

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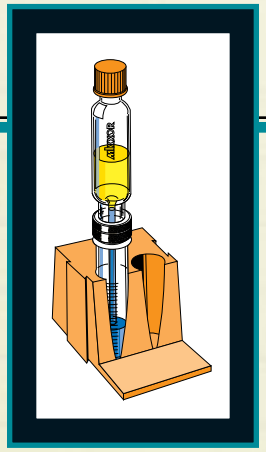

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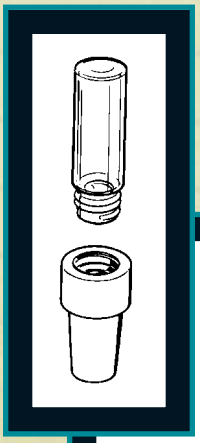

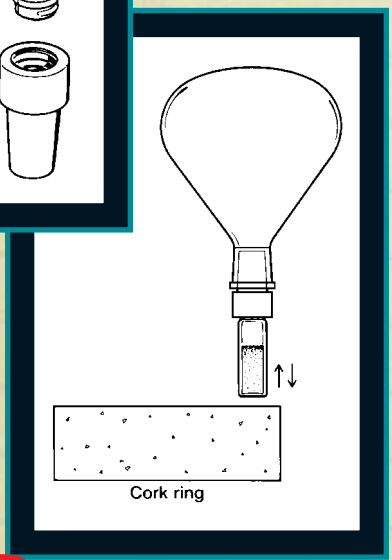

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	20-400	Z40,657-0	
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Acetone	Z41,007-1		
Ethyl alcohol	Z41,009-8		
Methanol	Z41,010-1		
Isopropanol	Z41,012-8		
Distilled water	Z41,013-6		
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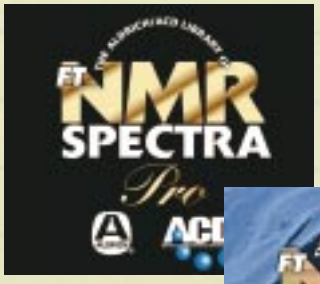

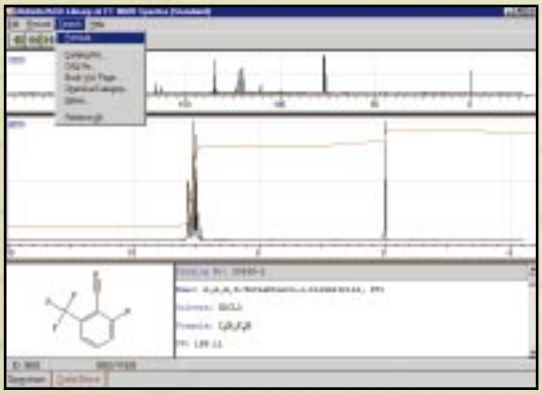

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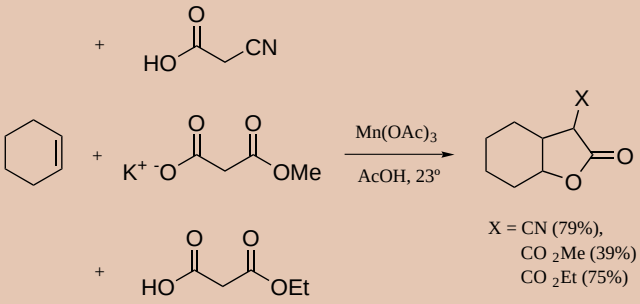
for pest control.[39] A chemoselective reaction with the double bond in 1,3-alkenynes is part of novel approaches toward the sex pheromones of the Japanese beetle[40] and the tomato worm.[41] Introducing acetic anhydride into the reaction mixture resulted in a preparative method for the long-chain 4-acetoxy-5-alkynoic acids.[42] The lactonizations with propionic acid leading to α-methylated butyrolactones (29-50%) have been developed to a lesser extent.[35] Along with monocarboxylic acids, derivatives of malonic acid have been used in the lactonization of alkenes.[35,43] These reactions have two major advantages: first, the enhanced acidity of proradicals allows the reaction to proceed at lower temperatures (23-70°C), and, second, the cyclic products are α-functionalized with cyano and alkoxycarbonyl groups (**eq 8**) suitable for secondary structural modifications. A new synthetic dimension is introduced by malondiamide in which cyclization can occur on the amino group and leads to the formation of pyrrolidinone derivatives.[44] The spirolactonization reaction of malonic acid with olefins can be regarded as one of the most graceful synthetic methods in manganese organic chemistry.[45] Polysubstituted spirolactones are formed in one step and high yield (**eq 9**), although the diastereoselectivity of the process needs further improvement.

Dihydrofuran synthesis[4] is the most versatile synthetic procedure applicable to the structurally diverse alkenes and β-dicarbonyl compounds or β-keto esters (**eq 10**). Its selectivity is dependent on the oxidation rate of the adduct radicals generated (**4, Scheme 1**), and requires the assistance of cupric acetate for nonstabilized alkyl radicals. While $Mn(OAc)_3$ has been widely employed, isolated reports have also appeared on the use of $Mn(acac)_3$ with yields of up to 97% (**eq 11**).[46] Results on the stereoselectivity of the cycloaddition to disubstituted alkenes, although limited to styrene derivatives,[47] point out the exclusive trans orientation of the 2,3-disposed substituents. A remarkable array of fused- and spirodihydrofurans has become accessible due to the introduction of enol ethers (**eq 12**) and enol lactones (**eq 13**) as unsaturated substrates.[48] Further developments of the parent reaction include detailed structural studies of the cycloadditions to 1,3-alkenynes[49] and 1,3-alkadienes,[16,19] as well as chemoselective reactions of transition-metal-protected 1,3-alkenynes.[50]

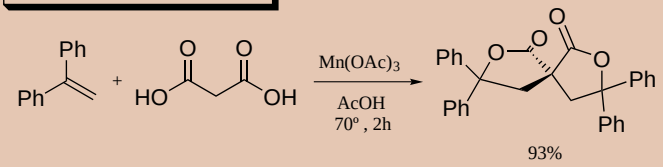
From the standpoint of practical applications, an important contribution to the field has become the development of radical addition and cycloaddition reactions with $Mn(OAc)_3$ *generated in situ.* This has allowed chemists to address environmental concerns[8] and to make the experimental protocols

Lactonization with Dicarboxylic Acid Derivatives



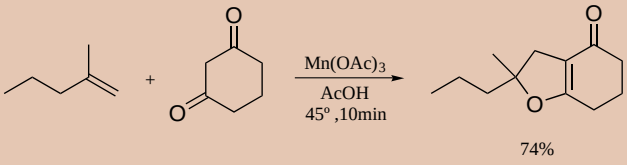
eq 8[35,43]

Spirolactonization Reaction

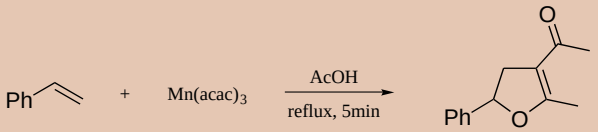


eq 9[45b]

Synthesis of 2,3-Dihydrofurans

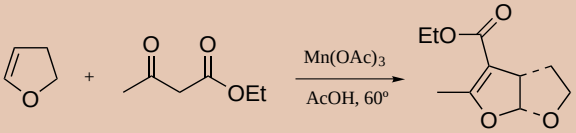


eq 10[101]

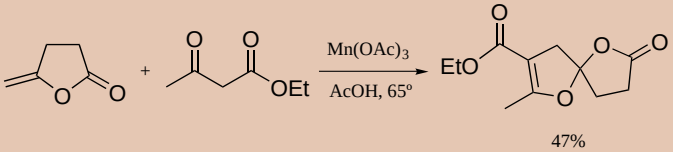


eq 11[46]

Enol Ethers and Enol Lactones as Substrates

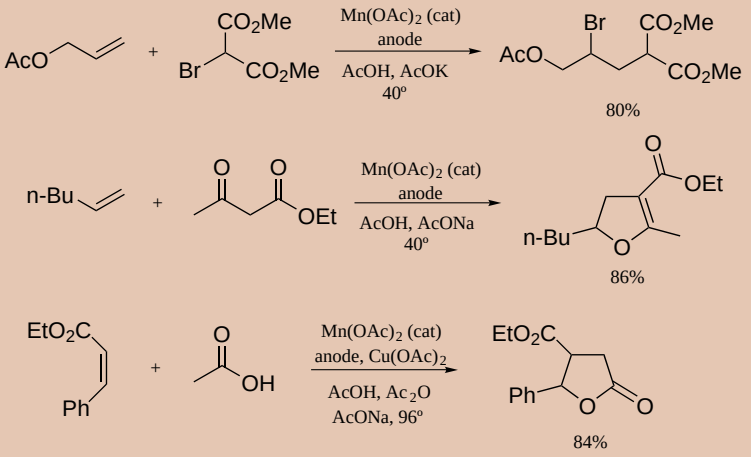


eq 12[48b]

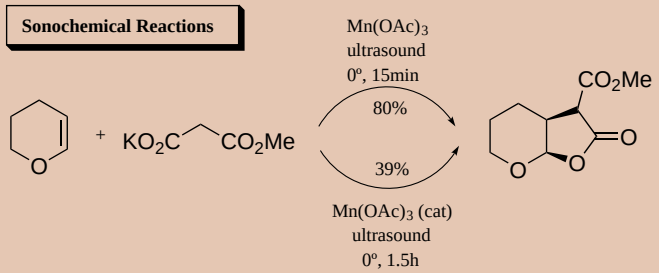


eq 13[48a]

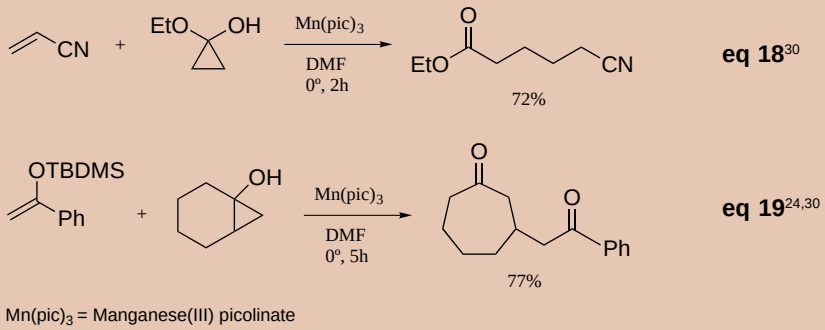
Electrochemically Generated $Mn(OAc)_3$—Addition and Cycloaddition Reactions



Sonochemical Reactions

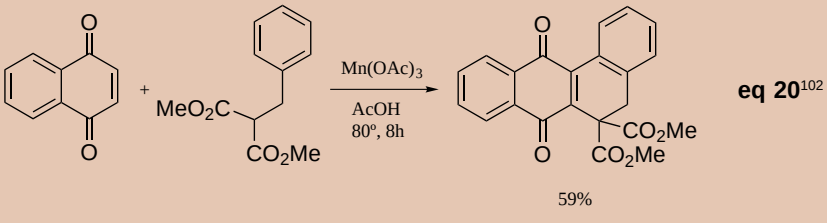


Cyclopropanol-Derived Alkyl Radicals: Intermolecular Additions



$Mn(pic)_3$ = Manganese(III) picolinate

Addition—Cyclization Reaction



compatible with a wider range of functional groups. Representative examples[51] include the high-yield addition reaction of bromomalonic ester (**eq 14**), the synthesis of substituted dihydrofurans (**eq 15**), and the low-temperature lactonization with acetic acid (**eq 16**). Monsanto has developed an electrochemical system for the synthesis of sorbic acid, a food preservative produced on a large commercial scale.[38] Moreover, potassium permanganate has been shown to regenerate the active manganese species at 70-75°C in the reactions of acetone and dimethyl malonate with olefins.[52] While its current scope is rather limited, the methodology looks promising and may become suitable for industrial use.

Sonochemical reactions represent a new avenue in manganese chemistry, and feature the lowest reaction temperature (0°C) ever reported.[53] Although lactonization of alkenes with malonic ester derivatives is the only type of sonochemical reactions studied, the method provides functionalized butyrolactones in high yields and allows the use of catalytic quantities of the metal oxidant (**eq 17**).

Manganese(III) picolinate has recently been introduced as a novel radical initiator for cyclopropanols, a new class of substrates.[24,30] The initial step includes ring opening and generation of alkyl radicals which add reductively to activated double bonds (**eq 18**) and enol ethers (**eq 19**). The potential of this methodology is best illustrated by the stereoselective intramolecular additions that have resulted in an array of bicyclic molecular assemblies.[54] A conceptually related process makes use of cyclobutanols, fused and spiro,[25,55] which undergo oxidative ring opening and subsequent intramolecular addition onto suitably located multiple bonds. Although still in its infancy, the oxidative cleavage of strained carbocycles looks especially promising as a novel synthetic methodology, and will probably attract more attention in the coming years.

Addition–cyclization reactions, a relatively unexplored dimension in manganese chemistry, have been designed in two ways (**Chart 2**). The unsaturated radical recipients are either tethered to each other or combined with a carbonyl-group-containing molecular fragment. Double[56-60] and triple[14,61] bonds act efficiently as recipients of attack of electrophilic educt radicals, whereas, in the second step, intramolecular additions of nucleophilic adduct radicals occur mostly upon aromatic rings (benzene, thiophene, pyridine, pyrrole).[14,56,57,61,62] Thus, a representative example includes a malonic ester moiety as a proradical with the double bond and the benzene ring receiving consecutive radical attacks (**eq 20**). The formation of tetralone,

tetralin®, indane, quinoline, isoquinoline, naphthalene, and carbazole derivatives[56,61-63] demonstrates the outstanding potential of manganese-based addition-cyclization processes.

Selected intermolecular reactions are listed in **Table 1** to illustrate the bewildering array of organic products accessible by manganese-based technology. This compilation of reactants, reactive pathways of adduct radicals, products, and bibliography should serve as a quick guide for chemists looking for novel synthetic methods that could solve their specific problems. Manganese(III) species have also been utilized in the functionalization of pyrimidine bases which are used in synthetic oligonucleoside probes.[64]

2.3 Intramolecular and Tandem Cyclizations

The extensive coverage of this topic by Snider,[3] the major contributor to the field, allows us to limit this discussion to some key mechanistic and selectivity issues. The main types of substrates for intramolecular cyclizations are shown in **Chart 3**. The disposition of the carbon-centered radical varies with respect to the multiple bond tethered to a β-dicarbonyl unit. Understandably, the synthetically most accessible starting materials—2- and 4-substituted β-keto esters and 1,3-diketones, O- and C-substituted malonic esters, and β-keto esters—were chosen first for in-depth synthetic studies.[3,4] The *regioselectivity* of the process, as represented by competing cyclization pathways, determines the ring size in the end products. The largest number of experimental data is available for *5-exo-* vs. *6-endo-*cyclization modes, with the former clearly dominating and leading to cyclopentane derivatives. From a preparative viewpoint, the formation of six-membered rings is best developed for salicylic acid derivatives.[65] While the *6-exo-* vs. *7-endo-*cyclization modes have been elaborated to a lesser extent, both cyclohexanes[29,66] and cycloheptanes[29] can be synthesized as major products. The level of predictability is higher for the *5-exo/6-endo* cyclizations since a larger database of such reactions is currently available. The *stereoselectivity* of intramolecular cyclizations is well studied for cyclopentanes and cyclohexanes, while it remains mostly unestablished in the case of larger ring sizes.[4] Sporadically tested *4-exo-* vs. *5-endo-*cyclizations are represented by two extreme cases, the highly regioselective formation of five-[15,67] and four-membered[68] rings, both driven by steric and electronic factors.

Tandem cyclizations include consecutive intramolecular additions upon suitably located unsaturated moieties. The greater diversity of

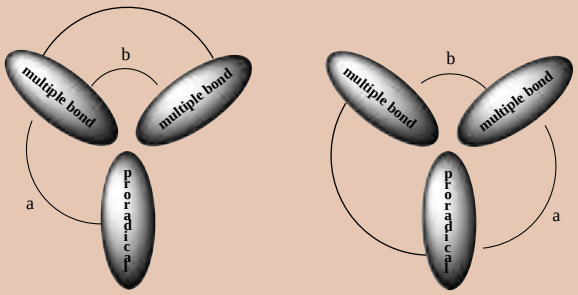


Chart 2. Addition–Cyclization Reactions: Phenomenology (a—educt radical attack; b—adduct radical intramolecular addition).

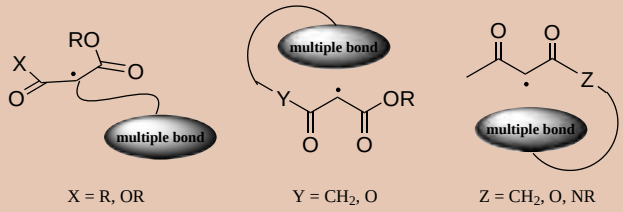


Chart 3. Topology of Intramolecular Reactions.

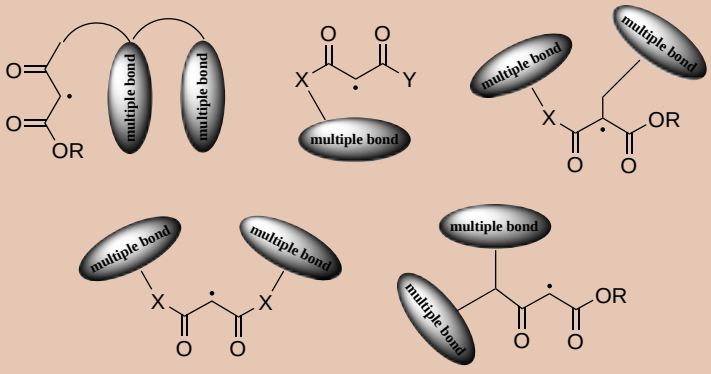


Chart 4. Topology of Tandem Cyclizations.

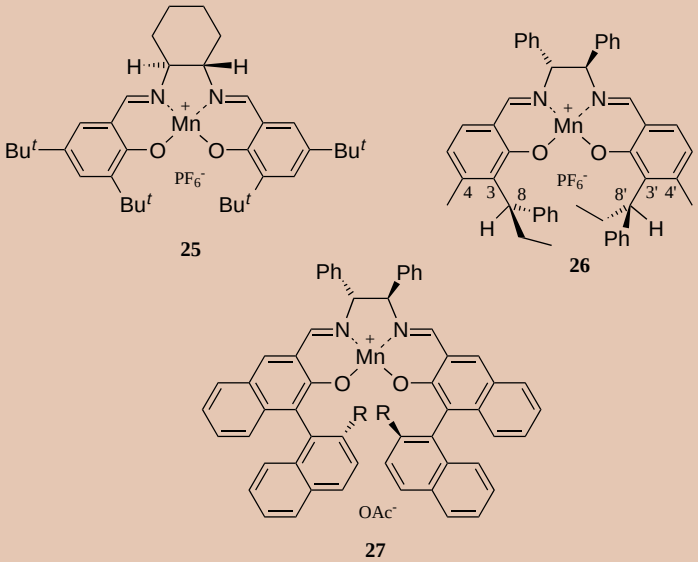
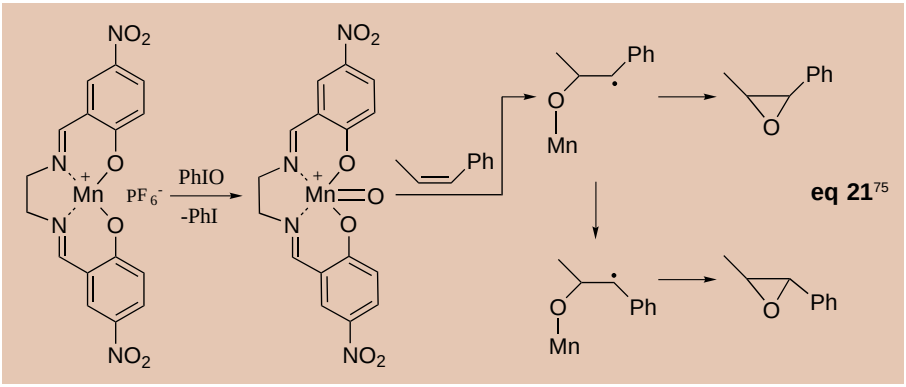
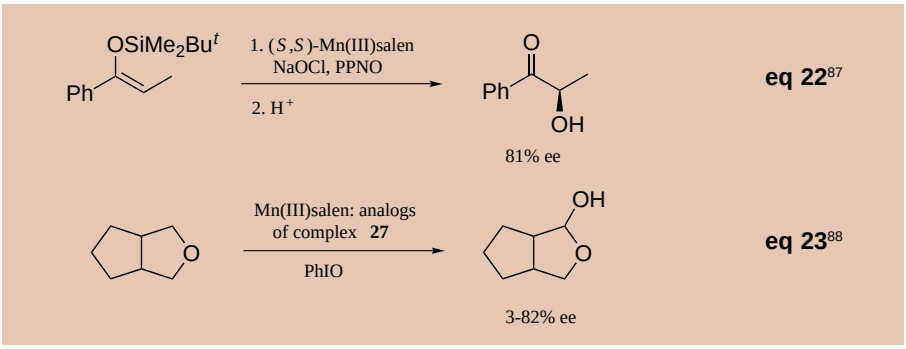
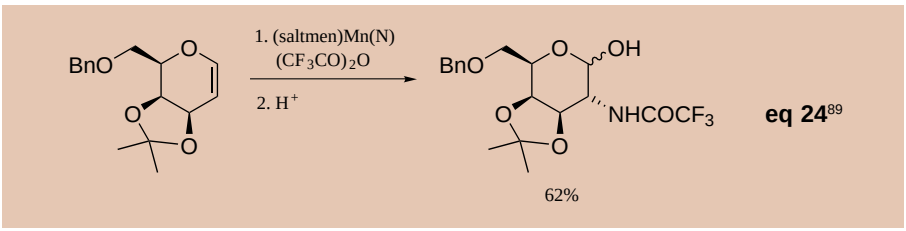
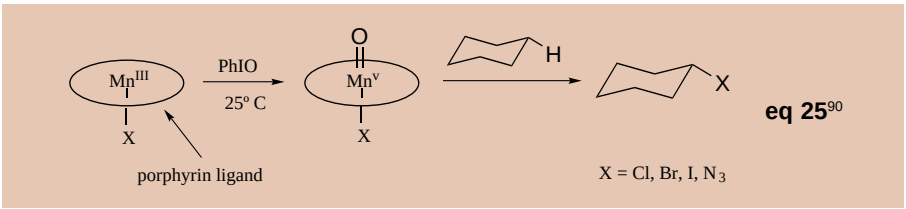


Chart 5. Chiral (Salen) Manganese(III) Complexes.









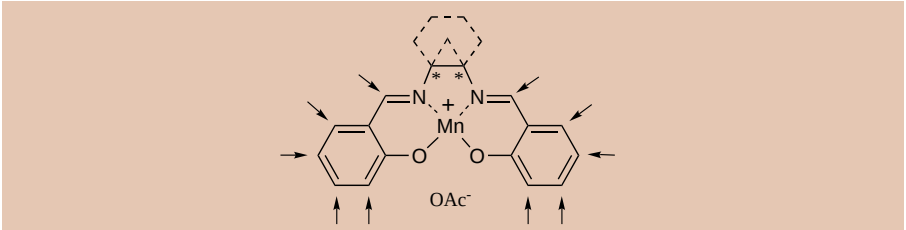


Chart 6. DNA-Cleaving Manganese(III) Cationic Complexes.

structures in **Chart 4** reflects the increased number of variables participating in molecular design. Malonic ester derivatives, β-keto esters and β-diketones have served as proradical moieties, and C=C, C≡C, C≡N, COOH, COOR, COO^- and Ar groups as the sites of attack of the radical/carbocation intermediates.[3,4] The specific combinations of unsaturated fragments studied so far are: double bond–double bond, double bond–benzene ring, triple bond–double bond, triple bond–benzene ring, double bond–carbalkoxy/carboxy/carboxylate, and double bond–nitrile group. Polycyclizations upon double bonds have also been reported.[3,4] A remarkable array of fused and bridged, di-, tri-, and tetracyclic molecules, rich in functionalities, has been synthesized in a regio- and stereoselective manner. Overall, the regioselectivity of the consecutive cyclization steps can be predicted more reliably than the stereochemical result. The current state of manganese(III)-based intramolecular cyclizations can be described as "mature" as demonstrated by the successful construction of complex natural products.[66,69-74]

3. Manganese (Salen) Complexes: Catalytic Asymmetric Epoxidation and Related Reactions

In 1986, Kochi[75] discovered that cationic (salen)Mn(III) complexes, generated by a one-electron oxidation of the parent species, act as effective catalysts for the conversion of alkenes to the corresponding epoxides. The reaction is characterized by high chemoselectivity (no allylic oxidation), stereospecificity, and good yields (50-75%). Iodosylbenzene, an oxidizing agent, converts cationic Mn(III) into Mn(V)-oxo species, which interact with the substrate by the oxygen rebound mechanism (**eq 21**). The involvement of radical intermediates was suggested based on several lines of evidence, in particular, the stereomutation of the cis double bond (up to 14%),[75] and the minimal inversion of 4% observed for the 5,5'-dinitro catalyst (**eq 21**).

Initially, metalloporphyrin complexes were used in various oxo transfer reactions,[76] even though the salen moiety is better suited for chiral design, since, unlike the porphyrin ligand, not all of its peripheral atoms are sp^2-hybridized. Most importantly, the chirality may be introduced in the ethano bridge, in a close proximity to a central Mn=O bond, as well as in selected positions of the benzene ring. This approach has been creatively exploited by Jacobsen[77] and Katsuki[78] in the construction of optically active (salen)manganese catalysts. Representative examples of these catalysts (**Chart 5**) include chiral centers in the 1", 2"-positions (**25**,[77c] **26**,[78c] **27**[78d]), achiral bulky groups in the 3,3'- and 5,5'-positions (**25**[77c]), as well as stereogenic centers in the 8,8'-positions (**26**[78c]). The methodology for the preparation of novel catalysts has been well elaborated, and the most widely used catalyst, Jacobsen's catalyst, is now commercially available in both enantiomerically pure forms.[79] Structurally diverse alkenes with different degrees of substitution and unsaturation have been extensively investigated[80] to gain a better understanding of the steric and electronic parameters responsible for the asymmetric induction. The mechanism of the reaction is mostly understood, although the intimate structural features of the reactive

Table 1. Compendium of Manganese(III)-Mediated Intermolecular Radical Reactions

Substrate	Proradical	Adduct Radicals Transformation Path	Product	Refs
alkene	aldehyde	β-deprotonation	α,β– and β,γ–alkenals	103
		H-atom abstraction	alkanal and alkanone	19,32,103a,104
		AcO-group transfer	γ-acetoxy alkanal	19
alkene	ketone	H-atom abstraction	alkanone	22,60,105
		β-deprotonation	telomeric alkenone	106
alkene	acetic acid	oxidative cyclization	γ-lactone	10,12,27,34b 36,37,107
	cyanoacetic acid	oxidative cyclization	γ-lactone	35,36,43
	malonic monoester	oxidative cyclization	γ-lactone	35,43
alkene	propionic acid	oxidative cyclization	γ-lactone	35,36
alkene	acid anhydride	β-deprotonation	4-alkenoic acid	108
		H-atom abstraction	alkanoic acid	109
alkene	β-diketone or	oxidative cyclization	2,3-dihydrofuran	46a,47,101
	β-keto ester	H-atom transfer	alkylated β-diketone	110
		Cl-atom transfer	γ-chloro-β-diketone	111
		β-deprotonation	γ,δ-unsat. β-keto ester	112
alkene	β-keto sulfoxide or β-keto sulfone	oxidative cyclization	2,3-dihydrofuran	17
alkene	malonic ester	Cl-atom transfer	γ-chloromalonic ester	111
		H-atom transfer	alkylated malonic ester	113
alkene	malonic acid	double oxidative cyclization	spirolactone	45
alkene	malonamide	oxidative cyclization	α,β-unsaturated γ-lactone	44
alkene	nitroaceto-phenone	cyclization upon NO_2 group	isoxazoline *N*-oxide	114
cycloalkene	acetic acid	oxidative cyclization	bicyclic, tricyclic, and bridged lactones	10,12,27, 35-37,115
enol acetate	ketone	β-elimination	1,4-diketone	34a
enol ether	β-diketone or β-keto ester	oxidative cyclization	fused/spiro 2,3-dihydrofuran	48b,48c, 116,117
enol lactone	β-diketone or β-keto ester	oxidative cyclization	spiro/fused 2,3-dihydrofuran	48a,48b,116

Table 1. Compendium of Manganese(III)-Mediated Intermolecular Radical Reactions (cont.)

Substrate	Proradical	Adduct Radicals Transformation Path	Product	Refs
allyl sulfide	ketone	β-elimination	γ,δ–alkenone	33
allyl sulfide	β-keto ester	β-elimination	γ,δ-unsat. β-keto ester	33
D-glucal	malonic ester	AcO-transfer	2-C analog of D-glucose	118
1,3-alkadiene	acetic acid	oxidative cyclization	γ-vinyl-γ-lactone	36,38,40,119
1,3-alkadiene	β-diketone or β-keto ester	oxidative cyclization	2-vinyl-2,3-dihydro furan	16,19,46b,49
1,5-alkadiene	malonamide	oxidative cyclization	fused pyrrolidinone spiro-γ-lactone	120
1,3-alkenyne	acetic acid	oxidative cyclization	5-alkyn-4-olide	40,41
	acetic anhydride	AcO-ligand transfer	5-alkynoic acid	42
	β-diketone or β-keto ester	oxidative cyclization	2,3-dihydrofuran and/or furan	49
1,3-alkadiyne	β-diketone or β-keto ester	oxidative cyclization	furan	121
arene	malonic acid	β-deprotonation	aromatic acid	122
			aromatic aldehyde	122

intermediates, their configuration, and the role of axial ligands are still debatable.[81] Among the recent important practical applications of the catalytic asymmetric epoxidation are the synthesis of pheromones,[82] paclitaxel side chain,[83] potassium channel activator BRL 55834,[84] and diltiazem.[85] Although not fully optimized, the first asymmetric epoxidation with an *achiral* (salen)manganese(III) complex and a *chiral ligand* has recently been reported.[86]

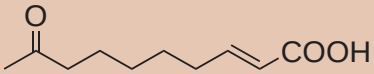
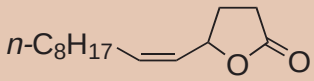
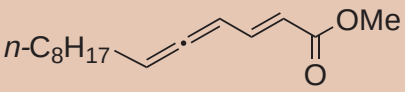
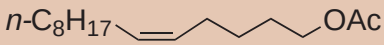
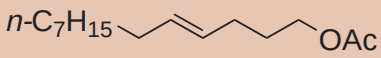
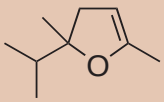
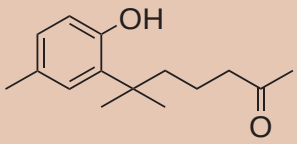
(Salen) manganese(III) complexes can also be used for reactions other than epoxidation of alkenes. These new avenues are represented by the asymmetric synthesis of α-hydroxy ketones (**eq 22**),[87] and the selective C-H bond oxidation in five- and six-membered cyclic ethers (**eq 23**).[88] A landmark achievement in manganese chemistry has been the use of novel nitrido complexes to deliver nitrogen to double bonds in glycals, thus producing β-amino alcohols via putative aziridine complexes.[89] The end products, the synthetically versatile 2-amino carbohydrates (**eq 24**), can be used in the total synthesis of natural products and polysaccharides.

4. Manganese(III) Porphyrins

The major impetus for the development of manganese porphyrin chemistry was provided by the nature-made monooxygenase enzymatic system, cytochrome P-450,[5,6] which is capable of oxidizing alkanes in a selective manner. The last two decades have been marked by intense research efforts directed at understanding the role of metalloporphyrins in biological oxidation processes, and elaboration, both catalytically and asymmetrically, of industrially important alkane-activation and alkene-epoxidation methodologies.[76] Iodosylbenzene is generally used to convert (tetraphenylporphinato)-manganese(III) derivatives into the active Mn(V)-species, which halogenate or oxidize an unactivated C-H bond in alkanes (**eq 25**).[90] The radical nature of the intermediates has been suggested by solid mechanistic evidence.[90] Substantial advances have also been made in expanding the scope of the oxidation reactions, in furthering our understanding of the key mechanistic issues,[76] and in developing an immobilized version of the Mn(III)-porphyrin catalyst, which should have important practical applications.[91]

A variety of novel manganese porphyrins has been synthesized and structurally characterized in attempts to develop a superoxide dismutase mimic,[92] site-specific DNA binding and cleaving agents[93] including a catalytic version,[94] and conjugates with bisbenzimidazole dye (Hoechst 33258).[95] A sequence-specific oxidative damage to RNA mediated by a cationic manganese porphyrin has also been reported.[96]

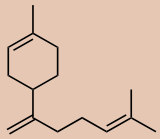
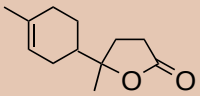
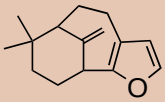
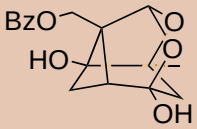
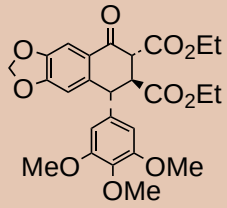
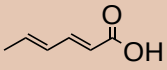
Table 2. Synthesis of Natural Bioactive Molecules

Structure / Origin	Mn(III)-Mediated Key Steps	Refs
 Queen substance	addition of acetone across double bond in alkene	123
 sex pheromone, *Popillia japonica*	lactonization of double bond in 1,3-enyne	40
 sex pheromone, *Acanthoscelides obtectus*	lactonization of double bond in 1,3-enyne	124
 sex pheromone, *Scotia exclamationis*	lactonization of double bond in 1,3-enyne	125
 sex pheromone, *Keiferia lycopersicella*	lactonization of double bond in 1,3-enyne	41
 sex pheromone, *Hylecoetus dermestoides*	addition of β-keto ester across double bond in 1,3-diene	126
 Himasecolone	addition of acetone across double bond in alkene	127

5. Novel Classes of DNA-Cleaving Agents

There is a consensus among chemists and biologists that the ability to cleave DNA is vital to the antitumor activity of therapeutic agents. A significant positive effect has been exhibited by purely organic molecules such as calicheamicin, esperamicin, and leinamycin,[97] and by transition-metal complexes such as bleomycin.[5,6,98] Recently, manganese(III)-salen complexes joined the family of DNA-cleaving agents with bioactivity revealed in the presence of a terminal oxidant.[99] Multiple structural variations of the ethano-bridged parent complex (**Chart 6**, arrows indicate positions of substituents) have allowed the establishment of the relationship between the stereoelectronic nature of the substituents and the mode of biological action. Alteration of the two-carbon bridge (dotted lines) and introduction of the two stereocenters in the cyclohexane ring (denoted with stars) reduce the desired activity and permit detection of enantiospecific recognition. Although limited in scope, these results are significant since they could become a starting point for the development of novel chiral manganese complexes with site-specific DNA cleaving capabilities as part of the ongoing search for transition-metal-based antitumor agents.

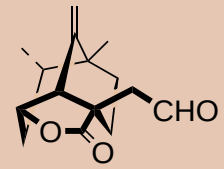
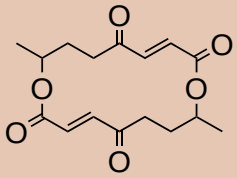
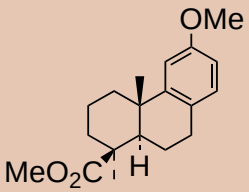
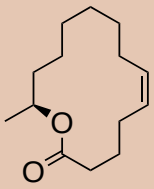
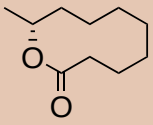
Table 2. Synthesis of Natural Bioactive Molecules (cont.)

Structure / Origin	Mn(III)-Mediated Key Steps	Refs
 β-Bisabolene	addition of acetic acid across double bond in alkene	128
 Norbisabolide	addition of acetic acid across double bond in alkene	128,129
 Dihydropallescensin D	intramolecular addition of β-keto ester across double bond	69
 (±)-Paeoniflorigenin	addition of cyanoacetic acid across double bond in cyclohexene	130
 Podophyllotoxin analogue	addition of β-keto ester across double bond in cinnamate	47
 Sorbic acid	conjugate 1,2-addition across double bond in 1,3-butadiene	38

6. Synthesis of Organic Molecules of Biological Relevance

In the past three decades, manganese chemistry has passed from infancy to adolescence and into maturity. As illustrated in **Table 2**, a remarkable diversity of organic molecules—acyclic and cyclic, fused and bridged, carbo- and heterocyclic, aromatic and aliphatic—has become accessible via manganese-mediated chemical transformations. The analysis of the key steps in total syntheses shows a disproportionate use of some of these reactions, such as the lactonization of alkenes or the addition of mono- and dicarbonyl compounds across double bonds, while other more feasible synthetic reactions still await practical applications. Other noteworthy accomplishments include manganese-induced polycyclizations, a one-step entry into spongian and marginatane furanoditerpenes,[71] the formal synthesis of upial, a natural sesquiterpene of unique topology,[72] and the construction of the bicyclic framework of huperzines.[74]

Table 2. Synthesis of Natural Bioactive Molecules (cont.)

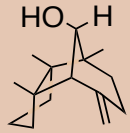
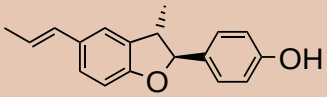
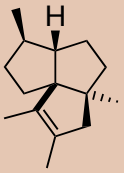
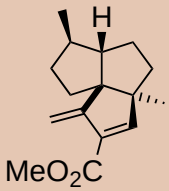
Structure / Origin	Mn(III)-Mediated Key Steps	Refs
 (±)-14-Epiupial	intramolecular addition of dimethyl malonate across double bond	70
 Pyrenophorin	addition of acetone across double bond in alkene	131
 (±)-Podocarpic acid precursor	intramolecular tandem cyclization of β-keto ester	66
 synergist of the aggregation pheromone, *Cryptolestes pusillus*	Mn-salen catalyzed asymmetric epoxidation of 1,3-alkenyne	82
 defensive pheromone, *Phoracantha synonyma*	Mn-salen catalyzed asymmetric epoxidation of 1,3-alkenyne	82

7. Concluding Remarks

In modern science manganese chemistry occupies a niche of considerable breadth and potential. Its importance has grown steadily in the past decades and has resulted in a large number of research papers and review articles. One of the important areas that is not discussed in this review is the chemistry of *manganese enzymoids*, i.e., the design and synthesis of dinuclear oxo- and acetate-bridged Mn(III)-Mn(IV) complexes for use as models for photosystem II (PSII), and the examination of their water-splitting and catalase activities. I would like to refer the interested reader to the recent reviews on this subject.[100]

What developments might take place in manganese chemistry in the near future? First, more in-depth mechanistic investigations, including the structural characterization of reactive intermediates, and the acquisition of complete stereocontrol in enantioselective radical reactions. Second, the design and synthesis of new chiral, tailor-made

Table 2. Synthesis of Natural Bioactive Molecules (cont.)

Structure / Origin	Mn(III)-Mediated Key Steps	Refs
 (±)-Gymnomitrol	intramolecular addition of ketone across triple bond	73
 (±)-Conocarpan	addition of enone across double bond in styrene	132
 (-)-Silphiperfol-6-ene	oxidative rearrangement of ethynyl cyclobutanol	55
 Methyl (-)-cantabradienate	oxidative rearrangement of ethynyl cyclobutanol	55

manganese complexes for such important applications as epoxidation and aziridination of unsaturated substrates and alkane activation. Third, the design and construction of novel mono- and dinuclear manganese complexes, which can be used as efficient enzyme mimics, in particular, those with highly developed catalase activity. Finally, more organic compounds, which become easily accessible through manganese-based methodologies, could find their way to the market. And fortunately, there will be important breakthroughs which cannot be predicted based on the current level of knowledge, but which constitutes the very beauty of science and without which the scientific endeavor would lose much of its fascination.

8. Acknowledgements

I wish to express my gratitude to all past and present graduate students and research associates who made our contribution to the field possible. I am indebted to the Office of Graduate Studies, Research and International Programs and University Corporation, California State University, Northridge, for generous financial support, and to my daughter Marina whose birth at the time of writing this review provided me with boundless inspiration.

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About the Author

Gagik G. Melikyan was born in Yerevan, Armenia. He received a B.Sc. degree in Chemistry from the Yerevan State University (Yerevan) in 1973 and a Ph.D. degree from the Institute of Elementorganic Compounds (Moscow) in 1977. He began his independent scientific career at the Institute of Organic Chemistry, National Academy of Sciences (Yerevan), where, as a Group Leader and Project Leader, he directed graduate students and junior research fellows. In 1990, he was awarded the second academic degree, Doctor of Science, for his contribution to the field of radical and ionic reactions of conjugated systems and their utilization for the synthesis of sex pheromones. From 1990 to 1992, he was an Alexander von Humboldt Fellow at the Institute of Organic Chemistry, University of Erlangen-Nürnberg (Erlangen). After relocation to the United States, he became an Adjunct Professor at the University of Oklahoma (Norman), and, in 1995, joined the faculty in the Department of Chemistry, California State University, Northridge, where he currently holds the rank of Associate Professor of Chemistry. His research interests include new synthetic methodologies based on organometallic radical chemistry, asymmetric reactions, stereocontrolled radical transformations of coordinated molecules, radical nucleotide chemistry, and organometallic probes for biomedical studies. Dr. Melikyan is author or coauthor of 6 review articles and 53 research publications in peer-reviewed scientific journals.

Lab Notes, continued from page 34.

Separating DMF from Alkylated Nucleosides by Silica Gel Flash Column Chromatography

Alkylation of nucleosides is often carried out in polar aprotic solvents such as *N,N*-dimethylformamide (DMF). A convenient way to get rid of DMF is to wash it out repeatedly with water. However, nucleoside adducts are themselves often more soluble in water than in solvents like ethyl acetate that are used for extracting the organic product. Evaporating DMF on high-vacuum pumps is not an easy proposition especially at room temperature. The stability of nucleoside adducts is never guaranteed even at slightly elevated temperatures.

We found that an extremely useful method in such cases is to load the entire reaction mixture on a column of silica weighing 40-50 times the weight of starting materials. DMF is easily eluted with chloroform. Since the adducts are quite polar, they are retained very well on silica. Once DMF is removed, the compounds can be eluted with chloroform-methanol mixtures. However, the polarity should be gradually increased viz., 5% MeOH in $CHCl_3$, 10% MeOH in $CHCl_3$, and so on, depending on the polarity of the compounds. If the polarity is increased suddenly, even compounds that are well-separated on TLC may elute as mixtures. The method works quite well even for DMF-H_2O mixtures and dimethyl sulfoxide (DMSO). We have successfully isolated alkylated adducts of 2'-deoxyadenosine and 2'-deoxycytidine using this method.

I hope this method proves as useful to other organic chemists working with nucleosides as it has to us.

Manvinder Wahi, Graduate Student
Department of Chemistry and Biochemistry
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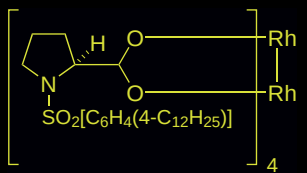
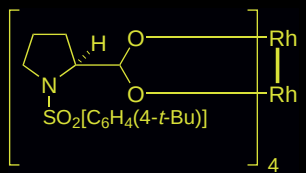
College Park, MD 20742

New Chiral Catalysts

Dirhodium(II) Tetracarboxylate Catalysts



Rh_2(*S*-DOSP)$_4$



Rh_2(*S*-TBSP)$_4$

47,461-4	**Rh_2(*S*-TBSP)$_4$**
47,462-2	**Rh_2(*R*-TBSP)$_4$**
47,044-9	**Rh_2(*S*-DOSP)$_4$**
47,114-3	**Rh_2(*R*-DOSP)$_4$**

Davies and co-workers have demonstrated the broad utility of chiral dirhodium tetracarboxylates, such as Rh_2(*S*-TBSP)$_4$ and Rh_2(*S*-DOSP)$_4$, as catalysts for asymmetric cyclopropanations by either vinyldiazoacetates[1] or phenyldiazoacetate derivatives.[2] A remarkable feature of these reactions is that the cyclopropanations occur with high diastereoselectivity and enantioselectivity. These transformations can be used in general methods for the asymmetric synthesis of vinylcyclopropanes,[1] cyclopropaneamino acids,[1] 4,4-diarylbutanoates,[3] cycloheptadienes, bicyclo[3.2.1]octadienes,[4] allyl- and benzylsilanes,[5] and other polycyclic compounds.[6]

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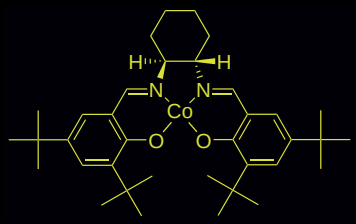
New Jacobsen's Catalyst

Chiral Co(II) Salen Complex

This new catalyst has been used for the hydrolytic kinetic resolution (HKR) of terminal epoxides[1] and for the enantioselective catalytic ring opening of meso epoxides.[2] Catalytic amounts (1 mol %) of the Co(II) salen complex are used in the reactions, and the catalyst can be easily recycled (regenerated with acid).

(1) Tokunaga, M. et al. *Science* **1997**, *277*, 936. (2) Jacobsen, E.N. et al. *Tetrahedron Lett.* **1997**, *38*, 773.



(*S,S*)

47,460-6 **(*S,S*)-(+)-*N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II)**

47,459-2 **(*R,R*)-(–)-*N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II)**

Aldolase Antibody 38C2

The first commercially available catalytic antibody

Antibody 38C2 catalyzes the following reactions:

- Aldol addition and, in some cases, the condensation reaction[1,2]
- Crossed aldol[1,2]
- Retro aldol[1,2]
- Self aldol[1,2]
- Decarboxylation of β-keto acids[2,3]
- Robinson annulation[4]
- Kinetic resolutions[5]

See Technical Bulletin AL-207 for full experimental details.

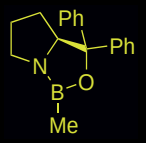
(1) Hoffmann, T. et al. *J. Am. Chem. Soc.* **1998**, *120*, 2768. (2) Barbas, C.F., III et al. *Science* **1997**, *278*, 2085. (3) Björnestedt, R. et al. *J. Am. Chem. Soc.* **1996**, *118*, 11720. (4) Zhong, G. et al. *ibid.* **1997**, *119*, 8131. (5) Lerner, R.A. et al. manuscript in preparation.

47,995-0 **Aldolase antibody 38C2, murine catalytic monoclonal antibody** (each vial contains 10 mg of lyophilized antibody plus 5-6 mg of phosphate buffer salts)

48,157-2 **Aldolase antibody 38C2, murine catalytic monoclonal antibody** (lyophilized from pure water)

CBS-Oxazaborolidine

The CBS (Corey-Bakshi-Shibata) oxazaborolidine catalyst has been used in the asymmetric reduction of prochiral ketones.[1]



Other applications include the enantioselective synthesis of α-hydroxy acids,[2] α-amino acids,[3,4] C_2 symmetrical 1,1'-ferrocenyl diols,[5] and propargyl alcohols.[6]

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45,769-8 **(*R*)-2-Methyl-CBS-oxazaborolidine,** 1*M* solution in toluene

45,770-1 **(*S*)-2-Methyl-CBS-oxazaborolidine,** 1*M* solution in toluene

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49,443-7	**Methyl alcohol**, biotech grade solvent, 99.93%
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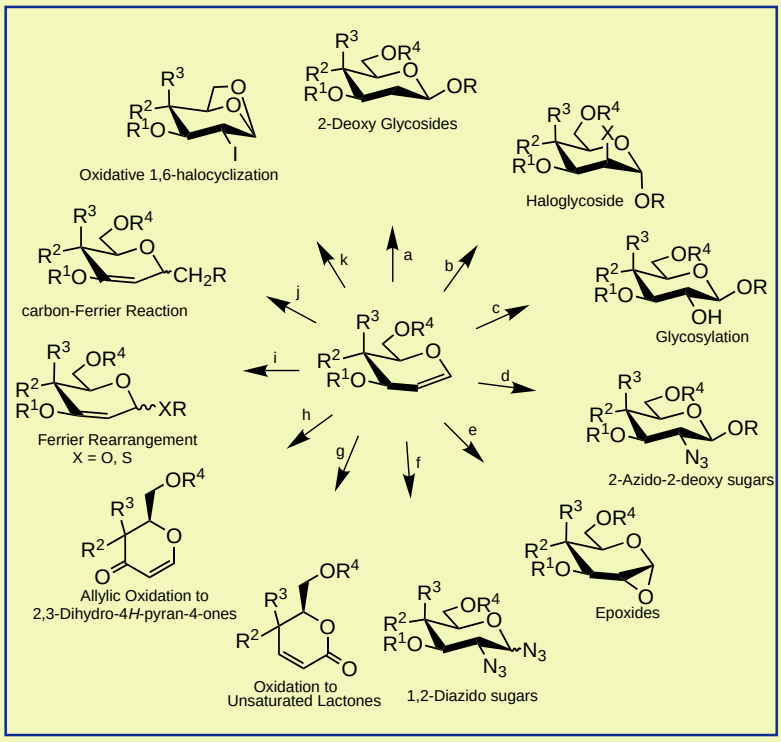
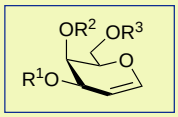
Carbohydrate Synthesis



Glycals, 1,2-unsaturated derivatives of pentoses and hexoses, are among the most versatile chiral building blocks. Not surprisingly, glycals have been the subject of considerable interest in carbohydrate chemistry,[1] oligosaccharide synthesis,[2] and the development of combinatorial synthesis of oligosaccharide libraries.[3] Glycals, as chiral building blocks, serve as precursors for a broad variety of optically active products.[4] The most important transformations involve Lewis acid induced rearrangements, addition of heteroatoms, cycloadditions, epoxidations, and oxidations. The Lewis acid catalyzed rearrangement of glycals in the presence of alcohols, known as the Ferrier rearrangement, is the method of choice for preparing 2,3-unsaturated glycosides.[1,5] Glycals have also shown tremendous utility as precursors for the synthesis of C-glycosides.[6] The promising synthetic potential of organometallic derivatives of glycals has been reported recently.[7] Glycals have also been used in the chemoenzymatic synthesis of oligosaccharides and rare sugars.[8] Glycal derivatives have been studied as glycosidase and glycosyl transferase inhibitors[9] and have been used as antigens to raise antibodies.[10]

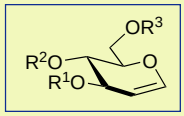
Galactals

R^1, R^2 = H; R^3 = TBDMS	**48,073-8**	**6-*O*-TBDMS-D-galactal**, 97%
R^1, R^2 = C(O); R^3 = TBDMS	**48,070-3**	**6-*O*-TBDMS-D-galactal cyclic carbonate**, 97%
R^1, R^2 = C(O); R^3 = H	**46,410-4**	**D-Galactal cyclic 3,4-carbonate**
R^1, R^2 = H; R^3 = TIPS	**46,409-0**	**6-*O*-TIPS-D-galactal**, 97%
R^1, R^2 = C(O); R^3 = TIPS	**46,411-2**	**6-*O*-TIPS-D-galactal cyclic carbonate**, 97%



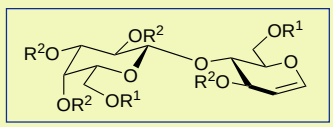
Glucals

R^1, R^3 = TBDMS; R^2=Ac	**47,282-4**	**4-*O*-Acetyl-3,6-di-*O*-TBDMS-D-glucal**, 97%
R^1, R^3 = TBDPS; R^2=Ac	**47,281-6**	**4-*O*-Acetyl-3,6-di-*O*-TBDPS-D-glucal**, 96%
R^1, R^2 = H; R^3 = Bz	**47,274-3**	**6-*O*-Benzoyl-D-glucal**, 98%
R^1, R^2 = H; R^3 = TBDPS	**47,278-6**	**6-*O*-TBDPS-D-glucal**, 95%
R^1, R^2 = Ac; R^3 = TBDMS	**47,277-8**	**3,4-Di-*O*-acetyl-6-*O*-TBDMS-D-glucal**, 96%
R^1, R^2 = Ac; R^3 = TBDPS	**47,279-4**	**3,4-Di-*O*-acetyl-6-*O*-TBDPS-D-glucal**, 97%
R^1, R^3 = Bz; R^2 = H	**47,284-0**	**3,6-Di-*O*-benzoyl-D-glucal**, 96%
R^1, R^3 = TBDMS; R^2 = H	**47,283-2**	**3,6-Di-*O*-TBDMS-D-glucal**, 97%
R^1, R^3 = TBDPS; R^2 = H	**47,280-8**	**3,6-Di-*O*-TBDPS-D-glucal**, 95%



Lactals

R^1 = TBDMS; R^2 = H	**47,285-9**	**6,6'-Di-*O*-TBDMS-D-lactal**, 97%
R^1 = TBDPS; R^2 = H	**47,286-7**	**6,6'-Di-*O*-TBDPS-D-lactal**, 97%
R^1, R^2 = H	**47,113-5**	**D-Lactal**, 97%
R^1 = TBDMS; R^2 = Ac	**47,288-3**	**Tetra-*O*-acetyl-6,6'-di-*O*-TBDMS-D-lactal**, 98%
R^1 = TBDPS; R^2 = Ac	**47,287-5**	**Tetra-*O*-acetyl-6,6'-di-*O*-TBDPS-D-lactal**, 97%



These products are manufactured exclusively for Aldrich Chemical Company by Sussex Research Laboratories, Inc., Ottawa, Ontario, Canada.

(a) Thiem, J.; Klaffke, W. *J. Org. Chem.* **1989**, *54*, 2006. (b) Lemieux, R.U.; Levine, S. *Can. J. Chem.* **1964**, *42*, 1473. (c) Friesen, R.W.; Danishesfky, S.J. *Tetrahedron* **1990**, *46*, 103. (d) Lemieux, R.U.; Ratcliffe, R.M. *Can. J. Chem.* **1979**, *57*, 1244. (e) Danishefsky, S.J.; Bilodeau, M.T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380. (f) Snider, B.B.; Lin, H. *Synth. Commun.* **1998**, *28*, 1913. (g) Rollin, P.; Sinay, P. *Carbohydr. Res.* **1981**, *98*, 1913. (h) Harders, J. et al. *Liebigs Ann. Chem.* **1997**, 2125. (i) Fraser-Reid, B. *Acc. Chem. Res.* **1996**, *29*, 57. (j) Ferrier, R.J.; Prasad, N. *J. Chem. Soc. (C)* **1969**, 570. Postema, M.H.D. *Tetrahedron* **1992**, *48*, 8545. Thom, S.N.; Gallagher, T. *Synlett* **1996**, 185. (k) Czernecki, S. et al. *Tetrahedron Lett.* **1992**, *33*, 221.

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30,697-5	***tert*-Butyl methyl ether,** 99.8%	**30ppm**
28,911-6	**Carbon tetrachloride,** 99+%	**20ppm**
28,830-6	**Chloroform,** 99+%	**10ppm**
27,099-7	**Dichloromethane,** 99.8%	**10ppm**
29,630-9	**1,4-Dioxane,** 99.8%	**30ppm**
NEW **45,984-4**	**Ethyl alcohol,** 99.5%, non-denatured (TAX-PAID)	**30ppm**
27,764-9	**Ethyl alcohol,** reagent, denatured	**30ppm**
25,952-7	**Ethylene glycol dimethyl ether,** 99.5%	**30ppm**
24,665-4	**Heptane**, 99%	**10ppm**
22,706-4	**Hexanes**	**20ppm**
29,699-6	**Methyl acetate,** 99.5%	**30ppm**
32,241-5	**Methyl alcohol,** 99.8%	**20ppm**
27,438-0	**Methyl sulfide,** 99+%	**30ppm**
31,032-8	**Propylene carbonate,** 99.7%	**30ppm**
27,097-0	**Pyridine,** 99.8%	**30ppm**
18,656-2	**Tetrahydrofuran,** 99.9%	**30ppm**
24,451-1	**Toluene,** 99.8%	**20ppm**

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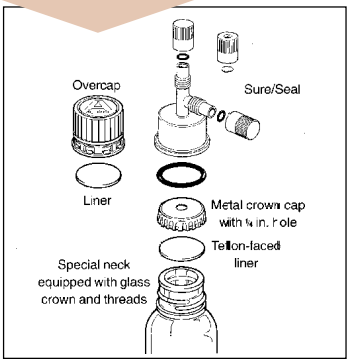

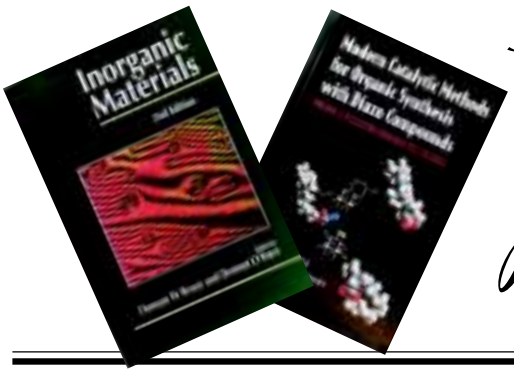

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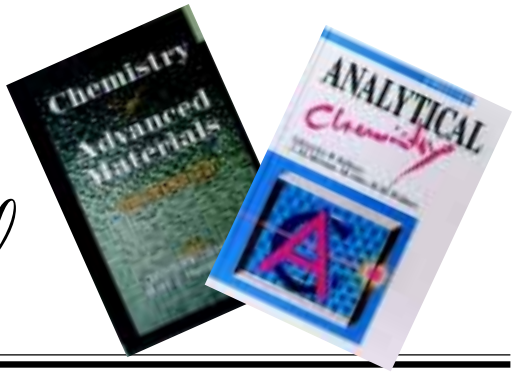

Strategies for Organic Drug Synthesis and Design

D. Lednicer, John Wiley & Sons, New York, NY, 1997, 500pp. Ideal for anyone learning or working in organic, medicinal, or pharmaceutical chemistry. This work offers a clear examination of the synthetic routes followed to prepare a range of compounds with assigned generic names. The book illustrates a variety of organic transformations and structural classes of compounds by presenting the chemistry used in the synthesis of the selected drugs.

Z40,856-5

Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides

M.P. Doyle, M.A. McKervey, and T. Ye, John Wiley & Sons, New York, NY, 1998, 652pp. This resource brings together a wealth of procedures for the synthesis and practical use of diazocarbonyl compounds. It features methods for the preparation of important catalysts and for applications of diazocarbonyl compounds within each of the main transformation categories—including in-depth coverage of cyclopropanation, C-H and X-H insertion, Wolff rearrangement, ylide formation, aromatic cycloaddition and substitution, and many other useful reactions.

Z40,857-3

Chemistry of Advanced Materials: An Overview

L.V. Interrante and M.J. Hampden-Smith, Eds., Wiley-VCH, New York, NY, 1998, 580pp. Advanced materials are substances such as composites, super alloys, and advanced ceramics. This is the first volume in a new series, *Chemistry of Advanced Materials*, devoted to providing a broad perspective on materials chemistry and helping scientists and engineers understand the importance of chemistry in material science and engineering.

Z40,863-8

α-Hydroxy Acids in Enantioselective Syntheses

G.M. Coppola and H.F. Schuster, Wiley-VCH, Weinheim, Germany, 1997, 513pp. Chiral α-hydroxy acids serve as starting materials in a wide variety of enantioselective conversions leading to commercially important products. This monograph, a stimulating source of ideas and an essential reference work for research chemists, focuses on the well-known lactic, mandelic, malic, and tartaric acids. Examples show how chiral centers inherent in these simple compounds can be used to control the introduction of further stereogenic centers. Readers can directly apply new transformations in their own work since reaction conditions are given in handy tables.

Z40,864-6

Inorganic Materials

2nd ed., D.W. Bruce and D. O'Hare, Eds., John Wiley & Sons, New York, NY, 1997, 593pp. This revised edition of a highly successful book addresses several of the vigorous areas of research in this field where inorganic materials are central to that research. Provides coverage of molecular inorganic superconductors, molecular inorganic magnetic materials, metal-containing materials for nonlinear optics, inorganic intercalation compounds, biogenic inorganic materials, clay chemistry, polymeric coordination complexes, metal-containing liquid crystals, and precursors for electronic materials.

Z40,867-0

A Practical Guide to Combinatorial Chemistry

A.W. Czarnik and S.H. DeWitt, Eds., American Chemical Society, Washington, DC, 1997, 450pp. Practical guide for both newcomers and specialists in small-molecule combinatorial chemistry. Tutorial-style chapters review computational tools to analyze molecular diversity, methods of solid-phase peptide and small-molecule synthesis, and approaches to synthesizing solid- and solution-phase libraries.

Z40,842-5

Analytical Chemistry

R. Kellner, J.-M. Mermet, M. Otto, and H.M. Widmer, Eds., Wiley-VCH, Weinheim, FRG, 1998, 530pp. This title offers students and newcomers to the field a modern, stimulating, clearly structured overview of analytical chemistry worldwide. The work will allow those individuals specializing in a particular aspect of analytical chemistry to learn about other aspects of the field.

Z40,854-9

Capillary Electrophoresis in Chiral Analysis

B. Chankvetadze, John Wiley & Sons, New York, NY, 1997, 572pp. Capillary electrophoresis (CE) allows separation on a very small scale: Chiral analysis is the separation of different molecules that are mirror images of one another. As regulations around the world demand increasing levels of purity of chiral molecules, CE is becoming a very important technique for safeguarding the public's health. This book is both an in-depth introduction and a comprehensive review of current technology regarding the applications of CE in chiral analysis.

Z40,869-7

Biotransformations in Organic Chemistry: A Textbook

3rd ed., K. Faber, Springer-Verlag, New York, NY, 1997, 402pp. Updated edition provides a basic introduction to the use of biocatalysts in modern preparative organic chemistry.

Z28,737-7

Biomedical Frontiers of Fluorine Chemistry

I. Ojima, J.R. McCarthy, and J.T. Welch, Eds., American Chemical Society, Washington, DC, 1996, 386pp. Reviews recent research on fluorine-containing molecules in biology and medicinal chemistry. Details applications for biomedical problems.

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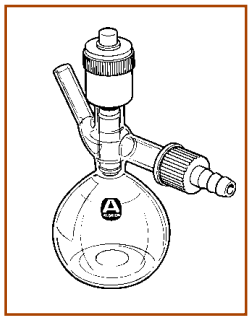

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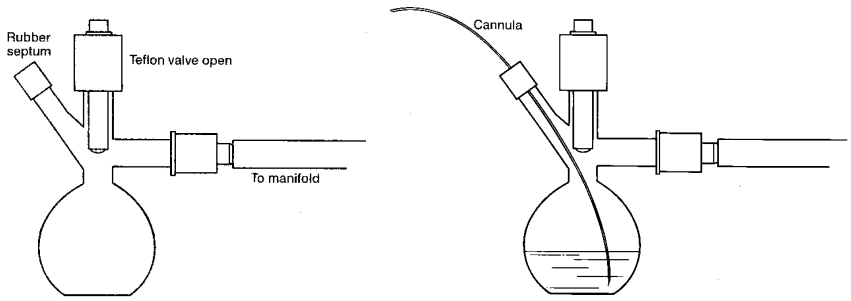

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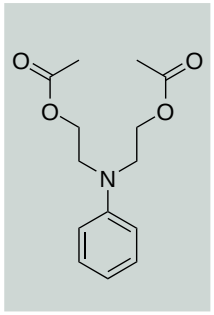
Aldrichimica Acta

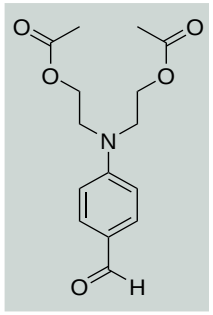
Volume 31, Number 3, 1998 (*Last issue in 1998*)

Transition-Metal-Based Lewis Acid Catalysts

New Products

Polymers with promising electro-optic features, including high second-order optical nonlinearity, good thermal and temporal stability, and low long-wavelength absorption, have been prepared from these two compounds.[1-3]



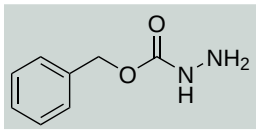


(1) Wang, P.N. et al. *Chem. Mater*. **1995**, *7*, 185. (2) Zhang, Y. et al. *Polymer* **1997**, *38*, 2893. (3) Sun, S.-S. et al. *Chem. Mater*. **1996**, *8*, 2539.

47,797-4 ***N*-Phenyldiethanolamine diacetate**, 97%

48,488-1 **4-[Bis[2-(acetyloxy)ethyl]amino]benzaldehyde**, 98%

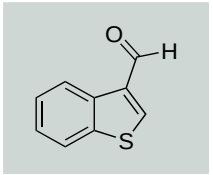
Benzyl carbazate is frequently used to prepare hydrazine-substituted compounds. Examples include azapeptides and hydrazine-substituted flavins.[1,2]



(1) Quibell, M. et al. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2843. (2) Kim, J.-M. et al. *J. Am. Chem. Soc*. **1995**, *117*, 100.

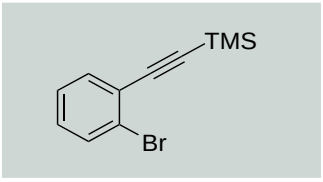
49,978-1 **Benzyl carbazate**, 98%

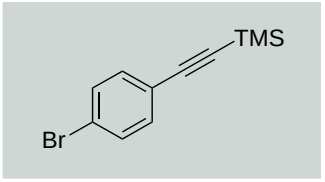
Benzo[*b*]naphtho[*d*]thiophene and [1]benzothieno[3,2-*h*]isoquinolines have been prepared from this aldehyde.[1,2]



(1) Castle, N. et al. *J. Heterocycl. Chem*. **1981**, *18*, 967. (2) Shafiee, A. et al. *ibid*. **1976**, *13*, 141.

49,496-8 **Thianaphthene-3-carboxaldehyde**, 95%



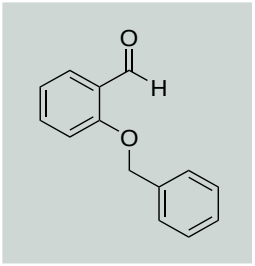


Molecular wires,[1] phenylethynyl oligomers,[2] angular phenylenes,[3] and dehydrobenzoannulenes[4] have been prepared from these arylacetylenes.

(1) Anderson, S. et al. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2383. (2) Hsung, R.P. et al. *Organometallics* **1995**, *14*, 4808. (3) Schmidt-Radde, R.H.; Vollhardt, K.P.C. *J. Am. Chem. Soc*. **1992**, *114*, 9713. (4) Haley, M.M. *Synlett* **1998**, 557.

48,469-5 **(2-Bromophenylethynyl)trimethylsilane**, 98%

49,401-1 **(4-Bromophenylethynyl)trimethylsilane**, 98%

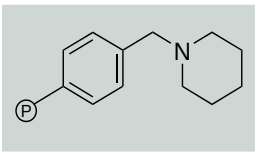


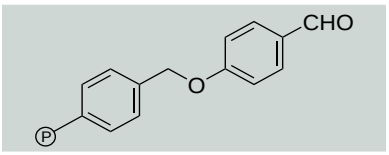
Leukotriene B_4 antagonists and blocking groups for rotaxanes have been prepared from these useful synthons.[1,2]

(1) Chan, W.K. et al. *J. Med. Chem*. **1996**, *39*, 3756. (2) Gibson, H.W. et al. *J. Org. Chem*. **1993**, *58*, 3748.

49,718-5 **2-(6-Chlorohexyloxy)tetrahydro-2*H*-pyran**, 95%

49,974-9 **2-Benzyloxybenzaldehyde**, 98%



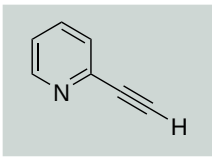


These polymer-bound reagents are used as scavengers in solid-phase organic synthesis. The polymer-bound piperidine is an acid scavenger, while the benzaldehyde is used to scavenge primary and secondary amines via formation of the imine.

Kaldor, S.W. et al. *Tetrahedron Lett*. **1996**, *37*, 7193.

49,461-5 **Piperidine, polymer-bound**
47,208-5 **4-Benzyloxybenzaldehyde, polymer-bound**

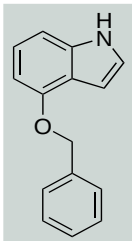
Polymers with interesting electrical properties have been prepared using ethynylpyridine.[1,2]



(1) Balogh, L. et al. *J. Polym. Sci., Part A: Polym. Chem*. **1998**, *36*, 703. (2) Gal, Y. et al. *Bull. Korean Chem. Soc*. **1998**, *19*, 22.

46,992-0 **2-Ethynylpyridine**, 98%

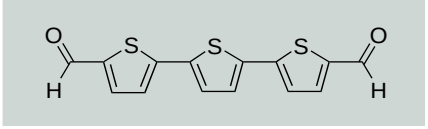
A number of heterocycles with promising pharmacological activity have been prepared from this indole.[1,2]



(1) Chan, W.K. et al. *J. Med. Chem*. **1996**, *39*, 3756. (2) Sheppard, G.S. et al. *ibid*. **1994**, *37*, 2011.

24,621-2 **4-Benzyloxyindole**, 98%

Oligothiophenes with interesting electronic and optical properties have been prepared from this terthiophene.[1,2]



(1) Novikova, T.S. et al. *Synth. Met*. **1996**, *83*, 47. (2) Wei, Y. et al. *Chem. Mater*. **1996**, *8*, 2659.

49,910-2 **2,2':5',2''-Terthiophene-5,5''-dicarboxaldehyde**, 97%

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About Our Cover

The Brown Family (oil on paper mounted on canvas, 23⅝ x 28½ in.) by the American artist Eastman Johnson (1824–1906) represents James Brown, whose father founded the international mercantile banking firm that still bears the name Brown Brothers and Company, with his wife Eliza and their grandson William in the parlor of their house on University Place in New York. It is at one time both a scene of everyday life and a group portrait, combining the two types of painting for which Johnson was best known. Signed and dated 1869, it is a record of the appearance of the home where the Browns had raised their family, commissioned from the artist in anticipation of a move further uptown to a new residence at Park Avenue and 37th Street.

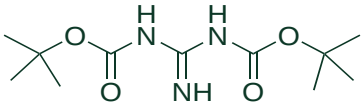
The Browns are shown seated by the fire in their comfortable parlor. Young William has interrupted his grandfather's reading of the evening paper, causing his grandmother to look up from her knitting. The room, with its paintings and other decorative objects, carved furniture, gilded frames, heavy red draperies, carved marble mantle, green wallpaper, strapwork ornament and figured carpet, reflects the affluence and social position of the Brown family. However, the appearance of this room was criticized as garish and tasteless when the painting was first exhibited. Nevertheless, when the Browns moved to their new Park Avenue home they had this room dismantled and reinstalled there, and their son John even later moved it into his own house.

This painting is a gift of David Edward Finley and Margaret Eustis Finley to the National Gallery of Art.

"Please Bother Us."

by

Jai Nagarkatti, President



Dr. Ganesan Vaidyanathan of the Department of Radiology at the Duke University Medical Center kindly suggested that we offer 1,3-bis(*tert*-butoxycarbonyl)guanidine. This reagent converts bromoalkanes to guanidines using sodium hydride,[1] and alcohols to guanidines using Mitsunobu's conditions.[2]

(1) Vaidyanathan, G.; Zalutsky, M.R. *J. Org. Chem.* **1997**, *62*, 4867.
(2) Dodd, D.S.; Kozikowski, A.P. *Tetrahedron Lett.* **1994**, *35*, 977.

49,687-1 1,3-Bis(*tert*-butoxycarbonyl)guanidine, 98%

Naturally, we made this useful reagent. It was no bother at all, just a pleasure to be able to help.

Lab Notes

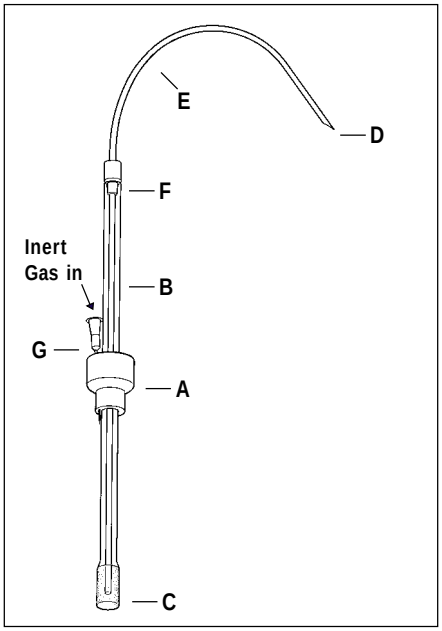
Moving Disc Filtration: Low-Temperature, Inert-Atmosphere Removal of Solvent from Low-Melting Crystals in an Ordinary, One-Neck Flask

The motivation for assembling this device came from our need to rapidly and efficiently remove mother liquors from crystalline, low-melting solids under conditions which allow maintenance of a low-temperature and/or dry, inert atmosphere. For finely divided crystals containing significant amounts of entrapped liquid, suction/pressure filtration was mandated. The several devices uncovered in a literature search,[1-5] while effective, require more specialized apparatus and complicated maneuvers than does the one described herein. This device differs from others in that it allows the crystalline solid to remain in the one-neck flask in which it has crystallized, and is easily adapted to fit a range of flask sizes. Furthermore, it can be assembled almost entirely from commercially available parts.

Assembly begins by boring a hole (cork borer) through rubber septum **A** (e.g., ⅋19/22, Aldrich **Z10,076-5**) to allow insertion (snug fit, inserted through the narrow end of the septum) of gas-dispersion tube **B** (**Z14,546-7**, porosity 170–220, 12mm o.d.). The length of protrusion of the fritted glass end (**C**) will be adjusted throughout the course of liquid removal. The noncoring tip **D** of an 18-inch, 12-gauge, double-ended needle (**E**) is pushed through the small end of "#3" rubber septum **F** (e.g., **Z10,072-2**), far enough to allow the flat end of the needle to reach the bottom of the inside of the gas-dispersion tube, with the #3 septum sealing the top of the gas-dispersion tube. The noncoring end of the needle is bent into a smooth ~120° arc. Syringe needle **G** (e.g., a B-D PrecisionGlide®, **Z19,250-3**) is inserted into the well of the ⅋19/22 septum, until the tip emerges through the bottom of the wall on the lower end of the septum. Needle **G** is connected to a gas line (e.g., N_2, Ar; needle-tubing connector w/male Luer Lok®). The apparatus is now ready to use.

The ⅋19/22 septum (**A**) fits snugly into a standard 50-mL Erlenmeyer flask. To adapt the apparatus to a larger flask (with or without a standard taper joint), conical neoprene rubber filter adapters (set: **Z25,423-1**) can be nested on the flask. We have thus removed mother liquors from 50- to 500-mL Erlenmeyer flasks.

Multiple crystallizations are needed to separate (2'*R*)-1'-(3'-bromo-2'-methylpropyl) (1*S*)-10-camphorsulfonate (mp 29 °C) from its higher-melting (2'*S*) diastereomer. In a typical procedure, a solution of these isomers in methanol is crystallized at 0 °C. The flask, held in an ice-water bath, is fitted with the



apparatus, with the inert gas flowing gently. The gas dispersion tube is held above the liquid, and the noncoring end of the needle is inserted about 1.5 inches into a receiver flask, to accommodate spitting. The gas dispersion tube is then pushed down to make and maintain contact with the liquid (immersion is not necessary). Gas pressure forces the liquid out through the needle. When the gas dispersion tube reaches the top of the crystalline solid, it is held in contact with the solid surface; wicking action continues to drain solvent from the crystals. When an acceptable level of dryness is attained, the crystals can be rinsed with additional cold solvent. We rinse these crystals with cold ether to facilitate drying. When the crystals are sufficiently dry that they will not melt/dissolve in the remaining solvent, the flask is removed from the cold bath, and the crystal drying is completed in any of the standard ways. We normally weigh and analyze the completely dry crystals, then redissolve them in the appropriate amount of solvent for the next crystallization, all without removing them from the flask. We have handled amounts of solid from ~1g to 100g in this way, and have used bath temperatures as low as -30°C; much lower temperatures should not be a problem.

The basic principle of this apparatus can be used in modified versions. For example, on a larger scale (larger, wider-mouth, or multiple-neck flask), the 18-inch needle can be omitted and the gas dispersion tube modified (bent at the receiver end, a larger-diameter fritted disc at the immersed end). With this modification, we have removed 1-2 liters of solvent from 200-300g of crystals in a beaker (in an ice bath) by aspirator suction, with an inert gas blanket to minimize moisture condensation. The fritted disk is easily moved around and used to tamp down the crystals while providing a wicking surface, thereby maximizing solvent removal.

(1) Czapkiewicz, J.; Tutaj, B. A Design for Low-Temperature Filtration of Strongly Hygroscopic Crystals. *J. Chem. Educ.* **1992**, *69*, 590. (2) Shaw, C.F., III; Allred, A.L. Crystallization and Filtration Apparatus for Low Temperatures and Inert Atmosphere. *J. Chem. Educ.* **1970**, *47*, 164. (3) Giese, R. Low Temperature Recrystallization Tube. *J. Chem. Educ.* **1968**, *45*, 610. (4) Holah, D.G. Apparatus for Preparations and Filtrations Under Inert, Dry Conditions. *J. Chem. Educ.* **1965**, *42*, 561. (5) Smith, F.E. *Aldrichimica Acta* **1989**, *22*, 58, and references therein.

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Transition-Metal-Based Lewis Acid Catalysts

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Outline

1. Introduction

In 1960, Yates and Eaton reported that molar equivalents of aluminum trichloride were capable of accelerating certain Diels–Alder reactions by as much as 10^5 times over the corresponding thermal reactions.[1] Whereas proton catalysis of these reactions had been reported,[2] the observation that Lewis acids were capable of accelerating the Diels–Alder cycloaddition was a seminal discovery which propelled the development of a variety of new reactions that relied on Lewis acid promotion. In addition to the classical Diels–Alder reaction (**eq 1**), these include the Mukaiyama[3] (**eq 2**) and Sakurai[4] (**eq 3**) reactions, the hetero-Diels–Alder cycloadditions[5] (**eq 4**), the ene reactions[6] (**eq 5**), and the nitrone–olefin [3+2] additions[7] (**eq 6**).

After the efficacy of aluminum trichloride was demonstrated, it was natural to investigate the halides of B(III), Sn(IV) and Ti(IV) as well as those of the lanthanides, Zn(II), and Mg(II) for Lewis acid promotion. Generally, stoichiometric or greater amounts of the Lewis acid were employed in order to achieve maximum acceleration and to compensate for the destruction of the Lewis acid by hydrolysis. Later, when these Lewis acids were modified for use in asymmetric synthesis, catalytic quantities began to be used. These modified chiral Lewis acids were usually prepared by addition of a chiral ligand to an appropriate Lewis acid precursor. Although notable successes have been reported by the use of these chiral catalysts, they present a number of disadvantages. Among these are their high sensitivity to water, the tendency of ligated Lewis acids to scramble their ligands and to form oligomeric species. The fact that the (achiral) Lewis acid precursor is usually more catalytically active than the chiral ligated species can lead to diminution of the observed enantiomeric excess unless the chiral catalyst is completely formed. As a consequence, great care and considerable effort is required in order to exclude these complications or to identify the catalytically active species. It was for these reasons that, some years ago, we began a search for transition-metal-based Lewis acid catalysts in the expectation that structurally defined, stable catalysts would be produced.

2. Background

Soon after we began our search for suitable transition-metal-based Lewis acids, there appeared three reports on such catalysts, **1**,[8] **2**,[9] and **3**.[10] Compound **1** is a very effective catalyst for the classical Diels–Alder reaction at low catalyst loading. However, it has a strong tendency to polymerize dienes and is moisture sensitive. Despite these problems, this was an important discovery because it indicated how a normally electron-rich metal, in this case d^6 tungsten (0), could be modified to act as a Lewis acid. The SbF_6 ligand in **1** is very labile and is readily replaced by the carbonyl functions of dienophile aldehydes, ketones, and esters; this results in the formation of cationic adduct complexes. Further, because the coordination of the adduct is trans disposed to the NO^+ ligand, the dienophile is labile by virtue of the strong trans-effect of NO^+. The lability of the adduct is important in catalysis because it assures that ligand dissociation will not be turnover-limiting.[11] Lewis acid induced activation of a substrate occurs because the Lewis acid withdraws electrons from the substrate and thereby activates it to reaction. A positively charged Lewis acid is expected to enhance the required electronic displacement over that provided by a similar neutral Lewis acid. The presence of charge in transition-metal Lewis acids may be generally necessary, at least for the classical Diels–Alder reaction, but is not sufficient to provide Lewis acidity. In the case of **1**, the electron-withdrawing π-acidic carbonyl and nitrosyl ligands are important in contributing to the tungsten Lewis acidity. Thus, we have replaced, successively, one and two of the carbonyl ligands of **1** by phosphines and have found that the Lewis acidity, as measured by the rates of a standard Diels–Alder reaction, is progressively reduced. This is consistent with the expectation that the replacement of electron-withdrawing carbonyl ligands by electron-donating phosphines will increase the negative charge on the metal, thereby diminishing its Lewis acidity. That charge alone is not necessarily sufficient to produce Lewis acidity is demonstrated by our observation that the cationic complex $[Ru(diphos)_2Cl]^+$ (diphos is $Ph_2PCH_2CH_2PPh_2$) is a very poor catalyst for most Diels–Alder reactions.

Professor Brice Bosnich (right) receiving the *1998 ACS Award in Inorganic Chemistry* from Dr. Mark A. Drezdzon, Manager–Techware, Sigma-Aldrich Research.

From the above discussion, it is obvious that **2** should be a powerful Lewis acid catalyst; it has two nitrosyl ligands, is dipositively charged, and has a vacant coordination position for substrate binding. This is the case,[9] but like **1**, it suffers from being a potent catalyst for polymerizing dienes. Compound **3**, on the other hand, is expected to be electron-rich but the presence of the positive charge might provide mild Lewis acidity. It was found that **3** is a useful catalyst for the (Danishefsky) hetero-Diels–Alder reaction, but the classical Diels–Alder reaction is not catalyzed by **3**. The principal reason for the latter inactivity is that dienophiles, which are generally electron-deficient olefins, displace the ethylene ligand of **3** to form stable π-olefin complexes which do not react with dienes.

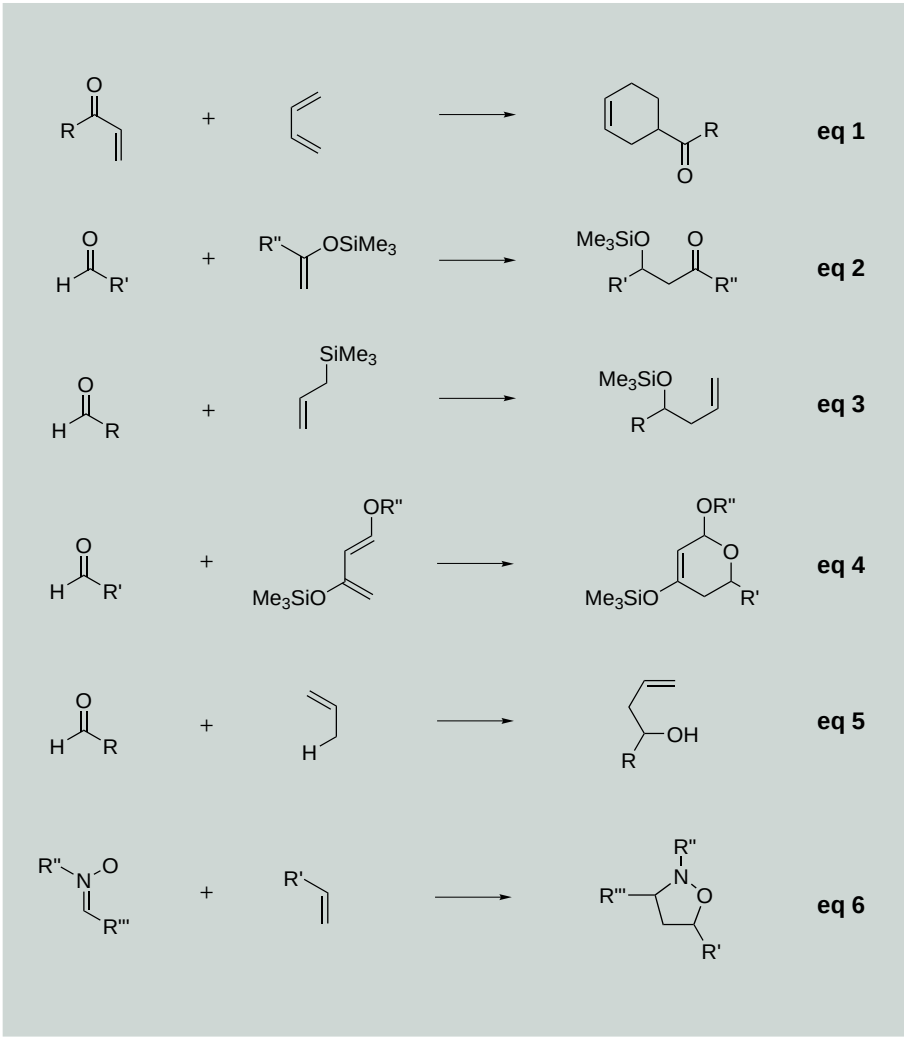
Thus, for the classical Diels–Alder reaction in particular, the problem of generating transition-metal Lewis acids resides in producing complexes where the electron density of the metal is such that diene polymerization does not

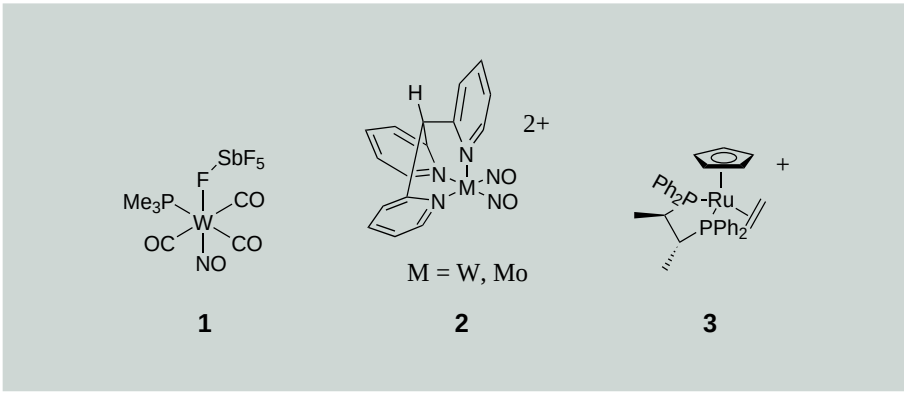
occur and where π-olefin coordination is suppressed. Tuning the Lewis acidity of the transition metal can be a fairly rational process and different reactions require varying degrees of Lewis acidity. For example, strong Lewis acids are generally required for the classical Diels–Alder reaction whereas milder Lewis acids are preferred for the Mukaiyama reaction and its variant, the (Danishefsky) hetero-Diels–Alder reaction.

3. Ruthenium and Titanium Complexes as Lewis Acids

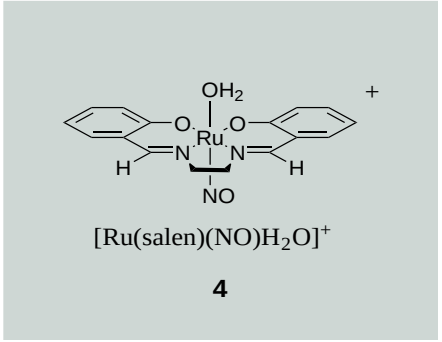
The complex $[Cp_2TiCl_2]$, where Cp is the cyclopentadienyl ligand, is a stable, robust complex which can be modified into chiral forms by appropriate substitution of the Cp ligands.[12] Although it has a vacant *d* orbital,[13] it does not form Lewis acid adducts because the vacant orbital is sterically inaccessible. With sterically less demanding ligands, such as acetonitrile, this remaining orbital is employed for coordination as occurs in the complex $[Cp_2Ti(NCCH_3)_3]^{2+}$. Titanium (IV), however, is an electropositive metal and it would be expected to act as a strong Lewis acid even in the presence of the electron-donating Cp ligands provided that the chloro ligands in $[Cp_2TiCl_2]$ were replaced by readily displaceable ligands such as H_2O or the triflate anion ($CF_3SO_3^-$ = OTf). The complexes $[Cp_2Ti(OTf)_2]$ and $[Cp'_2Ti(H_2O)_2](OTf)_2$, where Cp′ is the pentamethylcyclopentadienyl ligand, had already been prepared and characterized.[14] Both of these complexes are soluble in weakly coordinating solvents such as methylene chloride and nitroalkanes. We found that, in these solvents, organic aldehyde and ketone ligands readily replaced the OTf or H_2O ligands, and, moreover, the exchange is rapid and reversible. The latter condition is necessary for efficient catalysis,[11] otherwise the catalytic turnover could be controlled by the rates of substrate coordination and dissociation. The intrinsic Lewis acidity of these titanium (IV) centers will be enhanced by the fact that the substrate adducts will carry a positive charge. Thus, the complexes $[Cp_2Ti(OTf)_2]$ and $[Cp'_2Ti(H_2O)_2](OTf)_2$ have the necessary characteristics for catalytic Lewis acid activity. As we show presently, these complexes are efficient catalysts for the classical Diels–Alder reaction. A related zirconium (IV) complex, $[Cp_2Zr(O\text{-}t\text{-}Bu)\ THF]^+$, was also shown to act as a catalyst for the Diels–Alder reaction.[15]

Unlike titanium(IV), ruthenium(II) complexes are generally electron-rich at the metal center. Ruthenium(II) complexes are usually robust, air-stable, water-insensitive, diamagnetic (d^6) octahedral compounds. These are attractive characteristics if the complexes could be modified to act as Lewis acids. For this purpose, we prepared the stable and robust ruthenium(II) complex **4** as the weakly coordinating $SbCl_6^-$ salt.[16]





The characteristics which were expected to make **4** a Lewis acid were its positive charge, the presence of the electron-withdrawing ligand NO^+ trans disposed to the H_2O ligand, and the presence of hard donor ligands such as oxygen and nitrogen. Because of the trans-disposed NO^+ ligand, the water ligand was expected to be very labile. This proved to be the case, because, in nitromethane solutions, exchange with $^{17}OH_2$ at -25°C was rapid on a ^1H NMR time scale.



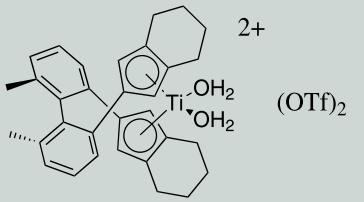
Further, addition of aldehydes or ketones to these solutions led to the formation of adducts which were stable but exchanged rapidly. It is interesting to note that these adducts became more stable with an increase in temperature.

4. The Diels–Alder Reaction

Some of the results obtained using the three catalysts $[Ru(salen)(NO)H_2O]^+$, $[Cp'_2Ti(H_2O)_2]^{2+}$ and $[Cp_2Ti(OTf)_2]$ are collected in **Table 1**. Many other dienes and aldehyde and ketone dienophiles are subject to catalysis by these complexes but the list in **Table 1** serves to exemplify the salient features. None of these three catalysts significantly accelerates the Diels–Alder reactions of α,β-unsaturated esters at these low catalyst loadings. Even at 1 mol % loadings these catalysts accelerate the reactions by a factor of 10^3 to $>10^5$ over the corresponding thermal reactions. As is nearly always observed in catalysis of the Diels–Alder reaction, the product isomer ratio is greater than in the corresponding thermal reactions. Whereas the ruthenium catalyst tends to have a lower turnover frequency, it has an advantage over the titanium catalysts in that no polymerization of the dienes is observed. For slow reactions, which take more than 50 h for 90% completion, the titanium complexes do cause small amounts of diene polymerization.

Unlike traditional Lewis acids, neither the $[Ru(salen)(NO)H_2O]^+$ nor the $[Cp'_2Ti(H_2O)_2]^{2+}$ catalyst is destroyed by water. Moreover, Diels–Alder catalysis can be carried out in the presence of water. Even in the presence of a 100-fold excess of water over the catalyst concentration, only a small retardation in turnover frequency is observed. Thus, as a practical matter, these two robust, air-stable catalysts can be used at low catalyst loadings without special precautions for the Diels–Alder reaction. Although the $[CpTi(OTf)_2]$ complex does undergo some hydrolysis in solution, it also can be used without special precautions for the Diels–Alder reaction. As we shall see presently, this hydrolysis is a significant feature for other reactions.

Unlike many other Lewis acid catalyzed reactions, the Diels–Alder reaction preserves the binding functionality of the dienophile in the product. In other words, for example, an aldehyde functionality in the dienophile produces an aldehyde product. As a consequence, it might be assumed that product inhibition in catalysis would be observed because of product binding to the catalyst. Perhaps surprisingly, only weak product inhibition is observed. In the presence of a 100-fold excess of product over the catalyst, the Diels–Alder reaction proceeds only three times more slowly than in the absence of initially added product. Presumably, the greater steric bulk of the product over that of the substrate accounts, to some extent, for the mild product inhibition.



[((*S*)-biphenacene)Ti$(H_2O)_2$](OTf)$_2$

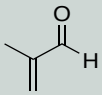
5

Although not commonly recognized as a problem in Lewis acid catalysis, there is a possible alternative origin for the catalysis. It could be argued that the aquo groups in the catalysts, whether incorporated initially or formed subsequently by hydrolysis, are acidic and that the observed catalysis is merely the result of proton catalysis. The exclusion of Brønsted over Lewis acid catalysis is not always easy to establish. An indication that the Diels–Alder reactions by the present catalysts are due to Lewis acid promotion is the observation that the strong acid CF_3CO_2H, at 1 mol % loadings, does not catalyze any of the Diels–Alder reactions studied in the times for the catalyzed reactions shown in **Table 1**. The most persuasive case against proton catalysis is the observation of enantioselection by chiral modifications of the titanium catalysts. The chiral diaquo complex **5** was prepared in enantiopure forms.[17] The Diels–Alder reaction (**eq 7**) was carried out in methylene chloride solution at -78 °C using 2 mol % of **5**.[18] The reaction was complete in 30 minutes and the enantiomeric excess (ee) of the major isomer (exo) was 75%. This result clearly indicates that the major, if not the sole, path for catalysis involves the activation of the dienophile by binding to the metal rather than the result of proton catalysis.

5. The Oxo–Ene Reaction

The ene reaction has traditionally been promoted by using stoichiometric or greater amounts of Lewis acids, although a number of catalytic systems using Zn(II)[19] and Ti(IV)[20] have been reported.

Table 1. Results of Diels–Alder Catalysis at 25°C Using 1 mol % of $[Ru(salen)(NO)H_2O]^+$, $[Cp'_2Ti(H_2O)_2]^{2+}$, and $[Cp_2Ti(OTf)_2]$.[a]

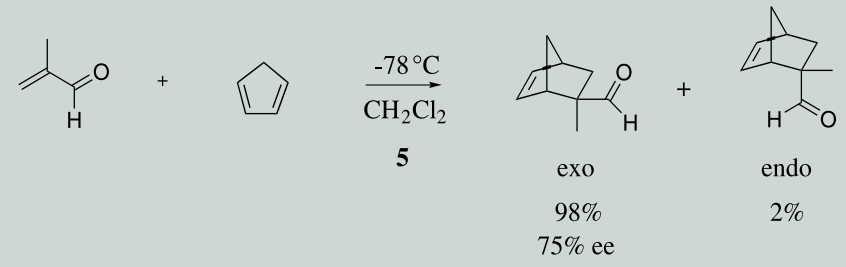
	Dienophile	Diene	Time in hours for 90% yield (isomer ratio)		
			$[Ru(salen)(NO)H_2O]^+$ [b]	$[Cp'_2Ti(H_2O)_2]^{2+}$ [c]	$[Cp_2Ti(OTf)_2]$ [c]
1			5 (99:1)	6.7(95:5)	18(87:13)
2			4.4 (98:2)	3.2 (94:6)	0.4 (97:3)
3			3 (93:7)	3.2 (91:9)	5.7 (92:8)
4			48 (70:30)	76 (75:25)	66 (80:20)
5			71 (91:9)	13 (94:6)	3.8 (92:8)
6			22 (99:1)	2.1 (95:5)	4.9 (93:7)

[a] Catalyses were carried out using 2.8 M concentrations of each substrate for the ruthenium catalyst, and using 1.0 M of each substrate for the two titanium catalysts. [b] In CH_3NO_2 solutions. [c] In CH_2Cl_2 solutions.

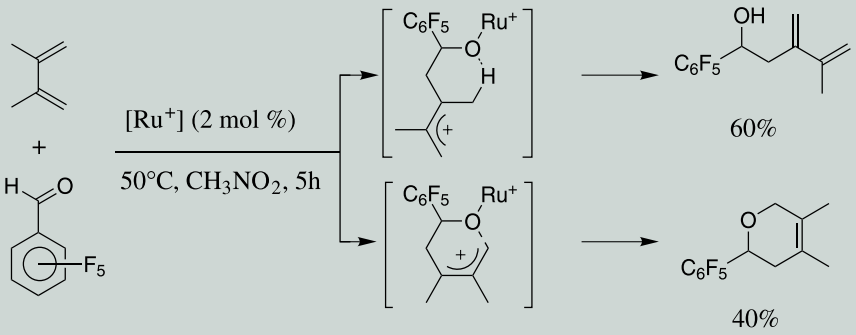
The intermolecular ene reaction is generally restricted to electron-deficient aldehydes. We have explored a number of these reactions using the ruthenium catalyst; some of the results are collected in **Table 2**.[21] Although catalysis is restricted to very activated carbonyl compounds, the results serve to illustrate that a d^6 transition metal can be modified to act as a catalyst for the normally sluggish ene reaction. These reactions are not catalyzed by 2 mol% CF_3CO_2H under the same conditions, indicating that the ruthenium center is the true catalyst.

We found that 1,3-dienes, unlike mono-olefins, undergo more facile catalysis, presumably by a stepwise process involving carbenium ion intermediates (**eq 8**). A number of dienes were investigated, and all gave a mixture of the ene and hetero-Diels–Alder products presumably because of the bifurcation caused by the two putative intermediates illustrated in **eq 8**.[21]

It is probable, however, that the ruthenium catalyst will find application for the intramolecular ene reaction. An example is the clean conversion of (+)-citronellal to l-isopulegol using 1 mol % of the ruthenium catalyst in CH_3NO_2 solution at 25°C. The catalyst gives 80% yield of l-isopulegol, the rest consisting of the other (three) isomers. This transformation is used in the industrial production of l-menthol, in which zinc bromide is used as the Lewis acid in stoichiometric amounts.



eq 7



eq 8

6. The [3+2] Nitrone–Olefin Cycloaddition

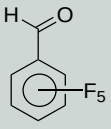
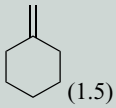
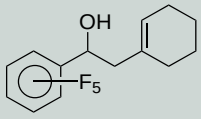
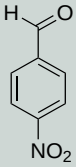
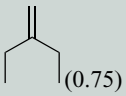
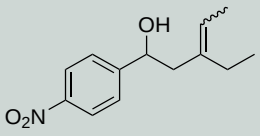
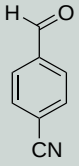
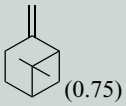
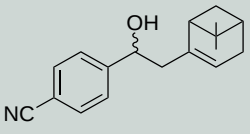
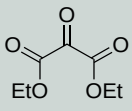
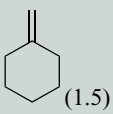
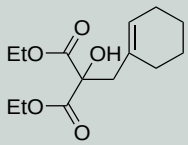
Traditionally, the [3+2] nitrone–olefin cycloaddition has been carried out thermally generally using electron-rich olefins. There have been a number of reports where traditional Lewis acids have been employed,[22] usually in amounts ≥ 20 mol %. The complex $[Cp_2Ti(OTf)_2]$ seemed ideally suited for this reaction because nitrones were expected to bind strongly to the titanium center by the oxygen atom and, after reaction, the oxygen atom would become a less strongly coordinating ether (**eq 6**). Thus product inhibition was not expected to be significant.

Using nitrone **6** and ethyl vinyl ether in CH_2Cl_2 solution in the presence of 4 mol % of $[Cp_2Ti(OTf)_2]$, the reaction depicted in **eq 9** occurred rapidly at 25°C .[23]

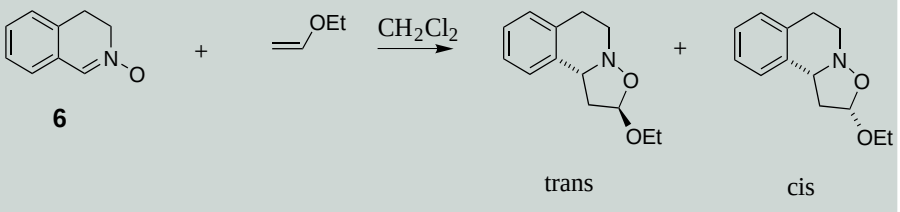
After a certain amount of experimentation, it was determined that the majority of the transformation was due to proton catalysis. It was found that very small concentrations of water, which remain even after drying the CH_2Cl_2 solvent, caused the formation of triflic acid by the process shown in **eq 10**.

The oligomeric species, "$[Cp_2TiO]$" is not a catalyst but HOTf is a very potent catalyst for this reaction. This hydrolysis reaction does not

Table 2. Results of the Intermolecular Oxo–Ene Reaction Using 2 mol % of $[Ru(salen)(NO)H_2O]^+$ in CH_3NO_2 Solution at 50°C.

	Enophile (0.5M)	Olefin (conc., M)	Product	t, h[a]
1		 (1.5)		5
2		 (0.75)		40
3		 (0.75)		41
4		 (1.5)		42

[a] Time required for 95% reaction.



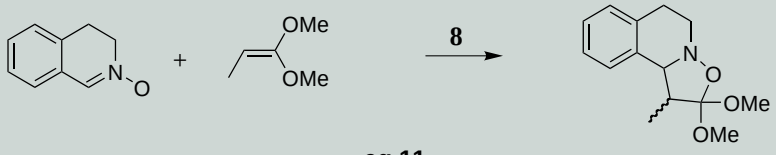
6

trans cis

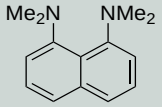
eq 9

$$[Cp_2Ti(OTf)_2] + H_2O \longrightarrow "[Cp_2TiO]" + 2HOTf$$

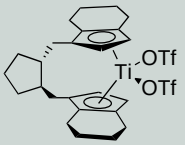
eq 10



eq 11

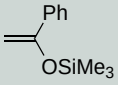


7

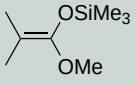


R, *R*-[Ti(*S*, *S*-cyclacene)$(OTf)_2$]

8

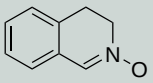
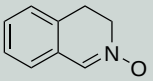
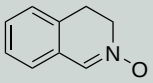
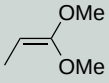
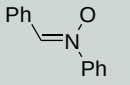
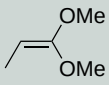
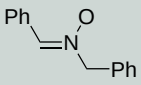
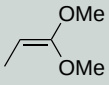


9



10

Table 3. Results of [3+2] Nitrone–Olefin Cycloadditions [a]

	Nitrone	Olefin	t for 95% Yield (h)	Isomer Ratio (trans:cis)
1			60	75:25
2			40	88:12
3			0.3	65:30
4			0.5	32:68
5			31	17:83

[a] Using 3 mol % $[Cp_2Ti(\mathbf{6})_2](OTf)_2$ in the presence of 6 mol % of proton sponge in CH_2Cl_2 solutions at 25°C. Concentrations of the nitrones are ~ 0.5 M and those of the olefins are 0.6–1.0 M.

appear to interfere in the Diels–Alder reaction as we noted earlier. Proton catalysis of the nitrone–olefin reaction occurs even with pyridinium triflate, and it was found necessary to use Proton-Sponge® **7** in order to suppress proton catalysis.

In the presence of the proton sponge, the titanium complex acts as a catalyst. It was found more convenient to use the nitrone adduct $[Cp_2Ti(\mathbf{6})_2](OTf)_2$ rather than $[Cp_2Ti(OTf)_2]$ as the catalyst. The bisnitrone adduct is readily prepared as stable crystals and its X-ray crystal structure is shown in **Figure 1**. In CH_2Cl_2 solutions, the catalyst exists as the bisnitrone complex and, under catalytic conditions where an excess of nitrone is present for the majority of catalysis, it is probable that the bisnitrone complex is the catalytically active species.

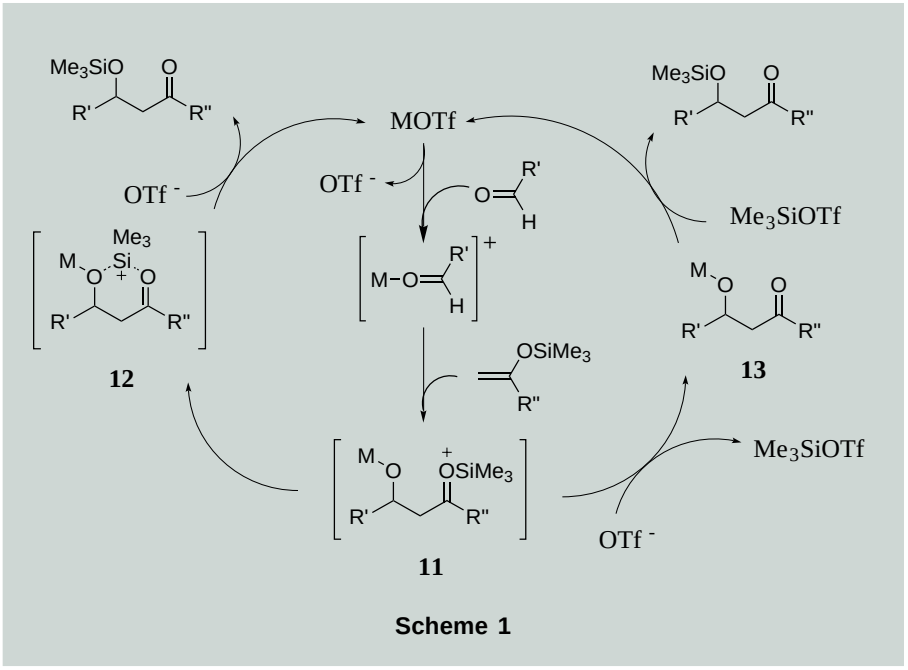
Some of the results are collected in **Table 3**. The rates of the cycloadditions depend on both the nature of the nitrone and olefin—the cyclic nitrone and the more electron-rich olefins are associated with faster rates. Compared to the corresponding thermal reactions, the dimethyl vinyl ethers react catalytically at least 10^4 times faster, whereas the monoethers are catalyzed about 10^3 times faster than the corresponding thermal reactions. Of course, the catalytic turnover rate can be increased by increasing the catalyst concentration.

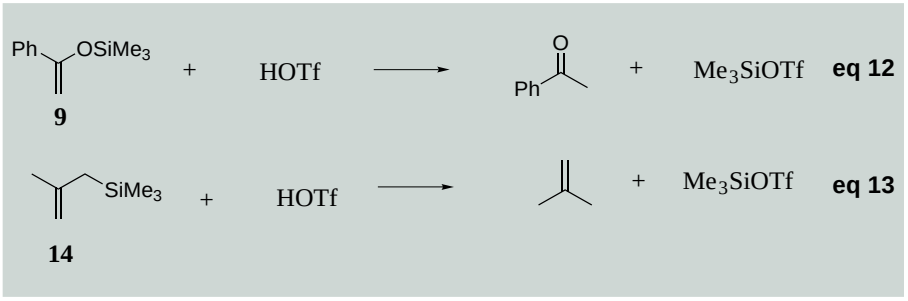
Given the strong proton catalysis observed for these reactions, it was useful to demonstrate that enantioselectivity could be observed. For this purpose, we employed the chiral catalyst *R*,*R*-[Ti(*S*,*S*)-cyclacene$(OTf)_2$] (**8**)[23] in the presence of a proton sponge in CH_2Cl_2 solutions at 25°C (**eq 11**). The major (trans) isomer of the product was isolated and found to have an ee of 14% suggesting that catalysis involves binding of the nitrone to the titanium center.

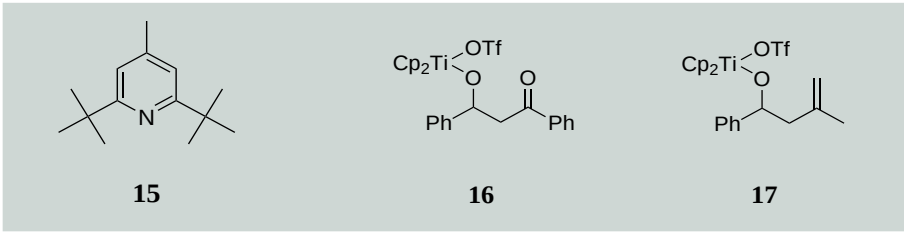
7. The Mukaiyama and Sakurai Reactions

Using a variety of aldehydes and ketones and silyl enol ether **9**, or ketene acetal **10**, the ruthenium catalyst was found to promote the Mukaiyama reaction (**eq 2**) at very low catalyst loadings, even as low as 0.1 mol %.[24] Although

it is not clear that the ruthenium complex is the real catalyst, the complex appears to undergo reduction by the vinyl ethers or vinyl acetals. The reduction is evidenced by a sudden color change in solution but the apparent reduction is unpredictable, occurring sometimes after 20 turnovers and at other occasions after 100 or more turnovers. Because of this and other reasons, the ruthenium complex is not a useful catalyst for this reaction and suggests that the Mukaiyama reaction may require oxidatively stable transition-metal Lewis acids. One would anticipate that the $[Cp_2Ti(OTf)_2]$ complex would be less likely to reduce during Mukaiyama catalysis. This proved to be the case and the titanium complex was found to catalyze the condensation of a variety of aldehydes and ketones with the olefins, **9** and **10**.[25] Similarly, this same complex catalyzed the Sakurai coupling (**eq 3**) of a variety of allylic silanes with aldehydes, ketones, acetals, ketals, and orthoesters.[26] We do not provide tables of these results because the $[Cp_2Ti(OTf)_2]$ complex is not the primary catalyst in any of these coupling reactions. In order to show how this conclusion was reached, it is necessary to understand the mechanism of these two reactions.







8. Mechanisms of the Mukaiyama and Sakurai Reactions

The Lewis acid catalyzed Mukaiyama reaction is generally assumed to proceed by the mechanism outlined in **Scheme 1**.

The aldehyde binds to the metal by displacement of the triflato ligand. The enol ether then attacks the bound, activated aldehyde to give the intermediate, **11**. It is the fate of this intermediate which determines if the catalysis proceeds by the expected path. If the trimethylsilyl group is transferred by way of an intermediate resembling **12**, the product will form and the catalyst (MOTf) will be regenerated. On the other hand, the trimethylsilyl group in **11** could be captured by triflate ion to give intermediate **13**. Were the Me_3SiOTf to capture the aldolate, **13**, the product would also be formed by an intermolecular pathway. Trimethylsilyl triflate, however, is known to be a very powerful catalyst for the Mukaiyama reaction[27] and the question arises as to whether the rate of capture of the enolate, **13**, by trimethylsilyl triflate will be faster than trimethylsilyl triflate catalysis. A similar scheme can be proposed for the Sakurai reaction.

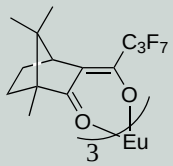
An extensive investigation of the mechanism of $[Cp_2Ti(OTf)_2]$ catalysis in CH_2Cl_2 solutions of both the Mukaiyama and Sakurai reactions revealed a number of disconcerting features of these catalyses which appear to have general applicability. Addition of the enol ether, **9**, or the allylic silane, **14**, to a CH_2Cl_2 solution of $[Cp_2Ti(OTf)_2]$ leads to the immediate formation of trimethylsilyl triflate. It was shown that all of the Mukaiyama and Sakurai reactions proceed by the Me_3SiOTf path. The formation of Me_3SiOTf has its origins in the formation of HOTf by the hydrolysis reaction shown in **eq 10**.

Trimethylsilyl triflate is formed by the very rapid representative reactions shown in **eq 12** and **eq 13**.

There are two obvious ways of suppressing the formation of triflic acid. One is to thoroughly dry the solvent, but this is an impractical proposition because Me_3SiOTf is such a potent catalyst that even very small concentrations of adventitious water, as little as 10^{-5} M, are sufficient to cause rapid catalysis. The other is to take normal precautions for exclusion of water but to carry out the catalysis in the presence of a hindered base such as **15**. The protonated form of this base does not induce the reactions shown in **eq 12** and **eq 13** and hence Me_3SiOTf will not form by this method.

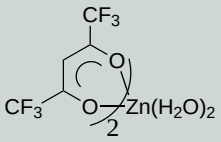
Following the catalysis by ^1H NMR spectroscopy using $[Cp_2Ti(OTf)_2]$, benzaldehyde, silyl enol ether **9**, and base **15** in CD_2Cl_2 at 25°C, revealed the formation of Me_3SiOTf and one equivalent of the aldolate, **16**. Under similar conditions, the Sakurai coupling between benzaldehyde and the allylic silane **14** also gave Me_3SiOTf and **17**.

In both cases, the aldolates, **16** and **17**, are stable in the presence of a molar equivalent of Me_3SiOTf. As a consequence, the $[Cp_2Ti(OTf)_2]$ complex merely serves as an initiator for the production of the real catalyst, Me_3SiOTf. These results, namely the formation of the Me_3SiOTf catalyst either by Lewis acid hydrolysis or as a result of the formation



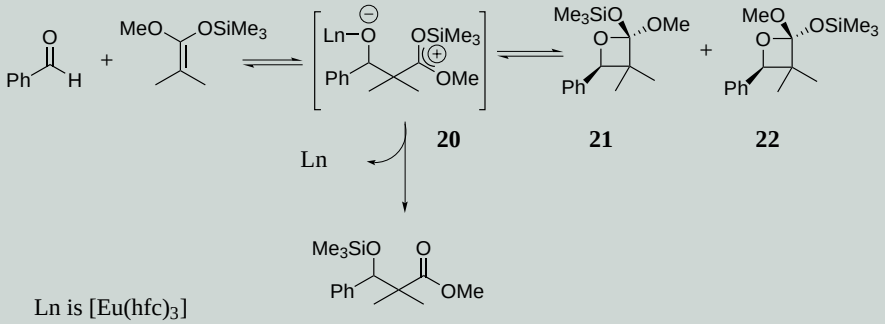
[Eu(hfc)$_3$]

18



[Zn(facac)$_2$(H$_2$O)$_2$]

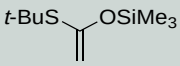
19



20 **21** **22**

23

Scheme 2



24

Figure 1. Structure of [Cp$_2$Ti(6)$_2$]$^{2+}$ [23b]

of a stable aldolate, are not peculiar to the present catalyst and appear to be widespread among many, but not all, reported catalysts.[28,29]

There are, however, a number of chiral Lewis acid catalysts which act as efficient enantioselective catalysts for the Mukaiyama reaction.[28,30,31] It is clear that these enantioselective reactions proceed via the chiral Lewis acid and not by way of the achiral, Me_3SiOTf catalyst. The question then arises as to what characteristics the Lewis acid must possess in order that the formation of Me_3SiOTf be suppressed. Inspection of **Scheme 1** suggests that if the Lewis acid–oxygen bond of the aldolate intermediate is weak and, if no kinetic impediments exist, the probability of Me_3Si^+ transfer, either intra- or intermolecularly, will be increased. Consequently, the probability of forming standing concentrations of Me_3SiOTf will be reduced. With these considerations in mind, we selected the two potential catalysts **18** and **19** for investigation. Both are neutral complexes and, unlike [Cp$_2$Ti(OTf)$_2$], are expected to form weak aldolate bonds. Additionally, the presence of electron-withdrawing fluorine groups in the ligands is expected to enhance the Lewis acidity of the metals. Because [Eu(hfc)$_3$] is expected to form 7-coordinate Lewis acid adducts and the [Zn(facac)$_2$(H$_2$O)$_2$] complex is expected to form 6-coordinate adducts after displacement of the water ligand, we might expect that the aldolate bonds will be especially weak in these neutral complexes. Generally, Lewis acidity decreases as the coordination number increases. Thus, both the neutral charge and the coordination number of the aldolates are expected to conspire to give weak adducts and weak aldolate metal bonds.

Using 4 mol % [Eu(hfc)$_3$] in benzene solution at 20°C, the reaction between benzaldehyde and the ketene acetal is represented in **Scheme 2**.[32] After one hour, equilibrium between the two oxetanes, **21** and **22**, is reached using 1M solutions of each substrate. The initial kinetic ratio of oxetane isomers is 48:52, which changes to a thermodynamic ratio of 38:62. (We were unable to identify the isomers.) The equilibrium constant between the substrates and oxetanes is 3. After several hours, the Mukaiyama product, **23**, begins to appear and is completely formed irreversibly after several days. Addition of the hindered base, **15**, does not alter the rate of catalysis indicating that protons are not involved in catalysis. Using the chiral [Eu(hfc)$_3$] catalyst, the Mukaiyama product, **23**, was found to have an ee of 15%. As required, the oxetanes are racemic after equilibration, but if the catalysis is quenched before equilibration of the oxetanes is obtained, a small ee of 5% is found. Although these enantiomeric excesses are modest, they indicate that the lanthanide complex is involved in catalysis.

The results outlined in **Scheme 2** are significant because the aldolate, **20**, is not detected and hence its unstable Me_3Si^+ group will not be captured by the aldehyde substrate. Rather, the aldolate collapses either to the oxetanes or to the starting substrates. For this particular case, this process occurs faster than the silyl transfer to give the Mukaiyama product. The fugacious nature of the putative intermediate and the stability of the silyl groups in oxetanes ensures that Me_3Si^+ will not enter into the catalytic cycle. The weak aldolate bond ensures that the carbenium ion of **20** is captured rapidly but the relative rates of formation of the oxetanes and Mukaiyama product depend on both the catalyst and the substrate.[32] Thus, we find that, with [Zn(facac)$_2$(H$_2$O)$_2$] under the same conditions and using benzaldehyde and the same ketene acetal, the formation of the Mukaiyama product occurs more quickly than in the case of the lanthanide complex. Although the oxetanes are observed, they do not achieve equilibration before the final product is formed. An extreme case is the reaction of benzaldehyde and substrate **24** using the zinc catalyst. In this case, no oxetanes are observed and only the Mukaiyama product is formed.

Although these weak Lewis acids are real catalysts for the Mukaiyama coupling reactions, they do not cause coupling of ketones with silyl ketene acetals nor coupling of silyl enol ethers with aldehydes or ketones. Further work is required to ascertain whether other Lewis acids can be devised which genuinely catalyze coupling of these less reactive substrates. For those concerned about the mechanism of enantioselection, it is clear that the origins of the chiral discrimination can be

very complex. The enantioselection will depend on the rates of equilibration of the oxetanes and on the rate of production of the Mukaiyama product. The most complicated condition is when the oxetanes are formed at a rate comparable to the rate of formation of the product.

9. Concluding Remarks

This review of our work is presented from the point of view of an inorganic chemist. Inorganic chemists tend to focus on the attributes of metal and on the mechanism of the catalysis. New transition-metal-based Lewis acids are likely to be discovered and become increasingly used. It is hoped that this review will provide some of the conceptual underpinnings for the development of new transition-metal Lewis acids.

10. Acknowledgments

This work was supported by grants from NIH. I am grateful to my coworkers for developing this field. Their names appear in the references.

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About the Author

Brice Bosnich, a native of Australia, completed his undergraduate degree at the University of Sydney and his Ph.D. at the Australian National University. He has held posts at University College, London, at the University of Toronto, and is now a professor of Chemistry at the University of Chicago. A common thread throughout his work has been an interest in inorganic stereochemistry, which has included the relationship between absolute structure and circular dichroism spectra, diastereoselective complexation, and molecular mechanics of organometallic complexes. His work in asymmetric catalysis has led him to develop new catalysts and to study their mechanisms. He is the recipient of a number of awards, including the Noranda Award of the Canadian Institute of Chemistry, the Organometallic Medal and the Nyholm Medal, both of the Royal Society of Chemistry. This review is the result of his receipt of the ACS Award in Inorganic Chemistry sponsored by Aldrich. His current interests are in cooperative bimetallic reactivity and in supramolecular recognition.

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M = Sc, Y, La, Ce, Pr, Nd, Gd, Tb, Er, Yb

References: (1) Kaltsoyannis, N.; Bursten, B.E. *J. Organomet. Chem.* **1997**, *528*, 19. (2) Strittmatter, R.J.; Bursten, B.E. *J. Am. Chem. Soc.* **1991**, *113*, 552. (3) Bougeard, P. et al. *Inorg. Chem.* **1985**, *24*, 93. (4) Birmingham, J.M.; Wilkinson, G. *J. Am. Chem. Soc.* **1956**, *78*, 42. (5) Idem *ibid.* **1954**, *76*, 6210. (6) Molander, G.A. *Chemtracts* **1998**, *2*, 237. (7) Watson, P.L.; Parshall, G.W. *Acc. Chem. Res.* **1985**, *18*, 51. (8) Qian, C. et al. *J. Organomet. Chem.* **1992**, *430*, 175. (9) Qian, C. et al. *J. Mol. Catal.* **1990**, *63*, L1. (10) Qian, C.; Zhu, D. *Synlett* **1990**, 417. (11) Greenwald, A.C. et al. *Mater. Res. Soc. Symp. Proc.* **1993**, *301*, 21. (12) Mine, Ph. et al. *Nucl. Instrum. Methods Phys. Res., Sect. A* **1997**, *387*, 171. (13) Tamai, H. et al. *Chem. Mater.* **1996**, *8*, 454. (14) Tanner, P.S. et al. *Chem. Ber./Recl.* **1997**, *130*, 155.

Lab Notes, continued from page 75

Stankovic Transfer Adapters

Transferring lyophilized solids, such as synthetic peptides, from a round-bottom flask to a vial is often difficult due to the light and fluffy nature of these solids. Such solids often float in air and are easily blown away by the slightest of air currents, making it nearly impossible to transfer them using standard weighing paper without substantial losses. To circumvent this problem, I developed a simple adapter which connects the round-bottom flask and the vial directly. To transfer the solid, one simply inverts the assembly and taps the vial on a soft surface such as a cork ring. This process effects the complete transfer of the solid with minimal losses. Use of the adapter also minimizes exposure of the compound to the air, making it ideal for use with moisture- or air- sensitive solids. Moreover, although originally designed to solve the problems associated with the transfer of lyophilized solids, I now use it to transfer any solid from a vial to a flask, since it eliminates the need to use some intermediate device such as a weighing boat or paper.

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Division of Warner–Lambert Co.
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Ann Arbor, MI 48105

Editor's Note: *Aldrich sells a variety of Stankovic transfer adapters, please see page 92 of this issue.*

Two-Dimensional Thin-Layer Chromatography of Caged Products

It is a common practice for us to attach a caging group (photoremovable group such as *o*-nitrobenzyl or desyl) to a biologically active substrate to block its activity. The caged substrate is then activated by light to study the effect of sudden influx of the substrate. This condition is otherwise difficult to achieve by typical diffusion processes.

The caging reaction usually generates a mixture of products, and the easiest way to identify a prospective caged product is by 2-D TLC analysis. The reaction mixture is applied to one corner of a square TLC plate (5 cm x 5 cm; silica gel 60 F254; aluminum-backed) at baseline distance from either edge. The plate is developed and irradiated with a bench-top UV lamp for a few minutes. The plate is then rotated 90°, spotted with the starting substrate at the baseline as a reference, and developed along the second dimension. After photolysis, the spot that generates the starting substrate along the second dimension is the desired caged product. To achieve maximum resolution, a different solvent system is usually used for developing the plate along each dimension.

This analytical technique has been successfully applied to a variety of substrates such as adenosine 5'-triphosphate, P3-(1-(2-nitrophenyl)ethyl) ester, disodium.

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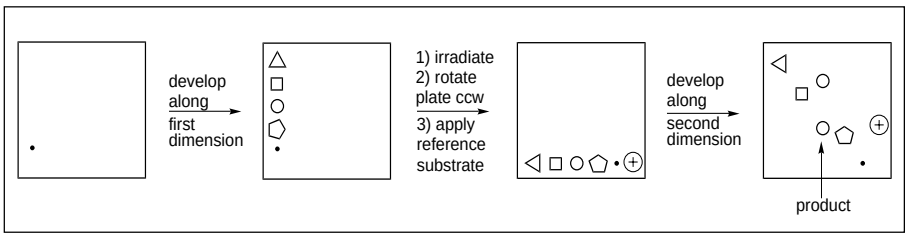

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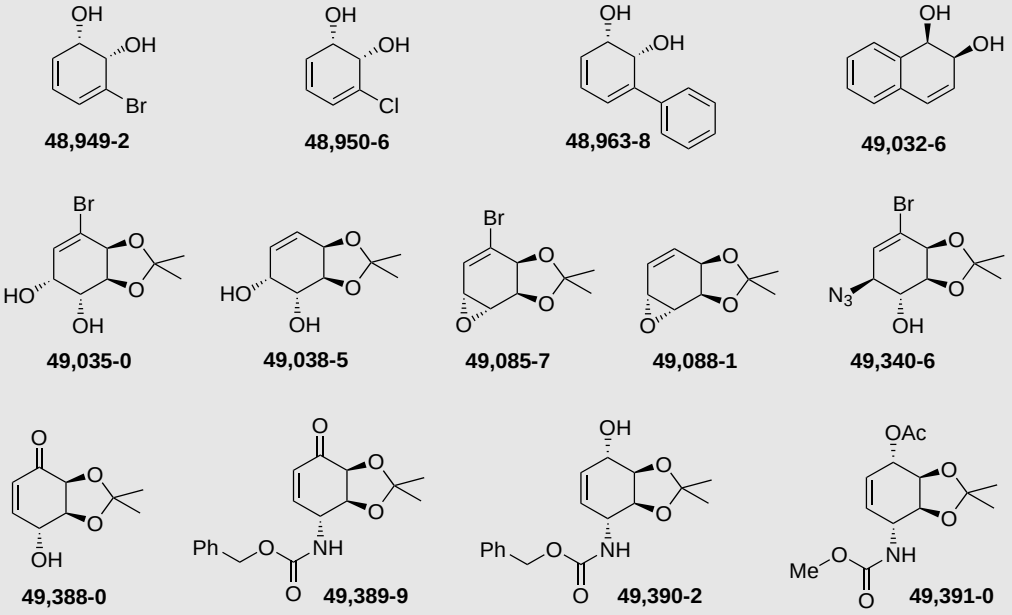
The *cis*-diene diol functionality offers researchers a fantastic opportunity for the manipulation of these building blocks into a variety of products. Chiral nonracemic *cis*-diene diols can undergo a variety of reactions such as oxidative cleavage, cycloadditions, electrophilic additions, and sigmatropic rearrangements.

Aldrich now offers an extensive line of *cis*-diene diols and their derivatives. All these products are offered as a suspension in phosphate buffer. The unit size corresponds to the actual amount of product and not the total volume. The label provides simple instructions regarding extraction of the product from the suspension prior to use. The chemical purity of each product was determined on the pure crystals prior to suspending them in the phosphate buffer. To place an order, please call **800-558-9160** (USA), or contact your local Sigma-Aldrich office.



48,949-2 **(1*S*-*cis*)-3-Bromo-3,5-cyclohexadiene-1,2-diol**, 96%
48,950-6 **(1*S*-*cis*)-3-Chloro-3,5-cyclohexadiene-1,2-diol**, 98%
48,963-8 **(1*S*-*cis*)-3-Phenyl-3,5-cyclohexadiene-1,2-diol**, 98%
49,032-6 **(1*R*-*cis*)-1,2-Dihydro-1,2-naphthalenediol**, 98%
49,035-0 **[3a*S*-(3aα,4α,5α,7aα)]-7-Bromo-3a,4,5,7a-tetrahydro-2,2-dimethyl-1,3-benzodioxole-4,5-diol**,99%
49,038-5 **[3a*S*-(3aα,4α,5α,7aα)]-3a,4,5,7a-Tetrahydro-2,2-dimethyl-1,3-benzodioxole-4,5-diol**, 98%
49,085-7 **[3a*S*-(3aα,5aβ,6aβ,6bα)]-4-Bromo-3a,5a,6a,6b-tetrahydro-2,2-dimethyloxireno[*e*]-1,3-benzodioxole**, 98%

49,088-1 **[3a*R*-(3aα,5aβ,6aβ,6bα)]-3a,5a,6a,6b-Tetrahydro-2,2-dimethyloxireno[*e*]-1,3-benzodioxole**, 96%
49,340-6 **[3a*S*-(3aα,4α,5β,7aα)]-5-Azido-7-bromo-3a,4,5,7a-tetrahydro-2,2-dimethyl-1,3-benzodioxol-4-ol**, 99%

49,388-0 **(3a*S*,7*R*,7a*S*)-7,7a-Dihydro-7-hydroxy-2,2-dimethyl-1,3-benzodioxol-4(3a*H*)-one**, 98%
49,389-9 **(3a*S*,7*R*,7a*S*)-7-(Carbobenzyloxyamino)-7,7a-dihydro-2,2-dimethyl-1,3-benzodioxol-4(3a*H*)-one**, 98%
49,390-2 **(3a*R*,4*S*,7*R*,7a*S*)-7-(Carbobenzyloxyamino)-3a,4,7,7a-tetrahydro-2,2-dimethyl-1,3-benzodioxol-4-ol**, 98%

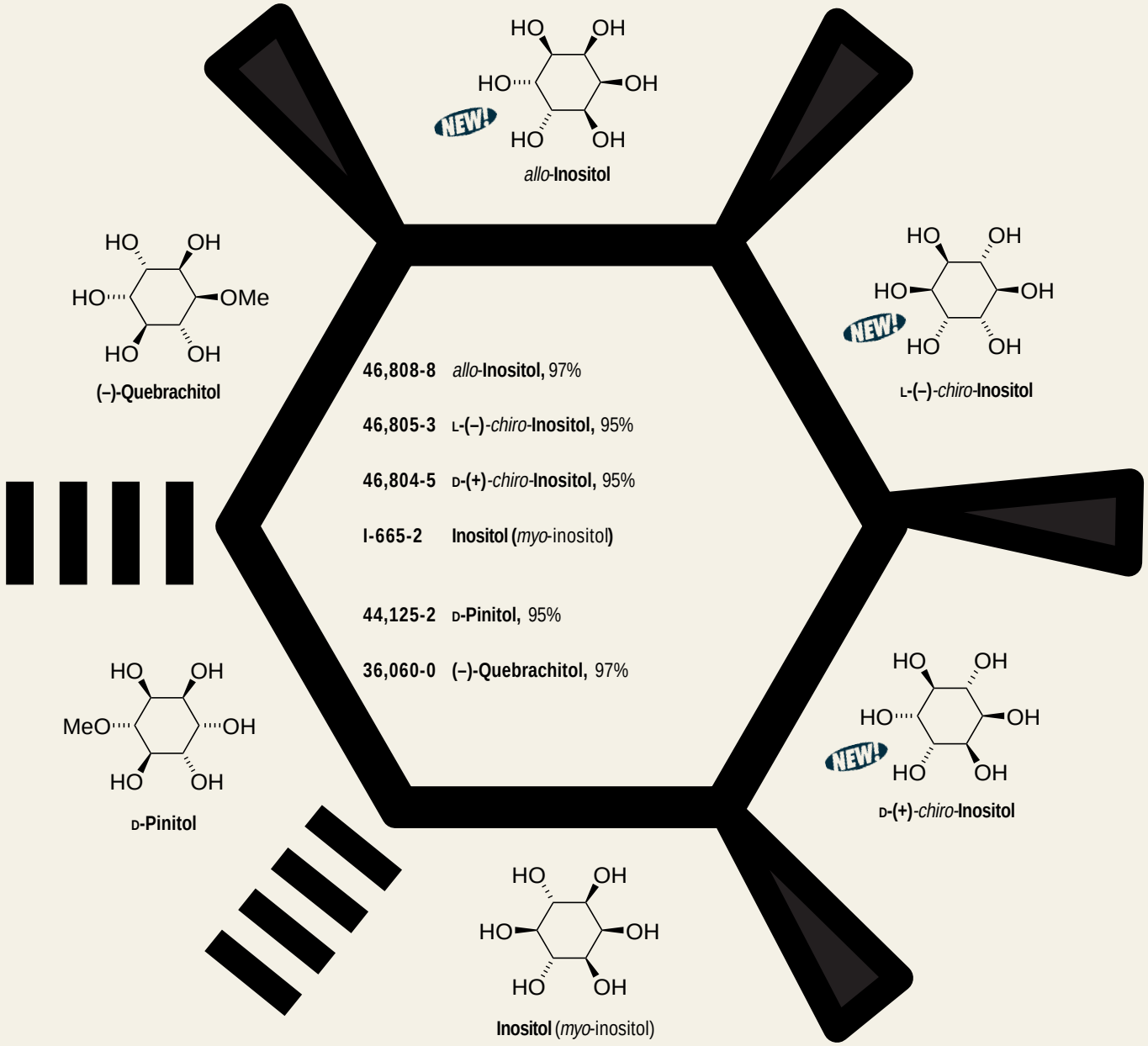
49,391-0 **(3a*R*,4*S*,7*R*,7a*S*)-3a,4,7,7a-Tetrahydro-7-(methoxycarbonylamino)-2,2-dimethyl-1,3-benzodioxol-4-ol 4-acetate**, 98%

Inositols

The inositols and their phosphates constitute an extremely important class of compounds. They have been used in the development of metabolically stable insulin mediators, inhibitors, and modulators of important metabolic functions such as glycolysis. Inositols are stable to degradative enzymes in vivo because they lack a hydrolytically labile glycosidic linkage. This feature is important for the development of metabolically stable insulin mediators.

Aldrich now offers a variety of the more rare inositols such as D-*chiro*- and *allo*-inositols; *neo*-inositol will soon be available. For more information, please call our Technical Services department at **800-231-8327** (USA).

References: (1) Potter, B.V.L. *Nat. Prod. Rep.* **1990**, *7*,1. (2) Bellington, D.C. *Chem. Soc. Rev.* **1989**, *18*, 83. (3) Berridge, M.J.; Irvine, R.F. *Nature* **1989**, *341*, 197. (4) Hudlicky, T.; Cebulak, M. *Cyclitols and Their Derivatives. A Handbook of Physical, Spectral, and Synthetic Data*; VCH: New York, 1993. (5) Hudlicky, T. et al. *Chem. Rev.* **1996**, *96*, 1195. (6) Hudlicky, T. et al. *Synthesis* **1996**, 897.



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Perspectives in Modern Synthetic Organic Chemistry

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- Professor **Yoshito Kishi**; *Harvard University*
  Recent Topics in Natural Product Synthesis
- Professor **Steven V. Ley**; *University of Cambridge*
  New Methods and Tools for Organic Synthesis
- Professor **Masakatsu Shibasaki**; *University of Tokyo*
  Recent Developments in Multifunctional Asymmetric Catalysis

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1999 ACS Award Recipients

Aldrich, a proud sponsor of three separate ACS awards, congratulates the following 1999 recipients for their outstanding contributions to chemistry.

ACS Award for Creative Work in Synthetic Organic Chemistry: Professor **Dale L. Boger**, The Scripps Research Institute

Selected for his outstanding contributions to, among others, the total synthesis of biologically important natural products, the studies of antitumor antibiotics that derive their biological properties from binding with DNA, the development of new synthetic methodologies in heterocyclic chemistry, and the early implementation of methods to carry out solution-phase combinatorial chemistry.

ACS Award in Inorganic Chemistry: Professor **Richard D. Adams**, the University of South Carolina

Chosen in recognition of his pioneering research on the chemistry of cluster complexes (polynuclear metal complexes). This includes the preparation and characterization of novel cluster complexes, the systematic investigation of these as powerful catalysts for the transformation of small organic molecules, and the development of new forms of catalysis by metal cluster complexes.

Herbert C. Brown Award for Creative Research in Synthetic Methods: Professor **Barry M. Trost**, Stanford University

As one of his nominating colleagues put it, Professor Trost has made "uniquely significant contributions to a broad spectrum of subjects in chemistry" and is a "pre-eminent contributor to synthetic methodology for over 33 years". Dr. Trost has fundamentally impacted such diverse research areas as the chemistry and biology of insect juvenile hormones, sulfur chemistry, the chemistry of strained rings, and transition-metal catalysis. He is credited with an impressive number of total syntheses of natural products and syntheses of important new materials such as pyracylenes.

Congratulations to each and all!

From the Aldrich Bookshelf

Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids

G.M. Coppola and H.F. Schuster, John Wiley & Sons, New York, NY, 1987, 393 pp. Focuses on the use of amino acids and their second-generation derivatives to produce chiral reagents, intermediates, and final products.

Z16,762-2

Stereoselective Synthesis

R.S. Atkinson, John Wiley & Sons, New York, NY, 1995, 600pp. Covers the majority of reaction types used in modern stereoselective synthesis. Introduces a simplified classification for reactions based on the number of chiral centers.

Z26,175-0

The Logic of Chemical Synthesis

E.J. Corey and X.-M. Cheng, John Wiley & Sons, New York, NY, 1995, 436 pp. Softbound. Discusses the logic underlying the analysis of complex synthetic problems.

Z27,174-8

Molecular Spectroscopy Workbench: Advances, Applications, and Practical Advice on Modern Spectroscopic Analysis

E.W. Ciurczak, John Wiley & Sons, New York, NY, 1998, 476pp. Compiles and updates the best articles to date from the eleven-year history of *Spectroscopy* magazine's successful "Molecular Spectroscopy Workbench" column. From the fundamentals of important techniques to novel time- and money-saving ideas, it draws from a broad spectrum of recent developments in the field of molecular spectroscopy. Includes information about near- and midrange infrared techniques, optical rotation/circular dichroism, UV/Vis and fluorescence, mass spectrometry, acousto-optic tunable filters, fiber optics, and new hardware.

Z40,865-4

Advanced Catalysts and Nanostructured Materials: Modern Synthetic Methods

W.R. Moser, Ed., Academic Press, New York, NY, 1996, 592pp. Provides a comprehensive review of the latest techniques for the preparation of advanced catalysts and solid-state materials of specific structure and morphology.

Z28,635-4

NMR Data Processing

J.C. Hoch and A.S. Stern, Wiley-Liss, New York, NY, 1996, 196pp. Complete information about how to process, present, and perform error analysis on data obtained from modern nuclear magnetic resonance (NMR) experiments. Includes extensive examples for maximum comprehension.

Z40,858-1

Applied Homogeneous Catalysis with Organometallic Compounds: A Comprehensive Handbook in Two Volumes

B. Cornils and W.A. Herrmann, Eds., VCH Publishers, Weinheim, FRG, 1996, 1,246pp. Comprehensive treatment of one of the most important topics in organometallic chemistry. Explores both basic research and industrial applications through treatment of catalytic reactions and processes.

Z40,230-3

The Encyclopedia of Reagents for Organic Synthesis

L.A. Paquette, Ed., John Wiley & Sons, New York, NY, 1995, 6234pp. Presents the facts in a "pros and cons" assessment of each reagent to give the complete picture. Where applicable, each entry includes: transformations recognized for the reagent; comparison of the specific properties of the reagent with those of other agents capable of equivalent chemistry; stereo-, regio-, and enantiocontrol qualifications.

8-volume set **Z24,805-3**

Metal and Ligand Reactivity: An Introduction to the Organic Chemistry of Metal Complexes

E.C. Constable, VCH Publishers, New York, NY, 1996, 308pp. Introduction to the reactions and interactions between metal ions and ligands. Provides useful information for organic synthesis.

Z28,938-8

Purification of Laboratory Chemicals

A must for any library!

4th ed., D.D. Perrin and W.L. Armarego, Eds., Butterworth, New York, NY, 1996, 450pp. Explains techniques of purification with specific methods for more than 4,000 chemicals and biochemicals.

Z28,581-1

Asymmetric Synthetic Methodology

D.J. Ager and M.B. East, CRC Press, Boca Raton, FL, 1996, 483pp. Implements asymmetric synthesis in an industrial chemistry environment. Provides methodology to perform specific asymmetric transformations with emphasis on scope and limitations.

Z27,403-8

Chiral Auxiliaries and Ligands in Asymmetric Synthesis

J. Seyden-Penne, John Wiley & Sons, New York, NY, 1995, 716pp. An in-depth guide for synthesis of chiral compounds in pharmaceutical and medical research. Provides an overview of the principles of physical organic chemistry governing stereoselection.

Z27,369-4

Reductions in Organic Chemistry

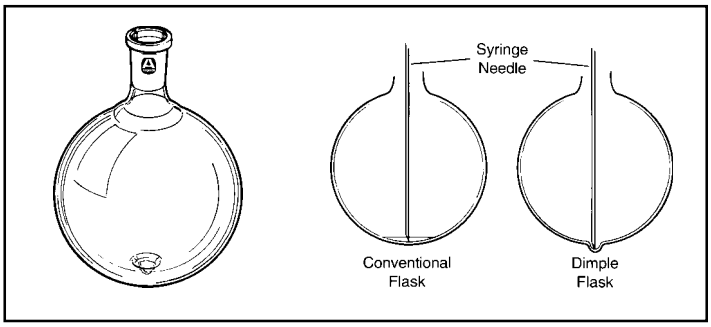
2nd ed., M. Hudlicky, American Chemical Society, Washington, DC, 1996, 429pp. A compilation of the types of reductions undergone by the various classes of organic compounds. Describes the methods, reactants, and products of reductions.

Z28,591-9

ALDRICH DIMPLE FLASKS

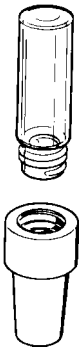
These flasks are designed to permit complete removal of liquids using noncoring type syringe needles, gauges 12 to 20, that are used for piercing rubber septa. A small indentation or "dimple" at the bottom of the flask acts as a reservoir to collect liquids which may then be drawn off via syringe. The dimple is small enough that it does not interfere with the use of egg-shaped magnetic stirring bars.

Cap. (mL)	14/20 Joint Cat. No.	24/40 Joint Cat No.
25	**Z40,632-5**	—
50	**Z40,633-3**	—
100	**Z40,634-1**	**Z40,636-8**
250	—	**Z40,637-6**
500	—	**Z40,638-4**
1,000	—	**Z40,639-2**



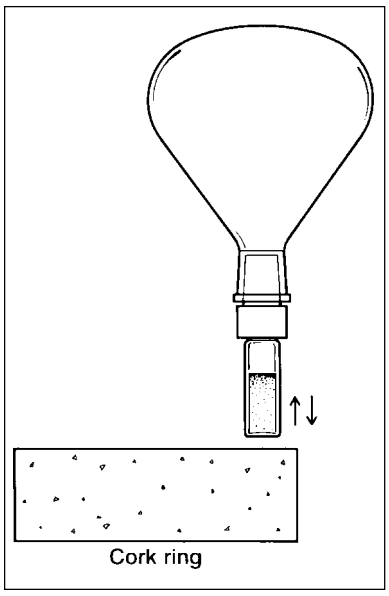
The design of these flasks was first published by Professor Brian E. Love of the East Carolina University Department of Chemistry in *Organic Preparations and Procedures International,* **1997**, *29*, 600-601.

STANKOVIC TRANSFER ADAPTERS



These unique adapters greatly simplify the transfer of solids from round-bottom flasks to vials. Precision-machined, chemically inert Teflon® PTFE adapters will not seize in the joint. A wide range of thread sizes are available to accommodate most sample vials including scintillation vials (22 mm threads).

- Transfers samples without exposure to air or moisture.
- Reduces sample losses due to air currents and static charge that can normally cause light solids to float or blow away when transferred open to the air.
- Excellent for transferring fluffy lyophilized samples, especially peptides.
- Transfers any freely flowing solid and eliminates the need for weighing paper or other intermediate devices.



Easy to Use:

Screw sample vial into bottle thread at top of adapter. Insert other end of adapter into flask joint. Invert assembly and gently tap* vial on a soft surface to transfer solids from flask into sample vial.

Joint	Bottle Thread	Cat. No.
14/20	13-425	**Z40,646-5**
24/40	13-425	**Z40,647-3**
	15-425	**Z40,648-1**
	20-400	**Z40,650-3**
	22mm	**Z40,658-9**
24/29	13-425	**Z40,651-1**
	15-425	**Z40,653-8**
	20-400	**Z40,654-6**
	22mm	**Z40,659-7**
29/32	13-425	**Z40,655-4**
	15-425	**Z40,656-2**
	20-400	**Z40,657-0**
	22mm	**Z40,660-0**

* Care must be used when tapping vial to prevent accidental breakage. Tapping on a cork ring or other soft surface is recommended.

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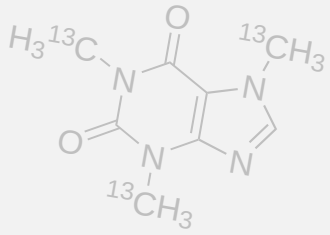

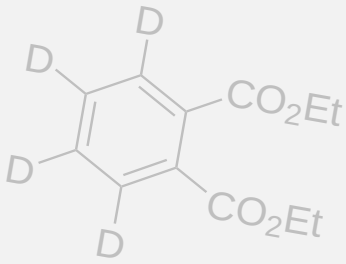

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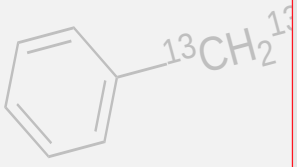

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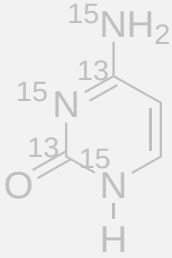

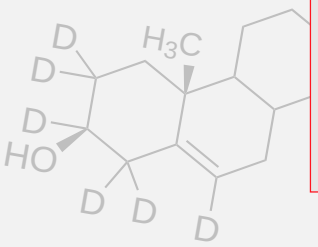

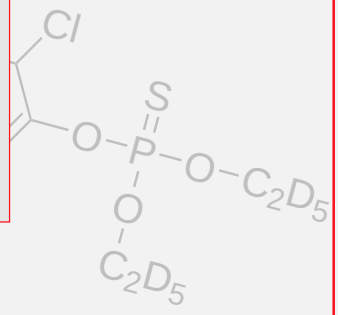

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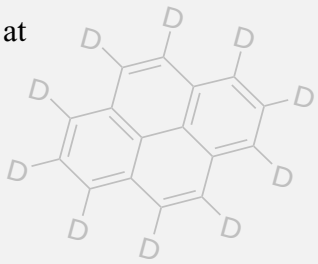

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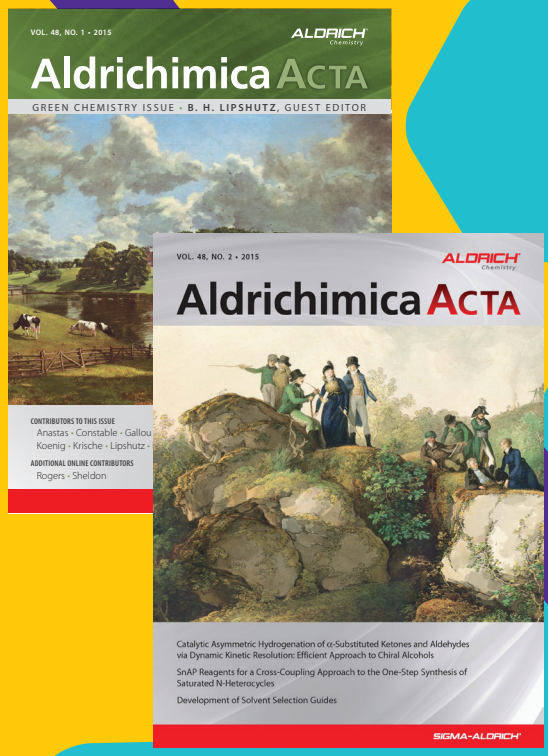

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