DEDICATED TO PROFESSOR H. C. BROWN ON HIS 90TH BIRTHDAY

Aldrichimica ACTA

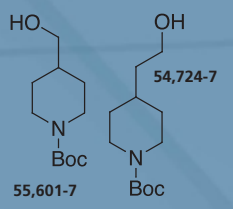
VOL. 35, NO. 1 • 2002

Herbert C. Brown and Aldrich

Asymmetric Reduction of Ketones and Ketimines

Pinane-Based "Allyl"boranes

NEW Products

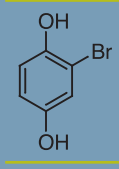


These Boc-protected piperidines have been utilized extensively in the drug discovery arena. Recent applications include their use in the synthesis of several types of GPIIb/IIIa antagonists[1-4] and of potent and selective inhibitors of acetylcholineesterase.[5]

(1) Hoekstra, W. J. et al. *J. Med. Chem.* **1999**, *42*, 5254. (2) Fisher, M. J. et al. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 835. (3) Egbertson, M. S. et al. *J. Med. Chem.* **1999**, *42*, 2409. (4) Xue, C.-B. et al. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3499. (5) Villalobos, A. et al. *J. Med. Chem.* **1994**, *37*, 2721.

55,601-7
***N*-Boc-4-piperidinemethanol**, 97%

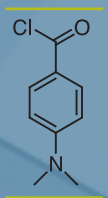
54,724-7
***N*-Boc-4-piperidineethanol**, 97%



This versatile hydroquinone has been employed as a building block for the synthesis of biologically active marine metabolites such as *ent*-chromazonarol,[1] 9,11-drimen-8α-ol,[2] and fulvanin.[2] It has also found applications in nonlinear optics as a monomer for phenylene–ethynylene oligomers.[3]

(1) Barrero, A. F. et al. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2325. (2) Barrero, A. F. et al. *Synlett* **2000**, *11*, 1561. (3) Wautelet, P. et al. *Macromolecules* **1996**, *29*, 446.

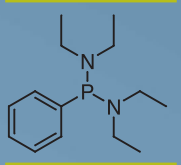
16,713-4
2-Bromohydroquinone, 97%



This convenient building block allows the facile preparation of 4-(dimethylamino)benzoyl-substituted compounds.

Purchase, T. S. et al. *Bioorg. Med. Chem.* **1997**, *5*, 739.

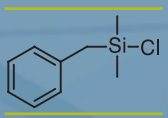
52,611-8
4-(Dimethylamino)benzoyl chloride, 97%



Utilized as a milder alternative to dichlorophenylphosphine (Aldrich catalog number D7,198-4).

(1) Nettekoven, U. *J. Org. Chem.* **1999**, *64*, 3996. (2) Tollefson, M. B. et al. *J. Am. Chem. Soc.* **1996**, *118*, 9052.

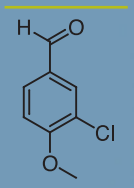
55,470-7
Bis(diethylamino)phenylphosphine, 97%



Employed in the synthesis of amino-substituted vinylsilanes, which were smoothly cyclized to the corresponding pyrrolidines.

Miura, K. et al. *Org. Lett.* **2000**, *2*, 385.

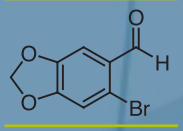
56,237-8
Benzylchlorodimethylsilane, 97%



Has been used in the synthesis of lycorine-type alkaloids[1] and substituted phthalazines.[2]

(1) Lida, H. et al. *J. Chem. Soc., Perkin Trans. I* **1975**, 2502. (2) Watanabe, N. et al. *J. Med. Chem.* **1998**, *41*, 3367.

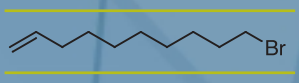
56,504-0
3-Chloro-4-methoxybenzaldehyde, 97%



This bromo aldehyde was employed in total syntheses of (–)-lycoricidine,[1] benzo[*c*]phenanthridines,[2] and the diaza analog of ellagic acid.[3]

(1) Keck, G. E. *J. Am. Chem. Soc.* **1999**, *121*, 5176. (2) Bernabe, P. *Tetrahedron Lett.* **1998**, *39*, 9785. (3) Kanojia, R. M. *ibid.* **1995**, *36*, 8553.

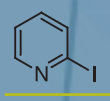
56,301-3
6-Bromopiperonal, 97%



Important intermediate for the preparation of macrocyclic ketones, such as (*R*)-(–)-muscone,[1] and biologically active macrocyclic lactones.[2]

(1) Kamat, V. P. et al. *Tetrahedron* **2000**, *56*, 4397. (2) Kobayashi, Y.; Okui, H. *J. Org. Chem.* **2000**, *65*, 612.

56,085-5
10-Bromo-1-decene, 97%



This versatile reagent has been used in Sonogashira[1] and Suzuki coupling reactions in the presence of carbon monoxide to produce α-pyridyl ketones,[2] as well as in coupling reactions with aryl thiols to produce heteroaromatic thioethers.[3]

(1) Koseki, Y. et al. *Tetrahedron Lett.* **2000**, *41*, 2377. (2) Couve-Bonnaire, S. et al. *ibid.* **2001**, *42*, 3689. (3) Schopfer, U.; Schlapbach, A. *Tetrahedron* **2001**, *57*, 3069.

55,876-1
2-Iodopyridine, 98%

Aldrichimica ACTA

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For worldwide contact information, please see the inside back cover.

About Our Cover

Le Château Noir (oil on canvas, 73.7 cm x 96.6 cm) was painted by Paul Cézanne between 1900 and 1904. At the center of the painting stands the chateau, with its Gothic windows, red door, and terra cotta and ochre walls contrasted with the deep green of the surrounding vegetation and the intense blue of the Provençal sky. The title, *The Black Chateau*, comes from the fact that the original owner, a manufacturer of lampblack (a pigment made from soot), had the house's interior walls painted black.

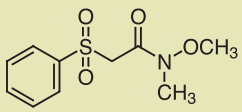
Cézanne was born in nearby Aix-en-Provence, and as a youth took long walks to the chateau and the surrounding estate. His father wanted him to study law, but in 1861 he abandoned his legal studies and went to Paris to devote himself to painting. There, he met the artist Camille Pissarro and became acquainted with the impressionists. He exhibited with these artists in 1874 and 1877, but his artistic aims were never entirely compatible with impressionism, which sought to capture through the analysis of color and light the effect of transitory visual sensation. The impressionist technique tends to dissolve any sense of solid form, but Cézanne declared that he wished "to make of impressionism something solid and durable, like the art of the museums". He wanted to "do Poussin over again, after nature", which is to say that he wanted to reconcile two seeming opposites, the immediacy of observed nature and the timeless order of the compositions of his seventeenth-century predecessor. He increasingly thought in terms of simple planes and volumes modeled in color, which he understood as the embodiment of the underlying forms of visible objects.

In *Le Château Noir*, the walls of the house, the path, the tree trunks and leafy branches, even the sky, are painted in planes of rich color. Cézanne had no interest in specific or picturesque details, but believed that a painting must succeed both as an illusion of depth and as a textural surface of heavy and vibrant pigments. The result of this approach was an ever-greater abstraction, and his influence on artists like Picasso and Braque, who in time almost completely abandoned any connection to the illusionism of traditional representation, was incalculable.

This painting is a gift of Eugene and Agnes Meyer to the National Gallery of Art, Washington, D.C.

"Please Bother Us."

Clint Lane, President



Dr. Indrapal Singh Aidhen and his research group at the Indian Institute of Technology Madras (Chennai, India) have developed *N*-methoxy-*N*-methyl-2-phenylsulfonyl-acetamide as a versatile reagent for the two-carbon homologation of alkyl halides under mild conditions (K_2CO_3 in DMF). Dr. Aidhen kindly suggested that we offer this valuable amide to our customers.

Satyamurthi, N.; Singh, J.; Aidhen, I. S. *Synthesis* **2000**, 375.
Satyamurthi, N.; Aidhen, I. S. *Carbohydr. Lett.* **1999**, *3*, 355.

56,108-8
***N*-Methoxy-*N*-methyl-2-phenylsulfonyl-acetamide**, 97%

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

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

Table of Contents

Herbert C. Brown and Aldrich

There is hardly any chemist today, who is not aware of Professor Brown's accomplishments in, and impact on, the field of chemistry. Perhaps no one is more keenly aware of his lasting contributions than we are at Aldrich Chemical Company.

When Professor Brown finally convinced a small chemical company (Aldrich) of the merits of commercializing his hydroboration technology,[1] a 30-year, highly successful collaboration began between Dr. Brown and Aldrich Chemical Company. Thus, the Aldrich-Boranes "acorn" was planted just over 30 years ago and has now grown into a tall, sturdy "oak". Some of the fruits of this collaboration have been the wide array of boron compounds that Aldrich has made available to chemists worldwide, and the financial rewards that the Purdue Research Foundation[2] and the recipients of the annual Herbert C. Brown Award[3] have reaped.

Photo courtesy of H.C. Brown

Sarah and Herbert Brown in front of the new building devoted to the production of air-sensitive compounds at the Aldrich plant near Sheboygan Falls, WI (October 14, 1999).

Brown served on the Aldrich Board of Directors (1972–1975), the Sigma-Aldrich Board of Directors (1975–1979), and has been retained as a consultant by Aldrich (1972–Present). A few of Brown's students came to work for Aldrich and made important contributions to the growth of the business, perhaps none more so than Clint Lane, Aldrich's current president.

No write-up about Professor Brown, however brief, would be complete without mentioning his lifelong passion for *chemistry*.[4] As attendees of professional meetings such as the ACS or the Boron Americas meetings can attest to, Nobel Laureate Brown still attends as many talks as he possibly can and unassumingly walks around the exhibition halls checking out exhibits, visiting vendors, and picking up chemical literature—just as an eager, young graduate student would do, except that Brown is nearly 90 years old! Professor Brown's other lifelong love is *Sarah Baylen Brown*, his wife of 65 years. As Brown put it "I take care of the chemistry, and Sarah takes care of the money and everything else". Brown relates a pertinent story that is dear to his heart: not long ago both of them were attending a professional function and were observed to treat each other affectionately. This prompted a couple, who didn't know them well, to ask them if they were newlyweds! After family and chemistry in general, Brown is perhaps most fond of *boron* and its compounds; he was particularly thrilled when he bought a laser pointer that emitted a green light—the color associated with the combustion of boron compounds. In fact, those very close to him know that just about the only way to get him off the subject of boron chemistry is to ask him about his two granddaughters.

In writing this piece about Professor Brown, we were hard-pressed to learn about any interests he might have outside of chemistry. The only one we could identify is photography. Of the few things he dislikes, doing chores that require physical exertion appears to be foremost.[5]

Professor Brown,

Your friends and admirers at Aldrich thank you for your lasting contributions to chemistry and to the success of Aldrich, and wish you a happy ninetieth birthday.[6] Many of us look forward to celebrating your birthday—with you, Sarah, your son Charles, your two granddaughters, Tamar and Ronni, and many of the more than 500 former Brown students—at a special symposium to be held on May 23–25, 2002 at Purdue University.

References and Notes: (1) Firsan, S. J. *Aldrichimica Acta* **2001**, *34*, 35. (2) Reference 1, p 44. (3) *The Herbert C. Brown Award for Creative Research in Synthetic Methods*, administered by the American Chemical Society (ACS) and co-sponsored by Aldrich Chemical Company. More information on this award is found on the ACS Web site at www.chemistry.org. (4) (a) Many anecdotes and fascinating information, particularly about Brown's early years, have been compiled in a book celebrating Brown's 66th birthday and retirement: *Remembering HCB: Memoirs of Colleagues and Students of Herbert C. Brown*; Bank, S., Ed.; Purdue University: West Lafayette, IN, 1978. (b) An essay honoring Professor Brown on the occasion of his 75th birthday has appeared in an earlier issue of this magazine: Brewster, J. H. *Aldrichimica Acta* **1987**, *20*, 3. (5) Reference 4a, p 5. (6) Herbert C. Brown's ninetieth birthday falls on May 22, 2002.

Boron-Based Reducing Agents for the Asymmetric Reduction of Functionalized Ketones and Ketimines†

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Department of Chemistry
Hallym University
1 Ockchon-Dong
Chunchon, Kangwon-Do 200-702, Republic of Korea
E-mail: btcho@hallym.ac.kr

Outline

1. Introduction

Optically active alcohols and amines are important compounds, which are utilized extensively as starting materials, intermediates, and chiral auxiliaries for preparing biologically active substances including natural products. One of the simplest and most useful methods for the preparation of these alcohols and amines is the asymmetric reduction of prochiral ketones and ketimines. Over the past three decades, a variety of asymmetric ketone-reducing reagents have been reported.[1] These reagents are mainly chirally modified aluminum and boron hydrides. However, most of the early experiments in this area gave disappointingly low optical yields.[2] Moreover, because the nature of the reducing system is generally unknown, there has been no reliable information on reproducibility and the mechanistic basis for enantioselectivity. In recent years, significant advances have been made in the area of asymmetric ketone reduction. In these cases, the use of stoichiometric or catalytic amounts of boron-based reagents has led to high enantioselectivities.[3-5]

In contrast to the enormous progress made in the asymmetric reduction of ketones, the reduction of imines with chiral reducing agents has been relatively neglected. Recently, we and others have reported the use of boron-based asymmetric reducing agents in the successful, highly enantioselective, asymmetric reductions of various functionalized ketones and ketimines to the corresponding alcohols and amines. This review focuses on the reducing characteristics of boron-based reagents that are useful for the asymmetric reduction of a wide variety of functionalized ketones and ketimines (**Figures 1** and **2**). The review will cover asymmetric reductions of ketones and ketimines reported between 1983 and March 2001. For literature coverage prior to this period, the reader should consult the excellent published reviews of asymmetric ketone reductions with boron-based reducing agents.[3-5] As compared to our similar but brief survey of the asymmetric reduction of α-functionalized ketones in reference 3c, the current review differs in scope (16 differently functionalized ketones and cyclic and acyclic ketimines) and in its treatment of the subject. To our knowledge, it is the first systematic compilation of these types of reductions.

2. Boron-Based Asymmetric Reducing Agents

2.1. Stoichiometric Reagents

Potentially useful asymmetric reductions using boron-based reducing agents involve stoichiometric and catalytic processes. Of the stoichiometric reagents reported, those that

are the most promising for the highly enantioselective reduction of various functionalized ketones are: monosaccharide-modified borohydrides—K-glucoride, **1**,[6] and K-xylide, **2**[7]—and α-pinene-based organoboranes including $^{d}Ipc_2BH$, **3**,[8a] $^{d}Ipc_2BCl$ [**4**, (–)-DIP-Chloride™],[4b] and *B*-^{d}Ipc-9-BBN (**5**, *R*-Alpine-Borane®)[4a] (**Figure 3**).[4,9] These reagents show extraordinary consistency and predictable stereochemistry in the reduction of ketones. This fact implies that the reducing agent in these cases is a single species. A chiral dialkoxyborane, **6**, was effectively used for the reduction of imines.[10] On the other hand, successful reductions of α- or β-keto esters and cyclic imines with lithium[11] or sodium acyloxyborohydrides, **7**–**9**,[12,13] modified with chiral amino acids or tartaric acid, have been reported. Although their reducing species are not known, these reagents are nevertheless practical and very effective. Despite much remarkable success using these stoichiometric reagents, and because at least one equivalent of each is required for the reduction, limitations to their widespread use remain: their availability and cost, and the

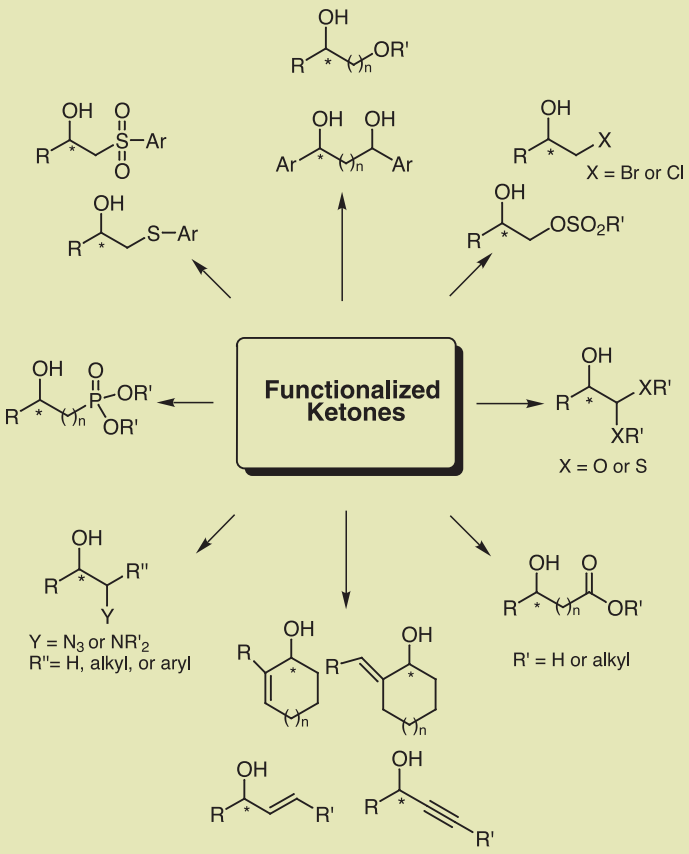


Figure 1. Asymmetric Reduction of Functionalized Ketones.

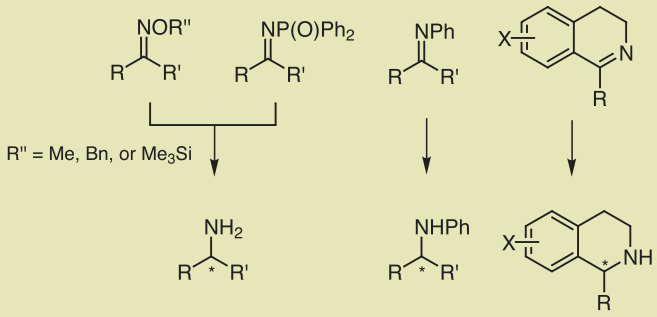


Figure 2. Asymmetric Reduction of Ketimines.

need for product purification and chiral auxiliary recovery in large-scale applications. Thus, it appeared desirable to develop catalytic processes for these types of reductions.

2.2. Catalytic Reagents

Since Itsuno[14a] and Corey[15] reported the first oxazaborolidine-catalyzed asymmetric borane reduction, a number of such reductions of prochiral ketones have been extensively studied.[5] These reductions furnish high enantioselectivities and predictable configurations even in the presence of 2 mol % of the oxazaborolidines. Of the reagents reported, oxazaborolidines **10**–**15**[14-19] **(Figure 4)** have been successfully applied to the reduction of functionalized ketones and imines. Borane-THF, borane-methyl sulfide (BMS), and catecholborane (CB) have so far been the most commonly used borane carriers for the catalytic reduction. However, these borane carriers have certain disadvantages for large-scale applications: high air- and moisture-sensitivity, low concentration and stability of borane-THF; and high volatility, flammability, and unpleasant odor of BMS. We[20] and others[21] overcame these drawbacks by using *N*-ethyl-*N*-isopropylaniline-borane complex (BACH-EI™) and *N*,*N*-diethyl-aniline-borane complex (DEANB) instead of borane-THF, BMS, or CB for the catalytic reduction. It has been known that such amine-borane complexes offer the advantages of being highly soluble in most common solvents and less sensitive to air and moisture. Moreover, chiral ligands that are useful for the catalytic asymmetric borane reduction have been reported: enantiopure β-hydroxysulfimine **16**,[22] phophinamide **17**,[23]

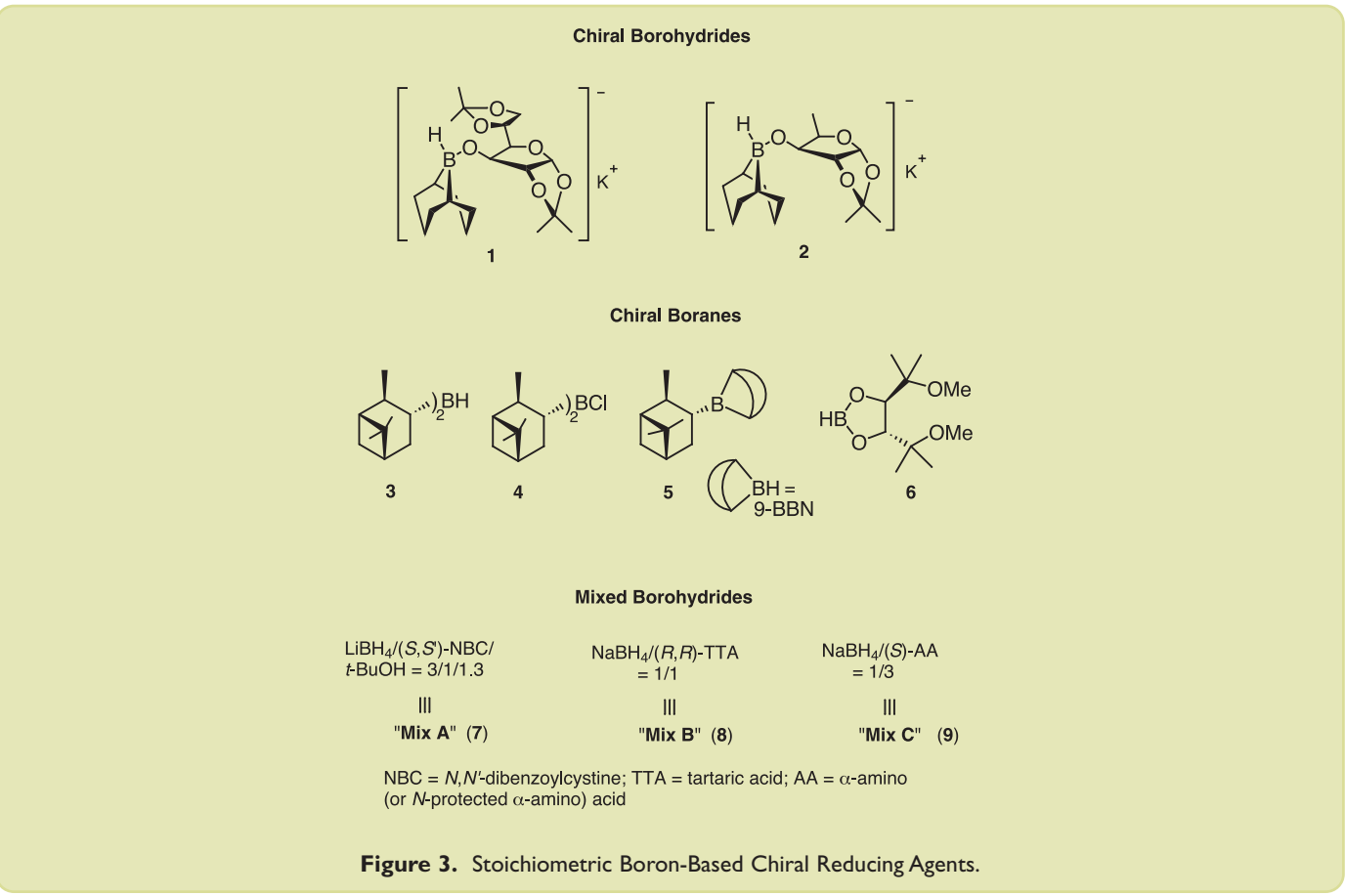


Figure 3. Stoichiometric Boron-Based Chiral Reducing Agents.

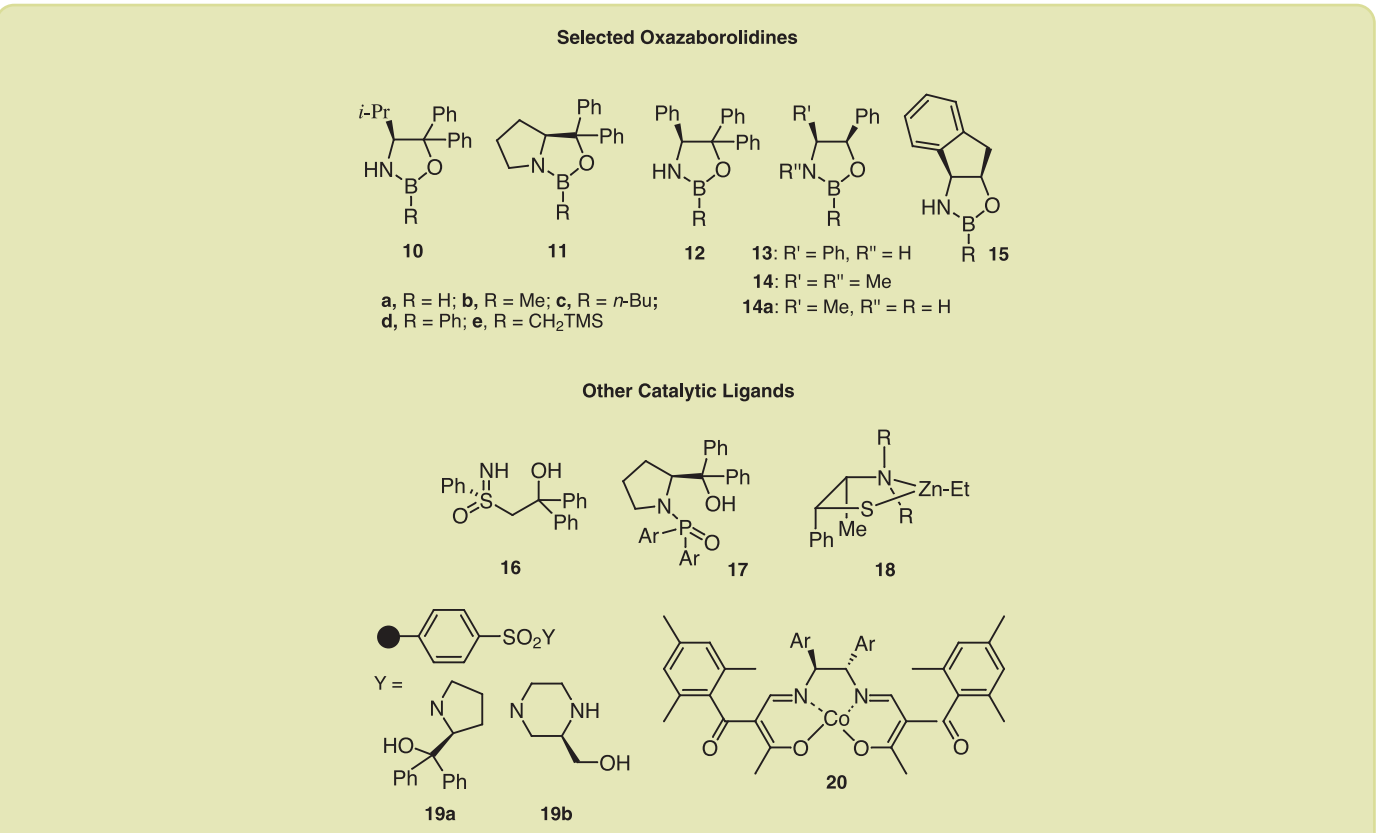
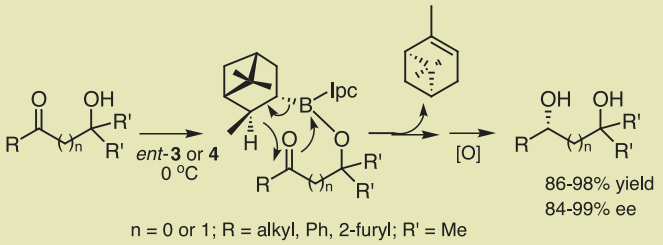
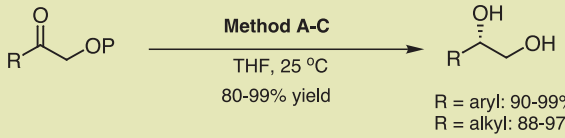


Figure 4. Catalytic Boron-Based Reagents.

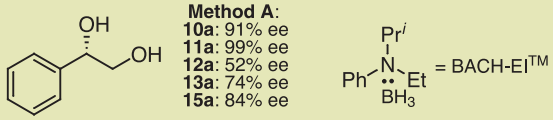


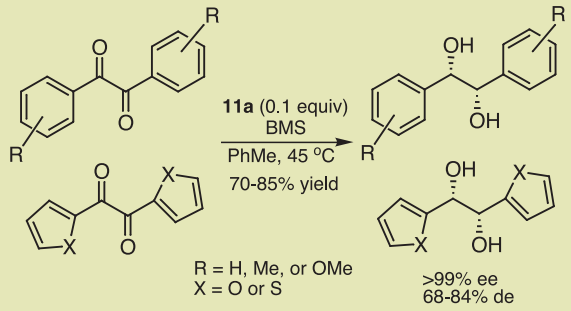
eq 1



eq 2

A: P = TBDMS or TIPS; (i) **10-15** (0.1 equiv), BH_3-THF (0.6 equiv); (ii) *n*-Bu_4NF
B: P = TBDMS or TIPS; (i) **11b** (0.1 equiv), BH_3-THF (0.6 equiv); (ii) *n*-Bu_4NF
C: P = THP; (i) **11b** (0.1 equiv), BACH-EI™ (1.0 equiv); (ii) HCl





eq 3

Reduction Conditions	Diol Yield (%)	Diol % de	Diol % ee
11 (*B*-OMe) (0.1 equiv), BMS (1.0 equiv), rt	91	>95	>98
13a (0.1 equiv), BMS (1.4 equiv), rt		58	94
4 (2 equiv), -78 °C to rt	93	>98	>98

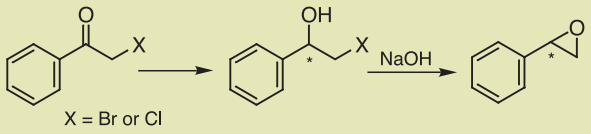
eq 4

thiazazincolidine complexes **18**,[24] and polymer-supported sulfonamidoalcohols **19**.[25] Recently, Mukaiyama and co-workers reported the highly enantioselective reduction of ketones and imines with sodium borohydride in the presence of 1 mol % of chiral β-oxoaldiminatocobalt(II) complexes **20**.[26]

3. Asymmetric Reduction of Functionalized Ketones

3.1. Hydroxy Ketones and Diketones

The stoichiometric, asymmetric reduction of α- and β-hydroxy ketones with *ent*-**3** or **4** proceeded in excellent enantiomeric excess (ee) via an intramolecular β-hydrogen shift (**eq 1**).[8b] Recently, we reported an efficient and very highly enantioselective method for the preparation of optically active terminal 1,2-diols via the oxazaborolidine-catalyzed borane reduction of α-silyloxy or tetrahydropyranyloxy ketones (**eq 2**).[20a,27] A comparison of the enantioselectivities of structurally diverse oxazaborolidines **10**–**15** in the reduction of 2-*tert*-butyldimethylsilyloxyacetophenone showed that **11a** provided the best result: 1-phenyl-1,2-ethanediol was obtained with near 100% ee. Very high ee's were also observed in the same reduction of aromatic analogs using **11a** as the catalyst. The first successful use of the more stable *N*-ethyl-*N*-isopropylaniline-borane complex (BACH-EI™), instead of BH_3 or BMS as the borane carrier (Method C), made the reduction more practical for large-scale applications.[20a] Chiral ligand **16** was employed as part of an effective catalyst for the reduction of α-protected hydroxy ketones.[22b] The CBS oxazaborolidine-catalyzed reduction of 1,2-diketones, in particular benzil derivatives and heterocyclic analogs, provided optically active (*S*,*S*)-hydrobenzoins with both high enantiomeric and diastereomeric excesses (ee and de) (**eq 3**).[28] Similarly, the oxazaborolidine-catalyzed



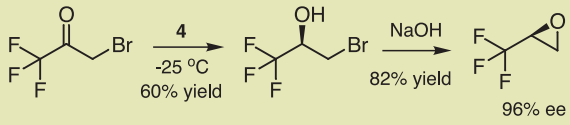
Reduction Conditions	Styrene Oxide Yield (%)	% ee
1 (1.1 equiv), -78 °C	82	77, *S*
2 (1.1 equiv), -78 °C	99	92, *S*
4 (1.2 equiv), -25 °C	90	96, *R*
5 (neat), rt	91	96, *R*
11a (0.02 equiv), BH_3:THF (0.5 equiv), rt	97	96, *S*
13a (0.1 equiv), BMS (0.5 equiv), -20 °C	>90	92, *S*
15b (0.1 equiv), BH_3:THF (0.8 equiv), -20 °C	>90	96, *S*
16 (0.1 equiv), BMS (1.2 equiv), rt	84	84, *S*
17 (0.1 equiv), BMS (1.0 equiv), 110 °C	91	94, *S*
19a (0.15 equiv), $NaBH_4$–TMSCl, 65 °C	98	96, *S*

eq 5

X	R	Reduction Conditions	Trihalomethyl Carbinols Yield (%)	% ee
F	aryl	**11c** (0.1 equiv), CB (1.5 equiv), PhMe, -78 °C or -20 °C	>90	94-100, *R*
F	aryl	**4** (neat, 1.1 equiv), 25 °C	48-93	78-90, *S*
F	alkyl	**4** (neat, 1.1 equiv), 25 °C	70-87	87-96, *S*
Cl	aryl	**11c** (0.1 equiv), CB (2.0 equiv), PhMe–THF, -70 °C	64-74	>98, *R*
Cl	alkyl	**11c** (0.1 equiv), CB (1.5 equiv), PhMe, -78 °C to 23 °C	94-97	92-98, *R*

CB = catecholborane

eq 6



eq 7

borane reductions[29,30] of 1,4-diphenyl-1,4-butanedione and its reduction with **4**[31] produced the corresponding 1,4-diol with high ee's and de's (**eq 4**).

3.2. α-Halo and α-Sulfonyloxy Ketones

The asymmetric reductions of α-bromo- and α-chloroacetophenone, among the α-halo ketones, have been the most studied (**eq 5**). Reductions with **4**,[9] **5**,[32] and most of the oxazaborolidine- and other-ligand-catalyzed reductions[19,22,23,25b,33,34] provided 2-halo-1-phenylethanols with high ee's. The chiral borohydrides **1** and **2** afforded 77% and 92% ee's, respectively.[6,7] Reductions of trihalomethyl ketones with **11c**/CB or with **4** afforded the corresponding trihalomethyl carbinols in 78–100% ee's (**eq 6**).[35,36a] **4** was also effectively employed for preparing 1,1,1-trifluorooxirane in high ee by reduction of 1-bromo-3,3,3-trifluoropropanone (**eq 7**).[36b]

Optically active halohydrins or styrene oxide derivatives, obtained by reduction of α-halo ketones, have been widely used as key intermediates in the synthesis of many chiral drugs containing the β-amino alcohol moiety **(Figure 5)**. Examples of such drugs include: (*R*)-denopamine (**21**),[37] (*R*)-isoproterenol (**22**),[38] (*R*)-salmeterol (**23**),[39] and (*R,R*)-formoterol (**24**).[40] However, the use of α-halo ketones as starting materials in commercial applications has severe drawbacks: α-halo ketones cause skin and eye irritation and are unstable to light. These disadvantages were successfully overcome by using the more stable and nonirritating α-sulfonyloxy ketones. The CBS oxazaborolidine-catalyzed reduction of α-sulfonyloxy ketones using BACH-EI™ as the hydride source provided the corresponding 1,2-diol monosulfonates and terminal epoxides in very high ee's (**eq 8**).[20e] The reduction with **4** also afforded high enantioselectivities.[41] Using this methodology, chiral drugs such as (*R*)-**21**, (*R*)-nifenalol (**25**), and (*R*)-pronethalol (**26**) were prepared highly enantioselectively by direct amination of the corresponding optically active 1,2-diol monosulfonates.[42] Moreover, enantiopure (1*S*,2*R*)-indene oxide (**27**)—which is a key starting material for the synthesis of indinavir (**28**), a highly effective HIV protease inhibitor—has been efficiently prepared by the same reduction from 2-(*p*-toluenesulfonyloxy)-1-indanone (**eq 9**).[20f]

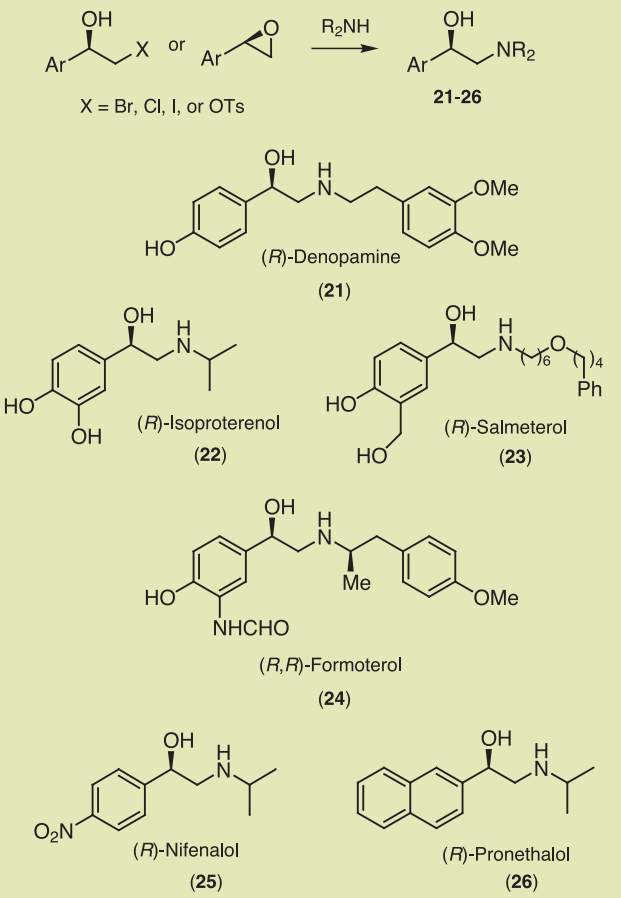
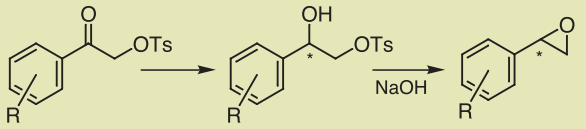


Figure 5. Applications of Optically Active Halohydrins to the Synthesis of Chiral Drugs.



eq 8

Reduction Conditions	Epoxides Yield (%)	Epoxides % ee
11b (0.1 equiv), BACH-El™ (1.0 equiv), 25 °C	94-96	94-99, *S*
4 (1.1 equiv), -25 °C	72-92	92-97, *R*

3.3. α-Keto Acetals and α-Keto Thioketals

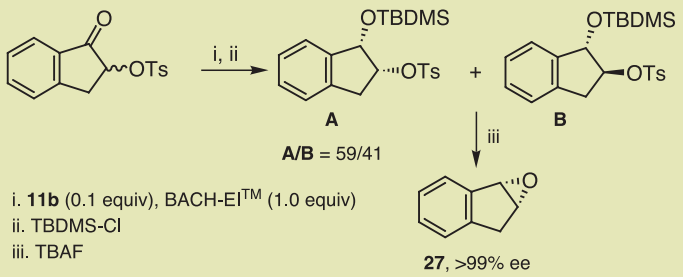
Chiral hydride **2** efficiently reduced aliphatic and aromatic α-keto acetals to the corresponding α-hydroxy acetals in 87–99% ee (**eq 10**).[43] The CBS reduction provided excellent ee's for aromatic analogs but moderate ee's for aliphatic ones.[20b] Similarly, the CBS reduction of both acyclic and cyclic α-keto thioketals was highly enantioselective (**eq 11**).[44]

3.4. Keto Acids, Esters, and Amides

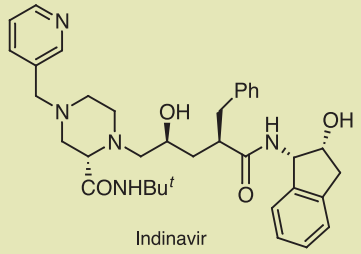
Treatment of α- and β-keto acids with **4** and triethylamine led to the corresponding α- and β-hydroxy acids in excellent ee's.[45] Similarly, **3** successfully reduced α-, β-, and γ-keto acids to the corresponding hydroxy acids with very high ee's (**eq 12**).[46] In the case of α-keto esters, both **1**[6] and **5**[32] produced high ee's (**eq 13**). However, these reagents failed to reduce β-keto esters.[9] In contrast, the reduction was successfully achieved by mixed borohydrides, "(*R*)-Mix A" [(*R*)-**7**] and "Mix B" (**8**), obtained from the reaction of $NaBH_4$ with (*R,R'*)-*N,N'*-dibenzoylcystine and (2*R*,3*R*)-tartaric acid, respectively. (*R*)-**7**[11] produced the desired aromatic β-hydroxy esters in 84–92% ee, while **8**[12] provided the aliphatic analogs in 68–84% ee (**eq 14**). "Mix C" (**9**), modified with (*S*)-*tert*-leucine, was effectively used to prepare the optically active α-hydroxy amide **29** as a key intermediate in the synthesis of chiral diltiazem (**30**), a potent calcium channel blocker (**eq 15**).[47]

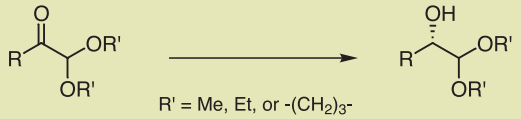
3.5. α,β-Enones and Ynones

The oxazaborolidine-catalyzed reduction of α,β-enones, using **11**[35a,48] or **12**[49] as the catalyst, has been extensively studied. The reduction is effective for all cases having acyclic, endocyclic, or exocyclic double bonds. To minimize the hydroboration of the C=C bond by borane, these reductions were carried out at low temperature. Interestingly, the olefinic portion in acyclic enones generally behaves as the large group for the reduction. The stoichiometric reagents, **1**, **4,**



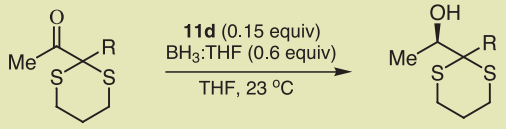
eq 9





R	Reduction Conditions	α-Hydroxy Acetals Yield (%)	% ee
aryl	**2** (1.1 equiv), -78 °C	80-87	92-96, *S*
alkyl	**2** (1.1 equiv), -78 °C	70-80	87-99, *S*
aryl	**11b** (0.1 equiv), DEANB (1.0 equiv), 25 °C	91-97	83-99, *S*
alkyl	**11b** (0.1 equiv), DEANB (1.0 equiv), 25 °C	65-98	42-71, *S*

eq 10

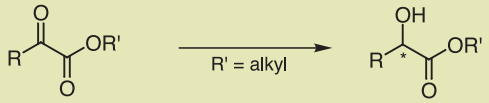


eq 11

3 (1.0 equiv), rt — 77-98% ee

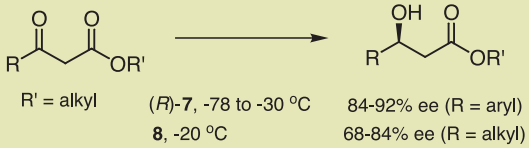
4 (1.2 equiv), Et_3N (1.0 equiv), -20 to 0 °C — 85-98% ee

eq 12

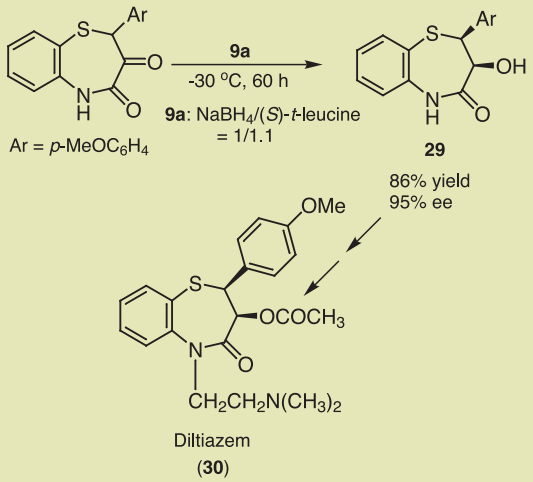


R	Reduction Conditions	α-Hydroxy Esters Yield (%)	% ee
aryl	**1** (1.1 equiv), -78 °C	78-85	89-96, *S*
alkyl	**1** (1.1 equiv), -78 °C	75-87	81-98, *S*
aryl	**5** (2.0 equiv, neat), 0 or 25 °C	89-95	83-92, *R*
alkyl	**5** (2.0 equiv, neat), 0 or 25 °C	50-98	75-92, *R*

eq 13



eq 14



eq 15

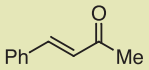
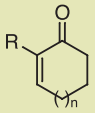
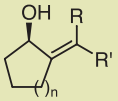
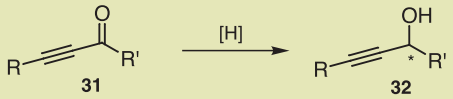
α,β-Enones	Reduction Conditions	Enols Yield (%)	Enols % ee
	**1** (1.1 equiv), -78 °C	92	60, *R*
	4 (1.1 equiv), -25 °C	65	81, *S*
	5 (1.3 equiv, neat), 25 °C	80	89, *S*
	11c (0.1 equiv), CB (1.5 equiv), -78 °C	>95	92, *R*
	12b (0.1 equiv), BMS (1.0 equiv), 0 °C	>90	82, *R*
	R = alkyl or Br; n = 0 or 1		
	11c (0.1 equiv), CB (1.5 equiv), -78 °C	>90	90-93, *R*
	R = H or alkyl; R' = alkyl or Ph; n = 0 or 1		
	11b (1.0 equiv), BMS (1.0 equiv), -20 °C	73-98	87-95, *R*

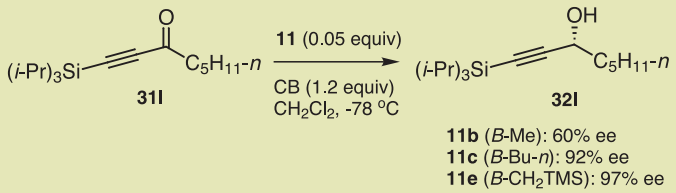
Figure 6. Asymmetric Reduction of α,β-Enones.



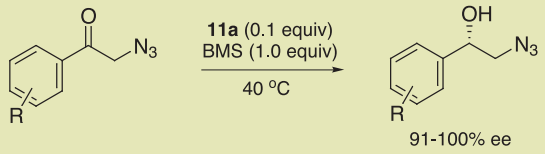
31, 32			% ee					
	R	R'	**1**	**4**	**5**	**11b**	**11e**	**12b**
a	H	Me	59	17	79			
b	H	*c*-C_6H_{11}				98		
c	*n*-C_5H_{11}	Me					68	
d	Ph	Me	61	21	100	71	87	
e	Ph	Et		28	97	88		
f	*n*-Oct	*t*-Bu		≥99				
g	Ph	*t*-Bu		≥99	80			
h	*t*-Bu	Me	86					
i	TMS	Me					87	
j	TMS	*c*-C_6H_{11}						93
k	TMS	1-Ad						97
l	(*i*-Pr)$_3$Si	*n*-C_5H_{11}					96	

Ad = adamantyl

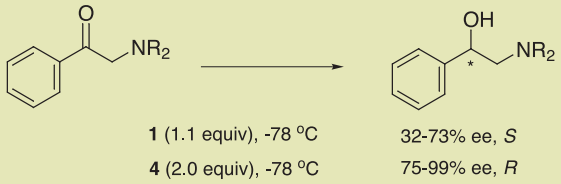
eq 16



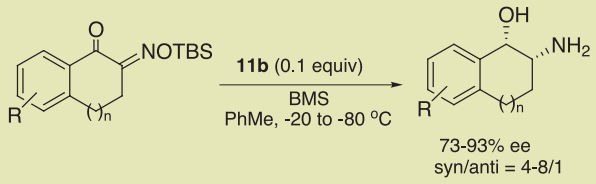
eq 17



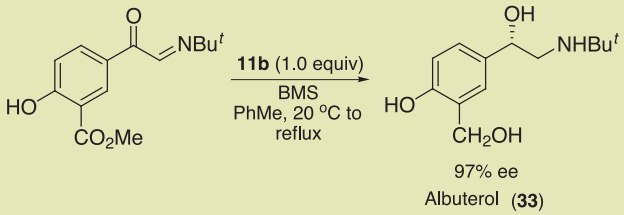
eq 18



eq 19



eq 20



eq 21

and **5** provided moderate ee's in the reduction of (*E*)-4-phenyl-3-buten-2-one (**Figure 6**).[9] On the other hand, enantioselectivities in the reductions of α,β-ynones are generally very sensitive to the steric size of the distal group of the alkyne and to the nature of the substituents on the carbonyl carbon. Ipc_2BCl (**4**) provided very high ee's of the sterically hindered propargyl alcohols **32f** and **32g**, but very low ee's of nonsterically hindered alcohols (**eq 16**).[50] Similarly, reductions with **1**[51] or **5**[32,50] were sensitive to steric effects. The catalytic reductions, using **11b**[52] or **12b**[53] at low temperatures, also furnished high ee's for hindered ketones. It was also observed that the enantioselectivity of the CBS oxazaborolidine reduction was dependent on the steric size of the boron substituents in the catalyst (**eq 17**).[54]

3.6. α-Azido, Amino, and Imino Ketones

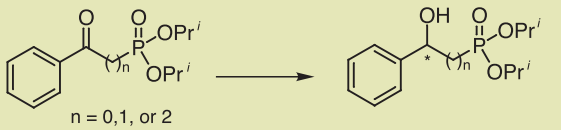
Asymmetric reduction of prochiral ketones containing nitrogen at the α position is one of the most convenient methods for preparing chiral β-amino alcohols, which are found as important structural units in many biologically active compounds. α-Azidomethyl aryl ketones are effectively reduced to the corresponding 2-azido-1-arylethanols in very high ee's by the CBS oxazaborolidine-catalyzed reduction (**eq 18**).[55] In the reduction of α-*N*,*N*'-dialkylamino ketones, **4** afforded high ee's,[56] whereas **1** provided moderate ee's (**eq 19**).[57] Moreover, the catalytic reduction of α-imino ketones has been successfully carried out (**eq 20**),[58] and has been applied to the highly enantioselective synthesis of chiral albuterol (**33**) (**eq 21**).[59]

3.7. Keto Phosphonates

Optically active α-hydroxyphosphonates are not only biologically active as inhibitors of different enzymes, but also serve as precursors in the synthesis of α-aminophosphonates, which are used as analogs of α-amino acids. **4** reduced aromatic α-ketophosphonates to the corresponding α-hydroxyphosphonates with moderate ee's.[60] CBS oxazaborolidine-catalyzed reduction, using **11c** as the catalyst and catecholborane as the borane carrier, provided moderate-to-high enantioselectivities. The reduction is also effective for β and γ analogs (**eq 22**).[61]

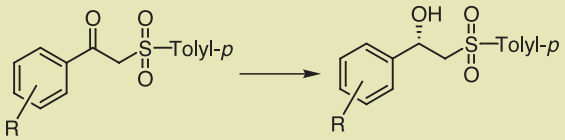
3.8. β-Keto Sulfones

Optically active β-hydroxy sulfones are extremely useful chiral building blocks, because the α-carbon atom can be further

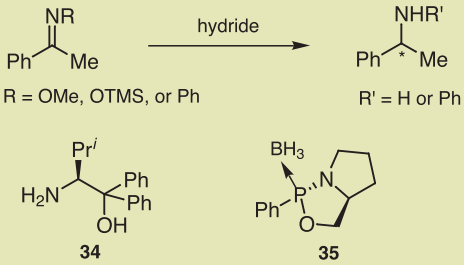


n	Reduction Conditions	α-Hydroxy Esters Yield (%)	% ee
0	**4** (1.1 equiv), -20 °C	58	60, *S*
0	**11c** (0.12 equiv), CB (1.1 equiv), -20 °C	92	65, *S*
1	**11c** (0.12 equiv), CB (1.1 equiv), -20 °C	66	91, *R*
2	**11c** (0.12 equiv), CB (1.1 equiv), -20 °C	58	68, *R*

eq 22



eq 23



Reagents	NOMe (% ee of the Amine Products)	NOTMS (% ee of the Amine Products)	NPh (% ee of the Amine Products)	References
34-BH_3, 30 °C	99 (52)[a]	62	73	14a, 64a-c
34-$NaBH_4$-$ZrCl_4$,[b] rt	(90)[a]			14c
11a-BH_3	86 (58)[a]	40	78 (37)[a]	64b,c
14-BH_3	58 (36)[a]	90	79 (38)[a]	64c,d
16 (0.1 equiv), BMS (1.2 equiv)	(33)[a]		(51)[a]	22a
19b (2.2 equiv), BH_3 (3.0 equiv), 50 °C	96			25a
6 (5.0 equiv), $MgBr_2$ (1.2 equiv)	NR		56	10
35 (0.1 equiv)-BMS, 110 °C			(63)[a]	65

[a] The figures in parentheses indicate % ee obtained from the use of 0.1 equiv of catalyst or ligand.
[b] [**34**]:[$NaBH_4$]:[$ZrCl_4$]:[imine] = 15:40:40:12.

eq 24

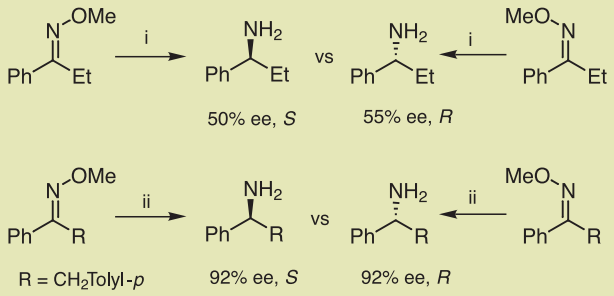
functionalized, and because the sulfonyl group can be easily cleaved without causing any racemization of the chiral center. Very recently, we prepared optically active β-hydroxy sulfones in 97–99% ee by the catalytic reduction of the corresponding β-keto sulfones using **11b** as the catalyst and BACH-EI™ as the borane source (**eq 23**).[62] The reduction is also very effective for hindered aliphatic analogs.[62]

4. Asymmetric Reduction of Prochiral Ketimines

In contrast to the large number of asymmetric ketone reductions that are known, only limited success has been achieved in the reduction of ketimines. This is due to the low electrophilicity of the imine carbon and the rapid equilibration between the *E* and *Z* isomers.[63] In addition, most chiral Lewis acids including oxazaborolidines are trapped by the basic nitrogen atoms of imines and/or product amines leading to less effective catalytic reactions.

4.1. Acyclic Prochiral Ketimines

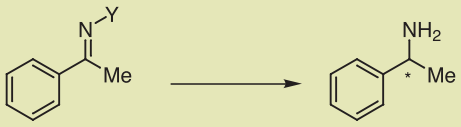
Itsuno and coworkers reported the successful asymmetric reduction of aromatic ketone oxime *O*-alkyl ethers with excess borane-THF[14a,b] or $NaBH_4$-$ZrCl_4$,[14c] in the presence of 1.2 equiv of **34**, to produce the corresponding amines in good-to-high ee's. They also obtained high ee's for the same reduction using a polymer-supported sulfonamido alcohol, **19b**, as a chiral inducer.[25b] We found that the stoichiometric borane reduction of aromatic *N*-phenyl imines using **10a** or **11a** proceeded with good enantioselectivity.[64a] When 0.1 equiv of **10a** or **11a** was used, lower enantioselectivities were obtained in cases of both the oxime ethers and *N*-phenyl imines.[14b,64b,c]



(i) **16** (0.1 equiv), BMS (1.2 equiv), PhMe
(ii) **14a**-BH_3 (2.5 equiv), THF, 20 °C

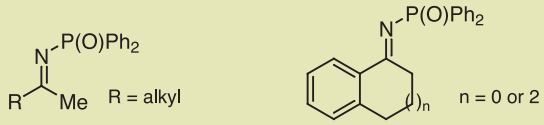
Scheme 1. Effect of Oxime Ether Geometry on Enantioselection.

Table 1. The Asymmetric Reduction of Activated Ketimines



Y	Reduction Conditions	Amine Yield (%)	Amine % ee
SPh	**16a** (0.1 equiv), BMS (1.2 equiv), rt	64	70, *S*
SO_2Tolyl-*p*	**16a** (0.1 equiv), BMS (1.2 equiv), rt	77	22, *S*
TBDMS	**12a** (2.0 equiv), BH_3:THF, -10°C	33	79, *R*
TBDMS	**14a** (2.0 equiv), BH_3:THF, -10 °C	71	50, *S*
$POPh_2$	**16a** (0.1 equiv), BMS (1.2 equiv), rt	70	16, *S*
$POPh_2$	**1** (1.2 equiv), -78 °C	54	15, *R*
$POPh_2$	**20a** (0.01 equiv), $NaBH_2(OR)_2$, 0 °C	90	97, *S*

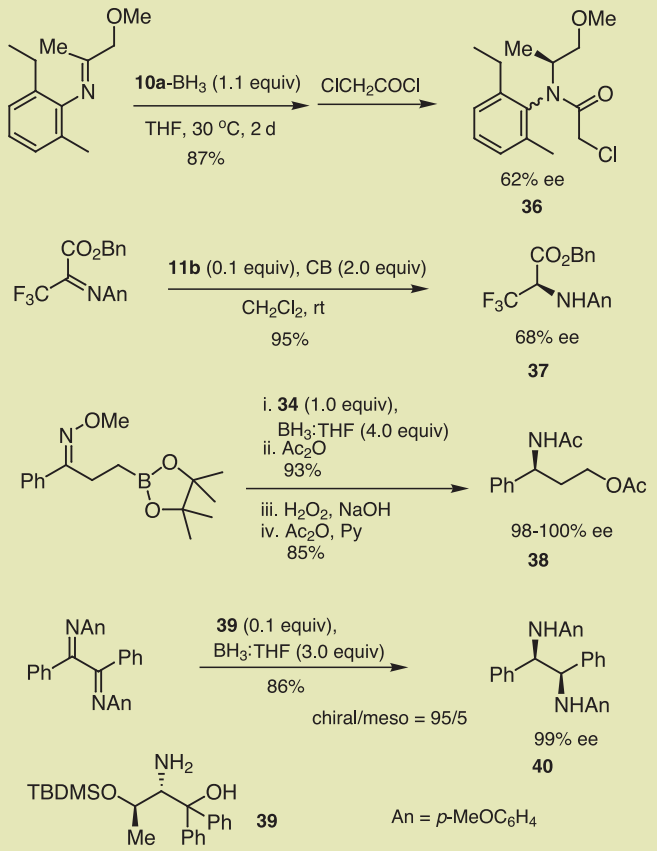
TBDMS = *t*-$BuMe_2Si$. **20a**: Ar = 2,4,6-$Me_3C_6H_2$



Other reductions using **14**,[64c,d] **16**,[22] or **35**[65] as chiral catalysts afforded moderate enantioselectivities. Reagent **6** reduced *N*-phenylimines to *N*-phenylamines with moderate ee's, but did not reduce oxime ethers.[10] Reagents **1**, **4**, and **5** did not reduce oxime ethers or *N*-phenylimines.[42,64a,c] All of these results are summarized in **eq 24**. In the borane reduction of oxime ethers using **14a** or **16** as chiral inducers, Sakito[66] and Bolm[22] independently found that the absolute configurations of the amines formed are dependent on the geometry of the oxime ethers: the *E* oxime led to the *S* amine, while the *Z* oxime gave rise to the *R* amine (**Scheme 1**). The asymmetric reduction of activated imines such as *N*-silyl-, *N*-sulfenyl-, *N*-sulfonyl-, or *N*-diphenylphosphinylimines under stoichiometric or catalytic conditions has also been studied (**Table 1**). The borane reduction of acetophenone *N*-*tert*-butyldimethylsilylimine using **14a** or **12a** under stoichiometric conditions provided the desired amine in moderate yields and ee's.[67] Reduction of acetophenone *N*-phenylsulfenylimine using **16** as catalyst gave 70% ee, while the *N*-tosyl- and *N*-diphenylphosphinylimine analogs provided much lower ee's under the same conditions.[22] The reduction of *N*-diphenylphosphinyl derivatives of alkyl methyl ketimines to the corresponding aliphatic amines has been successfully achieved in moderate ee's by using **1**.[68] Recently, Mukaiyama reported the very efficient reduction of *N*-diphenylphosphinylimines using the chiral cobalt(II) complex **20a** and sodium alkoxyborohydride as catalyst and hydride source, respectively. The reduction provided the desired amines with very high enantioselectivity even in the presence of 1 mol % of **20a**.[26] Such reductions have been effectively applied to the asymmetric synthesis of the herbicide metolachlor (**36**),[69] 3,3,3-trifluoroalanine (**37**),[70] γ-amino alcohol **38**,[71] and C_2-symmetric 1,2-diamine **40**[72] (**Scheme 2**).

4.2. Endocyclic Imines

The asymmetric reduction of 1-substituted 3,4-dihydroisoquinolines, **41**, is the most straightforward method for preparing nonracemic 1-substituted tetrahydroisoquinoline alkaloids such as salsolidine (**42a**), norlaudanosine (**42b**), and norcryptostylines (**42c,d**) (**Scheme 3**). Recently, a very effective and convenient dihydroisoquinoline reduction, using chiral sodium acyloxyborohydride ("Mix C", **9b**) modified with (*S*)-*N*,*N*-phthaloylisoleucine, gave the desired alkaloids in moderate yields and 94–99% ee.[13a] This reducing system has been successfully applied to the synthesis of



Scheme 2. Applications of the Asymmetric Reduction of Ketimines.

nonracemic 1-substituted 1,2,3,4-tetrahydro-β-carboline alkaloids, **44**. The mixed borohydride **9a**, modified with (*S*)-*N*-Cbz-proline, is similarly effective in the reduction.[13b] Chiral dialkoxyborane **6** rapidly reduced imines **41** and **43** to the corresponding amines in high yields, but low ee's.[10] On the other hand, **1**–**4** and borane complexes of **10a**, **11a**, and **16** did not reduce the same imines under stoichiometric conditions.[64a] Recently, we reported the catalytic asymmetric reduction of cyclic imines **41** with BH_3:THF in the presence of 0.2 equiv of a thiazazincolidine, **18**, to produce the desired amines in moderate yields and good ee's.[24] Unlike cyclic imines **41**, iminium salts **45** were easily reduced to the corresponding amines, **46**, with **1** and borane complexes of **10a** and **11a** under stoichiometric conditions. However, low ee's were obtained.[73] The reduction of cyclic imines was successfully applied to the synthesis of a potent quinolone antibacterial agent, (*S*)-ofloxacin (**47**) (**Scheme 4**).[74]

5. Conclusion

The present review was not designed to be comprehensive, but rather to summarize some of the recent advances in the stoichiometric and catalytic asymmetric reductions of functionalized ketones and ketimines using boron-based chiral reducing agents. Many boron-based reagents, proven to be very effective for the highly enantioselective reduction of various functionalized ketones, have been introduced. However, the development of effective reducing agents for the asymmetric reduction of ketimines remains a challenging target.

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7. References and Notes

(†) This review is dedicated to Professor Herbert C. Brown for his distinguished achievements in chemistry on the occasion of his 90th birthday.

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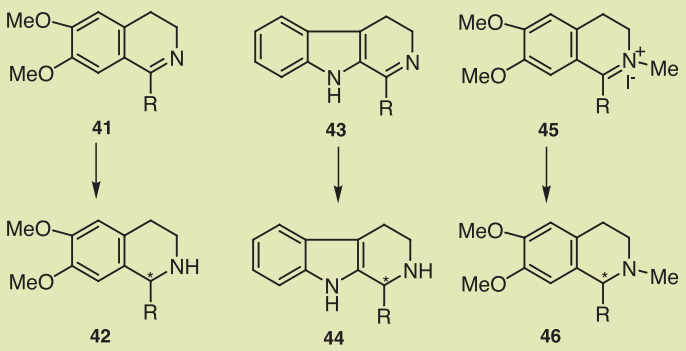
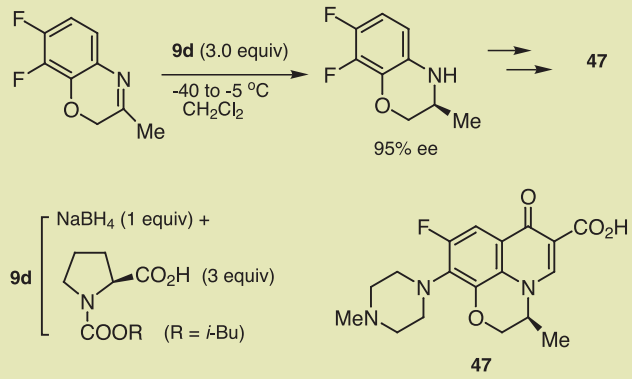


a = Me; **b** = 3,4-$(MeO)_2C_6H_3CH_2$; **c** = 3,4-$(MeO)_2C_6H_3$;
d = 3,4-$(OCH_2O)C_6H_3$; **e** = 3,4,5-$(MeO)_3C_6H_2$

9b = $NaBH_4$ (1) + *N*-Cbz-proline (3)
9c = $NaBH_4$ (1) + *N,N*-Phth-isoleucine (3)

Reduction Conditions	Products	Yield (%)	% ee
6 (5.0 equiv), 0 °C	**42a**	50	28, *R*
6 (5.0 equiv), 0 °C	**44a**	98	42, *R*
18 (0.2 equiv), BH_3:THF (2.0 equiv), -5 to 10 °C	**42**	25-87	24-86, *R*
9b (2.5 equiv), rt	**42**	85-90	70-86, *S*
9c (1.2 equiv), rt	**42**	83-90	93-100, *S*
9b (2.5 equiv), rt	**44a**	85	79, *S*
9c (1.2 equiv), rt	**44**	89-90	94-100, *S*
1 (1.1 equiv), -78 °C	**46**	67-86	37-52, *R*
10a (1.0 equiv), BH_3:THF (2.0 equiv), 30 °C	**46**	58-86	10-17, *R*

Scheme 3. Asymmetric Reduction of Endocyclic Imines.



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About the Author

Professor Byung Tae Cho was born in Seoul and grew up in Kang Nung, Republic of Korea. He received a B.S. degree in pharmacy from Seoul National University in 1967. After a three-year military service as a pharmacist officer in the Korean Air Force, he joined the Korea Institute of Science and Engineering (KIST) as a research chemist, and worked on the industrial synthesis of drugs including β-lactam antibiotics, antibacterial agents, and analgesics. In 1974, he joined Dong Wha Pharmaceutical Company as head of the synthetic division, and was promoted to director of the division in 1979. He obtained his Ph.D. degree in 1982 under the guidance of Professor Nung Min Yoon at Sogang University. His doctoral research studies focused on the exploration of boron hydride reductions. In 1982, he joined Hallym University as an assistant professor of chemistry. From 1985 to 1987, he undertook a postdoctoral fellowship with Professor Herbert C. Brown at Purdue University, where he worked on the development of new chiral borohydrides and their applications to the asymmetric reduction of ketones. Since 1993, he has been working at Hallym University as a full professor of chemistry.

His current research interests include the development of new chiral catalysts for asymmetric reductions and enantioselective carbonyl alkylations, and the use of catalytic enantioselective phase-transfer reactions in the synthesis of chiral drugs. He is the author of approximately 70 research publications.

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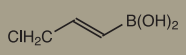
55,659-9
$C_3H_6BClO_2$



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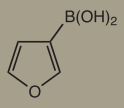
5g

51,216-8
$C_4H_5BO_3$



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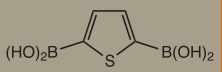
47,031-7
$C_4H_6B_2O_4S$



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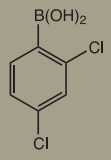
52,138-8
$C_6H_5BCl_2O_2$



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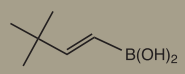
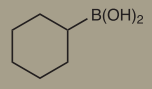
55,655-6
$C_6H_{13}BO_2$



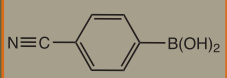
1g
5g

55,658-0
$C_6H_{13}BO_2$



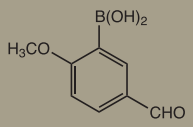
5g
10g

52,141-8
$C_7H_6BNO_2$



1g
10g

51,225-7
$C_8H_9BO_4$



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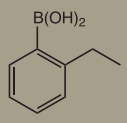
52,152-3
$C_8H_{11}BO_2$



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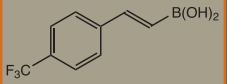
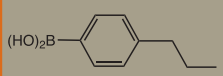
51,902-2
$C_9H_8BF_3O_2$



1g
5g

52,150-7
$C_9H_{13}BO_2$



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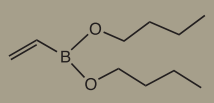
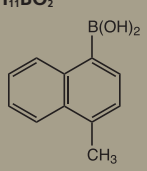
56,814-7
$C_{10}H_{21}BO_2$



1g
5g

52,145-0
$C_{11}H_{11}BO_2$



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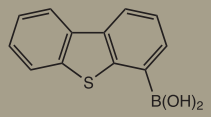
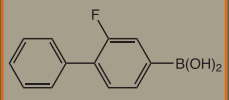
49,998-6
$C_{12}H_9BO_2S$



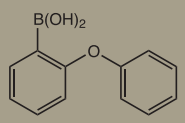
1g
5g

51,210-9
$C_{12}H_{10}BFO_2$



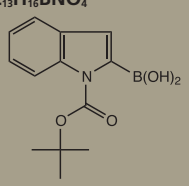
5g

52,148-5
$C_{12}H_{11}BO_3$



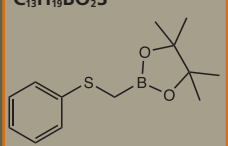
10g

56,233-5
$C_{13}H_{16}BNO_4$



1g

56,815-5
$C_{13}H_{19}BO_2S$



1g
5g

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- ***Experience in custom synthesis***

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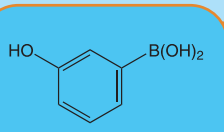
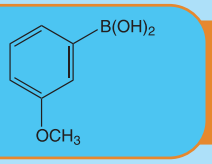
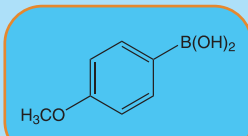


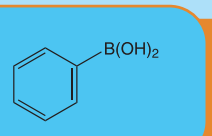
52,396-8 [87199-18-6]
3-Hydroxyphenylboronic acid
500kg to MT
MDL# 1074603



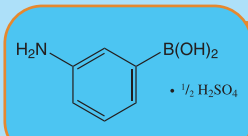
44,168-6 [10365-98-7]
3-Methoxyphenylboronic acid
250-500kg
MDL# 161359



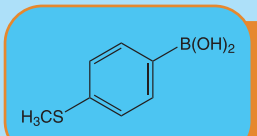
41,759-9 [5720-07-0]
4-Methoxyphenylboronic acid
250-500kg
MDL# 39139



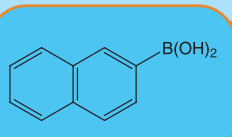
P2,000-9 [98-80-6]
Phenylboronic acid
250kg
MDL# 2013



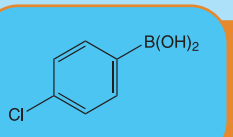
A7,175-1 [66472-86-4]
3-Aminophenylboronic acid hemisulfate
50-100kg
MDL# 13111



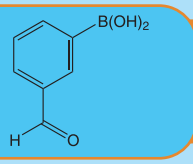
45,680-2 [98546-51-1]
4-(Methylthio)phenylboronic acid
25-50kg
MDL# 93410



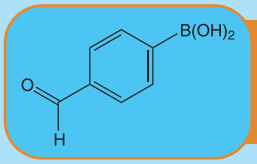
48,013-4 [32316-92-0]
2-Naphthaleneboronic acid
25-50kg
MDL# 236051



41,754-8 [1679-18-1]
4-Chlorophenylboronic acid
25-50kg
MDL# 39137

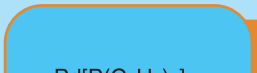


44,165-1 [87199-16-4]
3-Formylphenylboronic acid
25kg
MDL# 161356



43,196-6 [87199-17-5]
4-Formylphenylboronic acid
25kg
MDL# 151823

32,877-4 [52409-22-0]
Tris(dibenzylideneacetone)dipalladium(0)
kg quantities
MDL# 13310



21,666-6 [14221-01-3]
Tetrakis(triphenylphosphine)Pd(0)
kg quantities
MDL# 10012

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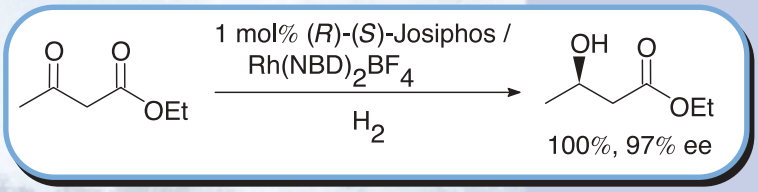


Chiral ligands for highly enantioselective hydrogenation and related reactions. The palladium-catalyzed substitution of allylic acetates by carbon nucleophiles proceeds rapidly, giving high enantioselectivity:[3,4]

43167	**(*R*)-1-((1*S*)-2-(Diphenylphosphino)ferrocenyl)ethyldicyclohexylphosphine** ((*R*)-(*S*)-Josiphos)	purum, ~97%	M_r 594.54	$C_{36}H_{44}FeP_2$	**100mg; 500mg** (155806-35-2)
43168	**(*S*)-1-((1*R*)-2-(Diphenylphosphino)ferrocenyl)ethyldicyclohexylphosphine** ((*S*)-(*R*)-Josiphos)	purum, ≥ 97.0%	M_r 594.54	$C_{36}H_{44}FeP_2$	**100mg; 500mg** (162291-02-3)

Chiral ligands for homogeneous catalysis:[5,6]

43164	**(*R*)-1-((1*S*)-2-(Diphenylphosphino)ferrocenyl)ethyldi-*tert*-butylphosphine**	purum, ≥ 97.0% (CHN/NMR)	M_r 542.46	$C_{32}H_{40}FeP_2$	**100mg; 500mg** (155830-69-6)
43166	**(*S*)-1-((1*R*)-2-(Diphenylphosphino)ferrocenyl)ethyldi-*tert*-butylphosphine**	purum, ≥ 97.0% (CHN/NMR)	M_r 542.46	$C_{32}H_{40}FeP_2$	**100mg; 500mg**

Chiral ligands for homogeneous catalysis:

36676	**(*R*)-1-((1*S*)-2-(Dicyclohexylphosphino)ferrocenyl)ethyldicyclohexylphosphine**	purum, amount Fe ~97%	M_r 606.63	$C_{36}H_{56}FeP_2$	**100mg; 500mg** (167416-28-6)
36677	**(*S*)-1-((1*R*)-2-(Dicyclohexylphosphino)ferrocenyl)ethyldicyclohexylphosphine**	purum, amount Fe ~97%	M_r 606.63	$C_{36}H_{56}FeP_2$	**50mg; 250mg** (158923-07-0)
36678	**(*R*)-1-((1*S*)-2-(Dicyclohexylphosphino)ferrocenyl)ethyldiphenylphosphine**	purum, ≥ 97.0% (CHN/NMR)	M_r 594.54	$C_{36}H_{44}FeP_2$	**50mg; 250mg** (158923-09-2)
36679	**(*S*)-1-((1*R*)-2-(Dicyclohexylphosphino)ferrocenyl)ethyldiphenylphosphine**	purum, ≥ 97.0% (CHN/NMR)	M_r 594.54	$C_{36}H_{44}FeP_2$	**50mg; 250mg** (162291-01-2)

(1) Blaser, A. H. U. *J. Organomet. Chem.* **2001**, *34*, 621. (2) Spindler, B F.; Blaser, A. H. U. *Adv. Synth. Catal.* **2000**, *68*, 1. (3) Togni, C. A. et al. *J. Am. Chem. Soc.* **1994**, *116*, 4062. (4) Bronco, S. et al. *Helv. Chim. Acta* **1995**, *78*, 883. (5) Pregosin, P. S. et al. *Organometallics* **1995**, *14*, 842. (6) Zanetti, N.C. et al. *ibid.* **1996**, *15*, 860.

Our range of products in this rapidly evolving field is continuously expanding. For more information, please visit our Web site at www.sigma-aldrich.com/fluka.

Fluka

A "Hand" for Professor Sharpless

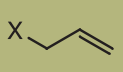
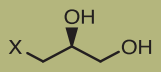
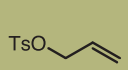
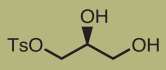
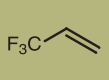
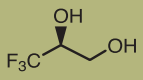
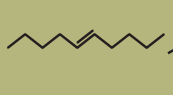
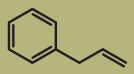
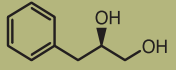
Aldrich Chemical Co. congratulates Professor K. Barry Sharpless of The Scripps Research Institute for receiving a share of the 2001 Nobel Prize in Chemistry for his practical research on "chirally catalyzed oxidation reactions". The laureate's work has been adapted to a number of industrial syntheses of antibiotics, antidepressants, anti-inflammatory drugs, and heart medicines.

Professor Sharpless has successfully developed three catalytic techniques to yield enantiomerically pure products. The first, the Sharpless asymmetric epoxidation (AE),[1] transforms allylic alcohols into epoxy alcohols using a novel titanium-based catalyst. The second, the Sharpless asymmetric dihydroxylation (AD),[2] uses an osmium-based catalyst to asymmetrically dihydroxylate olefins. The wide acceptance of this methodology has prompted researchers to develop a new class of ligands,$(DHQD)_2AQN$ and $(DHQ)_2AQN$, in order to expand the scope of the reaction.[3] These two are useful complements to the ligands we already offer: $(DHQD)_2PYR$/$(DHQ)_2PYR$ and $(DHQD)_2PHAL$/$(DHQ)_2PHAL$.[4]

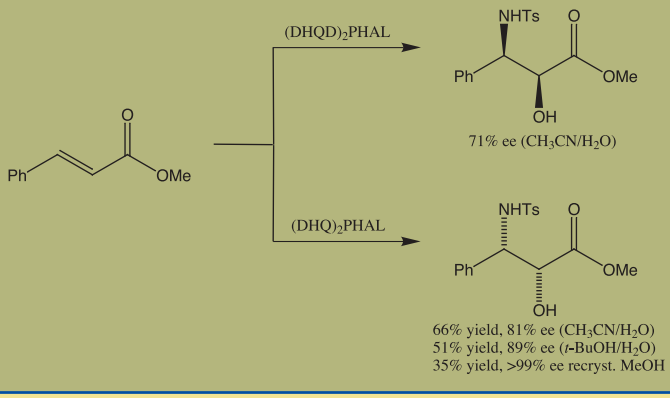
The success of AD led the way for Sharpless's third method, the Sharpless asymmetric aminohydroxylation (AA).[5] The key stoichiometric reagent in this method is the oxidant Chloramine-T, which is a nitrogen analog of sodium hypochlorite and formally acts as a reservoir of "sulfonyl nitrene". The transformation is illustrated by the synthesis of a Taxol® side chain from methyl cinnamate.

Along with asymmetric induction, the chiral ligand provides dramatic enhancements in regioselectivity as well as suppression of the path(s) responsible for the formation of the diol by-product.

Sharpless Asymmetric Dihydroxylation

Olefin	Product	% ee $(DHQD)_2AQN$	% ee Previous Best (Ligand)
		[X= Cl, Br, I] 90, 89, 83	63 $(DHQD)_2PHAL$
		83	40 $(DHQD)_2PHAL$
		81	64 $(DHQD)_2PYR$
		98	97 $(DHQD)_2PHAL$
		78	44 $(DHQD)_2PHAL$

Sharpless Asymmetric Aminohydroxylation



Products:

45,671-3 $(DHQD)_2AQN$, 95%
45,670-5 $(DHQ)_2AQN$, 95%
39,275-8 AD-mix-α
39,276-6 AD-mix-β
39,272-3 $(DHQ)_2PHAL$, 95+%
39,273-1 $(DHQD)_2PHAL$, 95+%
41,897-8 $(DHQ)_2PYR$, 97%
41,895-1 $(DHQD)_2PYR$, 97%
40,286-9 Chloramine-T trihydrate, 98%, A.C.S. reagent
85,731-9 Chloramine-T hydrate, 98%

References: (1) Katsuki, T.; Sharpless, K.B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (2)(a) Jacobsen, E.N.; Markó, I. Mungall, W.S.; Schröder, G.; Sharpless, K.B. *ibid.* **1988**, *110*, 1968. (b) Kolb, H.C.; VanNieuwenhze, M.S.; Sharpless, K.B. *Chem. Rev.* **1994**, *94*, 2483. (3) Becker, H.; Sharpless, K.B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 448. (4) Becker, H.; King, S.B.; Taniguchi, M.; Vanhessche, K.P.M.; Sharpless, K.B. *J. Org. Chem.* **1995**, *60*, 3940. (5) Li, G.; Chang, H.-T.; Sharpless, K.B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451.

Equipment for Air-Sensitive Chemistry

Serrated rubber septa NEW!

Closure has a turnover flange molded to grip outside of container neck, promoting a double seal in conjunction with annular serrations on a hollow plug. Annular serrations depress themselves against the inside wall of the bottle neck, making each serration a suction sealing point.

Fits container neck i.d. (mm)	For use with:	*White rubber* Cat. No.	*Red rubber* Cat. No.	*Blue rubber* Cat. No.
8.0	10/30	**Z51,217-6**	**Z51,216-8**	**Z51,264-8**
12.5	14/20	**Z51,212-5**	**Z51,211-7**	**Z51,267-2**
16.0	Sure/Seal	**Z51,219-2**	**Z51,218-4**	**Z51,269-9**
17.5	19/22	**Z51,221-4**	**Z51,220-6**	**Z51,270-2**
20.5	24/40	**Z51,214-1**	**Z51,213-3**	**Z51,272-9**
25.5	29/42	**Z51,223-0**	**Z51,222-2**	**Z51,275-3**

Sllicone Serrated Septa *(Shown above at right) are excellent for high-heat and sterile applications. See the Aldrich Handbook for a listing of these products.*

ALDRICH ATMOSBAGS

The Aldrich AtmosBag is a 0.003in. gauge PE bag that can be sealed, purged, and inflated with an appropriate inert gas, creating a portable, convenient, and inexpensive "glove box" for handling air-and moisture-sensitive, as well as toxic*, materials. Other applications include dust-free operations, controlled atmosphere habitat, and, for the sterile ethylene oxide-treated AtmosBag, immunological and microbiological studies. Small AtmosBags have one inlet per side. Includes instructions.

Two-hand AtmosBag shown here with PE benchtop base and Benchrack lattice system (see below).

Size	Uninflated dim. (in.) Opening	W x L	Inflated vol. (ft^3)	(L)	*Non-sterile* Cat. No.	*Sterile* Cat. No.
Two-hand AtmosBags						
S	12	27 x 30	1.74	350	**Z11,283-6**	**Z11,837-0**
M	24	39 x 48	39.84	280	**Z11,282-8**	**Z11,836-2**
L	36	51 x 58	18.52	520	**Z10,608-9**	**Z11,835-4**
Four-hand AtmosBag						
	30	45 x 58	–	–	**Z10,840-5**	

AtmosBag accessories

PE bench-top bases

Rigid, ½ in. thick. Keeps AtmosBag in place. Fits inside respective bag.

S	11 x 16in.	**Z11,286-0**
M	20 x 16in.	**Z11,285-2**
L	24 x 34½ in.	**Z10,691-7**

Mini-size Benchrack

Includes base and ⅝ in. diam. lattice rod sections.

No. of positions	No. of rods	Base dim. (in.)	Cat. No.
4	8	19 x 8	**Z22,565-7**

***CAUTION:** Always handle toxic materials in a hood or other controlled system to prevent and protect against exposure in case of leakage. All products made of PE may tear, break, or puncture. To assure that air-sensitive materials do not become exposed to air, follow instructions on package; also, test and monitor AtmosBag for leaks before and during use.

Equipment for Air-Sensitive Chemistry

KDS SYRINGE PUMPS

Advanced microprocessor-controlled syringe pumps designed especially for low, pulse-free flow rates. Easy setup:

1. Select syringe size

2. Enter volume to be dispensed

3. Enter flow rate, then press start button

Single-syringe pumps

Series 100 infusion pumps. Combine precision and simplicity with ease of use and exceptional durability. The 230V pumps are CE compliant. 9 x 6 x 5in. 4½lb.

Features:

- Holds any size syringe from 10mL to 60mL
- Automatic volume control and shutoff
- Last settings stored in memory
- Continuous dispense volume display
- Simple menu-driven setup:
  syringe diameter (selected from displayed table)
  dispense volume
  dispense flow rate

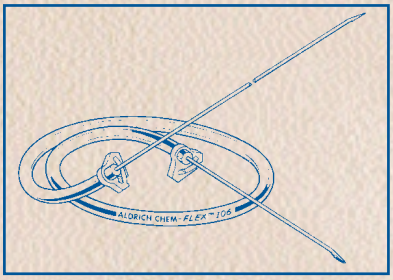
Volts	Cat. No.
115	**Z40,135-8**
230	**Z40,136-6**

Dual-syringe pumps

Series 200 infusion pumps. All the features of Series 100 pumps plus:

- Holds two syringes, sizes 10mL to 140mL each
- Settings can be reviewed or changed during operation
- Optical encoder stall detection
- Choice of unit selection
- RS-232C interface for computerizing up to 100 pumps
- TTL interface for foot switch, timer, relay control; outputs for run indicator, valve control
- 11 x 9 x 5½in. 9lb.

Volts	Cat. No.
115	**Z40,137-4**
230	**Z40,138-2**



Note: *For extra security when using large bore transfer needles, fasten septum to bottle or flask opening with a wrap-it tie. See the Septa Section of the Aldrich Handbook for a listing of these products.*

CHEM-FLEX transfer lines

Especially suited for transfer of products packed in Aldrich Sure/Seal bottles.These ready-to-use transfer lines incorporate CHEM-FLEX 106 tubing which has a chemically-inert, thin-wall PTFE inner tube sheathed in clear PVC for extra strong, flexible lines that are resistant to crushing or kinking. Two 12 gauge SS needles (6 and 18in.) are connected to the CHEM-FLEX 106 tubing with nylon clamps. Liquids contact only PTFE and SS during transfers.

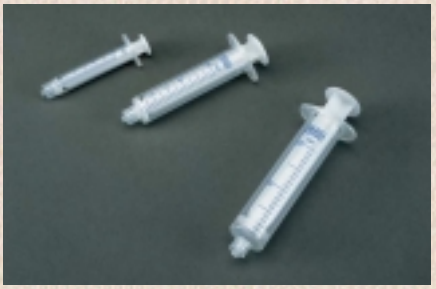
Tubing L (in.)	Cat. No.
30	**Z23,102-9**
60	**Z28,175-1**
120	**Z28,177-8**

Equipment for Air-Sensitive Chemistry

ALL POLYPROPYLENE LUER LOCK SYRINGES

Non-contaminating, sterile, disposable syringe has PP barrel and plunger with a safety stop to prevent plunger separation. Luer lock centered on barrel. Individually peel-packed. Order needles separately on next page.

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



MICRO-MATE INTERCHANGEABLE SYRINGES

Characteristics:

All are made from borosilicate glass; metal parts are chrome-plated brass. Syringes have male fittings. Order needles separately on next page.

- Interchangeable barrels and plungers
- Thermal shock and corrosion resistant
- Reinforced flanges, flat on two sides to prevent syringe rolling
- Precision shrinking ensures leakproof fit
- Graduations permanently fused into glass affording lifetime legibility
- Colored plunger ends, fused around bottom beveled rim of plunger, facilitate volume measurement

Three tip sizes available:

Needle-lock Luer – Tips fitted to heavy glass bases to ensure greater strength than glass-Luer tips. All Luer needles lock into needle-lock tips with an easy twist.

Metal Luer – Include all the same features as needle-lock tips, except for the special locking device. Fit all Luer needles and other female Luer fittings.

Glass Luer – Tips have reinforced glass bases to ensure strength and minimize breakage; beveled ends to reduce chipping.

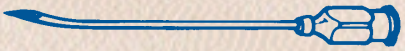
Cap. (cc)	Grad. int. (cc)	Tip style	Cat. No.
2	0.1	needle-lock Luer	**Z10,104-4**
		metal Luer	**Z18,113-7**
		glass Luer	**Z10,190-7**
5	0.2	needle-lock Luer	**Z10,105-2**
		metal Luer	**Z18,116-1**
		glass Luer	**Z18,118-8**
10	0.2	needle-lock Luer	**Z10,106-0**
		metal Luer	**Z18,121-8**
		glass Luer	**Z18,122-6**
20	1.0	needle-lock Luer	**Z10,107-9**
		metal Luer	**Z18,124-2**
		glass Luer	**Z18,125-0**
30	1.0	needle-lock Luer	**Z10,108-7**
		metal Luer	**Z18,126-9**
		glass/metal Luer	**Z18,127-7***
50	2.0	needle-lock Luer	**Z10,234-2**
		metal Luer	**Z18,128-5**
		glass/metal Luer	**Z18,129-3***

*Has glass tip with removable metal Luer tip adapter.

SYRINGE NEEDLES

Stainless steel syringe needles

304 SS needle with chrome-plated brass Luer hub.

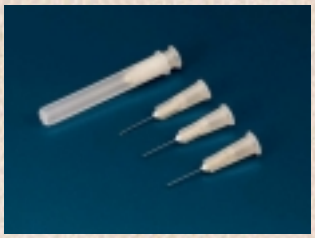


Noncoring point, ideal for piercing septa

Standard point

L (in.)	Gauge	*Noncoring point* Cat. No.	*Standard point* Cat. No.
2	22	**Z11,560-6**	**Z10,383-7**
	20	**Z11,303-4**	**Z10,110-9**
	18	**Z11,304-2**	**Z10,111-7**
	16	**Z11,706-4**	–
	14	**Z11,700-5**	**Z12,675-6**
	13	–	**Z12,676-4**
	12	**Z11,694-7**	**Z12,677-2**
3.5	17	**Z11,305-0**	**Z10,112-5**
4	22	**Z11,713-7**	
	20	**Z11,711-0**	
	18	**Z11,709-9**	
	16	**Z11,707-2**	
	14	**Z11,701-3**	
	12	**Z11,695-5**	
6	22	**Z11,614-9**	
	20	**Z10,270-9**	
	19	**Z21,934-7**	
	18	**Z10,271-7**	
	16	**Z10,878-2**	
	14	**Z11,702-1**	
	12	**Z11,696-3**	
10	22	**Z11,714-5**	
	20	**Z11,712-9**	
	19	**Z21,935-5**	
	18	**Z11,710-2**	
	16	**Z11,708-0**	
	14	**Z11,704-8**	
	12	**Z11,697-1**	
12	22	**Z11,615-7**	
	20	**Z10,113-3**	
	19	**Z21,936-3**	
	18	**Z10,114-1**	
	16	**Z10,879-0**	
	14	**Z11,705-6**	
	12	**Z11,699-8**	
24	19	**Z21,937-1**	
	18	**Z10,086-2**	
	16	**Z10,087-0**	
	14	**Z12,674-8**	
	12	**Z12,672-1**	
36	20	**Z15,242-0**	
	19	**Z21,939-8**	
	18	**Z15,241-2**	
	16	**Z15,240-4**	
	14	**Z15,239-0**	
	12	**Z15,238-2**	

PrecisionGlide disposable needles



- Regular bevel point
- SS needle with PP Luer hub
- Siliconized to reduce resistance

Gauge	L (in.)	Cat. No.
30	0.5	**Z19,234-1**
30	1.0	**Z19,236-8**
27	0.5	**Z19,238-4**
27	1.25	**Z19,237-6**
26	0.5	**Z19,239-2**
25	1.0	**Z19,240-6**
25	1.5	**Z19,241-4**
23	0.75	**Z19,244-9**
23	1.0	**Z19,245-7**
23	1.25	**Z19,243-0**
22	1.0	**Z41,213-9**
22	1.5	**Z19,247-3**
21	1.0	**Z19,248-1**
21	1.5	**Z19,250-3**
21	2.0	**Z19,257-0**
20	1.0	**Z19,251-1**
19*	1.0	**Z19,253-8**
19*	1.5	**Z19,254-6**
19**	1.5	**Z19,197-3**
18	1.0	**Z19,255-4**
18***	1.5	**Z19,200-7**
18**/***	1.5	**Z19,198-1**
16	1.0	**Z19,256-2**
16***	1.0	**Z19,201-5**

*Thin wall needle **5µm Filter needle
***No-Kor needle

Equipment for Air-Sensitive Chemistry

Double-tipped needles

304 SS with noncoring tips.

L (in.)	Gauge	Cat. No.
12	20	**Z17,559-5**
24	20	**Z10,109-5**
	18	**Z10,088-9**
	16	**Z10,089-7**
	14	**Z18,522-1**
	12	**Z18,521-3**
36	16	**Z10,090-0**
	12	**Z18,520-5**

Double-ended needles

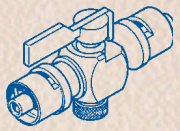
304 SS. One noncoring tip, one flat-cut end.

L (in.)	Gauge	Cat. No.
6	12	**Z11,639-4**
18	12	**Z11,640-8**
24	18	**Z10,242-3**
24	16	**Z10,243-1**
36	16	**Z10,245-8**

SYRINGE FITTINGS

PERFEKTUM one-way compression-nut stopcocks

Female Luer to male Luer lock, not unidirectional.
Z10,235-0
As above with large bore.
Z10,236-9



Male Luer lock to male Luer lock, not unidirectional.
Z10,237-7

PERFEKTUM high pressure stopcocks

NEW!

Chrome-plated brass body. High pressure rating up to 290psi.

One-way
Male needle-lock Luer to female Luer.
Z50,657-5

Three-way
Male needle-lock Luer to female Luer to side female Luer.
Z50,658-3

PERFEKTUM stainless steel stopcocks

NEW!

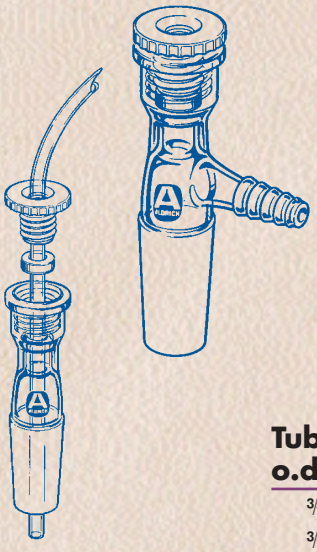
Made from corrosion-resistant 303 stainless steel.

One-way
Male needle-lock Luer to female Luer.
Z50,655-9

Three-way
Male needle-lock Luer to female Luer to side female Luer.
Z50,656-7

Glassware for Air-Sensitive Chemistry

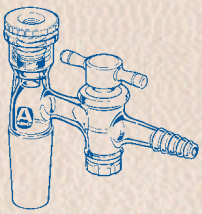
TUBING ADAPTERS WITH TORION CONNECTION



The unique Torion connection ensures an air-tight seal between tubing and reaction vessels when transferring air-sensitive materials.

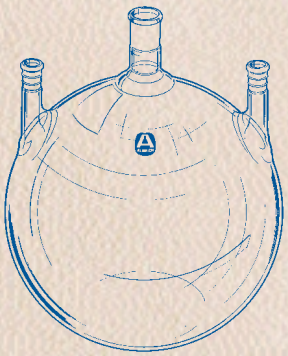
1. Hard-wall transfer tubing (e.g. PP or PTFE) is inserted through the threaded polypropylene bushing and PTFE-coated sealing ring of the adapter.
2. Turn the bushing to make an air-tight compression seal with the tubing.
3. Use the optional solid-glass plug to make an air-tight Torion seal when the transfer tubing is not in use.

Tubing o.d. (in.)	Inner ⅀ joint	*Straight* NEW! Cat. No.	*With hose barb* Cat. No.
3/16	14/20	**Z53,162-6**	**Z53,172-3**
3/16	19/22	**Z53,163-4**	**Z53,173-1**
5/16	14/20	**Z53,164-2**	**Z53,175-8**
5/16	19/22	**Z53,165-0**	**Z53,176-6**
5/16	24/40	**Z53,166-9**	**Z53,177-4**
5/16	29/32	**Z53,167-7**	**Z53,178-2**
1/2	24/40	**Z53,168-5**	**Z53,179-0**
1/2	29/32	**Z53,169-3**	**Z53,180-4**
1/2	34/45	**Z53,170-7**	**Z53,181-2**
1/2	45/50	**Z53,171-5**	**Z53,182-0**



Tubing adapters with stopcock NEW!

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



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

Solid glass plugs NEW!

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

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

Replacement PTFE-coated sealed rings

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

Glassware for Air-Sensitive Chemistry

ALDRICH SCHLENK-TYPE GLASSWARE

This system is specifically designed for additions, chemical reactions, distillations, drying/evaporation, extractions, filtrations, recrystallizations, washing, degassing, and transfers of solids and liquids. For small-scale manipulation of air- and moisture-sensitive reagents. Aldrich Schlenk-type glassware is available with greaseless threaded ₮14/20 ground-glass joints and is compatible with the Aldrich All-in-One Glassware Kit.

- Greaseless threaded ₮ joints require no clamps
- Narrow openings minimize infusion of air during manipulations
- Side-arm stopcocks for evacuation of air and purging with inert gas
- May be used with ordinary glassware with ₮ joints

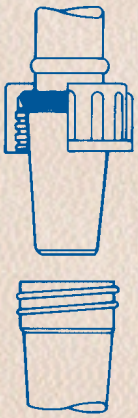
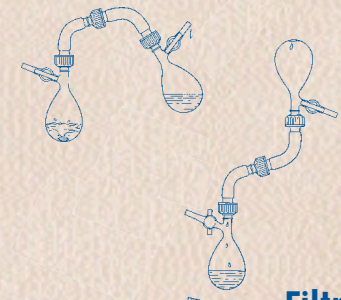


Fig. 1

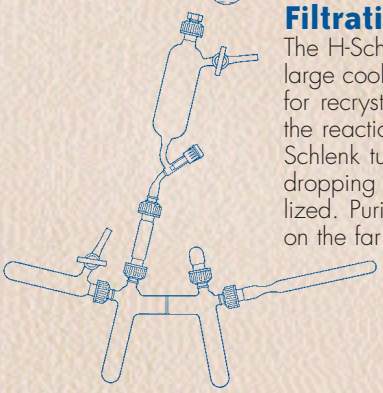
Fig. 1: Threaded joint consists of an externally threaded female ₮ joint and a corresponding male ₮ joint with a threaded plastic nut and O-ring that seals above the ground-glass joint to make a vacuum-tight, greaseless seal. A simple twist of the nut loosens the joint for safe disassembly.

TYPICAL OPERATIONS USING ALDRICH SCHLENK-TYPE GLASSWARE



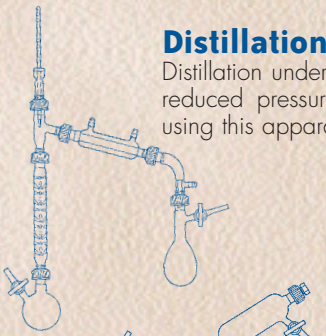
Chemical Reaction

After securing the reaction flask and initiating stirring, the apparatus is slowly rotated about the joint between the two adapters, allowing the reagent solution to flow into the reaction flask.



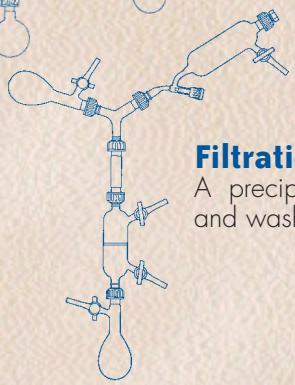
Filtration/Recrystallization

The H-Schlenk tube permits low-temperature filtration if a large cooling bath is used. The illustration shows a set-up for recrystallization. Starting material is transferred from the reaction and storage tube on the far left, into the H-Schlenk tube where it is dissolved with solvent from the dropping funnel, filtered into the right leg, and recrystallized. Purified material is transferred to the sealing tube on the far right.



Distillation

Distillation under inert atmosphere and/or reduced pressure is easily accomplished using this apparatus.



Filtration/ Washing

A precipitate may be collected and washed using this apparatus.

For additional Schlenk application diagrams and ordering information see the ***2001-2002 Aldrich Glassware catalog*** or visit our website at **www.sigma-aldrich.com/glassware**. To request your copy of the glassware catalog call **1-800-231-8327 (USA)**.

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Pinane-Based Versatile "Allyl"boranes†

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Outline

1. Introduction

The discovery of hydroboration by Brown and Subba Rao and the utilization of the resulting organoboranes as reactants or reagents marked the beginning of a new era in organic chemistry.[1] In the two decades that followed, Brown and others explored the new "continent" of organoboranes for functional group transformations and new carbon–carbon bond-forming reactions.[2] These developments laid the groundwork for several of the asymmetric synthetic methods that emerged during the past two decades.[3-5]

The pioneering report by Brown and Zweifel on the asymmetric hydroboration of (*Z*)-2-butene in high enantiomeric excess (ee) with α-pinene-derived diisopinocampheylborane (Ipc_2BH) is the first successful nonenzymatic asymmetric synthesis.[6] Ipc_2BH was the forerunner for a series of pinane-based versatile reagents (PVR) for asymmetric reduction, allyl- and crotylboration, ring opening of epoxides, homologation, enolboration, and other reactions (**Figure 1**). Several accounts of the chemistry of these reagents have appeared in the literature.[3,7] This review will focus on the "allyl"borating reagents derived from α-pinene.[8]

2. Allylboration: Characteristics

Almost four decades ago, Mikhailov and Bubnov pointed out that triallylborane, in marked contrast to the saturated trialkylboranes, undergoes a fast addition to carbonyl groups (**eq 1**).[9] Mikhailov and Pozdnev later showed that such reactions occur with allylic rearrangement.[10]

Mikhailov, Bubnov, and their coworkers studied this reaction in detail and included several other electrophilic carbons as substrates. Thus, imine derivatives, vinyl ethers, and even acetylenes were subjected to allylboration (**eq 2**).[11]

The homoallylic alcohol products contain hydroxyl and alkene moieties, which can be transformed into other functional groups (**Figure 2**).

It is possible to conceive of several substituted allylborating agents to achieve the synthesis of different types of homoallylic alcohols (**eq 3**). Hoffmann, Brown, Roush, and others have made significant contributions by systematically studying this aspect of "allyl"boration.[7,8] The stereoelectronics of the substituents at the α carbon (substituents 1 and 2) controls the stereochemistry of the olefins in the products. Selective formation of *E* and *Z* olefinic products has been achieved.[8b,12] Hoffmann and Zeiss showed that the reaction of (*E*)- or (Z)-butenylboronates (crotylboronates) with aldehydes results in the formation of anti or syn β-methyl homoallylic alcohols, respectively.[13]

It is crucial to control the allylic rearragements of crotylboranes (**eq 4**) in order to achieve maximum diastereoselectivity. Crotyldialkylboranes tend to rearrange more than crotylboronic acid esters. Conducting the reactions at low temperatures is essential to stopping the rearrangement and achieving high diastereoselectivity.[13,14]

Due to the similarity in their reaction pathways (involving allylic rearrangement), alkoxyallylboration (**eq 5**), crotylboration (**eq 6**), allenylboration (**eq 7**), and propargylboration (**eq 8**) can all be broadly classified under "allyl"boration. For convenience, the term "higher crotyl"boranes is used for those reactions involving homologs of 2-butenylboranes (**eq 6**).

The chemistry of boron enolates (enolboration, **eq 9**) is also very similar to allylboration. However, enolborinates do not undergo allylic rearrangement due to a strong

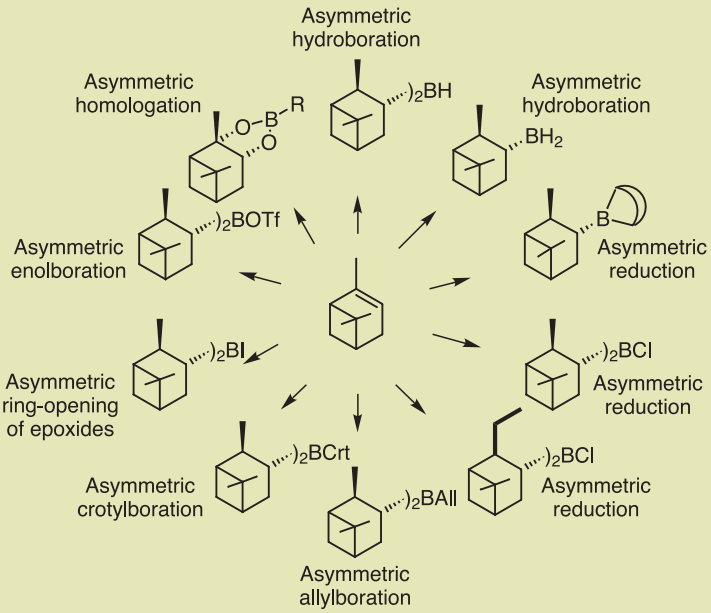
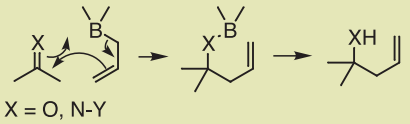
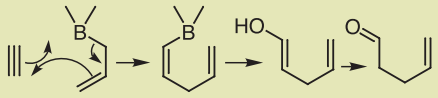


Figure 1. Pinane-Based Versatile Reagents (PVR).



eq 1



eq 2

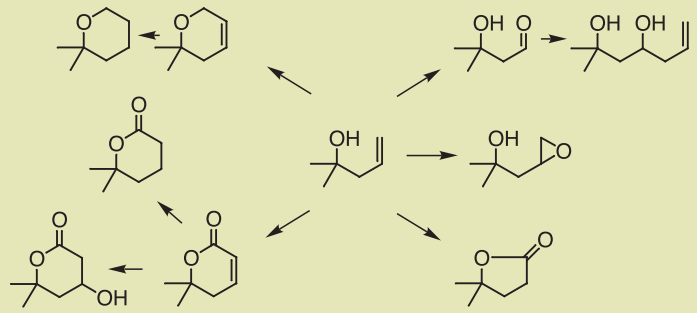
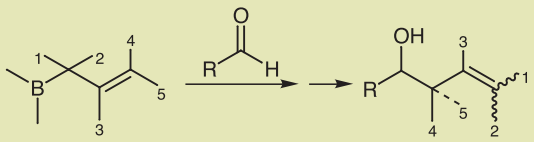
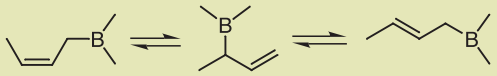


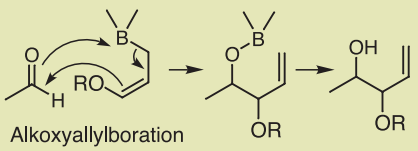
Figure 2. Elaboration of Allylboration-Derived Homoallylic Alcohols.



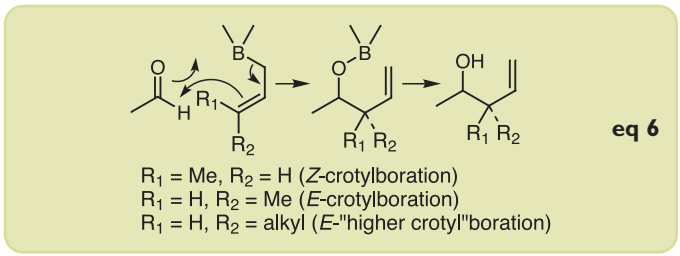
eq 3

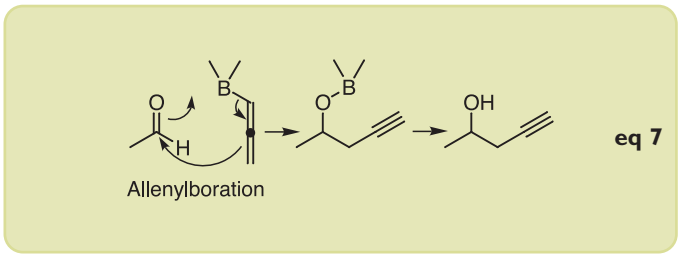


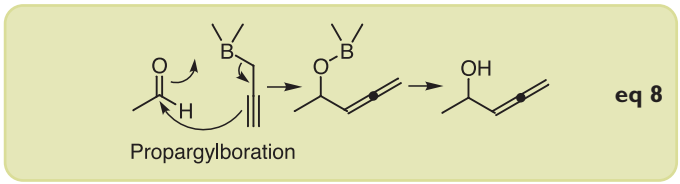
eq 4

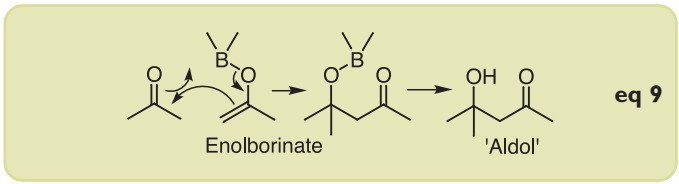


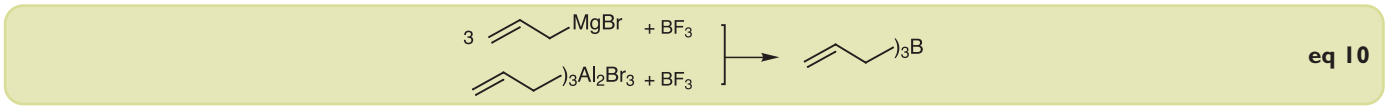
eq 5

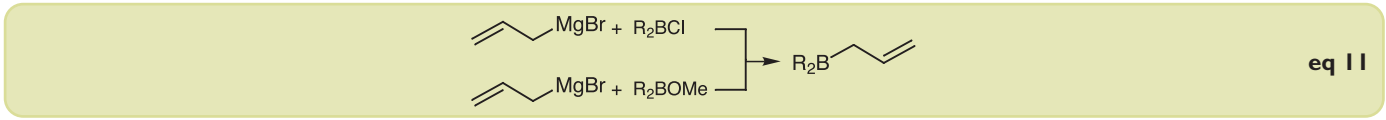


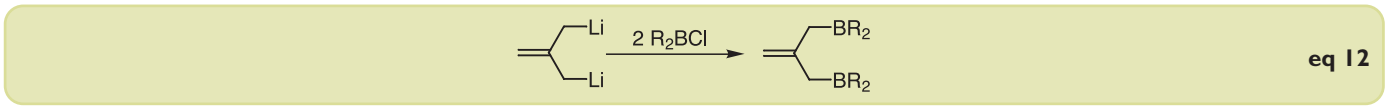


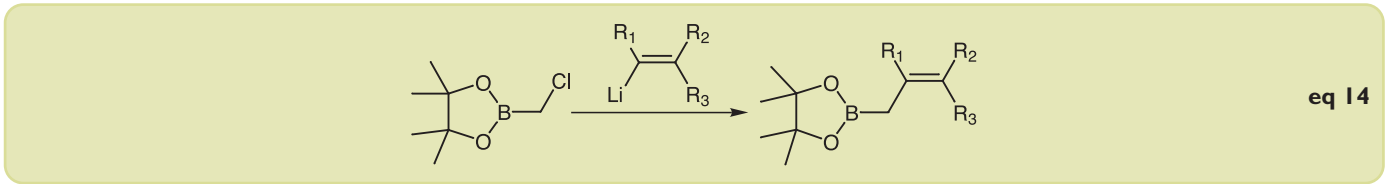












B–O bond.[15] The mechanism involves a similar six-membered cyclic transition state, and much success has been achieved with pinane-based chiral auxiliaries.[16]

3. Preparation of Allylboranes

The simplest synthesis of allylboranes involves the treatment of allylmetals with borane derivatives, such as haloboranes or alkoxyboranes (**eq 10**, **11**).[9] Bubnov and coworkers have reported the synthesis of bis(allylboranes) from dilithioisobutylene (**eq 12**).[17]

Allylboronates can be prepared by a one-carbon homologation (Matteson homologation) of vinylboronates with halomethyllithium (**eq 13**).[18] Treatment of vinyllithiums with halomethylboronates can also be used to prepare "crotyl"boronates stereospecifically (**eq 14**).[19]

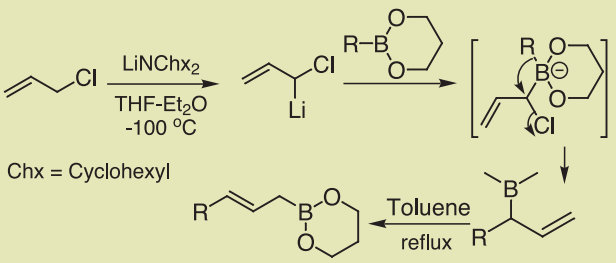
Brown and coworkers have reported a three-carbon homologation procedure for the preparation of higher crotylboronates (**Scheme 1**).[20]

Suzuki and coworkers have shown that catalytic hydroboration of 1,3-dienes with catecholborane in the presence of Pd(0) catalyst results in the formation of crotylborane derivatives (**eq 15**).[21] Another procedure for preparing stereospecific "crotyl"boranes involves the haloboration of terminal acetylenes, followed by Negishi coupling and Matteson homologation protocols (**Scheme 2**).[22]

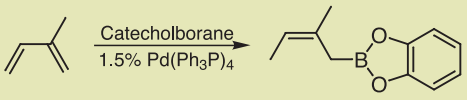
Yet another procedure for the preparation of "crotyl"boranes involves the hydroboration of substituted allenes. Although several hydroboration products are possible, the predominant product observed is the *E* "crotyl"borane (**eq 16**).[23]

4. Asymmetric Allylboration

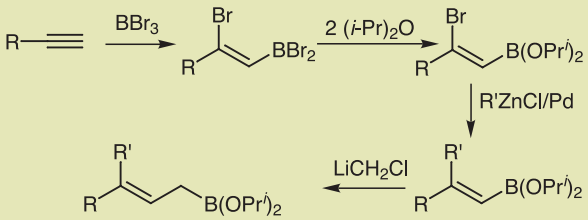
Asymmetric allylboranes that react with aldehydes to produce chiral homoallylic alcohols have attained considerable importance in the art of stereoselective synthesis of highly sophisticated, conformationally nonrigid systems.[5,8] Here, not only the enantioselectivity, but also the diastereoselectivity of the reaction is highly important. Accordingly, numerous searches



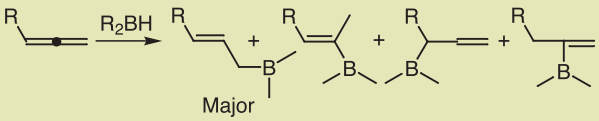
Scheme 1. Preparation of "Crotyl"boronates by a Three-Carbon Homologation.



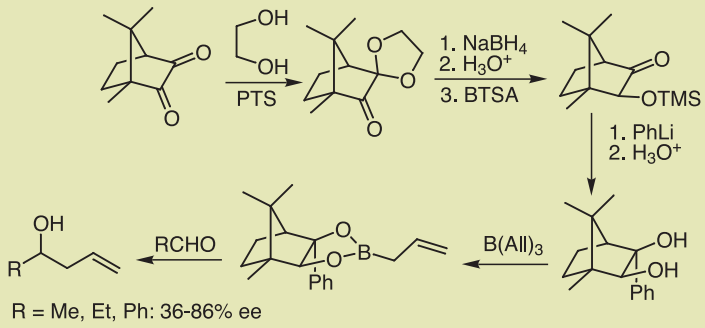
eq 15



Scheme 2. Preparation of Allylboronates via Haloboration–Homologation.



eq 16



Scheme 3. The First Asymmetric Allylboration.

for the most efficient reagent that can achieve both these selectivities in a single step have been carried out.[5,8]

Hoffmann and coworkers reported the first asymmetric allylboration utilizing a camphor-derived auxiliary (**Scheme 3**).[24] They studied various allyl- and crotylboration reactions using this auxiliary for both single and double asymmetric synthesis.[8a-d]

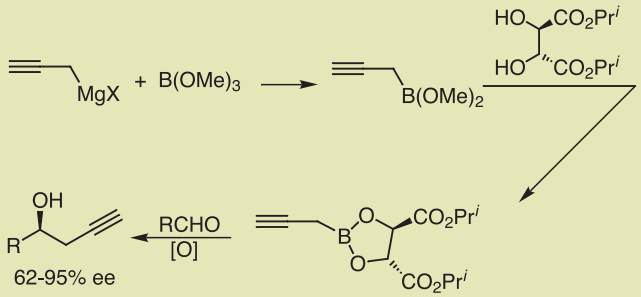
Yamamoto and coworkers introduced tartrate esters as chiral auxiliaries for propargylboration (**Scheme 4**).[25] Later, they utilized this approach for the allenylboration of aldehydes to produce homopropargylic alcohols in very high ee (**eq 17**).[26] They showed that the ee's of the alcohols depend on the alkyl group of the tartrate ester: ethyl and isopropyl tartrates lead to lower ee's, while cyclododecyl and 2,4-dimethylpentyl tartrates lead to higher ee's.

Isopropyl tartrate was used as a chiral auxiliary for allylborations by Roush and coworkers (**Scheme 5**),[27] who also used tartrates for crotylborations.[28] Tartramido-allylboronates provided better selectivity in allylborations than tartrate esters.[29]

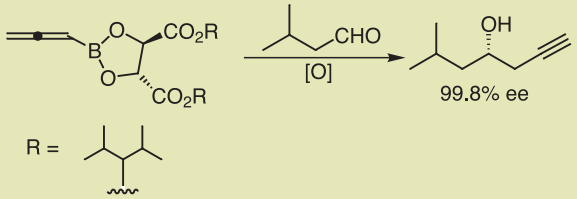
Figure 3 shows several "allyl"borating agents. These include allylboronates derived from chiral 1,2-diols,[30] functionalized allylboronates,[31] oxazaborolane,[32] and diaza-borolane.[33]

5. Asymmetric Dialkylallylboranes

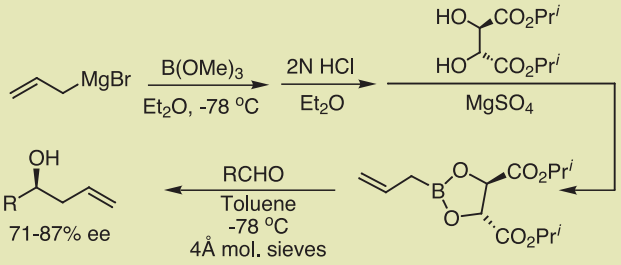
Brown and Jadhav put α-pinene to the test for allylboration and achieved an economical reaction with predictable stereochemistry and high enantioselectivity.[34] *B*-Allyldiiso-pinocampheylborane, prepared from either *B*-chlorodiisopinocampheylborane (DIP-Chloride™)[35] or *B*-methoxydiisopinocam-pheylborane and allyl Grignard reagent, provided high ee's for most of the aldehydes



Scheme 4. Tartrate Ester Auxiliary for Propargylboration of Aldehydes.



eq 17



Scheme 5. Tartrate Ester for Allylboration.

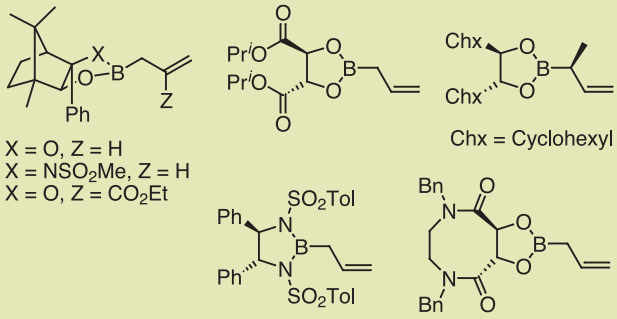
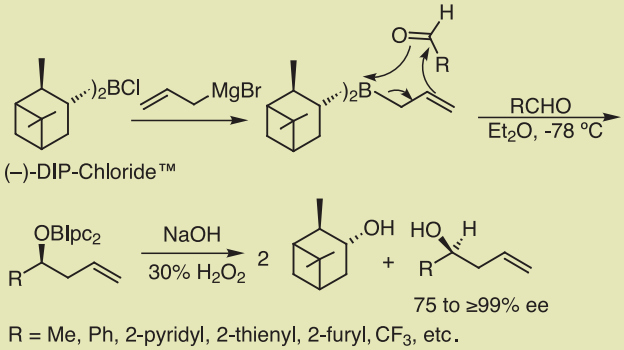


Figure 3. "Allyl"borating Agents.



Scheme 6. Preparation and Reactions of *B*-Allyldiisopinocampheylborane.

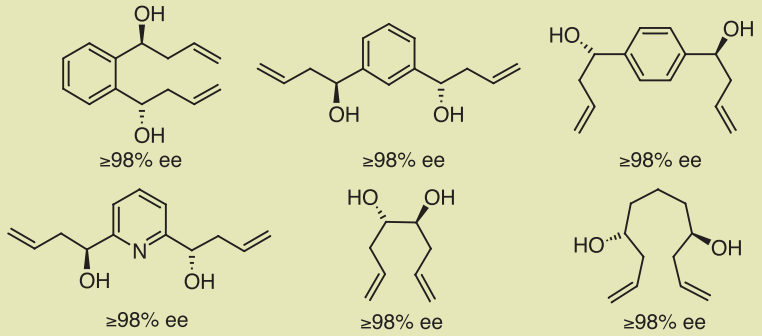
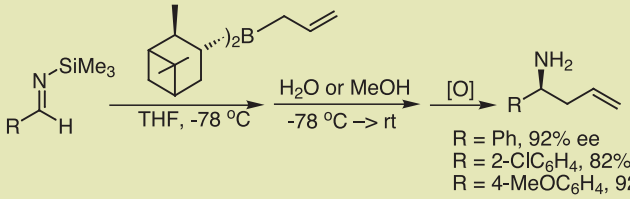
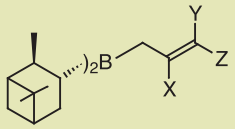


Figure 4. High Enantioselectivities in the Allylboration of Dialdehydes.

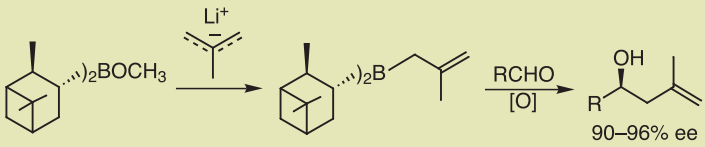


eq 18



X	Y	Z
H	H	H
H	H	Me
H	H	Cl
H	H	NPh_2
H	H	$B(OR)_2$
H	Me	H
H	OMe	H
H	Me	Me
Me	H	H
vinyl	H	H

Figure 5. Pinane-Based "Allyl"borating Reagents.



Scheme 7. Methallylboration of Aldehydes.

tested, including heterocyclic[36] and fluorinated aldehydes[37] (**Scheme 6**). With chiral aldehydes, the reagent controlled the diastereoselectivity leading to high de's and ee's.[38] High selectivities were also achieved in the allylboration of a series of dialdehydes (**Figure 4**).[39] Recently, it has been shown that this reagent provides high ee's of homoallylic amines produced by the allylboration of *N*-silyl imines (**eq 18**).[40]

Several remarkably successful "allyl"borating agents have been synthesized using pinane as the chiral auxiliary (**Figure 5**). Discussion of these reagents follows.

5.1. B-Methallyldiisopinocampheylborane

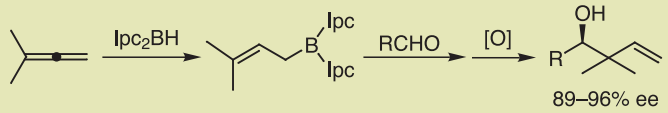
This reagent, readily prepared from Ipc_2BOMe and methallyllithium, converts aldehydes into methallyl alcohols in very high ee's (**Scheme 7**).[41] The alcohols are valuable intermediates, which can be elaborated into more complex acyclic compounds via diastereoselective epoxidation and iodocyclization.

5.2. 3,3-Dimethylallyldiisopinocampheylborane

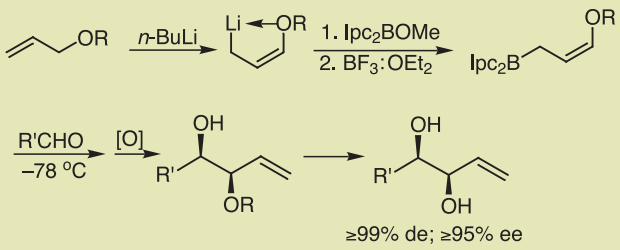
This reagent is synthesized by the hydroboration of 1,1-dimethylallene. Its allylboration reaction typically provides products with predictable configurations in 89–96% ee (**Scheme 8**).[42]

5.3. [(Z)-3-Alkoxyallyl]diisopinocampheylborane

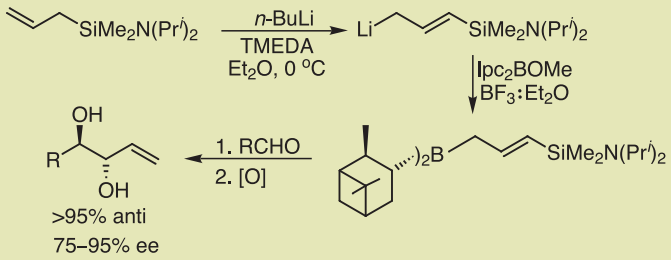
Metal salts of allyl alkyl ethers remain in the *Z* form due to chelation.[43] Transmetalation with boron retains the *Z* stereochemistry.[44] The synthesis of [(*Z*)-3-alkoxyallyl]diisopinocampheylborane was achieved by reaction of the lithium salt of allyl alkyl ether with *B*-methoxydiisopinocampheylborane, followed by treatment with BF_3:Et_2O.[45] The reaction of the title



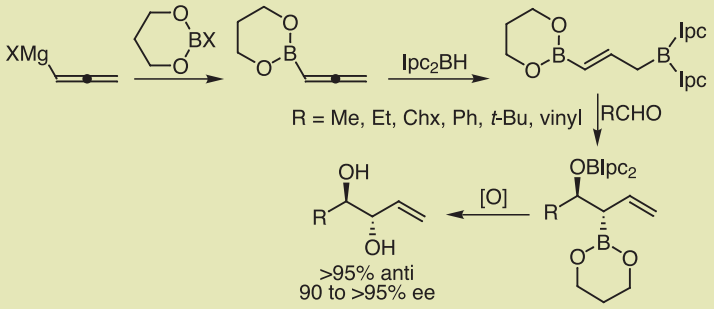
Scheme 8. Preparation and Reaction of (Dimethylallyl)diisopinocampheylborane.



Scheme 9. Asymmetric Synthesis of Vicinal syn Diols.



Scheme 10. Asymmetric Synthesis of Vicinal anti Diols.



Scheme 11. Asymmetric Synthesis of Vicinal anti Diols.

reagent with aldehydes at low temperatures exhibits a high syn selectivity, and allows the preparation of syn 1,2-diols in high ee's after removal of the alkyl protecting groups (**Scheme 9**).

5.4. B-[3-((Diisopropylamino)-dimethylsilyl)allyl]diisopino-campheylborane

Barrett and Malecha synthesized this γ-silylallyldiisopinocampheylborane as a surrogate for the preparation of anti 1,2-diols with excellent absolute and relative stereocontrol (**Scheme 10**).[46]

5.5. [(E)-3-(2,6-Dioxaborolyl)allyl]-diisopinocampheylborane

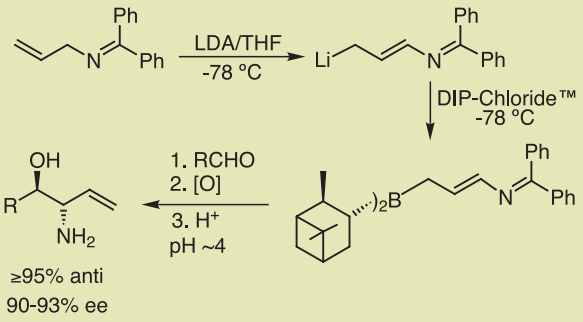
Brown and Narla achieved the synthesis of this γ-borolylallylborane reagent by hydroboration of allenylborane, which was prepared by treatment of allenylmagnesium bromide with a chloroborane. The title reagent achieves the synthesis of anti 1,2-diols in excellent isomeric and enantiomeric purities (**Scheme 11**).[47]

5.6. [(E)-3-(Diphenylimino)allyl]-diisopinocampheylborane

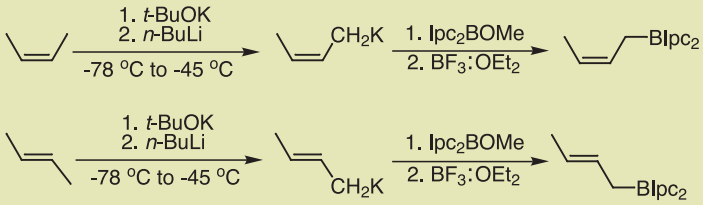
Barrett and coworkers reported the convenient synthesis of anti β-amino alcohols in high de and ee using an "imino" allylborane reagent (**Scheme 12**).[48]

5.7. B-(E)- and (Z)-Crotyldiiso-pinocampheylborane

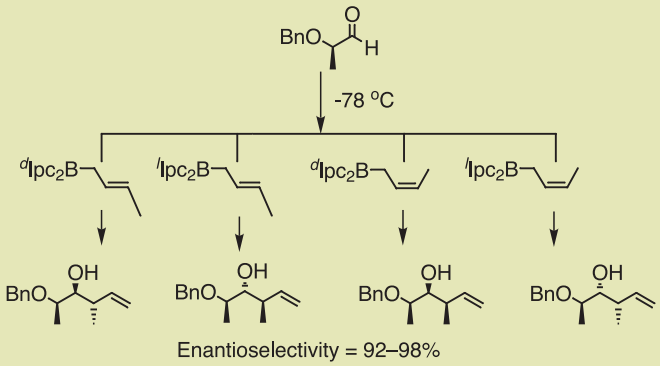
Hoffmann synthesized *E* and *Z* crotylboronates and reported that the stereochemistry is transferred during the crotylboration of aldehydes.[13] The preparation of isomerically pure *E* and *Z* crotylboronates from isomerically pure crotylpotassium was reported by Fujita and Schlosser.[49] Brown and Bhat utilized a similar procedure for the synthesis of



Scheme 12. Asymmetric Synthesis of Vicinal anti Amino Alcohols.



Scheme 13. Preparation of Crotyldiisopinocampheylboranes.



Scheme 14. Crotylboration of α-Substituted Chiral Aldehydes.

isomerically pure *B*-(*E*)- and *B*-(*Z*)-crotyldiisopinocampheylboranes (**Scheme 13**).[14]

The reaction of these derivatives with aldehydes achieved the synthesis of the four possible isomers of β-methylhomoallylic alcohols with remarkable enantiomeric and diastereomeric efficiencies. It is important, however, to maintain the reaction temperature below -45 °C to avoid scrambling the crotylboranes. Since the reagent controls the diastereoselectivity in reactions with chiral aldehydes, it is possible to prepare all eight diastereomeric homoallylic alcohols at will by the appropriate choice of reagent and chiral aldehyde (**Scheme 14**).[50]

5.8. B-2'-Isoprenyldiisopinocampheylborane

The success with crotylpotassium led Brown and Randad to the preparation of *B*-2'-isoprenyldiisopinocampheylborane from isoprenylpotassium and *B*-methoxydiisopinocampheylborane. Condensation of this reagent with aldehydes provided isoprenylated chiral alcohols, including the pheromones of the bark beetle *Ips paraconfusus* Lanier, ipsenol and ipsdienol (**Scheme 15**).[51]

5.9. Higher Crotylboranes

A series of higher crotylboranes were synthesized by the hydroboration of appropriate allenes with Ipc_2BH. The hydroboration produced essentially pure *E* crotylboranes, which provided the anti alcohols in high de's and ee's (**Scheme 16**).[23]

5.10. γ-Chloroallyldiisopinocampheylborane

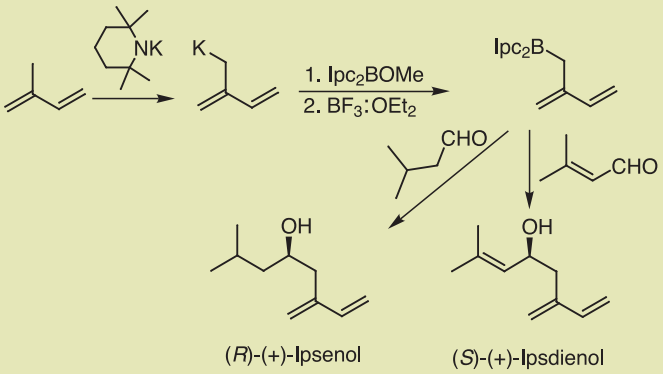
Oehlschlager and coworkers prepared a series of chlorohydrins in very high de's and ee's, by utilizing an α-pinene-based chloroallylborane. The chlorohydrins were readily converted into chiral vinyl epoxides (**Scheme 17**).[52]

5.11. B-2-Cyclohexen-1-yldiisopinocampheylborane

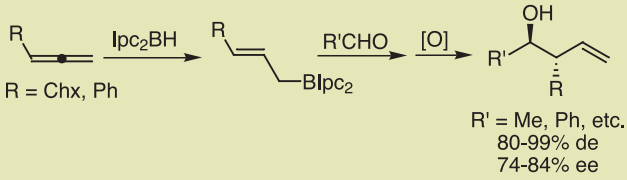
Brown and coworkers reported the synthesis of the title compound by hydroboration of 1,3-cyclohexadiene. "Allyl"boration using this reagent provided 1-(2-cyclohexenyl)-1-alkanols in high de's and ee's (**Scheme 18**).[53] This procedure was successfully applied to the synthesis of the C_2-symmetric chiral auxiliary, dicyclohexyl-1,2-ethanediol,[30] via reaction with glyoxal and hydrogenation (**Scheme 19**).[54]

5.12. Other Chiral Dialkylallylboranes

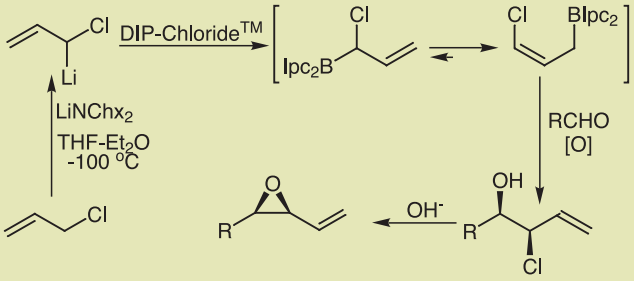
Brown and coworkers tested several other terpenes as chiral auxiliaries for allylboration (**Figure 6**).[55] Of these, the reagents prepared



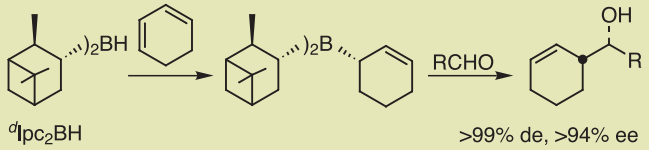
Scheme 15. Asymmetric Synthesis of Ipsenol and Ipsdienol.



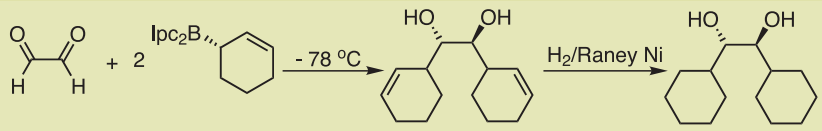
Scheme 16. Higher Crotylboration.



Scheme 17. Asymmetric Synthesis of Vinyl Epoxides via Chloroallylboration.



Scheme 18. Preparation of *B*-2-Cyclohexen-1-yldiisopinocampheylborane.



Scheme 19. Synthesis of the Chiral Auxiliary Dicyclohexyl-1,2-ethanediol.

from 2- and 3-carene turned out to be superior.[55,56] Other known chiral dialkylallylborating agents derived from synthetic chiral auxiliaries are also shown in Figure 6.[57]

6. Applications of Allyl- and Crotylboration

Asymmetric "allyl"boration is a very useful reaction for the synthesis of complex natural products and biologically active molecules. Both tartrate- and pinane-derived reagents have been widely exploited in synthesis. **Schemes 20–23** depict representative applications of pinane-derived reagents as reported in the literature.[58-62]

6.1. Allylboration–Ring-Closing-Metathesis Reactions for the Synthesis of α-Pyrones

Optically pure α-pyrones (5,6-dihydro-2*H*-pyran-2-ones) are structural features in several biologically active natural products.[63] Our protocol for the synthesis of α-pyrones involves the esterification of homoallylic alcohols with acryloyl chloride, followed by ring-closing metathesis (RCM)[64] using Grubbs's ruthenium catalyst.[65] Representative examples of our approach are shown in **Scheme 24**.[66]

Similar approaches were utilized for the synthesis of argentilactone (**Scheme 25**),[67] tarchonanthuslactone (**Scheme 26**),[68] and umuravumbolide (**Scheme 27**).[69]

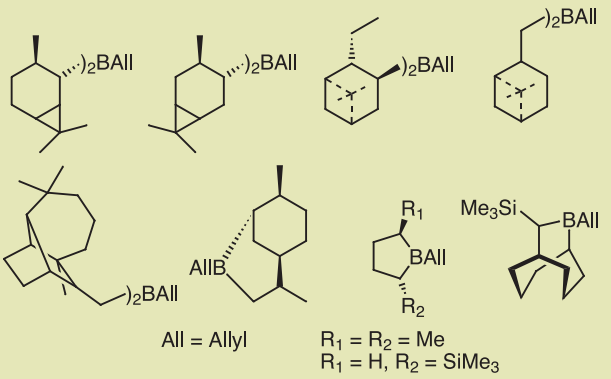
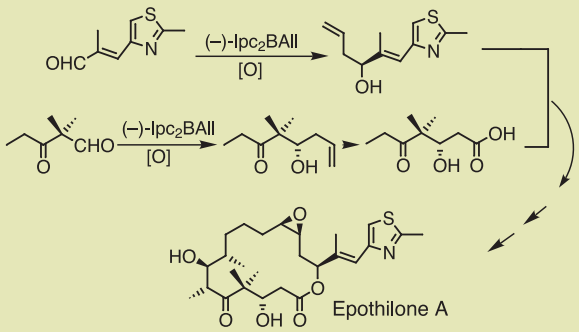
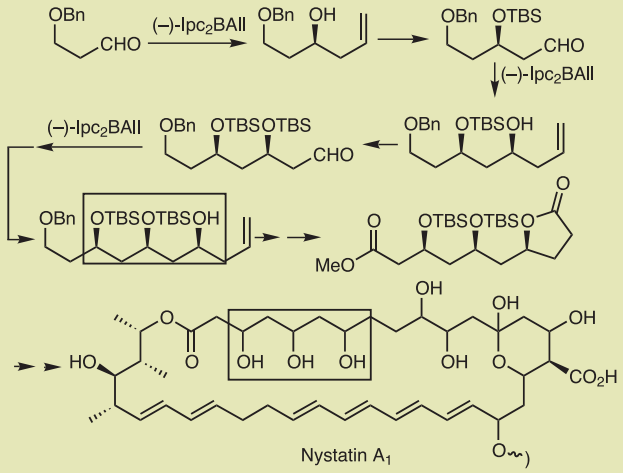


Figure 6. Chiral Dialkylallylboranes.



Scheme 20. Application of Allylboration. Synthesis of Epothilone A.



Scheme 21. Application of Allylboration. Synthesis of Nystatin A_1.

6.2. *HMG-CoA Reductase Inhibitor Analogs*

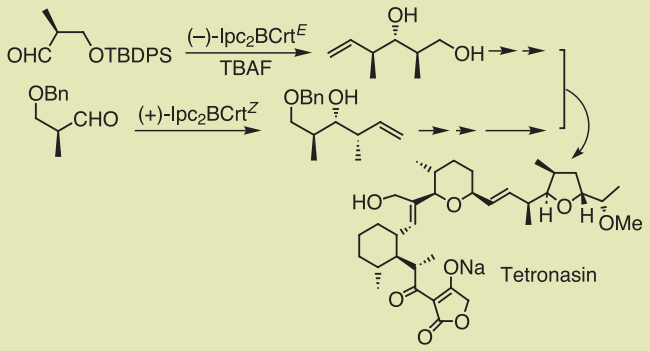
The discovery of compactin and mevinolin (**Figure 7**) two decades ago as inhibitors of hydroxymethylglutaryl coenzyme A reductase revolutionized research aimed at the treatment of hypercholesterolemia.[70] Systematic studies of the analogs of mevinolin have revealed that the key pharmacophore necessary for drug action is the β-hydroxy-δ-lactone unit.[71] Our synthesis of mevinolin analogs is shown in **Scheme 28**.[72]

7. Conclusion and Prospects

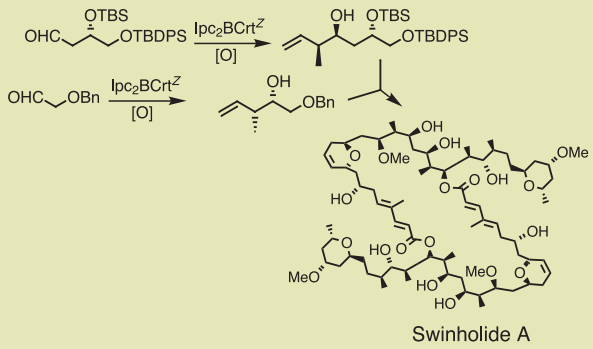
The borane continent that Professor Brown discovered is truly vast. Allylboration is only a small part of organoborane chemistry. This review has covered only a subsection of the still-developing area of asymmetric "allyl"boration. We are currently developing a variety of new "allyl"borating agents, and investigating substrates other than aldehydes.

8. Acknowledgments

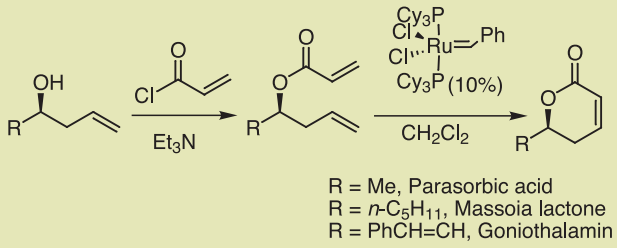
Financial support from the Herbert C. Brown Center for Borane Research[73] and Aldrich Chemical Company is gratefully acknowledged. Thanks are also due to the dedicated members of my research group, particularly Dr. M. Venkat Ram Reddy.



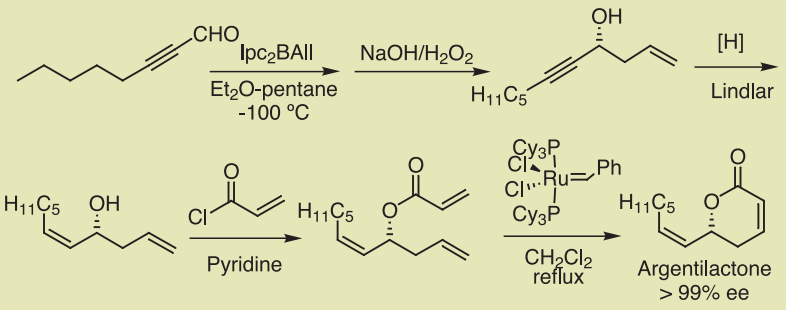
Scheme 22. Application of Crotylboration. Synthesis of Tetronasin.



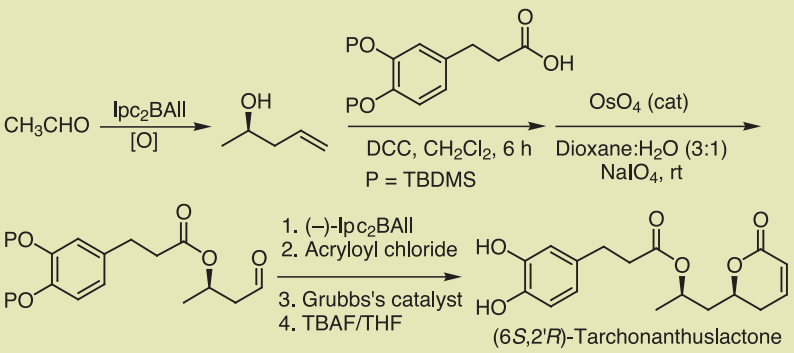
Scheme 23. Application of Crotylboration. Synthesis of Swinholide A.



Scheme 24. Synthesis of α-Pyrones via Ring-Closing Metathesis.



Scheme 25. Synthesis of Argentilactone.



Scheme 26. Synthesis of Tarchonanthuslactone.

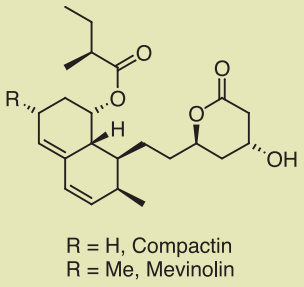
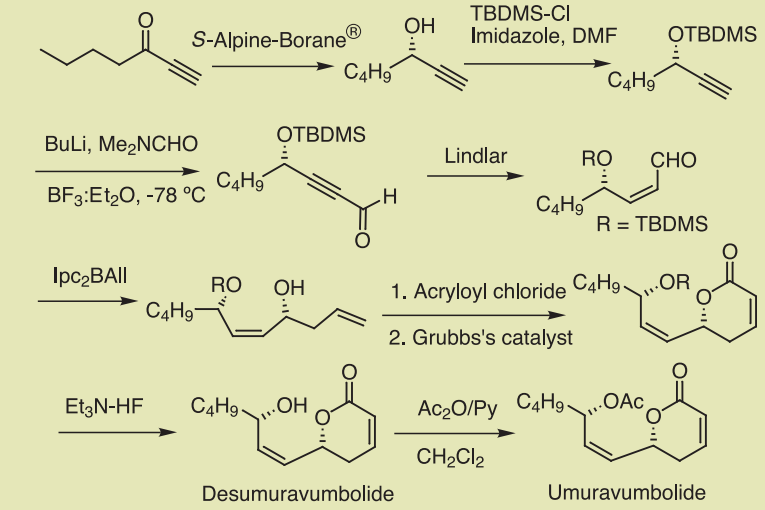
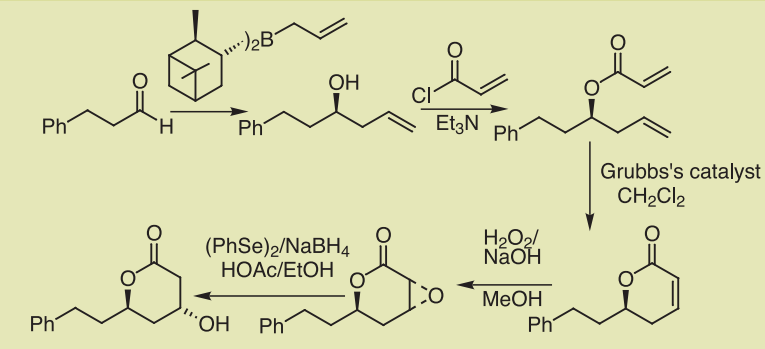


Figure 7. HMG-CoA Reductase Inhibitors.



Scheme 27. Synthesis of Umuravumbolide.



Scheme 28. Synthesis of Mevinolin Analogs via Ring-Closing Metathesis.

9. References and Notes

(†) This review is dedicated to Professor Herbert C. Brown on his ninetieth birthday.

(1) (a) Brown, H. C.; Subba Rao, B. C. *J. Am. Chem. Soc.* **1956**, *78*, 5694. (b) Brown, H. C. *Hydroboration*; Benjamin: New York, 1962.

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About the Author

P. V. Ramachandran (Chandran) received his Ph.D. degree in 1983 from the Indian Institute of Technology in Kanpur. In 1984, he joined Professor Herbert C. Brown's group as a postdoctorate. After two years, he became Brown's research assistant and continued in that position until 1997, when he joined the faculty of the Chemistry Department at Purdue University. He is a co-author of nearly 100 research publications, including several reviews and book chapters. He has also edited two books. He currently supervises an 18-member research group at the Herbert C. Brown Center for Borane Research. Apart from chemistry, Chandran likes to visit historic sites with his wife and two sons.

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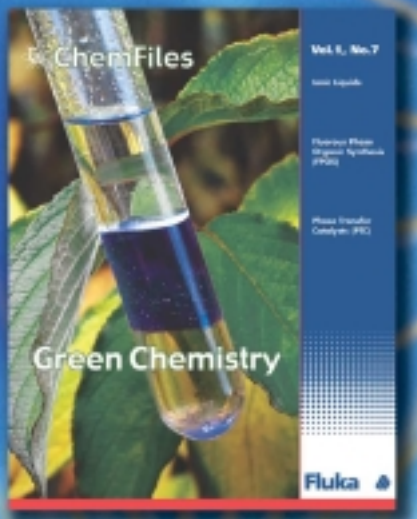

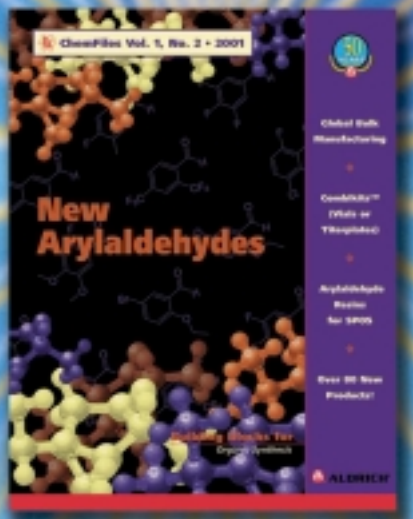

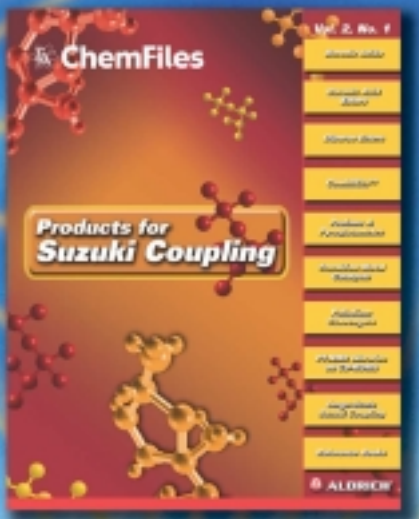

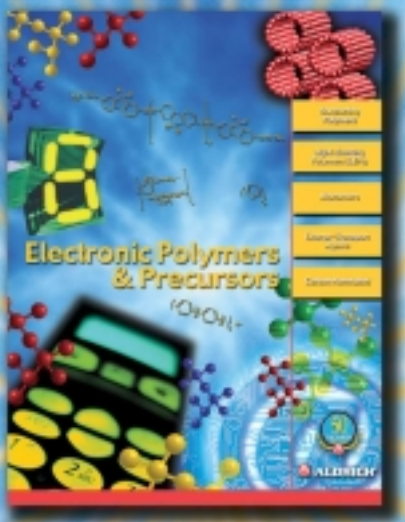

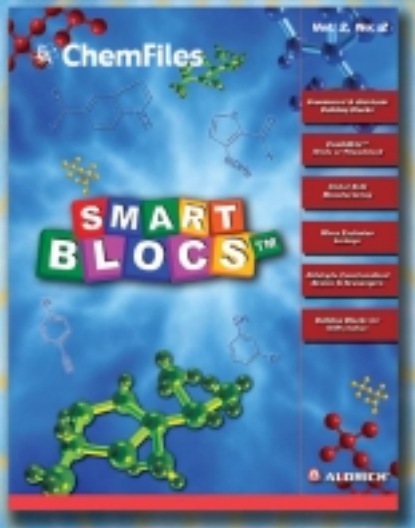

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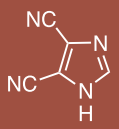

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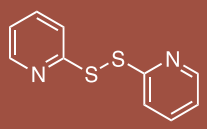
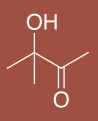
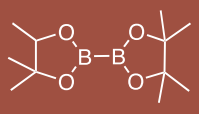
Oligonucleotide synthesis
[1122-28-7]



14,304-9 (Aldrithiol™-2)
Protein synthesis
[2127-03-9]

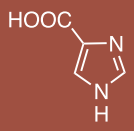


H3,960-4
Versatile intermediate
[115-22-0]



47,329-4
Suzuki coupling
[73183-34-3]

48,108-4 (Racemic BINAP)
Pd-catalyzed reactions
[98327-87-8]



42,584-2
Functionalized imidazole
[1072-84-0]

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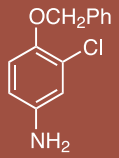

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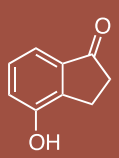

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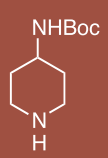

54,093-5
[73874-95-0]

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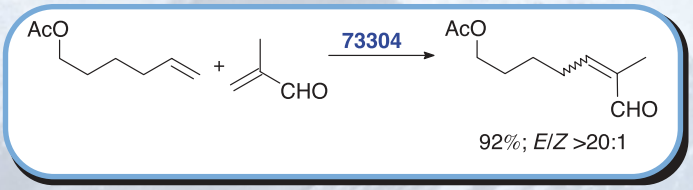

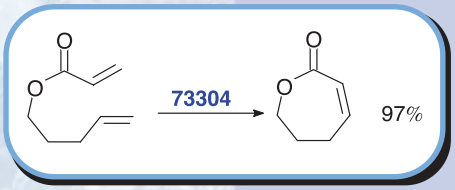

73304

New! **Benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium**
[Grubbs catalyst 2nd generation]

$C_{46}H_{65}Cl_2N_2PRu$ M_r 848.98 [246047-72-3] purum, ≥ 97.0% (C) **500mg**

New-generation catalyst with increased activity for olefin metathesis reactions; it often gives excellent yields in cases where the classic Grubbs catalyst fails;[2] even enol ethers undergo ring-closing metathesis (RCM) in excellent yield in the presence of this catalyst.[3]

91501

New! **Benzylidene-bis(tricyclohexylphosphine)dichlororuthenium**, polymer-bound
[Grubbs catalyst on polystyrene]

~0.1 mmol/g; cross-linked with 1% DVB; particle size: 100–200 mesh; may contain white polymer particles (polyethylene) **1g; 5g**

This polymer-supported Grubbs catalyst can be recovered from the reaction mixture after the reaction is completed and reused; this saves resources and avoids metal contamination of metathesis products, which is a serious problem in pharmaceutical chemistry.[4]

09587

Benzylidene-bis(tricyclohexylphosphine)dichlororuthenium
[Grubbs catalyst]

$C_{43}H_{72}Cl_2P_2Ru$ M_r 822.97 [172222-30-9] purum, ≥ 97.0% (C) **250mg; 1g; 5g**

Highly active and functional-group-tolerant catalyst for metathesis reactions,[5] in particular ring-closing of dienes to macrocycles[6] or ring-opening polymerization.[7] It is also the reagent used in preparing immobilized, 2nd generation Grubbs catalysts.[8]

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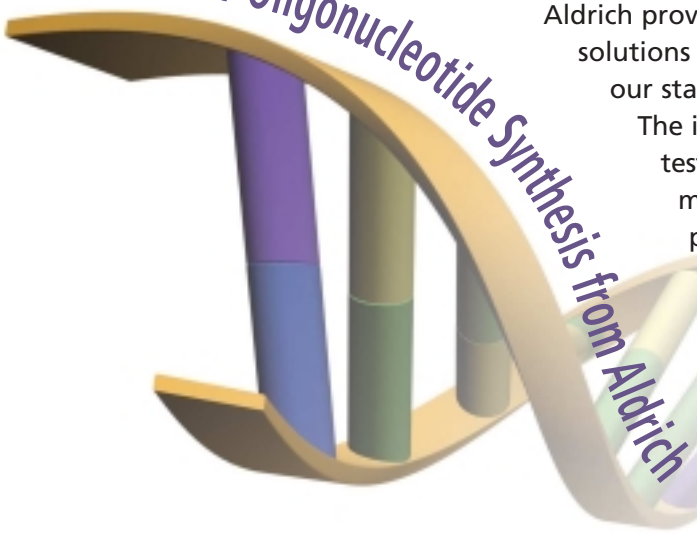


Aldrich provides a number of Capping, Deblocking, and Activator solutions for oligonucleotide synthesis. Each solution is blended in our state-of-the-art manufacturing facility in Sheboygan, Wisconsin. The integrity and quality of every solution is confirmed by rigorous testing to verify that our stringent product standards have been met. We have complete control over the manufacturing process, enabling superb quality and lot-to-lot consistency to be a norm rather than an exception. If you do not see a particular solution you are interested in from the list below, please contact our Technical Service department at **800-231-8327** with your suggestion. For information on these and other Aldrich products, please visit our Web site at **www.sigma-aldrich.com**.

Capping Solutions

Prevents further elongation of a growing oligonucleotide chain by "capping" unreacted 5′-hydroxyl ends of the chain. The 5′-hydroxyl end undergoes acetylation by acetic anhydride to prevent further reaction.

55,534-7 **Cap Mix A** **1L; 2L**
(Contains 90% tetrahydrofuran:10% acetic anhydride)

55,531-2 **Cap Mix A**, with 2,6-lutidine **1L; 2L**
(Contains 80% tetrahydrofuran:10% acetic anhydride: 10% 2,6-lutidine)

55,533-9 **Cap Mix A**, with pyridine **1L; 2L**
(Contains 80% tetrahydrofuran: 10% acetic anhydride: 10% pyridine)

55,532-0 **Cap Mix B** **1L; 2L**
(Contains 84% tetrahydrofuran: 16% 1-methylimidazole)

55,535-5 **Cap Mix B**, with pyridine **1L; 2L**
(Contains 80% tetrahydrofuran: 10% pyridine: 10% 1-methylimidazole)

Deblocking Solution

Removes the acid-labile dimethoxytrityl (DMT) protecting group from the 5′-hydroxyl of the previous nucleotide synthon added.

56,193-2 **Deblock** **1L; 2L**
(Contains 3% trichloroacetic acid in dichloromethane)

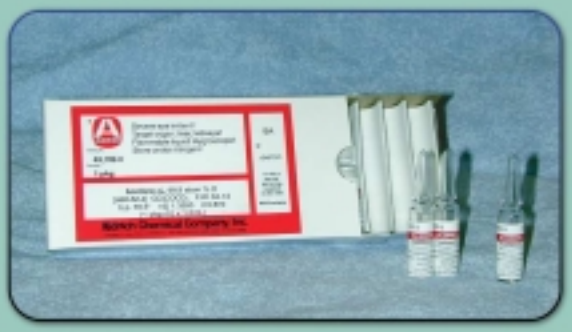
Activator Solution

Protonates the dialkylamino group of the phosphoramidite group, forming an active tetrazolophosphane intermediate. This intermediate can react directly with the free 5′-hydroxyl functionality of an oligonucleotide chain.

55,404-9 **1*H*-Tetrazole**, 3 wt.% solution in acetonitrile **1L; 2L**

NEW
Convenient Size!

5 x 1.0mL ampule packs from Aldrich



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Try our 5 x 1.0mL ampule packs today!

- **convenient** for those customers who are occasional NMR users
- **ideal** for solvents that may degrade naturally over time, such as chloroform-*d*
- **less** chemicals in the lab
- **same** convenient packaging as the larger pack size

All of the deuterated solvents at right are available in 10 x 1.0mL and 5 x 1.0mL ampule packs

Cat. No.	Description
43,192-3	Acetone-d_6, 99.9 atom % D
23,686-1	Acetonitrile-d_3, 99.8 atom % D
23,688-8	Benzene-d_6, 99.6 atom % D
23,689-6	Chloroform-*d*, 99.9 atom % D
26,980-8	*N*,*N*-Dimethylformamide-d_7, 99.5 atom % D
26,982-4	Methyl-d_3 alcohol-*d*, 99.8+ atom % D
23,692-6	(Methyl sulfoxide)-d_6, 99.9 atom % D

For a complete list of deuterated solvents that Aldrich offers, please refer to the *Products for NMR* brochure or the *Aldrich Handbook of Fine Chemicals and Laboratory Equipment*. Additional product information can be found on our Web site at **www.sigma-aldrich.com**.

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Professor of Chemistry

Kurashiki University of Science and the Arts

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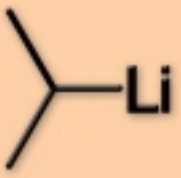
Professor Akira Suzuki received his Ph.D. degree (1959) from Hokkaido University, Sapporo, Japan, where he later became a professor in the Department of Applied Chemistry (1973–94). From 1963 to 1965, Dr. Suzuki worked as a postdoctoral associate in Professor Herbert C. Brown's research group investigating the stereochemistry of the hydroboration reaction. He was a visiting professor at several universities, including the University of Wales in 1988 and Purdue University in 2001. After his retirement from Hokkaido University in 1994, Professor Suzuki became a professor of chemistry at Okayama University of Science, and was appointed professor at Kurashiki University of Science and the Arts in 1995. He has received numerous awards; including a Testimonial from the Korean Chemical Society (1987), the Chemical Society of Japan Award (1989), the H. C. Brown Lecturer Award (Purdue University, 2000), and the 2001 Distinguished Lecturer Award (Queen's University, Canada, and Pfizer Inc.); and was made an Honorary Member of the Argentine Organic Chemistry Society in 2001.

Professor Suzuki's contributions to organoborane chemistry involve the discovery and development of new synthetic methodologies using organoboron compounds. The formation of organic radicals from organoboranes in the presence of catalytic amounts of oxygen was first discovered in the course of cooperative work with Professor Brown's research group. Professor Suzuki was also instrumental in the utilization of organoboron compounds as carbanions in synthesis. Organoboranes are also useful as a source of carbocations under electrochemical conditions, although a limited number of examples have been reported. More recent work by Suzuki and coworkers revolves around palladium-catalyzed cross-coupling reactions of various organoboron compounds with a number of organic electrophiles in the presence of bases. This reaction has become known as the Suzuki Coupling and is the focus of this book.

52,974-5

Isopropyllithium, 0.7 *M* solution in pentane

100mL; 1L



Useful in syntheses of nitroalkanes, hydroximoyl halides, and nitrile oxides by reaction with β-nitrostyrenes;[1] and of substituted alkenediols by alkylative, double-ring opening of dihydrofuran and dihydropyran epoxides.[2]

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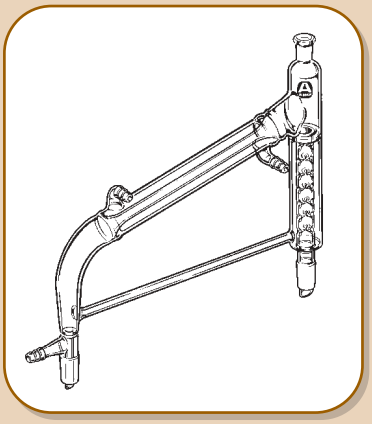
(1) Yao, C.-F. et al. *Tetrahedron* **1998**, *54*, 791.
(2) Hodgson, D. M. et al. *Org. Lett.* **2001**, *3*, 3401.

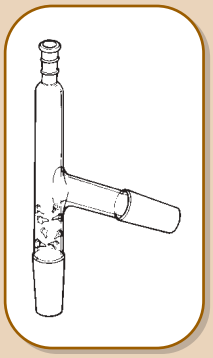
Aldrich Distillation Glassware

Heavy-Duty Vigreux Distillation Heads



These distillation heads are designed with heavier tubing and extra support to withstand the rigors of laboratory use. The one-piece jacketed design achieves greater distillation efficiency.

Joints	Thermometer joint	Immersion (mm)	O.d. (mm)	Condenser L (mm)	Cat. No.
14/20	10/18	40	25	150	**Z51,651-7**
24/40	10/30	75	38	300	**Z51,653-8**
29/32	10/30	75	38	300	**Z51,654-6**

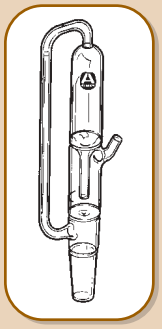


Short-Path Distillation Heads

Vigreux indents prevent bumping of fine or lightweight column packing into the condenser or fraction cutter when column is flooded.

Joints	Thermometer joint	Immersion (mm)	Cat. No.
14/20	10/18	40	**Z53,038-7**
19/22	10/18	40	**Z53,039-5**
24/40	10/30	75	**Z22,009-4**
29/32	10/30	75	**Z53,040-9**

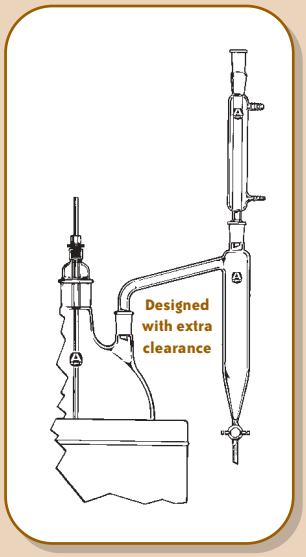
Reaction Vessel Bubblers



Capacity is 5 to 7mL. Excellent for closing off a reaction vessel from the atmosphere.

Joint	Cat. No.
14/20	**Z53,033-6**
19/22	**Z53,034-4**
24/40	**Z10,432-9**
29/32	**Z53,035-2**

Dean–Stark Traps

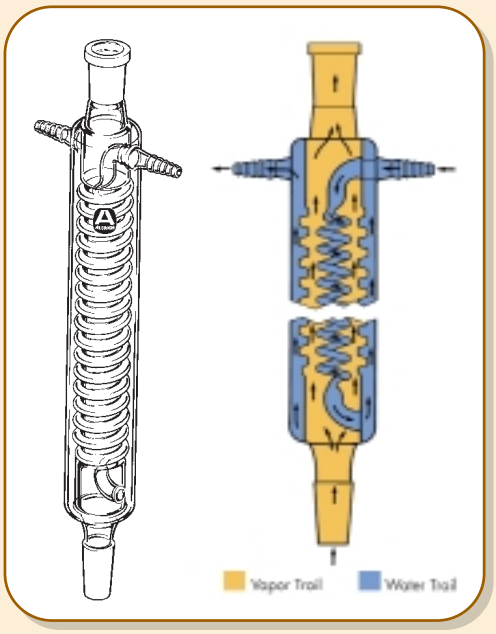


Provide ample clearance with thick-walled aluminum heating mantles

Designed specifically for azeotropic distillation using solvents lighter than water. Each Dean–Stark trap comes standard with a 4mm bore PTFE stopcock. The 12mL and 25mL traps use a 2mm bore stopcock.

Cap. (mL)	Overall H (mm)	Side-arm clearance (mm)	Suggested flask size	Joints	Cat. No.
12	205	80	50mL – 5L	14/20	**Z20,254-1**
25	255	80	50mL – 5L	14/20	**Z42,307-6**
25	280	80	50mL – 5L	24/40	**Z42,302-5**
25	280	80	50mL – 5L	29/32	**Z51,625-2**
100	350	100	5L – 12L	24/40	**Z42,303-3**
100	350	100	5L – 12L	29/32	**Z51,626-0**
300	440	170	22L – 50L	24/40	**Z42,304-1**
300	440	170	22L – 50L	29/32	**Z51,627-9**
500	455	170	22L – 50L	24/40	**Z42,306-8**
500	455	170	22L – 50L	29/32	**Z51,628-7**

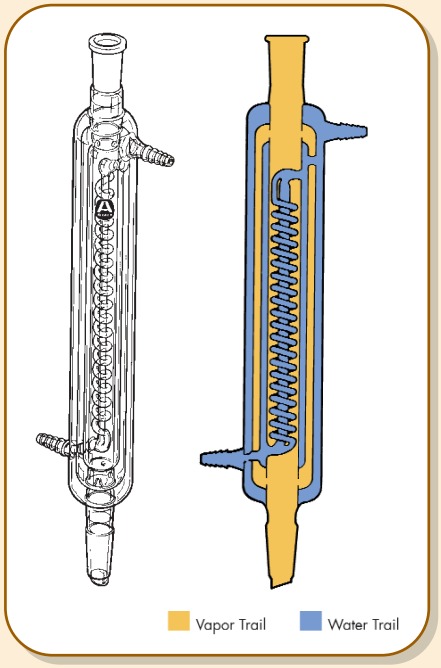
NEW Aldrich High-Efficiency Condensers



Jacketed Friedrichs Coil Condensers

The molded spiral condensing tube around the inner coil creates additional surface area for improved efficiency. 54mm o.d.

Overall H (cm)	24/40 joints Cat. No.	29/32 joints Cat. No.
26	**Z51,723-2**	**Z51,724-0**
41	**Z51,725-9**	**Z51,726-7**



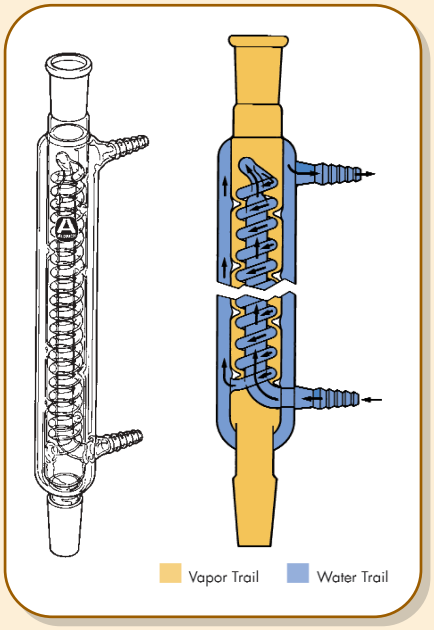
Triple-Jacket Coil Condensers

Excellent for Lower-Boiling Solvents

Features:

- Triple jacketing provides maximum cooling surface area
- Does not flood as readily during reflux surges
- Minimizes loss of volatile components
- Highly efficient while extremely compact

Overall H (cm)	Surface area (cm^2)	O.d. (mm)	24/40 joints Cat. No.	29/32 joints Cat. No.
44	1,230	60	**Z42,227-4**	**Z51,744-5**

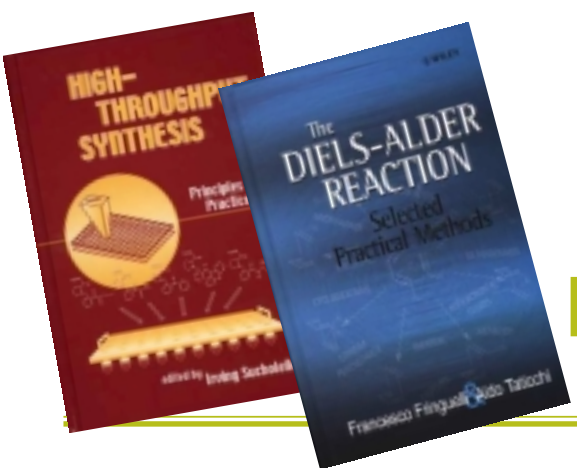


Super Condensers

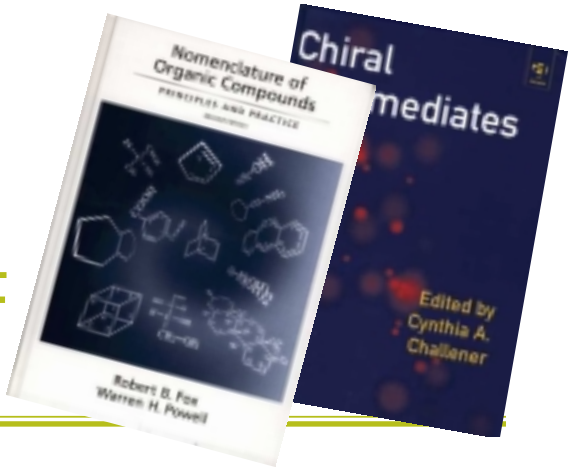
Extremely efficient condenser has a forced spiral path and a very large, water-cooled surface area. This design combines all these features into one condenser:

- cold-finger
- coiled
- Liebig
- Vigreux

Overall H (cm)	Surface area (cm^2)	O.d. (mm)	24/40 joints Cat. No.	29/32 joints Cat. No.
32	405	42	**Z22,497-9**	**Z51,740-2**
37	510	42	**Z22,498-7**	**Z51,741-0**
41	610	42	**Z22,499-5**	**Z51,742-9**
51	820	42	**Z22,500-2**	**Z51,743-7**



From the Aldrich Bookshelf



Advanced Organic Chemistry: Reaction Mechanisms

R. Bruckner, Academic Press, Orlando, FL, 2001, 512pp. Hardcover. A best-selling mechanistic organic chemistry text in Germany, this text's translation into English fills a long-existing need for a modern, thorough, and accessible treatment of reaction mechanisms for students of organic chemistry.

Z51,372-5

High-Throughput Synthesis

I. Sucholeiki, Ed., Marcel Dekker, New York, NY, 2001, 365pp. Hardcover. This reference text presents how-to methods, novel materials, and catalyst developments for creating new compounds. Background material on combinatorial chemistry is combined with cookbook-style directions and detailed case studies that emphasize the potential for reproducing experiments.

Z51,376-8

Chiral Drugs

C.A. Challener, Ed., Ashgate Publishing Co., Burlington, VT, 2001, 672pp. Hardcover. Part one provides an introduction to the types of sources and methods currently in use for obtaining chiral molecules, while part two gives a comprehensive listing of over 2,500 chiral drugs and includes structures and physical properties for each entry in the listing.

Z51,357-1

Chiral Intermediates

C.A. Challener, Ed., Ashgate Publishing Co., Burlington, VT, 2001, 832pp. Hardcover. *Chiral Intermediates* is an invaluable resource for information on available chiral molecules. Presents 4,700 commercially available chiral compounds with structures, physical properties, applications, manufacturers, and suppliers for each listing. Indexes, including a master index of names and synonyms and an index of custom manufacturing services for chiral compounds, are appended.

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Combinatorial Library Design and Evaluation: Principles, Software Tools, and Applications in Drug Discovery

A.K. Ghose and V.N. Viswanadhan, Eds., Marcel Dekker, New York, NY, 2001, 648pp. Hardcover. This book traces the latest advances in rational drug discovery and combinatorial library design, covering basic principles, design strategies, methodologies, software tools and algorithms, and applications. Specific topics include fast continuum electrostatics methods for structure-based ligand design, knowledge-based approaches for the design of small-molecule libraries for drug discovery, relative and absolute diversity analyses of combinatorial libraries, and design of combinatorial libraries that mimic biological motifs.

Z51,373-3

Fenaroli's Handbook of Flavor Ingredients

4th ed., G.A. Burdock, CRC Press, Boca Raton, FL, 2001, 1,864pp. Hardcover. With a new format and twice the information found in the third edition, it gives you easy access to synonyms, international codes, sensory information, permitted uses of ingredients, international regulations, and more. The handbook puts together the "wish lists" of food scientists, regulatory and safety officers, pharmacologists, and toxicologists to provide a one-stop source for both GRAS and non-GRAS flavoring substances.

Z51,367-9

Crystallization

4th ed., J.W. Mullin, Butterworth-Heinemann, Stoneham, MA, 2001, 600pp. Hardcover. Incorporates all the recent developments and applications of crystallization technology. Provides clear accounts of underlying principles, a review of the past and current research themes, and guidelines for equipment and process design. This new edition introduces and enlarges upon such subjects as: separation of polymorphs and chiral crystals, micro- and macromixing, and seeding and secondary nucleation in batch crystallization processes.

Z51,368-7

The Diels–Alder Reaction: Selected Practical Methods

F. Fringuelli and A. Taticchi, John Wiley & Sons, New York, NY, 2002, 350pp. Hardcover. This is the first book to collect together 70 years worth of experimental procedures that have been developed to perform the Diels–Alder reaction. It begins with the fundamental principles and contains numerous graphical abstracts to present the basic concepts in a concise and pictorial way. Covers theory and synthetic applications of the experimental methods, and includes reports on industrial applications.

Z51,385-7

Handbook of Organopalladium Chemistry for Organic Synthesis

Available May 2002!

Ei-ichi Negishi, John Wiley & Sons, New York, NY, 2002, 3,300pp. Hardcover. 2-vol. set. This handbook is the most comprehensive and authoritative reference available on organopalladium reagents and catalysts. The material is organized according to reaction type, rather than type of organopalladium compound.

Z51,386-5

Nomenclature of Organic Compounds: Principles and Practice

2nd ed., R.B. Fox and W.H. Powell, Eds., Oxford University Press, New York, NY, 2001, 464pp. Hardcover. The book is divided into two parts. The first is a general overview of organic nomenclature, the second uses concepts from the first part to answer the question "How do I name this compound?". Individual chapters are concerned with almost every class of organic derivative, stressing the relationship between structure and names.

Z51,355-5

The Nitro Group in Organic Synthesis

N. Ono, John Wiley & Sons, New York, NY, 2001, 392pp. Hardcover. This book focuses on reactions that proceed under mild conditions, important functional groups that can be synthesized by the conversion of nitro groups, and the stereoselectivity of reactions of nitro compounds. Emphasizes environmentally friendly methods for nitration, the importance of aliphatic nitro compounds, and modern preparations of nitro compounds.

Z51,365-2

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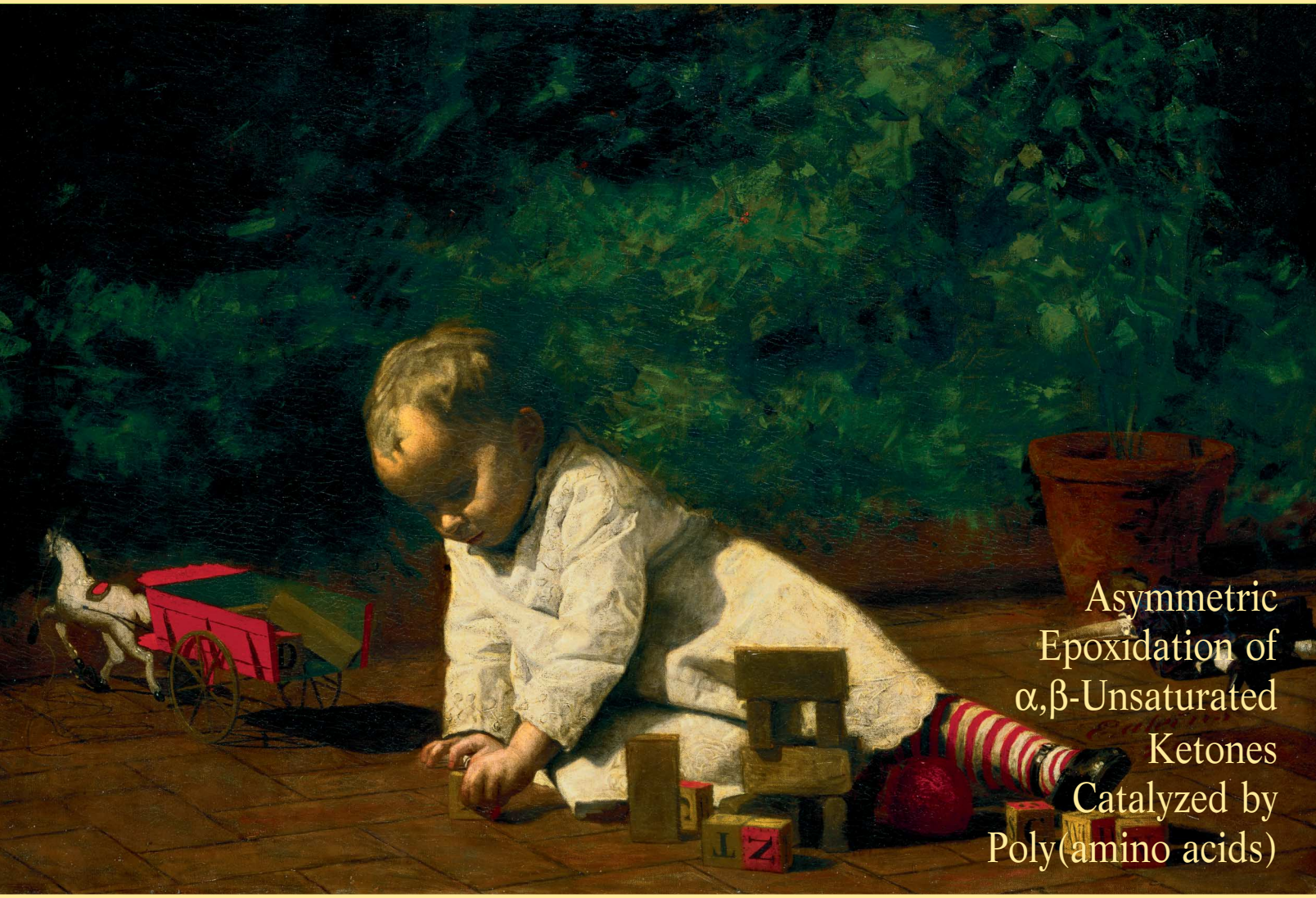

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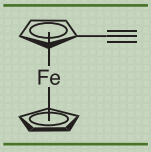
Borane–Amine Complexes for Hydroboration

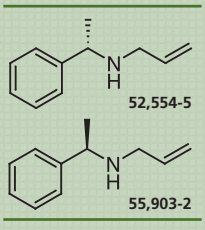
NEW products



Was employed in the synthesis of nonlinear optical polymers,[1] and served as a starting material for the construction of complex organometallics.[2]

(1) Buchmeiser, M.; Schrock, R.R. *Macromolecules* **1995**, *28*, 6642. (2) Buchmeiser, M.; Schottenberger, H. *J. Organomet. Chem.* **1992**, *441*, 457.

44,265-8
Ethynylferrocene, 97%

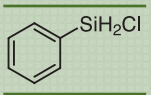


These chiral amines have been utilized in the asymmetric synthesis of β-lactams[1] and β-amino acids.[2]

(1) Bull, S. D. et al. *J. Chem. Soc., Perkin Trans. I* **2001**, 3106. (2) Davies, S. G.; Ichihara, O. *Tetrahedron Lett.* **1999**, *40*, 9313.

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

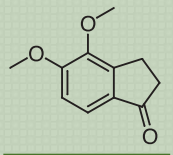
55,903-2
(*R*)-(+)-*N*-Allyl-α-methylbenzylamine, 97%



Utilized in the platinum-catalyzed hydrosilylation of olefins for the generation of dendrons with a chlorosilyl functional group.

Cuadrado, I. et al. *J. Am. Chem. Soc.* **1997**, *119*, 7613.

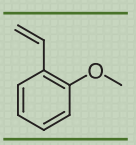
56,923-2
Chlorophenylsilane, 97%



Employed in the synthesis of cyclopentano-1,2,3,4-tetrahydroisoquinolines[1] and a novel 5-HT_{2c} receptor agonist.[2]

(1) Mathison, I. W. et al. *J. Org. Chem.* **1974**, *39*, 2852. (2) Adams, D. R.; Duncton, M. A. J. *Synth. Commun.* **2001**, *31*, 2029.

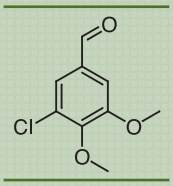
56,825-2
4,5-Dimethoxy-1-indanone, 97%



Has been employed to produce isoxazolidines through 1,3-dipolar cycloaddition reactions.

Chiacchio, U. et al. *Tetrahedron* **1994**, *50*, 6671.

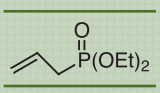
56,306-4
2-Vinylanisole, 98%



Basic building block for the synthesis of 1-aryl-2,3,4,5-tetrahydro-1*H*-3-benzazepines.[1,2]

(1) Weinstock, J. et al. *J. Med. Chem.* **1986**, *29*, 2315. (2) Gallagher, G., Jr. et al. Ger. Patent 2,802,087, Jul 1978; *Chem. Abstr.* **1978**, *89*, 163433v.

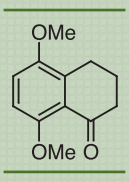
56,939-9
3-Chloro-4,5-dimethoxybenzaldehyde, 97%



Used in the preparation of 1,3-dienes with high *E*-isomer selectivity through the Horner–Wadsworth–Emmons reaction.[1,2]

(1) West, F.G.; Wang, Y. *Synthesis* **2002**, 99. (2) Maryanoff, B.E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

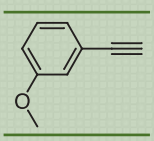
56,541-5
Diethyl allyl phosphonate, 98%



Tetralones have proven their synthetic versatility in the development of numerous biologically active compounds. 5,8-Dimethoxy-1-tetralone, for example, is a key intermediate in the synthesis of the antifungal and anticancer natural product (±)-diepoxin σ and related isomers.

Wipf, P.; Jung, J.-K. *J. Org. Chem.* **2000**, *65*, 6319.

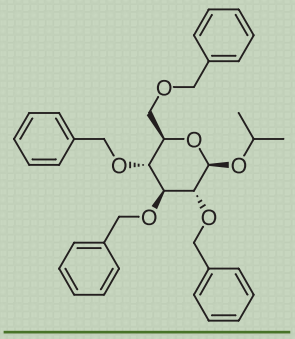
56,965-8
5,8-Dimethoxy-1-tetralone, 99%



Utilized in palladium-catalyzed coupling reactions that lead to vinylsilanes stereoselectively.

Chatani, N. et al. *J. Org. Chem.* **1995**, *60*, 1834.

51,941-3
3-Ethynylanisole, 96%



An excellent glycoside for the stereoselective synthesis of complex oligosaccharides and glycoconjugates.[1,2]

(1) Mereyala, H.B.; Reddy, G.V. *Tetrahedron* **1991**, *47*, 6435. (2) Garcia, B.A.; Gin, D.Y. *J. Am. Chem. Soc.* **2000**, *122*, 4269.

57,004-4
Isopropyl 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside, 98%

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About Our Cover

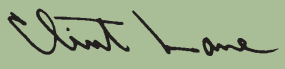
Photograph © Board of Trustees, National Gallery of Art, Washington.

Baby at Play (oil on canvas, 81.9 x 122.9 cm) was painted by Thomas Eakins in 1876. Eakins was born and grew up in Philadelphia. After taking courses at the Pennsylvania Academy of the Fine Arts, and studying anatomy there and at the Jefferson Medical College, he went in 1866 to Paris, where he attended the École des Beaux-Arts and studied independently with several artists, including Jean-Léon Gérôme. During the five or six years after his return to Philadelphia three years later, Eakins painted a number of both individual and group portraits of members of his family and that of his sister Frances, who married Eakins's boyhood friend, William J. Crowell. The subject of *Baby at Play* is Eakins's two-year-old niece, Ella Crowell. The low vantage point from which we see the figure, which is life-size, helps to draw attention to the child's almost solemn concentration on what she is doing. The painting is a good example of what the artist called "genre portraits", i.e., representations of people shown engaged in typical activities in their usual settings. It is probable that it is more than that, however.

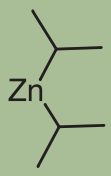
The picture was painted just at the time that educational reformers in Europe, especially the English social philosopher Herbert Spencer, whose *Education: Intellectual, Moral, and Physical* was published in New York in 1866, were having a great effect on educational thought and practice in America. Eakins, who was well-known for his serious dedication to the disciplined teaching of art, mentioned Spencer in a letter to his father just two years later. It is quite likely that this painting reflects Spencer's statement that "men are at last seeing that the spontaneous activity of the observing faculties in children has a meaning and a use. What was once thought mere purposeless action, or play, or mischief, as the case might be, is now recognized as the process of acquiring a knowledge upon which all after-knowledge is based." Eakins's acquaintance with Spencer's ideas means that this painting probably should not be considered as simply a representation of light-hearted childish play, but as a depiction of a more serious endeavor, the learning a child gains through experience and observation.

This painting is in the John Hay Whitney Collection at the National Gallery of Art, Washington, D.C.

"Please Bother Us."



Clint Lane, President



Professor Matthew H. Todd of the Department of Chemistry at Queen Mary, University of London, kindly suggested that we offer diisopropylzinc. This organometallic reagent undergoes an asymmetric autocatalytic reaction with substituted pyrimidines and a chiral initiator.

Shibata, T. et al. *J. Am. Chem. Soc.* **1998**, *120*, 12157.

56,811-2
Diisopropylzinc, 1.0*M* solution in toluene

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

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

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Lab Notes

A Simple Procedure for Polishing Circular and Rectangular Infrared Crystal Windows[1]

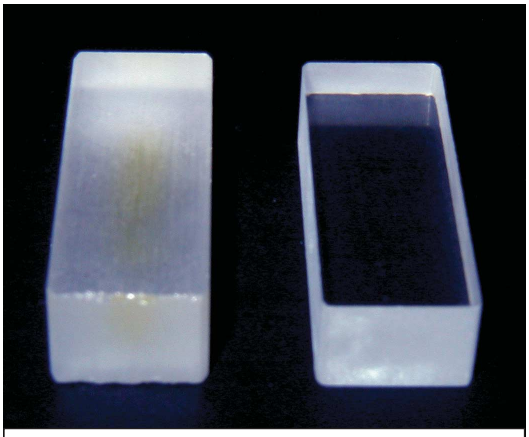


Figure 1. IR Crystal Window Before and After Polishing with the Current Procedure.

Polished crystal windows intended for use in infrared (IR) spectroscopy tend to fog even when not heavily used. The fogging is due primarily to ambient humidity and/or to trace amounts of water in the samples being analyzed.

In addition to the obvious cost saving on replacing windows (a pair of NaCl windows, the cheapest of all such windows, now costs about $20), the main reason for polishing IR windows is to improve the evenness of the crystal surface and thus the sample film or mull, resulting in an enhancement of the overall quality of the spectrum.

Assuming that the IR user does not have access to a crystal-polishing kit,[2] the materials needed to carry out the procedure described below are: (1) a flat, hard surface such as a bench top; (2) a laboratory paper towel (e.g., KIMTOWELS® wipers; Aldrich cat. no. Z23,678-0); (3) an ordinary piece of harsh, tan paper towels (the kind found in many bathrooms); (4) polishing compound (ferric oxide powder, Fe_2O_3; e.g., Aldrich cat. no. 31,005-0); and (5) a polishing solution (*i*-PrOH/H_2O 9:1).

Lay the laboratory and tan paper towels side by side on the lab bench. Place a small amount of the polishing compound on the tan paper towel and saturate the towel with the polishing solution. Using a spatula or spoon, smear the polishing compound over the soaked towel in such a way as to create a smooth, even layer of polishing compound. Grip the sample-free window firmly between the thumb and index finger, and rub its bottom side on the polishing compound using light pressure and tracing a figure 8. The number of times a figure 8 is traced will depend on how bad the window surface is. Lift the window off of the paper towel and trace figure 8's with it on the laboratory towel in order to dry it and rid it of excess ferric oxide.

Inspect the polished surface. If it looks transparent enough, repeat the above procedure with the opposite face of the window. When both surfaces are done, and only if needed, they can be rinsed with an anhydrous solvent such as anhydrous acetone. When not in use, the polished windows should be stored in a desiccator over a drying agent such as Drierite®.

This polishing procedure is routinely used in our laboratories, and is recommended mainly for NaCl or KBr windows—which are the most widely used types.

Notes: (1) If the IR crystal window is badly scratched or pitted, or if its surfaces are no longer flat from uneven polishing, the damaged window can be reclaimed as follows: It is first lapped on an ultrafine 600 grit sandpaper (e.g., 3M's TRI-M-ITE™ silicon carbide 600 TN4) to remove surface damage or flatten the entire window face. The window is then polished as described above. (2) For example, Aldrich cat. no. Z11,186-4.

KIMTOWELS and Drierite are registered trademarks of Kimberly-Clark Corp. and W. A. Hammond Drierite Co., respectively. TRI-M-ITE is a trademark of 3M Co.

***Editor's Notes*:** (1) Other, less detailed or related procedures for polishing cloudy infrared crystal windows have been reported: (a) Winston, A. *J. Chem. Educ.* **1991**, *68*, A124 (NaCl). (b) Gallego G., J. M. *J. Chem. Educ.* **1978**, *55*, 681 (NaCl, KCl). (c) Nemo, T. E. *Aldrichimica Acta* **1977**, *10*, 22 (AgCl). (d) Feairheller, W. R., Jr.; DuFour, H. *Appl. Spectrosc.* **1967**, *21*, 45 (CsI, CsBr). (e) Levine, M. A. *Appl. Opt.* **1966**, *5*, 1957 (CsI). (2) Customary lab safety precautions, such as the donning of suitable gloves, should be taken when using this polishing procedure.

James J. Brien
Laboratory Equipment Group
Aldrich Chemical Company, Inc.
1001 West Saint Paul Avenue
Milwaukee, WI 53233, USA
E-mail: jbrien@sial.com

Asymmetric Epoxidation of α,β-Unsaturated Ketones Catalyzed by Poly(amino acids)

*Christelle Lauret and Stanley M. Roberts**
Department of Chemistry
The University of Liverpool
Liverpool L69 7ZD
United Kingdom
E-mail: smrsm@liverpool.ac.uk

Outline

1. Introduction

Treatment of α,β-unsaturated ketones with hydrogen peroxide under basic conditions yields epoxy ketones, a transformation known as the Weitz–Scheffer reaction (**eq 1**). In recent years, considerable interest has centered on the asymmetric variants of this oxidation reaction. The reagents and catalysts used in some of the best-documented protocols for the oxidation of α,β-unsaturated enones are listed below (**Scheme 1**):[1]

- diethylzinc and a chiral alcohol under an atmosphere of oxygen
- a lanthanide in the presence of BINOL
- metal peroxides with diethyl tartrate
- chiral phase-transfer catalysts
- chiral dioxiranes
- *tert*-butylhydroperoxide and bovine serum albumin
- poly(amino acids)

The methodology that uses poly(amino acids), such as poly(L-leucine), has been the most popular for acyclic *E* enones and, in many cases, has advantages over alternative procedures.[1]

2. Juliá–Colonna Three-Phase Conditions

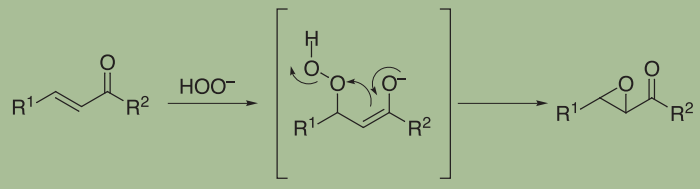
The original idea to use polyalanine or polyleucine as a catalyst for the epoxidation of α,β-unsaturated ketones can be attributed to Juliá (Barcelona) and Colonna (Milan). The Spanish and Italian teams studied the

reaction for a period of about four years in the early 1980s.[2] The catalyst was prepared in a conventional fashion[3] by synthesis of the amino acid *N*-carboxyanhydride and stimulating the polymerization of this activated system using an initiator, for example water or preferentially an amine.

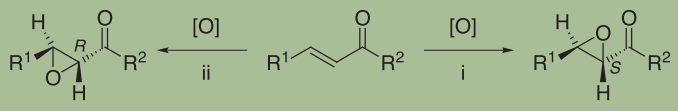
Subsequent to Juliá and Colonna's work, three other groups showed a significant interest in the reaction. Lantos and co-workers used the Juliá–Colonna reaction to prepare a precursor of a leukotriene antagonist;[4] the SmithKline group was able to demonstrate that the reaction can be scaled up to the multi-hundred-gram level. In South Africa, Bezuidenhoudt and co-workers prepared a series of optically active epoxides, using the Juliá–Colonna reaction as the key step in novel routes to flavonols.[5] Finally, Itsuno showed that cross-linked amino-methyl polystyrene could be used as the initiator of the polymerization, furnishing the first example of an immobilized poly(amino acid) catalyst.[6]

All the groups above employed the original Juliá–Colonna conditions for their epoxidation reactions. These conditions consist of aqueous hydrogen peroxide containing sodium hydroxide, a water-immiscible organic solvent such as hexane or toluene, and the insoluble poly(amino acid).

There are several reasons why the "three-phase" Juliá–Colonna reaction conditions did not gain more popularity. First, the optimum catalyst was not commercially available in large quantities and, undoubtedly, some of the published methods of preparation (for example, using water in a humidity cabinet)[4] were capricious. Secondly, the transformation appeared to be limited to enones of the type (*E*)-Ar^{1}CH=CHCOAr^2, i.e., close relatives of chalcone.[2] Thirdly, the catalyst forms a gel in the reaction mixture, which filters very slowly making difficult the recovery of the catalyst after completion of the reaction. Subsequently, it transpired that the three-phase reaction conditions can be used to epoxidize enediones (**eq 2**),[7] enone esters (**eq 3**),[7] and dienones (**eq 4**).[8] In addition, a limited number of alkyl groups *can* be accommodated on the carbonyl carbon or at the β position, *tert*-butyl (**eq 5**)[7] and cyclopropyl being two examples.[7] However, the range of substrates is still

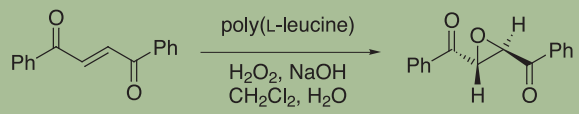


eq 1



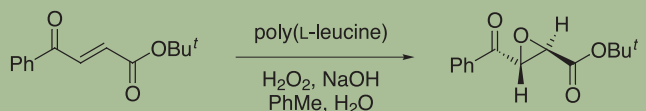
(i) Chiral catalyst promoting *si*-face attack at C-3
(ii) Chiral catalyst promoting *re*-face attack at C-3

Scheme 1. Asymmetric Oxidation of α,β-Unsaturated Ketones.



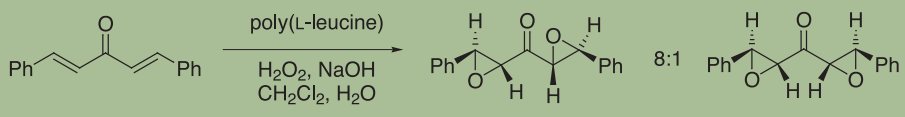
76%; 76% ee

eq 2



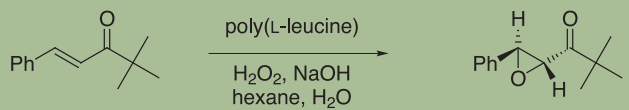
66%; >95% ee

eq 3



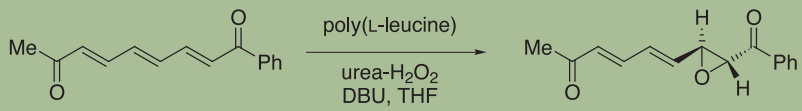
>98% ee

eq 4



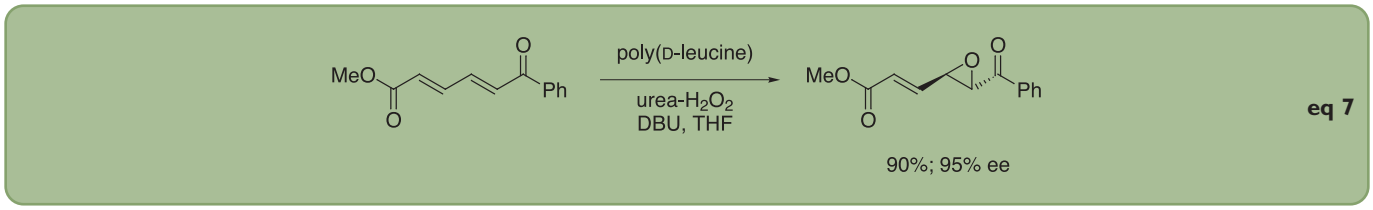
92%; 89% ee

eq 5

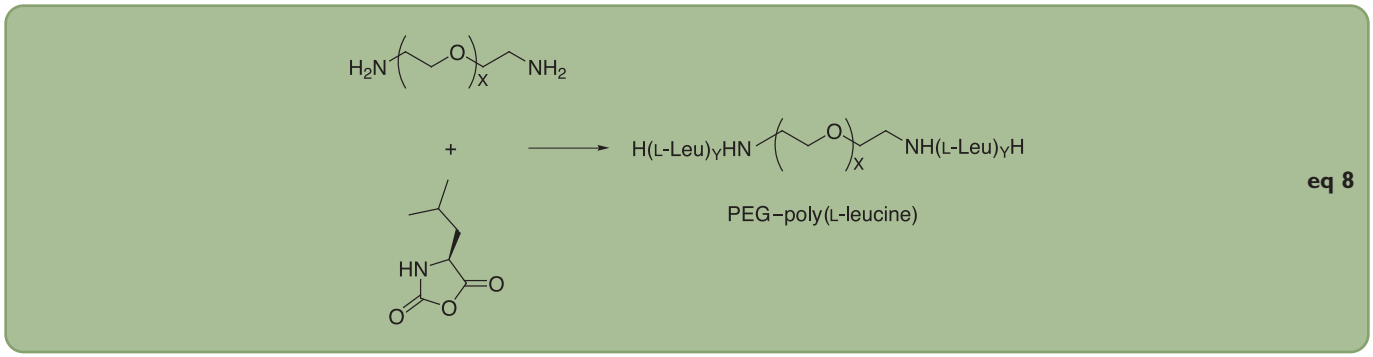


43%; 90% ee

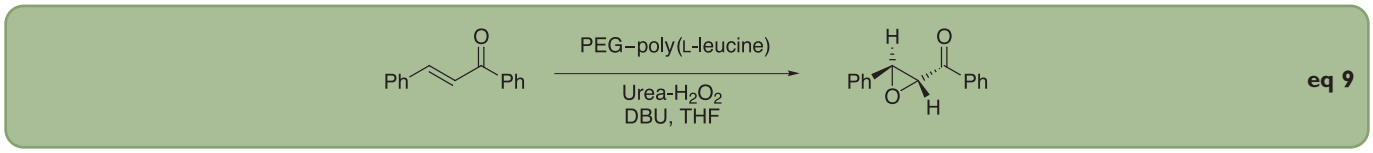
eq 6



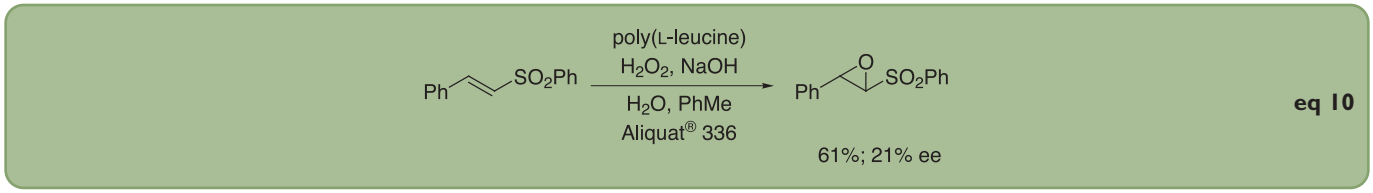
eq 7



eq 8



eq 9



eq 10

severely limited; for example, methyl styryl ketone is not oxidized under the "three-phase" conditions.[9]

3. Two-Phase Conditions

Several improvements to the Juliá–Colonna reaction have been described recently, which should help popularize the transformation. First, critically, a robust and reliable procedure for the preparation of poly(amino acids) is available, and is suitable for the synthesis of the chiral catalyst on a multikilogram level.[10] A simple washing procedure is used to "activate" the catalyst prior to use.

Another key improvement to the transformation was realized when it was shown that the asymmetric epoxidation reaction could be achieved under nonaqueous conditions, using the solid complex urea–hydrogen peroxide (UHP) as the oxidant, together with an organic base such as DBU.[9] As polyleucine remained insoluble in the organic solvent (for example, THF), the protocol was thought of as a "two-phase" system.

Under the "two-phase" conditions, the rate of oxidation of (*E*)-chalcone was increased by two orders of magnitude as compared to the original "three-phase" protocol.[9] Moreover, unlike in the "three-phase" system, most alkyl groups are tolerated at the β position and next to the ketone unit. However, alkyl vinyl ketones are still oxidized more slowly than aryl vinyl ketones (roughly by one order of magnitude), allowing the regioselective oxidation of selected trienediones to be achieved (**eq 6**).[11,12]

The "two-phase" system does not epoxidize simple ene esters, so that highly functionalized synthons may be constructed simply, rapidly, and in high optical purity (**eq 7**).[11]

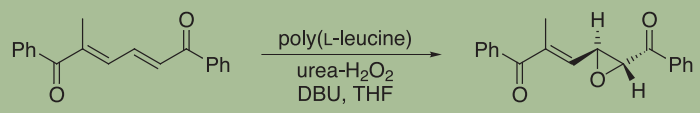
Polyleucine is a viscous paste in the "two-phase" reaction mixtures. The product can be separated from the catalyst by filtration; however, this process can be prohibitively slow on a larger scale, making the procedure unsuitable for use in a large-scale, multipurpose batch reactor.

This recovery problem was solved by adsorbing the polymeric catalyst onto commonly used "flash" silica.[13] The ratio of silica to polyleucine employed is ca. 3:1, and the amount of polyleucine needed to efficiently catalyze the asymmetric epoxidations is reduced by 75%. Presumably, the poly(amino acid) coats the surface of the silica, allowing a greater number of amino acid chains, and in particular *N*-terminal regions (vide infra), to be exposed to the reactants. Pleasingly, epoxidations using the silica-supported catalyst (Scat) give better rates of conversion and higher ee's of products as compared to the conventional catalyst.[14] At least as important is the fact that the catalyst retains the physical properties of silica, allowing the material to be filtered off, in practically quantitative yield, and recycled.

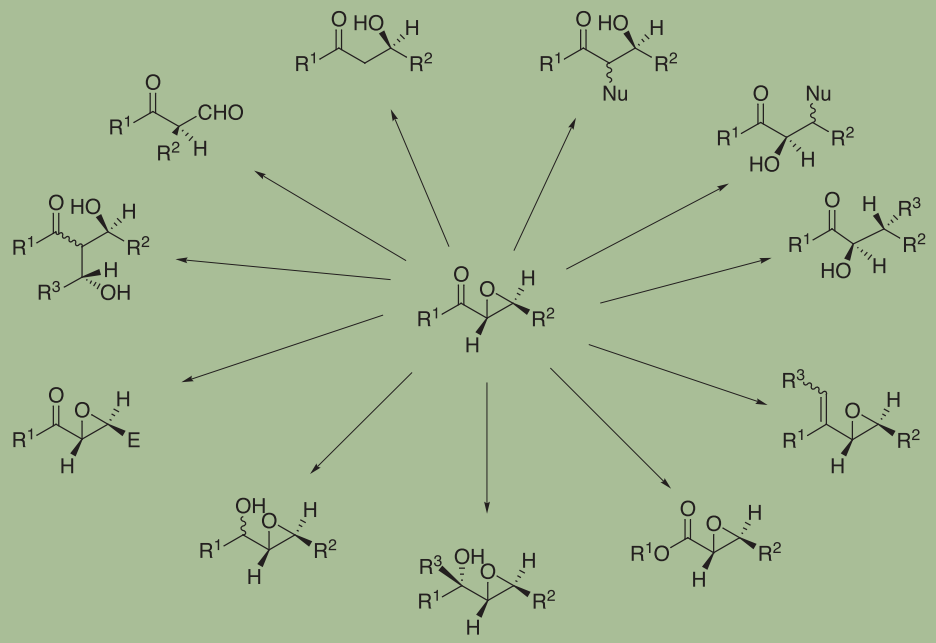
Very recently, a soluble version of the Juliá–Colonna catalyst has been developed, using amino poly(ethylene glycol) (PEG-NH_2) to initiate the polymerization of the amino acid *N*-carboxyanhydride (**eq 8**).[15] The resulting block copolymer may be dissolved in THF, and it catalyzes the stereoselective oxidation of chalcone in homogeneous solution (**eq 9**).

The present limitations of the Juliá–Colonna asymmetric epoxidation are as follows:

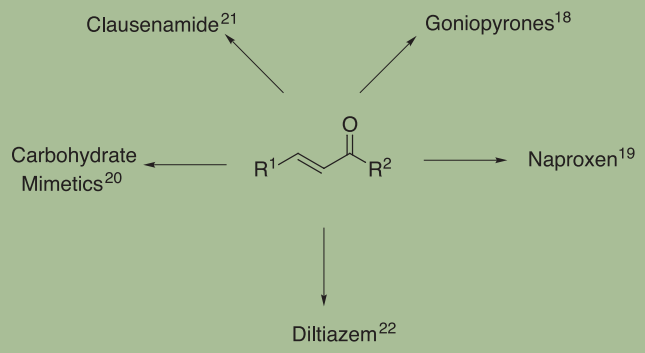
- electron-poor alkene systems other than α,β-unsaturated ketones are generally



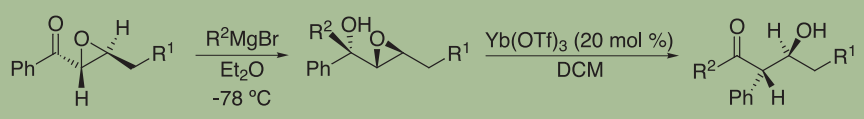
eq 11



Scheme 2. Known Chemistry of Epoxy Ketones.



Scheme 3. Applications of the Juliá–Colonna Reaction in Asymmetric Synthesis.



Scheme 4. Recent Application of the Juliá–Colonna Reaction.

unreactive: the only example involving a species other than an enone is the vinyl sulfone described in **eq 10**; the epoxide, however, was obtained in only a modest ee.[16]

- trisubstituted alkenones are generally unreactive. However, this can be used to advantage in differentiating alkene units within the same molecule (**eq 11**).[12a] Exceptionally, cyclic enones derived from tetralone, indanone, and related compounds do form epoxides, often in high yields and excellent ee's.[16]

4. Synthetic Applications

Given the rich chemistry of epoxy ketones (**Scheme 2**), it is not surprising that the development of the Juliá–Colonna reaction to access optically active materials has generated considerable interest among synthetic chemists. Indeed, some of the epoxides prepared using this methodology have already been used for the synthesis of natural products, biologically active compounds, and analogs in single-enantiomer form (**Scheme 3**).[17-22]

Recent additions to the downstream chemistry involve the synthesis of 2-aryl-3-hydroxy ketones by the stereoselective reaction of the epoxy ketone with a Grignard reagent, followed by a semipinacol rearrangement promoted by lanthanide triflates (**Scheme 4**).[23]

5. Mechanism

The mechanism by which simple poly(amino acids) catalyze an enzyme-like asymmetric oxidation reaction remains unclear. It has been established that not all poly(amino acids) may be employed in the Juliá–Colonna reaction; for example poly(L-phenylalanine) and, even more unexpectedly, poly(L-valine) are ineffective.[24] Synthesis of poly(amino acid) chains stepwise, using an automated peptide synthesizer, has established that the chiral matrix adjacent to the amino terminus determines the stereochemistry of the product.[25] In order to allow kinetic experiments to be undertaken to determine whether the enone or the peroxide (or both) are temporarily complexed to the polyamide network, PEG-based soluble catalysts with well-defined amino acid chains are now being prepared.[26]

6. Conclusion

Poly(amino acids) deposited on a simple solid support, for example flash silica, are robust, easily available, and readily recycled catalysts for the asymmetric epoxidation of a wide variety of α,β-unsaturated ketones. Other electron-poor alkenes are unreactive. The optically active epoxy ketones formed by the Juliá–Colonna reaction may be modified by a variety of transformations giving, inter alia, useful intermediates to natural products and biologically active analogs.

7. References and Notes

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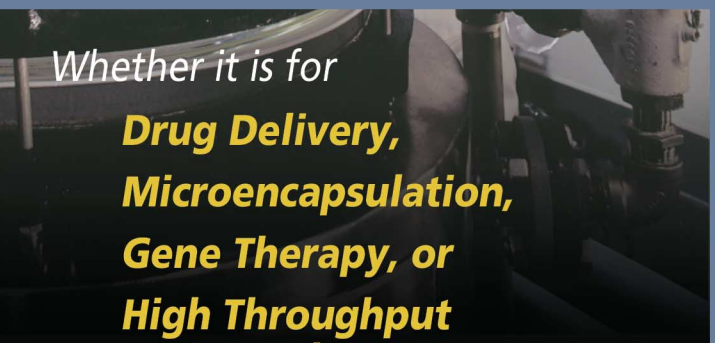
About the Authors

Stanley M. Roberts is currently Heath Harrison Professor of Organic Chemistry at the University of Liverpool. Prior to that, he was Lecturer/Reader at the University of Salford (1972–80), Head of Chemical Research, Glaxo Group Research, Greenford (1980–86), and Professor of Organic Chemistry at the University of Exeter (1986–95).

Christelle Lauret graduated in 1997 from the University of Poitiers, France, with her Maîtrise de Chimie, which included a one-year Erasmus exchange at the University of Liverpool. She is currently studying for her Ph.D. at the University of Liverpool under the supervision of Professor S. M. Roberts. Her doctoral research centers on the total synthesis of natural products, utilizing the Juliá–Colonna asymmetric epoxidation as a key step.



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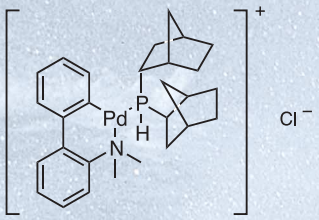

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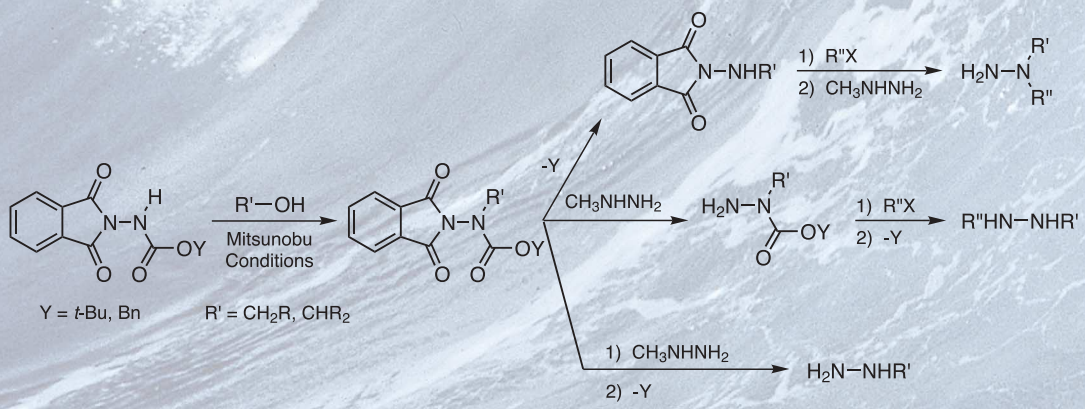

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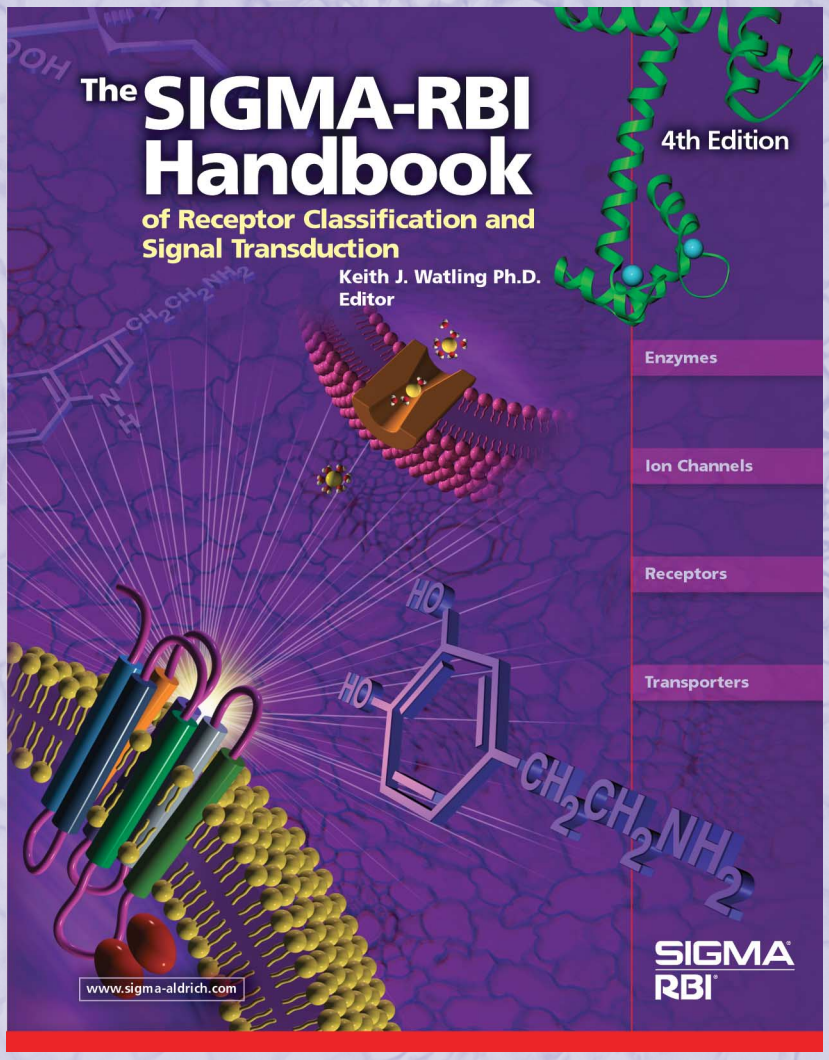

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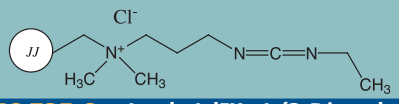
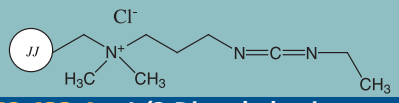
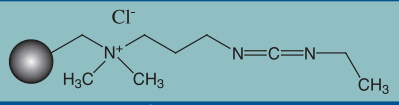
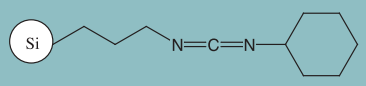
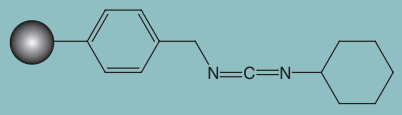
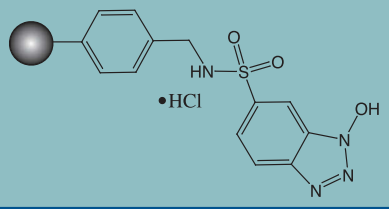
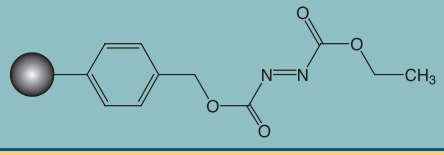
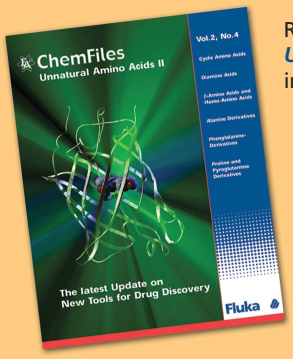
	0.5-1.0 mmol N/g	$R^1CO_2H + R^2NH_2 \rightarrow R^1CONHR^2$
56,725-6 **JandaJel™ -1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide,** 100-200 mesh		
	0.5-1.0 mmol N/g	$R^1CO_2H + R^2NH_2 \rightarrow R^1CONHR^2$
42,433-1 **1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide, polymer-bound,** 2% DVB, 200-400 mesh		
	~0.9 mmol carbodiimide/g	$R^1CO_2H + R^2NH_2 \rightarrow R^1CONHR^2$
56,988-7 **3-(1-Cyclohexylcarbodiimido)propyl,** functionalized silica gel, 200-400 mesh		
	~0.7 mmol carbodiimide/g	$R^1CO_2H + R^2NH_2 \rightarrow R^1CONHR^2$
56,184-3 ***N*-Benzyl-*N'*-cyclohexylcarbodiimide, polymer-bound,**[3] 1% DVB, 100-200 mesh		
	~1.7 mmol carbodiimide/g	$R^1CO_2H + R^2NH_2 \rightarrow R^1CONHR^2$
56,189-4 **1-Hydroxybenzotriazole-6-sulfonamidomethyl HCl, polymer-bound,**[4-10] 1% DVB, 100-200 mesh		
	0.8-1.0 mmol HOBt/g	$R^1CO_2H + R^2NH_2 \rightarrow R^1CONHR^2$
56,185-1 **Diethyl azodicarboxylate, polymer-bound,**[11,12] 1% DVB, 100-200 mesh		
	~0.7 mmol N/g	Mitsunobu reaction

References: (1) Desai, M.C. et al. *Tetrahedron Lett.* **1993**, *34*, 7685. (2) Buckman, B.O. et al. *ibid.* **1998**, *39*, 1487. (3) Weinshenker, N.M. et al. *Org. Synth.* **1988**, *Coll. Vol. VI*, 951. (4) Dendrinos, K.G.; Kalivretenos, A.G. *Tetrahedron Lett.* **1998**, *39*, 1321. (5) Kalir, R. et al. *Eur. J. Biochem.* **1975**, *59*, 55. (6) Chen, S.-T. et al. *J. Chem. Res. (S)* **1991**, 206. (7) Pop, I.E. et al. *J. Org. Chem.* **1997**, *62*, 2594. (8) Dendrinos, K. et al. *Chem. Commun.* **1998**, 499. (9) Dendrinos, K.G.; Kalivretenos, A.G. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1463. (10) Huang, W.; Kalivretenos, A.G. *Tetrahedron Lett.* **1995**, *36*, 9113. (11) Arnold, L.D. et al. *J. Am. Chem. Soc.* **1989**, *111*, 3973. (12) Mitsunobu, O. *Synthesis* **1981**, 1.



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Outline

1. Introduction

Diborane (B_2H_6) is a versatile reagent with a multitude of applications in organic and inorganic syntheses. Since it is a pyrophoric gas, borane complexes with Lewis bases are used instead, as they are more convenient to handle. Numerous applications of these borane complexes in the synthesis of pharmaceuticals and in other industrial applications have been reported.[1] Well-established borane–Lewis base complexes such as borane–tetrahydrofuran (H_3B–THF) and borane–dimethyl sulfide (BMS) have largely been used in these applications. However, the use of these important reagents has some disadvantages. For example, H_3B–THF is not stable for long periods, and its low concentration limits its applications to only one solvent. Although BMS does not have these drawbacks, its volatility, flammability, and the unpleasant odor of dimethyl sulfide give rise to safety and environmental concerns. On the other hand, borane–amine complexes are free of all these problems. Since the preparation of the first borane–amine adduct (H_3B–NEt_3) in 1937, almost all structural types of amines have been used for complexation with borane.[2] The borane–amine adducts have a wide range of physical and chemical properties and a variety of applications in, for example, the polymer, dye, metal plating, and pharmaceutical industries.[2b] Most of these applications are based on their reducing properties. Recently, attempts have also been made to increase their reactivity in hydrogenation reactions by using transition-metal catalysts.[3] In contrast, the scope of the hydroboration reaction with borane–amine adducts is rather limited due to the strong complexation between the borane and the amine. This results in a decreased reactivity of the borane–amines as compared to the borane adducts with ethers and sulfides.[4] However, the full range of reactivities of borane–amine adducts has not yet been defined. **Figure 1** shows some of the more popular borane–amine adducts, **1–9**, that have been reported in the literature.

Amines as borane carriers offer several advantages: they often form adducts of low sensitivity to moisture and air, and are readily soluble in a variety of solvents. The ease of recovery of the amine after the hydroboration reaction and the possibility of recycling it make borane–amines environmentally friendly reagents. The significance of these factors becomes more apparent with the growing importance of diborane for the

synthesis of pharmaceuticals and other compounds. The present review covers research published in the past five years that is aimed at developing new, highly reactive borane–amine adducts for hydroboration. A review covering the literature of borane–amines and phosphines up to 1997 concentrated mostly on the preparation and reducing properties of the borane–amines.[5] Since then, many new, highly reactive borane–amines have been reported for hydroboration. The effects of steric and electronic properties of these new amines on their complexations with borane and the influence of these properties on the hydroboration reaction have been systematically studied.

2. Borane–*N*,*N*-Dialkylanilines

A study by Brown and co-workers revealed that, in contrast to simple unhindered alkylamines, the less basic aniline derivatives form weaker and hence more reactive adducts with borane.[4a] For example, borane–triethylamine does not hydroborate 1-octene in tetrahydrofuran at room temperature, whereas borane–*N*,*N*-diethylaniline effects the hydroboration in 2 h under these conditions. Subsequently,

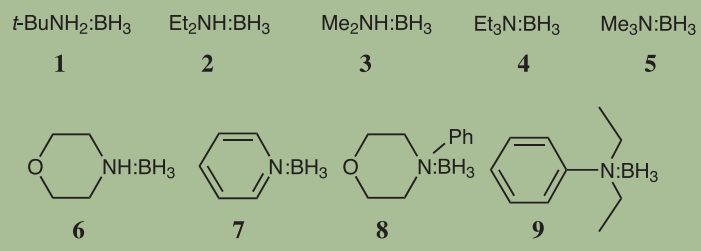


Figure 1. Some of the More Popular Borane–Amine Complexes.

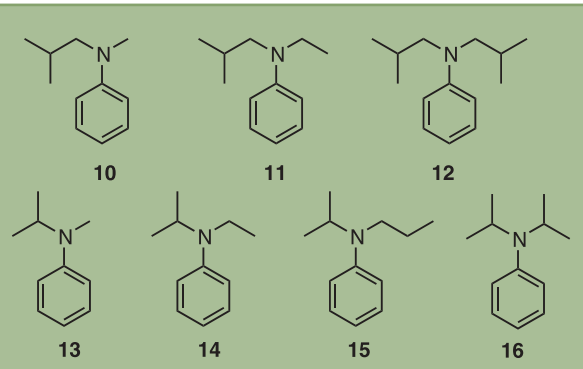
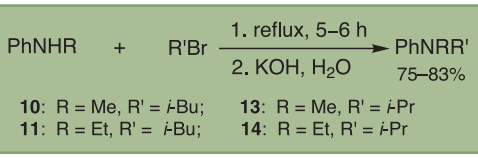
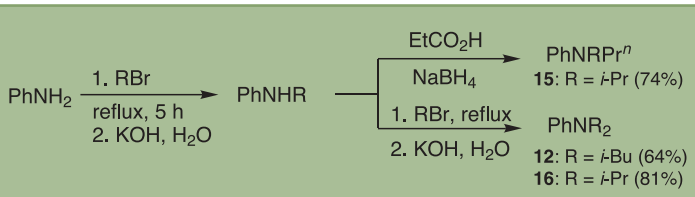


Figure 2. *N,N*-Dialkylanilines Differing in Their Steric Requirements.



eq 1



eq 2

Table 1. Preparation and Properties of Borane–*N,N*-Dialkylaniline Adducts

$PhNR^1R^2$				$H_3B:NPhR^1R^2$		
R^1	R^2	Compd No.	Exchange with $Me_2S:BH_3$ (%)[a]	Physical State at rt	$[BH_3]$[b] M	Hydroboration of 1-Octene in THF at rt[c]
Et	Et	–	66	liquid	4.8	2 h
i-Bu	Me	**10**	30	liquid	4.5	30 min
i-Bu	Et	**11**	19	liquid	4.0 → 3.2	15 min
i-Bu	*i*-Bu	**12**	0	liquid	0.9 → 0.6	15 min
i-Pr	Me	**13**	50	liquid	4.9	30 min
i-Pr	Et	**14**	36	liquid	4.7	15 min
i-Pr	*n*-Pr	**15**	25	liquid	4.1	15 min
i-Pr	*i*-Pr	**16**	0	solid	–	15 min

[a] The amine was mixed with $H_3B:SMe_2$ in a 1:1 molar ratio at rt; the percent exchange at equilibrium was determined by ^{11}B NMR. [b] Estimated by hydrolyzing the complex in 2 M HCl/glycerol/water (2:1:1) and measuring the volume of hydrogen evolved. [c] 3 M in 1-octene and 1 M in BH_3.

borane–*N,N*-diethylaniline was utilized by other groups for hydroborations and other reactions.[6] Moreover, this adduct was successfully applied to the stoichiometric reductions of representative functional groups such as aldehydes, ketones, carboxylic acids, tertiary amides, lactams, and imines, and to the oxazaborolidine-catalyzed enantioselective reduction of prochiral ketones.[7]

Borane adducts with *N*-phenylmorpholine and *N*-phenylaniline are even more reactive: each hydroborates 1-octene in tetrahydrofuran in less than 1 h at room temperature. However, because these two adducts are solids, they are less convenient to handle than liquid adducts in large-scale applications.[4a] Nevertheless, these examples clearly hint at the hydroboration potential of suitable borane adducts with *N,N*-dialkylanilines. More recently, a systematic study of the steric requirements of the *N,N*-dialkyl groups in *N,N*-dialkylanilines has been reported (**Figure 2**).[8]

2.1. Preparation of *N,N*-Dialkylanilines

The mixed amines **10, 11**, **13,** and **14** were prepared from low-cost *N*-methyl- or *N*-ethylaniline and isolated by fractional distillation in 75–83% yields (**eq 1**).[8a]

The other amines were prepared from aniline: **15** by reductive alkylation of an intermediate *N*-isopropylaniline; **12** and **16** by stepwise alkylation (**eq 2**).

2.2. Preparation of Borane–*N,N*-Dialkylaniline Adducts

The borane-complexing ability of the dialkylated anilines was tested by examining their exchange with BMS, as well as by preparing the corresponding borane adducts by passing diborane gas into the neat anilines.[8a] Borane–methyl sulfide is the only borane–Lewis base complex, other than borane–THF, that hydroborates representative olefins rapidly. Since borane does not form a 1:1 complex with THF, exchange reaction studies with borane–THF would be only qualitative. In contrast, methyl sulfide forms a 1:1 complex with borane and yields quantitative results in exchange experiments. These exchange experiments were carried out by mixing the aniline and borane–methyl sulfide in a 1:1 molar ratio under a nitrogen atmosphere. ^{11}B NMR was used to monitor the progress of the exchange by observing the rise of a new signal from the borane–*N,N*-dialkylaniline complex and the decrease in the signal from borane–methyl sulfide. If the aniline were to exchange more than 50% borane with borane–methyl sulfide, then this

would indicate preferential complexation of borane with the aniline. Consequently, this would imply a lower reactivity of the borane–aniline complex as compared to borane–methyl sulfide. Conversely, an exchange of less than 50% would indicate that the borane–aniline adduct is more reactive than borane–methyl sulfide.

The exchange experiments with various *N*,*N*-dialkylanilines reveal an interesting picture (**Table 1**).[8] The *N*-alkyl-*N*-isobutylanilines, in spite of both alkyl groups being primary, show lower complexing abilities than the *N*-isopropyl analogs. Apparently, the isobutyl group exerts slightly more steric hindrance than the isopropyl group in these equilibria. PhNBu^{i}Me and PhNBu^{t}Et form adducts that are 4.5 and 4.0 M in BH_3, respectively, but the molarity of PhNBu^{t}Et drops to 3.7 in 24 hours and to 3.2 in 4 days at room temperature.[8] Both adducts hydroborate 1-octene in THF at room temperature in less than 1 hour and under neat conditions in less than 2 hours. The corresponding *N*-alkyl-*N*-isopropylanilines complex borane slightly more strongly. The adducts of **13**–**15** are liquids above 0 °C, stable at room temperature, and are readily soluble in typical hydroboration solvents, such as diethyl ether, tetrahydrofuran, and dichloromethane.

The complexing ability of PhN(*i*-Bu)$_2$ (**12**) toward borane is much lower than that of the other *N*,*N*-dialkylanilines studied (Table 1, entry 4). Only a 0.9 M solution of the adduct forms at 0 °C, but loses almost half of its borane content within 24 hours at room temperature.[8] Interestingly, when treated with neat B_2H_6 gas, PhN(*i*-Pr)$_2$ forms a highly reactive and weak solid adduct that hydroborates 1-octene under neat conditions in less than 1 hour at room temperature.[8a] However, the solid adduct loses borane above its melting point (36–38 °C).

2.3. Reactivity in the Hydroboration Reaction

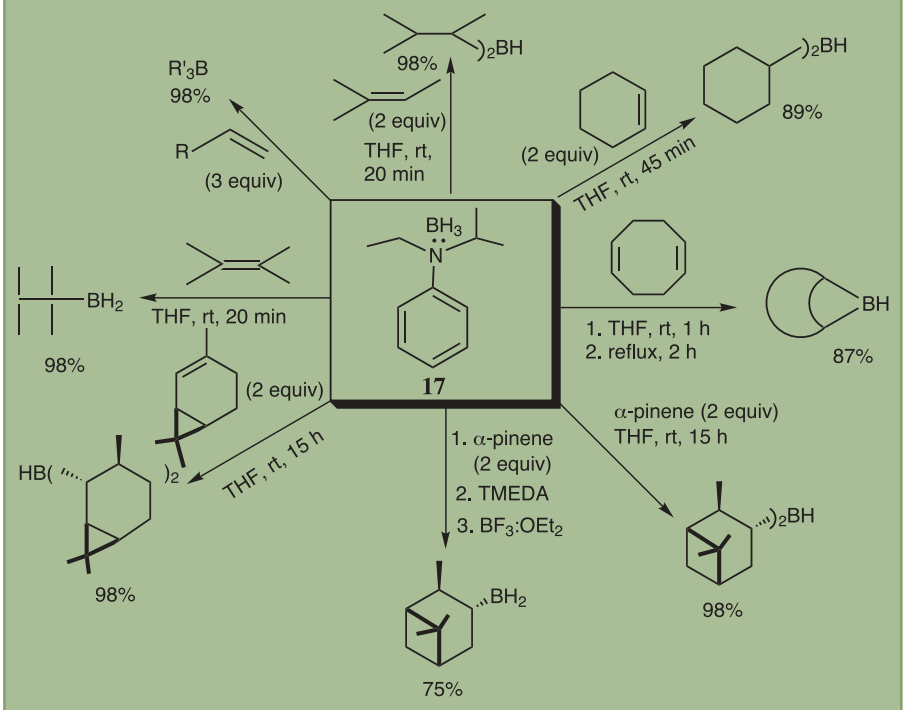
Of the *N*,*N*-dialkylanilines shown in Figure 2, the borane complexes of *N*-methyl-*N*-isopropylaniline (**13**) and *N*-ethyl-*N*-isopropylaniline (**14**) possess the qualities of a good hydroborating agent. The hydroboration properties of borane–*N*-ethyl-*N*-isopropylaniline (**17**, BACH-EI™) have been thoroughly studied.[8b] Its reactivity and regioselectivity are comparable to those observed for borane–THF, the fastest hydroborating borane–Lewis base complex known (**Table 2**). Moreover, the synthetic potential of this new, highly reactive, and environmentally benign borane–amine was further demonstrated in the facile and high-yielding preparations of several known but valuable dialkylboranes, such as the isomeric diisopinocampheylboranes (^{d}Ipc$_2$BH or ^{l}Ipc$_2$BH), (1*S*)-2-diisocaranylborane (^{d}Icr$_2$BH), 9-borabicyclo[3.3.1]nonane (9-BBN), dicyclohexylborane (Chx$_2$BH), and disiamylborane (Sia$_2$BH) (**Scheme 1**).[9]

Investigations of the reducing properties of **17** have also been carried out.[8b] They are not discussed here as they are beyond the scope of this review. Adduct **17** is also effective in catalytic asymmetric reductions.[10]

Table 2. Hydroboration of Various Olefins with Borane–*N*-Ethyl-*N*-isopropylaniline (17, BACH-EI™) vs Borane–THF[a]

	H_3B:THF		H_3B:NPhEtPr^i	
Olefin	React. Time (h)	Hydride Equiv Used[b]	React. Time (h)	Hydride Equiv Used[b]
1-Hexene	<0.5	3.00	<0.5	3.00
Styrene	0.5	3.00	0.5	3.00
β-Pinene	1.0	3.00	1.0	3.00
Cyclopentene	1.0	3.00	1.0	3.00
Norbornene	1.0	3.00	1.5	3.00
Cyclohexene	24	2.97	24	2.95
	0.58	2.00	0.75	2.00
2-Methyl-2-butene	24	2.94	24	2.90
	0.75	2.00	0.75	2.00
α-Pinene	24	1.96	24	1.93
	0.33	1.00	0.33	1.00
2,3-Dimethyl-2-butene	24	1.79	24	1.76
	0.33	1.00	0.33	1.00

[a] Reactions were carried out using 5 mmol of the borane complex and 15 mmol of the olefin in a total volume of 10 mL of solution. [b] Out of a total of 3.00 available hydrides.



Scheme 1. Preparation of Various Valuable Mono- and Dialkylborane Reagents Using **17**.

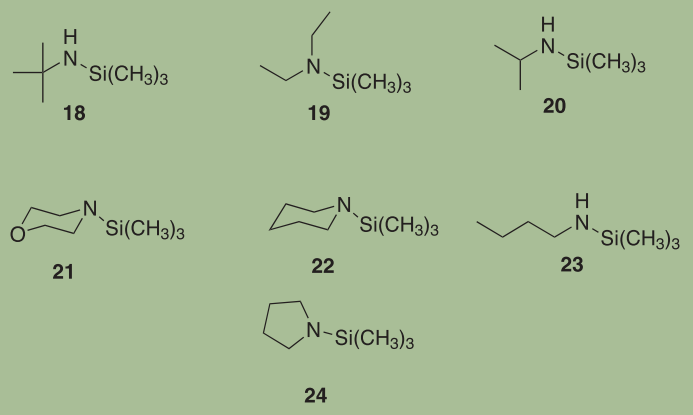
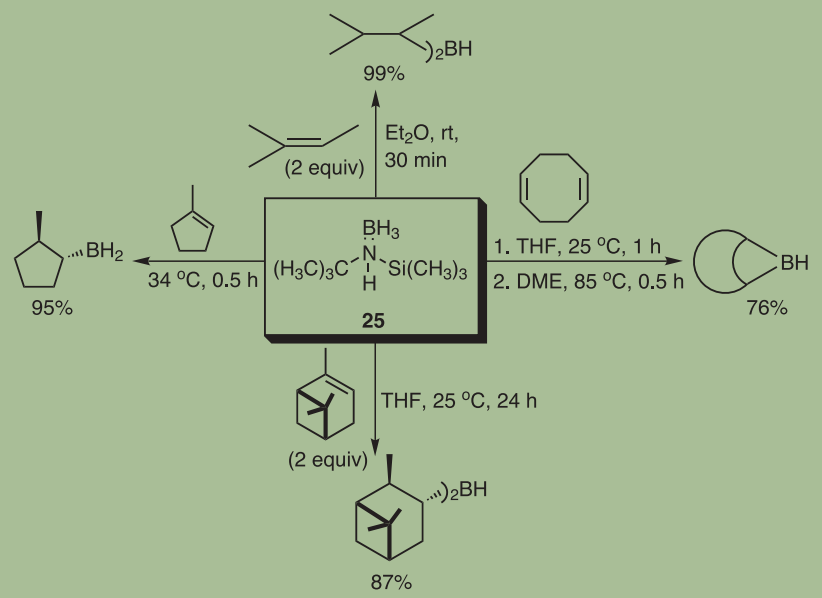


Figure 3. Hindered, Less Basic Amines: Trimethylsilylamines.

Table 3. Borane Adducts of Trimethylsilylamines

$(CH_3)_3SiNR^1R^2$			Amine:BH_3			
					Hydroboration of 1-Octene in THF[b]	
R^1	R^2	Compd No.	^{11}B NMR δ (J_{B-H})	Yield (%)[a]	Temp (°C)	Time (h)
H	*t*-Bu	**18**	-20 (99)	89	25	0.2
Et	Et	**19**	-14 (96)	89	25	2
H	*i*-Pr	**20**	-22 (95)	83	32	4
$CH_2CH_2OCH_2CH_2$		**21**	-18 (96)	85	25	22
$CH_2CH_2CH_2CH_2CH_2$		**22**	-17 (98)	94	25	72
H	*n*-Bu	**23**	-18 (94)	89	32	90
$CH_2CH_2CH_2CH_2$		**24**	-12 (98)	91	65	2

[a] Isolated yield of the borane–amine complex. [b] 3 equiv of 1-octene was used for 1 equiv of borane–amine.



Scheme 2. Preparation of Various Useful Mono- and Dialkylborane Reagents Using **25**.

3. Borane–Trimethylsilylamine Complexes

It is evident from the preceding studies on *N*,*N*-dialkylanilines that less basic amines form weaker borane complexes, making the latter more reactive towards olefins. Hindered and less basic amines can be synthesized by silylation of primary or secondary amines.[11] Recently, Soderquist and co-workers used this approach to prepare and investigate more reactive borane–amine adducts (**Figure 3**).[12]

3.1. Preparation of Borane–Trimethylsilylamine Complexes

Borane complexes of these trimethylsilylamines were prepared in 83–94% yields by the addition of diborane to the corresponding silylated amine in diethyl ether at –40 °C, followed by removal of the solvent under reduced pressure (**Table 3**). These complexes were identified by ^{11}B NMR and single-crystal X-ray diffraction analysis.[12a]

3.2. Hydroboration with Borane–Trimethylsilylamine Complexes

The reactivity of the borane adducts of amines **18–24** was examined in THF by employing 3 equiv of 1-octene. These studies revealed that the borane complex of trimethylsilyl-*tert*-butylamine (**18**) showed the best reactivity, hydroborating 1-octene in 12 min at 25 °C (Table 3, entry 1).[12a] In contrast, the borane complex of *N*-trimethylsilylpyrrolidine (**24**) required heating at 65 °C for 2 h. Among the other silylated amines tested, the borane adducts of **19** and **20** showed satisfactory reactivity, hydroborating 1-octene in 2 and 4 hours, respectively. The regioselectivity of these hydroborations was similar to that observed for borane–THF and borane–methyl sulfide complexes (94:6).[12a] Detailed hydroboration studies were then carried out on the most promising complex, borane–trimethylsilyl-*tert*-butylamine (**25**).[12b] Several known but useful mono- and dialkylboranes were thus prepared in 76–99% yields (**Scheme 2**).

4. Borane–Trialkylamines Possessing Isopropyl and Isobutyl Groups

The complexation of *N*,*N*-dialkylanilines with borane is governed by both electronic and steric factors around the nitrogen. A study was thus carried out to examine just the steric effect on the complexation of borane

with amines. Trialkylamines containing isopropyl and isobutyl groups of increasing steric requirements were investigated (**Figure 4**).[13] Trialkylamines **26–32** were prepared from low-cost and readily available starting materials (**eq 3–6**).

4.1. Preparation of the Borane Adducts

The borane–complexing ability of amines **26–32** was tested for the reasons and in the manner described in Section 2.2 (**Table 4**).[13a] The following reactivity order of these borane–amine adducts toward 1-octene emerges from the results in Table 4:

i-$Pr_2NEt:BH_3$ < *i*-$Bu_3N:BH_3$ <
i-$PrNBu^i_2:BH_3$ <
i-$Pr_2NCH_2CH_2OMe:BH_3$ <
i-$Pr_2NBu^i:BH_3$ < *i*-$Pr_3N:BH_3$ <
i-$Pr_2NBu^s:BH_3$

This reactivity pattern clearly shows the steric influence of alkyl groups around nitrogen on its complexing ability with borane. A simple change from *i*-Bu (**32**) to *i*-Pr (**28**), considerably increases the reactivity of the corresponding borane adduct (Table 4, entries 3 and 5). Similarly, changing *i*-Bu (**32**) to *s*-Bu (**30**) leads to an unstable borane adduct (Table 4, entries 3 and 7). The three borane adducts *i*-$Pr_2NBu^i:BH_3$, *i*-$Pr_3N:BH_3$ and *i*-$Pr_2NBu^s:BH_3$ are highly reactive—hydroborating 1-octene in THF at room temperature in 30 min or less. The adduct *i*-$Pr_2NBu^i:BH_3$ is a liquid above 0 °C; 4.6 M in BH_3; stable over long periods; and soluble in diethyl ether, *tert*-butyl methyl ether, tetrahydrofuran, dioxane, dichloromethane, and *n*-pentane. *i*-$Pr_3N:BH_3$ is a solid, while *i*-$Pr_2NBu^s:BH_3$ is an unstable liquid that slowly releases diborane at room temperature.

4.2. Hydroboration Characteristics

Of the preceding borane–trialkylamines, only borane–*N*,*N*-diisopropylisobutylamine (**33**) has the properties of a good hydroborating reagent. Hydroboration of representative olefins with **33** were carried out in a variety of solvents including dioxane and dichloromethane (**Table 5**).[13b] Hydroboration of simple unhindered olefins proceeded to the trialkylborane stage. Hindered olefins were rapidly hydroborated to the mono- or dialkylborane stage, but further hydroboration was slow. For a given alkene, the hydroborations were relatively fast in dioxane, THF, and pentane. However, an unusual rate retardation was observed in dichloromethane as compared to dioxane. Moreover, hindered olefins were hydroborated in preference to less hindered ones in dichloromethane. The product organoboranes were then oxidized to the corresponding alcohols and the carrier amine was recovered and recycled. The unusual reactivity in dichloromethane was explained in terms of the dipolar interactions between CH_2Cl_2 and the borane–amine, as described in **eq 7**.[14] These interactions hinder the approach of the olefin toward the borane–amine, resulting in initial slow reaction for any given olefin. In the case of less bulky olefins, the RBH_2 formed after the first hydroboration may coordinate with the carrier amine to form $RBH_2:NR_3$ leading to a slower second hydroboration by RBH_2. However, such coordination is minimal or absent in the case of olefins with bulkier alkyl groups, leading to faster hydroborations with a second and third equivalents of the olefin.

This unusual reactivity in dichloromethane makes possible for the first time the selective hydroboration of hindered olefins in the presence of terminal, less hindered olefins. Furthermore, the utility of adduct **33** was exploited in the preparation of various synthetically useful alkylboranes (**Scheme 3**).[13b]

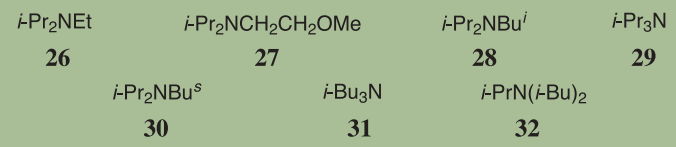


Figure 4. Trialkylamines with Increasing Steric Requirements.

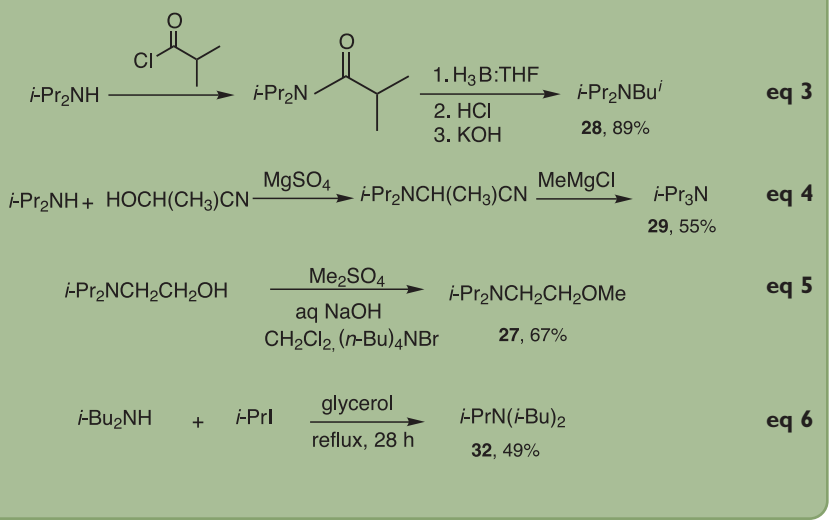


Table 4. Borane Adducts of Trialkylamines with Isopropyl and Isobutyl Groups

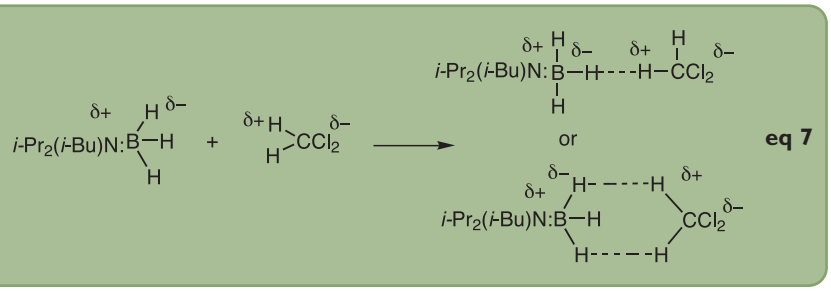
$R^1R^2NR^3$					Amine:BH_3		
R^1	R^2	R^3	Compd No.	Exchange with $Me_2S:BH_3$ (%)[a]	Physical State at rt	$[BH_3]$ M[b]	Hydroboration of 1-Octene in THF at rt[c]
i-Pr	*i*-Pr	Et	**26**	100	–	–	24 h (38%)
i-Pr	*i*-Pr	CH_2CH_2OMe	**27**	72	–	–	9 h
i-Pr	*i*-Bu	*i*-Bu	**32**	52	–	–	15 h
i-Bu	*i*-Bu	*i*-Bu	**31**	50	solid	–	24 h
i-Pr	*i*-Pr	*i*-Bu	**28**	42	liquid	4.6	30 min
i-Pr	*i*-Pr	*i*-Pr	**29**	18	solid	–	20 min
i-Pr	*i*-Pr	*s*-Bu	**30**	0	liquid	3.3 → 2.5	15 min

[a] The amine was mixed with $H_3B:SMe_2$ in a 1:1 molar ratio at rt; the percent exchange at equilibrium was determined by ^{11}B NMR. [b] Estimated by hydrolyzing the complex in 2 M HCl/glycerol/water (2:1:1) and measuring the volume of hydrogen evolved. [c] 3 M in 1-octene and 1 M in BH_3.

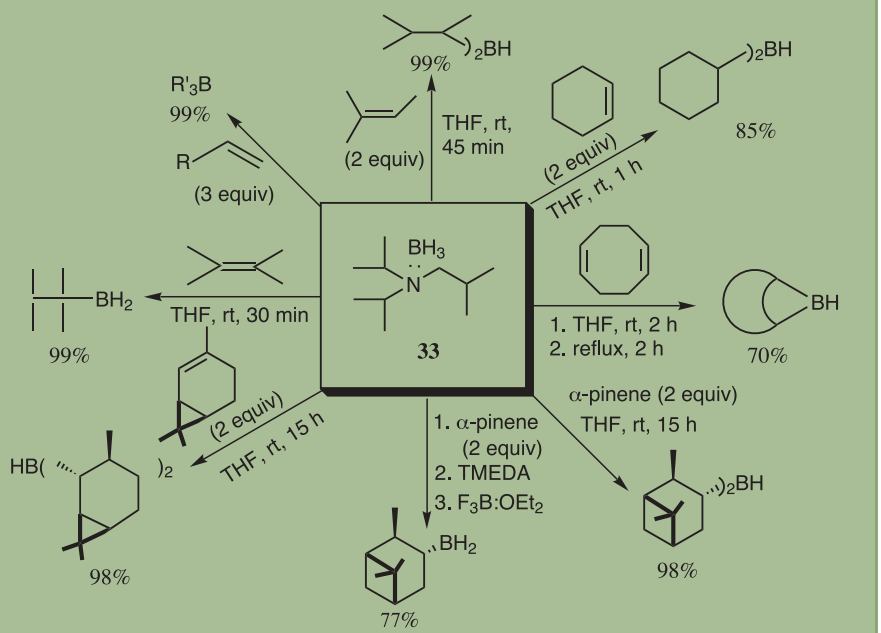
Table 5. Hydroboration of Olefins with Borane–*N,N*-Diisopropylisobutylamine (33)[a]

Olefin	Dioxane React. Time (h)	Dioxane Hydride Equiv Used[b]	Dichloromethane React. Time (h)	Dichloromethane Hydride Equiv Used[b]
1-Hexene	2.0	3.00	48	1.76
Styrene	2.0	3.00	48	1.92
β-Pinene	2.0	3.00	48	2.03
Cyclopentene	2.0	3.00	48	2.11
Norbornene	2.0	3.00	48	2.14
Cyclohexene	24	2.95	48	2.79
	0.83	2.00		
2-Methyl-2-butene	24	2.95	48	2.75
	1.83	2.00		
α-Pinene	24	2.00	48	1.54
	0.33	1.00		
2,3-Dimethyl-2-butene	24	1.71	48	1.64
	0.66	1.00		

[a] Reactions were carried out using 5 mmol of the borane complex and 15 mmol of the olefin in a total volume of 10 mL of solution. [b] Out of a total of 3.00 available hydrides.



eq 7



Scheme 3. Preparation of Known, Synthetically Useful Alkylboranes.

5. Borane Adducts of *tert*-Butyl-*N,N*-dialkylamines

The steric influence on the complexation of borane with trialkylamines was further elucidated by studying various *tert*-butyl-*N,N*-dialkylamines. Two series of amines, **34–38** and **39–43**, with increasing steric bulk of the alkyl groups within each series, were selected for the study (**Table 6**).[15]

5.1. Synthesis of the Amines

Amines **34**–**36**, having two primary unbranched alkyl groups, were prepared from *tert*-butylamine by standard alkylation procedures (**eq 8**).[15]

Amino ether **37** was obtained by methylation of *tert*-butyl(diethanol)amine with dimethyl sulfate in the presence of a phase-transfer catalyst (**eq 9**).

Amines **38**, **39**, **41**, and **42** were prepared from a common intermediate, *t*-BuNHBu^i (**eq 10**).[15] The alkylation of *tert*-butylamine with isobutyl bromide is very slow. A small amount of tetraalkylammonium bromide dissolved in adiponitrile markedly accelerates the reaction. Introduction of the second isobutyl group into *t*-BuNHBu^i by direct alkylation is difficult. Consequently, **38** was prepared by an acylation–reduction sequence.

Similarly, alkyl-*tert*-butylisopropylamines, **40** and **43**, were prepared from a common intermediate, *t*-BuNHPr^i (**eq 11**).[15]

5.2. Preparation of the Borane Adducts

The complexing ability of amines **34–43** was tested as described in Section 2.2.[15] The complexing ability of the amines in the two series examined decreased in the order shown below.

t-BuNR$_2$ series:

34 > **35** > **36** > **37** >> **38**

t-BuNRR^1 series:

39 > **40** > **41** > **42** >> **43**

The reactivity of the corresponding borane adducts toward 1-octene increased in the reverse order. Here also, steric factors play a crucial role in the stability and reactivity of the corresponding borane adducts. For example, *t*-BuNEt$_2$ (**35**) forms a strong complex with borane, making it unreactive in the hydroboration reaction. However, when one of the ethyl groups is replaced with an isopropyl group [*t*-BuNPr^{i}Et (**43**)], the corresponding borane adduct becomes unstable, as the nitrogen atom is too crowded in **43**. When the substitution on the alkyl chain is one carbon

away from nitrogen [*t*-BuNBu^{i}Et (**41**)], the corresponding borane adduct becomes stable, while the nitrogen is hindered enough to make it sufficiently reactive.

The following amines form highly reactive liquid borane adducts that hydroborate 1-octene in tetrahydrofuran at room temperature in less than 1 hour: **37**, **40**, and **41**. The lower limit of borane complexation among amines **34–43** is reached with **38**, which does not form an adduct with borane (**Table 7**).

5.3. Hydroboration Characteristics

Detailed hydroboration studies using the most promising adducts; *t*-Bu($CH_2CH_2OCH_3$)$_2$N:BH_3 (**44**), *t*-BuMePr^{n}N:BH_3 (**45**), and *t*-BuBu^{i}EtN:BH_3 (**46**) with representative olefins have been carried out in various solvents.[15] The observed hydroboration characteristics are similar to those found for **33**. The product organoboranes were oxidized to the corresponding alcohols, and the carrier amines were readily recycled.

6. Borane–*tert*-Alkyl-*N,N*-dialkylamines

tert-Butyl-*N,N*-diethylamine (**35**) takes 85% of borane away from BMS, but its borane adduct is relatively unreactive requiring 6 h for the complete hydroboration of 1-octene (Table 7, entry 2). In contrast, amines **40** and **41** form stable, highly reactive borane adducts that hydroborate 1-octene completely in 0.5 h and 0.3 h, respectively. On the other hand, *tert*-butyl-*N*-ethyl-*N*-isopropylamine (**43**) forms an unstable borane adduct, and *tert*-butyl-*N,N*-diisobutylamine (**38**) completely fails to complex with borane. These observations clearly show the dramatic effect of steric bulk around the amine nitrogen on its complexing ability with borane.

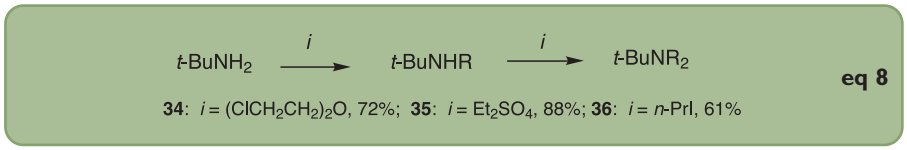
To get a clearer understanding of these steric effects, various *tert*-alkyl-*N,N*-diethylamines (**47**–**50**) were prepared[16] and studied, leading to the development of a new generation of hydroborating agents.

6.1. Synthesis of *tert*-Alkyl-*N,N*-diethylamines

N,N-Diethyl-*tert*-pentylamine (**47**) and *N,N*-diethyl-*tert*-octylamine (**50**) were prepared by reaction of diethyl sulfate with *tert*-pentyl- and *tert*-octylamines, respectively (**eq 12**). *N,N*-Diethyl-*tert*-hexyl- and *tert*-heptylamines (**48** and **49**) were prepared from the corresponding tertiary alcohols (**Scheme 4**).[17]

Table 6. *tert*-Butyl-*N,N*-dialkylamines with Increasing Steric Requirements

t-BuNR$_2$		*t*-BuNRR^1		
	R		R	R^1
34	$CH_2CH_2OCH_2CH_2$	**39**	Me	*i*-Bu
35	Et	**40**	Me	*i*-Pr
36	*n*-Pr	**41**	Et	*i*-Bu
37	CH_2CH_2OMe	**42**	*n*-Pr	*i*-Bu
38	*i*-Bu	**43**	Et	*i*-Pr



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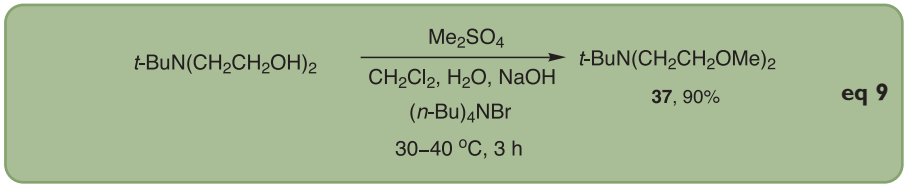

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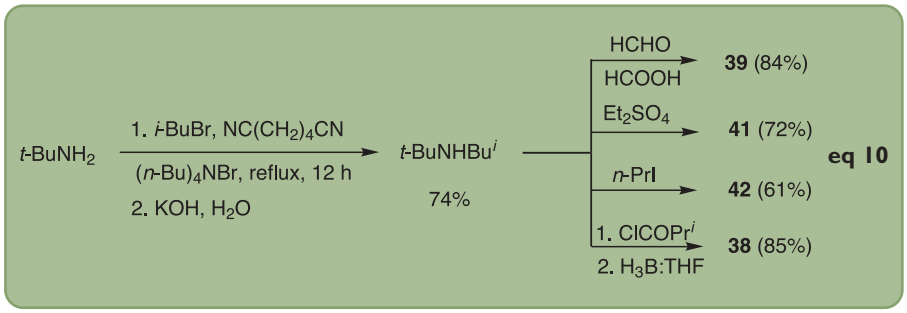

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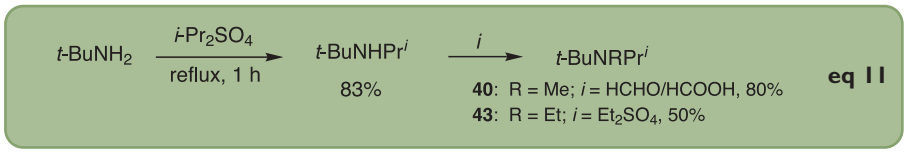
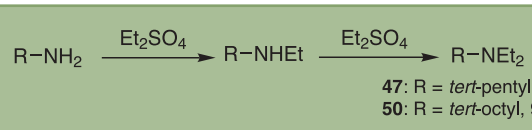


eq 11

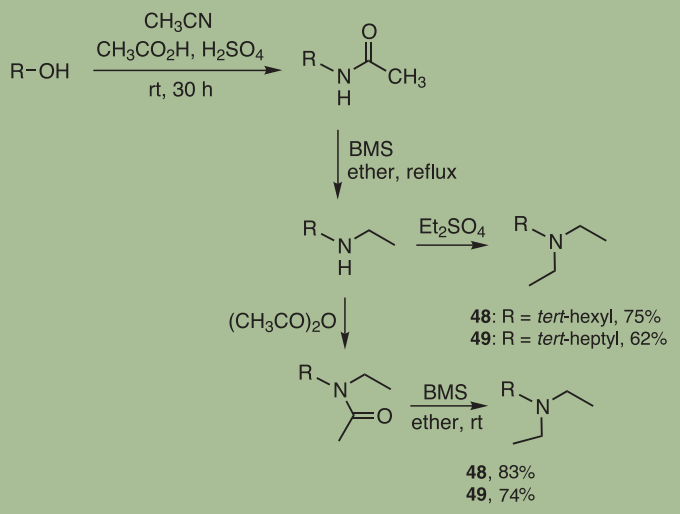
Table 7. Borane Adducts of *tert*-Butyl-*N,N*-dialkylamine Derivatives

t-BuNR^{1}R^2				H$_3$B:N(*t*-Bu)R^{1}R^2		
R^1	R^2	Compd No.	Exchange with $Me_2S:BH_3$ (%)[a]	Physical State at rt	[BH_3][b] M	Hydroboration of 1-Octene in THF at rt (h)[c]
$CH_2CH_2OCH_2CH_2$		**34**	100	–	–	6.0
Et	Et	**35**	85	–	–	6.0
n-Pr	*n*-Pr	**36**	70	–	–	3.0
CH_2CH_2OMe	CH_2CH_2OMe	**37**	50	liquid	4.5	0.5
i-Bu	*i*-Bu	**38**	0	–	–	–
i-Bu	Me	**39**	73	liquid	–	20
i-Pr	Me	**40**	50	liquid	5.3	0.5
i-Bu	Et	**41**	33	liquid	4.4	0.33
i-Bu	*n*-Pr	**42**	24	–	–	0.33
i-Pr	Et	**43**	0	liquid	5→3	0.25

[a] The amine was mixed with $H_3B:SMe_2$ in a 1:1 molar ratio at rt; the percent exchange at equilibrium was determined by ^{11}B NMR. [b] Estimated by hydrolyzing the complex in 2 M HCl/glycerol/water (2:1:1) and measuring the volume of hydrogen evolved. [c] 3 M in 1-octene and 1 M in BH_3.



eq 12

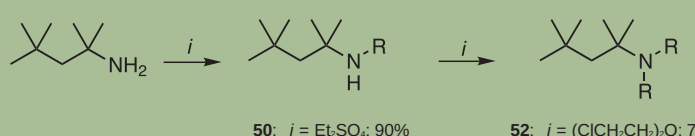


Scheme 4. Synthesis of *N,N*-Diethyl-*tert*-hexyl- and *tert*-heptylamines.

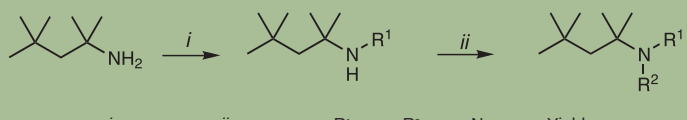
Table 8. Borane Adducts of *tert*-Alkyl-*N,N*-diethylamines

$RNEt_2$			Amine:BH_3		
R	Compd No.	Exchange with Me_2S:BH_3 (%)[a]	Physical State at rt	$[BH_3]$[b] M	Hydroboration of 1-Octene in THF at rt (h)[c]
t-Bu	**35**	85	liquid	–	6.0
t-Pent	**47**	83	–	–	4.0
t-Hex	**48**	40	liquid	4.3	0.5
t-Hept	**49**	80	–	–	3.5
t-Oct	**50**	38	liquid	4.0	0.3

[a] The amine was mixed with H_3B:SMe_2 in a 1:1 molar ratio at rt; the percent exchange at equilibrium was determined by ^{11}B NMR. [b] Estimated by hydrolyzing the complex in 2 M HCl/glycerol/water (2:1:1) and measuring the volume of hydrogen evolved. [c] 3 M in 1-octene and 1 M in BH_3.



eq 13



i	*ii*	R^1	R^2	No.	Yield
Et_2SO_4	$HCHO/HCO_2H$	Et	Me	**54**	76%
i-BuBr	$HCHO/HCO_2H$	*i*-Bu	Me	**55**	48%

eq 14

6.2. Borane Adducts of *tert*-Alkyl-*N,N*-diethylamines

The complexing ability of these amines toward borane was investigated as described in Section 2.2 (**Table 8**). *N,N*-Diethyl-*tert*-pentylamine (**47**) showed reactivities similar to those of the analogous *tert*-butyl compound (**35**), with only a marginal improvement in the rate of hydroboration of 1-octene. *N,N*-Diethyl-*tert*-heptylamine (**49**) formed a relatively strong borane adduct that hydroborated 1-octene in 3.5 h. In contrast, *N,N*-diethyl-*tert*-hexylamine (**48**) and *N,N*-diethyl-*tert*-octylamine (**50**) showed higher reactivities towards 1-octene.[16]

6.3. Preparation of *N,N*-Dialkyl-*tert*-octylamines

The preceding results demonstrated that *N,N*-diethyl-*tert*-octylamine (**50**) possessed the qualities of a good hydroborating reagent. To discover the optimal steric requirements in this *tert*-octyl system, several *N,N*-dialkyl-*tert*-octylamines (**50–55**), with increasingly bulky alkyl groups, were prepared (**eq 13** and **14**) and studied (**Table 9**).[16]

6.4. Borane Adducts of *N,N*-Dialkyl-*tert*-octylamines

As revealed by the exchange experiments summarized in Table 9, the dimethylamine derivative, **51**, formed a very stable borane adduct and thus, not surprisingly, the adduct was unreactive in the hydroboration of 1-octene. In contrast, **50** had a much lower affinity for borane and, consequently, was dramatically more reactive. The latter adduct is a liquid, with a borane concentration of 4.0 M, and is stable at room temperature. The borane adducts of **52** and **53** are both solids that have similar hydroboration reactivities in THF. Even though the adducts of **50**, **52**, and **53** are more reactive than those of the remaining amines, only the borane adduct of **50**, borane–*N,N*-diethyl-*tert*-octylamine (**56**), meets the requirements of a good hydroborating agent: It is a liquid at room temperature, has a high borane concentration, and hydroborates 1-octene rapidly at room temperature. Accordingly, the hydroboration behavior of this borane adduct toward representative olefins was studied in detail in various solvents.[16] **56** hydroborated olefins similarly to **33**. The product organoboranes were oxidized to the corresponding alcohols and the carrier amines were readily recycled. As in the case of **33**, an unusual rate retardation was observed for the hydroboration in dichloromethane, allowing for the selective hydroboration of hindered olefins in the presence of less hindered ones.[16]

7. Conclusions

The studies highlighted in this review identified a group of highly reactive borane–amine complexes, with varying physical and chemical properties and reactivities, that are now available for the first time. For example, these studies involved borane–amines with a wide range of boiling points. Thus, for a hydroboration of interest, a borane–amine can be selected that wouldn't interfere with the isolation of the product. These studies also examined the influence of steric factors around nitrogen on borane complexation. The hydroboration reactions were carried out in a variety of solvents or without solvent. Some interesting reactivity differences were noted for certain borane–amine complexes in dichloromethane, allowing for the selective hydroboration of hindered olefins in the presence of less hindered ones. Some of the most promising borane–amine reagents for hydroboration are shown in **Figure 5**.

The organoborane products from the hydroboration of representative olefins were readily oxidized, using hydrogen peroxide/sodium hydroxide, to the corresponding alcohols, and the carrier amines were readily recovered and recycled, resulting in a "green" process. In addition, these borane–amine complexes were utilized in the synthesis of several known but valuable dialkylboranes, such as the isomeric diisopinocampheylboranes ($^{d}Ipc_2BH$ or $^{l}Ipc_2BH$), (1*S*)-2-diisocaranylborane ($^{d}Icr_2BH$), 9-borabicyclo[3.3.1]nonane (9-BBN), dicyclohexylborane (Chx_2BH), and disiamylborane (Sia_2BH). Thus, these new-generation borane–amine complexes—free from the problems associated with previously reported borane–amine complexes and currently used borane–dimethyl sulfide and borane–tetrahydrofuran—should serve as environmentally friendly substitutes. Further studies are required to explore the full scope of this new generation of borane–amine complexes.

Table 9. Borane Adducts of *N,N*-Dialkyl-*tert*-octylamines

t-OctNR^{1}R^2				Amine:BH_3		
R^1	R^2	Compd No.	Exchange with $Me_2S:BH_3$ (%)[a]	Physical State at rt	$[BH_3]$[b] M	Hydroboration of 1-Octene in THF at rt (h)[c]
Me	Me	**51**	85	–	–	[d]
Et	Me	**54**	77	–	–	24
$CH_2CH_2OCH_2CH_2$		**52**	50	solid	–	0.33
Et	Et	**50**	38	liquid	4.0	0.33
i-Bu	Me	**55**	35	solid	–	1.5
n-Pr	*n*-Pr	**53**	25	solid	–	0.33

[a] The amine was mixed with $H_3B:SMe_2$ in a 1:1 molar ratio at rt; the percent exchange at equilibrium was determined by ^{11}B NMR. [b] Estimated by hydrolyzing the complex in 2 M HCl/glycerol/water (2:1:1) and measuring the volume of hydrogen evolved. [c] 3 M in 1-octene and 1 M in BH_3. [d] No appreciable reaction ocurred even after 24 h at room temperature.

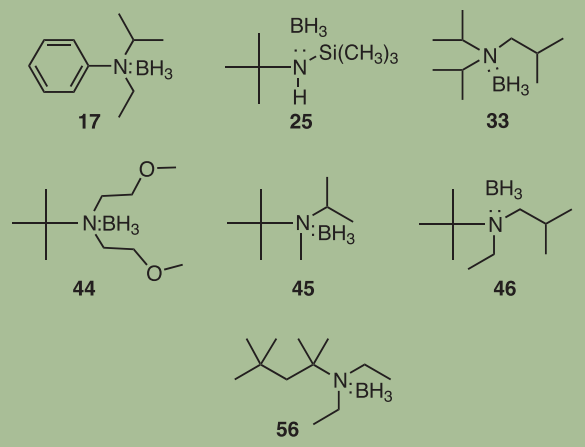


Figure 5. Most Promising New Borane–Amine Complexes for Hydroboration.

8. Acknowledgements

The author is highly thankful to Professor M. Zaidlewicz, a mentor and collaborator. Aldrich Chemical Company and the Purdue Borane Research Fund of Purdue University provided financial support for some of these studies. The help and support of Drs. Chris Hewitt and Peng Gao during the preparation of this manuscript are highly appreciated.

9. References and Notes

(†) Dedicated to Professor Herbert C. Brown, a great mentor and pioneer in organoborane chemistry, on the occasion of his 90th birthday.

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About the Author

Kanth V. B. Josyula was born in 1966 in Sanapallilanka, Andhra Pradesh, India. He received a Bachelor of Science degree in 1986 from Andhra-Nagarjuna University, Machilipatnam, India. He completed his master's (1988) and doctoral studies (1994) at the University of Hyderabad, India, working with Professor M. Periasamy. His doctoral work included the synthesis of chiral amines and amino alcohols and diols, and studies of their applications in catalytic asymmetric transformations. After receiving his Ph.D. degree, he worked briefly as a scientist in Dr. Reddy's Research Foundation, Hyderabad. In 1995–1996, he worked with Professor M. Zaidlewicz as a visiting scientist at Nicolaus Copernicus University, Torun, Poland. In 1996, he joined Professor Herbert C. Brown's research group at Purdue University as a postdoctoral associate. In 1998, he became research associate and continued his research on the synthesis and hydroboration and reduction reactions of new borane–amines, and on the synthesis of new, highly reactive chloroborane derivatives for selective hydroborations. In 2001, Kanth joined the New Products group in the R&D department at Aldrich Chemical Company. A common thread throughout his research carrier has been the applications of boranes and organoboranes in organic and asymmetric synthesis. His other research areas of interest include metal carbonyl chemistry, new methodology development, and reaction mechanisms. He has co-authored more than 25 research publications. In his free time, he and his wife, Sridevi, enjoy gardening and visiting friends.

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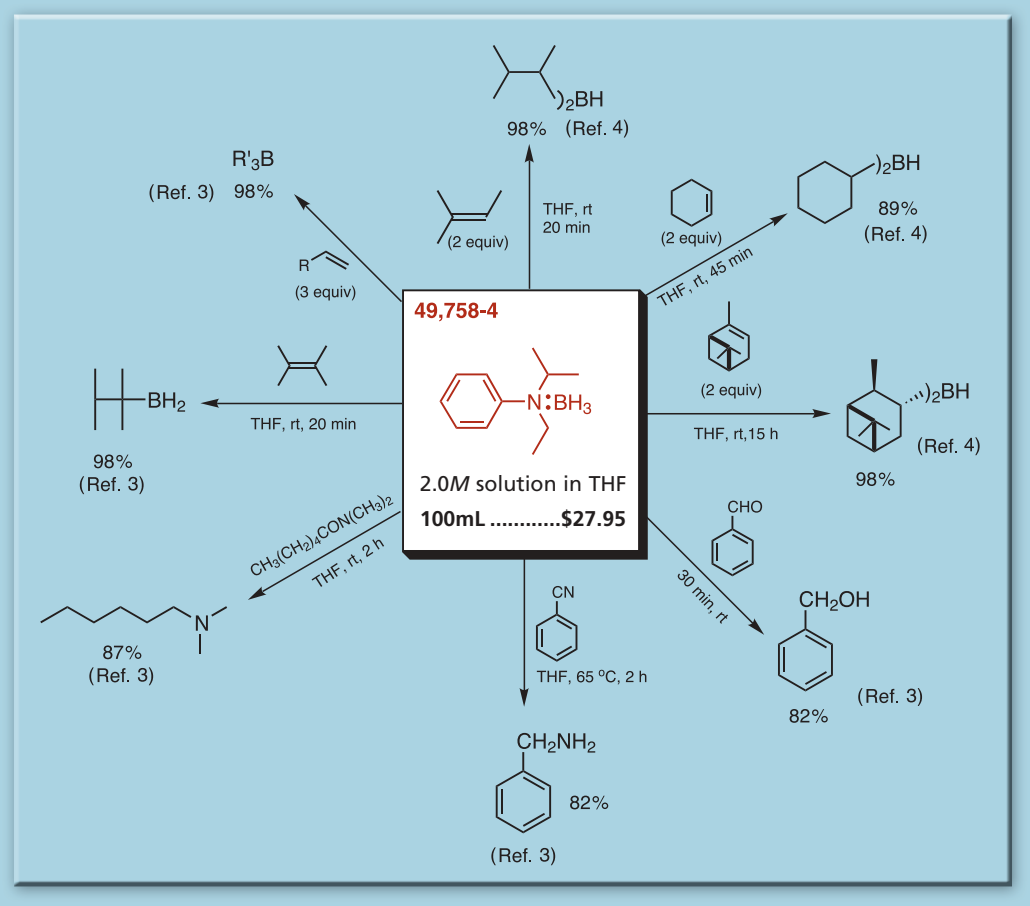

For an in-depth discussion of these amines and borane–amines, please refer to the preceding review by Dr. J. V. B. Kanth.

Additional Moderately Hindered Amines:

44,335-2	*N-tert*-**Butyl**-*N*-**ethylisobutylamine**, 98%
46,098-2	*N,N*-**Diethylbutylamine**, 97%
44,334-4	*N,N*-**Diethyl**-*tert*-**octylamine**, 98%
44,330-1	*N,N*-**Diisopropylisobutylamine**, 98%
44,333-6	*N*-**Ethyl**-*N*-**isopropylaniline**, 97%
44,332-8	*N*-**Isopropyl**-*N*-**methyl**-*tert*-**butylamine**, 98%

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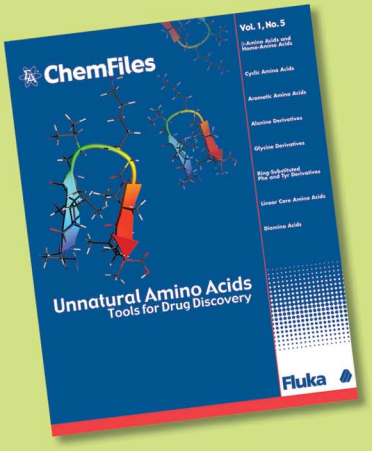

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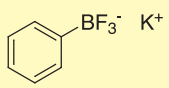
Aryl, alkyl, and alkenyl trifluoroborate salts are attractive alternatives to boronic acids in Suzuki coupling[1] and in rhodium-catalyzed carbon–carbon bond-forming reactions.[2] These salts are air- and water-stable,[3] and in many cases eliminate the need to introduce either additional ligands or base for cross-coupling. Whereas the boronic acids readily form cyclic anhydrides, these new salts do not form unwanted side products. In many cases, the trifluoroborate salt is more efficient and tolerant of functional groups than the corresponding boronic acid. Below is a list of potassium trifluoroborate salts available from Aldrich. For a comprehensive list of products for Suzuki coupling, please visit our website at **www.sigma-aldrich.com/aldrich** and select "Specialty Brochures" or email **girvine@sial.com**. Your new product suggestions are always welcome and appreciated.

References: (1) (a) Molander, G. A.; Biolatto, B. *Org. Lett.* **2002**, *4*, 1867. (b) Molander, G. A.; Rodriguez Rivero, M. *ibid.* **2002**, *4*, 107. (c) Molander, G. A.; Ito, T. *ibid.* **2002**, *4*, 393. (d) Xia, M.; Chen, Z.-C. *Synth. Commun.* **1999**, *29*, 2457. (e) Darses, S. et al. *Tetrahedron Lett.* **1998**, *39*, 5045. (f) Darses, S. et al. *ibid.* **1997**, *38*, 4394. (2) Batey, R. A. et al. *Org. Lett.* **1999**, *1*, 1683. (3) (a) Vedejs, E. et al. *J. Org. Chem.* **1995**, *60*, 3020. (b) Vedejs, E. et al. *J. Am. Chem. Soc.* **1999**, *121*, 2460.

56,395-1
Potassium phenyltrifluoroborate

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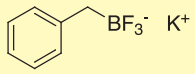
56,305-6
Potassium benzyltrifluoroborate

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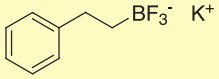
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57,155-5
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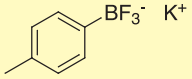
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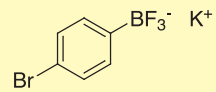
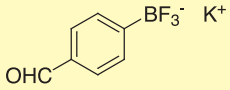
57,154-7
Potassium 4-bromophenyltrifluoroborate

1g
5g

57,609-3
Potassium 4-formylphenyltrifluoroborate

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57,613-1
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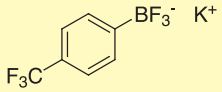
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57,159-8
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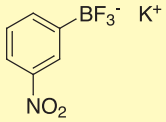
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57,611-5
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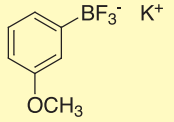
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57,156-3
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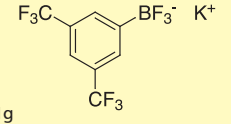
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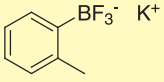
57,612-3
Potassium *o*-tolyltrifluoroborate

1g
5g

57,610-7
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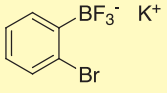
1g
5g

57,157-1
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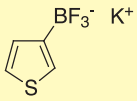
1g
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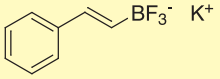
57,615-8
Potassium *trans*-styryltrifluoroborate

1g
5g

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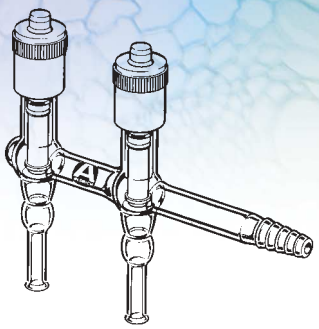
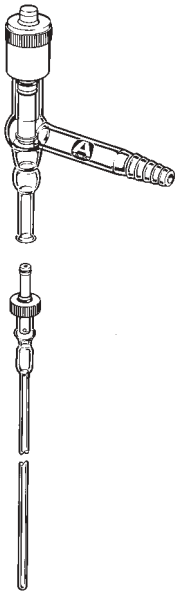
Aldrich NMR Tube Evacuation Manifolds



Designed to evacuate 5mm NMR tubes that have a PTFE valve. Once the NMR tube has been evacuated in the manifold, close the valve and place the tube in the NMR spectrometer. Manifolds have 0–10mm bore PTFE valves. The multiple evacuation station units allow removal of an NMR tube while the remaining tube(s) stay under vacuum.

Evacuation stations	L (mm)	Cat. No.
1	100	**Z51,647-3**
2	150	**Z51,648-1**
5	300	**Z51,650-3**



NMR Tubes with PTFE J Young Valves

Allow the easy handling of air-sensitive samples when used with Aldrich NMR tube manifolds. 5mm o.d., thin wall (0.38mm).

Length (in.)	Concentricity/ Camber (µm)	Wilmad® No.	Cat. No.
360MHz tubes			
7	51/25	507-JY-7	**Z51,419-5**
8	51/25	507-JY-8	**Z51,420-9**
400MHz tubes			
7	25/13	528-JY-7	**Z51,418-7**
8	25/13	528-JY-8	**Z51,421-7**
500MHz tubes			
7	13/6	535-JY-7	**Z51,416-0**
8	13/6	535-JY-8	**Z51,417-9**

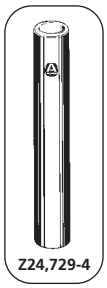
NMR Accessories

For vacuum–thaw applications, use the Aldrich NMR tube Dewar flask. When the tip-off technique is used, the MT-51 butane torch generates a 1,300 °C pinpoint flame.

Description	Cat. No.
NMR tube Dewar flask	**Z24,729-4**
MT-51 handheld torch	**Z26,506-3**
(Torch shipped empty, order butane separately)	
Butane fuel, 26g of butane fuel/can	**44,367-0**

Stainless steel NMR tube racks

Description	Cat. No.
10-tube rack	**Z51,431-4**
20-tube rack	**Z51,432-2**



Z24,729-4

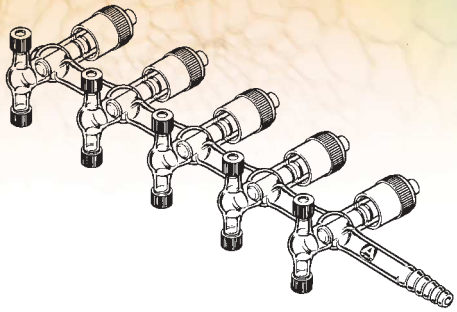
Z26,506-3

Stainless steel NMR tube racks

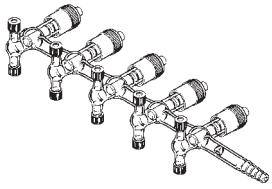
NMR Equipment

Aldrich 5mm NMR Tube Filling Manifolds

Convenient systems for preparing air- and moisture-sensitive NMR samples within a controlled manifold environment. Manifolds have 0–10mm bore PTFE valves. The multiple filling station units allow removal of an NMR tube while the remaining tube(s) stay under vacuum.

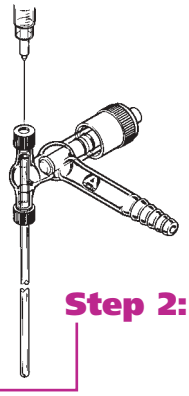


Filling Technique



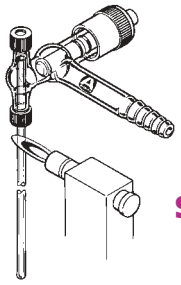
Step 1:

- Insert NMR tube through the open top cap and Viton® O-ring and evacuate NMR tube.



Step 2:

- Fill NMR tube with a syringe through the PTFE-faced silicone septum.



Step 3:

- Tip-off NMR tube or remove tube and cap.

Filling stations	L (mm)	Cat. No.
1	100	**Z51,644-9**
2	150	**Z51,645-7**
5	300	**Z51,646-5**

Replacement parts	Cat. No.
PTFE-faced silicone septa	**Z16,256-6**
Screw-caps	**Z16,253-1**
Viton® O-rings	**Z54,247-4**

Extra-long NMR Tubes

Special 9-in. tube length is recommended for use with Aldrich NMR tube tip-off manifolds.

Grade	Wilmad® No.	Cat. No.
360MHz	507-PP-9	**Z27,211-6**
400MHz	528-PP-9	**Z27,454-2**
500MHz	535-PP-9	**Z27,456-9**

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Matheson Gas Data Book

7th ed., C.L. Yaws, McGraw-Hill, Columbus, OH, 2001, 982pp. Hardcover. This updated edition is a comprehensive and convenient compendium of scientific data on gases. It includes a full spectrum of properties for 157 gases with unique temperature-dependency graphs and other handy charts. Also provides practical advice on equipment and procedures, including valves, leak detection, disposal of leaking cylinders, transport, safety equipment, and first aid.

Z51,454-3

The HPLC Solvent Guide

2nd ed., P.C. Sadek, John Wiley & Sons, New York, NY, 2002, 664pp. Hardcover. Reviews HPLC solvent selection and methodology. Provides detailed coverage of all commonly used HPLC solvents used in a wide variety of separations. Serves as an easy reference for solvent class, field of application, and specific analyte class. Focuses on practical applications and method optimization.

Z51,423-3

Solid-Phase Synthesis: A Practical Guide

S.A. Kates and F. Albericio, Eds., Marcel Dekker, New York, NY, 2000, 848pp. Hardcover. Provides the most up-to-date information needed to synthesize molecules by SPS employing polymeric supports, anchoring linkages, coupling reagents, and protection schemes. Thoroughly reviews small molecules, carbohydrates, peptides, and conjugates of biomolecules.

Z51,362-8

Compendium of Chiral Auxiliary Applications (3-Vol. Set)

G. Roos, Academic Press, Orlando, FL, 2001, 1,612pp. Hardcover. This is the first major reference work of its kind to look logically and sequentially at chiral auxiliaries, investigating their properties and applications in diastereoselective synthesis. This three-volume set includes more than 13,000 auxiliary reaction applications with complete reaction details for each auxiliary and over 2,700 references. The set is fully cross-referenced and compiled in a manner that facilitates making an informed selection of an auxiliary for a specific application.

Z51,324-5

Dendrimers and Dendrons: Concepts, Syntheses, Applications

G.R. Newkome, C.N. Moorefield, and F. Vogtle, John Wiley & Sons, New York, NY, 2001, 636pp. Hardcover. This book gives a comprehensive, up-to-date account of the topic, from the historical overview and theoretical background up to the most recent achievements. Includes sections on divergent and convergent syntheses, chiral dendritic macromolecules, metallodendimers, and much more. For special synthetic problems, a well-selected, detailed list of references is provided.

Z51,366-0

Catalytic Heterofunctionalization: From Hydroamination to Hydrozirconation

A. Tongi and H. Grutzmacher, Eds., John Wiley & Sons, New York, NY, 2001, 304pp. Hardcover. The first handbook on the subject of catalytic heterofunctionalization, presenting all the modern synthetic methods including hydroamination, hydrosilylation, hydrozirconation, hydroalumination, hydroboration, and hydrophosphination. An indispensable source for every researcher and practitioner of homogeneous catalysis as well as for all synthetic organic chemists in academia and industry.

Z51,378-4

Modern Organocopper Chemistry

N. Krause, Ed., John Wiley & Sons, New York, NY, 2002, 392pp. Hardcover. Presents the latest advances in organocopper chemistry and includes Zn–Cu, Sn–Cu, Si–Cu, and H–Cu reagents, and asymmetric reactions. Organized according to reaction type and selectivity problem, this book allows chemists to determine the optimal reagent for their needs.

Z51,429-2

Microscale Techniques for the Organic Laboratory

2nd ed., D.W. Mayo, R.M. Pike, and P.K. Trumper, John Wiley & Sons, New York, NY, 2001, 352pp. Softcover. Discusses the principal techniques used in the preparation, isolation, purification, and characterization of organic reaction products and naturally occurring materials.

Z51,426-8

Advanced Functional Molecules and Polymers (4-Vol. Set)

H.S. Nalwa, Taylor & Francis, London, England, 2001, 1,858pp. Hardcover. This four-volume set consolidates all the current knowledge of the science and technology of polymers into a single reference source. It covers every aspect of their science and engineering, drawing on two decades' worth of research. Includes the synthesis, processing, and spectroscopy of these compounds as well as their electronic, photonic, and physical properties and applications.

Z51,345-8

Organic Structures from Spectra

3rd ed., L.D. Field, S. Sternhell, and J.R. Kalman, John Wiley & Sons, New York, NY, 2002, 384pp. Hardcover. This introductory textbook includes all the major spectroscopic techniques that cover the derivation of structural information from spectroscopic data. It incorporates over 200 carefully selected problems that are graded to develop and consolidate the students' understanding of organic spectroscopy and of how structures are derived.

Z51,433-0

New Oxford Chemistry Primers!
(refers to the following 2 books only)

Protecting Group Chemistry

J. Robertson, Oxford University Press, New York, NY, 104pp. Softcover. Emphasizes the link between the mechanisms of organic chemistry and the choice of specific protecting groups that block chemical reactivity at those sites that must remain unaffected.

Z51,384-9

Stereoselectivity in Organic Synthesis

G. Procter, Oxford University Press, New York, NY, 96pp. Softcover. Reviews the general principles of stereoselectivity, especially stereoelectronic effects, and how these effects are applied to a wide range of modern stereospecific and stereoselective organic reactions.

Z51,381-4

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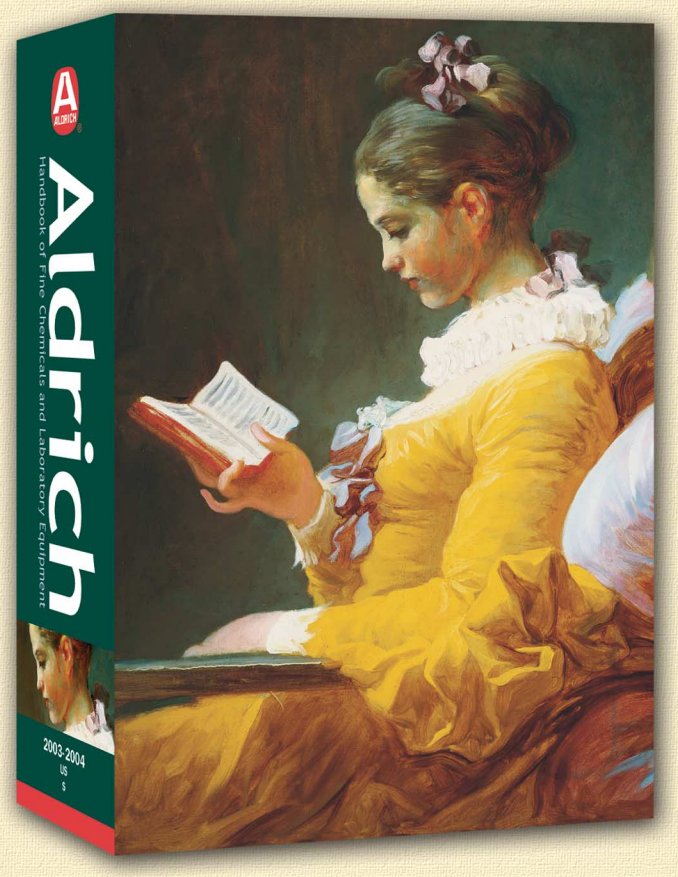

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Aldrichimica ACTA

VOL. 35, NO. 3 • 2002
(Last issue in 2002)

Applications of Ionic Liquids in Organic Synthesis

Novel Methods of Resolving Racemic Diols and Amino Alcohols

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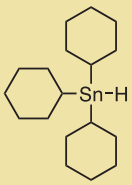
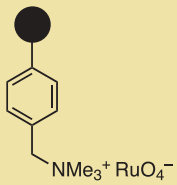
46,068-0 Tricyclohexyltin hydride, 97%



Utilized in the hydrostannation of a variety of functionalized alkenes in good yields.

Jousseaume, B. et al. *Organometallics* **1995**, *14*, 685.

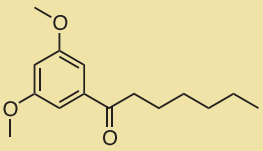
51,158-7 Perruthenate, polymer-bound



Has been used in the oxidation of pyridylcarbinols,[1] hydroxylamines,[2] benzylic alcohols,[3] and primary alcohols to their corresponding aldehydes.

(1) Habermann, J. et al. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1253. (2) Hinzen, B.; Ley, S.V. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1. (3) Haunert, F. et al. *ibid.* **1998**, 2235.

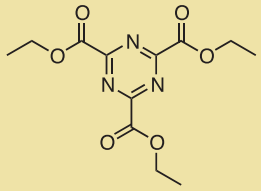
57,553-4 1-(3,5-Dimethoxyphenyl)heptan-1-one, 96%



An intermediate in the synthesis of functionalized cannabinoids.[1,2]

(1) Papahatjis, D. P. et al. *J. Med. Chem.* **1998,** *41,* 1195. (2) Harrington, P. E. et al. *J. Org. Chem.* **2000,** *65,* 6576.

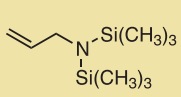
57,669-7 Triethyl 1,3,5-triazine-2,4,6-tricarboxylate, 97%



A reactive azadiene that is very useful in inverse-electron-demand Diels–Alder reactions for the efficient synthesis of highly functionalized pyrimidines.[1] Also utilized in the synthesis of purines and purine analogs via Diels–Alder reactions with aromatic dienophiles.[2]

(1) Dang, Q. et al. *J. Org. Chem.* **1996**, *61,* 5204. (2) Dang, Q. et al. *J. Am. Chem. Soc.* **1999,** *121,* 5833.

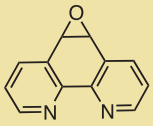
57,893-2 2-Allyl-1,1,1,3,3,3-hexamethyldisilazane, 97%



Was utilized to generate aminoalkylboronic acids.

Goeller, B. et al. *Main Group Metal Chemistry* **1997**, *20*, 795.

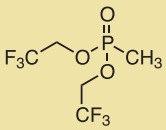
57,878-9 5,6-Epoxy-5,6-dihydro[1,10]phenanthroline, 98%



Versatile reagent that has been employed in syntheses of 5-substituted 1,10-phenanthrolines[1] and in the preparation of the marine alkaloid ascididemin.[2]

(1) Riklin, M. et al. *J. Chem. Soc., Dalton Trans.* **2001**, 1813. (2) Moody, C. J. et al. *Tetrahedron* **1992,** *48,* 3589.

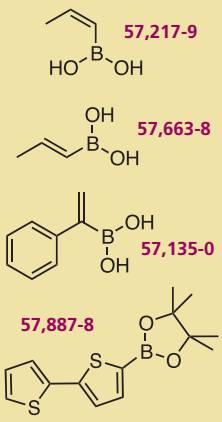
57,944-0 Bis(trifluoroethyl) methylphosphonate, 99%



An excellent starting material for the stereoselective synthesis of Z α,β-unsaturated esters[1] and ketones.[2]

(1) Still, W.C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405. (2) Yu, Y. et al. *ibid.* **1999**, *40*, 6725.

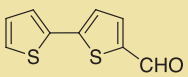
57,217-9 *cis*-Propenylboronic acid
57,663-8 *trans*-Propenylboronic acid
57,135-0 α-Phenylvinylboronic acid
57,887-8 5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2,2′-bithiophene



Vinyl boronic acids, like arylboronic acids, undergo facile Suzuki–Miyaura coupling with aromatic halides in the presence of palladium catalysts.[1] Several years ago, Miyaura and coworkers demonstrated the utility of cyclic pinacol esters of arylboronic acids in Suzuki–Miyaura coupling reactions.[2,3] Very recently, α-phenylvinylboronic acid was used for the preparation of the corresponding nonracemic alcohols via asymmetric hydrogenation, in the presence of a chiral rhodium catalyst, followed by oxidative cleavage.[4]

(1) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (2) Ishiyama, T. et al. *J. Org. Chem.* **1995**, *60*, 7508. (3) Ishiyama, T. et al. *Tetrahedron Lett.* **1997**, *38*, 3447. (4) Ueda, U. et al. *J. Organomet. Chem.* **2002**, *642*, 145.

57,670-0 2,2′-Bithiophene-5-carbaldehyde, 98%



Useful in medicinal chemistry[1,2] and materials science.[3,4]

(1) Rodriguez, M. J. et al. *J. Antibiot.* **1998**, *51,* 560. (2) Xu, W.-C. et al. *Bioorg. Med. Chem. Lett.* **1999**, *9,* 2279. (3) Kamal, M. R. et al. *Phosphorus, Sulfur Silicon Relat. Elem.* **1997**, *126,* 65. (4) Soudan, P. et al. *J. Mater. Chem.* **2001,** *11,* 773.

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About Our Cover

Cattleya Orchid and Three Brazilian Hummingbirds (oil on wood panel, 34.8 x 45.6 cm), signed and dated 1871, was painted by the American artist Martin Johnson Heade. Heade's earliest works were portraits, but by the early 1860s he had turned to landscape, a subject more attuned to his artistic personality. Using a limited number of pictorial elements: sky, clouds, water, perhaps some trees or rocks in an essentially flat landscape, Heade created an art of varied and shifting moods. Often his portrayal of natural phenomena such as shifting sunlight, approaching rain, lightning, dark clouds, and fog gives his paintings a dramatic and even disquieting character.

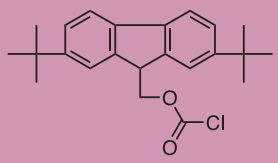
Photograph © Board of Trustees, National Gallery of Art, Washington.

During the 1860s, Heade turned to painting objects at close range, and produced a series of remarkably sensuous still life paintings of flowers. In 1863, he sailed to Rio de Janeiro to study and paint the major species of tropical hummingbirds for a book. The book was never published, but he made two other trips to Central and South America in 1866 and 1870, fascinated by the wildlife and the landscape. His approach was different from that of his friend Frederick Edwin Church, who also traveled to Latin America, but who sought to capture the grandeur of vast tropical landscapes, and it was different from that of naturalists like John James Audubon, whose purpose was to create an objective record of the birds and plants he saw. In *Cattleya Orchid and Three Brazilian Hummingbirds*, Heade carefully represents a specific kind of pink orchid and two particular species of hummingbird, one Sappho Comet, green with a yellow throat and red tail feathers, and two green-and-pink Brazilian Amethysts, but he sets these subjects in an evocative and mysterious tropical setting full of mist and diffuse light, combining the two kinds of painting at which he excelled, still life and landscape.

This painting is a gift of the Morris and Gwendolyn Cafritz Foundation to the National Gallery of Art, Washington, DC.

"Please Bother Us."

Clint Lane, President



Professor James S. Nowick of the University of California, Irvine, kindly suggested that we offer the amine-protecting group 2,7-di-(*tert*-butyl)-9-fluorenylmethyl chloroformate (Fmoc*-Cl) as an alternative to Fmoc-Cl. Dr. Nowick and coworkers have demonstrated that Fmoc*-protected amines have a greater solubility in common volatile organic solvents and fewer problems associated with byproduct removal than their Fmoc-protected counterparts.

Stigers, K. D.; Koutroulis, M. R.; Chung, D. M.; Nowick, J. S. *J. Org. Chem.* **2000**, *65*, 3858.

55,100-7
2,7-Di-(*tert*-butyl)-9-fluorenylmethyl chloroformate, 97% (Fmoc*-Cl)

Naturally, we made this valuable protecting group. It was no bother at all, just a pleasure to be able to help.

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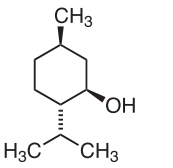
Table of Contents

Lab Notes

(1*R*,2*S*,5*R*)-(–)-Menthol: Proposed Calibration Standard for Polarimetry

Since its discovery in the early part of the nineteenth century,[1] polarimetry has been employed extensively in the sugar[2] and pharmaceutical industries,[3] and for the analysis of chiral compounds[4] and asymmetric synthesis products[5] and catalysts.[6] Polarimetry is also used in the teaching laboratory.[7,8]

While glucose and sucrose solutions are the most commonly utilized international standards for calibrating polarimeters,[9] their use suffers from the following disadvantages:



(1*R*,2*S*,5*R*)-(–)-Menthol

- Their solutions can become easily contaminated with bacteria or fungi.
- Sucrose can hydrolyze to a mixture of glucose and fructose, with a resulting reversal of the optical rotation.[10]
- Mutarotation is observed for solutions of glucose, which give constant rotations only after some hours.[11]

Thus, we thought it desirable to search for a new polarimetry standard, which ought to be stable, inexpensive, and easy to prepare and purify. We conducted preliminary tests on several candidates [(+)-tartaric acid, quinine sulfate, ephedrine, and *l*-menthol] and compared the results with those obtained with glucose and sucrose:

- Aqueous solutions of (+)-tartaric acid[12] and quinine sulfate racemized slowly and did not give stable readings.
- Aqueous solutions of ephedrine hydrochloride[13] (generated in situ from the free base and hydrochloric acid) gave stable readings, but, after three months, these readings changed due to racemization.

In contrast, we obtained good results with (1*R*,2*S*,5*R*)-(–)-menthol,[14] which may be obtained by resolving racemic synthetic menthol,[8] by asymmetric synthesis,[15] or, more commonly, from the essential oils of several species of mint, e.g., *Mentha piperita* or *Mentha herbensis*.[16] It is also commercially available,[17] inexpensive (much less so than ephedrine or quinine sulfate), and easy to purify by recrystallization or sublimation[14]—even easier than sucrose or glucose. We found ethanolic solutions of (–)-menthol to be stable for years.

We used samples of enantiomerically pure natural (–)-menthol[18] of constant melting point (41–42 °C), and checked their chemical purity by the method of Ligor and Buszewski.[19,20] The purities obtained fell in the range of >99.9 to 100%. We then measured the absolute optical rotation of a 10% solution of (–)-menthol in absolute ethanol on a JASCO DIP 370 digital polarimeter. 27 measurements were carried out at 25 °C over a period of 72 days. The average of these measurements, $[\alpha]_D^{25}$ = -50.40 ± 0.01 (c = 10, C_2H_5OH), compares very favorably with the reported value of $[\alpha]_D^{25}$ = -50 (c = 10, C_2H_5OH).[8,14,17]

We have been routinely using such an ethanolic solution of natural menthol (stored in a tightly closed vial) as a polarimeter calibration standard for over three years. We have obtained very stable readings during this period, and found no evidence of decomposition or loss by evaporation.

References and Notes

(1) (a) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley & Sons, Inc.: New York, 1994; pp 2–3. (b) The first practical polarimeter was constructed in 1840. Biot, J. B. *Ann. Chim. Phys.* **1840**, *74*, 401; http://museum.nist.gov/panels/bates/intro.htm (accessed May 14, 2002). (2) Ulber, R.; Faurie, R.; Sosnitza, P.; Fischer, L.; Stärk, E.; Arbeck, C.; Scheper, T. *J. Chromatogr., A* **2000**, *882*, 329. (3) Maier, N. M.; Pilar, F.; Lindner, W. *J. Chromatogr., A* **2001**, *906*, 3. (4) Goodall, D. M. *Trac-Trend Anal. Chem.* **1993**, *12*, 177; *Chem. Abstr.* **1993**, *119*, 155032m. (5) Huerta, F. F.; Minidis, A. B. E; Backvall, J. E. *Chem. Soc. Rev.* **2001**, *30*, 221. (6) Richards, C. J.; Locke, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2377. (7) Mosher, M. D.; Kelly, C. O.; Mosher, M. W. *J. Chem. Educ.* **1996**, *73*, 567. (8) Poiré, C.; Rabiller, C.; Chon, C.; Hudhomme, P. *J. Chem. Educ.* **1996**, *73*, 93. (9) National Institute of Standards and Technology (NIST). *Standard Reference Materials*; SRM No. 17e and 917b. http//www.srmcatalog.nist.gov/srmcatalog/tables/204-6.htm (accessed May 8, 2002). (10) Eggleston, G.; Vercelotti, J. R. *J. Carbohydr. Chem.* **2000**, *19*, 1305. (11) Yamabe, S.; Ishikawa, T. *J. Org. Chem.* **1999**, *64*, 4519. (12) Dippy, J. F. J.; Hughes, S. R. C.; Rozanski, A. *J. Chem. Soc.* **1959**, 2492. (13) Goss, C. A.; Wilson, D. C.; Welser, W. E. *Anal. Chem.* **1994**, *66*, 3093. (14) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: Oxford, U.K., 1988; p 215. (15) Milone, C.; Gangemi, C.; Neri, G.; Pistone, A.; Galvagno, S. *Appl. Catal. A, Gen.* **2000**, *199*, 239. (16) Veronese, P.; Li, X.; Niu, X. M.; Weller, S. C.; Bressan, R. A.; Hasegawa, P. M. *Plant Cell. Tiss. Organ Cult.* **2001**, *64*, 133. (17) For example, Aldrich Chemical Company. *Handbook of Fine Chemicals and Laboratory Equipment,* U.S. ed.; Milwaukee, WI, 2003–2004; p 1161, cat. no. M278-0. Also available at www.sigma-aldrich.com. (18) Brazilian standard pharmaceutical grade, which is equivalent to USP grade. The samples were obtained from Drogasil or Henrifarma). (19) Ligor, M.; Buszewski, B. *J. Chromatogr., A* **1999**, *847*, 161. (20) HP 5890 II gas chromatograph; HP5, cross-linked 5% methyl silicone capillary glass column (30 m x 0.32 mm x 0.25 μm); nitrogen carrier gas; the injector temperature (200 °C), the FID temperature (250 °C), and the heating program were the same as those reported by Ligor and Buszewski.

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Applications of Ionic Liquids in Organic Synthesis†

*Hua Zhao and Sanjay V. Malhotra**
Department of Chemistry and Environmental Science
New Jersey Institute of Technology
University Heights
Newark, NJ 07102, USA
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Outline

1. Introduction

An ionic liquid (IL) is a liquid consisting of ions only, but this definition is different from the classic definition of a molten salt.[1] The latter is a high-melting, highly viscous, and highly corrosive liquid, while an ionic liquid is liquid at a much lower temperature (< 100 °C) and has a lower viscosity. Currently, a major drive is underway in industry and academia to substitute more environmentally friendly technologies for traditional ones in which damaging and volatile organic solvents are heavily used. Ionic liquids are considered as environmentally friendly substitutes for volatile organic solvents, not only because of their low vapor pressures, but, more importantly, also because of their ability to act as catalysts. Moreover, ionic liquids possess several other attractive properties, including chemical and thermal stability, nonflammability, high ionic conductivity, and a wide electrochemical potential window.

Ambient-temperature, alkylpyridinium (RPy^+) chloroaluminate based ionic liquids were first reported in the early 1950s.[2] However, the report by Wilkes and co-workers[3a] of 1,3-dialkylimidazolium-based chloroaluminate ionic liquids, that possess favorable physical and electrochemical properties, provided the impetus for a dramatic increase in activity in this area.[3b] Ionic liquids usually consist of inorganic anions and nitrogen-containing organic cations, and their chemical and physical properties can be finely tuned for a range of applications by varying the cations or anions.[4] For example, varying the anion X in [EMIM][X] changes the melting point of the ionic liquid in the range of –14 to 87 °C.[5] The fact that they can now be produced with melting points at or below room temperature (as low as –96 °C) has been an important reason why ionic liquids have been explored in many applications.[1]

Recent reviews have surveyed the behavior of halogenoaluminate(III) ionic liquids in many reactions including dimerization, polymerization, and multiphase hydrogenation.[5,6] Since halogenoaluminate(III)-type ionic liquids are sensitive to moisture, their applications in chemical reactions have been limited. Stable, room-temperature ionic liquids (RTILs) have been studied in many chemical processes, for example, bio-processing operations,[7] as electrolytes in electrochemistry,[8,9] in gas separations such as the capturing of CO_2,[10] in liquid–liquid extractions,[11,12] and as heat-transfer fluids.[13] However, since most studies have employed ionic liquids as green solvents or catalysts for organic synthesis, this review will summarize recent research on the applications of RTILs in organic reactions.

2. Composition of Ionic Liquids

The most commonly used cations in room-temperature ionic liquids are alkylammonium, alkylphosphonium, *N*,*N*′-dialkylimidazolium ([RR′IM]), and *N*-alkylpyridinium ([RPy]) cations (**Figure 1**).[5] The most commonly utilized alkyl chains are methyl, ethyl, butyl, hexyl, octyl, and decyl. The most commonly investigated IL anions are shown in **Table 1**.[4,14-22]

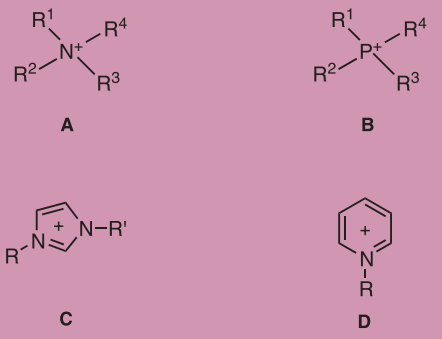
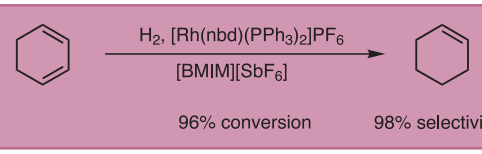


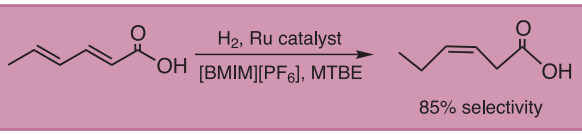
Figure 1. Important Cation Types in Room-Temperature Ionic Liquids.

Table 1. Examples of Anions Commonly Found in Ionic Liquids

Anion	Reference	Anion	Reference
BF_4^-	4	$(CF_3SO_2)_2N^-$	17
PF_6^-	14	$CF_3CO_2^-$	17
SbF_6^-	15	$HexBEt_3^-$	18
$CH_3CO_2^-$	4	OTs^-	19
HSO_4^-	16	$AuCl_4^-$	20
NO_3^-	4	$AlCl_4^-$	21
NO_2^-	4	Carborane anions	22
$CF_3SO_3^-$	17		



eq 1



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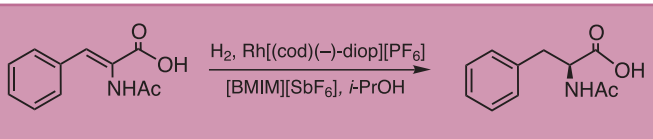

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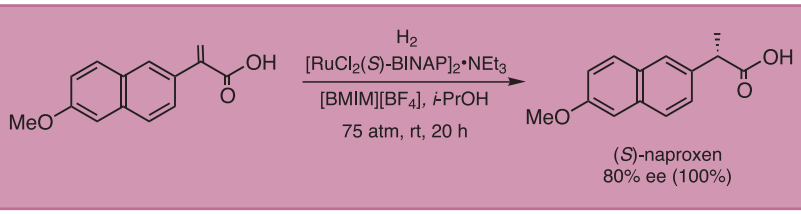


eq 4

3. Transition-Metal-Mediated Catalyses

3.1. Hydrogenation

Ionic liquids can dissolve organometallic compounds and provide a polar, weakly coordinating medium for transition-metal catalysts. In this case, ionic liquids are used as inert solvents or co-catalysts.

The [Rh(nbd)(PPh_3)$_2$][PF_6] (nbd = norbornadiene) catalyzed biphasic hydrogenation of 1-pentene in ionic liquids [BMIM][PF_6] (BMIM = 1-*n*-butyl-3-methylimidazolium) and [BMIM][SbF_6] was first reported in 1995 by Chauvin and co-workers.[23] The reaction rate in the IL was five times higher than the one obtained by using acetone as solvent. Furthermore, the catalyst solution in the ionic liquid was reused without significant loss of rhodium. Chauvin's group also reported a selective hydrogenation of 1,3-cyclohexadiene to cyclohexene (98% selectivity at 96% conversion) by taking advantage of the biphasic reaction system (**eq 1**):[24] the solubility of 1,3-cyclohexadiene in [BMIM][SbF_6] is about five times that of cyclohexene. It is worth noting that complete suppression of the hydrogenation activity was observed when ionic liquids containing Cl^- impurities were used.

Similarly, other rhodium- and cobalt-catalyzed hydrogenations, such as the hydrogenation of butadiene,[25] aromatic compounds,[26] or acrylonitrile–butadiene copolymers have been conducted successfully in ionic liquids.[27] More recently, a ruthenium-catalyzed stereoselective hydrogenation of sorbic acid to *cis*-3-hexenoic acid was performed in the biphasic [BMIM][PF_6]–MTBE system (**eq 2**).[28]

Enantioselective hydrogenation in ionic liquids has attracted special attention, since it provides a means for recycling metal complexes of expensive chiral ligands. In the presence of [Rh(cod)(–)-(diop)][PF_6] catalyst {cod = 1,3-cyclooctadiene; diop = 4,5-bis[(diphenylphosphanyl)methyl]-2,2-dimethyl-1,3-dioxolan-4,5-diol} in [BMIM][SbF_6], the enantioselective hydrogenation of α-acetamidocinnamic acid to (*S*)-phenylalanine was achieved with 64% enantiomeric excess (ee) (**eq 3**).[23]

Another successful example of enantioselective hydrogenation was reported by Monteiro et al., who used [$RuCl_2$(*S*)-BINAP]$_2$•NEt_3 as the chiral catalyst.[29] (*S*)-Naproxen was thus synthesized in 80% ee from 2-(6-methoxy-2-naphthyl)acrylic acid in [BMIM][BF_4] and isopropyl alcohol (**eq 4**).

Very recently, biphasic systems containing an ionic liquid and supercritical CO_2 ($scCO_2$) have been investigated for catalytic hydrogenation.[30,31] Tumas and co-workers[30] observed that the hydrogenation of olefins could be achieved in a biphasic [BMIM][PF_6]–$scCO_2$ system. The ionic liquid phase containing the catalyst was decanted and reused in up to four consecutive reactions. Jessop's group[31] performed the successful asymmetric hydrogenation of tiglic acid (**eq 5**) and the precursor of the anti-inflammatory drug ibuprofen (**eq 6**) by using Ru(OAc)$_2$((*R*)-tolBINAP) as catalyst. In both cases, the product was separated by $scCO_2$ extraction upon completion of the reaction.

Molecular hydrogen was found four times more soluble in [BMIM][BF_4] than in [BMIM][PF_6] at the same pressure.[32] Systematic studies of the effect of hydrogen concentration on enantioselectivity have been conducted by Berger et al. in the asymmetric hydrogenation of (*Z*)-α-acetamidocinnamic acid and the kinetic resolution of methyl (±)-3-hydroxy-2-methylenebutanoate by Rh(I) and Ru(II) catalysts.[32] The concentration of molecular hydrogen in the ionic liquid rather than its pressure in the gas phase was found to have the most significant influence on the conversion and enantioselectivity of these reactions.

3.2. Oxidation

Although ionic liquids are highly stable and have been evaluated as media for oxidation reactions,[17] surprisingly little attention has been focused on carrying out catalytic oxidations in ionic liquids. A recent publication by Song and Roh is one of the earliest studies of catalytic oxidations in ionic liquids.[33] In this study, asymmetric Jacobsen–Katsuki epoxidations were performed with NaOCl in [BMIM][PF_6] and were catalyzed by a chiral Mn complex (Jacobsen's catalyst) (**eq 7**). A clear improvement of the catalytic activity was observed by adding the ionic liquid to the dichloromethane solvent. The ionic liquid containing the catalyst was reused in four consecutive runs without significant loss in yield; however, after the 5th run, the conversion dropped from 83% to 53%. This drop in conversion is believed to be due to a degradation of the [Mn^{III}(salen)] complex.

Another example of catalytic oxidation is the methyltrioxorhenium (MTO)-catalyzed epoxidation of olefins with the urea–H_2O_2 adduct (UHP) in [EMIM][BF_4].[34] High conversions and yields were observed, except for 1-decene (46% conversion, > 99% yield), which was attributed to its lower solubility in the ionic liquid. In the case of sensitive epoxides, ring opening was observed in the presence of large amounts of water.

A more exciting study utilized a chiral Mn(salen) complex in [BMIM][PF_6] for the electroassisted biomimetic activation of molecular oxygen.[35] It was observed that a highly reactive oxomanganese(V) intermediate could transfer its oxygen to an olefin, which hints at a promising future for clean oxidations with molecular oxygen in ionic liquid media.

3.3. Hydroformylation

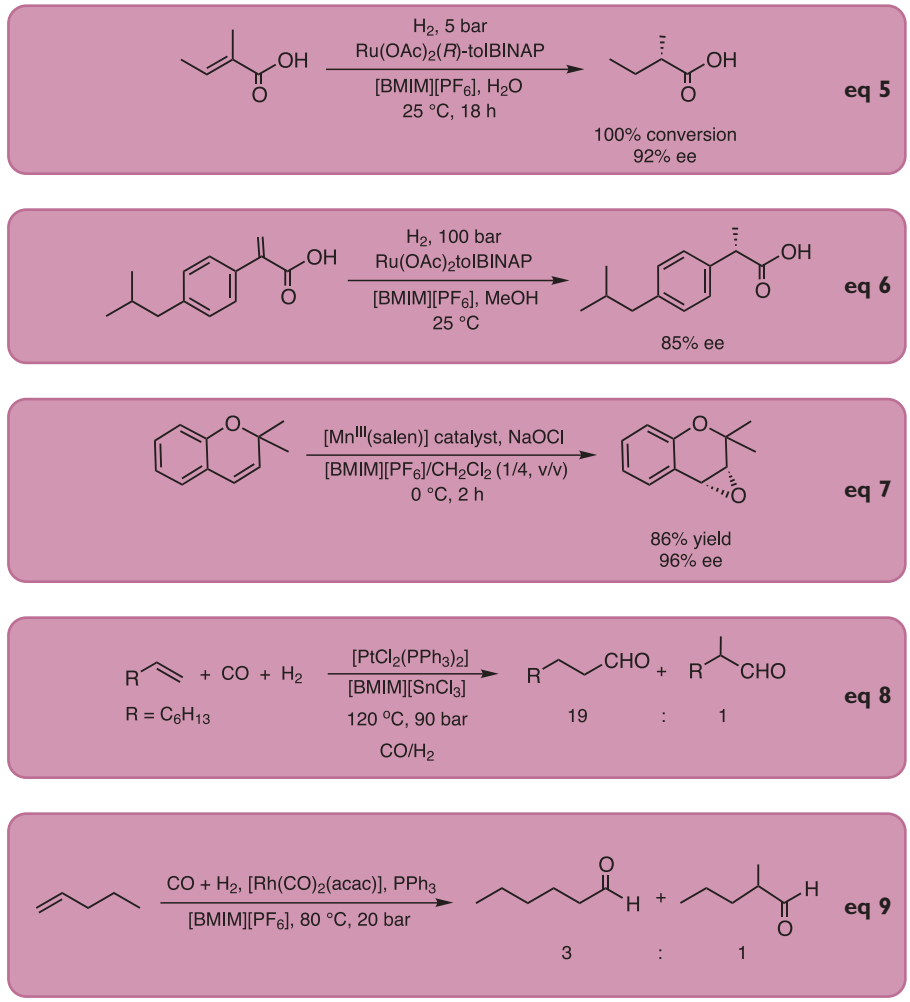
The platinum-catalyzed hydroformylation of ethene in tetraethylammonium trichlorostannate melts was conducted by Parshall as early as 1972.[36] The ionic liquid used in this case has a high melting point of 78 °C. Recently, Waffenschmidt and Wasserscheid reported the platinum-catalyzed hydroformylation of 1-octene in the room-temperature ionic liquid [BMIM][$SnCl_3$] (**eq 8**).[37] This biphasic system offered the advantage of simple product isolation and easy recovery of the platinum catalyst.

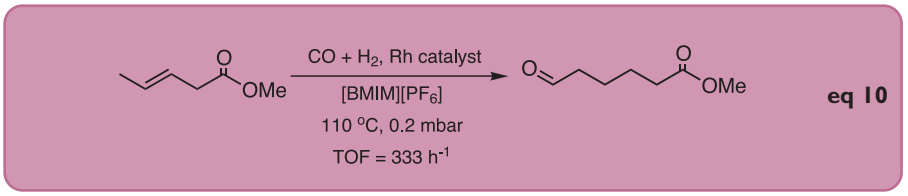
The ruthenium- and cobalt-catalyzed hydroformylation of internal and terminal alkenes in molten tetra-*n*-butylphosphonium bromide was reported by Knifton in 1987.[38] The rhodium-catalyzed hydroformylation of 1-hexene was investigated in higher-melting phosphonium tosylates, such as [Bu_3PEt][TsO] (mp 81–83 °C) and [Ph_3PEt][TsO] (mp 94–95 °C).[39] The product was easily separated from the solid catalyst medium at room temperature, and the catalyst was reused without loss of activity.

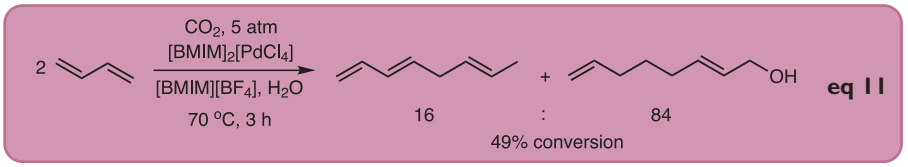
By employing room-temperature ionic liquid [BMIM][PF_6] as the reaction medium, the rhodium-catalyzed hydroformylation of 1-pentene was performed by Chauvin et al. (**eq 9**).[23] A higher activity [turnover frequency (TOF) = 333 h^{-1}] was observed as compared to the same reaction in toluene (TOF = 297 h^{-1}). Another report also indicated that a higher activity (TOF = 810 h^{-1}) and higher regioselectivity (*n/iso* = 16) were possible in the biphasic hydroformylation of 1-octene in [BMIM][PF_6] using a Rh-based catalyst.[40] Catalyst loss in the organic phase was less than 0.5%, and the ionic liquid catalyst solution was recycled. A high regioselectivity (20:1) was also obtained in the hydroformylation of 1-octene in [BMIM][PF_6] by using cationic guanidine-modified diphosphine ligands containing a xanthene backbone.[41]

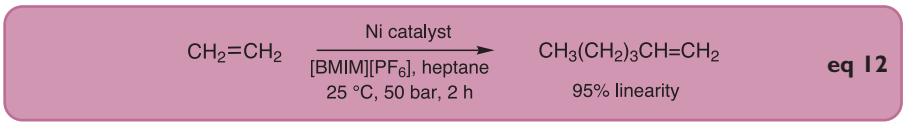
Not only have the biphasic hydroformylation reactions in ionic liquids shown their process advantages, but so has the rhodium-catalyzed monophasic reaction of methyl 3-pentenoate in [BMIM][PF_6] (**eq 10**).[42] The recovered catalyst was reused ten times under the same conditions without loss of activity.

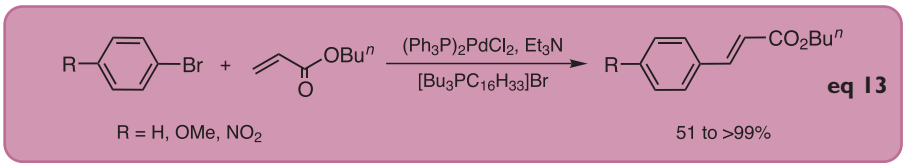
An interesting continuous flow process was utilized for the rhodium-catalyzed biphasic hydroformylation of 1-octene in [BMIM][PF_6]–$scCO_2$.[43] The product was synthesized at a fixed rate for 72 h with *n/iso* regioselectivity of 3.8, and only <1 ppm of Rh was lost in the organic phase.

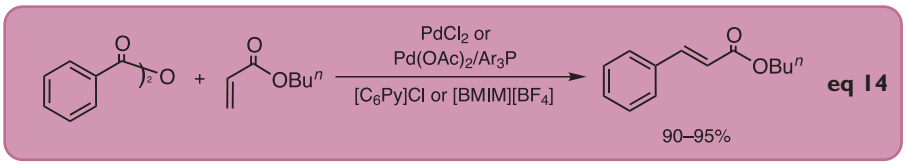


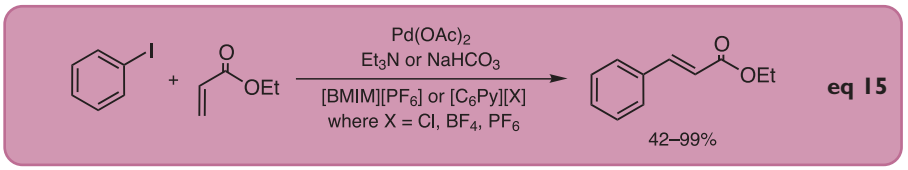












3.4. Hydrodimerization

Nickel(II)-catalyzed dimerization reactions in ionic liquids were first investigated in chloroaluminate(III) ionic liquid [BMIM][$AlCl_4$].[44] The product hexenes were separated from the ionic liquid by decantation. Due to the dissociation of ionic metal complexes caused by ionic liquids, it was believed that the ionic liquids were beneficial for the reactions. This application was extended to the oligomerization of butenes[45] and to the selective dimerization of ethene.[46]

Hydrodimerizations in ionic liquids can have many advantages over traditional hydrodimerizations, including higher selectivity for dimers due to their low solubility in ionic liquids, smaller reactor size, lower disposal costs, absence of corrosion, and wider applicability to less reactive and higher olefins.[15]

In recent years, chloroaluminate-free ionic liquids have become a new development in hydrodimerizations, because these new types of ionic liquids are more stable and easier to handle than the moisture-sensitive chloroaluminate(III) ionic melts. For example, [BMIM][BF_4] in water (1:1 v/v) was investigated in the hydrodimerization of 1,3-butadiene catalyzed by [BMIM]$_2$[$PdCl_4$].[47] In addition to the dimer, 1,3,6-octatriene, 2,7-octadienol was also produced (**eq 11**). However, by using $PdCl_2$/Ph_3P (1:4) as catalyst in [BMIM][X] (X = BF_4^-, PF_6^-, $CF_3SO_3^-$), the dimer, 1,3,6-octatriene, was obtained exclusively.[48]

Nickel(II)-catalyzed hydrodimerization reactions have also been studied in room-temperature ionic liquids. Wasserscheid and co-workers obtained a dimer selectivity of 98% and a TOF of 1240 h^{-1} at 25 °C in the linear dimerization (64% linearity) of 1-butene.[5,49] Recently, Wasserscheid, Gordon, and their co-workers also reported a biphasic oligomerization of ethene to higher α-olefins by nickel complexes in [BMIM][PF_6] (**eq 12**).[50] The product was separated easily as a clear layer, and the catalyst-containing ionic liquid layer was recovered without any detectable loss of catalyst activity.

3.5. Heck Reaction

The first use of ionic liquids as reaction media for the palladium-catalyzed Heck coupling was reported by Kaufmann et al. in 1996.[51] Moderate-to-high yields of butyl *trans*-cinnamates were obtained in molten tetraalkylammonium and tetraalkylphosphonium bromides by reaction of bromobenzenes with butyl acrylate (**eq 13**). The ionic liquid is believed to stabilize the palladium catalyst, and, in most reactions, no precipitation of palladium was observed even after complete conversion of the aromatic halide to the product.

Bohm and Hermann have extended this work to low-melting salts.[52] Their results indicate that molten [NBu_4][Br] (mp 103 °C) performs better in the Heck reaction than organic solvents such as DMF. In the reaction of bromobenzene with styrene, the yield of stilbene is increased from 20% in DMF to 99% in [NBu_4][Br] by using diiodobis(1,3-dimethylimidazolium-2-ylidene)palladium(II) as catalyst. Additional advantages of this solvent are the excellent solubility of all reacting molecules in it and its possible application as an inexpensive inorganic base. The authors also claim that the use of ionic liquids could become part of a standard method for carrying out Heck reactions in the future.

Earle, Seddon, and their co-workers described Heck couplings in [BMIM][PF_6] or *n*-hexylpyridinium hexafluorophosphate by using $PdCl_2$ or $Pd(OAc)_2$/Ar_3P as the catalyst (**eq 14**, **15**).[53] They reported a workup procedure in the three-phase system [BMIM][PF_6]/water/hexane. The products were soluble in the organic phase, while the used catalyst remained in the ionic layer. The salt formed as a by-product, [Hbase]X, dissolved in the aqueous phase.

The in situ identification of N-heterocyclic carbene complexes of palladium was performed by Xiao's group.[54] It was observed that [BMIM][Br] is more efficient in improving the Heck reaction rate than [BMIM][BF_4]. Two catalyst complexes, [PdBr(μ-Br)(bmiy)]$_2$ and [$PdBr_2$(bmiy)]$_2$, were isolated in [BMIM][Br] but not in [BMIM][BF_4] under the same reaction conditions. It was presumed that the stronger basicity of bromide as compared to tetrafluoroborate was a major factor in the formation of the carbene in [BMIM][Br]. Recently, Xiao and co-workers obtained >99% regioselectivity for the α-arylation

product in the Heck coupling of 1-bromonaphthalene with butyl vinyl ether in [BMIM][BF_4].[55] Similarly, [BMIM][BF_4] and [BMIM][PF_6] have also been employed in the palladium-catalyzed Stille[56] and Negishi couplings,[57] and in the nickel-catalyzed coupling of aryl halides.[58]

Other recent studies of the Heck coupling in ionic liquids include the Heck reaction of β-substituted acrylates in [NBu_4][Br] catalyzed by a palladium–benzothiazole carbene complex,[59] and the synthesis of pterocarpans by a Heck–oxyarylation reaction sequence in [BMIM][PF_6] in the presence of [$PdCl_2(PhCN)_2$]/Ph_3P/Ag_2CO_3 as the catalyst system.[60]

3.6. Alkoxycarbonylation

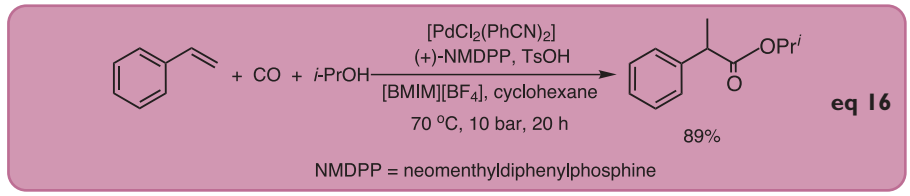
Carbonylation reactions in ionic liquids have received much less attention than the previously discussed transition-metal-catalyzed reactions. An example of palladium-catalyzed alkoxycarbonylation of styrene was reported by Monteiro and co-workers (**eq 16**).[61] In the reaction medium [BMIM][BF_4]/cyclohexane, styrene reacted with isopropyl alcohol and carbon monoxide to form isopropyl 2-phenylpropionate. Using (+)-neomenthyldiphenylphosphine [(+)-NMDPP] as ligand, the product was obtained in 89% yield and 99.5% regioselectivity, but with a very low asymmetric induction (ee < 5%).

A study of the palladium-catalyzed alkoxycarbonylation of aryl bromides and iodides in [BMIM][BF_4] and [BMIM][PF_6] was reported by Mizushima et al.,[62] who observed improved reactivities in the ionic liquids.

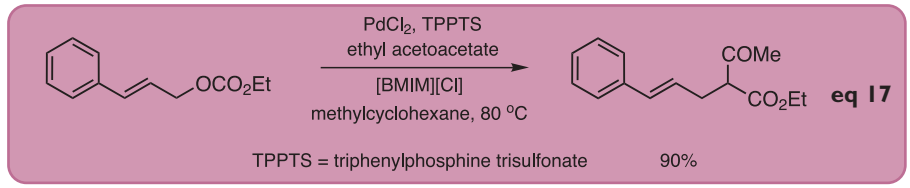
3.7. Trost–Tsuji Coupling

The Trost–Tsuji coupling is an important method for synthesizing carbon–carbon bonds through nucleophilic, allylic substitution. An interesting example is the monophasic reaction of 3-acetoxy-1,3-diphenylpropene with dimethyl malonate in [BMIM][BF_4].[63] The product is obtained in 91% yield after 5 h at room temperature using $Pd(OAc)_2$/PPh_3 as the catalyst system and K_2CO_3 as the base.

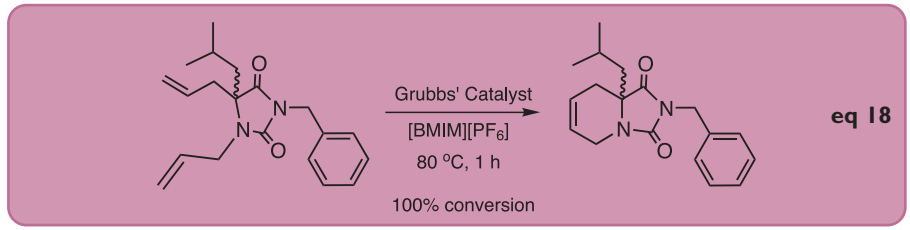
Biphasic Trost–Tsuji couplings have been conducted by de Bellefon et al. in [BMIM][Cl]/methylcyclohexane.[64] These workers observed a tenfold improvement in the catalytic activity due to the higher solubility of the substrates in the ionic liquid (**eq 17**). Enhanced selectivity was also achieved, since the formation of cinnamyl alcohol and phosphonium salts was suppressed.



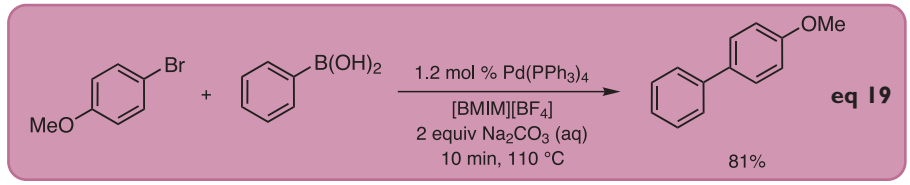
eq 16



eq 17



eq 18



eq 19

3.8. Ring-Closing Metathesis (RCM)

Ring-closing metathesis (RCM) is widely recognized as a powerful method for creating heterocycles, constrained peptides, and complex natural products.[65] [BMIM][PF_6] was used as an effective medium for ring-closing metathesis (RCM) that is induced by Grubbs' catalysts (**eq 18**).[66] After extraction of the product, [BMIM][PF_6] and the ruthenium catalyst were reused for three cycles. High conversions and a broad substrate tolerance were observed.

3.9. Suzuki Cross-Coupling

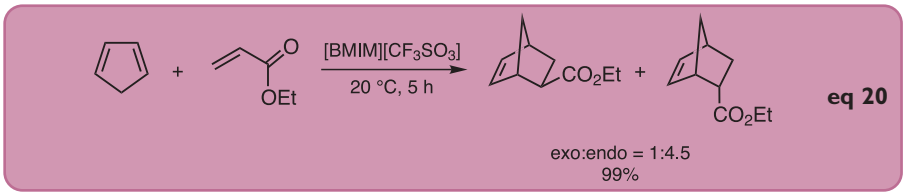
The Suzuki cross-coupling reaction is another versatile method for generating new carbon–carbon bonds. However, the traditional reaction suffers from several drawbacks such as incorporation of the catalyst into the product, decomposition of the catalyst, and/or poor reagent solubility. In order to overcome these drawbacks, a study of the palladium-catalyzed Suzuki cross-coupling reaction of aryl halides with arylboronic acids has recently been conducted in the room-temperature ionic liquid [BMIM][BF_4] (**eq 19**). Unprecedented reactivities were observed in addition to the easy isolation of product and recovery of catalyst.[67] This study identified several advantages of the Suzuki cross-coupling carried out in ionic liquids, namely: (a) a significant increase in reactivity is observed at a reduced catalyst concentration, especially for nonactivated aryl bromides; (b) homocoupling is avoided; (c) the reaction can be conducted under air without loss of yield or degradation of catalyst; and (d) repetitive runs can be performed without loss of catalyst activity.

4. Other Organic Reactions

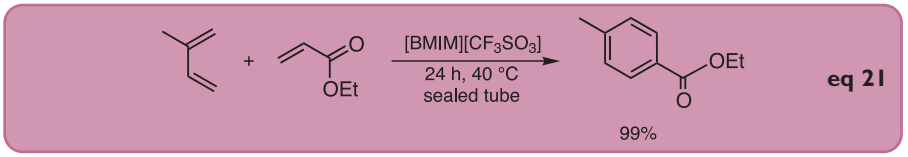
4.1. Diels–Alder Reaction

An early study of the Diels–Alder reaction of cyclopentadiene with methyl acrylate or methyl vinyl ketone in [$EtNH_3$][NO_3] was reported in 1989.[68] Although the reaction rate and selectivity were lower than those in water, the study showed that ionic liquids could be employed in this type of reaction. Encouraged by these findings, Diels–Alder reactions were conducted in several other ionic liquids such as [EMIM][PF_6],[69,70] [EMIM][BF_4],[70] [EMIM][CF_3SO_3],[70] [BMIM][ClO_4],[69] [EMIM][Cl]–$AlCl_3$,[71] and [BMIM][CF_3SO_3].[72] Two examples of these reactions are illustrated in **eq 20** and **21**.[72]

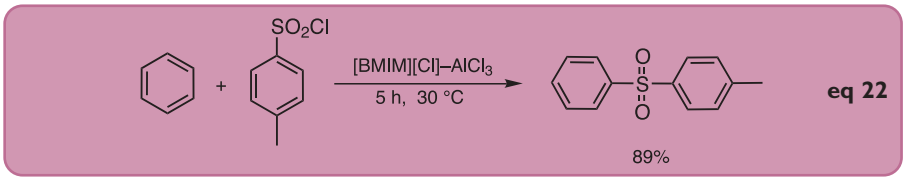
The use of $LiClO_4$ in diethyl ether has become one of the biggest developments in Diels–Alder chemistry. The $LiClO_4$–Et_2O



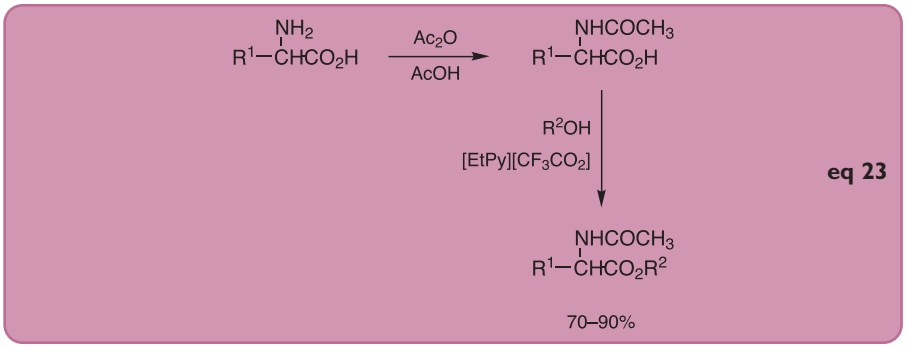
eq 20



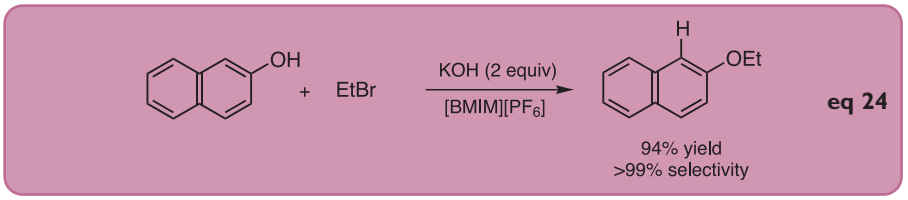
eq 21



eq 22



eq 23



eq 24

system can accelerate the Diels–Alder reaction due to the high concentration of electrolyte. By using ionic liquids instead of $LiClO_4$–Et_2O, reactivities can be improved and the need for potentially explosive perchlorate-based reaction media is eliminated.[72]

A recent study of the scandium triflate catalyzed Diels–Alder reaction investigated the use of ionic liquids as polar media for facilitating catalyst recovery and increasing reaction rate and selectivity.[73] For example, when 1,4-naphthoquinone was dissolved in [BMIM][PF_6] and reacted with 1,3-dimethylbutadiene in the presence of $Sc(OTf)_3$, the corresponding product was obtained in > 99% yield.

4.2. Friedel–Crafts Reaction

Friedel–Crafts acylations are of industrial importance and are associated with a massive consumption of aluminum(III) chloride. It has been demonstrated that acylation reactions can be carried out in acidic chloroaluminate(III) ionic liquids.[74,75] The regioselectivities and rates observed in these reactions are comparable to the best values known for the traditional acylations. The Friedel–Crafts acylation of benzene has been conducted in acidic chloroaluminate(III) ionic liquid.[75] The monoacylated products were obtained as a result of the deactivation of the aromatic ring by the acyl substituent. In addition to benzene and other simple aromatic rings, a range of organic and organometallic substrates (e.g., ferrocene) have been acylated in acidic chloroaluminate(III) ionic liquids.[76,77]

An in situ IR spectroscopic study was performed on the Friedel–Crafts acetylation of benzene in ionic liquids using $AlCl_3$ and $FeCl_3$.[78] The results revealed that the mechanism of the Friedel–Crafts acetylation of benzene in ionic liquids was exactly the same as that in 1,2-dichloroethane.

Another interesting development is the use of [BMIM][chloroaluminate] as Lewis acid catalyst for the Friedel–Crafts sulfonylation of benzene and substituted benzenes with TsCl (**eq 22**).[79] The substrates exhibited enhanced reactivity, and furnished the corresponding unsymmetrical diaryl sulfones in 83–91% yields under ambient conditions.

4.3. Esterification

Esterifications of alcohols and acetic acids in the room-temperature ionic liquid 1-butylpyridinium chloride–aluminum(III) chloride as a "green" catalyst have been reported by Deng et al.[80] Satisfactory conversions and selectivities were obtained, and most of the ester products were easily recovered due to their immiscibility with the ionic liquid.

Amino acid esters are very important intermediates in the chemical and pharmaceutical industry. They are usually difficult to prepare because amino acids exist as zwitterions (dipolar ions), in which the carboxyl group is not in the free form. Our group has recently developed a successful method for synthesizing amino acid esters using [EtPy][CF_3CO_2] (EtPy = *N*-ethylpyridinium) as a "green" catalyst.[81] Excellent conversions have generally been achieved for the ethyl and isopropyl esters of many amino acids (**eq 23**).

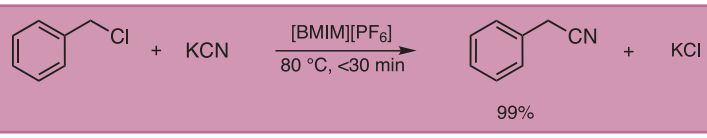
4.4. Regioselective Alkylation

Alkylation of indole or 2-naphthol is usually achieved by preformation of the ambident indolate[82] or 2-naphtholate[83] anion and subsequent treatment with alkyl halide. Regioselective alkylation at the heteroatom of these anions is solvent-dependent, and can be achieved by using a dipolar aprotic solvent such as DMF.[83,84] As an environmentally friendly alternative, [BMIM][PF_6] has been utilized for the regioselective alkylation at the heteroatom of indole and 2-naphthol (**eq 24**).[85] Advantages of this process include simple operation, easy product isolation, no measurable solvent vapor pressure, high regioselectivity, and the potential for recycling the solvent.

4.5. Displacement Reaction with Cyanide

Nucleophilic displacement reactions are often achieved using phase-transfer catalysis (PTC) to facilitate reaction between the organic reactants and the inorganic ionic

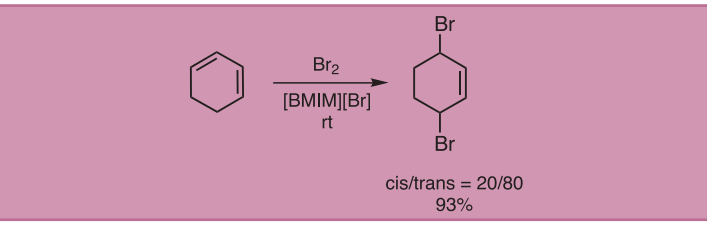
salts that provide the nucleophiles.[86] In conventional PTC, the typical organic solvents used, such as dichloroethane or *o*-dichlorobenzene, are environmentally undesirable. In addition, catalyst separation and recovery are very difficult. It has been demonstrated that the use of room-temperature ionic liquids as catalytic, environmentally benign solvents for the displacement of benzylic chloride with cyanide can replace phase-transfer-catalyzed biphasic systems (**eq 25**).[87] This eliminates the need for a volatile organic solvent and hazardous catalyst disposal.



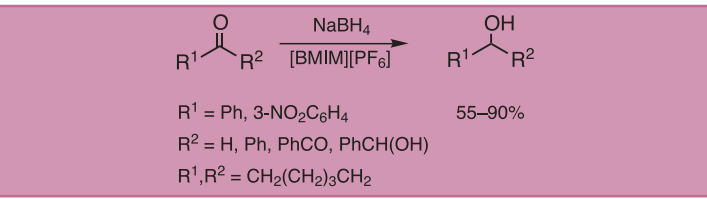
eq 25

4.6. Stereoselective Halogenation

The analysis of alkenes in a complex hydrocarbon mixture, such as gasoline, is a difficult process. The analysis of alkenes in the presence of alkanes, however, can be achieved after their transformation into the corresponding dihalo derivatives.[88] Several ionic liquids—[BMIM][PF_6], [BMIM][BF_4], [BMIM][Br], and [BMIM][Cl]—have been studied as alternatives to toxic chlorinated solvents for the stereoselective halogenation of alkenes and alkynes (**eq 26**).[89]



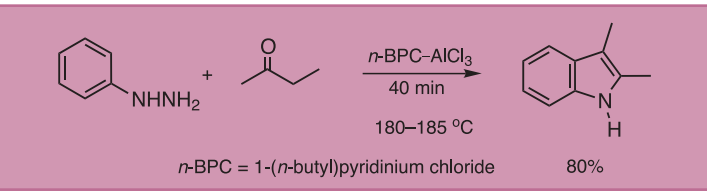
eq 26



eq 27

4.7. Reduction of Aldehydes and Ketones

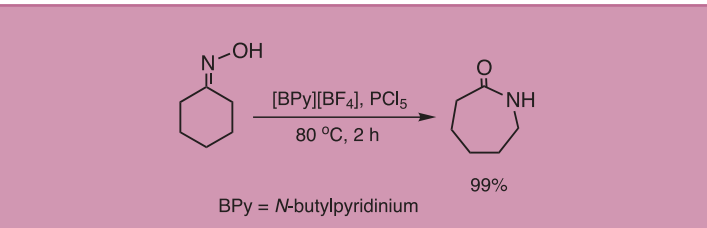
Howarth et al. have investigated the reduction of aldehydes and ketones with $NaBH_4$ in [BMIM][PF_6].[90] In this study, six common aldehydes and ketones were converted into the corresponding alcohols in moderate-to-high yields (**eq 27**). The ionic liquid was recycled, and, in some cases, the product alcohol was distilled directly from the ionic liquid.



eq 28

4.8. Fischer Indole Synthesis

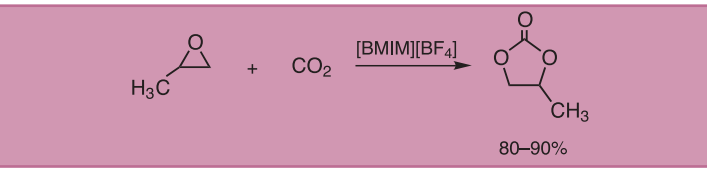
The Fischer indole synthesis using a chloroaluminate ionic liquid both as a solvent and catalyst was achieved with product yields in the 41–92% range (**eq 28**).[91] The amount of $AlCl_3$ used was much less than that of other reported catalysts such as $ZnCl_2$ or PPA, and the procedure followed proved safer with respect to the amount of catalyst employed, its hazard, and cost.



eq 29

4.9. Beckmann Rearrangement

The Beckmann rearrangement is typically carried out in strong Brønsted or Lewis acids, such as concentrated sulfuric acid, phosphorus pentachloride in ether, or hydrogen chloride in a mixture of acetic acid and acetic anhydride. These conditions give rise to significant amounts of by-products and serious corrosion problems.[92] In a recent study by Peng and Deng,[93] the catalytic Beckmann rearrangement of several ketoximes was achieved with satisfactory conversion and selectivity in 1,3-dialkyl-imidazolium or alkylpyridinium salts and phosphorated compounds (PCl_5, $POCl_3$, or P_2O_5) (**eq 29**).



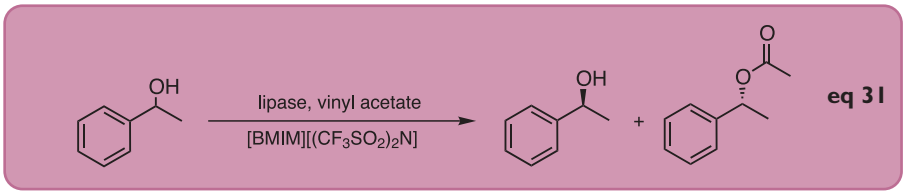
eq 30

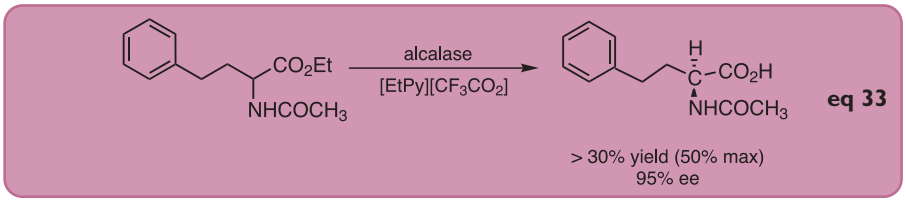
4.10. Cycloaddition

The cycloaddition of propylene oxide (PO) and carbon dioxide has been conducted in ionic liquids based on [BMIM] or [BPy] salts and in the absence of any organic solvent. Optimal results were obtained with [BMIM][BF_4] as catalyst (**eq 30**).[94] It was found that both the cations and anions of the room-temperature ionic liquids exerted a strong influence on catalytic activity, and a suitable CO_2/PO molar ratio was required for the reaction. The conversion of propylene oxide increased with increasing reaction temperature, and the ionic liquid catalyst was recycled.

5. Biocatalysis in Ionic Liquids

In recent years, a lot of attention has been focused on enzymatic reactions in ionic liquids. As early as 1984, it was observed that the enzyme alkaline phosphatase is relatively stable in a 4:1 (v/v) mixture of triethylammonium nitrate and water.[95] Erbeldinger et al. reported the first enzymatic synthesis of *Z*-aspartame in [BMIM][PF_6] containing 5% (v/v) water.[96] The enzyme





thermolysin exhibited excellent stability and a competitive rate in the same ionic liquid as compared to the enzymatic reaction in organic solvents.

Lipase has frequently been reported as a biocatalyst of organic reactions in ionic liquids. Nine lipases were investigated for the dynamic kinetic resolution of 1-phenylethanol by transesterification in various ionic liquids.[97] Improved enantioselectivities were observed as compared to when these same reactions were carried out in MTBE (**eq 31**). Kim et al. also obtained enhanced enantioselectivities in the transesterifications of alcohols using lipase in [BMIM][BF_4] and [BMIM][PF_6].[98] In the lipase-catalyzed enantioselective acylation of allylic alcohols in [BMIM][X] (X = PF_6^-, $CF_3CO_2^-$, TsO^-, SbF_6^-), Itoh et al. found that the anions of the imidazolium salts had a significant influence on the outcome of the reaction (**eq 32**).[99]

More systematic studies on lipase-catalyzed enantio- and regioselective acylations were conducted by Park and Kazlauskas in several imidazolium- and *N*-alkylpyridinium-based ionic liquids.[100] In these studies, the *Pseudomonas cepacia* lipase (PCL) catalyzed acylation of 1-phenylethanol with vinyl acetate proceeded with high enantioselectivity. Regioselective acetylation of β-D-glucose in ionic liquids yielded more 6-*O*-acetylglucose than 3,6-*O*-diacetylglucose (13–50:1), while the acetylation in organic solvents gave a selectivity of only 2–3:1. The epoxidation of cyclohexene by peroxyoctanoic acid, generated in situ by the immobilized enzyme Novozyme® 435 catalyzed reaction of octanoic acid with 60% aqueous H_2O_2, was achieved successfully.[101] Another study showed that the enantioselectivity of a lipase-catalyzed kinetic resolution could be increased at higher temperatures.[102] This study indicated that, for a galactosidase-catalyzed synthesis of a disaccharide, the secondary hydrolysis was suppressed thus doubling the yield. It was also observed that three different lipases exhibited both excellent activity and stability in the synthesis of an ester in [BMIM][PF_6].[103]

Recently, we showed that high enantioselectivities and yields could be achieved in the kinetic resolution of amino acid esters such as that of homophenylalanine in [EtPy][CF_3CO_2] by using the enzyme *Bacillus licheniforms* alcalase (**eq 33**).[104] This same alcalase also exhibited high selectivity and activity in low concentrations of ionic liquid in water.

6. Summary

The use of ionic liquids as solvents or catalysts has a profound effect on the observed activities and selectivities. As a result, there is growing interest in developing applications for them in a wide range of synthetic reactions. The present review was not designed to be comprehensive, but rather to summarize some of the recent advances in the application of ionic liquids in organic synthesis. We hope that readers will find it helpful in their day-to-day work.

7. References and Notes

(†) This review is dedicated to Professor Herbert C. Brown on his 90th birthday.

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Hua Zhao received both his B.S. degree in chemistry and M.S. degree in chemical engineering from Tianjin University (China). In 2002, he obtained his Ph.D. degree in chemical engineering from the New Jersey Institute of Technology under the direction of Professor Sanjay Malhotra. His research interests are focused on the study of ionic liquids in enzymatic reactions.

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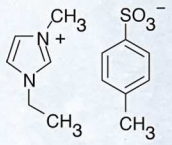
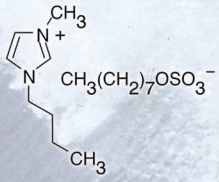
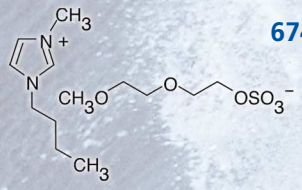


89155 1-Ethyl-3-methylimidazolium tosylate, [EMIM][Ts], purum, ≥98.0%
M_w 282.35 $C_{13}H_{18}N_2O_3S$ 5g; 50g



75059 1-Butyl-3-methylimidazolium octyl sulfate, [BMIM][$OctSO_4$], purum, ≥98.0%
M_w 348.50 $C_{16}H_{32}N_2O_4S$ 5g; 50g



67421 1-Butyl-3-methylimidazolium 2-(2-methoxyethoxy)ethyl sulfate, [BMIM][$MEESO_4$], ≥98.0%
M_w 338.42 $C_{13}H_{26}N_2O_6S$ 5g; 50g

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These contain highly fluorinated, hydrophobic anions, which create stable and absolutely water-immiscible ionic liquids for two-phase applications.

39056 1-Ethyl-3-methylimidazolium bis(pentafluoroethylsulfonyl)imide, [EMIM][BEtI], purum, ≥97.0%
M_w 491.33 [216299-76-2] $C_{10}H_{11}F_{10}N_3O_4S_2$ 1g; 5g

11291 1-Ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imidate, [EMIM][BMeI], purum, ≥97.0%
M_w 391.31 [174899-82-2} $C_8H_{11}F_6N_3O_4S_2$ 1g; 5g

50807 1,2-Dimethyl-3-propylimidazolium bis(trifluoromethylsulfonyl)imide, [DMPIM][BMeI], purum, ≥97.0%
M_w 419.36 [169051-76-7] $C_{10}H_{15}F_6N_3O_4S_2$ 1g; 5g

14654 1-Butyl-3-methylpyridinium bis(trifluoromethylsulfonyl)imide, [BMPy][BMeI], purum, ≥97.0%
M_w 316.40 [344790-86-9] $C_{12}H_{16}N_2O_4S_2$ 1g; 5g

30565 3-Methyl-1-propylpyridinium bis(trifluoromethylsulfonyl)imide, [PMPy][BMeI], purum, ≥97.0%
M_w 302.37 $C_{11}H_{14}N_2O_4S_2$ 1g; 5g

74305 1,2-Dimethyl-3-propylimidazolium tris(trifluoromethylsulfonyl)methide, [DMPIM][TMeM], purum, ≥97.0%
M_w 550.44 [169051-77-8] $C_{12}H_{15}F_9N_2O_6S_3$ 1g; 2.5g

* Products protected by U.S. Patent 5,827,602 assigned to Covalent Associates, Inc.

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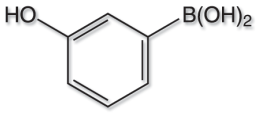
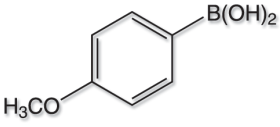


52,396-8 3-Hydroxyphenylboronic acid
CAS # 87199-18-6
MDL # 1074603



41,759-9 4-Methoxyphenylboronic acid
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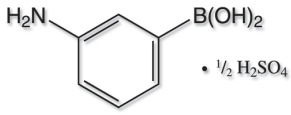
MDL # 39139



A7,175-1 3-Aminophenylboronic acid hemisulfate
CAS # 66472-86-4
MDL # 13111

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57,635-2 **Indium tin oxide coated glass slide**, 70–100-ohm resistance

57,827-4 **Indium tin oxide coated glass slide**, 8–12-ohm resistance

57,636-0 **Indium tin oxide coated aluminosilicate slide**, 5–15-ohm resistance

Product Number	57,635-2, 57,827-4	57,636-0
Slide Dimensions	25 x 75 x 1.1 mm	25 x 75 x 1.1 mm
Refractive Index	1.517	1.5290–1.5460
Strain Point	523 °C	666 °C
Typical Composition	72.6% SiO_2, 0.8% B_2O_3, 1.7% Al_2O_3, 4.6% CaO, 3.6% MgO, and 15.2% Na_2O	55.0% SiO_2, 7.0% B_2O_3, 10.4% Al_2O_3, 21.0% CaO, and 1.0% Na_2O
Passivation	passivated with 200+ Å SiO_2 applied directly to the glass slide prior to coating with ITO	no passivation layer is used, the ITO is applied directly to the substrate

Resistance is a factor of ITO thickness:

- 70–100 ohms = 150–300 Å ITO coating with a typical transmittance of 87%.

  Resistance may increase to as high as 375 ohms when exposed to temperatures of 300 °C for 30 minutes or more.

- 5–15 ohms = 1200–1600 Å ITO coating with a typical transmittance of 84%.

  Resistance may increase to as high as 30 ohms when exposed to temperatures of 300 °C for 30 minutes or more.

(1) Yan, C. et al. *Langmuir* **2000**, *16*, 6208. (2) Purvis, K.L. et al. *J. Am. Chem. Soc.* **2000**, *122*, 1808. (3) Biyikli, N. et al. *Appl. Phys. Lett.* **2001**, *79*, 2838. (4) Itoh, K. et al. *J. Phys. Chem.* **1988**, *92*, 7043. (5) Moriguchi, I. et al. *Chem. Mater.* **1998**, *10*, 2005. (6) Amako, J. et al. *Opt. Rev.* **1998**, *5*, 83. (7) Choi, W.B. et al. *Appl. Phys. Lett.* **1999**, *75*, 3129.

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Novel Methods of Resolving Racemic Diols and Amino Alcohols

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School of Chemistry
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Hyderabad – 500046, INDIA
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Outline

1. Introduction

In recent years, chiral amino alcohols and diols such as **1**[1,2], **2**,[3] and **3**[4] have been widely used as ligands to prepare catalysts employed in asymmetric synthesis. Whereas (*S*)-diphenylprolinol (**1**) and the chiral TADDOL derivative **2** can be readily synthesized starting from naturally occurring (*S*)-proline and (*R,R*)-tartaric acid, respectively, the widely used bi-2-naphthol (**3**) cannot be prepared starting from such natural chiral pool building blocks. Moreover, both enantiomers of any required starting material are generally not available from natural sources. Accordingly, there have been sustained efforts to develop synthetic methods for such useful chiral diols and amino alcohols.

While an asymmetric transformation may be contemplated for a crucial step in a multistep synthesis, the preparation of a racemic mixture followed by resolution can still be a viable and straightforward alternative, especially when both enantiomers are required. In recent years, very little effort has been made toward the development of new resolution methods for obtaining enantiomerically pure organic compounds, as compared to the immense efforts that have been spent toward the development of new asymmetric synthetic methods. Accordingly, we have undertaken research aimed at developing new resolution methods for diols and amino alcohols in order to facilitate the synthetic applications of these important compounds. In this review, recent developments in the methods of synthesis and resolution of some chiral diols and amino alcohols are surveyed.

2. Racemic Diols

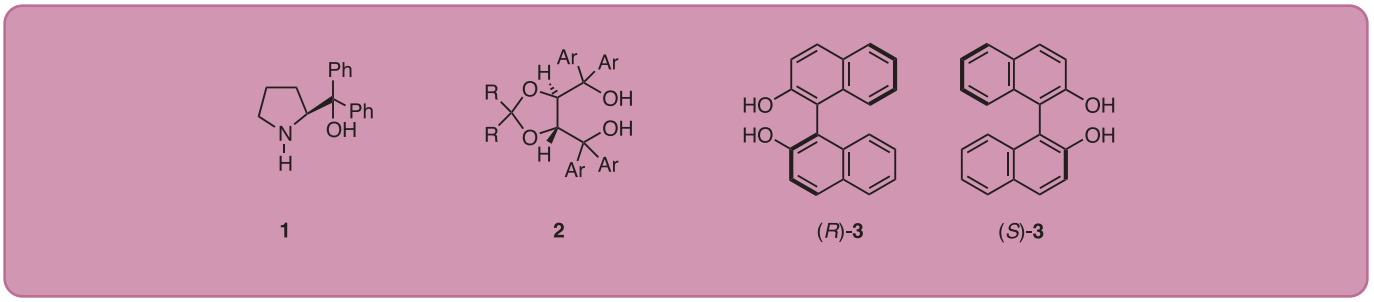
2.1. Resolution of Bi-2-naphthol

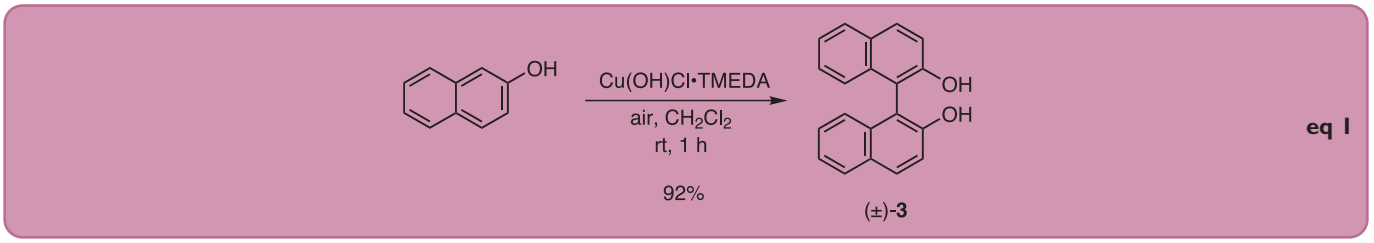
2.1.1. Via Diastereomeric Cyclic Phosphates

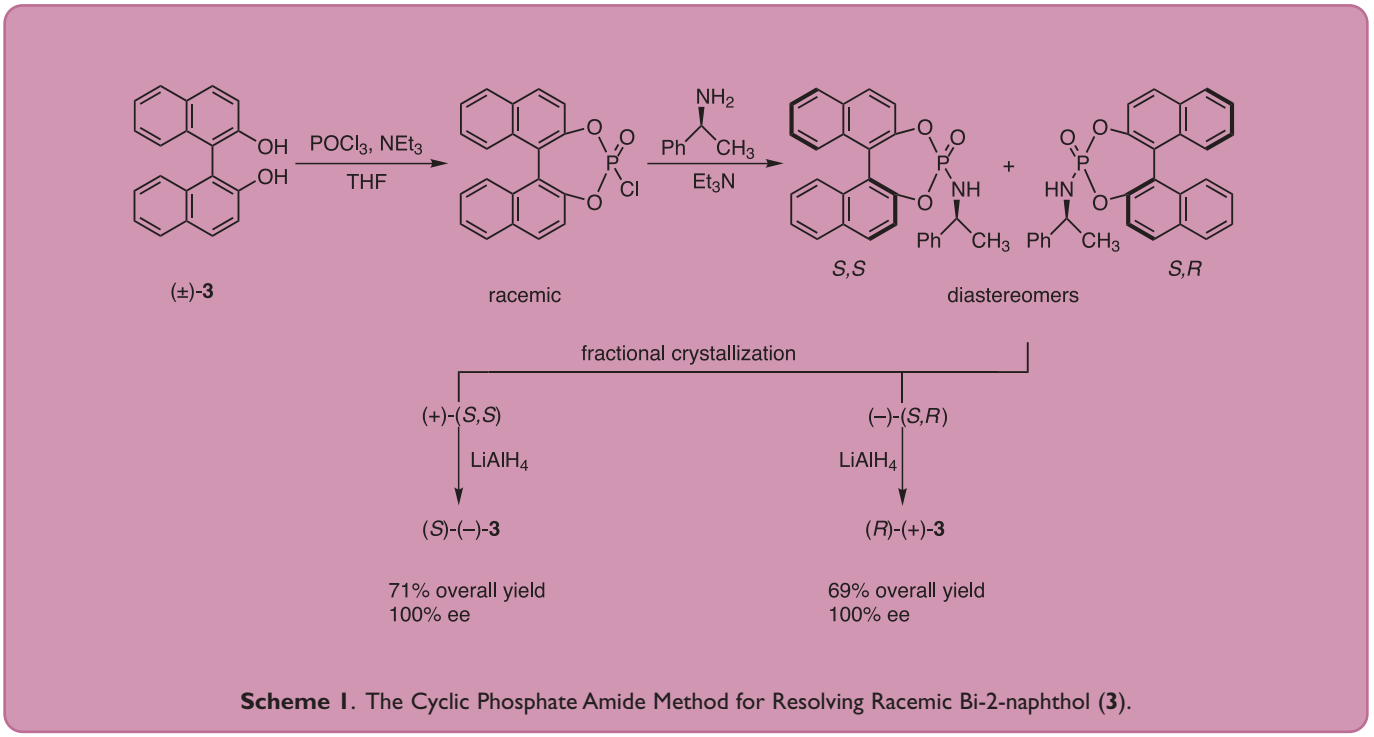
Even though asymmetric syntheses of bi-2-naphthol (**3**) have been reported,[5] this important chiral material and its substituted derivatives are generally obtained in enantiomerically pure forms by resolution of the racemic mixtures.[4] Racemic bi-2-naphthol can be readily prepared by Cu(II)-catalyzed oxidative coupling of 2-naphthol in the presence of air (**eq 1**).[5m]

Of the various resolution methods that have been reported for **3**, procedures involving the preparation of the corresponding racemic phosphoric acid derivatives have been widely utilized.[6] In the original procedure, the racemic cyclic binaphthyl phosphate was resolved via its cinchonine salt.[6] Later on, procedures were reported for the preparation of diastereomeric phosphate esters of chiral menthol,[7] or phosphate amides of commercially available chiral α-methylbenzylamine[8] (**Scheme 1**).

These methods can be readily adapted to large-scale synthesis. For example, the cyclic phosphate procedure has been utilized by Cram and coworkers on a molar scale to obtain chiral bi-2-naphthols for use in their studies of chiral host–guest complexes.[9] Several substituted bi-2-naphthols have also been resolved via the preparation of similar cyclic phosphate esters.[4] However, one drawback of this procedure is its use of $LiAlH_4$ to cleave the phosphate salts, amides, or esters, since $LiAlH_4$ is somewhat expensive and requires special handling. Accordingly, the search for more convenient procedures for the resolution of bi-2-naphthol is continuing.







Scheme 1. The Cyclic Phosphate Amide Method for Resolving Racemic Bi-2-naphthol (**3**).

2.1.2. Through Selective Enzymatic Hydrolysis of the Corresponding Esters

The enzymatic resolution of racemic alcohols through partial hydrolysis of the corresponding esters is one of the more widely applied methods for obtaining enantiomerically pure alcohols. Detailed studies on the resolution of racemic bi-2-naphthol esters have been reported, and a large-scale (0.7 mole) procedure has been described (**Scheme 2**).[10] This approach has also proven useful for resolving the corresponding octahydrobi-2-naphthol (**5**) and spirobiindanol **6**.[10]

Enantiomerically pure 1,2-cyclohexanediols have similarly been prepared by the enzymatic resolution of the corresponding diacetate **7** (**eq 2**).[11]

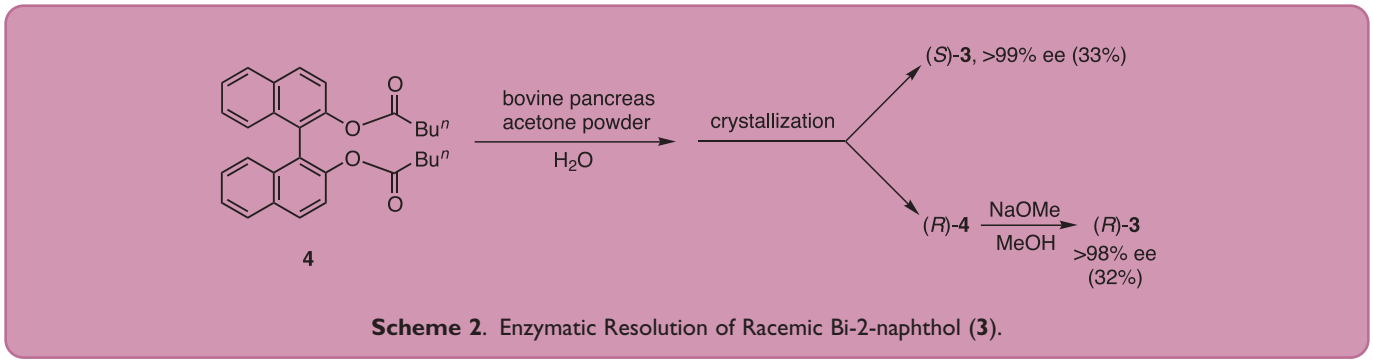
2.1.3. Via Diastereomeric Inclusion Complexes with Chiral Tartaric Acid Amides

Chiral host amides **9**, **10**, and **11**—which are derived from inexpensive, naturally occurring (*R*,*R*)-(+)-tartaric acid—form diastereomeric 1:1 inclusion complexes with guests bi-2-naphthol (**3**), 10,10'-dihydroxy-9,9'-biphenanthryl (**12**), and 2,2'-dihydroxy-9,9'-spirobifluorene (**13**), respectively.[12] Such complexes were utilized for the resolution of racemic **3** (**Scheme 3**) and racemic **12** (**Scheme 4**).[12]

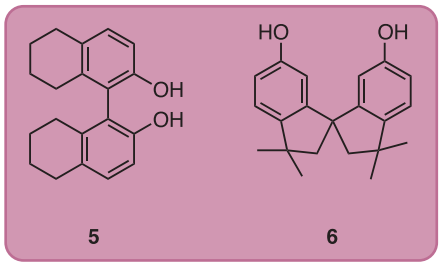
A diastereomeric 1:1 inclusion complex of diol **13** and amide **11** was similarly prepared in ethanol, crystallized from the same solvent, decomposed with dilute sodium hydroxide, and acidified with dilute hydrochloric acid to give (+)-**13** in 90% yield and >99% ee.[12]

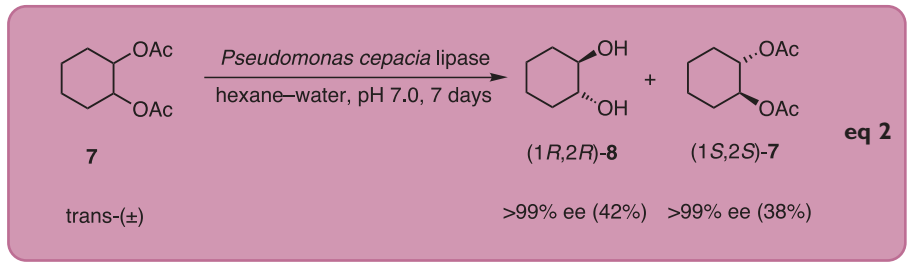
2.1.4. Via Diastereomeric Inclusion Complexes with Chiral Cinchonidium Halides

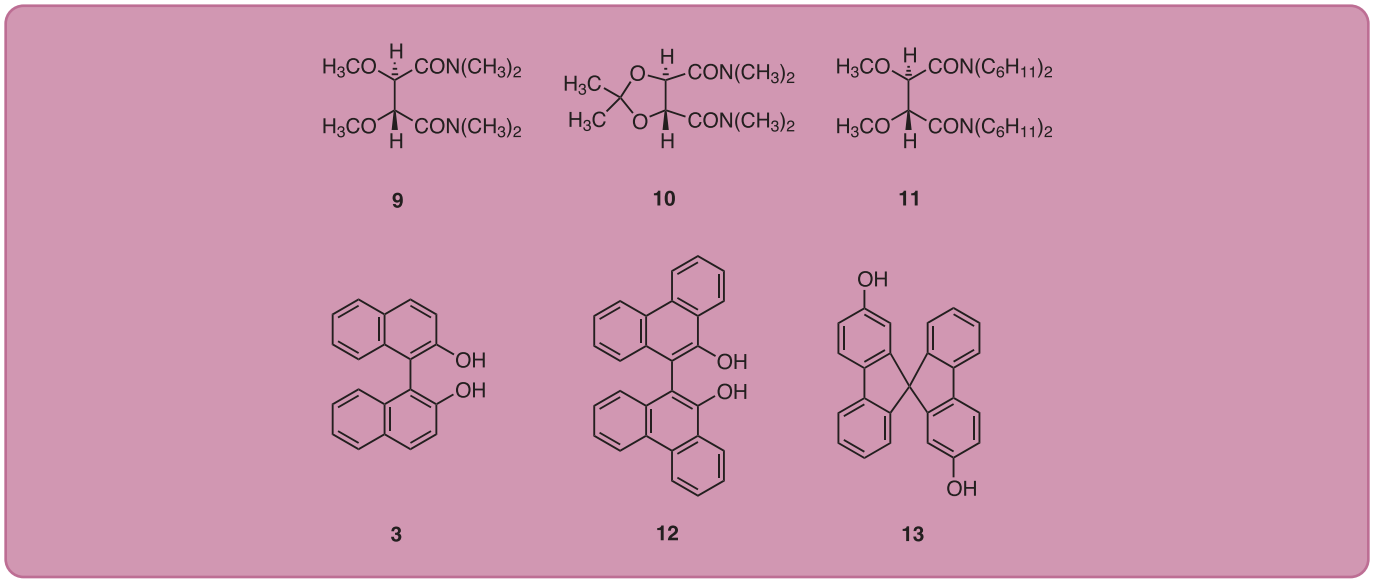
Inclusion complexes of bi-2-naphthol (**3**) with chiral *N*-benzylcinchonidium chloride (**14**) have been exploited in the resolution of



Scheme 2. Enzymatic Resolution of Racemic Bi-2-naphthol (**3**).







racemic **3** (**Scheme 5**).[13] (*R*)-**12** (>99% ee, 40% yield) and (*S*)-**12** (>58% ee, 60% yield) were similarly obtained from racemic **12** by employing *N*-butyl cinchonidium bromide (**15**) in methanol.[13] A slight modification of this procedure—using **14**, acetonitrile as solvent, and EtOAc/1N HCl to cleave the complex—afforded both enantiomers of **3** in ≥99% ee.[14]

2.1.5. With Chiral Diamines

Chiral 1,2-diaminocyclohexane (**16**) forms diastereomeric complexes with bi-2-naphthol (**3**).[15] Such derivatives were readily separated and crystallized to obtain both enantiomers of **3** in high enantiomeric purity (**Scheme 6**).[15]

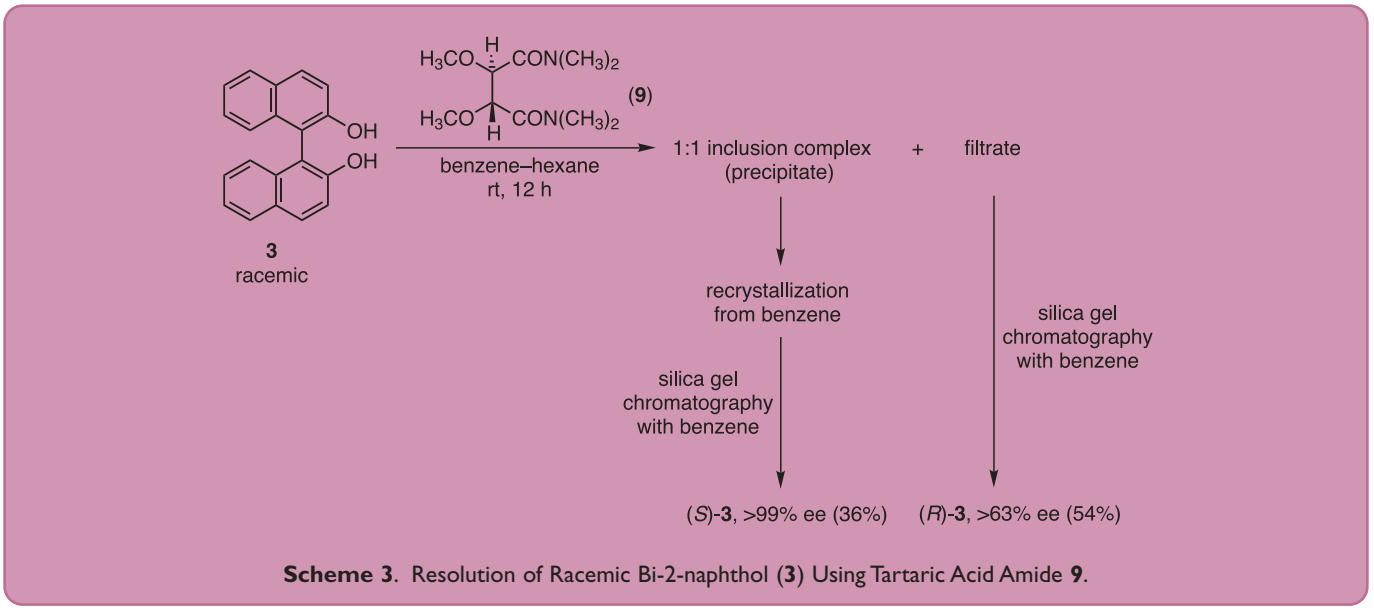
Similar results were obtained with chiral 1,2-diphenyl-1,2-diaminoethane.[12] Upon heating the mixture of diastereomeric complexes prepared from racemic **3** and the chiral amine, enantiomerically pure samples of **3** were obtained in 154–160% of the theoretical yields via a novel epimerization–crystallization process.[15]

2.1.6. With (S)-Proline

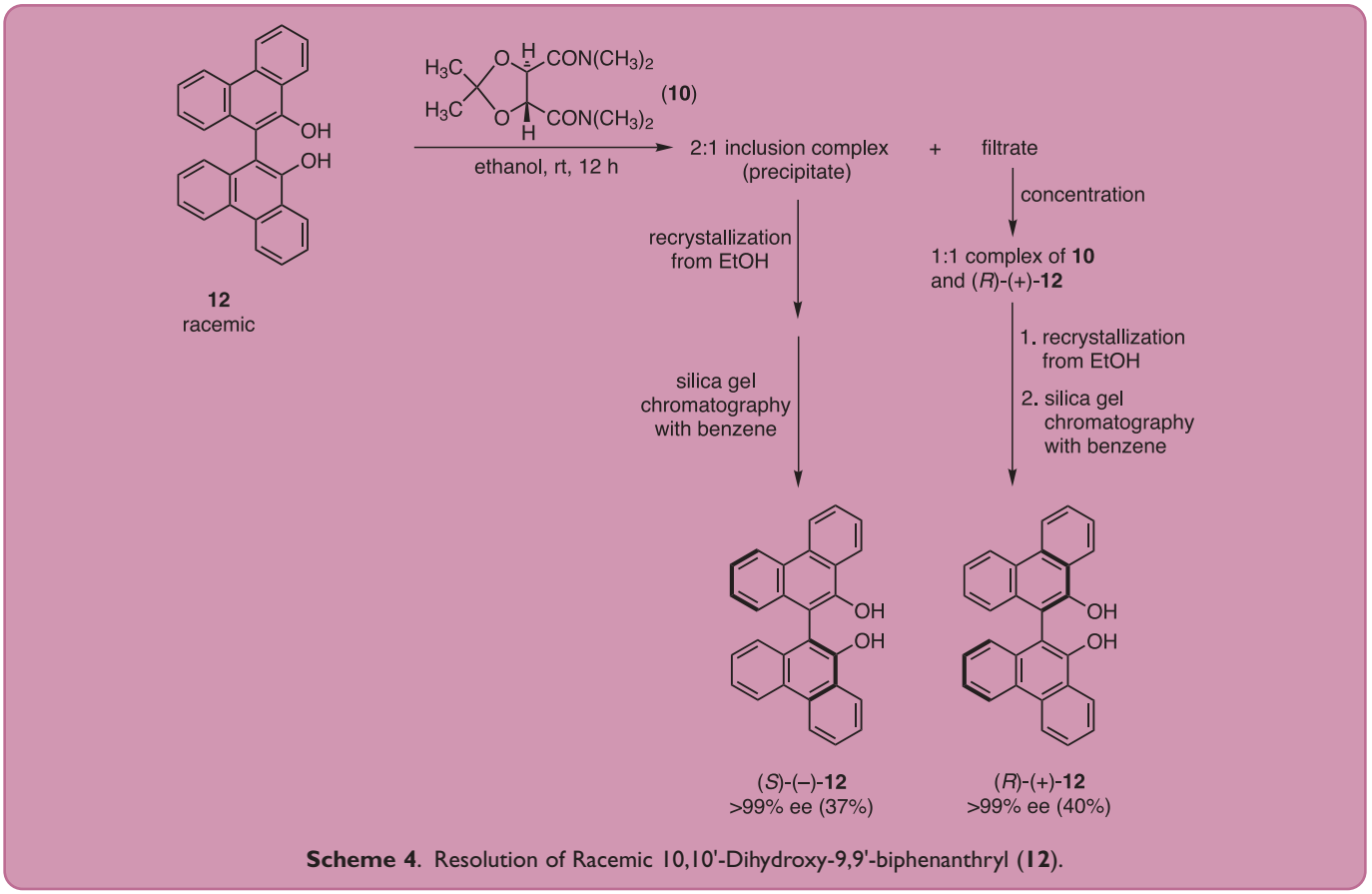
The cyclic phosphate derivatives of bi-2-naphthol (**3**) (Scheme 1) are hydrolytically stable, and hence require $LiAlH_4$ to regenerate **3**. In contrast, the corresponding diastereomeric borate complexes **17–20**, which are expected to be crystalline, should undergo hydrolysis readily. Such diastereomeric derivatives should also be easy to prepare from boric acid and amino acids, amino alcohols, or amines.

Hence, such a method would, in principle, be useful for the resolution of diols, amino acids, amino alcohols, and amines. Accordingly, systematic studies were undertaken to develop synthetic methods for such borate complexes using inexpensive boric acid, $B(OH)_3$.[16] The reaction of boric acid, bi-2-naphthol (**3**), and (*S*)-proline (**21**) did not give the corresponding borate derivative, **22**, as a major product. Instead, a 2:1 complex, **23**, of **3** and **21** formed under these conditions.[16,17] The partially resolved **3** was readily obtained by hydrolysis of **23** (**Scheme 7**).[17]

Complex **23** is also formed in other solvents such as methanol, dichloromethane,



Scheme 3. Resolution of Racemic Bi-2-naphthol (**3**) Using Tartaric Acid Amide **9**.



Scheme 4. Resolution of Racemic 10,10'-Dihydroxy-9,9'-biphenanthryl (**12**).

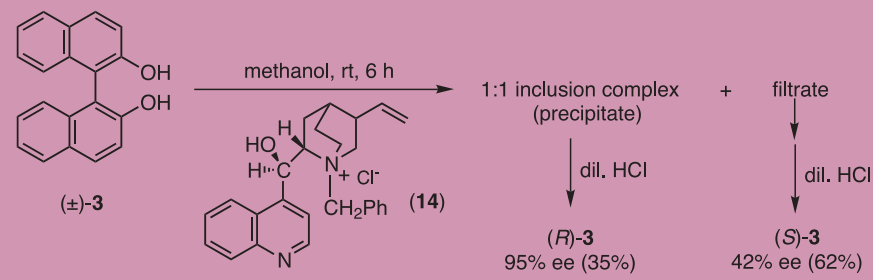
and acetonitrile.[18] The crystalline complex obtained in methanol has been characterized by X-ray crystallographic analysis. Samples of >99% ee are readily obtainable by repetition of the procedure starting from nonracemic **3**.[18]

Racemic diol **24**, and dicarboxylic acids **25** and **26** were also resolved via the corresponding diastereomeric complexes with (*S*)-proline, but without using boric acid.[19,20]

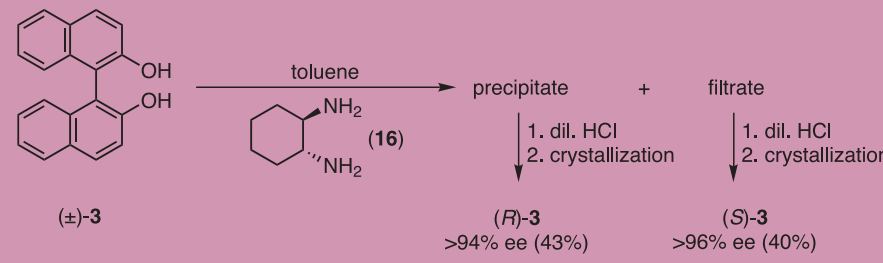
2.1.7. Via Diastereomeric Borate Complexes

An interesting procedure for the purification of nonracemic samples of **3** was devised by using boric acid and taking advantage of the predominant formation of homochiral complexes **19** or **20** (**Scheme 8**).[17,18]

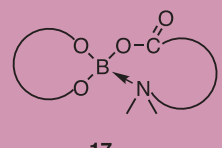
Subsequently, a simple and convenient procedure was developed for the resolution of racemic **3** by employing boric acid and (*R*)-(+)-α-methylbenzylamine (**Scheme 9**).[21] The intermediate borate complex of type **19** was characterized by single-crystal X-ray analysis.



Scheme 5. Resolution of Bi-2-naphthol (**3**) with Chiral *N*-Benzylcinchonidium Chloride (**14**) in Methanol.



Scheme 6. Resolution of Racemic Bi-2-naphthol (**3**) with Chiral 1,2-Diaminocyclohexane (**16**).



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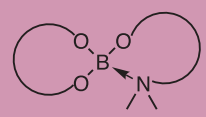

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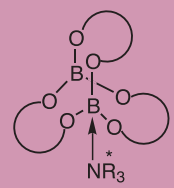
19



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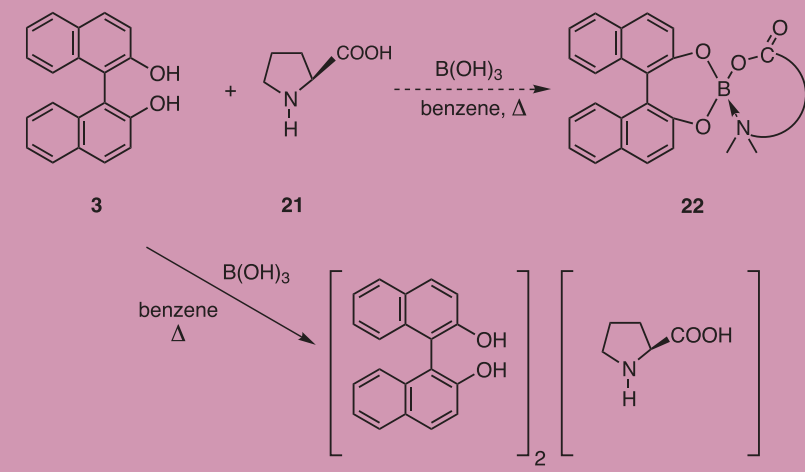
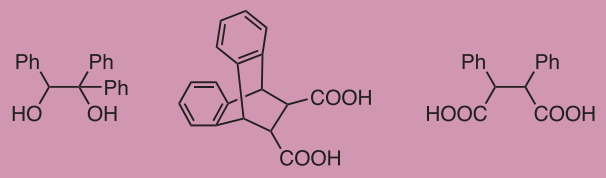
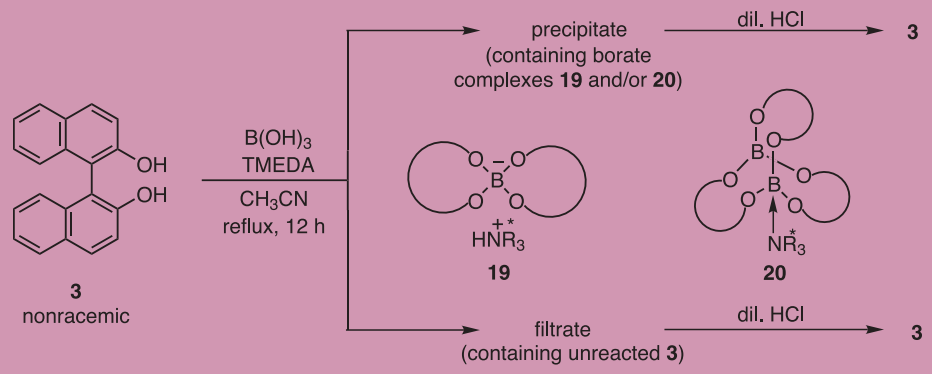


starting mat. (**3**)		**3** from precipitate			**3** from solution		
config.	ee, %	config.	ee, %	yield, %	config.	ee, %	yield, %
R+*S*	00	*S*	65	43	*R*	44	51
S	10	*S*	64	65	*R*	70	25
S	87	*S*	>99	77	*S*	35	11
R	44	*R*	90	45	*R*	06	41
R	90	*R*	>98	70	*R*	28	18

Scheme 7. Resolution of Racemic Bi-2-naphthol (**3**) with (*S*)-Proline (**21**).

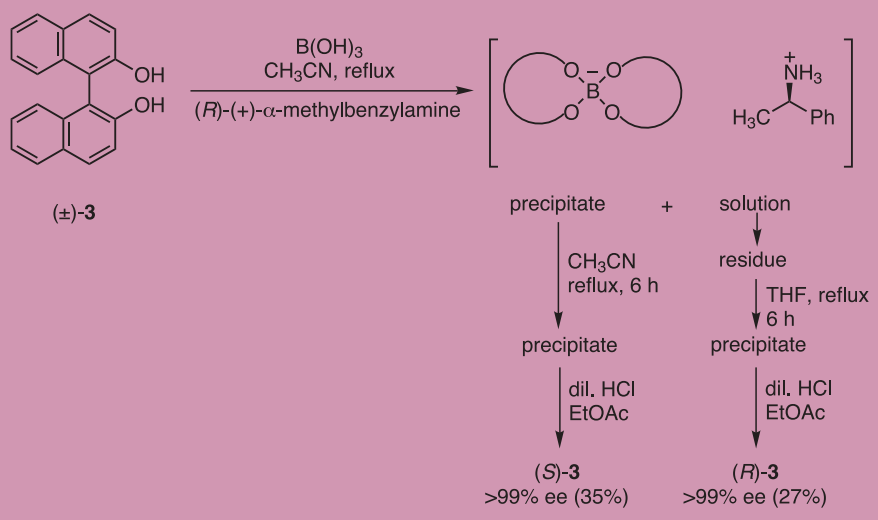


24 **25** **26**



starting mat. (**3**)		$B(OH)_3$	**3** from precipitate			**3** from filtrate		
config.	ee, %	(mmol)	config.	ee, %	yield, %	config.	ee, %	yield, %
R	17	0.57	*R*	88	11	*R*	03	76
R	34	1.14	*R*	92	31	*S*	05	55
R	79	2.67	*R*	93	77	*S*	06	10
S	18	0.60	*S*	89	13	*S*	05	75
S	34	1.10	*S*	95	28	*S*	01	54
S	75	2.50	*S*	95	77	*R*+*S*	00	10

Scheme 8. Purification of Nonracemic Bi-2-naphthol (**3**) Using Boric Acid.



Scheme 9. Resolution of Bi-2-naphthol (**3**) Using Boric Acid and Chiral α-Methylbenzylamine.

As discussed in Section 2.1.6, attempts at effecting the resolution of **3** using amino acids and amino alcohols, and through the intermediacy of borate complexes of type **17–20**, resulted in the discovery that **3** forms diastereomeric complexes with (*S*)-proline. Later on, such borate complexes were successfully prepared using borane and quinine; however, the structure of the borate–quinine complex was not established unambiguously (**Scheme 10**).[22]

The resolution can also be carried out via the corresponding "BOB"complexes and reaction of these with (*S*)-proline (**Scheme 11**).[23] Again, the structure of the complex formed under these conditions was not examined by X-ray analysis.

2.2. Resolution of Racemic 1,2- and 1,4-Diols Using Boric Acid and (S)-Proline

Racemic 1,2-diphenylethanediol (**29**) and 2,3-diphenyl-1,4-butanediol (**30**) were readily resolved via diastereomeric borate complexes using boric acid and (*S*)-proline (**Scheme 12**).[19] ^{1}H NMR studies provided support for the formation of the diastereomeric complex of type **17**.

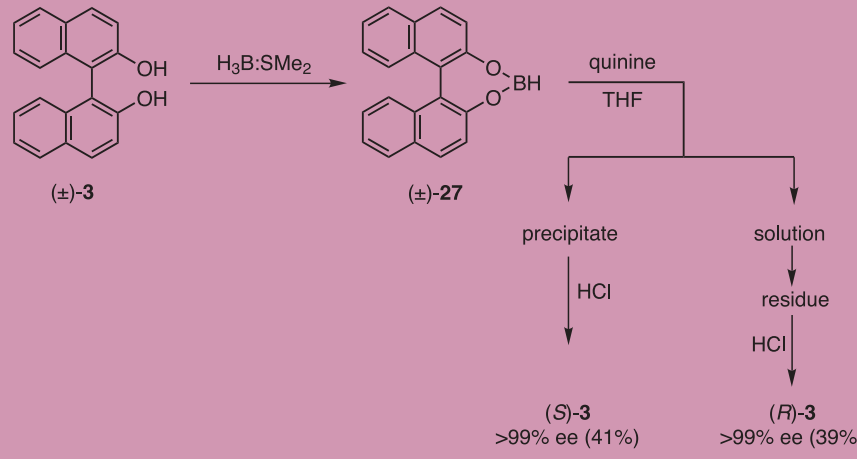
Racemic **30** is accessible by the $TiCl_4/Et_3N$ induced coupling of ethyl phenylacetate, followed by hydrolysis and reduction with borane (**Scheme 13**).[24]

3. Racemic Amino Alcohols

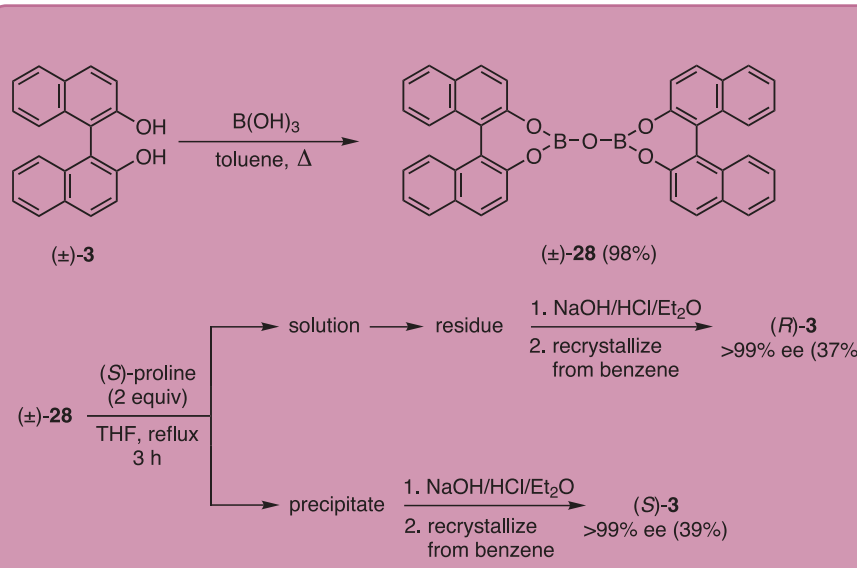
3.1. Resolution of Diphenylprolinol with Chiral Bi-2-naphthol and Boric Acid

Since chiral bi-2-naphthol became accessible, systematic investigations were undertaken to synthesize and resolve amino alcohols and derivatives, which were expected to form borate complexes of type **17–20** with chiral bi-2-naphthol and boric acid. The widely used diphenylprolinol (**1**) and other readily accessible amino alcohols were chosen for these studies. (*S*)-Diphenylprolinol [DPP, (*S*)-**1**] had been prepared by the addition of phenylmagnesium bromide to the N-protected (*S*)-proline ester.[25] Our preparation of (*S*)-**1** for application in large-scale synthesis was a slight modification and an improvement of the reported procedure (**Scheme 14**).[26]

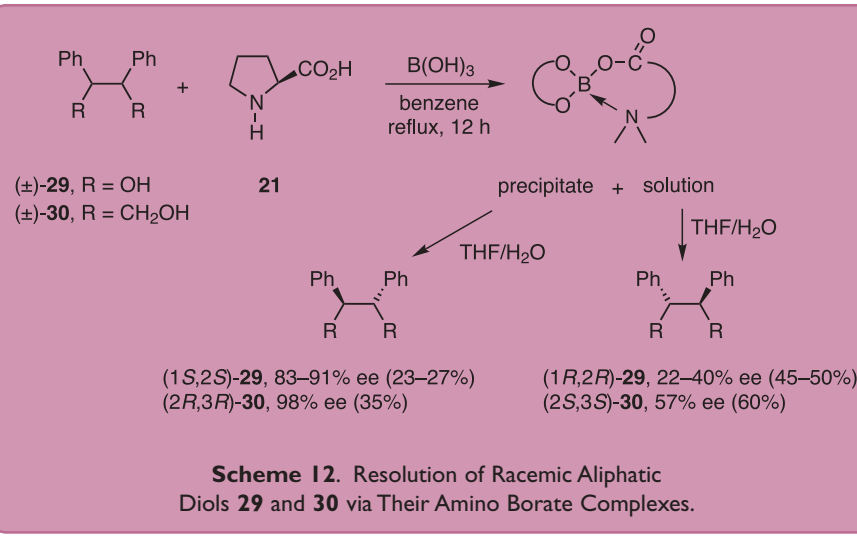
(*S*)-Diphenylprolinol is the precursor of the useful CBS oxazaborolidine catalyst that is utilized in the asymmetric borate reduction of ketones.[1] Accordingly, it was of interest to synthesize the enantiopode, (*R*)-diphenylprolinol, for applications in such oxazaborolidine reductions.[25] Since (*R*)-proline and racemic proline are somewhat



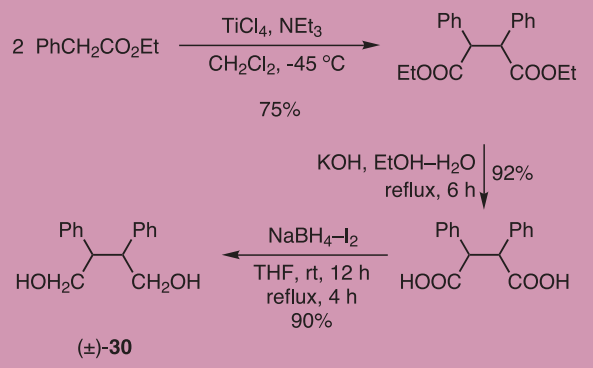
Scheme 10. Resolution of Bi-2-naphthol (**3**) Using Borane and Chiral Quinine.



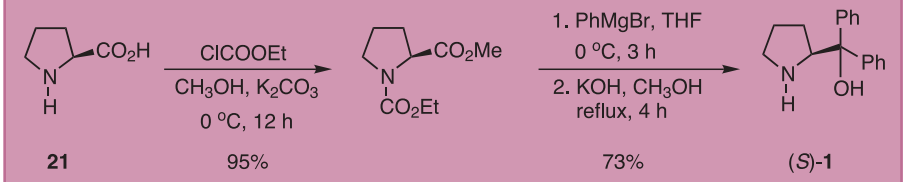
Scheme 11. Resolution of Bi-2-naphthol (**3**) through a "BOB" Complex.



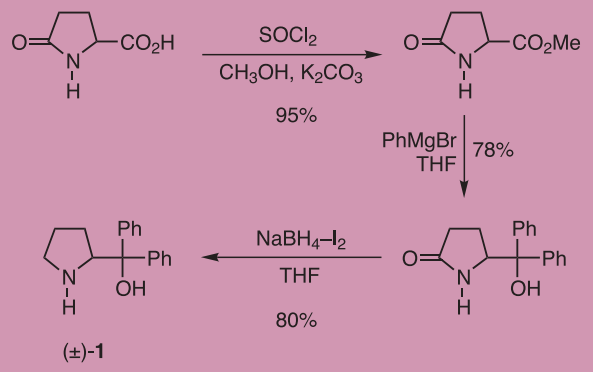
Scheme 12. Resolution of Racemic Aliphatic Diols **29** and **30** via Their Amino Borate Complexes.



Scheme 13. Preparation of Racemic 2,3-Diphenyl-1,4-butanediol (**30**).



Scheme 14. Synthesis of (*S*)-Diphenylprolinol.



Scheme 15. Alternative New Synthesis of Racemic Diphenylprolinol.

expensive, an alternative route had been developed by Corey and co-workers for the preparation of racemic diphenylprolinol starting from pyroglutamic acid.[25] The resulting racemic **1** was resolved using (*S*)-(+)- and (*R*)-(–)-*O*-acetylmandelic acids.[25b] We have reported an alternative new procedure for the synthesis of racemic diphenylprolinol, which employs a $NaBH_4$–I_2 reduction in a crucial step of the synthesis (**Scheme 15**).[27]

Racemic diphenylprolinol prepared in this way was resolved following the chiral bi-2-naphtholborate methodology (**Scheme 16**).[27] The intermediate borate complex was characterized by single-crystal X-ray analysis.

3.2. Resolution of Amino Alcohols Prepared from Cyclohexene Oxides

Racemic amino alcohols can be readily prepared through ring-opening of epoxides. For example, trans racemic amino alcohol **31** is obtained by heating cyclohexene oxide with pyrrolidine.[27,28] Racemic amino alcohol **31** formed borate complexes of type **19** with boric acid and bi-2-naphthol (**3**) in THF or acetonitrile. After a simple dilute hydrochloric acid workup of the precipitate and filtrate fractions, the nonracemic amino alcohol samples were obtained and were further purified by repetition of the procedure (**Scheme 17**).

The corresponding OMe derivative, **32**, gave better results: *trans*-(±)-**32** led with (*R*)-**3** to (1*R*,2*R*)-**32** (>44% ee, 63% yield) and (1*S*,2*S*)-**32** (83% ee, 30% yield).[27,28] The borate complex obtained in this case was crystalline, and the configurational assignments were confirmed by X-ray crystal-structure analysis.

3.3. Purification of Diastereomeric Amino Alcohols Obtained from Meyers' Lactam

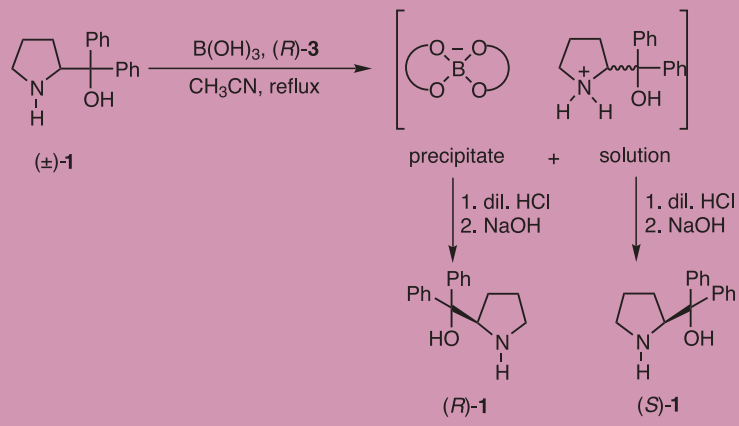
Nonracemic diastereomeric amino alcohol **34** is readily accessed by synthesis and cleavage of Meyers' lactam (**33**) (**Scheme 18**).[27] Diastereomeric amino alcohol **34**, prepared in this way, was purified using bi-2-naphthol (**3**) and boric acid (**Scheme 19**).[27] The intermediate borate complex was characterized by single-crystal X-ray analysis.

3.4. Resolution of Amino Alcohols with Chiral Bi-2-naphthyl-phosphoric Acid

Racemic amines are generally resolved using chiral resolving agents such as camphor-10-sulphonic acid, tartaric acid and its derivatives, and mandelic acid. Chiral bi-2-naphthylphosphoric acid—accessible through reaction of chiral bi-2-naphthol (**3**) with $POCl_3$ (Scheme 1)—is a promising resolving agent for racemic amino alcohols. For example, racemic diphenylpiperidinol (**35**) was resolved using (*S*)-(–)-bi-2-naphthylphosphoric acid [(*S*)-**36**] (**Scheme 20**).[6]

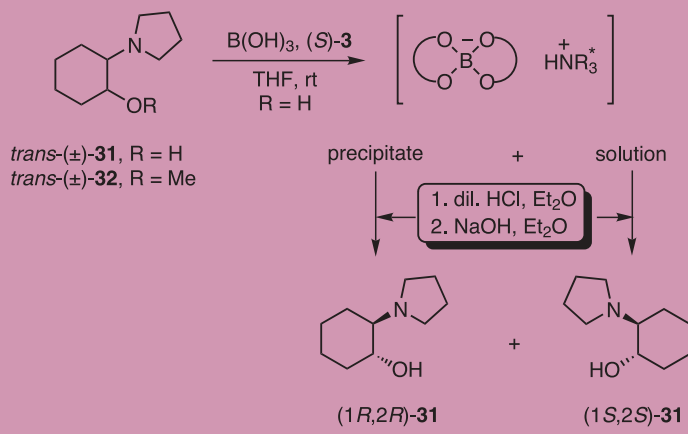
3.5. Resolution of Amino Alcohols Prepared by the Reduction of Oximes of α-Keto Esters

The $NaBH_4$–I_2 reduction of naturally occurring chiral amino acids **37** yields the corresponding *S* amino alcohols **38** (**eq 3**).[29] The corresponding racemic amino alcohols, **39**, are available by reduction of the oximes of α-keto esters with $NaBH_4$–I_2 (**eq 4**).[30] These amino alcohols form diastereomeric complexes with dibenzoyl-L-tartaric acid (**40**).[30] Nonracemic mixtures of the amino alcohols are obtained through precipitation of the complexes in acetone. The resolutions of phenylglycinol (**39a**) and phenylalaninol (**39b**) have been studied in detail. Interestingly, the nature of the nonracemic material obtained depends on the amount of resolving agent used. Thus, phenylglycinol samples of >90% ee are obtained by adding the resolving agent in portions (**Scheme 21**).[30] The nonracemic amino alcohols obtained in this way are readily purified further through crystallization using achiral dicarboxylic acids such as oxalic acid (**Scheme 22**).[30]



starting mixt. (**1**)		**1** from precipitate			**1** from solution		
config.	ee, %	config.	ee, %	yield, %	config.	ee, %	yield, %
R+*S*	0	*R*	90	18	*S*	20	80
R	42	*R*	>99	28	*S*	25	69
R	90	*R*	>99	78	*S*	30	20

Scheme 16. Resolution of Racemic Diphenylprolinol Using Boric Acid and Chiral Bi-2-naphthol.



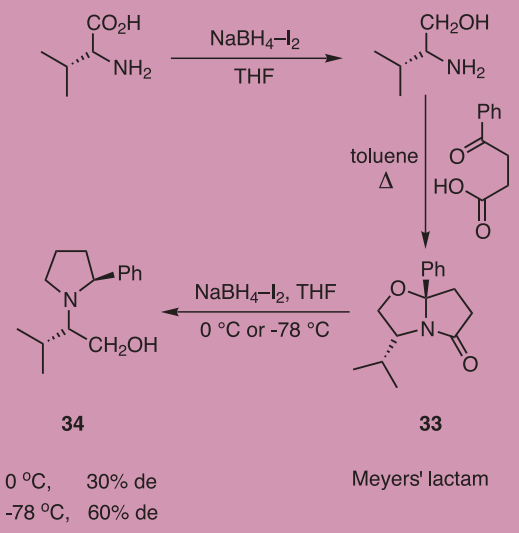
starting mixt. (**31**)		**31** from precipitate			**31** from solution		
config.	ee, %	config.	ee, %	yield, %	config.	ee, %	yield, %
racemic	0	1*R*,2*R*	38	40	1*S*,2*S*	36	45
1*R*,2*R*	38	1*R*,2*R*	79	40	1*R*,2*R*	11	55
1*R*,2*R*	79	1*R*,2*R*	>99	35	1*R*,2*R*	08	50

Scheme 17. Resolution of Racemic Amino Alcohol **31**.

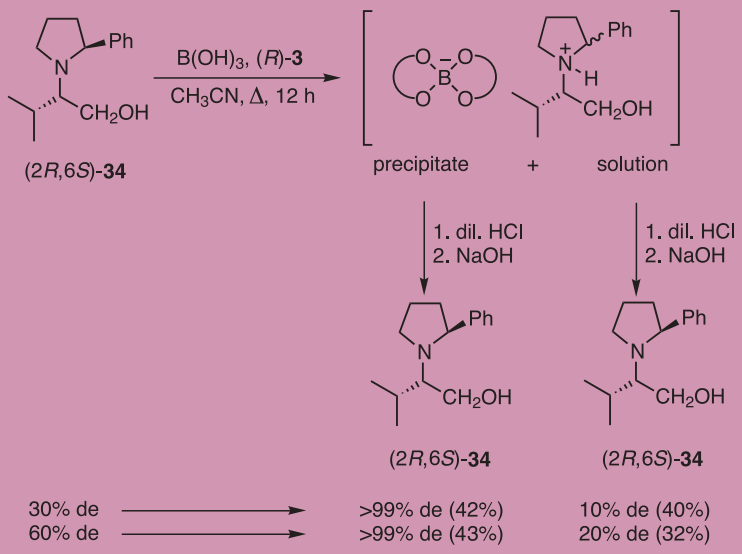
Nonracemic mixtures of phenylalaninol (**39b**) gave better results in the purification sequence that employs oxalic acid (**Scheme 23**).[30] Presumably, the oxalic acid forms predominantly homochiral aggregates, resulting in the precipitation of the complex enriched in the predominant isomer. X-ray crystal-structure analysis of the complexes is necessary for further understanding of the nature of the aggregates formed in these resolution processes.

4. Conclusions

Chiral diols and amino alcohols are widely used in asymmetric transformations both as building blocks and ligands for the preparation of catalysts. Although asymmetric syntheses are preferred for obtaining these compounds in enantiomerically pure forms, resolution methods of racemic or enriched mixtures, especially to attain both enantiomers, could become good alternatives, if they could be adapted to large scale. Resolution procedures involving the use of well-known resolving agents such as chiral camphor-10-sulphonic acid, tartaric acid, and mandelic acid have been available for a long time. New resolution methods that rely on enzymes, inclusion complexes, and phosphate and borate complexes would further expand the scope of the resolution approach. Novel methods for the purification of diols and amino alcohols using achiral reagents further illustrate the applicability of



Scheme 18. Synthesis of Diastereomeric Amino Alcohol **34**.



Scheme 19. Purification of Amino Alcohol **34** by Employing Boric Acid and Chiral Bi-2-naphthol.

this approach to the isolation of enantiopure organic compounds. Such a purification of partially resolved materials would involve selective formation of homochiral complexes and, hence, has relevance to nonlinear effects (i.e., a ligand with lower ee leading to a product with a higher ee) in asymmetric synthesis.[31] Accordingly, such concepts should further stimulate research in the exciting area of asymmetric synthesis.

5. Acknowledgement

The author is thankful to his students, whose names appear in the references, for their contributions to this research program. Financial support for this research program from the Department of Science and Technology, Government of India, is gratefully acknowledged.

6. References and Notes

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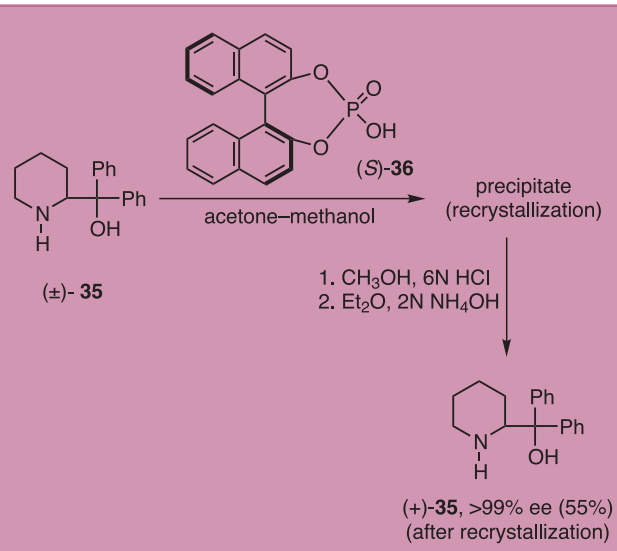
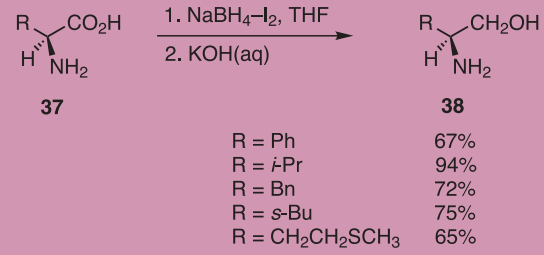


Scheme 20. Resolution of Racemic Amino Alcohol **35** with Chiral Bi-2-naphthylphosphoric Acid.



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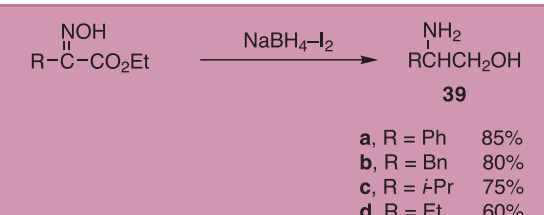

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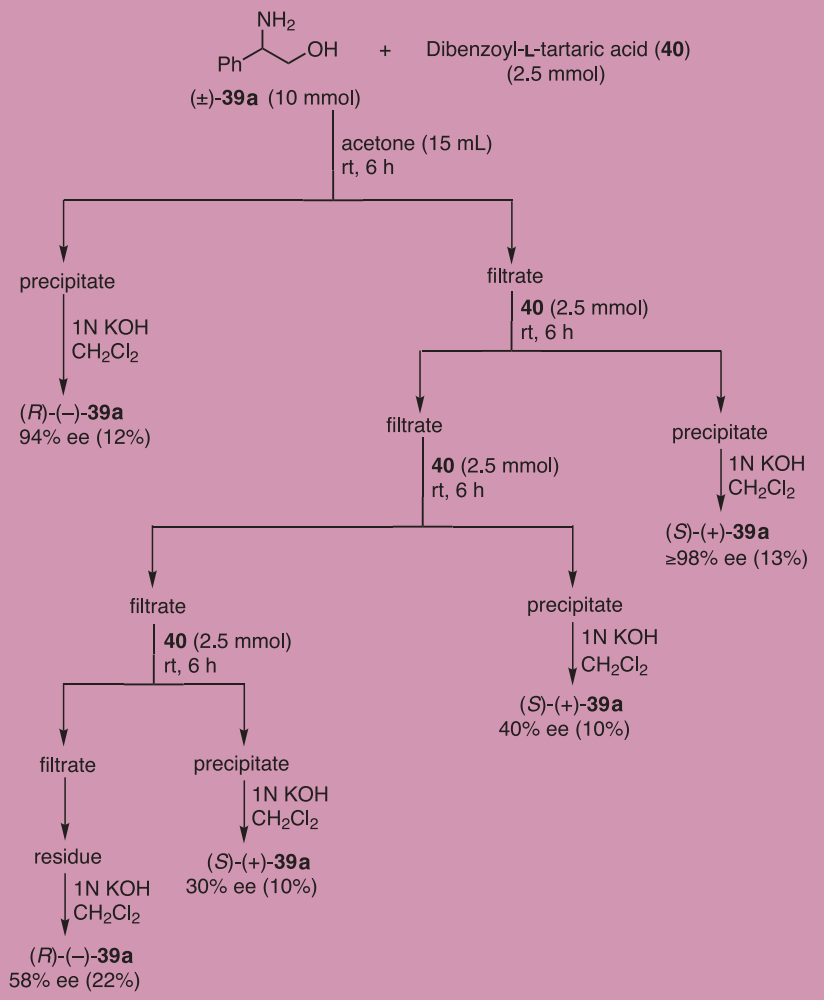
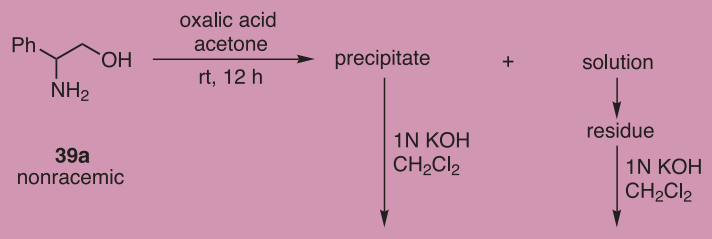


Scheme 21. Resolution of Racemic Phenylglycinol (**39a**) with Dibenzoyl-L-tartaric Acid (**40**).

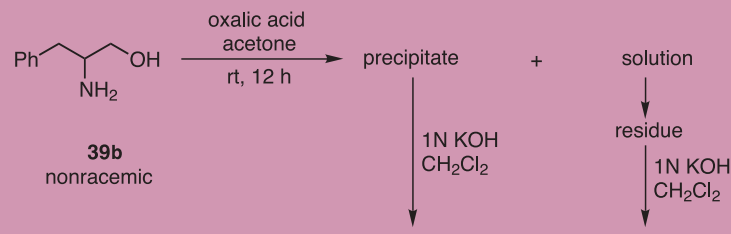


starting mixt. (**39a**)		**39a** from precipitate			**39a** from solution		
config.	ee, %	config.	ee, %	yield, %	config.	ee, %	yield, %
R	15	*R*	30	11	*R*	06	76
R	30	*R*	50	31	*R*	05	55
R	50	*R*	70	48	*S*	06	45
R	70	*R*	90	48	*S*	06	45
R	90	*R*	98	48	*S*	06	45

Scheme 22. Purification of Nonracemic Phenylglycinol (**39a**) Using Oxalic Acid.

About the Author

Mariappan Periasamy was born in Srivilliputtur, Tamil Nadu State, India. In the period 1970–1975, he studied for his B.S. (Special) and M.S. degrees at the American College, Madurai, India. He obtained his Ph.D. degree from the Indian Institute of Science, Bangalore, for his research work (1975–1979) in organic chemistry under the guidance of Professor M. Vivekananda Bhatt. After postdoctoral work with Professor Herbert C. Brown at Purdue University on the nonclassical ion problem (1979–1982), he joined the faculty of the School of Chemistry, University of Hyderabad, as a lecturer in July 1982. He was promoted to reader in February 1987, and became a full professor in April 1993. He was a visiting scientist/faculty at the Laboratory of Coordination Chemistry, Toulouse, France (1995), the University of Amsterdam (1996), the University of Marburg (1997), Purdue University (1999), and the University of Paris-Sud (2000). He is a recipient of the Shanti Swarup Bhatnagar Prize for Chemical Sciences (1996) awarded by the CSIR, Government of India, and was elected a fellow of the Indian Academy of Sciences, Bangalore, in 1994. His research interests are in the areas of organometallics and chiral reagents. Very recently, he has initiated a new research program on the conversion of farm waste to chemical feedstock, with the objective of developing viable, sustainable, renewable, and environmentally benign energy sources.



starting mixt. (**39b**)		**39b** from precipitate			**39b** from solution		
config.	ee, %	config.	ee, %	yield, %	config.	ee, %	yield, %
R	17	*R*	35	11	*R*	3	76
R	34	*R*	50	31	*R*	5	55
R	50	*R*	98	48	*S*	6	45
S	18	*S*	34	13	*S*	5	75
S	34	*S*	50	28	*R*+*S*	0	54
S	50	*S*	98	45	*R*+*S*	0	45

Scheme 23. Purification of Nonracemic Phenylalaninol (**39b**) Using Oxalic Acid.

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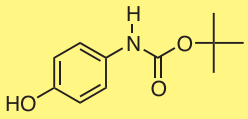
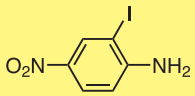
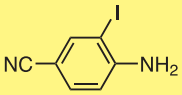
57,664-6
$C_{11}H_{15}NO_3$



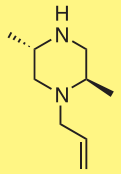
57,668-9
$C_6H_5IN_2O_2$



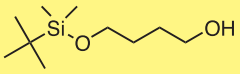
57,801-0
$C_7H_5IN_2$



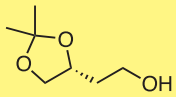
57,811-8
$C_9H_{17}N_2$



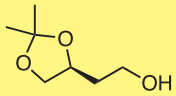
56,858-9
$C_{10}H_{24}O_2Si$



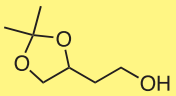
33,107-4
$C_7H_{14}O_3$



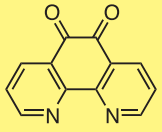
57,132-6
$C_7H_{14}O_3$



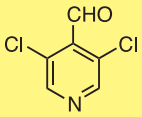
57,146-6
$C_7H_{14}O_3$



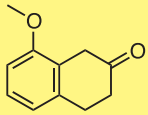
49,638-3
$C_{12}H_6N_2O_2$



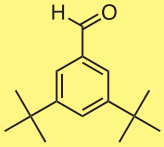
57,247-0
$C_6H_3Cl_2NO$



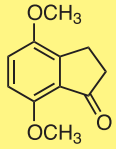
53,545-1
$C_{11}H_{12}O_2$



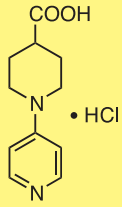
57,458-9
$C_{15}H_{22}O$



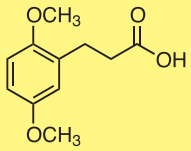
57,809-6
$C_{11}H_{12}O_3$



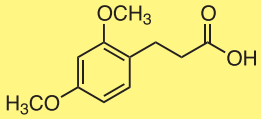
57,243-8
$C_{11}H_{14}N_2O_2 \bullet HCl$



57,565-8
$C_{11}H_{14}O_4$



57,566-6
$C_{11}H_{14}O_4$



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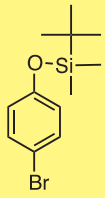
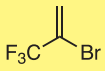
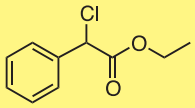
44,477-4
$C_{12}H_{19}BrOSi$



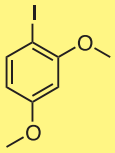
56,100-2
$C_3H_2BrF_3$



56,590-3
$C_{10}H_{11}ClO_2$



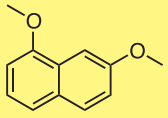
57,773-1
$C_8H_9IO_2$



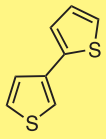
57,780-4
C_2H_2BrI

57,461-9
$C_6H_4Br_2O_2$

57,558-5
$C_{12}H_{12}O_2$



57,781-2
$C_8H_6S_2$



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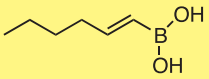
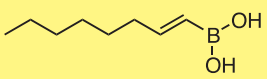
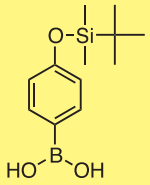
52,101-9
$C_6H_{13}BO_2$



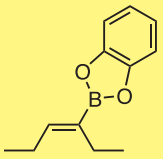
52,102-7
$C_8H_{17}BO_2$



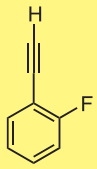
52,404-2
$C_{12}H_{21}BO_3Si$



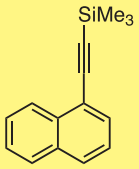
57,552-6
$C_{12}H_{15}BO_2$



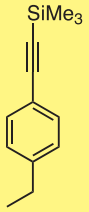
46,700-6
C_8H_5F



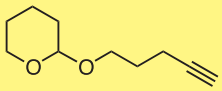
56,341-2
$C_{15}H_{16}Si$



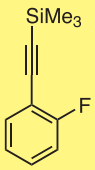
56,345-5
$C_{13}H_{18}Si$



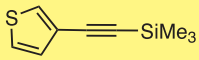
56,366-8
$C_{10}H_{16}O_2$



57,140-7
$C_{11}H_{13}FSi$

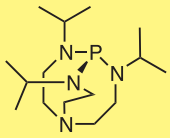


57,704-9
$C_9H_{12}SSi$



57,879-7
C_6H_4S

55,695-5
$C_{15}H_{33}N_4P$



56,588-1
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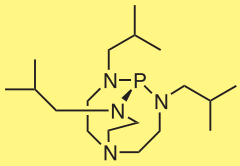
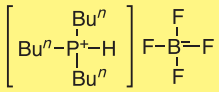


57,649-2
$C_{12}H_{28}BF_4P$



57,894-0
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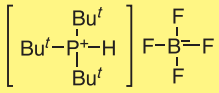
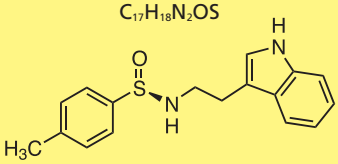


55,883-4
$C_{17}H_{18}N_2OS$



58,851-2
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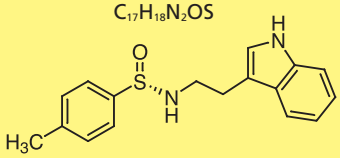
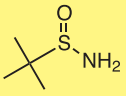


56,087-1
$C_4H_{11}NOS$



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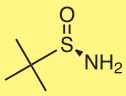
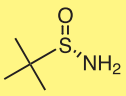
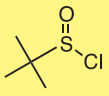


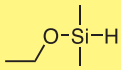
51,321-0
$C_4H_{11}NOS$



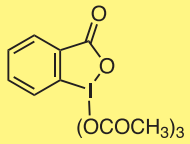
56,943-7
C_4H_9ClOS



57,863-0
$C_4H_{12}OSi$

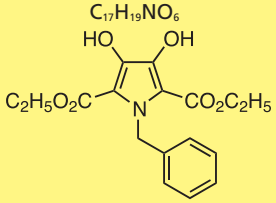


55,987-3
$C_{13}H_{13}IO_8$

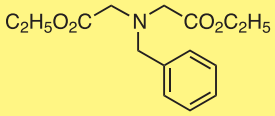


Dess–Martin Periodinane, 0.3*M* solution in dichloromethane

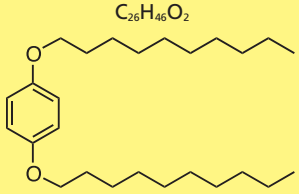
57,190-3
$C_{17}H_{19}NO_6$



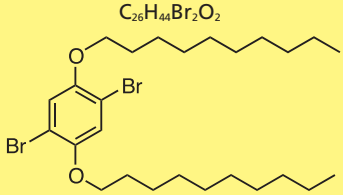
57,489-9
$C_{15}H_{21}NO_4$



57,651-4
$C_{26}H_{46}O_2$



57,837-1
$C_{26}H_{44}Br_2O_2$



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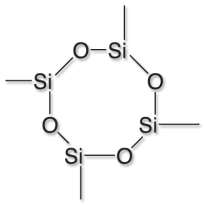
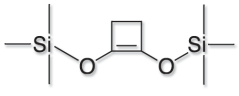
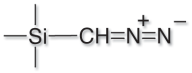


51,299-0
2,4,6,8-Tetramethylcyclotetrasiloxane, 99.5+%
CAS # 2370-88-9



29,383-0
1,2-Bis(trimethylsilyloxy)cyclobutene, 95+%
CAS # 17082-61-0



36,283-2
(Trimethylsilyl)diazomethane
2.0*M* solution in hexanes
CAS # 18107-18-1

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Fluka Is Proud to Announce That "DEAD" Is ALIVE!

Our **DEAD solution, 40% in toluene (11627)** is back again! As a result of new insights into its explosive properties, recent transport legislations made this very important reagent for the Mitsunobu reaction unavailable to customers for several months. Now, Fluka is able to offer **DEAD** again in a **stable** and **safe** 40% toluene solution.

Mitsunobu reactions, i.e., the combination of an azodicarboxylate (mostly DEAD) and a phosphine (such as triphenylphosphine or tributylphosphine) are currently widely applied in C–C bond-forming reactions in organic synthesis.[1-4] Many other applications are known, such as the preparation of *N*-alkylamides or imides starting from an alcohol and amide or imide, or the condensation of a carboxylic acid and an alcohol to form the corresponding ester. Also interesting, is the inversion of configuration that takes place in the case of a chiral secondary alcohol.

11627 **Diethyl azodicarboxylate solution** (DEAD), purum, ~ 40% in toluene (^{1}H NMR)[1-4]
M_w 174.16 [1972-28-7] $C_6H_{10}N_2O_4$ 50mL; 250mL; 500mL

Other Azodicarboxylic Acid Reagents Used in the Mitsunobu Reaction:

11625 **Di-*tert*-butyl azodicarboxylate** (DBAD), purum, ≥ 98.0% (GC)
M_w 230.27 [870-50-8] $C_{10}H_{18}N_2O_4$ 5g; 25g
An acid-labile reagent that allows facile isolation of the desired products;[5] useful in electrophilic amination and hydrazination of enolates and lithium alkyls.[6-8]

11626 **Diisopropyl azodicarboxylate** (DIAD), pract., ~ 95% (GC)[1]
M_w 202.21 [2446-83-5] $C_8H_{14}N_2O_4$ 25mL; 100mL
Useful for the preparation of aryl ethers.[9]

11632 **Azodicarboxylic acid dipiperidide** (ADDP), [1,1′-(azodicarbonyl)dipiperidine], purum, ≥ 98.0% (TLC)
M_w 252.32 [10465-81-3] $C_{12}H_{20}N_4O_2$ 5g; 25g
Versatile reagent for acids with high pKa's; excess reagent can be readily removed by filtration (after dilution with hexane).[10,11]

Auxiliary Reagents for the Mitsunobu Reaction:

93090 **Triphenylphosphine**, puriss., ≥ 98.5% (GC)
M_w 262.30 [603-35-0] $C_{18}H_{15}P$ 25g; 100g

93092 **Triphenylphosphine**, purum, ≥ 95.0% (GC)
M_w 262.30 [603-35-0] $C_{18}H_{15}P$ 50g; 250g; 1kg

93093 **Triphenylphosphine, polymer-bound**
~3 mmol triphenylphosphine/g resin cross-linked with 2% DVB; particle size 200–400 mesh
– [39319-11-4] Ⓟ-$C_6H_4P(C_6H_5)_2$ 1g; 5g; 25g
An easy and efficient way to completely remove the phosphine oxide at the end of the reaction.

90827 **Tributylphosphine**, pract., ~ 95% (GC)
M_w 202.32 [998-40-3] $C_{12}H_{27}P$ 25mL; 100mL; 500mL
This reactive phosphine gives better results than triphenylphosphine in the Mitsunobu reaction in a number of cases.[12,13]

90540 **Triethyl phosphite**, purum, ≥ 95.0% (GC)
M_w 166.16 [122-52-1] $C_6H_{15}O_3P$ 50mL; 250mL; 1L
Less reactive than triphenylphosphine, but can lead to a more favorable diastereomeric product ratio.[14,15]

(1) Hughes, D. L. *Org. React.* **1992**, *42*, 335. (2) Dodge, J. A. et al. *Org. Synth.* **1996**, *73*, 110. (3) Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127. (4) Mitsunobu, O. *Synthesis* **1981**, *1*. (5) Kiankarimi, M. et al. *Tetrahedron Lett.* **1999**, *40*, 4497. (6) Gennari, C. et al. *J. Am. Chem. Soc.* **1986**, *108*, 6394. (7) Evans, D. A. et al. *ibid.* **1986**, *108*, 6395. (8) Vicario, J. L. et al. *Tetrahedron Lett.* **1999**, *40*, 7123. (9) Carocci, A. et al. *Tetrahedron: Asymmetry* **2000**, *11*, 3619. (10) Tsunoda, T. et al. *Tetrahedron Lett.* **1993**, *34*, 1639. (11) Lai, J.-Y. et al. *ibid.* **1995**, *36*, 5691. (12) Rehnberg, N.; Magnusson, G. *J. Org. Chem.* **1990**, *55*, 5467. (13) Smith, A.B., III et al. *J. Am. Chem. Soc.* **1992**, *114*, 2567. (14) Townsend, C. A.; Nguyen, L.T. *Tetrahedron Lett.* **1982**, *23*, 4859. (15) Bose, A. K. et al. *Can. J. Chem.* **1984**, *62*, 2498.

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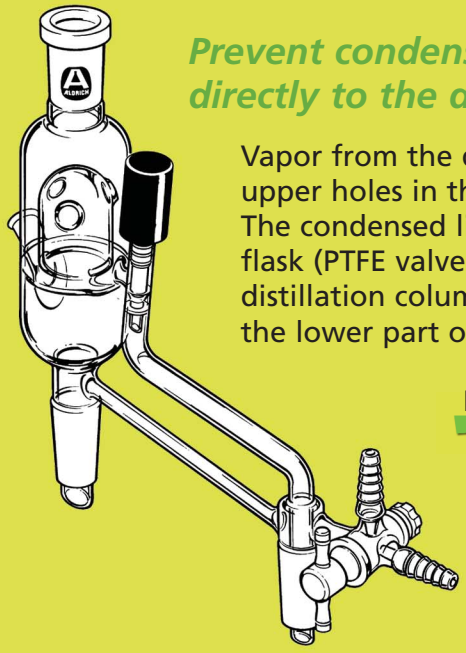
Aldrich High-Efficiency Variable Take-Off Heads



Prevent condensed liquids from returning directly to the distillation column.

Vapor from the distillation column passes through the upper holes in the take-off head and into the condenser. The condensed liquid can be drained into a side storage flask (PTFE valve open, Fig. 1) or allowed to return to the distillation column (PTFE valve closed) through a slot in the lower part of the head.

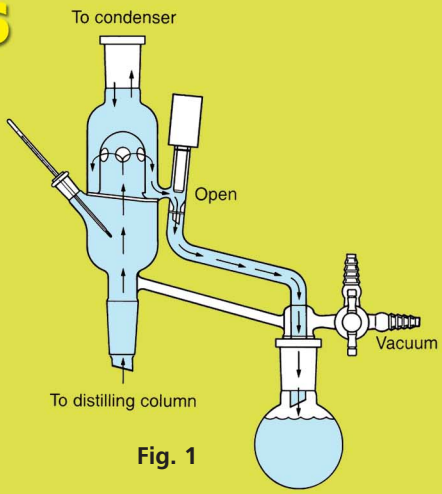


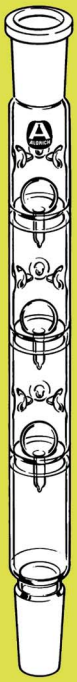
Fig. 1

Features:

- Upper and lower ⅀ joints permit the use of take-off head with different distillation columns and condensers
- Precision PTFE needle valve
- ⅀10/18 thermometer joint
- Vacuum/purge hose connections with PTFE stopcock

⅀ joints	Cat. No.
24/40	Z54,481-7
29/32	Z54,482-5

NEW!

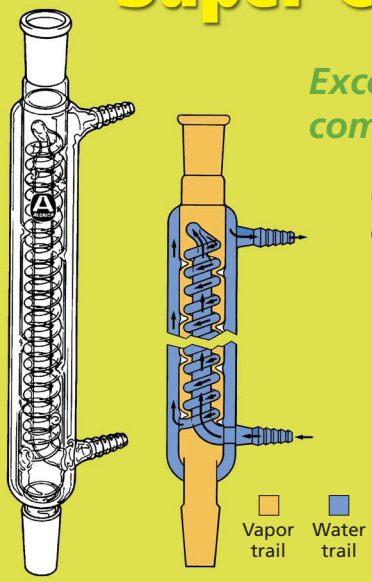


Generation II Snyder Distillation Columns

These improved floating-ball type columns feature robust, solid-glass constrictions for safer handling and integrity. Three sections.

⅀ joints	Cat. No.
14/20	Z54,483-3
24/40	Z54,484-1
29/32	Z54,487-6

Super Condensers



Excellent for volatile compounds.

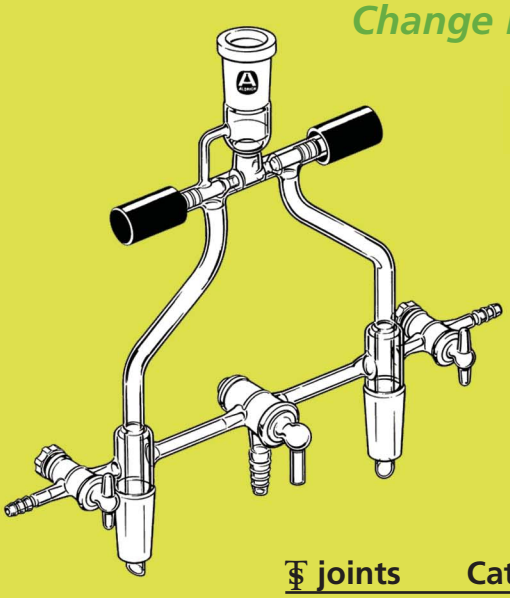
Combine all of these condenser types:

- Cold-finger
- Coiled
- Liebig
- Vigreux

Overall H (cm)	Surface area (cm^2)	⅀*24/40* Cat. No.	⅀*29/32* Cat. No.
32	405	Z22,497-9	Z51,740-2
37	510	Z22,498-7	Z51,741-0
41	610	Z22,499-5	Z51,742-9
51	820	Z22,500-2	Z51,743-7

NEW! Continuous-Receiving-Head Adapters

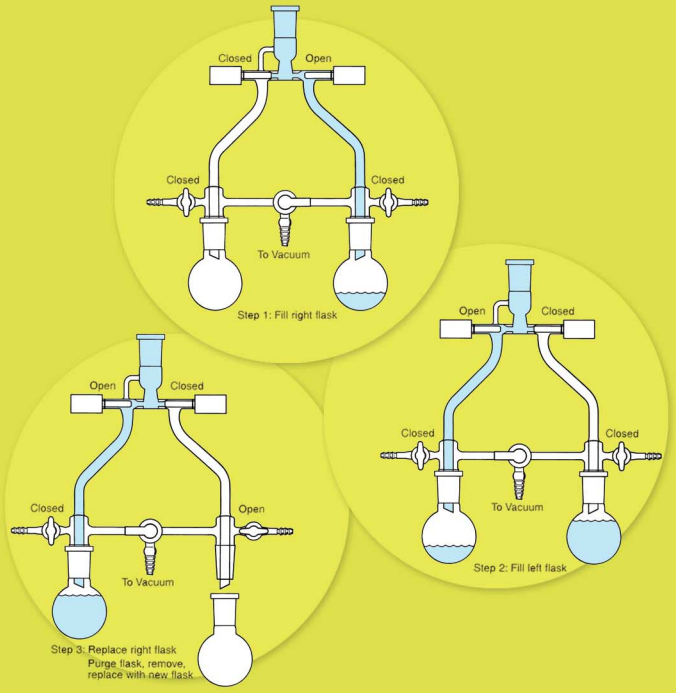
Change receiving flasks without stopping the distillation.



Features:

- Two high-vacuum PTFE needle valves
- One center, two side glass vacuum stopcocks

Ŧ joints	Cat. No.
24/40	Z54,479-5
29/32	Z54,480-9



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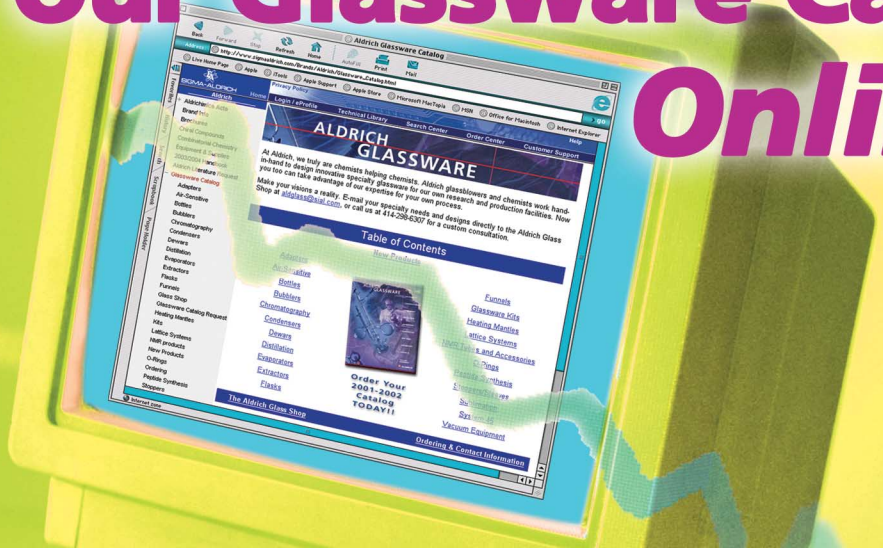

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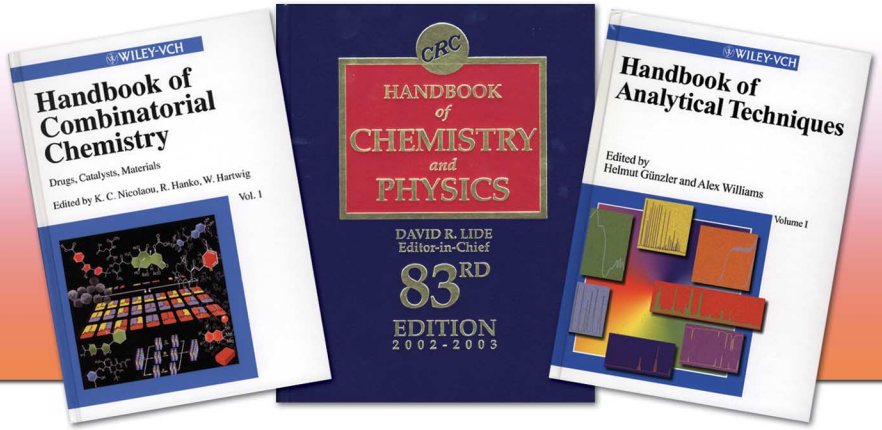

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P. Wasserscheid, Ed., John Wiley & Sons, New York, NY, 2002, 350pp. Hardcover. Ionic liquids not only have the potential to increase chemical reactivity and thus lead to more efficient processes, but also are non-flammable and less toxic than conventional solvents due to their low vapor pressure. This volume brings together the latest developments in this fascinating field and provides numerous practical tips.

Z51,514-0

Ionic Liquids: Industrial Applications for Green Chemistry

R. D. Rogers and K. R. Seddon, Eds., Oxford University Press, New York, NY, 2002, 464pp. Hardcover. One of the first books devoted to room-temperature ionic liquids. A useful guide for chemists interested in environmental protection, synthesis, catalysis, or the modern chemical industry.

Z51,496-9

Green Chemistry: An Introductory Text

M. Lancaster, Royal Society of Chemistry, Cambridge, UK, 2002, 302pp. Softcover. Outlines the basic concepts of the subject in simple language, looking at the role of catalysts and solvents, waste minimization, feedstocks, green-metrics, and the design of safer, more efficient processes. The inclusion of industrially relevant examples throughout demonstrates the importance of green chemistry in many industrial sectors.

Z51,527-2

Laboratory Automation in the Chemical Industries

D. G. Cork and T. Sugawara, Eds., Marcel Dekker, New York, NY, 2002, 384pp. Hardcover. This timely reference explores the broad range of automated techniques being employed by chemists. Written by academics, manufacturers, and practicing chemists in the pharmaceutical and fine chemical industries, the book is divided into two parts covering aspects of automation in chemistry discovery and process development. It features chapters on the design, implementation, and optimization of automated techniques for the production, purification, and analysis of new pharmaceutical and chemical compounds.

Z51,503-5

CRC Handbook of Chemistry and Physics

83rd ed., D. R. Lide, Ed., CRC Press, Boca Raton, FL, 2002, 2,664pp. Hardcover. Provides the widest and most complete coverage of data on properties of inorganic and organic compounds. Includes a new section that marries more contemporary resources, such as the Internet, with existing information.

Z51,474-8

Handbook of Analytical Techniques (2-Vol. Set)

H. Günzler and A. Williams, John Wiley & Sons, New York, NY, 2001, 1,198pp. Hardcover. Serves as a concise, one-stop reference for every professional, researcher, or student using analytical techniques. All relevant spectroscopic, chromatographic, and electrochemical techniques are described, including chemical and biochemical sensors, as well as thermal analysis, bioanalytical, nuclear, and radiochemical techniques. Special articles are devoted to general topics such as chemometrics, sampling, and sample preparation.

Z51,517-5

Handbook of Heterocyclic Chemistry

2nd ed., A. R. Katritzky and A. F. Pozharskii, Elsevier Science, New York, NY, 2000, 748pp. Hardcover. The highly systematic coverage given to the subject makes this one of the most authoritative single-volume accounts of modern heterocyclic chemistry available. Illustrated throughout with thousands of clearly drawn chemical structures. Contains over 1,500 chemical figures and reactions.

Z51,521-3

Handbook of Combinatorial Chemistry: Drugs, Catalysts, Materials (2-Vol. Set)

K. C. Nicolaou, R. Hanko, and W. Hartwig, Eds., John Wiley & Sons, New York, NY, 2002, 1,146pp. Hardcover. This two-volume set deals with synthetic chemistry in all of its forms, ranging from life sciences to materials science. An indispensable reference for synthetic, organic, and medicinal chemists, as well as material scientists.

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Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis

J. Tsuji, John Wiley & Sons, New York, NY, 2002, 496pp. Softcover. Provides complete coverage of nearly 35 years of transition-metal-complex chemistry. Includes an in-depth treatment of many innovative synthetic methodologies, a classification of all reactions according to substrates and reaction mechanisms, and examples of important applications of transition-metal-catalyzed reactions.

Z51,519-1

The Art of Writing Reasonable Organic Reaction Mechanisms

R. Grossman, Springer Verlag, New York, NY, 1998, 346pp. Hardcover. A classic textbook geared for advanced organic chemistry or special topics courses. The author uses a number of devices to help students understand the material. Also includes extensive problem sets at the end of all the chapters.

Z51,499-3

Chlorosulfonic Acid: A Versatile Reagent

R. J. Cremlyn, Springer Verlag, New York, NY, 2002, 300pp. Hardcover. This book provides a detailed, up-to-date account of the reactions of chlorosulfonic acid with aliphatic, aromatic, and heterocyclic compounds. Reactions with elements and inorganic compounds are also discussed, along with the use of the reagent as a powerful acid catalyst and dehydrating agent. Also reviews the commercial uses and manufacture of chlorosulfonic acid.

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Pharmaceutical Master Validation Plan: The Ultimate Guide to FDA, GMP, and GLP Compliance

S. I. Haider, CRC Press, Boca Raton, FL, 2001, 208pp. Hardcover + CD-ROM. An essential guide for establishing a master plan in compliance with FDA, GMP, and GLP requirements. Furnishes the building blocks for developing successful validation procedures and enables users to achieve regulatory compliance with time, money, and resource optimization. Provides a concise and easy-to-use reference tool for the testing and validation of pharmaceutical industry products and facilities.

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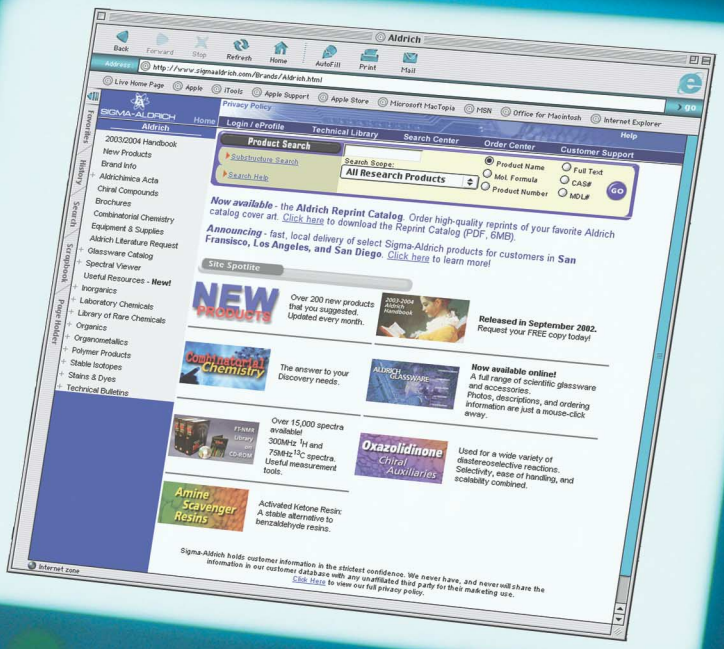

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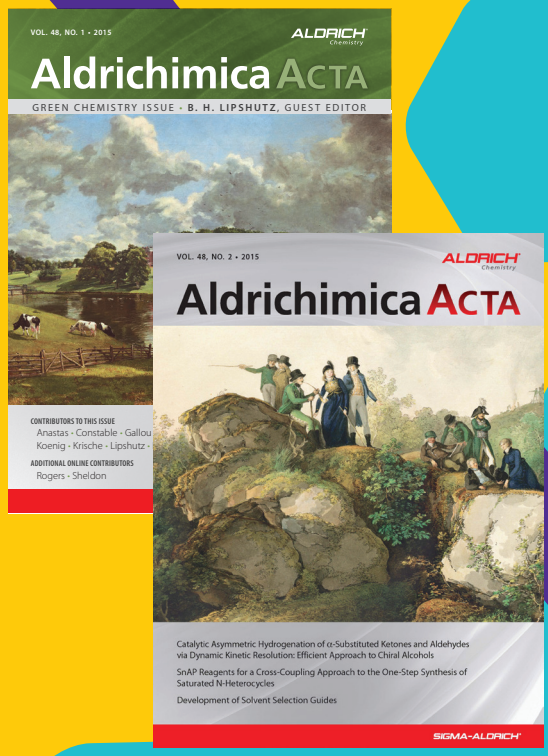

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