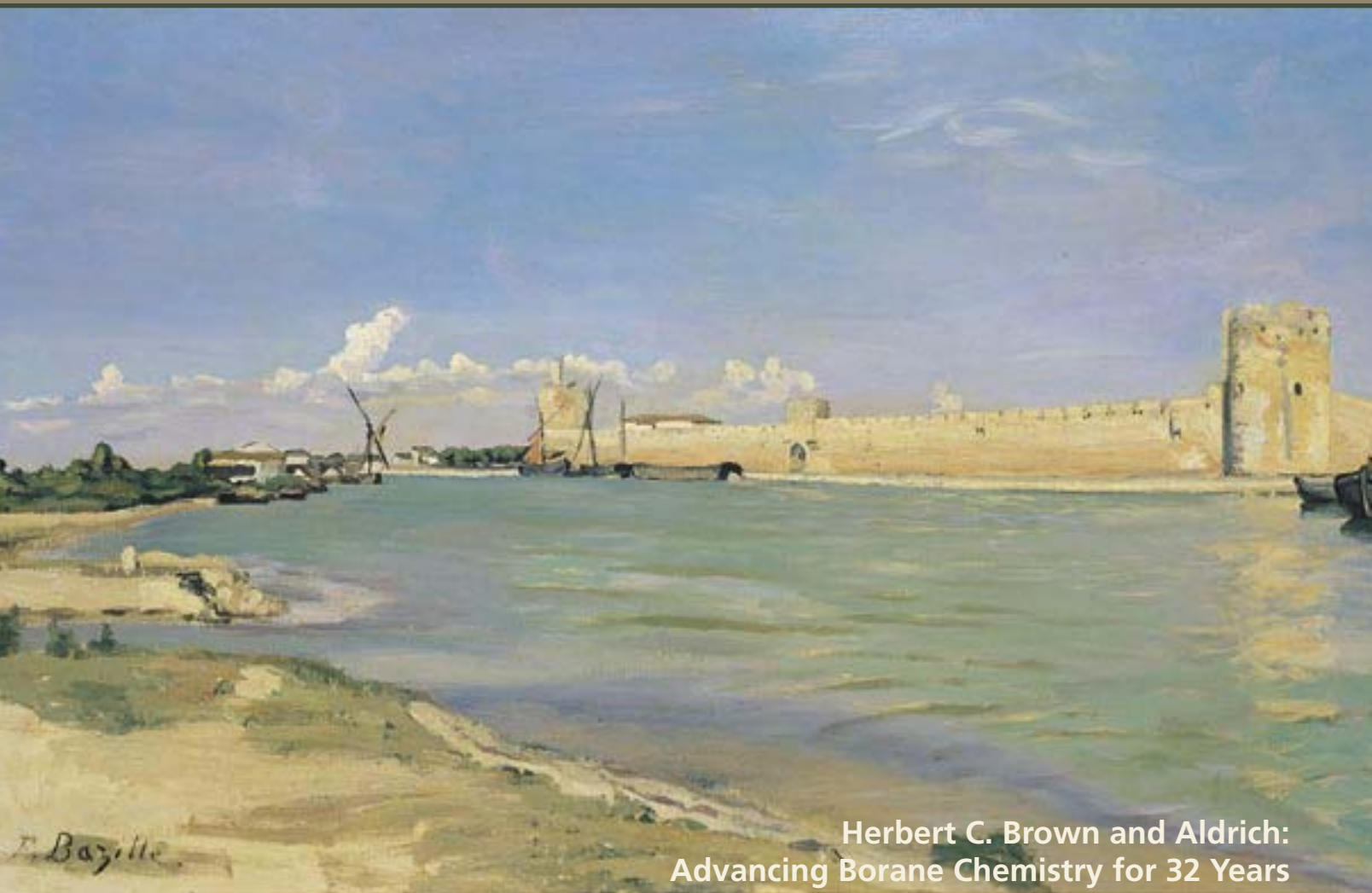


HONORING THE LIFE AND CONTRIBUTIONS OF H. C. BROWN

Aldrichimica ACTA

VOL. 38, NO. 2 • 2005



Herbert C. Brown and Aldrich:
Advancing Borane Chemistry for 32 Years

**Organotrifluoroborates:
Expanding Organoboron Chemistry**

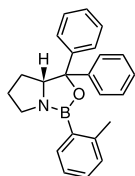
**Recent Advances in the Chemistry
of Lithium Aminoborohydrides**

New Products from Aldrich R&D

REAGENTS FOR ASYMMETRIC SYNTHESIS

(R)-(+)-*o*-Tolyl-CBS-oxazaborolidine solution, 0.5 M in toluene

65,429-9

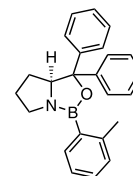


5 mL
25 mL

Excellent reagents for catalytic asymmetric transformations such as the Diels–Alder reaction¹ and the cyanosilylation of aldehydes.^{1,2} Chiral cationic oxazaborolidines, prepared from *o*-tolylloxazaborolidine and triflic acid, catalyze Diels–Alder reactions to provide high ee's.³ Recently, Corey and co-workers used these catalysts to synthesize several chiral natural products, otherwise synthesized in racemic form.⁴

(S)-(-)-*o*-Tolyl-CBS-oxazaborolidine solution, 0.5 M in toluene

65,430-2



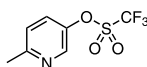
5 mL
25 mL

(1) Corey, E. J. et al. *J. Am. Chem. Soc.* **2002**, 124, 3808. (2) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, 126, 8106. (3) Ryu, D. H. et al. *J. Am. Chem. Soc.* **2002**, 124, 9992. (4) Hu, Q.-Y. et al. *J. Am. Chem. Soc.* **2004**, 126, 13708.

REAGENTS FOR CROSS-COUPLING REACTIONS

2-Methylpyridin-5-yl trifluoromethanesulfonate, 97%

64,848-5

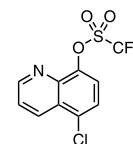


1 g
5 g

Activated triflates of this type have served as alternatives to aryl halides in a variety of palladium-catalyzed coupling reactions.¹⁻³

5-Chloroquinolin-8-yl trifluoromethanesulfonate, 97%

64,850-7



1 g
5 g

(1) Matthews, D. P. et al. *Tetrahedron Lett.* **1994**, 35, 5177. (2) Tilley, J. W.; Zawoiski, S. *J. Org. Chem.* **1988**, 53, 386. (3) Ellingboe, J. W. et al. *J. Med. Chem.* **1994**, 37, 542.

LIGANDS FOR CATALYSIS

Tri-*tert*-butylphosphine solution, 1 M in toluene

65,532-5

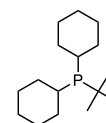


10 mL
50 mL

This low-melting, air-sensitive, and pyrophoric solid is now available as an easier-to-use toluene solution in a Sure/Seal™ bottle.

tert-Butyldicyclohexylphosphine, 97%

65,160-5



1 g
5 g

This novel phosphine was used to prepare catalysts for the ring-opening metathesis polymerization of cyclooctene.

Jan, D. et al. *J. Organomet. Chem.* **2000**, 606, 55.

REAGENT FOR C–X BOND FORMATION

Dimethyl thiophosphonate, 97%

65,531-7



1 g
5 g

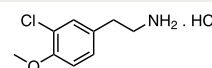
Reacts with imines under mild conditions and without demethylation to form α -aminophosphonothionates.

Tongcharoensirikul, P. et al. *J. Org. Chem.* **2004**, 69, 2322.

BUILDING BLOCK

3-Chloro-4-methoxyphenethylamine hydrochloride

65,632-1



5 g

A useful starting material for the synthesis of many natural products, such as 1,2,3,4-tetrahydroisoquinolines¹ and 2,3,4,5-tetrahydro-1*H*-3-benzazepines.²

(1) Charifson, P. S. et al. *J. Med. Chem.* **1988**, 31, 1941. (2) Chumpradit, S. et al. *J. Med. Chem.* **1991**, 34, 877.

Please see pages 56, 58, and 59 for additional new products.

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

SAFC™

Inspiring Science™

Aldrichimica ACTA

VOL. 38, NO. 2 • 2005

Aldrich Chemical Co., Inc.
6000 N. Teutonia Ave.
Milwaukee, WI 53209, USA

To Place Orders

Telephone 800-325-3010 (USA)
FAX 800-325-5052 (USA)
or 414-438-2199
Mail P.O. Box 2060
Milwaukee, WI 53201, USA

Customer & Technical Services

Customer Inquiries	800-325-3010
Technical Service	800-231-8327
SAFC™	800-244-1173
Custom Synthesis	800-244-1173
Flavors & Fragrances	800-227-4563
International	414-438-3850
24-Hour Emergency	414-438-3850
Web site	sigma-aldrich.com
Email	aldrich@sial.com

General Correspondence

Editor: Sharbil J. Firsan, Ph.D.
P.O. Box 355, Milwaukee, WI 53201, USA

Subscriptions

To request your **FREE** subscription to the *Aldrichimica Acta*, please contact us by:

Phone: 800-325-3010 (USA)
Mail: **Attn: Mailroom**
Aldrich Chemical Co., Inc.
P.O. Box 355
Milwaukee, WI 53201-9358
Email: **sams-usa@sial.com**

International customers, please contact your local Sigma-Aldrich office. For worldwide contact information, please see the inside back cover.

The *Aldrichimica Acta* is also available on the Internet at sigma-aldrich.com.

Aldrich brand products are sold through Sigma-Aldrich, Inc. Sigma-Aldrich, Inc., warrants that its products conform to the information contained in this and other Sigma-Aldrich publications. Purchaser must determine the suitability of the product for its particular use. See reverse side of invoice or packing slip for additional terms and conditions of sale.

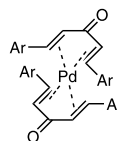
Aldrichimica Acta (ISSN 0002-5100) is a publication of Aldrich. Aldrich is a member of the Sigma-Aldrich family. © 2005 Sigma-Aldrich Co.

"PLEASE BOTHER US."

Joe Porwoll
Joe Porwoll, President

Dr. Ian J. S. Fairlamb of the University of York, U.K., kindly suggested that we offer this Suzuki-Miyaura cross-coupling palladium catalyst in our catalog. Palladium-catalyzed cross-coupling reactions constitute some of the most important and applied transformations for the synthesis of natural products, pharmaceutical targets, and conjugated materials.¹ This palladium catalyst has shown a higher activity over Pd₂(dba)₃ in the Suzuki-Miyaura cross-coupling of organic halides with arylboronic acids.²

(1) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: Hoboken, NJ, 2002.
(2) Fairlamb, I. J. S.; Kapdi, A. R.; Lee, A. F. *Org. Lett.* **2004**, *6*, 4435.



Ar = 3,5-dimethoxyphenyl

65,693-3 Bis(3,5,3',5'-dimethoxybenzylidene)acetone)-palladium(0) [Pd(dm-dba)₂] 1 g
5 g

Naturally, we made this useful catalyst. 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 and on the inside back cover.

TABLE OF CONTENTS

Herbert C. Brown and Aldrich: Advancing Borane Chemistry for 32 Years	43
<i>Clinton F. Lane, Northern Arizona University</i>	
Organotrifluoroborates: Expanding Organoboron Chemistry	49
<i>Gary A. Molander* and Ruth Figueroa, University of Pennsylvania</i>	
Recent Advances in the Chemistry of Lithium Aminoborohydrides	61
<i>Lubov Pasumansky and Bakthan Singaram,* University of California, Santa Cruz; and Christian T. Goralski, CTG Consulting</i>	

ABOUT OUR COVER

The Ramparts at Aigues-Mortes (oil on canvas, 60 × 100 cm) was painted and signed by the artist Frédéric Bazille in 1867. Probably few tourists who visit the famous classical ruins at Nîmes and Arles in southern France are aware that nearby is the best-preserved medieval fortress in Europe, the subject of this painting. In 1246, King Louis IX began the tower seen just to the left of the center of this picture and had a five-mile channel dug through the estuary of the Rhone river to the Mediterranean for ships embarking on the Seventh and Eighth Crusades. His son, Philippe III, started the enormous adjoining battlements in 1272, but, within less than a century, silting closed the passage to the sea and the structure was abandoned.



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

Bazille was born not far away at Montpellier to a well-to-do family and was expected to become a doctor. While still in medical school, however, he convinced his father to subsidize his artistic education in Paris. He soon became fast friends with Alfred Sisley, Auguste Renoir, and Claude Monet, who suggested to Bazille and the others that they paint out-of-doors directly in front of their subjects, thus initiating the essential aspect of impressionist painting. When in the spring of 1867 Bazille went to paint *The Ramparts at Aigues-Mortes*, he wrote to his mother that he intended to paint "a very simple painting" of "the walls of the city reflected in a pond at sunset". The composition of the picture is indeed very simple, defined by the diagonal of the sandbar in the foreground and the almost equal areas of water and sky on either side of the long horizontal of the ramparts. The view is to the east, with the late afternoon sun striking the walls of the fortress. A tower near the right edge of the painting is reflected in the water, and the pink tinge of the clouds suggests the coming sunset.

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

Organoboranes for Asymmetric Synthesis

From Sigma-Aldrich

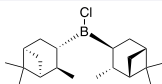
DIP-Chloride™ and DIP-Bromide™

Since its introduction 20 years ago, DIP-Chloride™ (*B*-chlorodiisopinocampheylborane, Ipc_2BCl , DIP-Cl) has become one of the most effective reagents for the asymmetric reduction of prochiral ketones, especially aralkyl and α -hindered ketones.¹ The reagent has found popular use in the asymmetric synthesis of ligands,² β -amino alcohols,³ and alkaloids,⁴ and is also capable of effecting asymmetric aldol reactions.⁵ Furthermore, asymmetric allylations can be achieved when DIP-Cl is reacted with allylmagnesium bromide, allowing for further elaboration of the reduced product. We are now offering this valuable reagent also as an easier-to-handle solution in three different solvents: heptane, hexane, and α -pinene.

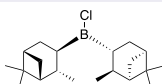
DIP-Bromide™ has been used for the asymmetric reduction of ketones, in enolboration reactions, and for the ring opening of meso epoxides.⁶ Sigma-Aldrich is pleased to offer these excellent reagents for asymmetric synthesis to our customers.

- (1) (a) Chandrasekharan, J. et al. *J. Org. Chem.* **1985**, 50, 5446. (b) Srebnik, M.; Ramachandran, P. V. *Aldrichimica Acta* **1987**, 20, 9.
- (2) Drury, W. J., III et al. *Angew. Chem., Int. Ed.* **2004**, 43, 70.
- (3) Beardsley, D. A. et al. *Tetrahedron Lett.* **1994**, 35, 1511.
- (4) Felpin, F.-X.; Lebreton, J. *J. Org. Chem.* **2002**, 67, 9192.
- (5) Stocker, B. L. et al. *Eur. J. Org. Chem.* **2004**, 330.
- (6) Dhar, R. K. *Aldrichimica Acta* **1994**, 27, 43.

(+)-DIP-Chloride™

31,701-2		5 g 25 g 100 g 1 kg
-----------------	---	------------------------------

(-)-DIP-Chloride™

31,702-0		5 g 25 g 100 g
-----------------	---	----------------------

(-)-DIP-Chloride™ solution, 65–75 wt. % in α -pinene

65,529-5	25 mL 100 mL
-----------------	-----------------

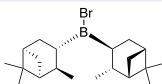
(-)-DIP-Chloride™ solution, 50–65 wt. % in heptane

64,841-8	25 mL 100 mL
-----------------	-----------------

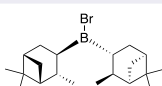
(-)-DIP-Chloride™ solution, 50–65 wt. % in hexanes

64,842-6	25 mL 100 mL
-----------------	-----------------

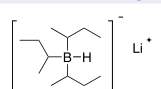
(+)-DIP-Bromide™, 95%

41,427-1		5 g 25 g
-----------------	--	-------------

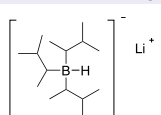
(-)-DIP-Bromide™, 95%

41,099-3		5 g 25 g
-----------------	---	-------------

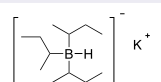
L-Selectride® solution, 1.0 M in tetrahydrofuran

17,849-7		100 mL 800 mL 8 L 18 L
-----------------	---	---------------------------------

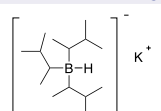
LS-Selectride® solution, 1.0 M in tetrahydrofuran

22,592-4		100 mL
-----------------	---	--------

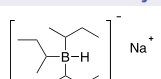
K-Selectride® solution, 1.0 M in tetrahydrofuran

22,076-0		100 mL 800 mL
-----------------	---	------------------

KS-Selectride® solution, 1.0 M in tetrahydrofuran

22,077-9		100 mL
-----------------	---	--------

N-Selectride® solution, 1.0 M in tetrahydrofuran

21,340-3		100 mL 800 mL
-----------------	---	------------------

The Selectride® Family

The Selectride® family of boranes is a group of powerful reagents for the asymmetric reduction of ketones on complex scaffolds. These reagents have been used in the synthesis of many natural products,⁷ in the stereoselective reduction of hemiacetals in various nucleoside syntheses,⁸ and are capable of effecting reductive cyclization⁹ and rearrangement reactions.¹⁰

- (7) Some recent examples: (a) Bahia, P. S.; Snaith, J. S. *J. Org. Chem.* **2004**, 69, 3226. (b) Thede, K. et al. *Org. Lett.* **2004**, 6, 4595. (c) Banwell, M. G. et al. *Org. Lett.* **2004**, 6, 2737. (d) Lichtenhaler, F. W. et al. *Tetrahedron: Asymmetry* **2003**, 14, 727. (e) Nelson, T. D. et al. *Tetrahedron Lett.* **2004**, 45, 8917.
- (8) (a) Hanessian, S.; Machaalani, R. *Tetrahedron Lett.* **2003**, 44, 8321. (b) Navarre, J.-M. et al. *Tetrahedron Lett.* **2003**, 44, 2199.
- (9) Nagaoka, Y. et al. *Tetrahedron Lett.* **2002**, 43, 4355.
- (10) (a) Chen, W. et al. *J. Org. Chem.* **2003**, 68, 1929. (b) Appendino, G. et al. *Eur. J. Org. Chem.* **2003**, 4422.

For competitive quotes on larger quantities of all of these organoboranes, please contact us at 800-244-1173 (USA) or at safcglobal.com.

Herbert C. Brown and Aldrich: Advancing Borane Chemistry for 32 Years



The author presenting Professor Brown with the first ACS H. C. Brown Award for Creative Research in Synthetic Methods (1998).

Clinton F. Lane
Department of Chemistry and Biochemistry
Northern Arizona University
P.O. Box 5698
Flagstaff, AZ 86011-5698, USA
Email: clint.lane@nau.edu

Outline

1. Introduction
2. Before 1972
3. Aldrich-Boranes, Inc.
4. Early Borane Reagents
5. Boranes on a Large Scale
6. Latest Borane Reagents
7. Philanthropy
8. Conclusions
9. References and Notes

1. Introduction

Nobel Laureate Herbert C. Brown (HCB), the R. B. Wetherill Research Professor Emeritus of Chemistry at Purdue University, died on December 19, 2004, at age 92. He will long be remembered at Aldrich and by the scientific community for his extensive contributions to borane chemistry. Brown and Aldrich maintained a close working relationship that started in 1972 and continued until his death. Interested readers are directed to his published obituary¹ and to the HCB pages on the Purdue University Department of Chemistry Web site.² A number of essays and notes have also appeared in this magazine, which provide biographical information and additional details about HCB and his 32-year relationship with Aldrich.³

This account will give a personal perspective of a career-long relationship with HCB as a thesis adviser and mentor and then as a consultant and friend, and of how he and I were able to help Aldrich advance borane chemistry.

2. Before 1972

The late 1960s were exciting times in HCB's research group at Purdue. We were actively investigating hydroboration and the reactions of organoboranes. The work was being quickly published as a series of communications in various journals.⁴ However,

Brown knew his developments would not be widely used until his new borane reagents were made available commercially.

The Schlesinger–Brown process for preparing metal borohydrides was developed on a laboratory scale at the University of Chicago in the early 1940s.^{5a} In the 1950s, Brown worked closely with Metal Hydrides (a start-up company in Massachusetts) on the scale-up of the process he, Schlesinger, and Finholt had discovered to produce NaBH_4 .^{5b} As expected, this valuable reagent was widely used by scientists only after it had become commercially available.

Encouraged by the success of NaBH_4 in research and commerce, Brown contacted a number of companies about licensing and developing his organoborane technology. Between 1969 and 1971, he successively approached the following companies: Ventron Corporation (the successor to Metal Hydrides), Ethyl Corporation, Eastman Kodak, Arapahoe Chemicals, and G. D. Searle and Company. In each case, the R&D scientists and the technical management groups at these companies were very interested and could see the potential for his new technology. However, once the proposals went higher in the organization, the business development staff would carry out market research only to find a complete absence of any sales numbers for the products. This was hardly surprising, since the products were not yet commercially available.

Professor Brown never shared the details of his aforementioned contacts with me when I was one of his Ph.D. students. However, he did ask me many times if I would be interested in working in industry to further the development of his borane technology. I always expressed an interest, but I could not wait for HCB to find an industrial partner. I left Purdue University in the fall of 1971, with my Ph.D. degree still pending, and joined Professor William T. Miller's research group at Cornell University as a postdoctoral research assistant to work on the chemistry of organofluorine compounds.

3. Aldrich-Boranes, Inc.

Early in 1972, HCB approached Alfred Bader, the cofounder and then president of Aldrich Chemical Co., and suggested that Aldrich consider offering a number of Brown's boron-containing reagents. Dr. Bader (Harvard Ph.D. with Louis Fieser) recognized the potential for Brown's technology, and offered to establish a subsidiary, Aldrich-Boranes, Inc., to commercialize all of Brown's discoveries. In the summer of 1972, Brown and Bader recruited me to become the first outside employee of this new company. I started my career with Aldrich in September of 1972, and first worked for Harvey Hopps, an existing Aldrich employee who had been appointed manager of Aldrich-Boranes. HCB became a director of Aldrich and a consultant to Aldrich-Boranes, Inc. His existing patents and all future ones covering all of his discoveries in boron-based chemistry were assigned to Aldrich-Boranes.

4. Early Borane Reagents

Aldrich-Boranes occupied first one, then two, and finally three laboratories in Aldrich's 940 West Saint Paul Avenue Building in Milwaukee, Wisconsin. During the period from 1972 to 1977, HCB called at least once or twice a week to discuss our progress. He often followed up the phone conversations with long and detailed letters. As usual, he was always very positive and optimistic about the chemistry, and would never accept a poor result for any scale-up of his chemistry. He contributed greatly to our success and remained interested and available. He visited us in Milwaukee at least two or three times a year, and I visited him at Purdue many times each year.

Within a year, ALHB (internal vendor code for Aldrich-Boranes) was successful in scaling up and developing many organoborane-based products for listing in the Aldrich catalog. However, we lost money. The following year (1973), we broke even. By the end of the third year, we made enough money to offset all previous losses, and the operations have been profitable ever since. The borane reagents developed during this period (**Figure 1**) now account for many millions of dollars in annual sales, with a few being among Aldrich's best-selling products.

HCB was not only a great scientist, but also a good businessman. He took an interest in all aspects of our business, especially the advertising and promotion of our products. He encouraged me to expand some of our advertisements into detailed reviews suitable for publications. These were published in various refereed journals and then condensed into shorter reviews for this magazine.⁶ In addition, HCB contributed a review on the subject and encouraged one of his

postdoctoral assistants to submit another.⁷ These helped promote our borane products and contributed greatly to our early success.

5. Boranes on a Large Scale

By our fourth year (1976), ALHB was starting to outgrow the space it occupied in Milwaukee, and desperately needed additional space to meet the market demand for borane reagents. Fortunately, we were able to purchase a small chemical plant in rural Sheboygan County about 50 miles north of downtown Milwaukee. ALHB moved to this new site in early 1978, and has continued to show strong growth to this day. My three chemist associates from Milwaukee (John Daniels, Wayne Adler, and Jim Sarafin) joined me in our move to the Sheboygan site. The three are currently part of the management team at the Sheboygan site of Sigma-Aldrich, Aldrich's successor company. HCB's long-term relationship with Aldrich is thus reflected in the long-term careers of many of Aldrich's chemists.

Today, Sigma-Aldrich operates five major plants on the 513-acre Sheboygan site. The production, packaging, and utilization of air-sensitive reagents remain an important part of operations at the site (**Figure 2**). Various borane reagents remain key compounds in production there, and new borane reagents continue to be developed at the site.

6. Latest Borane Reagents

Hundreds of additional and useful boron-based reagents were discovered in Brown's laboratories at Purdue in the 20+ years following his winning of the Nobel Prize in 1979. Sigma-Aldrich's R&D scientists worked very hard, with steady encouragement from HCB, to scale up and offer as many of his new borane reagents as possible. It is impossible to list all of these newer reagents in this short account, but **Figure 3** gives a representative sample. Brown continued to write and encourage his co-workers to write reviews for this magazine to promote his latest borane discoveries.⁸ It is interesting to note that the majority of HCB's work on reagents for asymmetric synthesis occurred after he received the Nobel Prize. The α -pinene-derived reagents could prove to be the most useful yet (**Figure 4**).^{8c}

7. Philanthropy

In 1960, Brown was promoted to R. B. Wetherill Research Professor. A significant part of the promotion package stipulated that HCB would be given personal ownership of all his existing and future patents. This was quite an unusual arrangement, but it enabled Brown to easily work with Alfred Bader on the

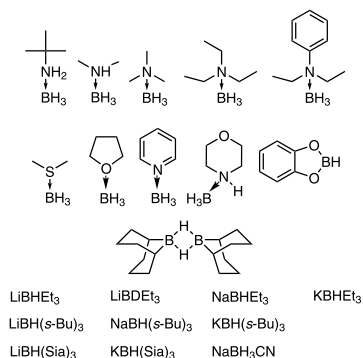


Figure 1. Early Borane Reagents Developed and Offered by Aldrich.



Figure 2. Herbert and Sarah Brown in 1999 near PRO I, the Building Dedicated to the Production of Air-Sensitive Compounds at the Sigma-Aldrich Site near Sheboygan, WI.

establishment of Aldrich-Boranes, Inc. Brown personally received royalty payments on the sales of all borane reagents sold by Aldrich. It might appear that Purdue gave up significant financial gains to keep a rising star. However, rewards come to those who wait.

In 1983, Herb and Sarah Brown endowed a special fund to establish and finance the Herbert C. Brown Lectures at Purdue. Every year since 1984, 3–5 world-class chemists are invited to Purdue to present a lecture on a Saturday in April. Interestingly, when the Department of Chemistry at Purdue first proposed these lectures, the plan was to seek financial contributions from HCB's former students and friends. Sarah rejected this idea and proposed that she and Herb provide all the necessary funds.

HCB was the first winner of the American Chemical Society Herbert C. Brown Award for Creative Research in Synthetic Methods (1998). Aldrich proposed this award to the ACS, and the endowment funds came from Herb and Sarah and the Purdue Borane Research Fund. Even though HCB provided the funding, it was a well-deserved honor for Herb to be the first recipient.

The following year, Herb and Sarah endowed the Herbert C. Brown Professorship of Chemistry at Purdue and provided all the financing to establish the Herbert C. Brown Center for Borane Research at Purdue. The funds for both have come from past royalty payments from Aldrich. Continuing royalty payments will be used to provide future financial support of these two entities.

8. Conclusions

It is generally believed that Brown's body of work in boron chemistry (the hydroboration reaction, reactions of organoboranes, selective reductions using boron hydrides, and asymmetric synthesis using borane reagents) represents the single most important individual accomplishment of the 20th century in synthetic chemistry. Aldrich is very proud to have played a part in achieving this accomplishment.


In 1972, Aldrich's motto was "Craftsmen in Chemistry", which was very appropriate for both HCB and the Aldrich chemists at that time. Later, Aldrich changed its motto to "Chemists Helping Chemists in Research and Industry", which was how HCB also approached his contributions to synthetic chemistry. He always wanted his reagents to be used by others in their research. Today,

Aldrich's motto is "Advancing Science". There is no question that Herbert C. Brown worked his entire life to advance borane science. He will be missed, but we will continue to explore and develop the borane chemistry he first discovered.

9. References and Notes

- (a) Jacoby, M. *Chem. Eng. News* **2005**, 83 (January 3), 8. (b) Perks, B. *Chem. World* **2005**, 2 (February), 10.
- <http://www.chem.purdue.edu/hcbrown/> (accessed February 2005). Please note especially the links to Biography, HCB Story (autobiographical); Purdue Lecture; 1979 Nobel Prize with a PDF file of the HCB Nobel lecture of December 8, 1979; and a bibliographical archive listing all of HCB's patents (total of 63), publications (total > 1200), the 22 M.S. degree theses, and the 141 Ph.D. theses of HCB's former students.
- (a) Brewster, J. H. *Aldrichimica Acta* **1987**, 20, 3. (b) Davenport, D. A. *Aldrichimica Acta* **1987**, 20, 25. (c) Firsan, S. J. *Aldrichimica Acta* **2001**, 34, 35. (d) Herbert C. Brown and Aldrich (*Editor's note*). *Aldrichimica Acta* **2002**, 35, 2.
- For a review covering this early period of organoborane research, see Brown, H. C. *Organic Syntheses via Boranes*; Wiley-Interscience: New York, 1975. (Reprinted as *Organic Syntheses via Boranes, Volume 1* by Aldrich Chemical Company, Inc.; Cat. No. Z40,094-7.)
- (a) Schlesinger, H. I.; Brown, H. C. *J. Am. Chem. Soc.* **1940**, 62, 3429. (b) Schlesinger, H. I.; Brown, H. C.; Finholt, A. E. *J. Am. Chem. Soc.* **1953**, 75, 205.
- (a) Lane, C. F. *Aldrichimica Acta* **1973**, 6, 21. (b) Lane, C. F. *Aldrichimica Acta* **1973**, 6, 51. (c) Lane, C. F. *Aldrichimica Acta* **1975**, 8, 3. (d) Lane, C. F. *Aldrichimica Acta* **1975**, 8, 20. (e) Lane, C. F. *Aldrichimica Acta* **1977**, 10, 41. (f) Lane, C. F. *Synthesis* **1975**, 135. (g) Lane, C. F. *Chem. Rev.* **1976**, 76, 773.
- (a) Brown, H. C. *Aldrichimica Acta* **1974**, 7, 43. (b) Krishnamurthy, S. *Aldrichimica Acta* **1974**, 7, 55.
- (a) Brown, H. C.; Campbell, J. B., Jr. *Aldrichimica Acta* **1981**, 14, 3. (b) Srebnik, M.; Ramachandran, P. V. *Aldrichimica Acta* **1987**, 20, 9. (c) Dhar, R. K. *Aldrichimica Acta* **1994**, 27, 43. (d) Cho, B. T. *Aldrichimica Acta* **2002**, 35, 3. (e) Ramachandran, P. V. *Aldrichimica Acta* **2002**, 35, 23. (f) Kanth, J. V. B. *Aldrichimica Acta* **2002**, 35, 57.

About the Author

Clinton F. Lane was born on January 29, 1944, in Iowa City, Iowa. He received his B.S. degree in chemistry in 1966 from Iowa State University of Science and Technology and his Ph.D. degree in 1972 from Purdue University, where he studied under the direction of Professor Herbert C. Brown. After one year of postdoctoral studies at Cornell University, Clint joined Aldrich Chemical Company as an R&D chemist with the goal of commercializing the organoborane technology discovered in HCB's laboratories. He was personally involved, or led teams, in new-product R&D, process R&D, scale-up, market development, and the manufacturing of hundreds of boron hydride, metal hydride, organoboron, and organometallic reagents that are now commercially available from Sigma-Aldrich, Inc. In later years at Aldrich, he was involved extensively in business development and technology licensing. Clint led a team that negotiated and set up a spin-off joint venture (Aldrich-APL, LLC); he also negotiated the terms of, and led the integration teams for, two acquisitions (Carbolabs, Inc., and Isotec, Inc.). In recognition of his service of over 30 years to the chemical community, Clint received several awards, and eventually became President of Aldrich in 1999. He retired in 2003, and is presently a research professor at Northern Arizona University. 

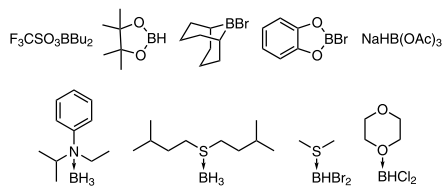


Figure 3. Representative List of the Latest Borane Reagents.

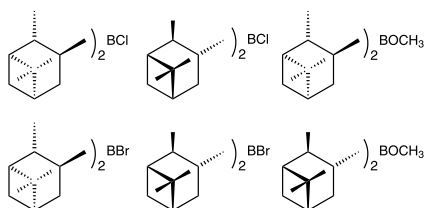


Figure 4. α -Pinene-Derived Borane Reagents.

Sigma-Aldrich: Promoting Online Customer Solutions

Life Science Industry Awards
The Science Choice
Sigma-Aldrich
2004



We are very pleased to announce that Sigma-Aldrich recently won first place for Customer Service at the 2004 Life Science Industry Awards in Washington, DC. This achievement truly reflects our everyday commitment and attitude towards providing world-class service to our customers. As part of this commitment, Sigma-Aldrich offers many fast and easy online services including price quotations, ordering, and shipment tracking. We invite you to visit us at sigma-aldrich.com and explore!

Ready to get started online? To support our online services, we have assembled a team of highly trained individuals to assist you and answer your questions. Our PIVOT (Providing the Internet's Value Over the Telephone) team provides several services, including:

- Customize and tailor your eProfile to fit your specific business needs.
- Demonstrate how to place online orders and quotes.
- Demonstrate how to check product availability, check the status of an order, and get tracking information for shipped orders.
- Demonstrate how to obtain technical information such as MSDS's, C of A's, and technical bulletins.
- Provide ongoing support for occasional and routine users.

Please call us at 1-800-286-2635 (USA), or email us at pivot@sial.com for all of your Sigma-Aldrich Web site needs.

We look forward to speaking with you and are confident you will share our enthusiasm, once you experience the benefits our Web site has to offer.

sigma-aldrich.com

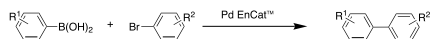
LEADERSHIP IN LIFE SCIENCE, HIGH TECHNOLOGY AND SERVICE
SIGMA-ALDRICH CORPORATION • BOX 14502 • ST. LOUIS • MISSOURI • USA



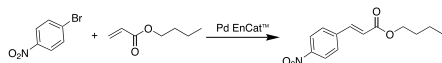
SIGMA-ALDRICH

Pd EnCat™ Experience the Latest in Palladium Catalyst Technology

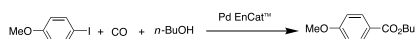
Suzuki Coupling



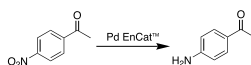
Heck Reaction



Carbonylation



Transfer Hydrogenation



Benefits of Using Pd EnCat™

- Low residual metal levels in final crude product (typically <10 ppm before purification)
- Easy recovery of catalyst by filtration
- Safer and easier to handle than palladium-on-carbon
- Compatibility with a wide range of process technology options, e.g., fixed-bed, fluidized-bed, trickle-bed, and microwave reactors

References: (1) Yu, J.-Q. et al. *Chem Commun.* **2003**, 678. (2) Bremeyer, N. et al. *Synlett* **2002**, 1843. (3) Ley, S. V. et al. *Chem Commun.* **2002**, 1134. (4) Chandrashekar, R. et al. *Chem Commun.* **2002**, 1132. (5) Vickerstaffe, E. et al. *Org. Biomol. Chem.* **2003**, *1*, 2419. (6) Ley, S. V. et al. *Org. Lett.* **2003**, *5*, 4665. (7) Pears, D. A.; Smith, S. C. *Aldrichimica Acta* **2005**, *38*, 23.

Cat No.	Name	Matrix Content (%)	%Pd (mmol/g)	P (mmol/g)	Ligand	Units		
64,472-2	Pd EnCat™ 40	40	3.9–4.6 (0.4)	N/A	N/A	1 g	10 g	100 g
64,471-4	Pd EnCat™ 30	30	3.9–4.6 (0.4)	N/A	N/A	1 g	10 g	100 g
64,470-6	Pd EnCat™ TPP30	30	3.9–4.6 (0.4)	0.26–0.35	Ph ₃ P	1 g	10 g	100 g
64,469-2	Pd EnCat™ TOTP30	30	3.9–4.6 (0.4)	0.15–0.20	(<i>o</i> -Tol) ₃ P	1 g	10 g	100 g
65,366-7	Pd(O) EnCat™ 30NP, Wet (45% water, unit weight excludes water)	30	3.7–4.6 (0.4)	N/A	N/A	1 g	10 g	100 g

Request a FREE copy of the EnCat™ User Guide CD by contacting cdavis1@sial.com (USA) or your local Sigma-Aldrich office.

For bulk inquiries, please call us at 800-244-1173 (USA) or visit us at safcglob.com.

LEADERSHIP IN LIFE SCIENCE, HIGH TECHNOLOGY AND SERVICE
ALDRICH • BOX 355 • MILWAUKEE • WISCONSIN • USA

Reaxa
www.reaxa.com

ALDRICH®
Advancing Science

sigma-aldrich.com

Get Results FAST...

PEPscreen®: Custom Peptide Libraries

Sigma-Genosys has developed a proprietary peptide synthesis platform using state-of-the-art technology. This technology allows the fastest and most efficient high-throughput parallel synthesis of milligram quantities of peptide libraries. The PEPscreen® service provides researchers with the ability to order large numbers of extremely affordable custom peptides delivered in less than 7 business days.

Product Specifications

- Quantity: 0.5–2 mg
- Length: 6–20 amino acids
- QC: MALDI-TOF MS on 100% of the peptides
- Format: lyophilized in 96-well tube racks
- Shipped with electronic PDF files of QC data and peptide sequence directory
- Minimum order size is 48 peptides

Features and Benefits

- Delivery: 7 business days or less
- Compatible with robotic automation for resuspension and dispensing in screening applications
- Ideal for performing solution-phase assays
- Suitable for robotic production of peptide microarrays
- N-Terminal modifications and nonstandard residue availability allows for maximum flexibility in project design

Modifications Available

- N-Terminal acetylation
- N-Terminal biotin
- N-Terminal fluorescein
- D-Amino acids
- Nonstandard residues
- Phosphorylated residues
- C-Terminal acid or amide



Ordering Information

For more information, please refer to sigma-genosys.com/acta205.

For technical inquiries, please contact peptides@sial.com.

Place your order by emailing your sequences in an 8-channel orientation (peptide #1 = A1, peptide #2 = B1, peptide #8 = H1, peptide #9 = A2, etc.).

NEW Aldrich® Zipper-Lock AtmosBag™

Fast, easy access to contents with a reliable, gas-tight seal

AtmosBag™ is a flexible, inflatable polyethylene chamber with built-in gloves that lets you work in a totally isolated and controlled environment. It is an inexpensive, portable alternative to the glove box, and is well suited to a variety of tasks and materials. It comes with the new **Technical Bulletin AL-211**, which contains instructional information and a listing of AtmosBag™ accessories.

- Manipulation of air- and moisture-sensitive materials
- Sampling and weighing operations
- Desiccating or constant-humidity chamber
- Controlled habitat for botany and life sciences
- Field sampling and testing



Two-Hand, Zipper-Lock AtmosBag™

Size	Opening (in.)	Inflation Vol. (L)	Cat. No.
S	12	50	Z53,020-4
M	24	280	Z53,021-2
L	36	520	Z53,022-0

sigma-aldrich.com

LEADERSHIP IN LIFE SCIENCE, HIGH TECHNOLOGY AND SERVICE
ALDRICH • BOX 355 • MILWAUKEE • WISCONSIN • USA

ALDRICH
Advancing Science

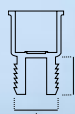
AtmosBag and Aldrich are a trademark and a registered trademark, respectively, of Sigma-Aldrich Biotechnology, L.P.

Suba•Seal® Rubber Septa Exclusively from Sigma-Aldrich

The Suba•Seal® name is well-known as the best-quality fold-over closure with serrated stopper. Sigma-Aldrich is now the exclusive worldwide source for genuine Suba•Seal® products. We have increased your choice of colors to give you more options to color-code your applications, and are offering a silicone rubber version for higher-temperature use. Check out the product table below for more information that will help you choose the best Suba•Seal® closure for your application.

Suba•Seal® rubber septa—ideal for air- and moisture-sensitive chemistry procedures. After piercing with non-coring needle, the rubber closes puncture, providing air- and moisture-tight seal to protect contents of vessel or container from the atmosphere. This closure has a fold-over flange molded to grip the outside of the container neck, promoting a double seal in conjunction with the annular serrations on the hollow plug. The annular serrations depress themselves against the inside wall of the neck of the flask, making each serration a suction sealing point. **Note:** For extra security when using large-bore transfer needles, fasten septum to bottle or flask opening with a wrap-it tie.

See the new 2005–2006 Aldrich catalog or visit our Web site at sigma-aldrich.com/labequipment for additional Suba•Seal® colors and listings, Schlenk glassware, wrap-it ties, and accessory tools.



Suba•Seal® No.	Fits Neck I.D. (mm)	Length (mm)		Use with	White Rubber Cat. No.	Red Rubber Cat. No.
		A	B			
13	9.5	9.6	9.3	10/30 joints	Z16,725-8	Z12,456-7
25	14.0	14.1	12.5	14/20 joints	Z16,728-2	Z12,459-1
33	17.5	18.0	12.7	Sure/Seal™ bottles	Z16,729-0	Z12,461-3
37	19.0	20.4	15.7	19/22 joints	Z16,730-4	Z12,462-1
45	22.0	23.0	20.4	24/40 joints	Z16,732-0	Z12,465-6
57	27.0	28.3	20.5	29/42 joints	Z16,735-5	Z12,468-0

sigma-aldrich.com

LEADERSHIP IN LIFE SCIENCE, HIGH TECHNOLOGY AND SERVICE
ALDRICH • BOX 355 • MILWAUKEE • WISCONSIN • USA

ALDRICH
Advancing Science

Suba•Seal is a registered trademark of William Freeman & Co., Ltd. Sure/Seal is a trademark of Sigma-Aldrich Biotechnology, L.P.

Organotrifluoroborates: Expanding Organoboron Chemistry



Dr. Gary A. Molander



Dr. Ruth Figueroa

Gary A. Molander* and Ruth Figueroa
Roy and Diana Vagelos Laboratories
Department of Chemistry
University of Pennsylvania
231 South 34th Street
Philadelphia, PA 19104-6323, USA
Email: gmolandr@sas.upenn.edu

Outline

1. Introduction
2. Preparation of Potassium Organotrifluoroborates
3. Suzuki Cross-Coupling Reactions
 - 3.1. Alkyltrifluoroborates
 - 3.2. Aryltrifluoroborates
 - 3.3. Heteroaryltrifluoroborates
 - 3.4. Alkenyltrifluoroborates
 - 3.5. Alkynyltrifluoroborates
 - 3.6. Synthetic Application
4. Oxidation Reactions
 - 4.1. Epoxidation
 - 4.2. Ozonolysis
5. Conclusions
6. References and Notes

1. Introduction

Boronic acids, boronate esters, and organoboranes have been employed for many years as the principal organoboron partners in Suzuki–Miyaura-type cross-coupling reactions.¹ However, these reagents possess many limitations. Boronic acids are notorious for being difficult to purify and for having an uncertain stoichiometry. Even though the use of boronate esters is more attractive from this point of view, these reagents lack atom economy and are more expensive to employ. Organoboranes are limited by the inherent characteristics of the in situ hydroboration reaction used to create them. These latter reagents also suffer from high sensitivity to air and poor functional-group compatibility in some cases. In contrast, organotrifluoroborates are unique compounds that have been shown to overcome these limitations. These reagents can be easily prepared from inexpensive materials. They are stable to air and moisture, allowing storage for long periods of time without noticeable degradation. In fact, their high versatility and stability has made them excellent partners in Suzuki–Miyaura-type coupling reactions.

Even though the chemistry of organotrifluoroborates has been comprehensively reviewed elsewhere,² the recent growth

in the application of these compounds warrants another look. The present review outlines the utility and versatility of organotrifluoroborates in cross-coupling reactions. Additionally, the ability of these reagents to resist chemical oxidation will be highlighted. This feature of organotrifluoroborates offers a unique opportunity to preserve the carbon–boron bond in the oxidation of remote functionality within the same molecule.

2. Preparation of Potassium Organotrifluoroborates

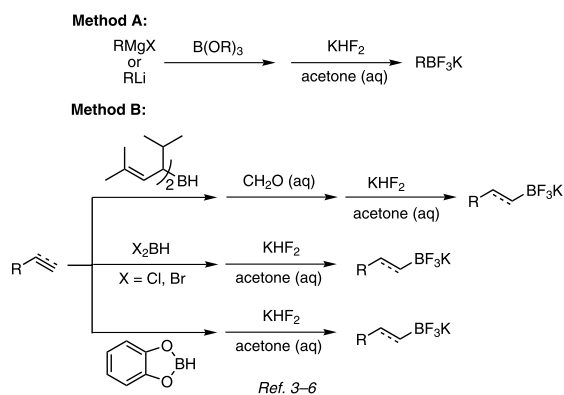
Although potassium organotrifluoroborates have been known for some time, Vedejs and co-workers were the first to report the most convenient synthesis of these materials from boronic acids and derivatives utilizing the readily available and inexpensive KHF_2 .³ In combination with this facile process, potassium organotrifluoroborates are thus accessed by two general methods (**Scheme 1**).^{3–6} They can be readily prepared by starting with the transmetalation of organolithium or Grignard reagents with trialkylborates.⁴ Alternatively, they can be synthesized ultimately by various catalyzed or uncatalyzed hydroborations of alkynes or alkenes,^{5,6} taking advantage of the unique selectivity associated with each version of this process.

3. Suzuki Cross-Coupling Reactions

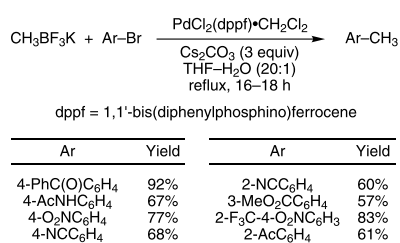
Early studies by the groups of Genêt⁷ and Xia⁸ demonstrated the potential of organotrifluoroborates in palladium-catalyzed coupling reactions to form biaryls using arenediazonium salts or diaryliodonium salts as electrophiles. It should be noted that organotrifluoroborates led to superior yields and reactivity in side-by-side comparisons with boronic acids.⁹ Since those early studies, the scope of cross-coupling reactions that utilize organotrifluoroborates has expanded considerably.

3.1. Alkyltrifluoroborates

The first cross-coupling reactions of alkyltrifluoroborates with aryl halides were efficiently performed using $\text{PdCl}_2(\text{ddpf})$ as the catalyst, Cs_2CO_3 as the base, and $\text{THF-H}_2\text{O}$ as the solvent system, and showed tolerance of a number of functional groups (**eq 1**).^{10,11}

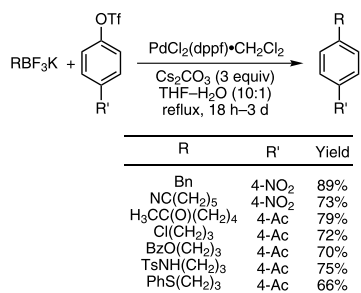


Scheme 1. The Two General Methods for Preparing Organotrifluoroborates.



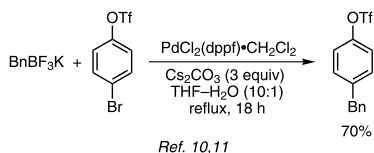
Ref. 11

eq 1

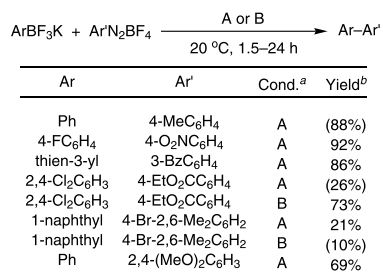


Ref. 10,11

eq 2



eq 3



^a Conditions A: Pd(OAc)₂, 1,4-dioxane;

conditions B: Pd₂(μ-OAc)₂[P(*o*-tolyl)₃]₂, MeOH.

^b Isolated yields. GC yields are in parentheses.

Ref. 7a

eq 4

Aryl halides are attractive partners because of their ready availability and economy. Interestingly, the presence of water is essential for the efficiency of the reaction. This requirement for water and added base has elicited several mechanistic studies on the actual species involved in the coupling process.^{12,13}

Aryl triflates, common coupling partners in palladium-catalyzed cross-coupling reactions, were as efficient as the aryl halides (eq 2).^{10,11} Surprisingly, the nitro group survived the basic reaction conditions, when *p*-nitrophenyl triflate was reacted with potassium benzyltrifluoroborate. By contrast, the nitro group is reduced to the corresponding aniline product in Suzuki reactions with *B*-alkyl-9-BBN.¹⁴ The electrophiles employed showed the same relative reactivity order as that observed with organotin¹⁵ and *B*-alkyl-9-BBN¹⁴ reagents, i.e., Br > OTf >> Cl (eq 3).¹⁰ The use of secondary alkyltrifluoroborates was prohibited by the predominance of β-elimination and dehydroboration pathways.

3.2. Aryltrifluoroborates

The use of aryltrifluoroborates in Suzuki-type reactions was first reported by Genêt's and Xia's groups. Genêt and co-workers⁷ reported the reaction of arenediazonium tetrafluoroborates with aryltrifluoroborates using two catalyst systems: Pd(OAc)₂ in 1,4-dioxane (A) and Pd₂(μ-OAc)₂[P(*o*-tolyl)₃]₂ in MeOH (B) (eq 4).^{7a} These systems were tolerant of different functional groups and, in the case of the *ortho*-chloro-substituted aryltrifluoroborate, only conditions B were efficient due to the precipitation of metallic palladium when using conditions A. The reaction was also chemoselective toward the arenediazonium salt in the presence of halides or triflates.

Chen and Xia also reported the use of diaryliodonium salts (eq 5) and 2-thienyl(tosyloxy)iodobenzene (eq 6) as coupling partners of organotrifluoroborates to provide biaryls in excellent yields.⁸ The scope of the reaction was extended to palladium catalysts with or without phosphine ligands. Similar results were obtained with Koser's reagent, PhI(OH)OTs, as the coupling partner.

Subsequently, the reaction of aryltrifluoroborates with aryl halides as coupling partners was developed (eq 7).^{12,16} Specifically, a key point was the discovery that the use of a base was required. As previously observed by Xia, many of the reactions could be performed under ligandless conditions. A variety of trifluoroborates were reacted using Pd(OAc)₂ as the catalyst and inexpensive K₂CO₃ as the base. The choice of solvent for these cross-couplings was critical because of solubility issues associated with trifluoroborates. Another added feature of these reactions was their insensitivity to oxygen: excellent results were obtained whether the reactions were carried out in an inert atmosphere or in the air. The coupling of potassium phenyltrifluoroborate with a variety of electron-rich aryl halides afforded the corresponding biaryls in good-to-excellent yields. The slight decrease in yield using amide or amine substituents might be due to their complexation with the palladium catalyst.¹⁷

The reaction of 4-bromobenzonitrile (an electron-poor aryl bromide) with electron-deficient aryltrifluoroborates also afforded excellent yields (eq 8).¹² The reaction of 2,6-difluoro- and pentafluorophenyltrifluoroborate (and electron-deficient organoboron partners in general) revealed an inherent advantage of the organotrifluoroborates. In both of these cases, the corresponding boronic acids have failed to couple under a variety of different reaction conditions owing to competitive protodeboration.^{12,18}

The reaction of *ortho*-substituted aryltrifluoroborates and aryl bromides required longer reaction times, revealing the inhibitory effects of steric hindrance (Scheme 2).¹² In the case of the halide

partner, very hindered substrates are not well tolerated. For example, the reaction of 4-methoxyphenyltrifluoroborate with 2-bromomesitylene produced the coupled product in only a 52% yield. Homocoupling of the trifluoroborate was a competing pathway. Hindered aryltrifluoroborates are more readily coupled with aryl halide partners.

The Suzuki-type cross-coupling of heteroaryl bromides afforded the biaryls in modest-to-excellent yields (eq 9).¹² The reaction between 1-phenyltrifluoroborate with 2-bromopyridine did not proceed to completion, presumably due to complexation of the nitrogen moiety to the catalyst.¹⁷ Longer reaction times only increased the homocoupling of the trifluoroborate. Dependence on the reactivity of the substrate was demonstrated, when higher yields were observed as in the case of the acyl-substituted thiophene and furan. Reactions with the more sterically hindered 1-naphthyltrifluoroborate were also high-yielding. In fact, the effective reaction with 2-chloropyrazine represented another example wherein trifluoroborates display improved reactivity over analogous boronic acids.

Batey and Quach showed that tetrabutylammonium trifluoroborates, which are more soluble in organic solvents than the potassium salts, can also be used in cross-coupling reactions using ligand-added conditions (eq 10).¹³

3.3. Heteroaryltrifluoroborates

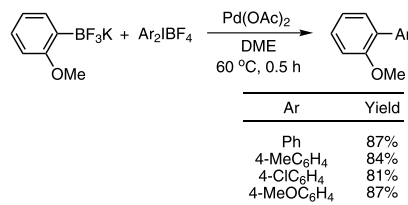
The Suzuki-type reactions were expanded to the use of heteroaryltrifluoroborates and a number of diverse heteroaryl bromides as coupling partners (eq 11).¹² Activated heteroaryl halides such as 3-bromopyridine require a shorter reaction time than 2-bromopyridine. These heteroaryl halides also reacted under ligandless conditions. Unactivated thiophenes and thiazoles required longer reaction times and the use of PdCl₂(dppf)•CH₂Cl₂. In some cases, this led to homocoupling of the trifluoroborate. It is of interest that reaction of the unprotected 7-bromoindole gave 77% of the expected biaryl. It is believed in this case that the basic, ligand-added conditions inhibited complexation of the indole nitrogen to the palladium.¹²

The cross-coupling of tetrabutylammonium thien-3-yltrifluoroborate with 4-bromoacetophenone has also been accomplished in 91% yield.¹³

3.4. Alkenyltrifluoroborates

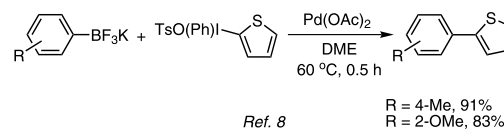
Alkenyltrifluoroborates are exceptional partners in the Suzuki cross-coupling reaction, providing advantages over other organoboron counterparts. Although alkenyldialkylboranes are efficient substrates in this reaction,¹⁹ their high molecular weight and the requirement to remove the two “dummy” groups on the boron make them less atom-economical. Lower molecular weight alkenylboronic acids, such as vinyl and propenylboronic acids,²⁰ readily polymerize and cannot be easily isolated.

Initial studies with functionalized aryl electrophiles demonstrated that the coupling reaction using PdCl₂(dppf)•CH₂Cl₂ could be accomplished using both halides and triflates (eq 12).^{21,22} The reactions were run in *i*-PrOH–H₂O using *t*-BuNH₂ as the inexpensive base. It is important to mention that the conditions developed for the coupling of alkenyltrifluoroborates [PdCl₂(dppf)•CH₂Cl₂, Cs₂CO₃, THF–H₂O] were also efficient. A variety of functional groups (e.g., nitro, cyano, aldehyde, ketone, ether) were tolerated in these reactions. The reactions were efficient with variously substituted alkenyltrifluoroborates, from the parent vinyltrifluoroborate to trisubstituted analogs (eq 13).²² The double-bond geometry of the trifluoroborate was retained with complete stereospecificity in these reactions. Batey and Quach have reported that tetrabutylammonium



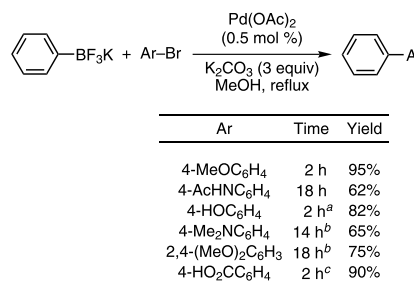
Ref. 8

eq 5



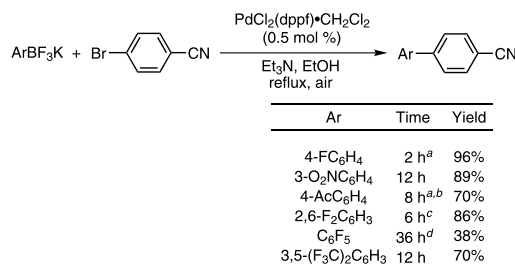
Ref. 8

eq 6

^a H₂O, 65 °C, air.^b Cat. (1 mol %), PPh₃ (0.5 mol %).^c H₂O, rt, air.

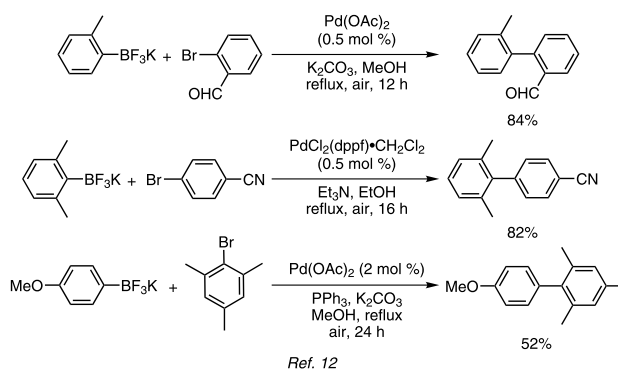
Ref. 12

eq 7

^a Pd(OAc)₂, K₂CO₃, MeOH, reflux.^b PPh₃. ^c Cat. (1 mol %).^d Cat. (5 mol %), THF.

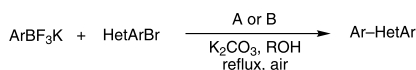
Ref. 12

eq 8



Ref. 12

Scheme 2. Effect of Steric Hindrance in Aryltrifluoroborate Coupling Reactions.

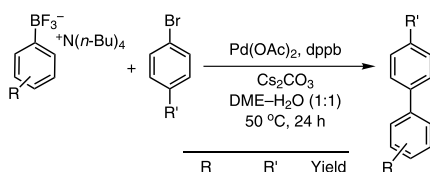


Ar	HetAr	Cond. ^a	Time	Yield
Ph	pyridin-2-yl	A	5 h	70%
Ph	pyridin-3-yl	A ^b	2 h	90%
Ph	pyrimidin-5-yl	A ^b	5 h	92%
Ph	2-acetylthien-5-yl	A	0.8 h	93%
Ph	2-carboxyfuran-5-yl	A ^c	6 h	67%
1-naphthyl	thien-2-yl	B	13 h	83%
1-naphthyl	thien-3-yl	B	13 h	72%
1-naphthyl	furan-3-yl	B	9 h	68%
1-naphthyl	thiazol-2-yl	B	13 h	80%
1-naphthyl	pyrazin-2-yl	B ^d	9 h	85%

^a Conditions A: Pd(OAc)₂ (0.5–1.0 mol %), MeOH; conditions B: PdCl₂(dppf)•CH₂Cl₂ (1–2 mol %), Et₃N, EtOH. ^b Pd(OAc)₂ (1.0 mol %). ^c H₂O, 65 °C. ^d HetArCl.

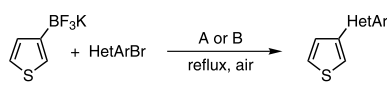
Ref. 12

eq 9



Ref. 13

eq 10

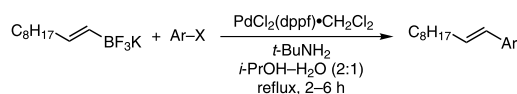


HetAr	Cond. ^a	Time	Yield
pyridin-2-yl	A	15 h	60%
pyridin-3-yl	A	7 h	68%
thiazol-2-yl	B	14 h	67%
thien-2-yl	B	13 h	63%
2-carboxyfuran-5-yl	B	10 h ^b	70%
pyrazin-2-yl	B	12 h ^{b,c}	83%
pyrimidin-5-yl	B	18 h	75%
indol-7-yl	B	10 h	77%

^a Conditions A: Pd(OAc)₂ (0.5–1 mol %), K₂CO₃, MeOH; conditions B: PdCl₂(dppf)•CH₂Cl₂ (0.5–2 mol %), NEt₃, EtOH. ^b K₂CO₃ used instead of Et₃N. ^c HetArCl.

Ref. 12

eq 11



Ar	X	Yield
4-MeOC ₆ H ₄	I	60%
4-O ₂ NC ₆ H ₄	Br	71%
4-O ₂ NC ₆ H ₄	OTf	76%
4-AcC ₆ H ₄	Br	69%

Ref. 22

eq 12

octen-1-yltrifluoroborate reacts readily with 4-bromoacetophenone to give the coupling product in 87% yield.¹³

The cross-coupling reaction of alkenyltrifluoroborates has been extended to heteroaryl bromides (**eq 14**)²² and, as mentioned above, cross-coupling reactions using potassium vinyltrifluoroborate are particularly important (**eq 15**).²² In contrast to its boronic acid and boronate ester counterparts, potassium vinyltrifluoroborate can be prepared in large quantities and stored indefinitely.²⁰

Cross-coupling of alkenyltrifluoroborates with alkenyl halides results in the preparation of conjugated dienes which are important synthetic units. Conjugated dienes are present in many biologically active compounds, and serve as starting materials in the highly useful Diels–Alder reaction. Although many other methods of synthesis of conjugated dienes are available, these have many limitations. The Kumada²³ and Negishi²⁴ coupling reactions sometimes provide low chemoselectivities and yields, and often create operational difficulties as well. For example, both are air-sensitive and the starting materials are usually prepared in situ. The tin reagents utilized in the Stille coupling are toxic, and the tin-containing byproducts formed in the coupling are difficult to remove. Some of the limitations of alkenylboronic acid derivatives have been mentioned above. Additionally, the added requirement of having to use excess amounts of toxic thallium bases to achieve efficiency in cross-coupling reactions of alkenylboronic acids and alkenylboronate esters with alkenyl halides further limits the usefulness of these organoboron reagents.²⁵

The Suzuki-type reactions of alkenyltrifluoroborates with alkenyl halides were performed using optimized conditions [Pd(OAc)₂, 2 PPh₃, Cs₂CO₃, THF–H₂O] (**eq 16**).²⁶ The system was sensitive to air and thus inert atmosphere conditions were required. Initial studies revealed that the process is completely stereospecific. Thus, the reaction of (*E*)- and (*Z*)-4-phenyl-1-buten-1-yltrifluoroborate with (*E*)- and (*Z*)-1-bromo-5-chloro-1-pentene resulted in the synthesis of the four possible isomers in a stereodefined manner (>99%). Interestingly, the reaction was not susceptible to steric hindrance within the halide partner. Highly substituted alkenyl bromides afforded the dienes in high yields. Additionally, many functional groups (e.g., formyl and cyano) were tolerated.²⁶ In particular, the reaction with 2-bromo-3-methyl-2-cyclopenten-1-one was of interest, because α-bromoenones were previously found to be unreactive under other coupling conditions.²⁷

The trifluoroborate counterpart was similarly versatile with regard to steric and functional-group tolerance (**eq 17**).²⁶ A special case is the reaction of the trifluoroborate bearing a methyl ester with 3-bromo-3-buten-1-ol. Under the reaction conditions developed, hydrolysis of the ester and/or transesterification might be expected, but neither was observed. This has been attributed to the use of a heterogeneous base.²⁸

The synthesis of diene functionalities incorporated within many natural products often involves the use of various silyl protecting groups along the way. Therefore, the compatibility of the silyl protecting group with organotrifluoroborates, an obvious source of fluoride, was also evaluated (**eq 18**).²⁶ Somewhat surprisingly, dienes were obtained in high yields with the silyl ether groups surviving the reaction conditions intact.²⁶

3.5. Alkynyltrifluoroborates

The reaction of potassium alkynyltrifluoroborates with aryl halides and triflates complements the usual Sonogashira coupling reaction.²⁹ Other organoboron compounds have been used in similar coupling reactions, but many limitations are associated with their use.^{30–32} Genêt was the first to attempt the cross-coupling

of potassium alkynyltrifluoroborates with arenediazonium salts.⁷ However, the major reaction pathway in this case was simple reduction of the diazonium salts.

Subsequently, a successful protocol for the Suzuki cross-coupling of potassium alkynyltrifluoroborates with the more accessible aryl halides and triflates was developed. Thus, the cross-coupling reaction of potassium 1-hexyn-1-yltrifluoroborate, using $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ as the catalyst, with various aryl bromides proceeded in good yields (eq 19).³³ Surprisingly, alcohols and carboxylic acids were tolerated in the reaction, even though, in principle, protodeboronation of the alkynyltrifluoroborate with these functional groups is a distinct possibility.^{2,12,34} Heteroaryl bromides were also effective coupling partners.

The reaction was expanded to the use of aryl triflates.³³ Moderate-to-excellent yields were obtained with both electron-deficient and electron-rich triflates. In addition, a number of diversely substituted alkynyltrifluoroborates were also evaluated (eq 20).³³ Satisfactory-to-excellent yields were observed, even in the presence of silyl ethers, which are normally quite labile in the presence of fluoride ions.

3.6. Synthetic Application

The first application of organotrifluoroborates in natural product synthesis was demonstrated in the formal total synthesis of oximidine II.³⁵ Oximidines are natural products with a diverse biological activity.³⁶ The challenge in these targets was the construction of the highly strained macrolide. The key step in this synthesis was the macrocyclization of an alkenyltrifluoroborate to accomplish the formation of the 12-membered ring (Scheme 3).³⁵ The reaction was performed under previously developed Suzuki-type reaction conditions as discussed above. This approach afforded several advantages over traditional macrolactonization reactions that had been attempted previously, and its success was due to the ease of access of the trifluoroborate functionality via the Snieckus hydroboration³⁷ and the inherent stability of the resulting boron derivative.

4. Oxidation Reactions

Organoboron compounds are generally incompatible with oxidants, which readily cleave the labile carbon–boron bond.³⁸ Organotrifluoroborates can be utilized to overcome this limitation. The first indication of this unexpected stability was the oxidation of thioether **1** to sulfone **2** using *m*-CPBA (eq 21).³⁹ Both the oxidative strength of the peracid and the acidity of the resulting carboxylic acid byproduct were well tolerated in this process.

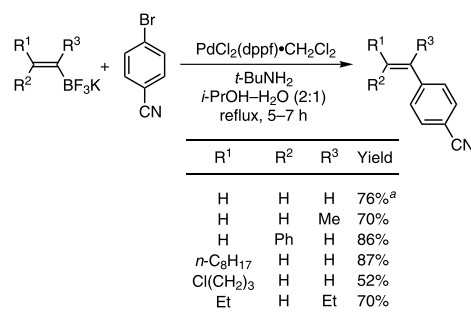
4.1. Epoxidation

Organotrifluoroborates have been epoxidized using dimethyldioxirane (eq 22).³⁹ The scope of the reaction was demonstrated by the use of a variety of alkenes bearing the trifluoroborate unit. The remarkable stability of the product as compared with the highly reactive oxiranyl anions was attributed to two factors: (i) α -elimination was inhibited by the covalent nature of the carbon–boron bond, and (ii) the strength of the boron–fluorine bond prevents hydrolysis of the boron species and provides resistance also to oxidation and α -transfer reactions.^{2a,2c,40,41}

Epoxytrifluoroborates are promising substrates in Suzuki-type reactions. The reaction conditions for the coupling can be manipulated to achieve preservation of the oxirane ring or its opening (Scheme 4).³⁹

4.2. Ozonolysis

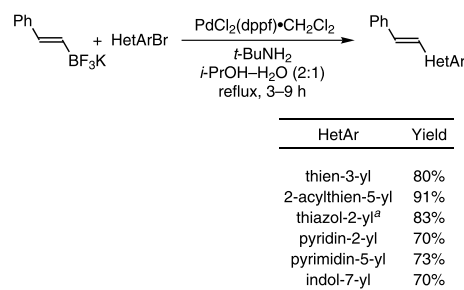
Ozonolysis of organotrifluoroborates has also been a part of ongoing studies of the oxidation of these substrates. These studies



^a Et₃N used as base.

Ref. 22

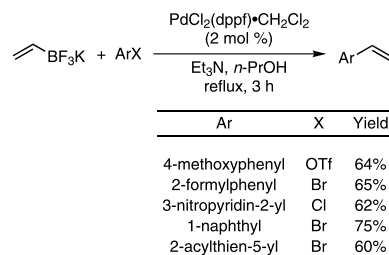
eq 13



Ref. 22

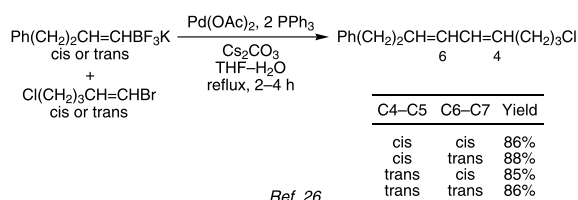
^a Et₃N used as base.

eq 14



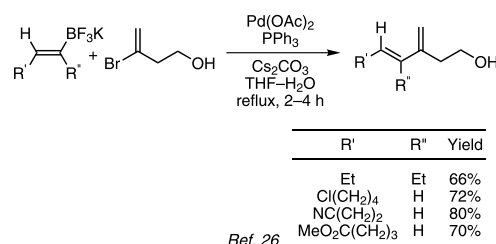
Ref. 21

eq 15



Ref. 26

eq 16



Ref. 26

eq 17

have shown that potassium trifluoroborates are stable to strong oxidative conditions. For example, the oxidation of the alkene functionality in unsaturated alkyl- or aryltrifluoroborates has been accomplished by bubbling ozone through an acetone–water or acetone–dichloromethane solution. The resulting ozonides were reduced using either dimethyl sulfide or zinc in acetic acid to provide the expected carbonyl groups, while preserving the trifluoroborate unit.⁴² Ozonolysis of the carbon–carbon double bonds in unsaturated tetrabutylammonium trifluoroborates takes place just as readily and produces the corresponding aldehydes and ketones in excellent yields (Scheme 5).⁴²

5. Conclusions

Organotrifluoroborates are a unique class of organoboron compounds that have emerged as promising synthetic reagents. Their easy access and inherent stability has led to the accomplishment of diverse and challenging Suzuki–Miyaura-type reactions. Their remarkable behavior toward oxidative conditions has resulted in the development of unprecedented epoxidation and ozonolysis reactions. Therefore, organotrifluoroborates are able to overcome many limitations associated with the use of boronic acids or boronate esters, thereby expanding the role of organoboron compounds in selective organic synthesis.

6. References and Notes

- (1) For recent reviews of the Suzuki–Miyaura cross-coupling, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (c) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; pp 49–97.
- (2) Darses, S.; Genêt, J.-P. *Eur. J. Org. Chem.* **2003**, 4313.
- (3) (a) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020. (b) Vedejs, E.; Fields, S. C.; Hayashi, R.; Hitchcock, S. R.; Powell, D. R.; Schrimpf, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 2460.
- (4) Matteson, D. S. *Tetrahedron* **1989**, *45*, 1859.
- (5) Brown, H. C.; Bhat, N. G.; Somayaji, V. *Organometallics* **1983**, *2*, 1311.
- (6) (a) Burgess, K.; Ohlmeyer, M. J. *Chem. Rev.* **1991**, *91*, 1179. (b) Pereira, S.; Srebnik, M. *J. Am. Chem. Soc.* **1996**, *118*, 909. (c) Kabalka, G. W.; Narayana, C.; Reddy, N. K. *Synth. Commun.* **1994**, *24*, 1019. (d) Männig, D.; Nöth, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 878. (e) Garrett, C. E.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 3224.
- (7) (a) Darses, S.; Genêt, J.-P.; Brayer, J.-L.; Demoute, J.-P. *Tetrahedron Lett.* **1997**, *38*, 4393. (b) Darses, S.; Michaud, G.; Genêt, J.-P. *Eur. J. Org. Chem.* **1999**, 1875.
- (8) Chen, Z.-C.; Xia, M. *Synth. Commun.* **1999**, *29*, 2457.
- (9) (a) Batey, R. A.; Thadani, A. N.; Smil, D. V.; Lough, A. J. *Synthesis* **2000**, 990. (b) Batey, R. A.; Thadani, A. N.; Smil, D. V. *Org. Lett.* **1999**, *1*, 1683. (c) Batey, R. A.; Thadani, A. N.; Smil, D. V. *Tetrahedron Lett.* **1999**, *40*, 4289.
- (10) Molander, G. A.; Ito, T. *Org. Lett.* **2001**, *3*, 393.
- (11) Molander, G. A.; Yun, C.-S.; Ribagorda, M.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 5534.
- (12) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302.
- (13) Batey, R. A.; Quach, T. D. *Tetrahedron Lett.* **2001**, *42*, 9099.
- (14) Oh-e, T.; Miyaura, N.; Suzuki, A. *Synlett* **1990**, 221.
- (15) (a) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033. (b) Echavaren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478.
- (16) Molander, G. A.; Biolatto, B. *Org. Lett.* **2002**, *4*, 1867.
- (17) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12051.
- (18) Thiemann, T.; Umeno, K.; Ohira, D.; Inohae, E.; Sawada, T.; Mataka, S. *New J. Chem.* **1999**, 1067.
- (19) (a) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 32. (b) Miyaura, N.; Satoh, M.; Suzuki, A. *Tetrahedron Lett.* **1986**, *27*, 3745. (c) Suzuki, A.; Brown, H. C. *Suzuki Coupling*; Organic Syntheses via Boranes, Volume 3; Aldrich Chemical Company: Milwaukee, 2003; p 37.
- (20) Matteson, D. S. *J. Am. Chem. Soc.* **1960**, *82*, 4228.
- (21) Molander, G. A.; Rivero, M. R. *Org. Lett.* **2002**, *4*, 107.
- (22) Molander, G. A.; Bernardi, C. R. *J. Org. Chem.* **2002**, *67*, 8424.
- (23) Huo, S.; Negishi, E. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., de Meijere, A., Eds.; Wiley-Interscience: New York, 2002; Vol. 1, pp 335–409.
- (24) (a) Negishi, E.; Ay, M.; Gulevich, Y. V.; Noda, Y. *Tetrahedron Lett.* **1993**, *34*, 1437. (b) Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445. (c) Duffault, J.-M.; Einhorn, J.; Alexakis, A. *Tetrahedron Lett.* **1991**, *32*, 3701. (d) Lipshutz, B. H.; Lindsley, C. *J. Am. Chem. Soc.* **1997**, *119*, 4555.
- (25) (a) Armstrong, R. W.; Beau, J.-M.; Cheon, S. H.; Christ, W. J.; Fujioka, H.; Ham, W.-H.; Hawkins, L. D.; Jin, H.; Kang, S. H.; Kishi, Y.; Martinelli, M. J.; McWhorter, W. W., Jr.; Mizuno, M.; Nakata, M.; Stutz, A. E.; Talamas, F. X.; Taniguchi, M.; Tino, J. A.; Ueda, K.; Uenishi, J.; White, J. B.; Yonaga, M. *J. Am. Chem. Soc.* **1989**, *111*, 7525. (b) Kobayashi, S.; Mori, K.; Wakabayashi, T.; Yasuda, S.; Hanada, K. *J. Org. Chem.* **2001**, *66*, 5580. (c) Scheidt, K. A.; Bannister, T. D.; Tasaka, A.; Wendt, M. D.; Savall, B. M.; Fegley, G. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 6981. (d) Pazos, Y.; Iglesias, B.; de Lera, A. R. *J. Org. Chem.* **2001**, *66*, 8483. (e) Mergott, D. J.; Frank, S. A.; Roush, W. R. *Org. Lett.* **2002**, *4*, 3157.
- (26) Molander, G. A.; Felix, L. A. *J. Org. Chem.* **2005**, in press.
- (27) (a) Negishi, E.; Owczarczyk, Z. R.; Swanson, D. R. *Tetrahedron Lett.* **1991**, *32*, 4453. (b) Lee, J.; Snyder, J. K. *J. Org. Chem.* **1990**, *55*, 4995. (c) Malleron, J. L.; Bacqué, E.; Desmazeau, P.; M'houmadi, C.; Paris, J. M.; Peyronel, J. F. *Synth. Commun.* **1995**, *25*, 2355.
- (28) The reaction using *t*-BuNH₂ as the base gave only 33% of the product owing to hydrolysis of the ester group.
- (29) (a) Campbell, I. In *Organocopper Reagents. A Practical Approach*; Taylor, R. J. K., Ed.; Oxford University Press: Oxford, 1994; p 217. (b) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 3, p 521. (c) Farina, V. In *Transition Metal Organometallics in Organic Synthesis*; Hegedus, L. S., Ed.; Comprehensive Organometallic Chemistry II Series; Pergamon: Oxford 1995; Vol. 12, p 222. (d) Miyaura, N. In *Cross-Coupling Reactions. A Practical Guide*; Miyaura, N., Ed.; Springer-Verlag: New York, 2002.
- (30) Soderquist, J. A.; Matos, K.; Rane, A.; Ramos, J. *Tetrahedron Lett.* **1995**, *36*, 2401.
- (31) Fürstner, A.; Seidel, G. *Tetrahedron* **1995**, *51*, 11165.
- (32) Castanet, A.-S.; Colobert, F.; Schlama, T. *Org. Lett.* **2000**, *2*, 3559.
- (33) Molander, G. A.; Katona, B. W.; Machrouhi, F. *J. Org. Chem.* **2002**, *67*, 8416.
- (34) (a) Suzuki, A. *Pure Appl. Chem.* **1994**, *66*, 213. (b) Suzuki, A. *Pure Appl. Chem.* **1991**, *63*, 419. (c) Suzuki, A. *Acc. Chem. Res.* **1982**, *15*, 178.
- (35) Molander, G. A.; Dehmel, F. *J. Am. Chem. Soc.* **2004**, *126*, 10313.
- (36) Yet, L. *Chem. Rev.* **2003**, *103*, 4283.
- (37) Kalinin, A. V.; Scherer, S.; Snieckus, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 3399.
- (38) (a) Johnson, J. R.; Van Campen, M. G., Jr. *J. Am. Chem. Soc.* **1938**, *60*, 121. (b) Matteson, D. S.; Moody, R. J. *J. Org. Chem.* **1980**, *45*, 1091.
- (39) Molander, G. A.; Ribagorda, M. *J. Am. Chem. Soc.* **2003**, *125*, 11148.
- (40) (a) Cragg, G. M. *Organoboranes in Organic Synthesis*; Marcel Dekker: New York, 1973. (b) Brown, H. C. *Organic Syntheses via Boranes*; Wiley-Interscience: New York, 1975. (Reprinted as

- Organic Syntheses via Boranes, Volume 1* by Aldrich Chemical Company, Inc.; Cat. No. Z40,094-7.)
- (41) (a) Brown, H. C.; Zaidlewicz, M. *Organic Syntheses via Boranes Volume 2*; Aldrich Chemical Company: Milwaukee, 2001. (b) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; pp 1–53. (c) Matteson, D. S. *Stereodirected Synthesis with Organoboranes*; Springer-Verlag: Berlin, 1995. (d) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (e) Ollivier, C.; Renaud, P. *Chem. Rev.* **2001**, *101*, 3415. (f) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169.
- (42) Molander, G. A.; Cooper, D. G. University of Pennsylvania, Philadelphia, PA. Unpublished work, 2005.


About the Authors

Gary Molander was born in Cedar Rapids, Iowa. He received his B.S. degree at Iowa State University in 1975, working with Professor Richard C. Larock. He entered the graduate chemistry program at Purdue University in 1975, obtaining his Ph.D. degree in 1979 under the direction of Professor Herbert C. Brown. In 1980, he joined Professor Barry Trost's group at the University of Wisconsin, Madison, as a National Institutes of Health postdoctoral fellow and, in 1981, he accepted an appointment at the University of Colorado, Boulder, as an assistant professor of chemistry. He was promoted to associate professor in 1988 and professor of chemistry in 1990. In 1999, he joined the faculty at the University of Pennsylvania and, in 2001, was appointed Allan Day Professor of Chemistry.




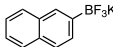
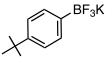

Professor Molander's research interests center on the development of new methods for organic synthesis and natural product synthesis. A major focus of his research has been the application of organolanthanide reagents and catalysts to selective organic synthesis. To date, more than 170 research papers have emanated from his research program. He has received several

honors for his work, including an Alfred P. Sloan Foundation Fellowship (1987), the American Cyanamid Academic Award (1989), the Arthur C. Cope Scholar Award from the American Chemical Society (ACS) in 1998, a Japanese Society for the Promotion of Science Fellowship (2002), and the Philadelphia Section Award of the ACS (2003). He has been a Visiting Professor at the Université de Paris-Sud, Orsay, France (1989, 1997); Philipps Universität, Marburg, Germany (1989); École Supérieure de Physique et de Chimie Industrielles de Paris (1993); Universidade Federal da Paraíba, Brazil (1998); Universidade Federal de Pernambuco, Brazil (1998); Universidad Nacional del Litoral, Santa Fe, Argentina (1998); Institute of Organometallic Chemistry, Russian Academy of Sciences, Nizhny Novgorod, Russia (1998); the Institut de Recherche en Chimie Organique Fine, Rouen, France (1999), and the Universidade Federal de Santa Maria, Brazil (2001).

He has served on the NIH Medicinal Chemistry Study Section and the ACS Division of Organic Chemistry Executive Committee. In 2001, he was the Executive Director for the 37th National Organic Symposium, and currently serves as the Secretary–Treasurer of the Organic Division of the ACS. He has been on the editorial advisory boards of *Organometallics*, *Tetrahedron*, *Tetrahedron Letters*, and *Current Topics in Medicinal Chemistry*, and is currently an associate editor of *Organic Letters*.

Ruth Figueroa obtained her B.S. degree in industrial chemistry from the University of Puerto Rico. She received her Ph.D. degree in organic chemistry at The Ohio State University under the supervision of Dr. David J. Hart. Her studies were directed toward the synthesis of the tetrahydropyran rings of the natural product lasonolide A. She joined Professor Molander's research group in October 2004 as a postdoctoral research associate, and is currently engaged in ongoing studies related to the oxidation of organotrifluoroborates. 

New Trifluoroborate Salts for Suzuki Coupling from Aldrich R&D

<p>Potassium vinyltrifluoroborate, 95%</p> <p>65,522-8  1 g 5 g</p>	<p>Potassium 2-methoxyphenyltrifluoroborate</p> <p>65,493-0  1 g 5 g</p>
<p>Potassium 5-methyl-2-thiophenetrifluoroborate</p> <p>65,494-9  1 g 5 g</p>	<p>Potassium 2-naphthalenetrifluoroborate</p> <p>65,701-8  1 g 5 g</p>
<p>Potassium 4-tert-butylphenyltrifluoroborate, 95%</p> <p>65,472-8  1 g 10 g</p>	<p>Potassium 2,4-difluorophenyltrifluoroborate</p> <p>65,699-2  1 g 5 g</p>

Trifluoroborates are air-stable alternatives to boronic acids in palladium-catalyzed Suzuki–Miyaura cross-coupling reactions.^{1,2} They are more robust, easier to handle, and less prone to protodeboronation.¹ They display a remarkably uniform behavior.²

(1) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302. (2) Molander, G. A. et al. *J. Org. Chem.* **2003**, *68*, 5534.

For additional information, please contact cdavis1@sial.com.
For competitive quotes on larger quantities, contact safglobal.com.

sigma-aldrich.com

LEADERSHIP IN LIFE SCIENCE, HIGH TECHNOLOGY AND SERVICE
ALDRICH • BOX 355 • MILWAUKEE • WISCONSIN • USA

 **ALDRICH**[®]
Advancing Science

Introducing science beyond the ordinary



Flavors & Fragrances

Naturals

Essential Oils

Synthetics

Techware

Kits

SAFC Specialties™
Inspiring Science™

Contact us for your new 2005–2006
Flavors & Fragrances catalog!

Tel.: 1-800-227-4563 (USA) or 414-438-3850

Fax: 414-438-4216

Email: ff@sial.com

SAFC, SAFC Specialties, and Inspiring Science are trademarks of Sigma-Aldrich Biotechnology, L.P.

www.safcspecialties.com

Member of the Sigma-Aldrich Group

PRECISION SEAL® SEPTA

Exceptional Fit, Feel, and Performance

ALDRICH, the leader in air-sensitive chemistry, announces the first complete family of rubber septa that are engineered for a precision fit in standard taper glassware joints and tubes. Precision Seal® septa are manufactured under "White Room" conditions, from one certified raw material formulation for absolute lot-to-lot consistency in all sizes.

Precision Seal is a registered trademark of Sigma-Aldrich Biotechnology, L.P.

	White Rubber	Red Rubber
For Use With:	Cat. No.	Cat. No.
7-mm o.d. glass tubing	Z55,390-5	Z55,402-2
8-mm o.d. glass tubing	Z55,391-3	Z55,403-0
10-mm o.d. glass tubing	Z55,392-1	Z55,404-9
13-mm i.d. tubing	Z55,394-8	Z55,405-7
⌀10/30 joints	Z55,395-6	Z55,406-5
⌀14/20 joints	Z55,396-4	Z55,407-3
⌀19/22 joints	Z55,397-2	Z55,408-1
⌀24/40 joints	Z55,398-0	Z55,410-3
⌀29/42 joints	Z55,399-9	Z55,411-1
Mixed set (145 each)	Z55,400-6	Z55,413-8

sigma-aldrich.com

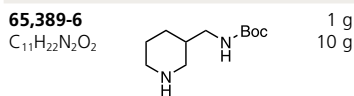
LEADERSHIP IN LIFE SCIENCE, HIGH TECHNOLOGY AND SERVICE
ALDRICH • BOX 355 • MILWAUKEE • WISCONSIN • USA

ALDRICH
Advancing Science

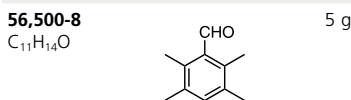
More New Products from Aldrich R&D

Organic Reagents and Building Blocks

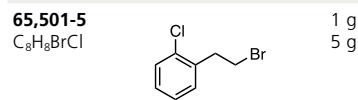
3-(Boc-aminomethyl)piperidine, 95%



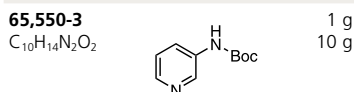
2,3,5,6-Tetramethylbenzaldehyde



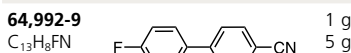
2-Chlorophenethyl bromide, 97%



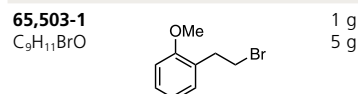
3-(Boc-amino)pyridine, 97%



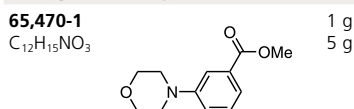
4-(4-Fluorophenyl)benzonitrile, 97%



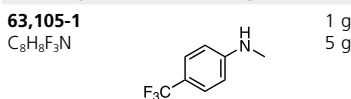
2-Methoxyphenethyl bromide, 97%



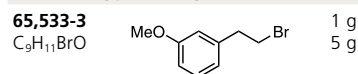
Methyl 3-(4-morpholino)benzoate, 97%



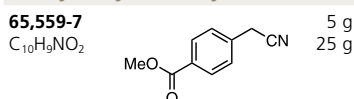
N-Methyl-4-trifluoromethylaniline, 97%



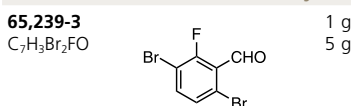
3-Methoxyphenethyl bromide, 97%



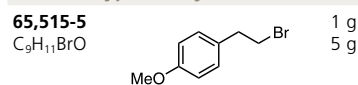
Methyl 4-(cyanomethyl)benzoate, 96%



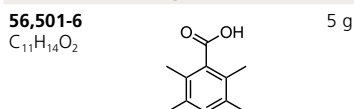
3,6-Dibromo-2-fluorobenzaldehyde



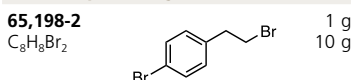
4-Methoxyphenethyl bromide, 97%



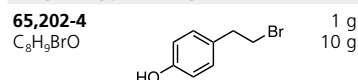
2,3,5,6-Tetramethylbenzoic acid



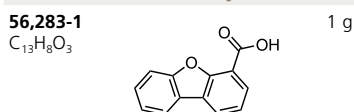
4-Bromophenethyl bromide, 96%



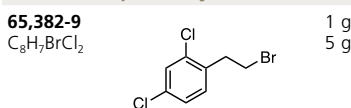
4-Hydroxyphenethyl bromide, 96%



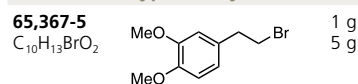
Dibenzofuran-4-carboxylic acid, 97%



2,4-Dichlorophenethyl bromide, 96%



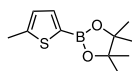
3,4-Dimethoxyphenethyl bromide, 97%



Boronic Acids and Esters

2-(5-Methylthien-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 95%

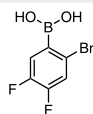
65,507-4
C₁₁H₁₇BO₂S



1 g
10 g

2-Bromo-4,5-difluorophenylboronic acid

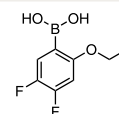
64,528-1
C₆H₄BBrF₂O₂



1 g
5 g

4,5-Difluoro-2-ethoxyphenylboronic acid

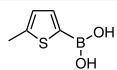
65,094-3
C₈H₉BF₂O₃



1 g
5 g

5-Methyl-2-thiopheneboronic acid

51,219-2
C₅H₆BO₂S



1 g
5 g

3-Bromo-5-methylphenylboronic acid

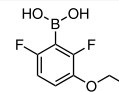
64,531-1
C₇H₈BBrO₂



1 g
5 g

2,6-Difluoro-3-ethoxyphenylboronic acid

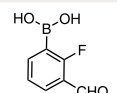
65,095-1
C₈H₉BF₂O₃



2 g
10 g

2-Fluoro-3-formylphenylboronic acid

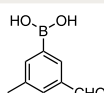
64,578-8
C₇H₆BF₂O₃



1 g
5 g

3-Formyl-5-methylphenylboronic acid

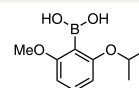
64,533-8
C₈H₉BO₃



1 g

2-Isopropoxy-6-methoxyphenylboronic acid

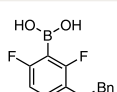
65,097-8
C₁₀H₁₅BO₄



2 g
10 g

3-Benzyloxy-2,6-difluorophenylboronic acid

63,570-7
C₁₃H₁₁BF₂O₃



1 g
5 g

3-Bromo-5-fluorophenylboronic acid

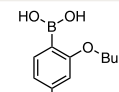
64,534-6
C₆H₅BBrFO₂



1 g
10 g

2,4-Dibutoxyphenylboronic acid

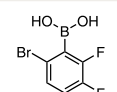
65,099-4
C₁₄H₂₃BO₄



1 g
5 g

6-Bromo-2,3-difluorophenylboronic acid

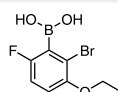
63,577-4
C₆H₄BBrF₂O₂



1 g
5 g

2-Bromo-3-ethoxy-6-fluorophenylboronic acid

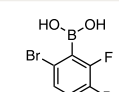
64,571-0
C₈H₉BBrFO₃



1 g
5 g

3,6-Dibromo-2-fluorophenylboronic acid

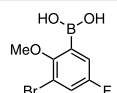
65,108-7
C₆H₄BBr₂FO₂



2 g
10 g

3-Bromo-5-fluoro-2-methoxyphenylboronic acid

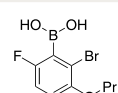
64,517-6
C₇H₇BBrFO₃



1 g
5 g

2-Bromo-6-fluoro-3-propoxyphenylboronic acid

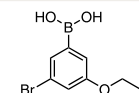
64,572-9
C₉H₁₁BBrFO₃



1 g
5 g

5-Bromo-3-ethoxyphenylboronic acid

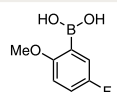
65,119-2
C₈H₁₀BBrO₃



1 g
5 g

4,5-Difluoro-2-methoxyphenylboronic acid

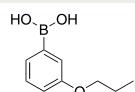
64,518-4
C₇H₇BF₂O₃



1 g
5 g

3-Isobutoxyphenylboronic acid

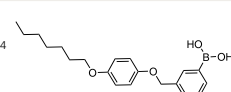
64,573-7
C₁₀H₁₅BO₃



1 g
5 g

3-(4'-Heptyloxyphenoxymethyl)phenylboronic acid

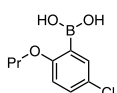
65,121-4
C₂₀H₂₇BO₄



1 g
5 g

5-Chloro-2-propoxyphenylboronic acid

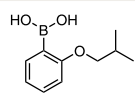
64,519-2
C₉H₁₂BClO₃



1 g
5 g

2-Isobutoxyphenylboronic acid

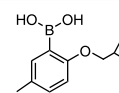
64,574-5
C₁₀H₁₅BO₃



1 g
5 g

2-Isobutoxy-5-methylphenylboronic acid

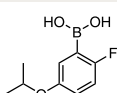
65,123-0
C₁₁H₁₇BO₃



2 g
10 g

2-Fluoro-5-isopropoxyphenylboronic acid

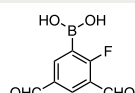
64,520-6
C₉H₁₂BF₂O₃



1 g
5 g

3,5-Diformyl-2-fluorophenylboronic acid

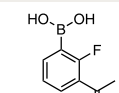
64,579-6
C₈H₆BF₂O₄



1 g
5 g

3-Acetyl-2-fluorophenylboronic acid

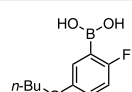
65,124-9
C₈H₈BF₂O₃



2 g
10 g

5-Butoxy-2-fluorophenylboronic acid

64,523-0
C₁₀H₁₄BF₂O₃

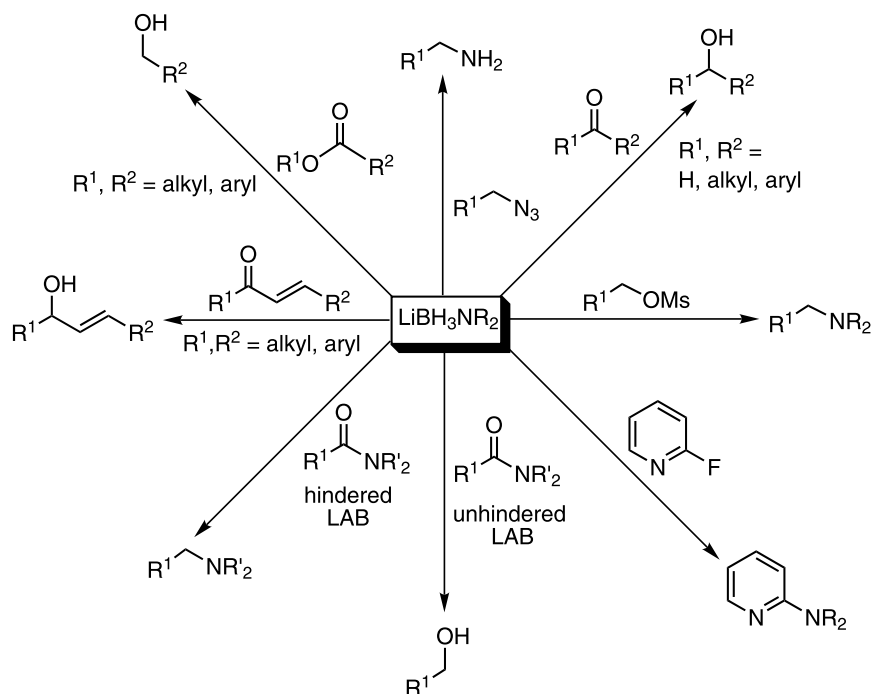


1 g
5 g

To view more new products, visit sigma-aldrich.com/newprod.
For competitive quotes on larger quantities, please contact safcglob.com.

Lithium Aminoborohydride (LAB) Reagents

Powerful, Air-Stable, and Selective Reducing Agents



Sigma-Aldrich is pleased to offer a number of lithium aminoborohydrides (LAB), which are readily applied to a range of reductions and aminations.¹ LABs are highly reactive yet air-stable reagents, and liberate hydrogen only slowly in protic solvents above pH 4. Developed in the laboratory of Professor Bakthan Singaram at the University of California, Santa Cruz, these new reagents are an attractive and safer alternative to LiAlH_4 due to their selectivity, ease of handling, and simple workup procedures.¹

(1) For a broader coverage of these topics, please see the review that starts on the facing page: Pasumansky, L.; Singaram, B.; Goralski, C. T. *Aldrichimica Acta* **2005**, 38, 61.

Lithium dimethylaminoborohydride solution, 1 M in THF

65,823-5		25 mL
$\text{C}_2\text{H}_9\text{BLiN}$	$\text{LiBH}_3\text{NMe}_2$	100 mL
FW 64.85		

Lithium morpholinoborohydride solution, 1 M in THF

65,830-8		25 mL
$\text{C}_4\text{H}_{11}\text{BLiNO}$	LiBH_3NR_2 ($\text{NR}_2 = 4\text{-morpholino}$)	100 mL
FW 106.89		

Lithium pyrrolidinoborohydride solution, 1 M in THF

65,824-3		25 mL
$\text{C}_4\text{H}_9\text{BLiN}$	LiBH_3NR_2 ($\text{NR}_2 = 1\text{-pyrrolidino}$)	100 mL
FW 90.89		

For additional information about these LABs or others that will be available soon, please contact our Technical Services department at 800-231-8327 (USA) or at aldrich@sial.com.

For inquiries about larger quantities, please contact us at safcglobal.com or 800-244-1173 (USA).

Recent Advances in the Chemistry of Lithium Aminoborohydrides[†]



Ms. Lubov Pasumansky



Dr. Bakthan Singaram

*Lubov Pasumansky and Bakthan Singaram**
 Department of Chemistry and Biochemistry
 University of California, Santa Cruz
 1156 High Street
 Santa Cruz, CA 95064, USA
 Email: singaram@chemistry.ucsc.edu

Christian T. Goralski
 CTG Consulting, LLC
 Midland, MI 48642, USA



Dr. Christian T. Goralski

Outline

1. Introduction
2. Reduction of *N*-Alkylactams and Amides
3. Reduction of Primary Alkyl Sulfonates to Hydrocarbons
4. Conversion of Primary Alkyl Methanesulfonates to Amines
5. Tandem Amination–Reduction Reactions
6. Synthesis of 2-(Dialkylamino)pyridines
7. Theoretical Calculations on LABs
8. Conclusions
9. Acknowledgements
10. References and Notes

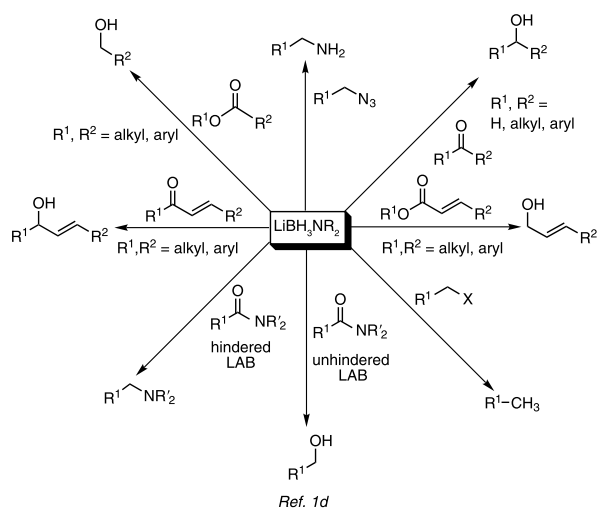
1. Introduction

Lithium aminoborohydrides (LABs) are a new class of powerful, selective, and air-stable reducing agents. LABs can be prepared as solids or 1–2 M THF solutions, or can be generated in situ for immediate use.¹ Since LABs can be synthesized from any primary or secondary amine, the steric and electronic environments of these reagents can be easily controlled. Solid LAB reagents can

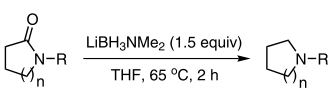
be used in dry air as easily as sodium borohydride, and they maintain their chemical reactivity for at least 6 months when stored at 25 °C under nitrogen or dry air. THF solutions of LABs retain their chemical reactivity for at least 9 months when stored at 25 °C under nitrogen. LABs are capable of reducing a variety of functional groups (**Scheme 1**),^{1d} and their use as reducing agents has been the subject of several reviews.² The present survey covers relevant research that has been published in the past five years.

2. Reduction of *N*-Alkylactams and Amides

N-Alkylactams are reduced with 1.5 equivalents of LiBH₃NMe₂ in THF at 65 °C in 2 hours, affording the corresponding cyclic amines in good-to-excellent yields (**eq 1**).³ The method is general for both five- and six-membered *N*-alkylactams. LAB reagents can perform a reagent-controlled reduction of amides to give either the corresponding alkanols or aminoalkanes. It is believed that, in sterically less demanding LABs, the boron moiety complexes the N-atom of the amide, making it a better leaving



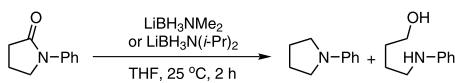
Scheme 1. Summary of the Reduction Reactions of LABs.



n	R	Yield
1	Bn	86%
1	Cy	80%
1	1-octyl	89%
1	1-dodecyl	96%
-a	-	96%
-b	-	75%

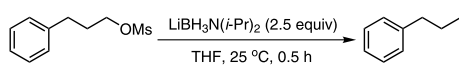
Ref. 3

eq 1



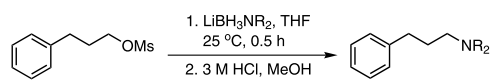
Ref. 3

eq 2



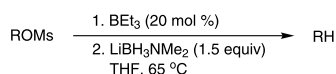
Ref. 4

eq 3



Ref. 4

eq 4



R	Time	Yield
Ph(CH ₂) ₃	0.25 h	94%
cyclohexyl	4 h	95%

Ref. 4

eq 5

group. This leads to an aldehyde, which is reduced further to the primary alcohol. In the case of sterically more demanding LABs, an imine is formed as an intermediate, which is then reduced to the aminoalkane. For example, 1-pyrrolidinooctanamide can be reduced either to 1-octanol (71%) with $\text{LiBH}_3(1\text{-pyrrolidino})$ or 1-pyrrolidinooctane (95%) with the sterically bulky $\text{LiBH}_3\text{N}(i\text{-Pr})_2$.^{1c} Based on these observations, it was thought that lactams might behave similarly and lead to the corresponding cyclic amines or ring-opened amino alcohols. Unfortunately, only 1-phenyl-2-pyrrolidinone gave any ring-opened product with either $\text{LiBH}_3\text{NMe}_2$ or $\text{LiBH}_3\text{N}(i\text{-Pr})_2$ (eq 2).³

3. Reduction of Primary Alkyl Sulfonates to Hydrocarbons

Primary alkyl sulfonates undergo facile reduction to the corresponding hydrocarbons with sterically hindered LABs (eq 3).⁴ Unfortunately, a sterically hindered LAB reagent will not reduce secondary alkyl sulfonates, which are recovered unchanged even after prolonged exposure at reflux temperature. For example, cyclohexyl methanesulfonate was completely recovered after treatment with 2.5 equivalents of $\text{LiBH}_3\text{N}(i\text{-Pr})_2$ in THF at 65 °C for 5 days.⁴

4. Conversion of Primary Alkyl Methanesulfonates to Amines

In contrast to the result shown in equation 3, when primary alkyl methanesulfonates were treated with sterically unhindered LAB reagents at 0 °C or 25 °C, no reduction products were formed. Instead, the corresponding tertiary amines were observed by GC analysis. Unexpectedly, under the reaction conditions, LABs behave exclusively as amine-transfer agents. For example, when treated with a variety of LAB reagents, 3-phenylpropyl methanesulfonate provides tertiary amines in excellent yields after an acidic methanolic workup (eq 4).⁴

The reduction of alkyl methanesulfonates with unhindered LAB reagents is possible, however, in the presence of Et_3B . Under these reaction conditions, LiBHEt_3 is generated in situ. Using 1.5 equiv of $\text{LiBH}_3\text{NMe}_2$ and 20 mol % of Et_3B , the reduction of both primary and secondary alkyl mesylates is accomplished in very high yields (eq 5).⁴

5. Tandem Amination–Reduction Reactions

The reaction of LABs with benzonitriles containing ring halogens has provided some very interesting results. Treatment of 2-chlorobenzonitrile with $\text{LiBH}_3\text{NMe}_2$ in refluxing THF afforded a 90% isolated yield of a 70:30 mixture of 2-(dimethylamino)benzylamine (the product of nucleophilic aromatic substitution of the chlorine by the dimethylamino group—another example of nitrogen transfer—followed by reduction of the cyano group) and 2-chlorobenzylamine (Scheme 2).^{5,6} Reaction of 2-chlorobenzonitrile with lithium pyrrolidinoborohydride under similar conditions gave analogous results: a 70:30 mixture of 2-(pyrrolidino)benzylamine and 2-chlorobenzylamine. Treatment of 2-chlorobenzonitrile with pyrrolidine under similar conditions gave only recovered starting material.

The tandem amination–reduction was further studied with other halogenated benzonitriles. Reaction of 2-bromobenzonitrile with lithium dimethylaminoborohydride gave 2-bromobenzylamine as the major product and the tandem amination–reduction product as the minor product (Scheme 3).⁶ This is not surprising in light of the known order of reactivity of aryl halides in $\text{S}_\text{N}\text{Ar}$ substitution reactions, with the bromo being the least reactive and the fluoro the most reactive.

Treatment of 2- and 4-fluorobenzonitriles with lithium pyrrolidinoborohydride in THF at reflux afforded 84% and 89% yields, respectively, of the corresponding pyrrolidinobenzylamines—the tandem amination–reduction products (**Scheme 4**).⁶ The reaction of 2-fluorobenzonitrile with various lithium *N,N*-dialkylaminoborohydrides is fairly general and gives the corresponding 2-(*N,N*-dialkylamino)benzylamines in very good yields (**eq 6**).⁶ Thus, a wide variety of amines, from the very nucleophilic, such as pyrrolidine, to the less nucleophilic, such as morpholine, undergo *N*-substitution with 2-fluorobenzonitriles via LAB reagents.^{5a,6}

6. Synthesis of 2-(Dialkylamino)pyridines

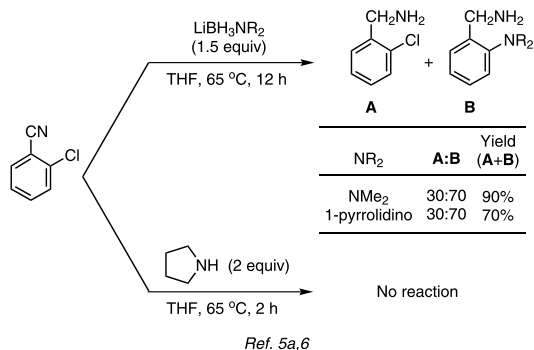
Aminopyridines are attractive synthetic targets, since many are biologically active molecules. For example, several aminopyridine-based pharmaceuticals are used to treat a range of disorders.^{7a–c} In addition, and because of their chelating properties, aminopyridines are commonly used as ligands in inorganic and organometallic chemistry.^{7f,g} Aminopyridines substituted with optically active groups could also serve as chiral auxiliaries or chiral ligands in asymmetric reactions.

We have extended the amination capabilities of LABs to 2-fluoropyridine. The direct amination of 2-fluoropyridine with LABs was first attempted to determine if an amination reaction analogous to that of 2-fluorobenzonitrile was indeed possible. The same reaction conditions that had been optimized for the amination of 2-fluorobenzonitrile were employed. Upon addition of 2-fluoropyridine to a THF solution of $\text{LiBH}_3\text{NMe}_2$, the colorless solution turned deep red in color. Meisenheimer complexes, the anionic intermediates formed during an $\text{S}_{\text{N}}\text{Ar}$ reaction, are known to form highly colored solutions. In fact, a similar deep-red color change in the $\text{S}_{\text{N}}\text{Ar}$ reactions of LABs with 2-halobenzonitriles had been observed. Gratifyingly, 2-(dimethylamino)pyridine was isolated in 59% yield. After these initial findings, attempts were made to optimize the reaction conditions. We discovered that elevated reaction temperatures were unnecessary and only 1.1 equiv of LAB reagent was required for the desired transformation. When 2-fluoropyridine was reacted at room temperature with 1.1 equiv of lithium homopiperidinoborohydride in THF for 1 h, 2-(homopiperidino)pyridine was isolated in 97% yield after employing the modified workup procedure. The products of the reaction of various LAB reagents with 2-fluoropyridine are shown in **equation 7**.⁸ The optically active LAB reagent prepared from (*S*)-(+)-2-methylpiperidine gave the lowest yield (60%), presumably as a result of increased steric requirements. 2-Chloropyridine reacted similarly with $\text{LiBH}_3\text{NMe}_2$ (THF, 65 °C, 1 h) and led to 2-dimethylaminopyridine in 87% yield.⁸

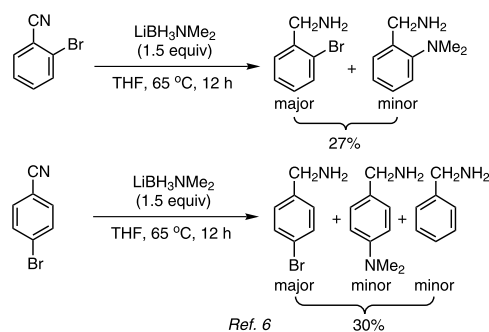
It is important to note that when 2-fluoropyridine is heated with a free amine such as homopiperidine at reflux temperature, the substrate remains intact even after an extended period of time. Other amines, specifically, sterically hindered lithium amides such as LDA, do not promote the amination of 2-halopyridines; instead, these reagents lead to ortho lithiation.⁹

Our investigations of the possible mechanism of the reaction of 2-fluoropyridine with LABs led us to hypothesize that the pyridine could be activated by coordination to boron during the reaction.¹⁰ To test this hypothesis, we treated 2-fluoropyridine with $\text{BH}_3\cdot\text{SMe}_2$ to form a 2-fluoropyridine–borane complex. We then reacted the complex with LiNPr_2 (formed from dipropylamine and *n*-BuLi) at 0 °C; 2-dipropylaminopyridine was isolated from this reaction in 50% yield (**Scheme 5**).¹⁰

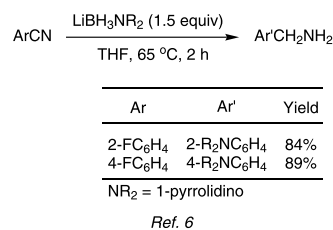
This unexpected result led us to investigate the importance of pre-activating 2-fluoropyridine with BH_3 . When 2-fluoropyridine



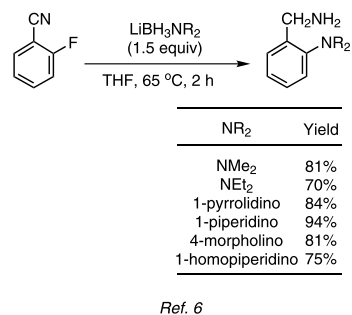
Scheme 2. Tandem Amination–Reduction of 2-Chlorobenzonitrile.



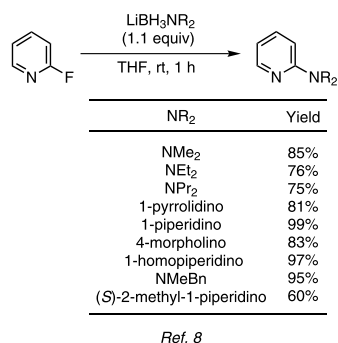
Scheme 3. Tandem Amination–Reduction of 2- and 4-Bromobenzonitriles.



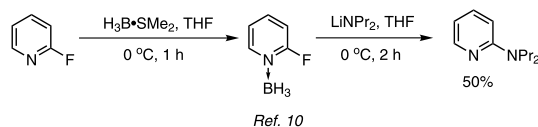
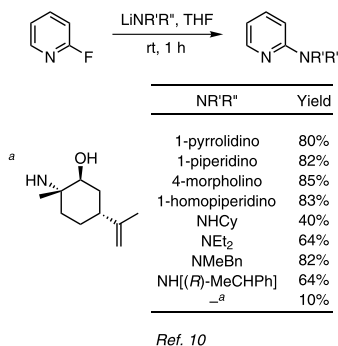
Scheme 4. Tandem Amination–Reduction of 2- and 4-Fluorobenzonitriles.



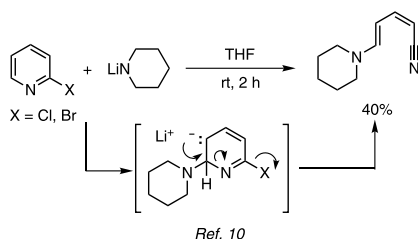
eq 6



eq 7

Scheme 5. Activation of 2-Fluoropyridine with H₃B·SMe₂.

eq 8



eq 9

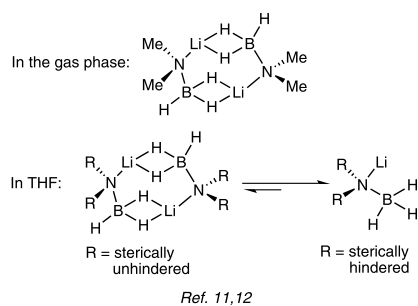


Figure 1. Hydrogen-Bridged LAB Dimer (Gas Phase) and Monomer (in THF).

was reacted with lithium pyrrolidide, in the absence of BMS, we were pleasantly surprised to find that 2-pyrrolidinopyridine was obtained in 80% yield. To determine the scope of this new amination method, a series of primary and secondary lithium amides were reacted with 2-fluoropyridine, which led to the corresponding 2-aminopyridines in 10–85% yields (eq 8).¹⁰ Interestingly, treatment of 2-chloro- and 2-bromopyridines with lithium amides under the same conditions led to the opening of the pyridine ring (eq 9).¹⁰

Clearly, the amination of 2-halopyridines with LABs operates under a different mechanism than the amination of 2-halopyridines with non-sterically hindered lithium amides. The reaction of 2-fluoropyridine with both LABs and lithium amides provides the same amination product. On the other hand, the reaction of 2-chloro- and 2-bromopyridines with LABs generates an aminopyridine, while the use of a lithium amide causes the opening of the pyridine ring.

7. Theoretical Calculations on LABs

Theoretical calculations of the equilibrium geometries and energies of LABs, carried out by Pratt and co-workers, indicate that LiBH₃NMe₂ exists largely as a hydrogen-bridged dimer in both the gas phase and as the bis(dimethyl ether) microsolvate (Figure 1).¹¹ More recently, this group utilized Density Functional Theory (DFT) calculations to determine the effects of ethereal solvents on the aggregation state of LiBH₃NMe₂. The calculations suggest that the dimer might coexist with the monomer in tetrahydrofuran. More hindered lithium dialkylaminoborohydrides exist primarily as monomers in ethereal solutions.¹² The kinetics (pseudo-first order in 1-chlorodecane) of the amination of 1-chlorodecane with LiBH₃NMe₂ (THF, 25 °C) showed no detectable change in reaction rate with time, suggesting that LiBH₃NMe₂ exists primarily as a monomer in THF, although the possibility of monomer–dimer equilibration cannot be ruled out.

8. Conclusions

Lithium aminoborohydrides are a new class of powerful yet selective reducing agents that reproduce, in air, virtually all of the transformations for which LiAlH₄ is now used. The reactivity of LABs is comparable to that of both LiAlH₄ and Vitride®. LABs are air-stable, nonpyrophoric, thermally stable, and liberate hydrogen only slowly in protic solvents above pH 4. LABs, whether solid or as THF solutions, retain their chemical activity for at least 6 months when stored under nitrogen at 25 °C. LABs can be synthesized from any primary or secondary amine, thus allowing precise control of the steric and electronic environments of these reagents.

The spectrum of reactions of lithium aminoborohydrides is not limited to their reducing properties, since, in several cases (e.g., reaction with halopyridines), LABs can also transfer their amine moiety. Both hydride and amine can be transferred in tandem amination–reduction reactions of halobenzonitriles.

In undergraduate teaching laboratories, transformations that would seldom be attempted because of the need to use LiAlH₄ or borane—such as the reduction of tertiary amides or esters—may become routine experiments with the use of LABs. For example, for the past four years, students at the University of California, Santa Cruz, who have taken the introductory organic chemistry laboratory class, have employed 1 M THF solutions of LABs to reduce aliphatic, aromatic, and α,β-unsaturated esters to the corresponding aliphatic, aromatic, and allylic alcohols, in air, in 70–98% isolated yields without incident or difficulty. In academic research laboratories, the short reaction time, ease of generation and handling, and simple workup procedure of reductions with

LABs make these new reagents attractive alternatives to LiAlH_4 or LiAlHET_3 (Super-Hydride[®]) reductions.

9. Acknowledgements

Professor H.C. Brown had a long association with UC Santa Cruz. In the nineties, he often visited UCSC, and the students, both in our research group and undergraduates at UCSC, enjoyed a great deal his visits and their interaction with him. Professor Brown gave his last public lecture (on General Asymmetric Syntheses via Organoboranes) here at UCSC in May of 2003 at the Bunnett Lectures. It would be difficult to imagine modern organic chemistry without the numerous and significant contributions from Brown's laboratories, as attested to by a look at any current organic chemistry journal or textbook. Some of us were very fortunate to have experienced a long association with Professor Brown, and will dearly miss him. His legacy will be carried on by his many former students and organoborane chemists.

10. References and Notes

- (f) Dedicated to Professor Herbert C. Brown, who passed away on December 19, 2004.
- (1) (a) Fisher, G. B.; Harrison, J.; Fuller, J. C.; Goralski, C. T.; Singaram, B. *Tetrahedron Lett.* **1992**, *33*, 4533. (b) Fuller, J. C.; Stangeland, E. L.; Goralski, C. T.; Singaram, B. *Tetrahedron Lett.* **1993**, *34*, 257. (c) Fisher, G. B.; Fuller, J. C.; Harrison, J.; Goralski, C. T.; Singaram, B. *Tetrahedron Lett.* **1993**, *34*, 1091. (d) Fisher, G. B.; Fuller, J. C.; Harrison, J.; Alvarez, S. G.; Burkhardt, E. R.; Goralski, C. T.; Singaram, B. *J. Org. Chem.* **1994**, *59*, 6378. (e) Singaram, B.; Fisher, G. B.; Fuller, J. C.; Harrison, J.; Goralski, C. T. U.S. Patent 5,466,798, November 14, 1995.
- (2) (a) Godjoian, G.; Fisher, G. B.; Goralski, C. T.; Singaram, B. In *Reductions in Organic Synthesis*; Abdel-Magid, A. F., Ed.; ACS Symposium Series 641; American Chemical Society: Washington, DC, 1996; pp 153–166. (b) Goralski, C. T.; Singaram, B.; Collins, C. J.; Cuzens, J. R.; Lanz, M. In *Organoboranes for Syntheses*; Ramachandran, P. V., Brown, H. C., Eds.; ACS Symposium Series 783; American Chemical Society: Washington, DC, 2001; pp 18–32.
- (3) Flaniken, J. M.; Collins, C. J.; Lanz, M.; Singaram, B. *Org. Lett.* **1999**, *1*, 799.
- (4) Thomas, S.; Huynh, T.; Enriquez-Rios, V.; Singaram, B. *Org. Lett.* **2001**, *3*, 3915.
- (5) (a) Thomas, S.; Collins, C. J.; Goralski, C. T.; Singaram, B. *Chem. Innov.* **2000**, *30* (August), 31. (b) The isolation of 2-aminonitriles at low temperatures was consistent with the nitrogen transfer taking place before reduction of the cyano group.
- (6) Thomas, S.; Collins, C. J.; Cuzens, J. R.; Spiciarich, D.; Goralski, C. T.; Singaram, B. *J. Org. Chem.* **2001**, *66*, 1999.
- (7) (a) Schtve, S. R.; Petrie, M. D.; McDermott, M. P.; Tierney, D. H.; Maso, D. H.; Goodman, A. D. *Neurology* **1997**, *48*, 817. (b) Sllin, L. C. *Med. Biol.* **1981**, *59*, 11. (c) Davidson, M.; Zemishlany, J. H.; Mohs, R. C. *Biol. Psychiatry* **1988**, *23*, 485. (d) Segal, J. L.; Warner, A. L.; Brunnenmann, S. R.; Bunten, S. C. *Am. J. Therapeutics* **2002**, *9*, 29. (e) Cacchi, S.; Carangio, A.; Fabrizi, G.; Moro, L.; Pace, M. *Synlett* **1997**, 1400. (f) Kempte, R.; Brenner, S.; Arndt, P. *Organometallics* **1996**, *15*, 1071. (g) Fuhrmann, H.; Brenner, S.; Arndt, P.; Kempe, R. *Inorg. Chem.* **1996**, *35*, 6742.
- (8) Thomas, S.; Roberts, S.; Pasumansky, L.; Gamsey, S.; Singaram, B. *Org. Lett.* **2003**, *5*, 3867.
- (9) (a) Choppin, S.; Gros, P.; Fort, Y. *Eur. J. Org. Chem.* **2001**, 603. (b) Radinov, R.; Haimova, M.; Simova, E. *Synthesis* **1986**, 886.
- (10) Pasumansky, L.; Hernandez, A. R.; Gamsey, S.; Goralski, C. T.; Singaram, B. *Tetrahedron Lett.* **2004**, *45*, 6417.


- (11) Mogali, S.; Darville, K.; Pratt, L. M. *J. Org. Chem.* **2001**, *66*, 2368.
- (12) Pratt, L. M.; Mogali, S.; Glington, K. *J. Org. Chem.* **2003**, *68*, 6484.

Super-Hydride is a registered trademark of Sigma-Aldrich Biotechnology, L.P. Vitride is a registered trademark of Rutherford Chemicals, LLC.

About the Authors

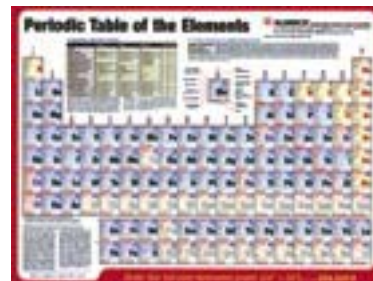
Lubov Pasumansky was born in St. Petersburg, Russia. She received her Bachelor of Science degree in chemistry from the University of California, Santa Cruz, in 2001. She is currently studying for her Ph.D. degree at the University of California, Santa Cruz, under the supervision of Professor B. Singaram. Her doctoral research focuses on developing synthetic methodologies that utilize lithium aminoborohydrides and lithium amides.

Bakthan Singaram was born in 1950 in Madanapali, India. He received his Bachelor of Science degree in chemistry in 1969 from the University of Madras, India. He completed his master's (1971) and doctoral studies (1977) at the University of Madras, working with Professor James Verghese. He did his postdoctoral research first at Purdue University with Professor H. C. Brown and later at the University College of Swansea, Wales, with Andrew Pelter. He returned to Purdue University in 1982 as assistant research scientist to H. C. Brown. In 1987, he became associate research scientist and, in 1989, joined the faculty at the University of California, Santa Cruz, as an assistant professor of chemistry. He was promoted to associate professor in 1995 and then full professor in 1999. He is a recipient of the Excellence in Teaching Award from the University of California, Santa Cruz (1995). His research interests include organoborane chemistry, asymmetric catalysis, glucose detection with boronic acid receptors, and materials chemistry.

Christian T. Goralski was born in 1942 in Cleveland, Ohio. He received his Bachelor of Science degree in chemistry from Case Institute of Technology in 1964. He then moved to Purdue University and received his Ph.D. degree in organic chemistry in 1969 under the direction of Professor William E. Truce. He joined the Dow Chemical Company in November of 1968. During the fall of 1985 and the spring of 1986, he spent 6 months as an industrial postdoctoral scholar in the laboratory of Professor Herbert C. Brown at Purdue University investigating the asymmetric hydroboration of enamines. He retired from the Dow Chemical Company in July 2004 after 30 years of working in the area of organic process research for the manufacture of pharmaceuticals. He is a member of the editorial advisory board of *Organic Process Research and Development*, and, in 2002, received a Distinguished Alumnus Award from the School of Science at Purdue University. 

Do you have an innovative shortcut or unique laboratory hint you'd like to share with your fellow chemists? If so, please send it to Aldrich (Attn.: Lab Notes, *Aldrichimica Acta*). For submitting your idea, you will receive a complimentary Aldrich periodic table poster (Cat. No. **Z54,320-9**). If we publish your lab note, you will also receive an Aldrich periodic table mouse pad (Cat. No. **Z54,323-3**). It is Teflon[®]-coated, 8.5 × 11 in., with a full-color periodic table on the front. We reserve the right to retain all entries for future consideration.

Teflon is a registered trademark of E. I. du Pont de Nemours & Co., Inc.

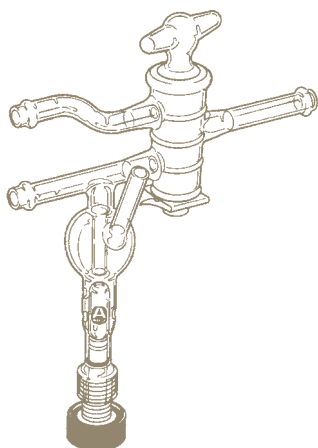
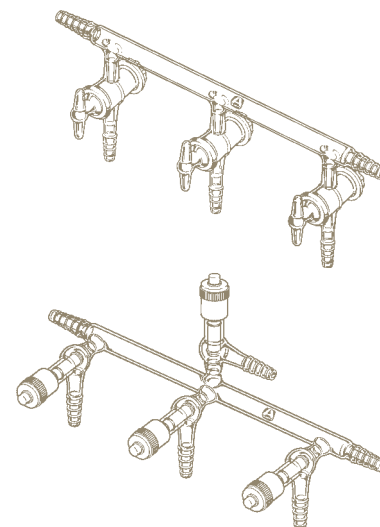


Aldrich Glassware for Air-Sensitive Chemistry

Aldrich Single-Bank Manifolds

A vacuum-gauge port is available as a means for relieving pressure buildup. Manifolds come with either 4-mm-bore glass stopcocks or 0–10-mm-bore high-vacuum PTFE J. Young valves.

No. of Positions	Overall L (mm)	Glass Stopcocks Cat. No.	High-Vacuum PTFE Valves Cat. No.
Standard manifold			
3	300	Z53,213-4	Z53,219-3
4	400	Z53,214-2	Z53,220-7
5	500	Z53,215-0	Z53,221-5
Manifold with vacuum-gauge port			
3	300	Z53,216-9	Z53,222-3
4	400	Z53,217-7	Z53,223-1
5	500	Z53,218-5	Z53,225-8



Aldrich Firestone Valve

Connect reaction vessel, house vacuum, and purge gas to the Firestone valve via 10-mm o.d. connections. A rapid and efficient purge valve for 100% replacement of air in reaction vessels. Automatically control gas flow and pressure. Conserve expensive gases by decreasing flow to almost zero after purging.

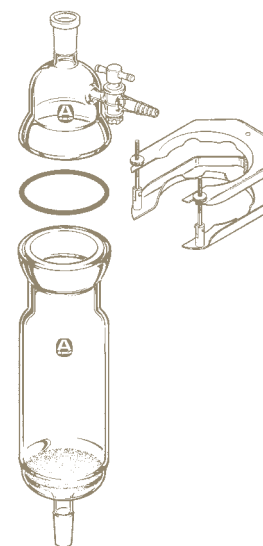
Z10,361-6

Aldrich Fritted Filter Funnels

Filter large volumes of air- and moisture-sensitive compounds quickly. With porosity C frit, 75-mm O-ring top and $\text{F}24/40$ or $\text{F}29/32$ bottom joint. Choose the 75-mm O-ring top that fits your application (see facing page).

Cap. (L)	Frit Diam. (mm)	Diam. × H ^a (mm)	$\text{F}24/40$ Cat. No.	$\text{F}29/32$ Cat. No.
1	90	95 × 340	Z51,728-3	Z51,734-8
2	120	130 × 360	Z51,729-1	Z51,735-6
4	150	165 × 420	Z51,730-5	Z51,736-4
6	150	165 × 540	Z51,731-3	Z51,737-2
10	150	165 × 800	Z51,732-1	Z51,738-0

^a Dimensions of bottle.



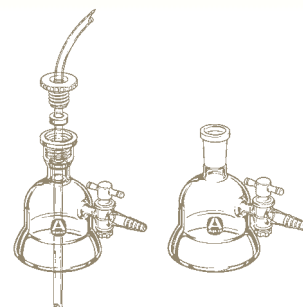
Aldrich 75-mm O-Ring Tops

Each top comes with a 4-mm PTFE stopcock. Use the stainless steel clamp listed below.

Torion™ inlet style—Use ½ in. hard-wall transfer tubing (e.g., PP or PTFE) for the airtight transfer of air-sensitive materials.

Standard taper—The $\text{F}24/40$ and $\text{F}29/32$ joints can accommodate a transfer adapter or a filter funnel.

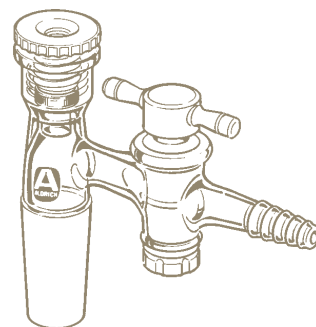
Description	Cat. No.
Torion™ inlet top	Z51,712-7
$\text{F}24/40$ top	Z51,713-5
$\text{F}29/32$ top	Z51,739-9
Stainless steel 75-mm clamp	Z51,727-5
Replacement Viton® O-Ring (pack of 3)	Z54,300-4



Torion™ Tubing Adapters with Stopcock

The unique Torion™ connection ensures an airtight seal between hard-wall tubing and reaction vessels, when transferring air-sensitive materials. Glass and PTFE stopcocks are threaded for additional safety and have a 2-mm bore for 3/16 in. tubing connection and 4-mm bore for 1/4 in. and 1/2 in. tubing connections.

Tubing O.D. (in.)	Inner F 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



Sigma-Aldrich: Premier Supply Partner for PYREX® Glassware

2005 marks a 20-year partnership between Sigma-Aldrich and Corning Life Sciences, that continues to bring premium-quality glassware to the scientific community.

Sigma-Aldrich introduces an expanded range of PYREX® glassware from Corning and is now a full-range supplier of glassware for your research and chemistry stockroom requirements.

For a complete listing of Corning products, please contact Sigma-Aldrich at (800) 325-3010 (USA), or visit our Web site at sigma-aldrich.com/corning1.



SafetyBarb™ Glass

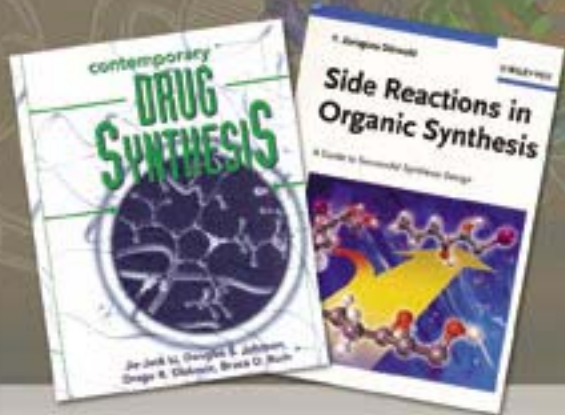
- Virtually eliminates breakage when installing or removing hoses.
- Reduces the incidence of personal injury.
- Costs no more than standard glassware.

See the new 2005–2006 Aldrich catalog for a listing of these products, or visit our Web site at sigma-aldrich.com/labequipment.

sigma-aldrich.com



SIGMA-ALDRICH



SciBook™ Select

Best Books for the Best Minds
sigma-aldrich.com/books

CHEMICAL SYNTHESIS TITLES

Organic Syntheses via Boranes, Volume 1

H. C. Brown, Aldrich Chemical, 1997, 283pp. Hardcover. This is a reprint of H. C. Brown's 1975 title containing a detailed discussion of organoboranes in organic synthesis.

Z40,094-7

Organic Syntheses via Boranes, Volume 2 Recent Developments

M. Zaidlewicz and H. C. Brown, Aldrich Chemical, 2001, 374pp. Hardcover. This book provides an account of recent developments in organoborane chemistry. Topics include hydroboration with borane and borane derivatives, organoborane conversions to functional groups, and carbon-carbon-bond formation via organoboranes.

Z40,095-5

Organic Syntheses via Boranes, Volume 3 Suzuki Coupling

A. Suzuki and H. C. Brown, Aldrich Chemical, 2003, 314pp. Hardcover. In this volume, various aspects of the Suzuki coupling reaction are discussed such as preparation of organoboranes for Suzuki coupling and coupling with alkyl-, alkenyl-, alkynyl-, and arylboranes.

Z51,430-6

Dead Ends and Detours: Direct Ways to Successful Total Synthesis

M. Sierra, M. de la Torre, K. C. Nicolaou (foreword), Wiley, 2005, 290pp. Softcover. In almost all publications, the valuable information provided is almost always based on successful organic reactions. But, it would be useful to have access to those syntheses that do not work, since they also provide important results of great importance for further synthesis. This book fills just such a gap. Using major total syntheses, the authors explain a variety of problems and recommend ways out of such dilemmas: Problems at the start and end of a synthesis, difficult and unexpected reactivities of functional groups, problems due to steric properties and much more.

Z70,336-2

Catalysts for Fine Chemical Synthesis, Volume 1, Hydrolysis, Oxidation and Reduction

S. Roberts and G. Poignant, Eds., Wiley, 2002, 224pp. Hardcover. In this volume, the review section contains a report on the integration of biotransformations into the catalyst portfolio. The procedure section contains a wide variety of synthetic protocols, such as epoxidations of unsaturated ketones and esters, asymmetric reductions of carbon-oxygen double bonds, asymmetric hydrogenations of carbon-carbon double bonds and other types of reaction. The featured catalysts include a wide range of different materials such as poly-D-leucine, D-fructose-based dioxiranes, oxaborolidine borane, some important titanium and ruthenium complexes as well as baker's yeast. For each reaction, there is one or several detailed protocols on how to prepare and employ the various catalysts.

Z54,160-5

Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals, Second Edition, 2-Volume Set

M. Beller and C. Bolm, Eds., Wiley, 2004, 1334pp. Hardcover. Over 70 internationally renowned authors cover the vast range of possible applications for transition metals in industry as well as academia. This two-volume work presents the current state of research and applications in this economically and scientifically important area of organic synthesis as well as in the production of fine chemicals. Over 1,000 illustrations and the balanced presentation allow readers fast access to the thorough compilation of applications.

Z70,345-1

Reductions by the Alumino- and Borohydrides in Organic Synthesis, Second Edition

J. Seyden-Penne, H. C. Brown (foreword), Wiley, 1997, 224pp. Hardcover. This updated second edition is a guide to the selection of reducing reagents in organic synthesis. It is the only reference focusing exclusively on aluminohydrides and borohydrides and their derivatives.

Z40,496-9

Side Reactions in Organic Synthesis: A Guide to Successful Synthesis Design

F. Z. Dörmwald, Wiley-VCH, 2005, 389pp. Softcover. Most syntheses in the chemical research laboratory fail, and usually require several attempts before proceeding satisfactorily. Many failures may, however, be avoided by understanding the structure-reactivity relationship of organic compounds. This textbook highlights the competing processes and limitations of the most important reactions used in organic synthesis. By allowing chemists to quickly recognize potential problems, this book will help improve their efficiency and success rate.

Z70,335-4

DRUG DISCOVERY TITLE

Contemporary Drug Synthesis

J.-J. Li, D. S. Johnson, D. R. Sliskovic, and B. D. Roth, Wiley, 2004, 221pp. Hardcover. This book examines how leading researchers and manufacturers have integrated chemistry, biology, pharmacokinetics, and a host of other disciplines in the creation and development of leading drugs. This timely volume focuses on the processes that resulted in high-profile drugs. It provides an in-depth introduction to each drug, followed by a detailed account of its synthesis, and organizes the drugs into fourteen therapeutic areas for clarity and ease of use.

Z70,353-2

SPECIAL TOPICS TITLE

Candid Science: Conversations with Famous Chemists

I. Hargittai, Imperial College Press, 2000, 516pp. Softcover. Thirty-six famous chemists, including Linus Pauling and Herbert C. Brown, tell about their lives in science, the beginnings of their careers, their aspirations, and their hardships and triumphs. NMR spectroscopy, computational chemistry, the drama of buckminsterfullerene, the story of the Pill, the politics of atmospheric chemistry and resonance theory, and the beginnings of molecular mechanics and modern stereochemistry are examples of the topics discussed.

Z55,383-2

View table of contents, search, browse, or order
from our entire library at sigma-aldrich.com/books.

Free bookmark! For details, visit our Web site.



SIGMA-ALDRICH

Sigma-Aldrich Worldwide Locations

Argentina

SIGMA-ALDRICH DE ARGENTINA, S.A.
Tel: 54 11 4556 1472
Fax: 54 11 4552 1698

Australia

SIGMA-ALDRICH PTY., LIMITED
Free Tel: 1800 800 097
Free Fax: 1800 800 096
Tel: 612 9841 0555
Fax: 612 9841 0500

Austria

SIGMA-ALDRICH HANDELS GmbH
Tel: 43 1 605 81 10
Fax: 43 1 605 81 20

Belgium

SIGMA-ALDRICH NV/SA.
Free Tel: 0800-14747
Free Fax: 0800-14745
Tel: 03 899 13 01
Fax: 03 899 13 11

Brazil

SIGMA-ALDRICH BRASIL LTDA.
Tel: 55 11 3732-3100
Fax: 55 11 3733-5151

Canada

SIGMA-ALDRICH CANADA LTD.
Free Tel: 800-565-1400
Free Fax: 800-265-3858
Tel: 905-829-9500
Fax: 905-829-9292

China

SIGMA-ALDRICH CHINA INC.
Tel: 86-21-6386 2766
Fax: 86-21-6386 3966

Czech Republic

SIGMA-ALDRICH s.r.o.
Tel: +420 246 003 200
Fax: +420 246 003 291

Denmark

SIGMA-ALDRICH DENMARK A/S
Tel: 43 56 59 10
Fax: 43 56 59 05

Finland

SIGMA-ALDRICH FINLAND
Tel: (09) 350 9250
Fax: (09) 350 92555

France

SIGMA-ALDRICH CHIMIE S.à.r.l.
Tel appel gratuit: 0800 211 408
Fax appel gratuit: 0800 031 052

Germany

SIGMA-ALDRICH CHEMIE GmbH
Free Tel: 0800-51 55 000
Free Fax: 0800-649 00 00

Greece

SIGMA-ALDRICH (O.M.) LTD
Tel: 30 210 9948010
Fax: 30 210 9943831

Hungary

SIGMA-ALDRICH Kft
Tel: 06-1-235-9054
Fax: 06-1-269-6470
Ingyenes zöld telefon: 06-80-355-355
Ingyenes zöld fax: 06-80-344-344

India

SIGMA-ALDRICH CHEMICALS
PRIVATE LIMITED
Telephone
Bangalore: 91-80-5112-7272
New Delhi: 91-11-5165 4255
Mumbai: 91-22-2570 2364
Hyderabad: 91-40-5584 5488
Fax
Bangalore: 91-80-5112-7473
New Delhi: 91-11-5165 4266
Mumbai: 91-22-2579 7589
Hyderabad: 91-40-5584 5466

Ireland

SIGMA-ALDRICH IRELAND LTD.
Free Tel: 1800 200 888
Free Fax: 1800 600 222
Tel: 353 1 4041900
Fax: 353 1 4041910

Israel

SIGMA-ALDRICH ISRAEL LTD.
Free Tel: 1-800-70-2222
Tel: 08-948-4100
Fax: 08-948-4200

Italy

SIGMA-ALDRICH S.r.l.
Telefono: 02 33417310
Fax: 02 38010737
Numero Verde: 800-827018

Japan

SIGMA-ALDRICH JAPAN K.K.
Tokyo Tel: 03 5796 7300
Tokyo Fax: 03 5796 7315

Korea

SIGMA-ALDRICH KOREA
Tel: 031-329-9000
Fax: 031-329-9090

Malaysia

SIGMA-ALDRICH (M) SDN. BHD
Tel: 603-56353321
Fax: 603-56354116

Mexico

SIGMA-ALDRICH QUÍMICA, S.A. de C.V.
Free Tel: 01-800-007-5300
Free Fax: 01-800-712-9920

The Netherlands

SIGMA-ALDRICH CHEMIE BV
Tel Gratis: 0800-0229088
Fax Gratis: 0800-0229089
Tel: 078-6205411
Fax: 078-6205421

New Zealand

SIGMA-ALDRICH PTY., LIMITED
Free Tel: 0800 936 666
Free Fax: 0800 937 777

Norway

SIGMA-ALDRICH NORWAY AS
Tel: 23 17 60 60
Fax: 23 17 60 50

Poland

SIGMA-ALDRICH Sp. z o.o.
Tel: +4861 829 01 00
Fax: +4861 829 01 20

Portugal

SIGMA-ALDRICH QUÍMICA, S.A.
Free Tel: 800 202180
Free Fax: 800 202178
Tel: 21 9242555
Fax: 21 9242610

Russia

SIGMA-ALDRICH RUSSIA
000 SAF-LAB
Tel: +7 (095) 975-1917/3321
Fax: +7 (095) 975-4792

Singapore

SIGMA-ALDRICH PTE. LTD.
Tel: 65-6779-1200
Fax: 65-6779-1822

South Africa

SIGMA-ALDRICH
SOUTH AFRICA (PTY) LTD.
Free Tel: 0800 1100 75
Free Fax: 0800 1100 79
Tel: 27 11 979 1188
Fax: 27 11 979 1119

Spain

SIGMA-ALDRICH QUÍMICA S.A.
Free Tel: 900 101376
Free Fax: 900 102028
Tel: 91 661 99 77
Fax: 91 661 96 42

Sweden

SIGMA-ALDRICH SWEDEN AB
Tel: 020-350510
Fax: 020-352522
Outside Sweden Tel: +46 8 7424200
Outside Sweden Fax: +46 8 7424243

Switzerland

FLUKA CHEMIE GmbH
Swiss Free Call: 0800 80 00 80
Tel: +41 81 755 2828
Fax: +41 81 755 2815

United Kingdom

SIGMA-ALDRICH COMPANY LTD.
Free Tel: 0800 717181
Free Fax: 0800 378785
Tel: 01747 833000
Fax: 01747 833313
SAFC (UK): 01202 712305

United States

SIGMA-ALDRICH
P.O. Box 14508
St. Louis, Missouri 63178
Toll-free: 800-325-3010
Call Collect: 314-771-5750
Toll-Free Fax: 800-325-5052
Tel: 314-771-5765
Fax: 314-771-5757

Internet:

sigma-aldrich.com

Introducing science beyond the ordinary

Process Development and Production-Scale Raw Materials in
Returnable Containers

A few of the chemicals that SAFC™ offers in bulk quantities are:

- Allyl Alcohol
- Allyl Chloride
- Chlorosilanes
- Chlorosulfonic Acid
- Dimethyl Sulfate
- Epichlorohydrin
- Solvents, Anhydrous
- Solvents, HPLC-Grade

Packaged under an inert nitrogen atmosphere in a variety of cylinders and portable tanks in 18- to 1,000-L sizes.

A safe, easy, and cost-effective way to purchase and transfer high-hazard, air-sensitive, and high-purity chemicals to your process vessels.

SAFC™

Inspiring Science™

For more information, please call **Dan Zagrodnik**
at **800-213-1206 (USA)** or **414-438-3869**.

SAFC, the SAFC logo, and Inspiring Science are trademarks of Sigma-Aldrich Biotechnology, L.P.

www.safcglobal.com

Member of the Sigma-Aldrich Group

Introducing science beyond the ordinary



SAFCTM

Inspiring Science™

SAFC™—where innovative scientists come to find the science they need to develop innovative products. Organic or biochemical, we offer integrated solutions throughout the product development plan, supporting you right through to commercialization. Applying years of chemistry know-how, process development and scale-up experience to bring your products to market faster.

No ordinary science here, but science beyond the ordinary.
Be inspired—by SAFC™.

www.safcglob.com

Member of the Sigma-Aldrich Group

 **ALDRICH**®

P.O. Box 14508
St. Louis, MO 63178
USA