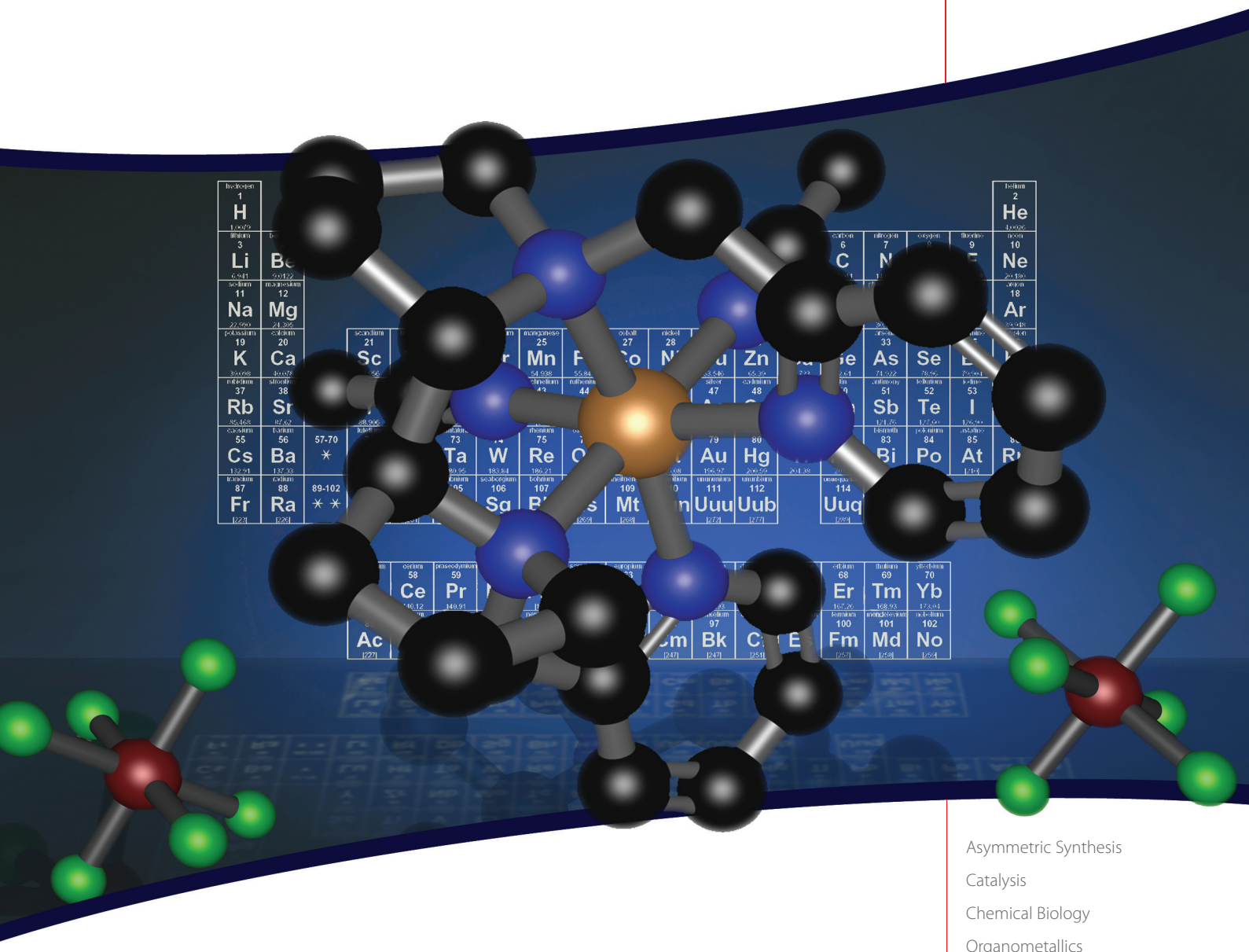
Aldrich CHEMFILES

Volume 10, Number 4 • 2010



Fe(S,S-PDP) - an electrophilic iron catalyst for site-selective C-H oxidation

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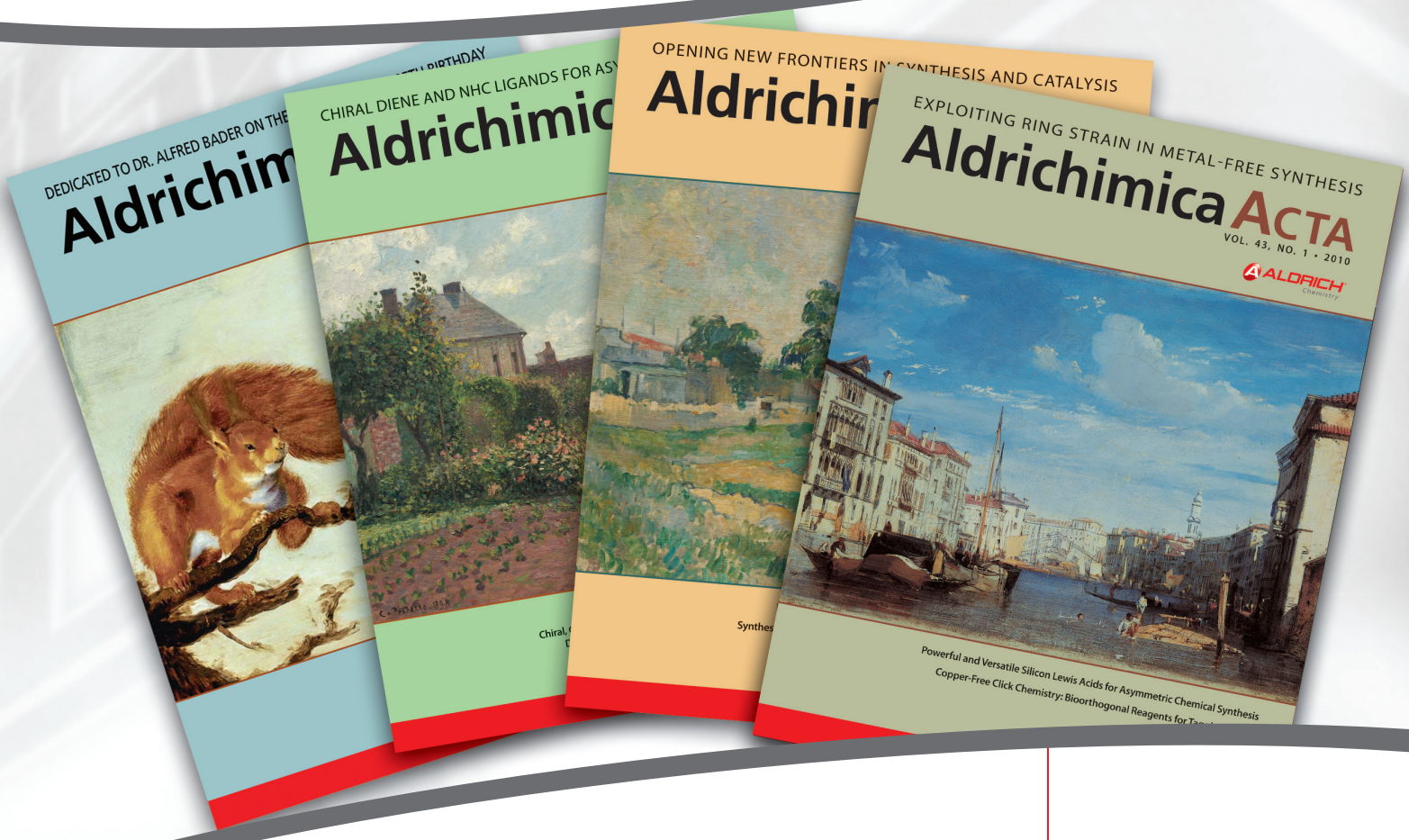

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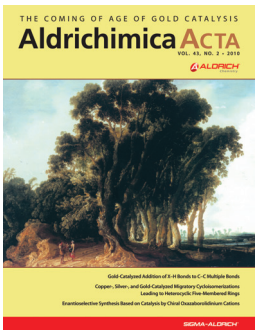

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Introduction

Haydn Boehm, Ph. D.
Global Marketing Manager: Chemical Synthesis
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Dear Chemists

Firstly I would like to offer congratulations from all of us here at Sigma-Aldrich to Prof. Richard Heck of the University of Delaware in Newark, US, Prof. Ei-ichi Negishi of Purdue University, US, and Prof. Akira Suzuki of Hokkaido University in Japan, who were awarded the 2010 Nobel Prize for chemistry. These three pioneers of synthetic organic chemistry were acknowledged for their eponymous palladium-catalyzed cross-coupling reactions, which form new carbon-carbon bonds under mild conditions, and are now indispensable to both research laboratories and industrial processes around the world.

Indeed this news has proven very timely as Prof. Negishi was our second speaker in the new Aldrich Chemistry Webinars series, and his ZACA Reaction Webinar was broadcast live from the 5th Annual Negishi-Brown and CAOSS Lectures from Purdue University on Tuesday, October 12, in partnership with the American Chemical Society and *C&EN* Webinars. If you were unable to attend the webinar then you can access it via ***aldrich.com/cheminars***.

The cover molecule of our fourth edition of the new *Aldrich ChemFiles* is Fe(*S,S*-PDP), which was originally reported by Prof. Christina White, and is now available from Aldrich Chemistry as part of our chiral 2,2′-bipyrrolidines portfolio (Asymmetric Synthesis). In *Aldrich ChemFiles* 10.4 we also introduce the latest building blocks for chemical biology (Chemical Biology), PEMB for reductive aminations (Synthetic Reagents), new gold catalysts (Catalysis), new organotins and organozincs (Organometallic Reagents), and our new oxetane portfolio (Building Blocks).

I hope that *Aldrich ChemFiles* 10.4 keeps you informed of the new Aldrich Chemistry products that facilitate the latest research methodologies and trends, and allows you to access key starting materials and reagents more efficiently.

Thanks for reading,

HBoehm

Haydn Boehm, Ph. D.

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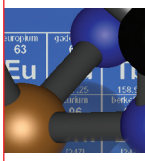


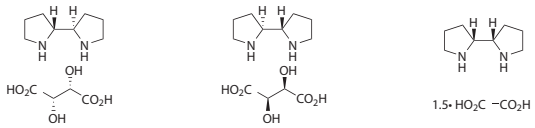
Asymmetric Synthesis

Daniel Weibel, Ph.D. European Market Segment Manager, Chemistry

daniel.weibel@sial.com

Chiral 2,2′-Bipyrrolidines

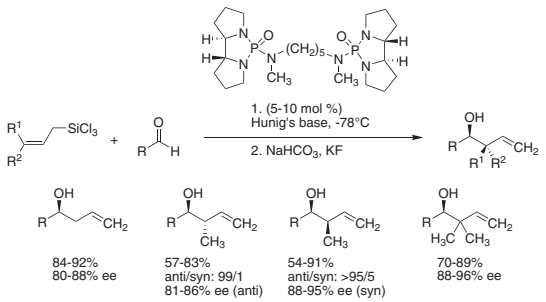
C_2-symmetrical, chiral 2,2′-bipyrrolidines have recently emerged as interesting structural chiral motifs in a number of ligands for asymmetric transformations (**Figure 1**). When the two nitrogen atoms function either in a bidentate chelate ligand or are covalently bonded to another atom, the two pyrrolidines adopted a stair-like structure, which creates a highly asymmetric environment.



688622 **688746** **712116**

Figure 1. Commercially available chiral 2,2′-bipyrrolidines.

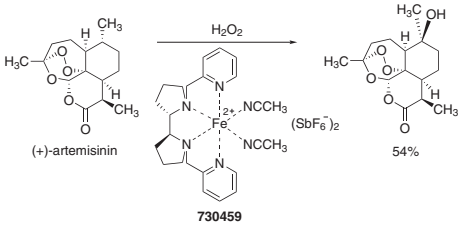
Prof. Denmark has exploited this feature in the development of a highly selective catalyst for asymmetric allylations.[1] The addition of allylic trichlorosilanes to unsaturated aldehydes can be catalyzed by chiral bisphosphoramide derived from 2,2′-bipyrrolidine (for the corresponding chiral bisphosphoramide catalyst derived from *N,N′*-dimethyl-1,1′-binaphthyldiamine, (**715549**) to give homo-allylic alcohols with excellent diastereo- and enantioselectivities (**Scheme 1**).



Scheme 1: Highly selective asymmetric allylic allylations using a bisphosphoramide organocatalyst

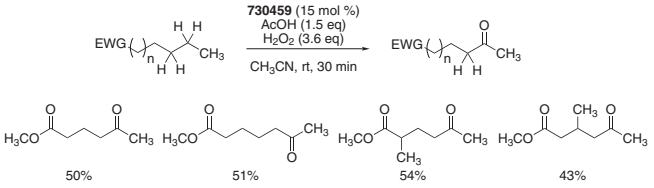
In 2007, Prof. Christina White reported on an iron-based small molecule catalyst Fe(S,S-PDP) (**730459**) bearing the (*S,S*)-1,1′-bis(2-pyridinylmethyl)-2,2′-bipyrrolidine (**712361**) moiety as chelating ligand that uses hydrogen peroxide to oxidize a broad range of substrates.[1] Predictable selectivity is achieved solely on the basis of the electronic and steric properties of the C–H bonds, without the need for directing groups. This type of general and predictable reactivity stands to enable aliphatic C–H oxidation as a method for streamlining complex molecule synthesis (**Scheme 2**).

On the basis of this set of selectivity rules the preferential oxidation of the electron-rich and sterically unencumbered tertiary C–H bond at C-10 of antimalarial tetracyclic compound (+)-artemisinin (**361593**) was predicted. In addition to the site selectivity issue posed in this substrate, a chemoselectivity challenge is present in the form of a sensitive endoperoxide moiety known to be prone to Fe(II)-mediated cleavage.[3] (+)-10β-Hydroxyartemisinin was generated in diastereomerically pure form as the major product in 54% yield (after recycling of artemisinin). Interestingly, (+)-artemisinin (**361593**) has previously been transformed enzymatically with microbial cultures of *Cunninghamella echinulata* to 10β-hydroxyartemisinin in 47% yield with substantially longer reaction times and a 10-fold lower volume throughput.[3] The ability of the simple, small molecule iron catalyst Fe(S,S-PDP) (**730459**) with broad substrate scope to achieve P-450-like tailoring enzyme selectivities is remarkable.



Scheme 2: Selective aliphatic iron-catalyzed C–H oxidation

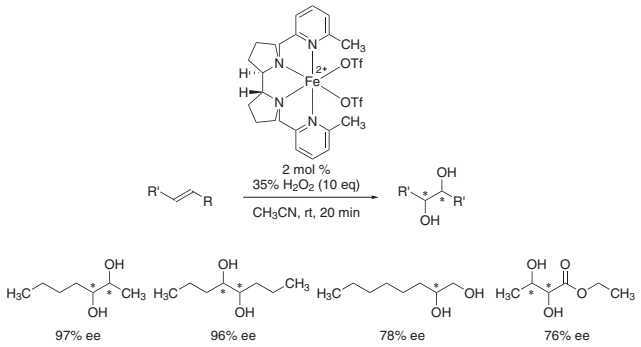
Recently, Prof. White reported the same bulky, electrophilic iron catalyst is capable of site-selective oxidation of isolated, unactivated secondary C–H bonds to afford mono-oxygenated products in preparatively useful yields without the use of directing or activating groups (**Scheme 3**).[4]



Scheme 3: Selective iron-catalyzed methylene oxidation

In 2008, Prof. Lawrence Que developed an iron catalyst bearing the optically active 6-Me_2-BPBP ((*R,R*)-1,1′-bis(6-methyl-2-pyridinylmethyl)-2,2′-bipyrrolidine) ligand (**712337**) for asymmetric olefin dihydroxylation.[5] This complex is hitherto one of the most effective reported to date achieving up to 97% enantiomeric excess of the *syn*-diol product from *cis*-disubstituted olefins (**Scheme 4**). These ee values are comparable to those obtained with the osmium-based AD α or β mixes (**392758** or **392766**).

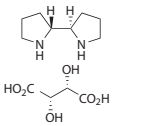
These results demonstrate for the first time that a synthetic nonheme iron catalyst can approach the high enantioselectivity found in *syn*-dihydroxylating enzymatic systems.



Scheme 4: Iron-catalyzed asymmetric olefin *cis*-dihydroxylation

References (1) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2001**, *123*, 9488. (2) Chen, M. S.; White, M. C. *Science* **2007**, *318*, 783. (3) Zhan, J.; Guo, H.; Dai, J.; Zhang, Y.; Guo, D. *Tetrahedron Lett.* **2002**, *43*, 4519. (4) Chen, M. S.; White, M. C. *Science* **2010**, *327*, 566. (5) Suzuki, K.; Oldenburg, P. D.; Que, L, Jr. *Angew. Chem. Int. Ed.* **2008**, *47*, 1887.

Chiral 2,2′-Bipyrrolidines



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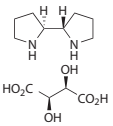

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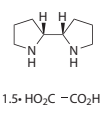

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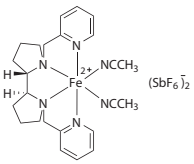

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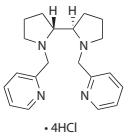

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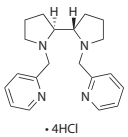

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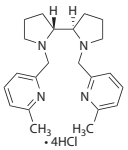

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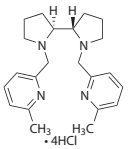

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Catalysis

Josephine Nakhla, Ph.D.
Market Segment Manager
Organometallics & Catalysis

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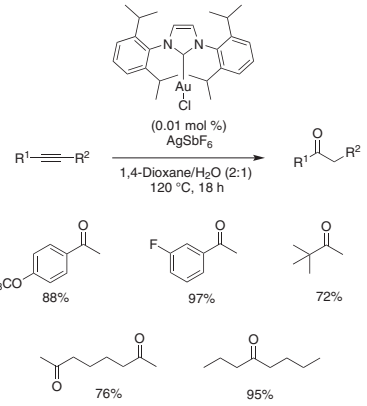
Alkyne Hydration

The hydration of alkynes has been extensively studied for more than 100 years. This reaction allows access to various carbonyl derivatives from alkyne precursors. Nolan and coworkers reported alkyne hydration using a gold catalyst. Nolan, a pioneer in the use of N-heterocyclic carbenes (NHCs) as ligands in various catalytic transformations with different metals, developed conditions employing a gold-NHC complex and silver hexafluoroantimonate for the hydration of alkynes (**Scheme 1**). It is important to note that an acid is not needed for this transformation and the reaction was feasible at low catalyst loadings (10 ppm).

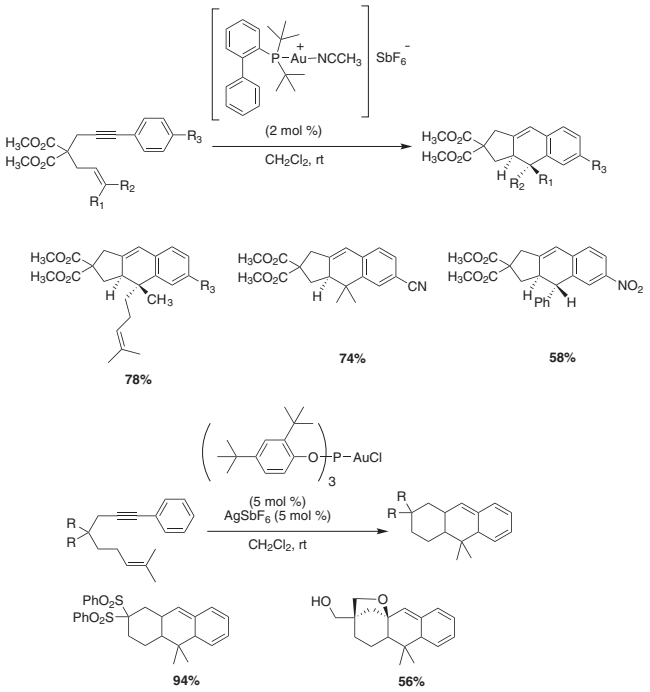


Scheme 1: Hydration of alkynes using gold-NHC complex

Reference (1) Marion, N.; Ramón, R. S.; Nolan, S. P. *J. Am. Chem. Soc.* **2009**, *131*, 448.

Intramolecular Cycloaddition of 1,3-Enynes with Alkenes

Echavarren and co-workers employed a crystalline gold complex containing either the *o*-biphenyl phosphine ligand JohnPhos, or a bulky aryl ether phosphine under mild conditions to effect the [4+2] cycloaddition of 1,3-enynes with olefins. A family of bi- and tricyclic scaffolds were prepared in good yields (**Scheme 2**). Both electron-withdrawing and electron-donating groups were tolerated on the aryl moiety.



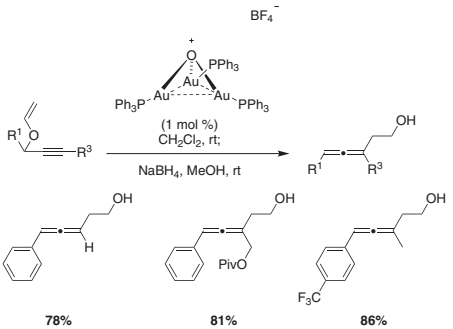
Scheme 2: Intramolecular cycloaddition of 1,3-enynes with alkenes

Reference (1) Nieto-Oberhuber, C.; Pèrez-Galán, P.; Herrero-Gómez, E.; Lauterbach, T.; Rodriguez, C.; López, S.; Bour, C.; Rosellón, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 269.

Propargyl Claisen Rearrangement

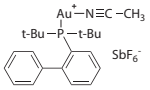
Toste and coworkers reported the use of the gold catalyst $[(Ph_3PAu)_3O]BF_4$ for the rapid two-step, one-pot sequence of a Claisen rearrangement of a propargyl vinyl ether followed by a reduction of the resulting aldehyde functionality to provide a variety of homoallenic alcohols. The reactions are generally high yielding and the robust catalyst system is able to induce almost complete chirality transfer (in most cases, ee's were ≥90%). Low catalyst loadings (1 mol %) and substitution at the alkyne is well tolerated generating the desired allenes in high yields (**Scheme 3**).

Reference (1) Sherry, B. S.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 15978.



Scheme 3: Preparation of homoallenic alcohols via Claisen rearrangement/ reduction sequence

Gold Catalysts from Sigma-Aldrich



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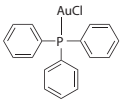

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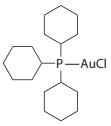

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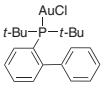

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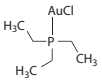

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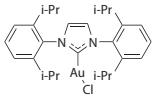

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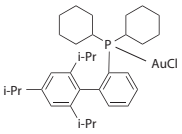

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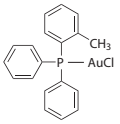

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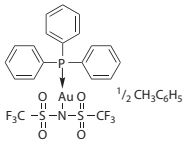

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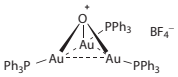

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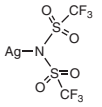

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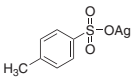

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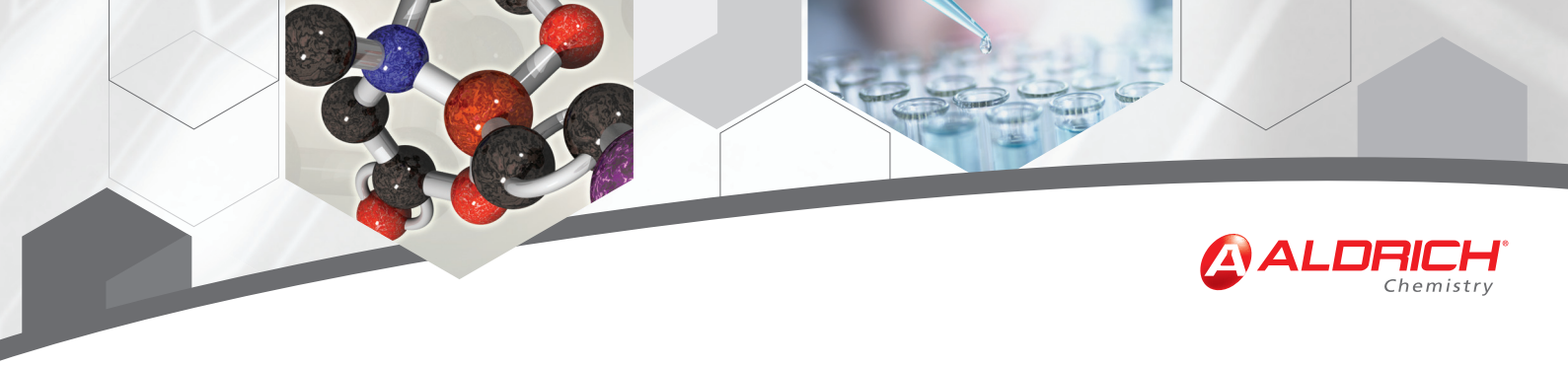

ALDRICH Chemistry

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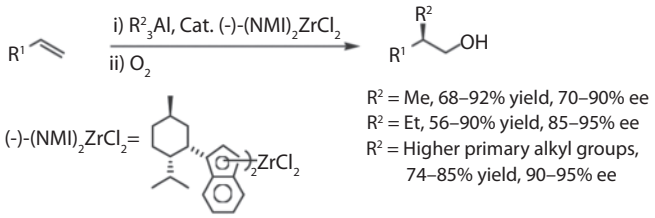
Overview: Many, if not the majority, of the organic compounds that are of interest and importance to mankind are chiral or optically active. Until recently, the major route to such chiral compounds and biocatalysts was the biosynthesis performed by nature, which employed enzymes as synthetic tools. Slowly but surely, other methods have emerged and their significance was predicted to increase significantly during the 21st century, when W. Knowles, R. Noyori, and K. B. Sharpless were awarded the 2001 Nobel Prize for their pioneering research using non-biological asymmetric methods for C–H and C–O bond formation.

What about the all-important C–C bond formation for asymmetric organic skeleton formation? This webinar introduces the discovery, development and application of the ZACA reaction, and showcases how its efficient, selective, potentially green and economical syntheses of biologically and medicinally important chiral organic compounds can benefit mankind.



R^2 = Me, 68–92% yield, 70–90% ee
R^2 = Et, 56–90% yield, 85–95% ee
R^2 = Higher primary alkyl groups, 74–85% yield, 90–95% ee

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- Relevant events and conferences are also highlighted.

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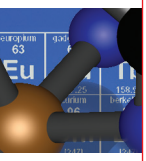

Chemical Biology

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Product Manager

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New Building Blocks for Chemical Biology

Modern automated synthesis protocols allow the fast and efficient production of biopolymers like peptides and even proteins, or oligonucleotides. In recent years, even the automated synthesis of complex carbohydrates has been described.[1] Automated synthesis procedures build the bridge to Chemical Biology. It does not require a fully trained chemist to perform automated synthesis. Even groups with a primary focus on biology research can utilize synthesizers to produce primers, test molecules, probes, etc., quickly and efficiently. On the other hand, chemistry benefits equally from automated procedures. Synthesis challenges that used to take weeks or months can today be completed in a matter of hours or a few days accelerating research tremendously. Fast and efficient synthesis is only possible if all necessary tools are readily available. Sigma-Aldrich is proud to offer a leading choice of tools and building blocks for advancing science in the "omics" era (genomics, proteomics, glycomics, metabolomics – to name just a few). This issue of *Aldrich ChemFiles* highlights some examples of recent additions to our portfolio.

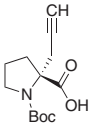
Beta Amino Acids

Although they are less abundant than their α-analogues, β-amino acids occur in nature both in free form and bound to peptides. Oligomers composed exclusively of β-amino acids (so-called β-peptides) might be the most thoroughly investigated peptidomimetics. Besides being remarkably stable to metabolism, exhibiting slow microbial degradation, and inherently stable to proteases and peptidases, they fold into well-ordered secondary structures consisting of helices, turns, and sheets. In this respect, the most intriguing effects have been observed when β^2-amino acids are present in the β-peptide backbone.[2] A whole new "world" has emerged from the design of fascinating new peptidic macromolecules from β- and γ-homologated proteinogenic amino acids and other components. Sigma-Aldrich has a history as a leading supplier of β^3-amino acids. Now, the portfolio of β^2-amino acids is significantly increased with members that had not yet been available commercially.

Proline Analogs

Proline is a non-polar, natural amino acid that forms a tertiary amide when incorporated into peptides. Thus, it is the only proteinogenic amino acid that does not act as a hydrogen bond donor in a peptide chain. Proline is known as a classical breaker of both the α-helical and β-sheet secondary structures in proteins and peptides, and it plays a crucial role in protein folding. Synthetic proline derivatives, mimetics and analogs offer further options to tune the biological, pharmaceutical, or physicochemical properties of peptides and proteins.

In recent years proline derivatives and analogs have also found increasing popularity as organocatalysts in asymmetric synthesis.[4]



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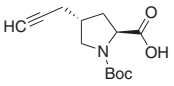

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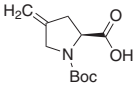

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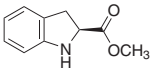

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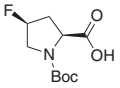

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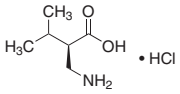
Unsaturated Amino Acids

Recent developments in Chemical Biology research have increased the demand of amino acid building blocks with unsaturated side chains. Alkyne moieties can be used in bioorthogonal synthesis strategies to form hybrid structures, introduce chemical probes into biomolecules, or link large fragments with each other. The most prominent technique relies on the Huisgen dipolar cycloaddition reaction between an azide and an alkyne.

Olefin moieties open amino acids and peptides to metathesis reactions and a full range of other bioorthogonal synthesis routes. Olefin metathesis is a key to the production of hydrocarbon stapled peptides.[5] Stapled peptides are currently in discussion as a new class of superpotent drugs or magical bullets promising to make peptide α-helices more potent and cell permeable by locking them in the most active conformation.[6]

References: (1) Timmer, M.S.M.; Adibekian, A.; Seeberger, P.H. *Angew. Chem. Int. Ed.* **2005**, *44*, 7605. (2) Lelais, G.; Seebach, D. *Biopolymers* **2004**, *76*, 206. (2) Seebach, D.; Beck, A.K.; Bierbaum, D.J. *Chem. Biodiv.* **2004**, *1*, 1111. (4) (a) Vignola, N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 450. (b) Dalko, P.I.; Moisan, L.; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138. (5) Walensky, L.D. et al. *Science* **2004**, *305*, 1466. (6) Kritzer, A.K. *Nature Chemical Biology* **2010**, *6*, 566.

New Amino Acid Building Blocks



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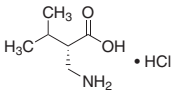

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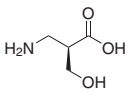

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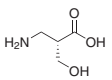

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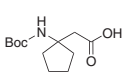

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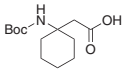

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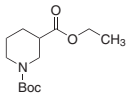

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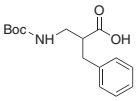

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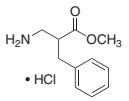

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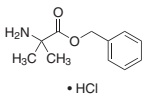

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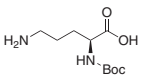

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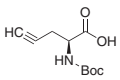

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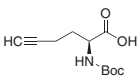

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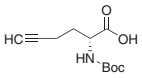

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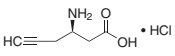

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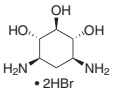

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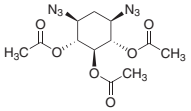

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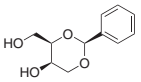

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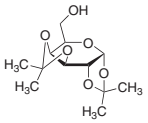

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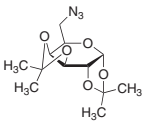

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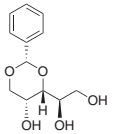

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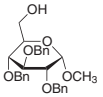

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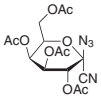

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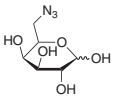

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Organometallics

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Market Segment Manager
Organometallics & Catalysis
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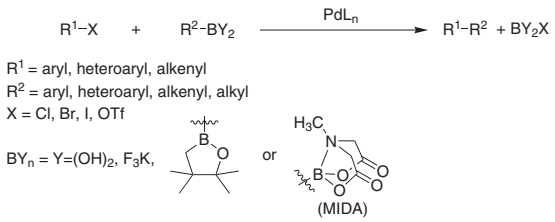
Suzuki Coupling

The cross-coupling of organoborons with organic electrophiles in the presence of a palladium catalyst (**Scheme 1**), is one of the most widely utilized methods for C–C bond formation in transition metal chemistry. Organoboron reagents are readily prepared or are commercially available, relatively non-toxic, and do not react with common functional groups. Several new product additions to our boron portfolio are highlighted below.



Scheme 1: The Suzuki reaction

Reference: Wolfe, J. P.; Nakhla, J. S. **The Suzuki Reaction.** Name Reactions for Homologations. John Wiley & Sons, Inc. (2009), (Pt. 1), 163–184.

New Boronic Acids and Boronate Esters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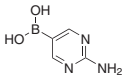
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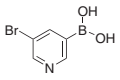
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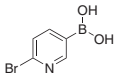
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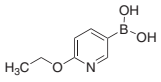
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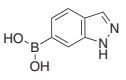
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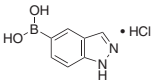
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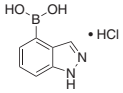
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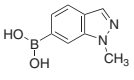
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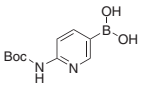
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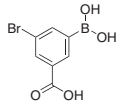
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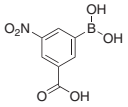
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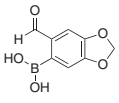
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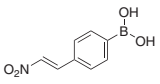
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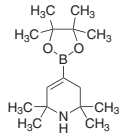
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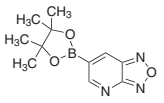
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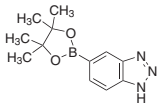
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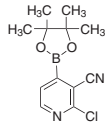
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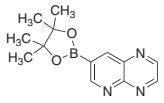
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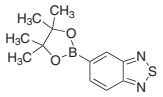
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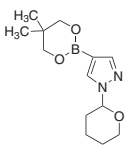
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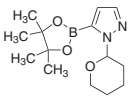
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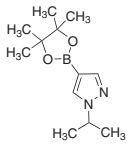
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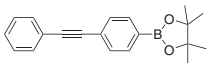
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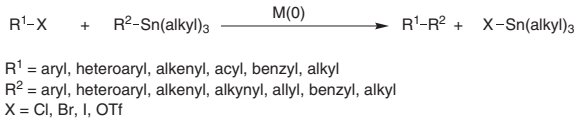
For a complete list of boron reagents available from Aldrich Chemistry, please visit *aldrich.com/boron*

Stille Coupling

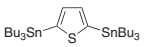
The cross-coupling of organotins with organic electrophiles in the presence of a transition-metal catalyst (**Scheme 2**), remains one of the most viable methods for the formation of C–C bonds in organic chemistry, particularly with heterocyclic nucleophiles. The Stille reaction, like other commonly used cross-couplings, has been employed in methodology development, countless elegant natural product syntheses, and in materials science.



Scheme 2: The Stille reaction

Reference: Mascitti, Vincent. **Stille coupling.** Name Reactions for Homologations. John Wiley & Sons, Inc. (2009), (Pt. 1), 133–162.

Organotin Reagents from Aldrich



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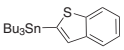

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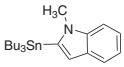

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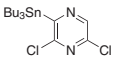

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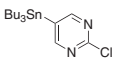

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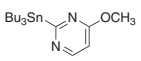

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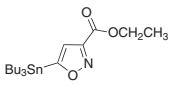

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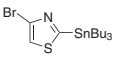

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675679

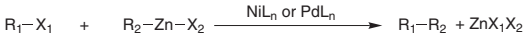
719501

718793

For a complete list of organotin reagents available from Aldrich Chemistry, please visit *aldrich.com/organotin*

Negishi Coupling

The cross-coupling of organozincs with organic electrophiles in the presence of a transition-metal catalyst (**Scheme 3**), is widely utilized due to the mild, yet reactive nature of organozinc halides.



R_1 = aryl, alkenyl, acyl
R_2 = aryl, heteroaryl, alkenyl, allyl, benzyl, homoallyl, homopropargyl
X_1 = Cl, Br, I, OTf
X_2 = Cl, Br, I

Scheme 3: The Negishi reaction

Reference: Yet, Larry. **Negishi Cross-Coupling Reaction**. Name Reactions for Homologations. John Wiley & Sons, Inc. (2009), (Pt. 1), 70–99.

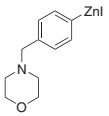
Organozincs

680982

680966

499382

710261



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710326

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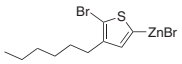

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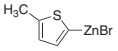

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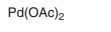
For a complete list of organozinc reagents available from Aldrich Chemistry, please visit *aldrich.com/zinc*

Common Catalysts Employed for Cross-Coupling



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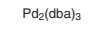

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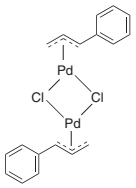
New Palladium Catalysts from Aldrich Chemistry



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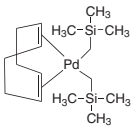

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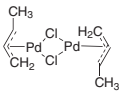

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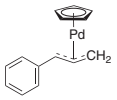

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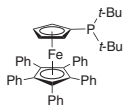
Common Ligand or Catalyst Families



675784
Hartwig

675709
Guram

570958
Fu

638439
Buchwald

709042
Nolan

For a complete list of catalysts available from Aldrich Chemistry, please visit *aldrich.com/catalysis*

Building Blocks

Mark Redlich, Ph.D.
Product Manager

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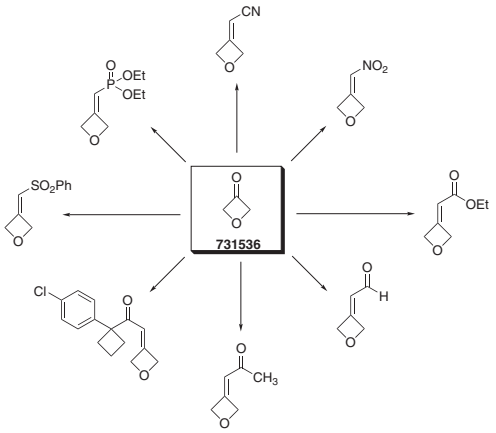
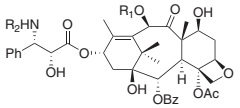
Oxetanes

Oxetanes are the closest homologs to epoxides, but historically have received far less attention than their three-membered-ringed brethren. However, oxetanes have received increasing exposure as attractive modules for drug discovery, largely due to a recent series of reports from Rogers-Evans, Carreira, and coworkers. They have demonstrated the improved physico- and biochemical properties of a molecular scaffold when an oxetane unit replaces a *gem*-dimethyl unit[1] and also reported an oxetane ring can function as a surrogate for a carbonyl group.[1b,2] More recently, they have demonstrated the use of 1,6-substituted azaspiro[3.3]heptanes containing an oxetane ring as alternatives to unstable 1,3-heteroatom substituted cyclohexanes.[3] In most cases, 3-oxetanone, **731536**, was the principal building block employed by the authors to install the oxetane unit (**Scheme 1**).



Scheme 1: Oxetane Derivatives Synthesized from 3-Oxetanone

The presence of the oxetane moiety in drug-like and biologically active molecules is nothing new to synthetic and medicinal chemists. Perhaps the best-known examples of oxetane-containing drugs are the natural product paclitaxel (Taxol®) and its synthetic analog docetaxel (**Figure 1**). Joëlle Dubois and coworkers studied the effect of the deletion of the oxetane ring in analogs of docetaxel and found the analogs to be less active than docetaxel in biological assays.[4] Merrilactone A (**Figure 2**) shows promise as a nonpeptidal neurotropic agent, [5] and the β-amino acid oxetin (**Figure 3**) has demonstrated both herbicidal and antibiotic activity.[6]



Paclitaxel: R_1 = Ac, R_2 = Bz
Docetaxel: R_1 = H, R_2 = Boc

Figure 1: Paclitaxel (Taxol®) and Docetaxel

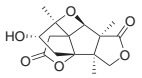


Figure 2: Merrilactone A

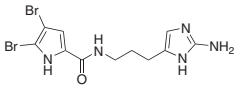


Figure 3: β-Amino Acid Oxetin

We are pleased to now offer a wide selection of new oxetane building blocks for a variety of applications in synthetic and medicinal chemistry.

New Oxetanes

731536

733296

731560

731579

733091

731544

731587

731609

For a complete list of oxetanes available from Aldrich Chemistry, please visit *aldrich.com/oxetane*

Halogenated Pyridines

Pyridines continue to be extremely popular building blocks for synthetic chemists across a number of disciplines. The pyridine moiety is found in a wide range of synthetic targets with applications in catalysis, drug design, molecular recognition, and natural product synthesis. Halogenated pyridines in particular are attractive building blocks for various cross-coupling methodologies. Sigma-Aldrich is pleased to offer these useful halogenated pyridines for your research.


722170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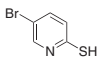
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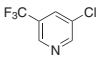
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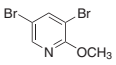
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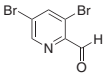
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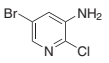
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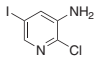
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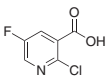
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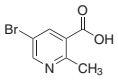
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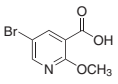
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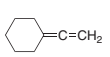
For a complete list of halogenated pyridines available from Aldrich Chemistry, please visit *aldrich.com/hal-pyr*

Other New Building Blocks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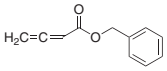
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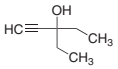
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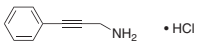
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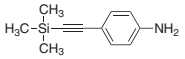
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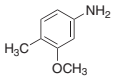
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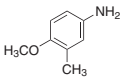
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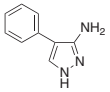
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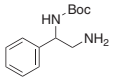
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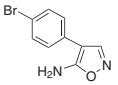
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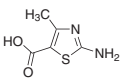
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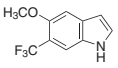
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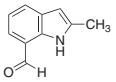
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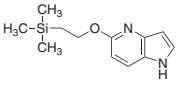
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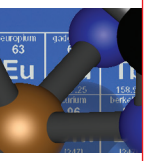
724378

For a complete list of building blocks available from Aldrich Chemistry, please visit *aldrich.com/bb*

References: (1) (a) Wuitschik, G. et al. *Angew. Chem., Int. Ed.* **2006**, *45*, 7736. (b) Wuitschik, G. et al. *J. Med. Chem.* **2010**, *53*, 3227. (2) Wuitschik, G. et al. *Angew. Chem., Int. Ed.* **2008**, *47*, 4512. (3) Burkhard, J. A. et al. *Org. Lett.* **2010**, *12*, 1944. (4) Deka, V. et al. *Org. Lett.* **2003**, *5*, 5031. (5) (a) Birman, V. B.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2080. (b) Huang, J.-M. et al. *Tetrahderon Lett.* **2000**, *41*, 6111. (c) Huang, J.-M. et al. *Tetrahderon* **2001**, *57*, 4691. (6) Omura, S. et al. *J. Antibiot.* **1984**, *37*, 1324.



Synthetic Reagents

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Product Manager

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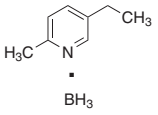
5-Ethyl-2-methylpyridine borane (PEMB): A New Reagent for Reductive Aminations

PEMB

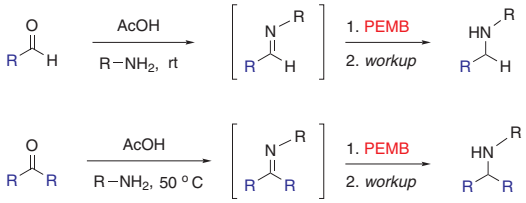


5-Ethyl-2-methylpyridine borane (PEMB)
725080

Figure 1: Structure of the new reductive amination reagent, PEMB (**725080**).

The reaction of a primary amine with an aldehyde or ketone in the presence of an appropriate hydride source provides quick access to an array of secondary amines. Critical to the success of this transformation is the nature of the reducing agent. Highly reactive hydrides will be intolerant not only with the weak Brönsted acid catalysts commonly employed but also with water generated upon iminium ion formation.

Useful Applications of PEMB

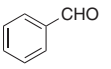
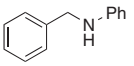
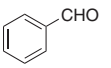
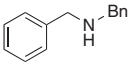
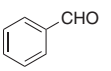
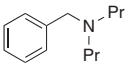
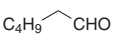
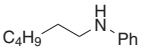
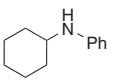
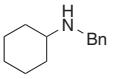
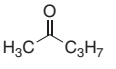
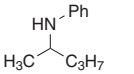
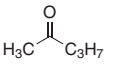
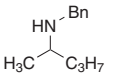
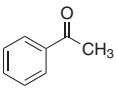
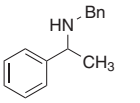


Scheme 1: Representative transformation conditions for reduction amination with PEMB.

5-Ethyl-2-methylpyridine (PEMB) exhibits enhanced shelf stability relative to other amine-boranes for reductive aminations (**Scheme 1**). Studies have shown solvolysis is slow (less than 7% daily) in water/THF or methanol solutions.

Reductive aminations with PEMB can be run in methanol. However, solvent can be eliminated completely and the reactions can be run neat, often with better yield than when run in solution (**Scheme 2**). Unlike some other hydride reducing agents, two of the three borane hydrides are utilized and usually an excess of reagent is not required.

Selected Examples

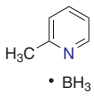
Carbonyl	Amine	Product	Yield (%) MeOH	Yield (%) neat
	$PhNH_2$		72	80
	$BnNH_2$		87[a]	92[a]
	Pr_2NH		0[b]	96
	$PhNH_2$		92	94
	$PhNH_2$		92	93
	$BnNH_2$		83[a]	70[a]
	$PhNH_2$		74	94
	$BnNH_2$		84	83
	$BnNH_2$		62[c]	70

[a] Isolated as the dialkylammonium acetate
[b] No reductive ammination product, benzyl alcohol generated
[c] Percent conversion in 1 h

Scheme 2: Selected reductive amination examples run in methanol and neat.

References: Burkhardt, E. R.; Coleridge, B. M. Tetrahedron Lett. **2008**, 49, 5152–5155.

Amine Boranes



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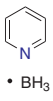

• BH_3

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$PhNEt_2$

• BH_3

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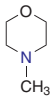

• BH_3

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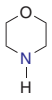

• BH_3

180203

Me_2NH

• BH_3

180238

$i\text{-}Pr_2NEt$

• BH_3

253111

$t\text{-}BuNH_2$

• BH_3

197939

Et_3N

• BH_3

178977

Me_3N

• BH_3

178985

H_3N

• BH_3

287717

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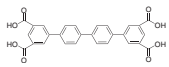

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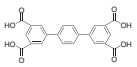

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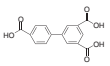

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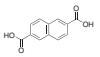

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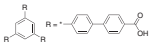

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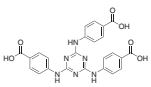

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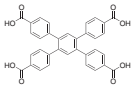

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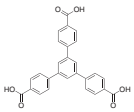

686859

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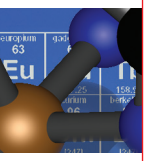
230006	**203696**	**467855**	**229415**
$Ni(NO_3)_2 \cdot 6H_2O$	$Cu(NO_3)_2 \cdot xH_2O$	$Co(NO_3)_2 \cdot 6H_2O$	
203874	**229636**	**203106**	



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Market Segment Manager
Solvents

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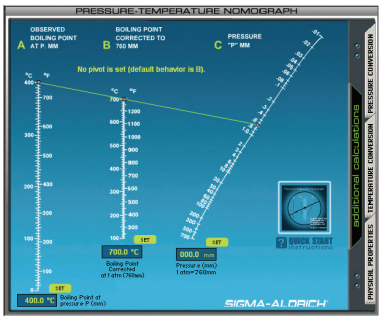

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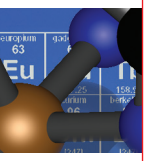

Labware Notes

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Product Manager

labware@sial.com

Distillation Adapter for On-The-Fly Sampling

Distillation is the most widely used bulk separation method used in the laboratory as well as industry. Beyond purification, it is widely used to characterize complex fluids (such as fuels) through measurement of the distillation curve, a plot of the boiling temperature against volume distilled. A common theme in both of these applications is the desire to understand the composition. In purification, the goal is to monitor the distillation progress, and in fluid characterization, one seeks to relate the composition to the temperature data.

The distillate sampling adapter (**Figure 1**) installed following a condenser or distillation column, can provide this important capability without the need for cumbersome, expensive and often unreliable fraction collectors.[1–3] The flow of the distillate is focused to drop into a 0.05 mL "hammock" that is positioned directly below the flow path. The sampling port, equipped with a vacuum tight valve, allows access to the hammock with a standard chromatographic syringe, through a septum. To sample the distillate, one simply positions the chromatographic syringe, preferably equipped with a blunt tipped needle, in the well of the hammock. It is a simple matter to withdraw samples as the distillation progresses. The sample can then be directly injected into the gas chromatograph or spectrometer, or injected into an autosampler vial for analysis later. Indeed, any analytical technique that is applicable for liquid samples ranging in volume from 1 to 50 microliters can be used to characterize the distillate.

This adapter has been used for many complex fluid analyses, including gasolines, diesel fuels, rocket kerosenes, jet fuels, crude oils, transformer fluids, waste oils and arson accelerants. Some of the analytical techniques applied to distillate fraction analysis include gas chromatography (with mass selective, flame ionization and chemiluminescence detection), FTIR spectroscopy, Karl Fischer coulombic titrimetry and refractometry. The ability to couple quantitative analysis with the distillation opens the door to thermochemical determinations such as the enthalpy of combustion of fuels, as a function of distillate cut. The adapter has also been used to measure corrosivity of crude oil fractions, with a copper coupon test performed at various distillate cuts.

Figure 1: Distillate sampling adapter.

For a complete list of adapters available from Aldrich Chemistry, please visit *aldrich.com/labware*

Aldrich GC sampling adapter, with vacuum connection and PTFE valve

Joint size	Cat. No.
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24/40	Z569909
29/32	Z569917
Replacement valve septa	33310-U
Septum inserter for valve	33311

References: (1) Bruno, T. J., Ott, L.S., Lovestead, T.M., Huber, M.L., The composition explicit distillation curve technique: relating chemical analysis and physical properties of complex fluids. *J. Chromatogr.* **2010**, A1217, 2703–2715. (2) Bruno, T. J., Ott, L.S., Lovestead, T.M., Huber, M.L., Relating complex fluid composition and thermophysical properties with the advanced distillation curve approach. *Chemical Eng. Tech.* **2010**, 33, (3), 363–376. (3) Bruno, T. J., Ott, L.S., Smith, B.L., Lovestead, T.M., Complex fluid analysis with the advanced distillation curve approach. *Anal. Chem.* **2010**, 82, 777–783.

Hamilton® Syringe, 700 Series

This syringe is a good choice for use with the sampling adapter. volume 10 µL, needle size 22s ga (blunt tip)

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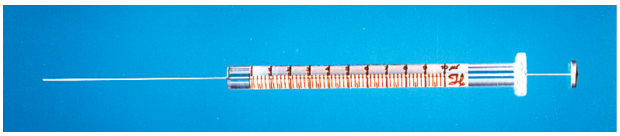

Aldrich Distillation Glassware

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News and Innovation

New Aldrich Condenser Design Eliminates Puddling on Equipment

Condensate cup catches water that forms on the outer surface of the condenser during use and eliminates puddling on reactor and equipment. Tubing connects to cup's hose barb to drain away water automatically.

Z568945 overall H 60 mm, Joint: ST/NS 14/20

Z568953 overall H 100 mm, Joint: ST/NS 14/20

Z568961 overall H 200 mm, Joint: ST/NS 14/20

Z568988 overall H 200 mm, Joint: ST/NS 24/40

Z568996 overall H 200 mm, Joint: ST/NS 29/32

Z569003 overall H 300 mm, Joint: ST/NS 14/20

Z569038 overall H 300 mm, Joint: ST/NS 29/32

Z569011 overall H 300 mm, Joint: ST/NS 24/40

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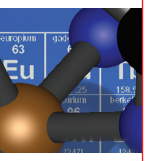

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Mike Willis
Market Segment Manager

mike.willis@sial.com

ChemNavigator® 3DPL™ (3-Dimensional Protein-Ligand Search)

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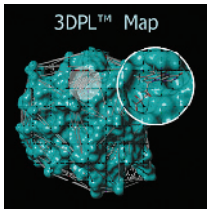
3DPL offers a rapid approach for selecting a population of targeted molecules from starting sets of millions of small molecule structures. 3DPL technology uses a protein structure and large databases of small molecule structures to perform rapid, flexible virtual screening against all likely binding sites on the protein surface. 3DPL is used to identify highly targeted sets of small molecule structures likely to bind the protein surface. Discovery companies can assay sets of hundreds to low thousands of high value structures and avoid screening larger sets of tens of thousands of diverse compounds.

3DPL is designed to allow drug discovery companies to identify a target-focused set of chemistry and move to bioassay and lead identification as quickly and efficiently as possible. 3DPL has several major advantages that allow for rapid identification of potential active molecules:

Advantages of 3DPL Searching



- **Knowledge of active site not required:** 3DPL includes technology for automated identification of all sites on the protein surface of appropriate size for binding with a therapeutic molecule. This Convex Hull technology identifies all potential binding sites that can be used in flexible screening, and it eliminates the need for an identified binding site as input for the screening experiment.

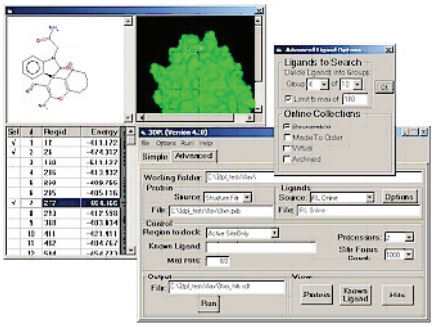
- **Entire protein surface may be considered:** Each small molecule is compared against all potential binding sites on the 3D protein surface to look for potential binding interactions. This approach offers the opportunity to identify ligands that would have been overlooked by virtual screening technologies that focus on only one or more pre-defined active sites on the protein surface.

- **Automatic conformational analysis:** Each small molecule ligand is flexed, in an energetically directed approach, and re-oriented thousands of times in the search for potential matches between the ligand and the protein surface.

- **Speed enables *in silico* screening of millions of small molecules:** 3DPL employs a unique and patented derivative field grid to direct small molecules to favorable binding conformations. The use of these grids significantly reduces computational time. Running on a single 1.4 GHz server, 3DPL is able to evaluate over 8 million chemical structures for binding across the entire protein surface in less than 4 days—a 600-fold increase over the fastest technology available today. Much larger structure sets can be run, which eliminates the need to filter out large numbers of potentially valuable samples before the virtual screening experiment.

- **3D Version of on-line iResearch™ Library included:** iResearch Subscribers may now access a special on-line version of the iResearch Library that is configured to use with 3DPL. This provides access to over 20 million 3D ligands for use in virtual screening.

Input to the system is a 3D protein model and a set of 3D small molecule structures; output is a selection of scored small molecule structures that have been calculated to show binding affinity for the protein surface. 3DPL can be used with ChemNavigator's iResearch Library of over million unique structures to provide access to the greatest diversity of commercially available small molecule compounds.



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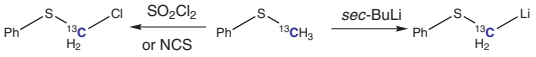
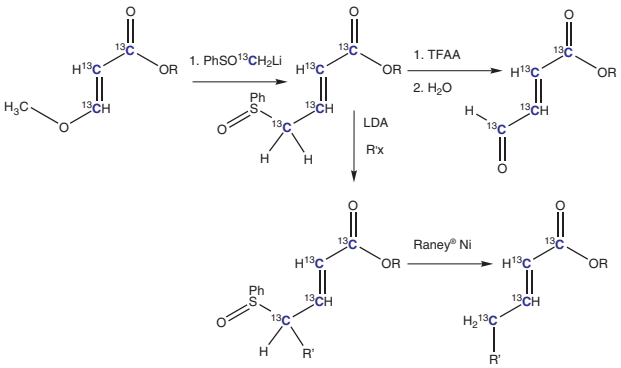
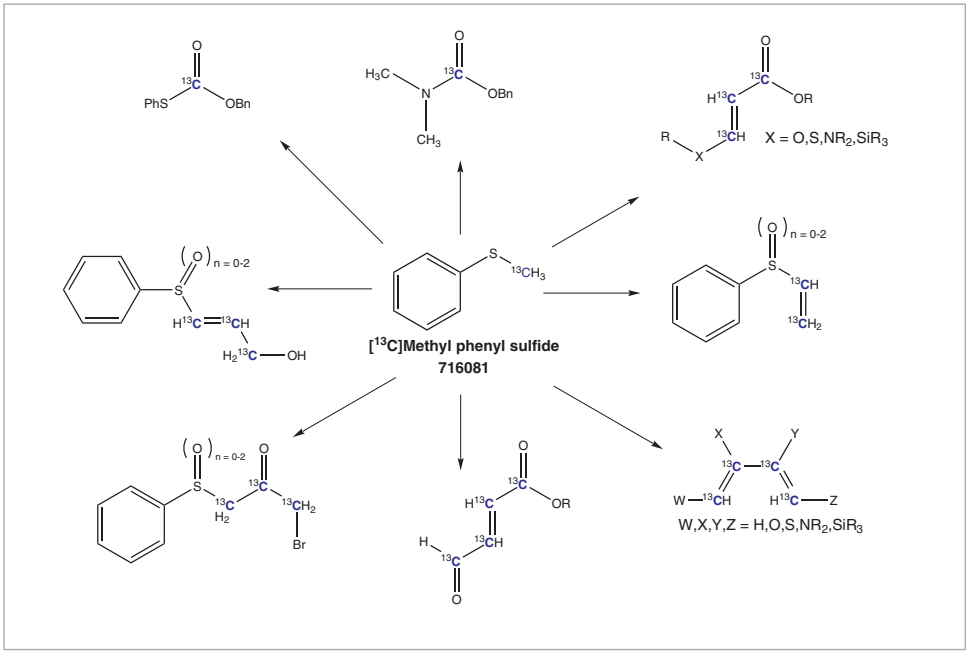
Reference: Martinez, R. A.; Alvarez, M. A.; Velarde, S. P.; Silks, L. A. P.; Stotter, P. L.; Schmidt, J. G.; Unkefer, C. J. Large-Scale Preparation of [^{13}C]-Methyl Phenyl Sulfide from [^{13}C]Methanol by a One-Step Process. *Org. Process Res. Dev.* **2002**, *6*, 851.

Some of the most versatile compounds in the collection include the methyl addition reagents of which methyl-^{13}C phenyl sulfide (**716081**) is a notable example. Methyl phenyl sulfide has a rich chemistry and, if prepared with carbon and deuterium labels in the methyl group, is a versatile labeling precursor easily converted into a nucleophilic or an electrophilic synthon.



Labeled methyl phenyl sulfide can be oxidized, adjusting the pK_a and allowing for subsequent modifications. A Raney® Ni mediated desulfurization can be used to remove the sulfur, leaving a labeled methylene group. Alternatively, a ^{13}C-labeled aldehyde, carboxylic acid, or carboxylic ester can be prepared directly.





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