ALDRICH CONGRATULATES THE 2006 ACS AWARD WINNERS

Aldrichimica ACTA

VOL. 39, NO. 1 • 2006

Organic Synthesis with Light-Fluorous Reagents, Reactants, Catalysts, and Scavengers

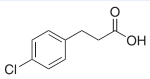
Synthetic Applications of Buchwald's Phosphines in Palladium-Catalyzed Aromatic-Bond-Forming Reactions

New Products from Aldrich R&D

Phenylpropionic Acid Derivatives

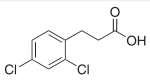
3-(4-Chlorophenyl)propionic acid, 97%

656151 1 g
[*2019-34-3*] 5 g
$C_9H_9ClO_2$



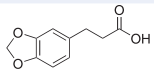
3-(2,4-Dichlorophenyl)propionic acid, 97%

656186 1 g
[*55144-92-8*] 5 g
$C_9H_8Cl_2O_2$



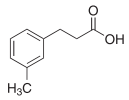
3-(3,4-Methylenedioxyphenyl)propionic acid, 97%

657565 1 g
[*2815-95-4*] 5 g
$C_{10}H_{10}O_4$



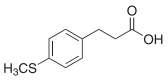
3-(3-Methylphenyl)propionic acid, 97%

656178 1 g
[*3751-48-2*] 5 g
$C_{10}H_{12}O_2$



3-(4-Methylthiophenyl)propionic acid, 97%

656135 1 g
$C_{10}H_{12}O_2S$ 5 g



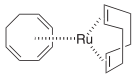
Versatile building blocks employed in the synthesis of several biologically active compounds, including γ-secretase inhibitors[1,2] and antagonists of human vanilloid receptor 1,[3,4] adenosine A_1 receptor,[5] and dopamine D_4 receptor.[6]

(1) Owens, A. P. et al. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4143. (2) Churcher, I. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 179. (3) Jetter, M. C. et al. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3053. (4) McDonnell, M. E. et al. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 531. (5) Van Calenbergh, S. et al. *J. Med. Chem.* **2002**, *45*, 1845. (6) Unangst, P. C. et al. *J. Med. Chem.* **1997**, *40*, 4026.

Organometallic Reagents

(1,5-Cyclooctadiene)(1,3,5-cyclooctatriene)ruthenium, Ru(cod)(cot)

654418 1 g
[*127382-91-6*]
$C_{16}H_{22}Ru$

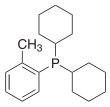


Highly selective catalyst for amine alkylations, [2+2] cycloadditions, and enyne generation;[1] and key precursor for the preparation of stabilized Ru nanoparticles.[2]

(1) (a) Mitsudo, T. et al. *J. Am. Chem. Soc.* **1999**, *121*, 1839. (b) Watanabe, Y. et al. *J. Org. Chem.* **1996**, *61*, 4214. (2) (a) Pelzer, K. et al. *Chem. Mater.* **2004**, *16*, 4937. (b) Pan, C. et al. *J. Am. Chem. Soc.* **2001**, *123*, 7584.

Dicyclohexyl(2-methylphenyl)phosphine, 95%

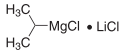
651885 1 g
[*173593-25-4*] 10 g
$C_{19}H_{29}P$



Bulky ligand in catalyst systems utilized in coupling reactions.

Isopropylmagnesium chloride–lithium chloride complex solution, 1.0 M in tetrahydrofuran

656984 10 mL
[*807329-97-1*] 100 mL
$C_3H_7Cl_2LiMg$



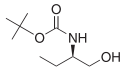
Performs halogen–magnesium exchange better than its counterparts, isopropylmagnesium chloride and diisopropylmagnesium.

Ren, H. et al. *Org. Lett.* **2004**, *6*, 4215.

1,2-Amino Alcohols

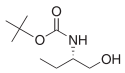
N-Boc-(*R*)-(+)-2-amino-1-butanol, 96%

660108 1 g
$C_9H_{19}NO_3$ 5 g



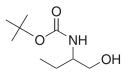
N-Boc-(*S*)-(–)-2-amino-1-butanol, 96%

660116 1 g
$C_9H_{19}NO_3$ 5 g



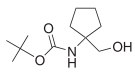
N-Boc-DL-2-amino-1-butanol, 97%

657786 1 g
[*138373-86-1*] 5 g
$C_9H_{19}NO_3$



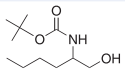
N-Boc-1-amino-1-cyclopentanemethanol, 97%

657689 1 g
$C_{11}H_{21}NO_3$ 5 g



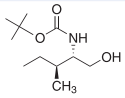
N-Boc-DL-2-amino-1-hexanol, 90%

657794 1 g
$C_{11}H_{23}NO_3$ 10 g



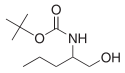
N-Boc-(2*S*,3*S*)-(–)-2-amino-3-methyl-1-pentanol, 96%

660205 2 g
$C_{11}H_{23}NO_3$ 10 g



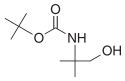
N-Boc-DL-2-amino-1-pentanol, 97%

657808 1 g
[*179684-02-7*] 5 g
$C_{10}H_{21}NO_3$



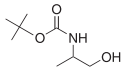
N-Boc-2-amino-2-methyl-1-propanol, 97%

657778 1 g
[*102520-97-8*] 5 g
$C_9H_{19}NO_3$



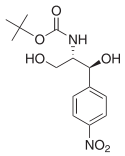
N-Boc-DL-2-amino-1-propanol, 95%

657816 1 g
[*147252-84-4*] 5 g
$C_8H_{17}NO_3$



N-Boc-(1*R*,2*R*)-(–)-2-amino-1-(4-nitrophenyl)-1,3-propanediol

660213 1 g
$C_{14}H_{20}N_2O_6$ 5 g



Versatile building blocks for the synthesis of aldehydes,[1] carboxylic acids,[2] aziridines,[3] azides,[4] and oxathiazolidines.[5]

(1) Tietze, L. F.; Burkhardt, O. *Synthesis* **1994**, 1331. (2) (a) Kokotos, G. et al. *J. Med. Chem.* **2004**, *47*, 3615. (b) Sasaki, N. A. *Tetrahedron Lett.* **1987**, *28*, 6069. (3) (a) Wessig, P.; Schwarz, J. *Synlett* **1997**, 893. (b) Braga, A. L. et al. *Org. Lett.* **2003**, *5*, 2635. (4) Benalil, A. et al. *Tetrahedron* **1991**, *47*, 8177. (5) Posakony, J. J. et al. *J. Org. Chem.* **2002**, *67*, 5164.

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General Correspondence

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

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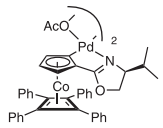
"PLEASE BOTHER US."

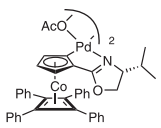
Joe Porwoll, President
Aldrich Chemical Co., Inc.

Professor Larry Overman of the University of California, Irvine, kindly suggested that we offer these cobalt(I) oxazoline palladacycle enantiomers. These acetate-bridged dimers (COP-OAc) effectively promote the asymmetric rearrangement of allylic trichloroacetimidates to allylic trichloroacetamides.[1] This grants ready access to valuable allylic amines of high enantiomeric purity, following the removal of the trichloroacetyl group under basic, acidic, or reductive conditions.

(1) Kirsch, S. F.; Overman, L. E.; Watson, M. P. *J. Org. Chem.* **2004**, *69*, 8101.



661716



661708

661716	(*S*)-(+)-COP-OAc Catalyst, 95%	250 mg 1 g
661708	(*R*)-(–)-COP-OAc Catalyst, 95%	250 mg 1 g

Naturally, we made these useful catalysts. 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.

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ABOUT OUR COVER

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

Family Group (oil on canvas, 182.8 × 213.3 cm) was painted by the American painter William Glackens in 1910–1911. Glackens was one of a number of artists whose works reflected the rapid changes that were occurring in America in the early years of the twentieth century. America was evolving from a predominantly agricultural society into an industrial power, people were moving from the country to the cities, and massive immigration was rapidly increasing the population. These artists strove to document the realism of everyday life, painting scenes in fashionable cafés and restaurants, immigrant life on New York City's Lower East Side, theatergoers emerging from popular shows on Broadway, and views in Central Park and the city's streets. Rejecting any self-conscious aestheticism or romanticism, eight of them joined together in 1908 to stage their own independent exhibition, repudiating the prevailing academicism of the time. The culmination of this movement occurred in 1913 with The Armory Show, a huge exhibition of modern American and European art in New York, in which Glackens's *Family Group* was first shown.

The painting records a visit to the artist's Fifth Avenue apartment by Grace Morgan, a family friend who had recently returned to New York from France. Mrs. Edith Glackens leans on her sister Irene's chair, while Ira Glackens, the artist's son, stands between his mother and a table on which their visitor rests her elbow. The light streaming in from the window in the background illuminates the diverse colors and patterns in the room, and the casual arrangement of the figures and their closeness to the viewer underscore the naturalness of the artist's approach. Even the fact that the bottom edge of the picture cuts off the diagonal of the carpet implies that the carpet extends into the space occupied by the viewer, further enhancing the immediacy and realism of Glackens's representation of a singular, but otherwise ordinary event in the life of his family.

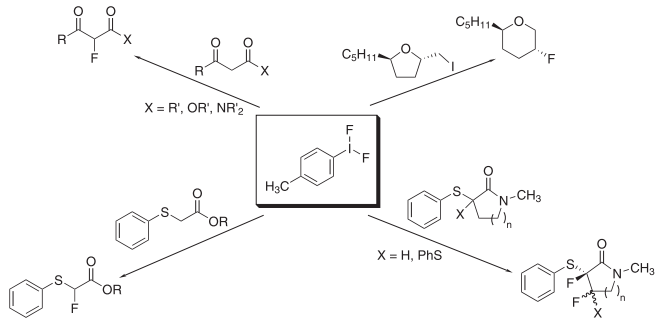
This painting is a gift of Mr. and Mrs. Ira Glackens to the National Gallery of Art, Washington, DC.

Fluorinating Reagents from Sigma-Aldrich

The importance of selectively fluorinating compounds in medicinal chemistry, biology, and organic synthesis is well appreciated and provides a major impetus to the discovery of new and mild fluorinating agents that can operate safely and efficiently. Elemental fluorine and many electrophilic fluorinating agents have been used in synthesis; however, most of these fluorinating agents are highly aggressive, unstable, and require special equipment and care for safe handling. Sigma-Aldrich is pleased to offer the following alternatives, which lack these drawbacks.

NEW 4-Iodotoluene Difluoride (Tol-IF_2)

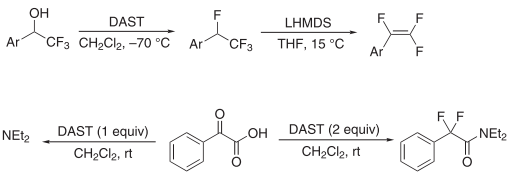
4-Iodotoluene difluoride (Tol-IF_2) is easy to handle and less toxic than many fluorinating agents. Selective monofluorination of β-keto esters, β-keto amides, and β-diketones takes place under mild conditions without the use of HF–amine complexes.[1] A new methodology for the synthesis of fluorinated cyclic ethers was recently reported, which utilized Tol-IF_2 to achieve a fluorinative ring-expansion of four-, five-, and six-membered rings.[2] When one equivalent of Tol-IF_2 is reacted with phenylsulfanylated esters, the α-fluoro sulfide results through a fluoro-Pummerer reaction.[3] When phenylsulfanylated lactams were treated with two equivalents of Tol-IF_2, the lactams were fluorinated in the α and β positions, resulting in diastereomeric difluorides.[4]



Diethylaminosulfur Trifluoride (DAST)

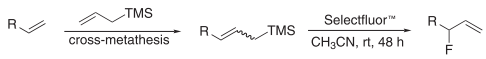
DAST has been regularly employed in selective fluorinations of alcohols, alkenols, carbohydrates, ketones, sulfides, epoxides, thioethers, and cyanohydrins. In addition, some novel organic cyclizations are possible when DAST is employed as a reagent.[5] 1,2,2-Trifluorostyrenes can be synthesized by fluorination of the parent α-(trifluoromethyl)phenylethanol with DAST, followed by dehydrohalogenation with lithium bis(trimethylsilyl)amide (LHMDS). This method leads to the trifluorostyrene without requiring a palladium-catalyzed coupling.[6]

The one-pot synthesis of α,α-difluoroamides via direct fluorination was recently reported using DAST as the fluorinating reagent. Decreasing the molar ratio of DAST to substrate resulted in the formation of the corresponding α-keto amide.[7]



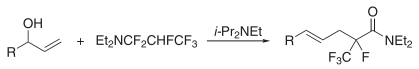
Selectfluor™ Fluorinating Reagent (F-TEDA)

Selectfluor™ fluorinating reagent [(1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), or F-TEDA)] is a user friendly, mild, air- and moisture-stable, non-volatile reagent for electrophilic fluorination. Selectfluor™ is capable of introducing fluorine into organic substrates in one step, with a remarkably broad scope of reactivity, often with excellent regioselectivity.[8] For example, allylic fluorides can be prepared using Selectfluor™ via a sequential cross-metathesis–electrophilic fluorodesilylation route. This route avoids the formation of byproducts that result from allylic transposition, which is observed when nucleophilic displacement or ring-opening reaction with DAST is attempted.[9]



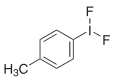
Ishikawa's Reagent

Ishikawa's reagent [(*N*,*N*-diethyl-1,1,2,3,3,3-hexafluoropropylamine) has also demonstrated its utility in fluorination reactions. In a recent example, Ishikawa's reagent has been used in a clean and reproducible fluorination protocol on an intermediate in the total synthesis of 26-fluoroepothilone B.[10] Ishikawa's reagent also displays the ability to insert a fluoro(trifluoromethyl)methylene moiety into unsaturated alcohols.[11]



References: (1) Yoshida, M. et al. *Arkivoc* [Online] **2003**(vi), 36. (2) Inagaki, T. et al. *Tetrahedron Lett.* **2003**, *44*, 4117. (3) Motherwell, W. B. et al. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2809. (4) Greaney, M. F. et al. *Tetrahedron Lett.* **2001**, *42*, 8523. (5) For a review, see Singh, R. P.; Shreeve, J. M. *Synthesis* **2002**, 2561. (6) Anilkumar, R.; Burton, D. J. *Tetrahedron Lett.* **2003**, *44*, 6661. (7) Singh, R. P.; Shreeve, J. M. *J. Org. Chem.* **2003**, *68*, 6063. (8) For a review, see Singh, R. P.; Shreeve, J. M. *Acc. Chem. Res.* **2004**, *37*, 31. (9) Thibaudeau, S.; Gouverneur, V. *Org. Lett.* **2003**, *5*, 4891. (10) Koch, G. et al. *Synlett* **2004**, 693. (11) Ogu, K.-i. et al. *Tetrahedron Lett.* **1998**, *39*, 305.

4-Iodotoluene difluoride



p-Tolyliododifluoride
[*371-11-9*] $CH_3C_6H_4IF_2$ FW 256.03
mp . . . . . 102–106 °C
R: 34 S: 26-36/37/39-45

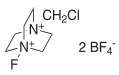
651117-1G	1 g
651117-5G	5 g

(Diethylamino)sulfur trifluoride

DAST
[*38078-09-0*] $(C_2H_5)_2NSF_3$ FW 161.19
Feiser **6**, 183; **10**, 142; **12**, 183; **13**, 110; **16**, 128
bp. . . . . .30–32 °C/ 3 mm Hg
density . . . . . 1.22 g/mL at 25 °C
R: 11-14-20/21/22-34 S: 16-26-36/37/39-45

235253-1G	1 g
235253-5G	5 g
235253-25G	25 g
235253-125G	125 g
235253-250G	250 g

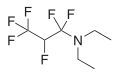
Selectfluor™ fluorinating reagent



F-TEDA
[*140681-55-6*] $C_7H_{14}B_2ClF_9N_2$ FW 354.26
>95% in F+ active
mp . . . . . 260 °C
R: 22-36/37/38-41 S: 26-36/37/39

439479-5G	5 g
439479-25G	25 g

Ishikawa's Reagent



N,*N*-Diethyl-1,1,2,3,3,3-hexafluoropropylamine
[*309-88-6*] $CF_3CF_2CHFN(C_2H_5)_2$ FW 223.16
bp. . . . . 56–57 °C n_D^{20} 1.3460
density . . . . . 1.230 g/mL at 25 °C
R: 10-34 S: 16-26-36/37/39-45

564990-25G	25 g
564990-100G	100 g

Organic Synthesis with Light-Fluorous Reagents, Reactants, Catalysts, and Scavengers

Dennis P. Curran
Department of Chemistry
University of Pittsburgh
Pittsburgh, PA 15260, USA
Email: curran@pitt.edu

Outline

1. Introduction

The need for rapid synthesis of small organic molecules in high purity has spawned a number of new approaches to conducting reactions and separations in recent years.[1] Among these, the fluorous approach has emerged as an especially general and powerful alternative to traditional solution-phase synthesis and to solid-phase synthesis, because it unites many of the most attractive features of both types of synthesis.[2,3] This review covers recent developments in the use of light-fluorous reagents, reactants, catalysts, and scavengers for the synthesis of small organic molecules and biomolecules.[4] The use of light-fluorous components in small-molecule organic reactions is typically coupled with a separation based on fluorous solid-phase extraction.[5]

In 1994, Horváth and Rábai launched the fluorous field with the introduction of "fluorous biphasic catalysis".[6,7] This liquid–phase, catalyst-immobilization technique uses "heavy fluorous molecules", containing large numbers of fluorines (often 63 or more), to impart high partition coefficients to these molecules and cause them to move out of organic solvents and into fluorous solvents. The fluorine atoms are supported on multiple tags (often also called "ponytails") that comprise perfluorohexyl (C_6F_{13}), perfluorooctyl (C_8F_{17}), or other perfluorinated or highly fluorinated groups. Spacers, such as $(CH_2)_n$ chains, are often present to insulate the reactive functionality from the strongly electron-withdrawing nature of the perfluoroalkyl group. Research on methods of fluorous biphasic catalysis for large-scale synthesis has flourished in recent years, and the techniques developed show excellent promise for industrial applications.

Introduced by our group in 1999,[8] "light fluorous chemistry" is more commonly employed in such small-scale, discovery-oriented applications as drug discovery and natural product synthesis. Light-fluorous molecules often bear a single perfluorohexyl or, more commonly, perfluorooctyl group. Such molecules have a low solubility in fluorocarbon solvents[9] and high solubility in many organic solvents, causing traditional liquid–liquid extractions in these cases to be inefficient. Light-fluorous molecules, however, can readily and reliably be separated from other organic molecules by the simple technique of fluorous solid-phase extraction (see Section 3).

2. Features of the Light-Fluorous Approach

Organic synthesis typically involves reaction, separation, and analysis and identification. The light-fluorous approach provides attractive features at each of these key stages. At the reaction stage, light-fluorous molecules are often soluble in a broad range of common organic solvents; this leads to clean solution-phase reactions with standard kinetics and reliable scalability. Generally speaking, there is little or no "reaction development" with light-fluorous reagents and catalysts: one simply utilizes, without modification, the established reaction conditions for the nonfluorous variant. Light-fluorous techniques are compatible with standard laboratory equipment and glassware, and they can be used synergistically with techniques such as supercritical carbon dioxide reactions and instruments such as microwave reactors. Fluoroalkyl groups are highly chemically inert, so fluorous tags outshine all other classes of tags in terms of chemical stability to reactions of all types.

At the separation stage of a synthetic process, fluorous tags expand rather than limit the separation options. In syntheses utilizing light-fluorous molecules, the preferred separation technique is fluorous solid-phase extraction, but all traditional separation techniques such as crystallization, distillation, and standard chromatography can still be used. This is in contrast to solid-phase synthesis, where all the traditional techniques are replaced by the single technique of filtration. This is fine if filtration does the job, but there are no good options if it does not. If desired, the fluorous components of a synthetic reaction can almost always be recovered and recycled.

At the analysis and identification stage, fluorous techniques involve discrete molecules, not oligomeric or polymeric materials; therefore, all traditional small-molecule analytical techniques are

suitable. Reaction mixtures and products can be analyzed by standard TLC and HPLC techniques and, again, both fluorous and nonfluorous options are available. Even GC is a powerful option for analyzing light-fluorous compounds because of their stability and volatility. For identification, solution-phase variants of standard spectroscopic techniques like NMR and IR are directly applicable. Fluorous molecules are compatible with the full range of modern small-molecule mass spectrometric techniques.

In short, if you are a practitioner of small-molecule organic synthesis, then you already know all of the experimental, analytical, and instrumental techniques that you need to know for light-fluorous synthesis, with the possible exception of fluorous solid-phase extraction.

3. Fluorous Solid-Phase Extraction

Fluorous solid-phase extraction (FSPE) is a simple experimental technique that resembles chromatography, but with key differences. Instead of using a standard stationary phase like silica gel, FSPE uses silica gel with a fluorocarbon- (or other fluorous-) bonded phase. Fluorous silica gel selectively retains polyfluorinated molecules, and this allows for a simple bifurcation of reaction mixtures containing fluorous and organic (nonfluorous) reaction components.

Figure 1 shows a photograph of the stages of a fluorous solid-phase extraction with two dyes. A mixture containing an organic (blue) and a fluorous (orange) dye is loaded onto the fluorous silica gel, and the column is eluted first with a fluorophobic solvent such as aqueous acetonitrile or methanol ("organic pass"). Water is the fluorophobic solvent *par excellence*, so only small amounts of it (5–20 vol %) are typically added to the water-miscible organic solvent. During this organic pass, the fluorous components are extracted (adsorbed) onto the silica gel, while the organic components are extracted off. A subsequent "fluorous pass" with a fluorophilic solvent (ether and THF are commonly used, among many others) extracts the fluorous components off the column.

These solid-phase extractions are fast, efficient, reliable, and, perhaps most importantly, they are generic. In other words, many different types of organic and light-fluorous molecules can be separated by substantially the same method. These features recommend FSPE for the standard "one-at-a-time" synthesis of organic molecules, as well as for manual or automated parallel synthesis. While a number of publications from our group provide experimental details about FSPE,[4,5] the best single source for detailed information on how to execute a successful FSPE in the laboratory is contained in an online application note.[10]

Finally, we have very recently introduced the technique of reversed-phase fluorous solid-phase extraction.[11] Here, the roles of the liquid and solid phases in a standard FSPE are reversed—a polar stationary phase (standard silica gel) is used with a (partially) fluorous mobile phase. The technique is nascent, and it may not have the generality of standard FSPE, but it is simple to test by TLC and simple to execute and, consequently, its use as a complement to FSPE merits consideration.

4. Examples of Light-Fluorous Reactions and Reaction Components in Small-Molecule Synthesis

Despite its relative youth, the field of light-fluorous chemistry has expanded rapidly, and a comprehensive treatment is already beyond the scope of this short review. In the following sections, topical areas, where light-fluorous chemistry has been utilized advantageously, will be presented along with illustrative reactions and reagents. This high-level overview is intended to give the reader a grasp of the many possibilities and applications. Many of the fluorous reagents, reactants, catalysts, and scavengers described below are now commercially available, and both the original literature and commercial application notes[10] provide extensive experimental details on their use.

4.1. Light-Fluorous Reagents

Reactions that use fluorous reagents to promote the transformation of a small-molecule substrate into a product are probably the most common among all classes of light-fluorous reactions. Two prototypical examples, a Mitsunobu reaction[12] and a Staudinger reaction,[13] are shown in **Scheme 1**. The Mitsunobu reaction is a rather challenging one between a nucleophile of relatively low acidity (*p*-methoxyphenol, **1**) and a secondary alcohol (2-octanol, **2**). The coupling is effected in solution by a combination of a fluorous Mitsunobu reagent (^{F}DEAD) and a fluorous phosphine (^{F}TPP-1) under the standard conditions of solvent, temperature, and time for the traditional Mitsunobu reaction. Simple fluorous solid-phase extraction then provides the coupled aryl alkyl ether, **3**, from the organic pass along with the spent reagents from the fluorous pass. The light-fluorous Staudinger reduction of azide **4** to amine **5** is comparably facile. Both the Mitsunobu and the Staudinger reactions have broad scopes, and the generic nature of the separation is especially attractive in parallel synthesis applications.

The relative reactivity of light-fluorous reagents compared to traditional reagents has not often been studied in detail; however, reactions of fluorous phosphines are a significant exception. A series of light-, medium-, and heavy-fluorous triarylphosphines exhibited comparable reactivities to triphenylphosphine in an assortment of typical phosphine reactions.[14] This study supports the assumption that the reactivities of light-fluorous reagents will be readily predictable from data on their nonfluorous counterparts.

Figure 2 shows some of the known fluorous reagents including phosphines, organic tin reagents and catalysts, selenenic acids, ketones, hypervalent iodine reagents and sulfoxides. The phosphines have many and varied uses,[15] while the tin reagents[16] have been employed for radical and ionic reductions and allylations as well as for azide displacements. The tin oxides promote the selective functionalization of diols,[17] while the ladder-like distannoxanes are excellent esterification catalysts.[18] The selenenic acids are powerful oxygenating reagents,[19,20] while the ketones can be used for in situ dioxirane generation.[21] The hypervalent iodine reagents[22] promote many kinds of interesting oxidations, while the sulfoxide can be used in an odorless variant of the Swern oxidation.[23]

The activation and coupling of acids for reaction with nucleophiles to make amides, esters, and related molecules is arguably the most common reaction class in drug discovery research, and is important in many other areas as well. An assortment of fluorous reagents, some of which are newly minted, are available to conduct these types of transformations. For example, the coupling of acids with both amines and alcohols by using Mukaiyama's pyridinium reagent is a powerful transformation that is underused, perhaps because of the problems associated with removing the reagent-derived pyridone byproduct. However, the fluorous Mukaiyama reagent[24] promotes smooth coupling and the resulting fluorous pyridone byproduct can readily be separated from the amide product (**eq 1**). An assortment of fluorous variants of popular coupling reagents are now available to carry out coupling reactions leading to amides, esters, and other functional groups (**Figure 3**).[25]

4.2. Organometallic Catalysts with Fluorous Ligands

The use of catalysts rather than stoichiometric reagents to promote organic transformations is increasingly important, and many

heavy-fluorous catalysts are already known. These are very useful for large-scale synthesis, but some reaction development may be needed. However, essentially any heavy-fluorous catalyst bearing multiple "ponytails" can be re-engineered into a light-fluorous one simply by reducing its fluorine content.

Several fluorous ruthenium and palladium catalysts are known. First- and second-generation fluorous Grubbs–Hoveyda catalysts are crystalline solids that promote metathesis reactions under standard conditions.[26] Separation and recovery of both the product and the catalyst are readily achieved by FSPE, as illustrated by the ring-closing metathesis of **9** to give the cyclic ether **10** (**Scheme 2**, **Part A**). The fluorous "pincer" complex (**Scheme 2**, **Part B**) efficiently promotes Heck reactions like the coupling of **11** to **12** to give **13** under standard thermal conditions, or even more rapidly and conveniently by microwave heating.[27] Bifurcation of the product mixtures as usual by FSPE provides the Heck product along with the recovered complex. However, the results suggest that the complex does not catalyze the reactions, but instead leaches very small amounts of highly active palladium metal into the reaction medium. As such, the "pincer" complex can be considered as a reusable catalyst reservoir. Fluorous nickel catalysts can also be recovered and recycled by FSPE.[28]

4.3. Fluorous Scavengers

Scavenging is a popular technique in medicinal chemistry and related areas for cleaning up crude reaction mixtures in which one of the key reaction components has been used in excess to promote a rapid, high-yielding reaction. The clean, solution-phase kinetics and the ease of separation by FSPE recommend fluorous scavengers for general use and, indeed, a number of scavenging applications have been described.[29] **Figure 4** shows representative examples of scavengers for nucleophiles,[30] electrophiles,[31] and trace metals.

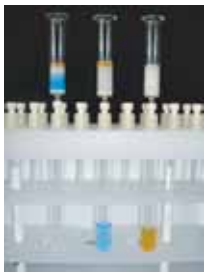
The functionalization of an isocyanate illustrates a typical use of a fluorous electrophilic scavenger (**eq 2**).[30b] Reaction of excess piperazine **14** with a limiting amount of phenyl isocyanate (**15**) is followed by addition of a fluorous isocyanate to scavenge the unreacted amine. Fluorous solid-phase extraction then provides the pure urea product, **16**, from the organic pass, while the fluorous pass with the scavenged fluorous urea, **17**, is usually discarded. The tables can be turned by using excess isocyanate to derivatize a limiting amount of amine; in this case, a fluorous amine is used to scavenge the remaining isocyanate.

4.4. Fluorous Protecting Groups

In multistep synthesis, it is often attractive to use substrates bearing fluorous protecting groups (sometimes called tags or labels) along with traditional nontagged reagents. A single fluorous protecting group renders a subsequent series of individual compounds fluorous, and this makes each succeeding reaction product susceptible to the same convenient fluorous solid-phase extraction.[32,33] Of course, the convenience is further amplified in parallel synthesis.

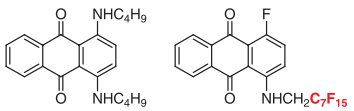
Scheme 3 shows two typical examples of coupling reactions of amines with fluorous-tagged carboxylic acids. (For similar coupling reactions with fluorous reagents, see Section 4.1.) In Part A, γ-amino acid **18**, bearing a fluorous *t*-butoxycarbonyl (^{F}Boc) group, is coupled with excess tetrahydroisoquinoline (**19**) in dichloromethane in the presence of EDCI and HOBt.[34] Fluorous solid-phase extraction removes all the excess and spent reagents in the organic pass and provides the amide product, **20**, in the fluorous pass.

The variant with fluorous carbobenzyloxy (^{F}Cbz) groups (Scheme 3, Part B) illustrates the extension of this approach to quasi-racemic synthesis.[35] Here, L-phenylalanine (Phe) is



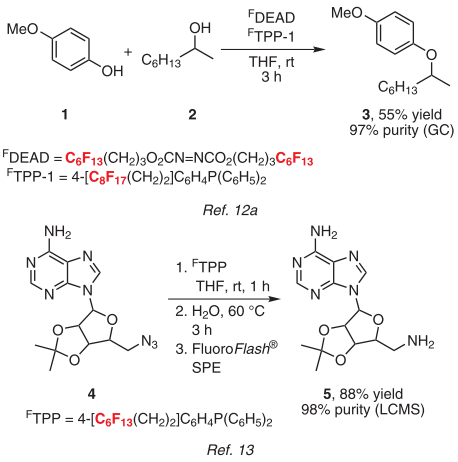
Left tube: Loading of dye mixture and beginning of fluorophobic elution with 80:20 MeOH:H_2O.
Middle tube: Completion of fluorophobic elution.
Right tube: Completion of fluorophilic elution (THF).

The dyes are:



blue dye orange dye

Figure 1. A Fluorous Solid-Phase Extraction of Organic (Blue) and Fluorous (Orange) Dyes over Fluoro*Flash*® Silica Gel.



^{F}DEAD = $C_6F_{13}(CH_2)_3O_2CN{=}NCO_2(CH_2)_3C_6F_{13}$
^{F}TPP-1 = 4-[$C_8F_{17}(CH_2)_2$]$C_6H_4P(C_6H_5)_2$

Ref. 12a

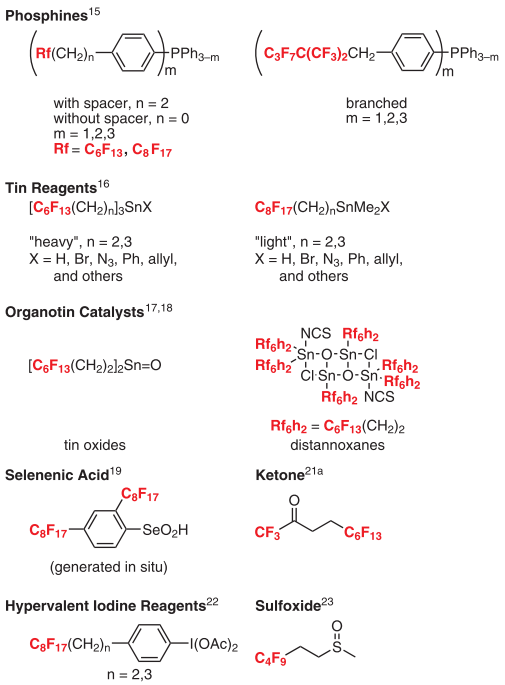
4

^{F}TPP = 4-[$C_6F_{13}(CH_2)_2$]$C_6H_4P(C_6H_5)_2$

5, 88% yield
98% purity (LCMS)

Ref. 13

Scheme 1. Light-Fluorous Mitsunobu (Top) and Staudinger (Bottom) Reactions.



Phosphines[15]

with spacer, n = 2
without spacer, n = 0
m = 1,2,3
Rf = C_6F_{13}, C_8F_{17}

branched
m = 1,2,3

Tin Reagents[16]

"heavy", n = 2,3
X = H, Br, N_3, Ph, allyl, and others

"light", n = 2,3
X = H, Br, N_3, Ph, allyl, and others

Organotin Catalysts[17,18]

tin oxides

Rf_6h_2 = $C_6F_{13}(CH_2)_2$
distannoxanes

Selenenic Acid[19]

(generated in situ)

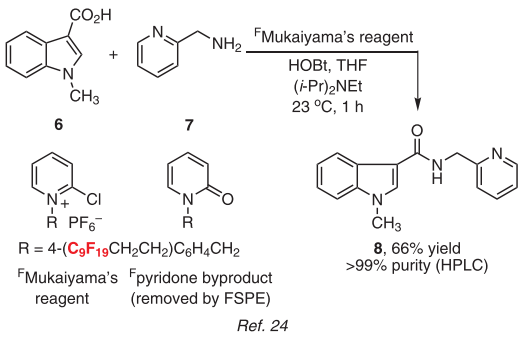
Ketone[21a]

Hypervalent Iodine Reagents[22]

n = 2,3

Sulfoxide[23]

Figure 2. Some of the Known Fluorous Reagents and Catalysts.



eq 1

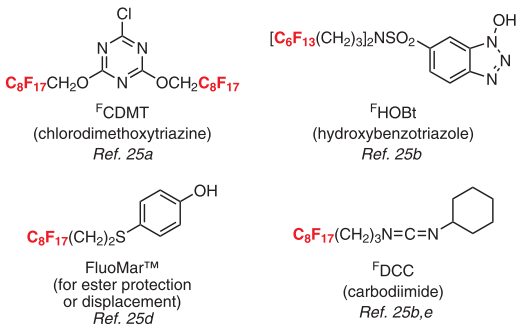
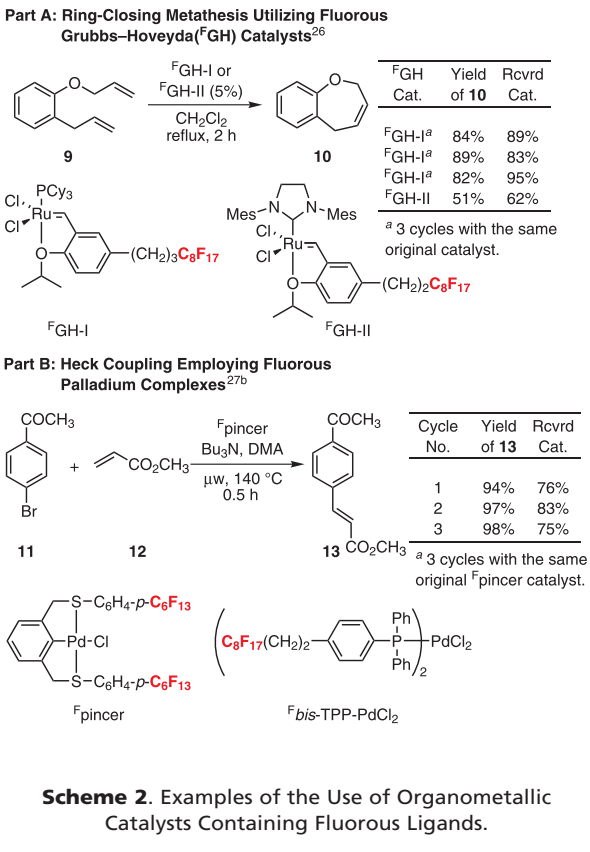


Figure 3. Fluorous Reagents for the Preparation of Peptides, Amides, and Esters.



Scheme 2. Examples of the Use of Organometallic Catalysts Containing Fluorous Ligands.

tagged with an FCbz group bearing a C_8F_{17} fragment, whereas D-Phe is tagged with a shorter C_6F_{13} fragment.[36] The mixture of fluorous-protected phenylalanine starting materials, **21**, is not a true racemate—hence the name quasi-racemate—because its components are not isomers. However, **21** behaves like a racemate in most respects, except, of course, when a fluorous separation is applied. Coupling of **21** with tetrahydroisoquinoline (**19**) is followed by charging the crude product onto an FSPE column and subsequent fluorophobic pass to elute the nonfluorous reagent- and reactant-derived byproducts. Flash chromatography with standard fraction collection is then applied to the same FSPE column, leading to D-quasi-enantiomer **22** in earlier fractions and L-quasi-enantiomer **23** in later fractions.

This process of resolving products based on fluorous tag size is called demixing or sorting, and it is usually applied after a multistep sequence to pull out individual compounds from a differentially tagged mixture in a process called fluorous-mixture synthesis.[37] In quasi-racemic synthesis—the simplest of fluorous-mixture synthesis techniques—a pair of enantiomers are tagged with different fluorous tags.[35] But it is also possible to tag diastereomers and even analogs (non-isomers) for fluorous-mixture synthesis. These techniques all leverage a synthesis by providing more compounds per unit effort.

Many other light-fluorous protecting groups have been introduced recently, and a selection of reagents that are used to install these groups is shown in **Figure 5**.[38–48] In addition to nitrogen-protecting groups such as FBoc, FCbz, and FFmoc;[38] there are also Fsilyl,[39] FPMB,[40] Fbenzyl,[41] and FTHP[42] protecting groups for alcohols; a fluorous ketonic protecting group for diols,[43a] and a fluorous sulfonate group for phenols.[43b] A number of these groups double as protecting groups for acids, and fluorous alcohols[44] also serve this function. The FluoMar™ reagent, a fluorous analog of the Marshall resin, doubles as a protecting group during a synthesis stage and as an activating group for subsequent displacement.[25d] These and other groups provide a broad spectrum of opportunities for rapid and efficient multistep synthesis under solution-phase conditions.

4.5. Fluorous Tagging in Multicomponent Reactions and Heterocycle Synthesis

A second use of fluorous tagging of substrates is in multicomponent reactions, especially those directed towards pharmaceutically relevant heterocycles.[3c] The use of a key fluorous-tagged component as the limiting reagent in a multicomponent reaction allows one to quickly isolate the tagged product away from what can often be complex mixtures containing unreacted reagents and products derived from the partial combination of several, but not all, of the reaction components. After the multicomponent reaction is completed, the tag is generally displaced in a cyclization (cyclative cleavage), is replaced by a proton (traceless tag) or, even more valuably, is replaced by another diversity element in a phase switch that provides a further purification gate for removing undesired products.[45]

The pairing of the advantages of fluorous tagging with microwave reactions is illustrated by the simple two-step synthesis of diverse quinoxalinones **26** (**Scheme 4**).[46] An initial Ugi reaction with mono FBoc-protected *o*-phenylenediamine (**24**) as the limiting reagent provides keto amides **25** after 20 min irradiation and FSPE. In this first FSPE, the desired products are in the fluorous fraction. Cleavage of **25** with TFA provides products **26** with moderate-to-high purities, this time from the organic fraction. Both steps (reaction and separation) can easily be conducted in parallel in less than half a workday. In contrast, a solution-phase approach using polymer-bound scavengers requires about 3–4 days to conduct

the same sequence, in part because a microwave is not used and in part because the polymer-bound scavengers react slowly (the scavenging reactions take more time than the target reactions). The use of fluorous tags in place of scavengers, the switch to fully solution-phase methods, and the use of microwave irradiation considerably expedite the creation of small, high-quality libraries by parallel synthesis.

5. Examples of Light-Fluorous Reactions and Reaction Components in Biomolecule Synthesis

Biomolecules, such as peptides and oligonucleotides, are typically prepared by solid-phase synthesis. Therefore, it might seem that fluorous techniques have no role to play in this important area, but this is not the case. In the long term, solution-based techniques may supplant solid-phase synthesis for some kinds of molecules. In the short term, fluorous techniques are already supplementing solid-phase syntheses in important ways.

Wipf and co-workers described the first union of solid-phase synthesis and fluorous-synthesis techniques in a small-molecule setting,[47] and applications in both peptide and oligonucleotide synthesis show great promise. For example, Van Boom completed a standard solid-phase peptide synthesis by capping the *N*-terminus with a fluorous Cbz or methanesulfonylethoxycarbonyl [$CH_3SO_2CH_2CH_2OC(=O)$; Msc] group.[48] Removal of the product from the solid phase provided a mixture of the target amino acid sequence, which was fluorous-tagged, and truncated sequences and other impurities, which were not. This mixture was then purified by fluorous HPLC rather than the usual reversed-phase HPLC, and the fluorous tag functioned as a powerful chromatographic shift agent, thereby rendering very easy an otherwise difficult separation. Oligopeptides of superior purity should be generally available by this method.

Pearson and co-workers, as well as others, have simplified the process even further in oligonucleotide synthesis by using solid-phase extraction instead of HPLC (**Figure 6**).[49] In this approach, a standard solid-phase synthesis of a DNA fragment by the phosphoramidite method is completed by coupling the last oligonucleotide with a fluorous dimethoxytrityl (^{F}DMT) group rather than a standard one. The sample is then removed from the solid phase, and the fluorous-tagged (target) oligonucleotide is separated from the untagged impurities by solid-phase extraction with a FLUORO-PAK® cartridge. After the fluorophobic pass to elute the nontagged impurities, an ammonia solution is added to clip the ^{F}DMT group. At the same time, this elutes the target oligonucleotide off the cartridge, while leaving the residual fluorous protecting group behind.

The experimental procedure is very simple to conduct, yet increases the purity of oligonucleotides obtained by solid-phase synthesis significantly. Despite the relatively small size of the fluorous group on the DMT tag, the method has been used for oligos containing as many as 50–100 nucleotides, which demonstrates the unique power of fluorous interactions.

6. Making Fluorous Reaction Components

The field of fluorous chemistry is young, and there is a chance that a needed fluorous material is not yet commercially available or even known. Preparing this fluorous material does not entail starting with the incredibly reactive elemental fluorine. Indeed, in over a decade of fluorous research in our group, we have never had the occasion to do the defining reaction in organofluorine chemistry (the formation of a carbon–fluorine bond). **Figure 7** illustrates some of the most popular and commercially available fluorous building blocks that can be fashioned into a diverse array

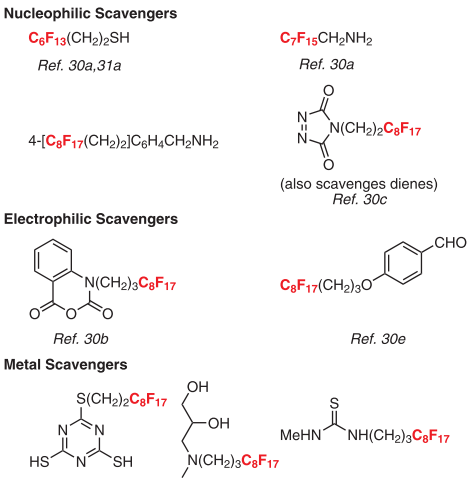
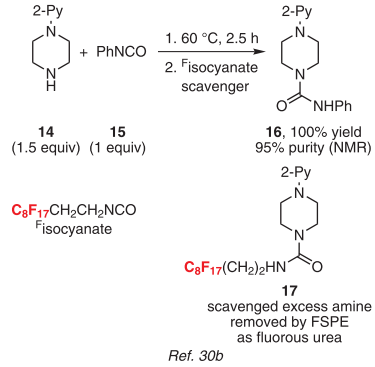
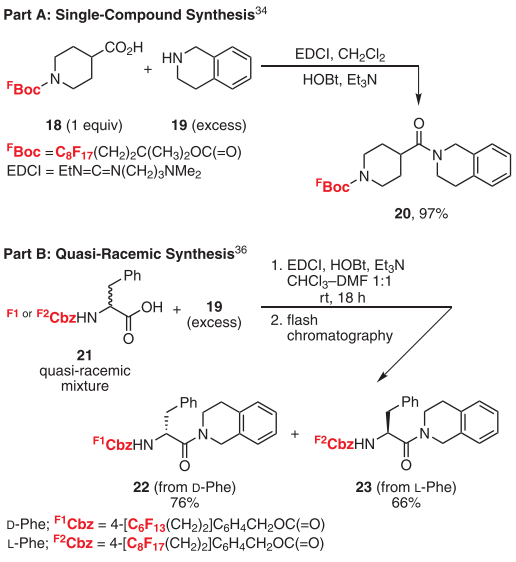


Figure 4. Representative Fluorous Scavengers.



eq 2



Scheme 3. Examples of Fluorous Protecting Groups in Single-Compound (Part A) and Quasi-Racemic (Part B) Syntheses.

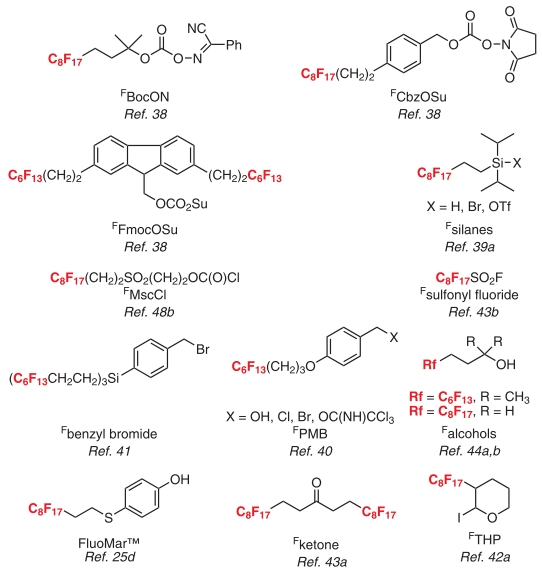
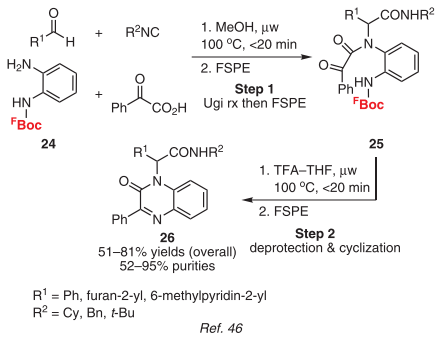


Figure 5. Representative Reagents That Are Employed to Install Fluorous Protecting Groups.



Scheme 4. A Rapid, Two-Step Heterocycle Synthesis with Fluorous Tagging.

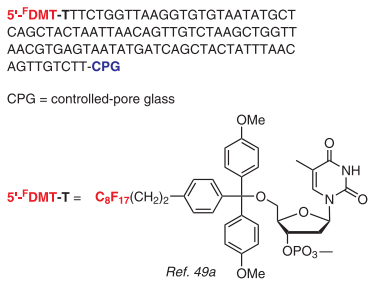


Figure 6. 100-mer Oligonucleotide Made by SPS with Fluorous Tagging and SPE Purification.

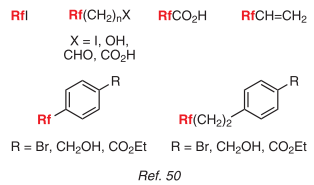


Figure 7. Representative Commercially Available Fluorous Building Blocks.

of new fluorous molecules by using established methods and reactions.[50]

7. Acknowledgments

I warmly thank my current and former co-workers at the University of Pittsburgh and the team at Fluorous Technologies, Inc., for their enthusiastic and enjoyable collaborations and especially for their many experimental and intellectual contributions. The National Science Foundation supported our initial foray into fluorous chemistry, and, since then, we have been supported consistently by the National Institutes of Health and the Merck Company. We are most grateful for the financial support of these institutions.

8. References and Notes

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About the Author

Dennis P. Curran received his B.S. degree in 1975 from Boston College. His Ph.D. was granted in 1979 by the University of Rochester, where he worked under Professor Andrew S. Kende. After a two-year postdoctoral stay with Professor Barry M. Trost at the University of Wisconsin, Dr. Curran joined the faculty of the chemistry department at the University of Pittsburgh in 1981. He now holds the ranks of Distinguished Service Professor and Bayer Professor of Chemistry, and is the founder of Fluorous Technologies, Inc. Dr. Curran has received the Pittsburgh Magazine Innovators Award (2003), the American Chemical Society Award for Creative Work in Synthetic Organic Chemistry (2000), the Cope Scholar Award (1988), and the Janssen Prize for Creativity in Organic Synthesis (1998). He is currently an ISI® "Highly Cited Researcher" (www.isihighlycited.com). Dr. Curran has authored over 300 papers, 20 patents, and two books. Beyond fluorous chemistry, he is well known for his work on radical reactions in organic synthesis.

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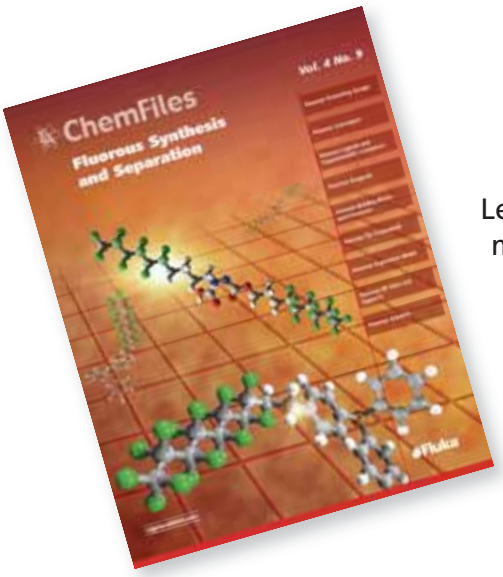

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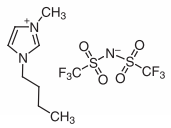
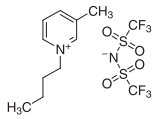
[*174899-83-3*]
$C_{10}H_{15}F_6N_3O_4S_2$
FW 419.35



77896-1G-F	1 g
77896-5G-F	5 g

1-Butyl-3-methylpyridinium bis(trifluoromethylsulfonyl)imide, purum, ≥97% (NMR)

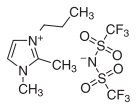
[*344790-86-9*]
$C_{12}H_{16}F_6N_2O_4S_2$
FW 430.39



14654-1G-F	1 g
14654-5G-F	5 g

1,2-Dimethyl-3-propylimidazolium bis(trifluoromethylsulfonyl)-imide, purum, ≥97% (NMR)

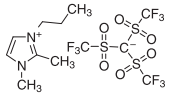
[*169051-76-7*]
$C_{10}H_{15}F_6N_3O_4S_2$
FW 419.36



50807-1G-F	1 g
50807-5G-F	5 g

1,2-Dimethyl-3-propylimidazolium tris(trifluoromethylsulfonyl)-methide, purum, ≥97% (NMR)

[*169051-77-8*]
$C_{12}H_{15}F_9N_2O_6S_3$
FW 550.44



74305-1G-F	1 g
74305-2.5G-F	2.5 g

1-Ethyl-3-methylimidazolium bis(pentafluoroethylsulfonyl)-imide, purum, ≥97% (NMR)

[*216299-76-2*]
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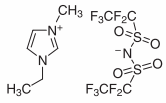
FW 491.33



39056-1G-F	1 g
39056-5G-F	5 g

1-Ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide, purum, ≥97% (HPLC)

[*174899-82-2*]
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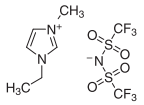
FW 391.31



11291-1G-F	1 g
11291-5G-F	5 g

3-Methyl-1-propylpyridinium bis(trifluoromethylsulfonyl)imide, purum

[*817575-06-7*]
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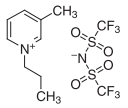
FW 416.36



30565-1G-F	1 g
30565-5G-F	5 g

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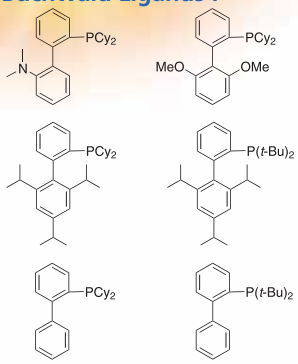

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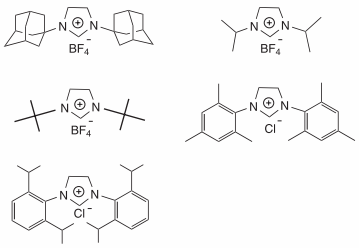

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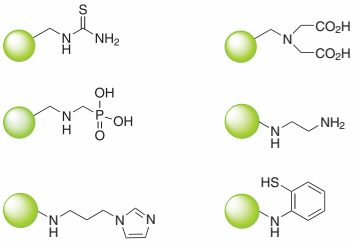

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659940-1KT	1-g bottles

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Pd EnCat™ 30 • Pd EnCat™ 40 • Pd EnCat™ TPP30 • Pd EnCat™ TOTP30 • Pd EnCat™ BINAP30 • Pd EnCat™ 30 NP

659959-1KT	1-g bottles

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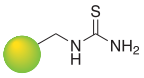
Sigma-Aldrich and Reaxa Ltd. Partner to Distribute QuadraPure™ Metal Scavengers

Functionalized Resins Solving Your Problems with Metal Contamination

The QuadraPure™ functionalized macroporous and microporous resins are designed to solve problems associated with the metal contamination that occurs during pharmaceutical or fine chemical processing from laboratory scale through to manufacturing. The very low levels of extractable impurities make QuadraPure™ products particularly suitable for use in GMP-compliant applications. QuadraPure™ Metal Scavengers are available in 5-g, 25-g, and 100-g units, as well as larger quantities.

Macroporous Resins

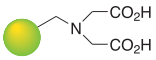


QuadraPure™ TU
655422
400–600 µm

Typical Experimental Capacity	Effective in Acid/Base
0.19 mmol/g (based on $Pd(OAc)_2$ in CH_2Cl_2)	Y/Y

Metals Removed

Pd, Pt, Ru, Au, Ag, Cu, Ni, Zn, Hg, Pb, and Cd



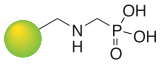
QuadraPure™ IDA
657026
350–750 µm

Typical Experimental Capacity	Effective in Acid/Base
0.16 mmol/g (based on $Cu(acac)_2$ in CH_2Cl_2)	Y[a]/Y

Metals Removed

Fe, Al, Ga, In, Cu, V, Pb, Ni, Zn, Cd, Be, Mn, Ca, Mg, Sr, and Ba

[a] pH < 2 gives poor scavenging.



QuadraPure™ AMPA
657611
350–750 µm

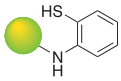
Typical Experimental Capacity	Effective in Acid/Base
0.17 mmol/g (based on $Ni(acac)_2$ in CH_2Cl_2)	Y[a]/Y

Metals Removed

Fe, Cu, Ni, Pb, V, Al, Sn, Zn, Cd, Co, Pd, Ca, Mg, Sr, and Ba

[a] pH < 2 gives poor scavenging.

Microporous Resins

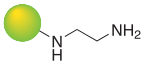


QuadraPure™ MPA
657662
100–400 µm

Functional Group Loading	Effective in Acid/Base
1.5 mmol/g	Y/Y

Metals Removed

Pd, Ru, Rh, Hg, Au, Ag, Cu, Pb, Ir, Pt, Cd, Co, and Sn

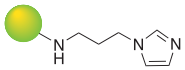


QuadraPure™ AEA
657646
100–400 µm

Functional Group Loading	Effective in Acid/Base
1.3 mmol/g	N/Y

Metals Removed

Pd, Sn, Ru, Pt, Ni, Cu, Zn, and Co



QuadraPure™ IMDAZ
657654
100–400 µm

Functional Group Loading	Effective in Acid/Base
1.5 mmol/g	N/Y

Metals Removed

Ni, Pd, Os, Rh, Co, V, Fe, Cu, and Sn

To inquire about larger quantities for any of the products listed above, call 800-244-1173 (USA) or visit us at **sigma-aldrich.com/quadrapure**. For technical support, please contact Reaxa at **info@reaxa.com**.

Reaxa
www.reaxa.com

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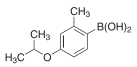
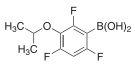
More New Products from Aldrich R&D

Boronic Acids and Esters

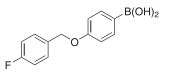
4-Isopropoxy-2-methylphenylboronic acid
657328 1 g, 5 g
$C_{10}H_{15}BO_3$



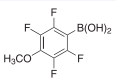
3-Isopropoxy-2,4,6-trifluorophenylboronic acid
657360 1 g, 5 g
$C_9H_{10}BF_3O_3$



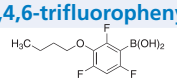
4-(4′-Fluorobenzyloxy)phenylboronic acid
658073 2 g, 10 g
$C_{13}H_{12}BFO_3$



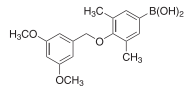
4-Methoxy-2,3,5,6-tetrafluorophenylboronic acid
657301 2 g, 10 g
$C_7H_5BF_4O_3$



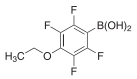
3-Butoxy-2,4,6-trifluorophenylboronic acid
657352 1 g, 5 g
$C_{10}H_{12}BF_3O_3$



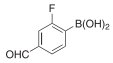
4-(3′,5′-Dimethoxybenzyloxy)-3,5-dimethylphenylboronic acid
652121 1 g, 5 g
$C_{17}H_{21}BO_5$



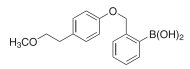
4-Ethoxy-2,3,5,6-tetrafluorophenylboronic acid
657298 2 g, 10 g
$C_8H_7BF_4O_3$



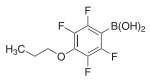
2-Fluoro-4-formylphenylboronic acid
657344 2 g, 10 g
$C_7H_6BFO_3$



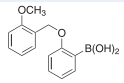
2-[(4′-(2-Methoxyethyl)phenoxy)methyl]-phenylboronic acid
658065 2 g, 10 g
$C_{16}H_{19}BO_4$



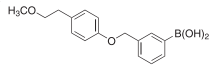
4-Propoxy-2,3,5,6-tetrafluorophenylboronic acid
657271 2 g, 10 g
$C_9H_9BF_4O_3$



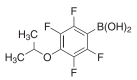
2-(2′-Methoxybenzyloxy)phenylboronic acid
657409 2 g, 10 g
$C_{14}H_{15}BO_4$



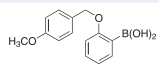
3-[(4′-(2-Methoxyethyl)phenoxy)methyl]-phenylboronic acid
657506 2 g, 10 g
$C_{16}H_{19}BO_4$



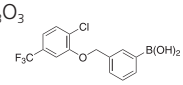
4-Isopropoxy-2,3,5,6-tetrafluorophenylboronic acid
657263 2 g, 10 g
$C_9H_9BF_4O_3$



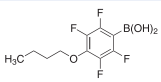
2-(4′-Methoxybenzyloxy)phenylboronic acid
657417 2 g, 10 g
$C_{14}H_{15}BO_4$



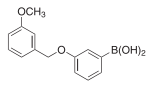
3-[(2′-Chloro-5′-(trifluoromethyl)phenoxy)-methyl]phenylboronic acid
657530 1 g, 5 g
$C_{14}H_{11}BClF_3O_3$



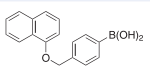
4-Butoxy-2,3,5,6-tetrafluorophenylboronic acid
657255 2 g, 10 g
$C_{10}H_{11}BF_4O_3$



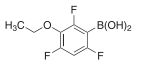
3-(3′-Methoxybenzyloxy)phenylboronic acid
657395 2 g, 10 g
$C_{14}H_{15}BO_4$



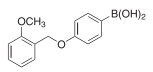
4-[(1-Naphthyloxy)methyl]phenylboronic acid
657522 2 g, 10 g
$C_{17}H_{15}BO_3$



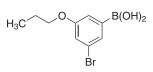
3-Ethoxy-2,4,6-trifluorophenylboronic acid
657247 1 g, 5 g
$C_8H_8BF_3O_3$



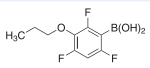
4-(2′-Methoxybenzyloxy)phenylboronic acid
657387 2 g, 10 g
$C_{14}H_{15}BO_4$



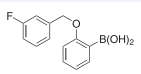
3-Bromo-5-propoxyphenylboronic acid
657514 1 g, 5 g
$C_9H_{12}BBrO_3$



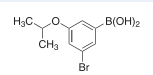
3-Propoxy-2,4,6-trifluorophenylboronic acid
657379 1 g, 5 g
$C_9H_{10}BF_3O_3$



2-(3′-Fluorobenzyloxy)phenylboronic acid
657492 2 g, 10 g
$C_{13}H_{12}BFO_3$

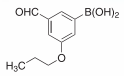


3-Bromo-5-isopropoxyphenylboronic acid
657735 1 g, 5 g
$C_9H_{12}BBrO_3$



3-Formyl-5-propoxyphenylboronic acid

657638 1 g 5 g
$C_{10}H_{13}BO_4$

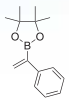


1-Phenylvinylboronic acid

571350 1 g 5 g
[*14900-39-1*]
$C_8H_9BO_2$

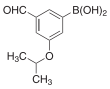
1-Phenylvinylboronic acid pinacol ester, 96%

659193 1 g
$C_{14}H_{19}BO_2$



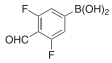
3-Formyl-5-isopropoxyphenylboronic acid

657557 1 g 5 g
$C_{10}H_{13}BO_4$



3,5-Difluoro-4-formylphenylboronic acid

635782 1 g 5 g
$C_7H_5BF_2O_3$



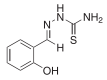
Organic Building Blocks

2-Bromo-3,3,3-trifluoro-1-propene, 97%

561002 1 g 5 g
[*1514-82-5*]
$C_3H_2BrF_3$

Salicylaldehyde thiosemicarbazone, 95%

658774 1 g 10 g
[*5351-90-6*]
$C_8H_9N_3OS$



2,4-Dihydroxy-6-methylbenzaldehyde, 97%

657603 1 g 5 g
[*487-69-4*]
$C_8H_8O_3$

2-Fluorophenethyl bromide, 97%

655023 1 g 5 g
[*91319-54-9*]
C_8H_8BrF

1,3-Diisopropoxybenzene, 97%

658766 5 g 25 g
[*79128-08-8*]
$C_{12}H_{18}O_2$

1-Indanone-6-carboxylic acid, 97%

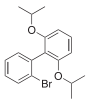
657549 5 g
[*60031-08-5*]
$C_{10}H_8O_3$

3-Chlorophenethyl bromide, 97%

655058 5 g 10 g
[*16799-05-6*]
C_8H_8BrCl

2-Bromo-2′,6′-diisopropoxy-1,1′-biphenyl, 95%

660221 5 g 25 g
$C_{18}H_{21}BrO_2$

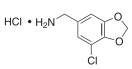


3,3′-Bithiophene-5-carboxaldehyde, 97%

657824 1 g 5 g
$C_9H_6OS_2$

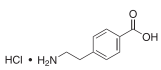
5-Aminomethyl-7-chloro-1,3-benzodioxole hydrochloride, 95%

658227 1 g 5 g
[*350480-53-4*]
$C_8H_8ClNO_2 \bullet HCl$



4-(2-Aminoethyl)benzoic acid hydrochloride, 97%

656380 1 g 5 g 25 g
[*60531-36-4*]
$C_9H_{12}ClNO_2$



9-Fluorenecarboxaldehyde diethyl acetal, 97%

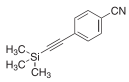
660566 1 g 5 g
$C_{18}H_{20}O_2$

4-Methylresorcinol, 97%

657581 1 g 5 g
[*496-73-1*]
$C_7H_8O_2$

4-(Trimethylsilylethynyl)benzonitrile

658391 1 g 10 g
[*75867-40-2*]
$C_{12}H_{13}NSi$



1-(Cyclopropylmethyl)piperazine, 97%

658839 1 g
[*57184-25-5*]
$C_8H_{16}N_2$

6-Chloro-1-indanone, 96%

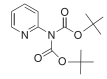
656828 1 g 5 g
[*14548-38-0*]
C_9H_7ClO

2-Amino-5-bromobenzonitrile, 96%

642827 1 g 5 g
[*39263-32-6*]
$C_7H_5BrN_2$

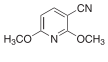
2-(*N*,*N*-BisBoc-amino)pyridine, 97%

659096 1 g 10 g
$C_{15}H_{22}N_2O_4$



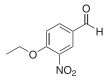
2,6-Dimethoxypyridine-3-carbonitrile, 97%

659266 1 g 5 g
[*121643-45-6*]
$C_8H_8N_2O_2$



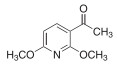
4-Ethoxy-3-nitrobenzaldehyde, 97%

650757 1 g 5 g
[*132390-61-5*]
$C_9H_9NO_4$



3-Acetyl-2,6-dimethoxypyridine, 97%

658316 5 g
$C_9H_{11}NO_3$



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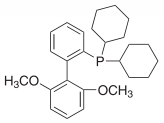
Buchwald's Phosphines for Forming C–C, C–N, and C–O Bonds

The Suzuki–Miyaura coupling is among the most powerful methodologies available to form C–C bonds, as it enjoys a broad scope and a wide functional group tolerance. Recently, notable advances have been made in the laboratories of Professor Stephen Buchwald at M.I.T. Sigma-Aldrich is proud to offer a series of Buchwald's phosphines that have been successfully utilized in the Suzuki–Miyaura coupling; in amination, amidation, and enolate arylation reactions; in the Sonogashira coupling; and in C–O-bond formation.

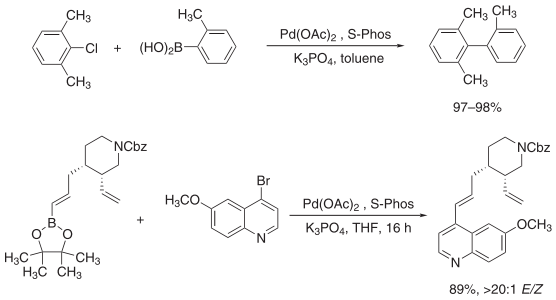
2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (S-Phos), 97%

638072
$C_{26}H_{35}O_2P$



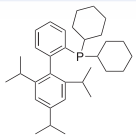
1 g
5 g
25 g

Recent work has shown that application of S-Phos leads to a Pd-catalyst system with unprecedented scope, reactivity, and stability for Suzuki–Miyaura coupling processes—successful with respect to aryl chloride substrates, the generation of truly hindered biaryls, and heteroaryl cross-couplings.[1] Furthermore, S-Phos was utilized in the synthesis of a key intermediate in catalytic, asymmetric total syntheses of quinine and quinidine.[2]



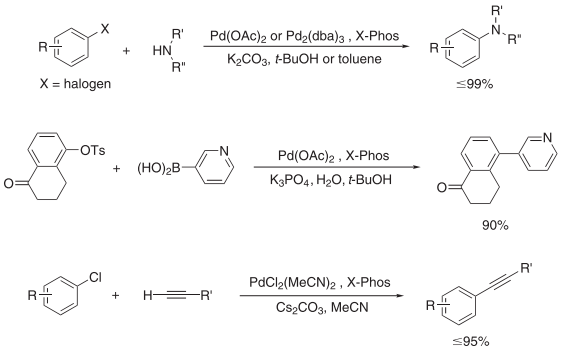
2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (X-Phos), 97%

638064
$C_{33}H_{49}P$



1 g
5 g
25 g

X-Phos has recently emerged with key applications in Pd-catalyzed C–N-bond formation.[3] It has also been successfully utilized in the Suzuki–Miyaura coupling of arene and vinyl sulfonates,[4] as well as in the Sonogashira coupling of alkynes.[5]

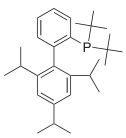


References: (1) Walker, S. D. et al. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871. (2) Raheem, I. T. et al. *J. Am. Chem. Soc.* **2004**, *126*, 706. (3) Huang, X. et al. *J. Am. Chem. Soc.* **2003**, *125*, 6653. (4) Nguyen, H. N. et al. *J. Am. Chem. Soc.* **2003**, *125*, 11818. (5) Gelman, D.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 5993.

Other Buchwald Phosphines

2-Di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl (*tert*-Butyl X-Phos), 97%

638080
$C_{29}H_{45}P$

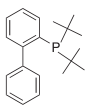


1 g
5 g
25 g

tert-Butyl X-Phos is an excellent ligand for the Pd-catalyzed coupling of phenols with aryl chlorides and bromides,[6] as well as the formation of C–O bonds and *O*-glycosylation using glycals.[7]

2-Di-*tert*-butylphosphinobiphenyl (JohnPhos), 97%

638439
$C_{20}H_{27}P$

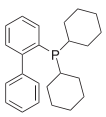


1 g
5 g
25 g

JohnPhos has been used in the amination of aryl halides and triflates,[8] as well as the intramolecular formation of C–O bonds.[9]

2-Dicyclohexylphosphinobiphenyl (Cyclohexyl JohnPhos), 97%

638099
$C_{24}H_{31}P$

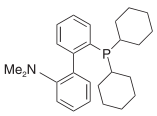


1 g
5 g
25 g

Cyclohexyl JohnPhos has been effective in C–N-bond-forming reactions, including the amination of aryl halides and triflates[8] and the amination of aryl halides containing hydroxy, amido, or enolizable keto groups.[10]

2-Dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl (DavePhos), 97%

638021
$C_{26}H_{36}NP$



1 g
5 g
25 g

DavePhos has proven useful in the amination of aryl halides containing hydroxy, amido, or enolizable keto groups.[10]

References: (6) Burgos, C.; Buchwald, S. L. Private communication, 2005. (7) Kim, H. et al. *J. Am. Chem. Soc.* **2004**, *126*, 1336. (8) (a) Ali, M. H.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2560. (b) Wolfe, J. P. et al. *J. Org. Chem.* **2000**, *65*, 1158. (9) (a) Kuwabe, S. et al. *J. Am. Chem. Soc.* **2001**, *123*, 12202. (b) For the intermolecular synthesis of aryl ethers: Torraca, K. E. et al. *J. Am. Chem. Soc.* **2001**, *123*, 10770. (10) Harris, M. C. et al. *Org. Lett.* **2002**, *4*, 2885.

Synthetic Applications of Buchwald's Phosphines in Palladium-Catalyzed Aromatic-Bond-Forming Reactions†


Dr. Christelle C. Mauger


Dr. Gérard A. Mignani

Christelle C. Mauger and Gérard A. Mignani*
Rhodia Recherches et Technologies
Centre de Recherches et de Technologies de Lyon
85 Rue des Frères Perret, BP 62
69192 Saint-Fons Cedex, France
Email: christelle.mauger@eu.rhodia.com

Outline

1. Introduction

Aromatic amines are important substructures in natural products as well as in industrially produced bulk and fine chemicals. As a consequence, interest in aromatic-bond-forming reactions (ABF), specifically in palladium-catalyzed carbon–nitrogen coupling reactions, has grown steadily during the last few years.[1] Since 1998, major advances in this area have been described by a number of research groups.[1c–e] However, the lack of a general, palladium-based catalyst for substitution reactions on aryl chlorides, as well as the elevated temperatures often required, have prompted research groups to search for new and more active catalysts. Catalysts based on bulky, electron-rich biarylphosphines (**1**–**10**)—discovered by Buchwald's group—are particularly mild and versatile in this regard (**Figure 1**).[2,3] The accessibility of these catalysts by practical synthesis has led to their widespread use in palladium-catalyzed carbon–carbon- and carbon–heteroatom-bond-forming reactions.

2. Buchwald's Phosphines

2.1. Preparation

The laboratory-scale synthesis of MePhos (**2**) and related phosphines, as reported by Buchwald and co-workers,[4] begins by forming the Grignard reagent from 2-bromotoluene or other aryl bromides. The resulting magnesium reagent is then added to the aryne generated from *o*-bromochlorobenzene and magnesium. The resulting biarylmagnesium bromide is reacted with dicyclohexylphosphine chloride under copper(I) chloride catalysis to form the required carbon–phosphorus bond of the Buchwald phosphine product (**Scheme 1**). The synthesis of biarylphosphines **2** and **4** has been successfully scaled up (250-liter reactor) and satisfactory isolated yields obtained: 55% for **2** and 56% for **4**.[3]

The corresponding 2',6'-diisopropoxybiphenyl ligand, **6**, has been synthesized by utilizing a modified one-pot protocol.[5] In the first step, 1,3-diisopropoxybenzene undergoes ortho lithiation at 80 °C in hexanes in the presence of *n*-butyllithium. *o*-Bromochlorobenzene is added dropwise over 50 min to generate the intermediate, 2-bromo-2',6'-diisopropoxybiphenyl, via a tandem benzyne condensation–bromine atom transfer sequence. Phosphine **6** is afforded after cooling the mixture to –78 °C, halogen–lithium exchange with *n*-butyllithium, and treatment with dicyclohexylphosphine chloride (**Scheme 2**). This method offers several advantages over the approach described in Scheme 1: it is faster and cleaner, avoids the use of copper salts and thus the treatments needed to remove them, and eliminates the need to prepare the aryl chloride starting materials.

2.2. Characteristics and Reactivity

The steric and electronic environments of dialkyl(biphenyl-2-yl)phosphines can generally be easily varied, since it is possible to

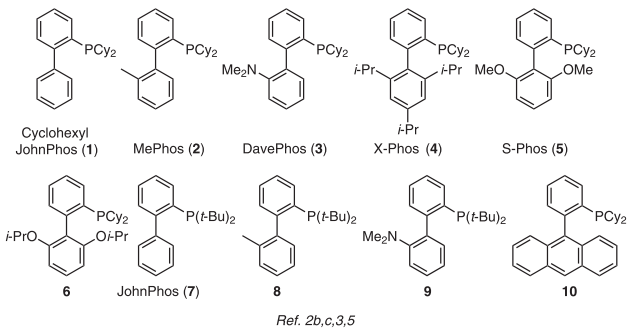
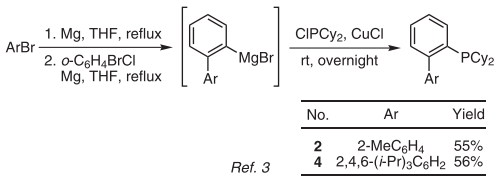
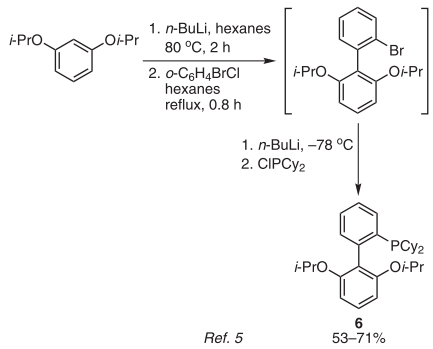


Figure 1. Bulky, Electron-Rich Dialkyl(biaryl)phosphine Ligands.



Scheme 1. Kilogram-Scale Synthesis of MePhos (**2**) and X-Phos (**4**).



Scheme 2. The One-Pot Modified Protocol for the Synthesis of Phosphine **6**.

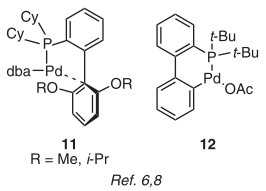
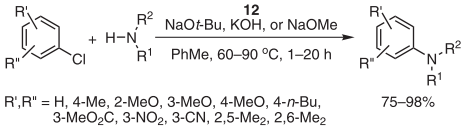


Figure 2. Palladium–Dialkyl(biaryl)phosphine Complexes.



eq 1

introduce different substituents on the benzene rings and to replace the benzene ring by a heteroaromatic ring.[6] Thus, a number of substituted dialkyl(biaryl)phosphines have been prepared and successfully utilized in Pd-catalyzed coupling reactions.[7] The observed high reactivity of ligands **1**, **2**, **3**, **7**, **8**, and **9** is a function of their steric bulk and high electron densities. It has been postulated that the π systems of the biaryl group interact with the Pd center, thereby strongly impacting the catalytic activity. This interaction may lead to cyclopalladation, which decreases the lifetime of the catalyst. Ligands **4**, **5**, and **6** are prevented from achieving this cyclometallation by the presence of two substituents at the 2' and 6' positions of the biaryl group. Moreover, substituents such as methoxy or isopropoxy can increase both the steric bulk and the electronic density of the biphenyl moiety, thus stabilizing the corresponding palladium complex, **11**, by the interaction of the lone pair of electrons on oxygen with the metal center (**Figure 2**).[8]

Zim and Buchwald have found that simply stirring **7** with $Pd(OAc)_2$ in toluene at room temperature led to the formation of palladacycle **12** in 94% yield. Palladium complex **12** possesses several desirable properties, such as being air-, moisture-, and heat-stable, and has proven to be a versatile precatalyst for the high-yield (75–98%) amination of various substituted chlorobenzenes (**eq 1**).[8]

Faller and Sarantopoulos have prepared and characterized a new allylpalladium–(Buchwald) phosphine complex (**13**) resulting from the reaction of DavePhos (**3**) with [(η^3-allyl)PdCl].[9] They demonstrated that, when a Pd–N bond is present, the phosphine ligand is hemilabile and a low barrier (<10 kcal/mol) exists for rupture of the Pd–N bond. They also showed that the preference for P,N vs P,C bonding is controlled by subtle electronic and steric effects (**Figure 3**): P–Pd–N bonding is preferred in the case of $ArPPh_2$ (**14**), whereas P–Pd–C bonding is preferred in the $ArPCy_2$ analogue (**13**). Such complexes might form as intermediate species in the catalytic cycles of aromatic-bond-forming reactions

3. Carbon–Nitrogen-Coupling Reactions

3.1. Synthesis of Anilines

3.1.1. Ammonia Synthetic Equivalents

The Pd-catalyzed, aromatic C–N-bond formation has become a convenient and general method for synthesizing arylamines from aryl halides. Nevertheless, while ammonia is the simplest amine, its use in such coupling reactions has only been reported in a copper-catalyzed reaction.[10] In the presence of a palladium catalyst, the reaction can be accomplished in two steps using ammonia equivalents, such as benzophenone imine, as first reported by Buchwald.[11] 2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene (BINAP) was the ligand of choice in this case. A few years later, Hartwig and co-workers described a simple palladium-catalyzed conversion of aryl halides into the corresponding anilines using lithium bis(trimethylsilyl)amide as an ammonia equivalent.[12] The reaction is catalyzed by $Pd(dba)_2$ in the presence of a phosphine ligand, and can be run with as little as 0.2 mol % of catalyst. While tri-*tert*-butylphosphine, $P(t\text{-}Bu)_3$, displayed the best catalytic activity in this reaction at room temperature, some biphenylylphosphine ligands developed by Buchwald and co-workers[13] were suitable at high temperatures (**eq 2**).[12]

Huang and Buchwald have also reported the use of several silylated amine derivatives as ammonia equivalents in the Pd-catalyzed amination reaction with commercially available **1** as the ligand.[14] While LiHMDS is effective in the amination of meta- and para-substituted aryl bromides and chlorides (>94% yields), the use of aminotriphenylsilane (Ph_3SiNH_2) permits the efficient reaction of ortho-substituted substrates (85–98% yields). In addition to

these results, the two authors showed that di- and triarylamines can be prepared in good-to-excellent yields (64–95%) from various substituted aryl halides using $LiNH_2$ as the nucleophile, NaO*t*-Bu as the base, and **7** as the ligand.

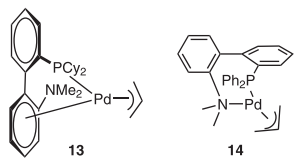
3.1.2. Reaction of Primary and Secondary Amines with Aryl Halides

In 1998, Buchwald demonstrated that **3** was generally superior to BINAP as a ligand in palladium-catalyzed amination reactions.[15] This highly active catalyst effected the reaction of primary alkyl amines with aryl bromides at room temperature and with aryl chlorides at 80 °C or 100 °C using NaO*t*-Bu as the base. Catalyst levels as low as 0.05 mol % Pd have been achieved in the reaction of chlorotoluene with di-*n*-butylamine. A weak base, such as K_3PO_4, could even replace sodium *tert*-butoxide, allowing the reaction conditions to be compatible with sensitive functional groups such as esters. A two-step procedure was then developed for the synthesis of unsymmetrical alkyldiarylamines from primary amines and two different aryl bromides.[16] The combination of $Pd(OAc)_2$ and (*rac*)-BINAP was found to be an excellent catalyst system for the coupling of primary amines with aryl bromides. Utilizing a second catalyst system, the palladium-catalyzed arylation of the resulting secondary amine afforded the expected alkyldiarylamine. The efficiency of each catalyst in the second step was shown to depend on the electronic nature of both coupling partners. 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (XantPhos) was effective in the coupling of electron-deficient (e.g., F_3C-, NC-, or Cl-substituted) and electron-neutral (e.g., Ph-substituted) *N*-alkylanilines with electron-deficient aryl bromides, while DavePhos (**3**) was more active with electron-rich *N*-alkylanilines (e.g., Me- or MeO-substituted) and totally independent of the electronic properties of aryl bromides (**Figure 4**).[16] This method is reasonably general and is compatible with base-sensitive functional groups.

Using **7** or MePhos (**2**) as ligand, a variety of unsymmetrical triarylamines have been prepared using a one-pot procedure by sequentially coupling an aniline with an aryl bromide and an aryl chloride (**Scheme 3**).[17] This method capitalizes on the selective and faster reaction of the aniline with the aryl bromide, and is versatile and compatible with electron-rich systems, ortho-substituted aryl halides, and multiple couplings. A modification of this method—employing a higher quantity of catalyst and carried out as a two-step, one-pot procedure—has been applied to the synthesis of triarylamines containing a heterocyclic moiety such as furan, thiophene, and pyridine.[17]

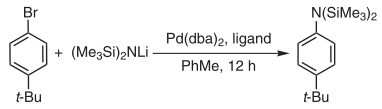
Following further developmental work on the palladium-catalyzed coupling between amines and aryl halides,[18,19] Buchwald described a general method for the direct coupling of amines with aryl halides that bear hydroxyl, amido, hydroxyalkyl, or oxoalkyl groups (**eq 3**).[20] This method is particularly interesting, because it allows the use of substrates bearing sensitive functional groups without employing protecting group strategies. Thus, in a typical procedure, using $LiN(TMS)_2$ as the base in the presence of $Pd_2(dba)_3$ and a bulky electron-rich ligand such as **1** or **3**, substituted aryl halides have been coupled with cyclic amines or anilines in moderate-to-excellent yields (56–95%).

The corresponding palladium-catalyzed amination of heteroaryl chlorides was first reported in 1996,[13,21] and has since been widely studied (**eq 4**).[22] For example, different chloropyridines, 2-chloroquinoline, and 2-chloropyrazine reacted with *N*-(arylethyl)piperazines, in the presence of **3** as the phosphine ligand, to afford the corresponding aminated products in moderate-to-good yields (50–75%). A higher selectivity for the 2 position was



Ref. 9

Figure 3. Subtle Steric and Electronic Effects Influencing the Binding of Palladium to Nitrogen vs Carbon.



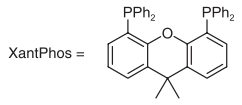
Ligand	T, °C	Yield[a]
P(*t*-Bu)$_3$	rt	95%
1	rt	82%
ArPCy$_2$[b]	90	92%

[a] GC yield. [b] Ar = 2',4',6'-trimethylbiphenyl-2-yl

Ref. 12

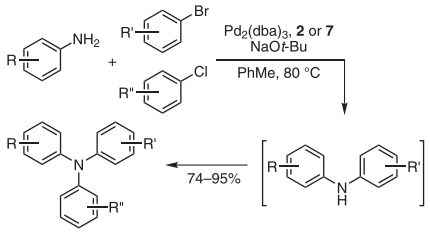
eq 2

	ArNHR	
Ar'Br	Electron-Poor	Electron-Rich
Electron-Poor	XantPhos	**3**
Electron-Rich	N/A	**3**



Ref. 16

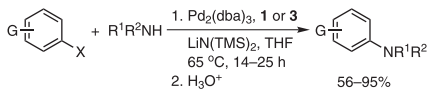
Figure 4. The Choice of Phosphine Ligand in the Pd-Catalyzed Cross-Coupling of *N*-Alkylanilines with Aryl Bromides.



R = 3-Me, 4-Me, 4-MeO, 3-NH$_2$, 2,4-Me$_2$
R' = 4-*t*-Bu, 3-MeO, 4-MeO, 4-NMe$_2$, 2,5-Me$_2$, 3,5-Me$_2$
R" = 3-Me, 4-Me, 4-*n*-Bu, 2-MeO, 3-MeO, 4-MeO, 2,5-Me$_2$

Ref. 17

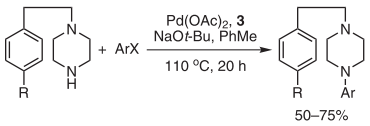
Scheme 3. One-Pot Synthesis of Simple Triarylamines.



X = Cl, Br
G = 2-Me, 4-*t*-Bu, 3-OH, 4-OH, 3-Ac, 3-HNAc, 4-HNAc, 3-(CH$_2$CH$_2$OH), 4-(CH$_2$CH$_2$OH), 4-(OCH$_2$CH$_2$OH) 4-(CH$_2$CH$_2$C(O)Me)
R^{1}R^{2}NH = Bu$_2$NH, PhNHMe, 4-MeC$_6$H$_4$NH$_2$, 4-MeOC$_6$H$_4$NH$_2$, 3,4-(MeO)$_2$C$_6$H$_3$NH$_2$, morpholine, 1-methylpiperazine, 4-hydroxypiperidine

Ref. 20

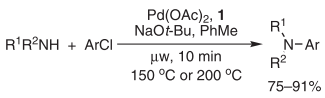
eq 3



R = H, F; X = Cl, Br
Ar = Ph, 4-$CF_3C_6H_4$, pyridin-2-yl, 5-chloropyridin-2-yl, 5-trifluoromethylpyridin-2-yl, quinolin-2-yl, isoquinolin-1-yl, pyrazin-2-yl

Ref. 22

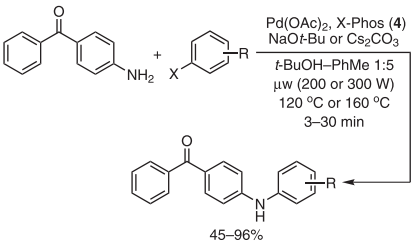
eq 4



Ar = 4-MeC_6H_4, 2-$MeOC_6H_4$, pyridin-2-yl, pyridin-3-yl, quinolin-2-yl, pyrazin-2-yl
R^1R^2NH = PhNHMe, 4-TolNHMe, morpholine

Ref. 23

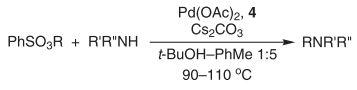
eq 5



X = Cl, Br, I, OTf
R = 2-Me, 4-Me, 2-MeO, 4-CN, 3-CF_3, 3-NO_2, 4-NMe_2, 4-F, 4-Cl, 2,4-F_2, 3-(1,3-dioxolan-2-yl)
3-Chloro- and 3-bromopyridines were also used.

Ref. 25

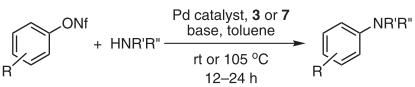
eq 6



R	R'		R"	Yield
4-*t*-BuC_6H_4	H		H	94%
4-*t*-BuC_6H_4	H		Ph	96%
4-*t*-BuC_6H_4	Ph		Ph	92%
4-*t*-BuC_6H_4	*n*-Bu		*n*-Bu	88%
4-*t*-BuC_6H_4		–$(CH_2)_4$–		98%
4-*t*-BuC_6H_4		indol-1-yl		>99%
2-MeC_6H_4	H		Ph_2C=N	90%
2-$MeOC_6H_4$	H		Bn	88%
2-$MeOC_6H_4$	H		*n*-Hex	88%
2-$MeOC_6H_4$	H		Ph_2C=N	97%
4-$MeOC_6H_4$		–$(CH_2)_4$–		85%
3-$MeO_2CC_6H_4$		(–CH_2CH_2)$_2$O		>99%
3-$MeO_2CC_6H_4$	H		Ph_2C=N	86%
4-NCC_6H_4	H		Ph_2C=N	94%
cyclohex-1-en-1-yl		indol-1-yl		>99%

Ref. 26

eq 7



Pd Catalyst = $Pd_2(dba)_3$ or $Pd(OAc)_2$
Base = NaO*t*-Bu or K_3PO_4
R'R"NH = 1° or 2° amine

R = 2-Me, 4-*t*-Bu, 2,6-$Me_2C_6H_3$, 4-MeO, 2-MeO_2C, 4-MeO_2C, 2-NO_2, 4-CN, 4-Ac, 2-Cl, 4-Cl, 2-Br, 4-Br

Nf = nonafluoro-*n*-butanesulfonate (nonaflate) = $CF_3(CF_2)_3SO_2$

Ref. 28

eq 8

observed in the amination of 2,5-dichloropyridine, with only 8% of the C2–Cl regioisomer being formed.

The microwave-assisted, high-speed Buchwald–Hartwig amination of unactivated (azahetero)aryl chlorides with anilines has been reported by Maes and co-workers.[23] These aminations, carried out under temperature-controlled microwave heating at 150 °C or 200 °C and employing **1** as ligand, reached completion in 10 minutes (**eq 5**). The reaction has been extended to primary and secondary aliphatic amines,[24] and has successfully been carried out in the presence of phosphine ligands **1**, **3**, or **7**. Similarly, p38 MAP kinase inhibiting, aniline-substituted benzophenones were synthesized by a palladium-catalyzed amination of aryl halides and triflates under microwave irradiation and in the presence of **4** and palladium acetate. The aniline-substituted benzophenones were isolated in moderate-to-excellent yields (45–96%) after short reaction times (3 to 30 min) (**eq 6**).[25]

3.1.3. Reaction of Amines with Aryl Sulfonates

The first room-temperature catalytic aminations of aryl triflates were reported using catalysts derived from **7** and NaO*t*-Bu as the base.[13] While this protocol was effective for the amination of electron-rich or electron-neutral aryl triflates, the use of electron-deficient aryl triflates resulted in the base-promoted cleavage of the triflate. High yields (76–92%) were obtained, however, for both electron-rich and electron-deficient aryl triflates by using K_3PO_4 as the base at 80 °C in the presence of a catalyst system comprised of Pd and **7**. Arylation of anilines (1.5–16 h) were generally faster than those of aliphatic amines (17–26 h). Later on, a general catalytic system was developed for the amination of aryl sulfonates.[26] Of all the biphenylylphosphines tested, X-Phos (**4**) displayed the highest catalytic activity. While tosylates were often good substrates, benzenesulfonates typically provided higher yields or shorter reaction times. This set of conditions can be used to arylate primary and secondary (both cyclic and acyclic) aliphatic amines, anilines, diarylamines, indoles, benzophenone imine, and benzophenone hydrazone (**eq 7**).[26] Aryl nonaflates, which can be prepared from the corresponding phenols, are an attractive alternative to triflates due to their increased stability under the coupling reaction conditions.[27] Both electron-rich and electron-neutral aryl nonaflates have been easily coupled with both primary and secondary amines in high yields at room temperature using ligands **3** or **7** and NaO*t*-Bu as the base (**eq 8**).[28] Using aryl substrates bearing both nonaflate and halide groups, selective substitution of the nonaflate was achieved in moderate-to-good yields (59–88%) using **3**, **7**, or BINAP.

Very recently, phosphines **1**, **3**, and **4** have been employed as ligands in the palladium-catalyzed amination of nucleoside aryl sulfonates to yield analogues of N^6-aryl-2,6-diaminopurine nucleosides in moderate-to-excellent yields.[29] The authors also demonstrated the importance of the nature of the ligand and the aryl sulfonate substituents to the outcome of the reaction.

3.2. Synthesis of N-Arylamides

A novel, efficient, and intramolecular Pd-catalyzed amination reaction has been utilized for the synthesis of the pharmaceutical key intermediate *N*-(1-benzylpiperidin-4-yl)-1,3-dihydroindol-2-one (**eq 9**).[30] X-Phos (**4**) was found to be superior to XantPhos and P(*o*-Tol)$_3$ in this reaction, resulting in a high reaction rate and an excellent yield (90%).

Ghosh et al. have reported the first efficient cross-coupling of aryl chlorides with oxazolidinones using cesium carbonate as the base (**eq 10**).[31] The use of a weak base allows the cheaper aryl chlorides—containing sensitive functionalities such as enolizable

ketones or amides, which are incompatible with other coupling methods—to be utilized. This coupling reaction provides access to the important *N*-aryl-β-amino alcohols building blocks, by hydrolysis of the oxazolidinone ring in the product with ethanolic NaOH. The authors have also observed a higher catalytic activity for dialkylphosphanylbiphenyl ligands **1**, **3**, and **7**, as compared to the classical BINAP, DPPF, P(*t*-Bu)$_3$, and XantPhos.

3.3. Synthesis of Heterocycles

Less reactive nitrogen nucleophiles, such as indoles, have been successfully coupled with a variety of aryl halides and triflates, in the presence of bulky electron-rich phosphines **1**, **3**, **7**, and other $ArPR_2$ ligands, to afford the desired *N*-arylindoles in moderate-to-high yields (43–95%) (**eq 11**).[32] Edmondson and co-workers have reported the first application of the Buchwald–Hartwig coupling to the synthesis of *N*-aryl enaminones in generally high yields in the presence of **3** and $Pd_2(dba)_3$ (**Scheme 4**).[33] The reaction is widely applicable to a variety of electron-rich, electron-poor, and electron-neutral aromatic halides. Moreover, the first tandem Buchwald–Hartwig–Heck cyclization has been achieved by the same group and applied to the synthesis of 2,3-disubstituted indole derivatives.

3.4. Synthesis of N-Arylhydrazones

A general, efficient, and safely scalable synthesis of *N*-arylhydrazones from the corresponding unsubstituted hydrazones and aryl chlorides or bromides has been developed (**eq 12**).[4,34] This palladium-catalyzed cross-coupling was successfully achieved with a low catalyst loading (<0.1 mol %) in good-to-excellent yields (85–97%). *N*-Arylhydrazones are particularly interesting, because they can be easily converted into pharmaceutical intermediates such as arylhydrazines and azaheterocycles.

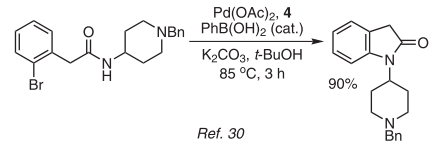
Recently, Haddad and co-workers have reported a versatile synthesis of 1-heteroarylpyrazoles from deactivated heteroaryl halides by a transhydrazonation–cyclization tandem process.[35] In the reaction of 5-bromo-2-methoxypyridine with benzophenone hydrazone, the use of **3** or **7** gave rise to the *N*-arylhydrazone in excellent yields (95% in both cases), while the use of DPPF or BINAP resulted in low yields (<10%). The reaction was successfully applied to the coupling of benzophenone hydrazone with 2-bromopyrimidine and 2-chloropyrazine, giving rise to the corresponding *N*-heteroarylhydrazones in 75% and 85% yields, respectively.

4. Carbon–Carbon-Coupling Reactions

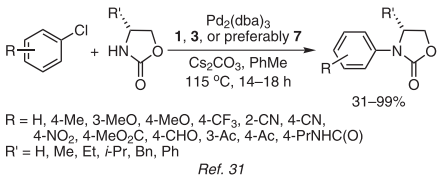
4.1. The Suzuki–Miyaura Coupling

Buchwald and co-workers have examined the use of biphenylylphosphine ligands in the Suzuki coupling of aryl halides with arylboronic acids. They demonstrated that the reaction of aryl bromides and chlorides proceeded in excellent yields (90–94%) at room temperature by using Pd(II)–**3** and CsF in dioxane (**eq 13**).[15] These conditions allowed the coupling of both electron-rich and electron-deficient aryl chlorides, and tolerated the presence of base-sensitive functional groups. This was the first example of a room-temperature Suzuki coupling of an aryl chloride.

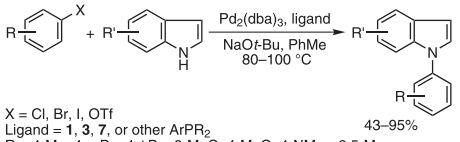
The new ligand 2-dicyclohexylphosphanyl-2',6'-dimethoxybiphenyl, S-Phos (**5**), has been utilized in the Suzuki coupling of 2,6-dimethylchlorobenzene with 2-methylphenylboronic acid.[36] Using only 0.2 mol % of catalyst, 2,2',6-trimethylbiphenyl was obtained in excellent yield (98%) after 0.2 h at 90 °C. The reaction proceeded even at room temperature. While classical dialkylphosphanylbiphenyls



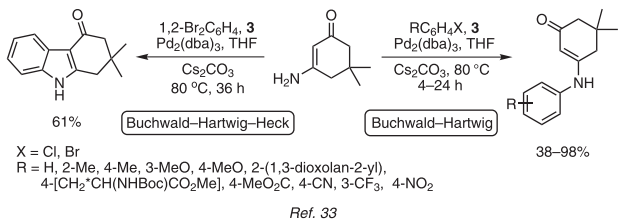
eq 9



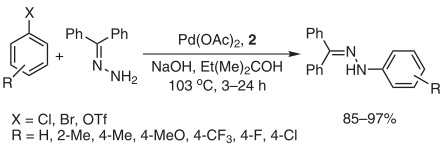
eq 10



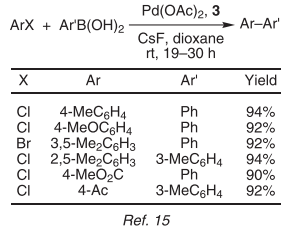
eq 11



Scheme 4. The Buchwald–Hartwig Coupling in the Synthesis of *N*-Aryl Enamines and Heterocycles.



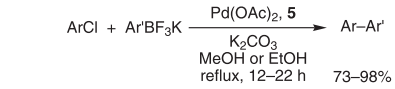
eq 12



X	Ar	Ar'	Yield
Cl	4-MeC$_6$H$_4$	Ph	94%
Cl	4-MeOC$_6$H$_4$	Ph	92%
Br	3,5-Me$_2$C$_6$H$_3$	Ph	92%
Cl	2,5-Me$_2$C$_6$H$_3$	3-MeC$_6$H$_4$	94%
Cl	4-MeO$_2$C	Ph	90%
Cl	4-Ac	3-MeC$_6$H$_4$	92%

Ref. 15

eq 13

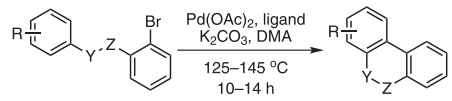


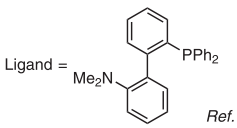
Ar = 4-*n*-BuC_6H_4, 4-$MeOC_6H_4$, 3-$MeO_2CC_6H_4$, 3,5-$(MeO)_2C_6H_3$, 2,6-$Me_2C_6H_3$, 2-Me-3-PhC_6H_3, 4-(pyrrol-1-yl)phenyl, pyridin-3-yl, pyrazin-2-yl, 2-formylthien-5-yl, 3,6-dimethylpyrazin-2-yl, quinolin-2-yl

Ar' = 2-MeC_6H_4, 4-*t*-BuC_6H_4, pyridin-3-yl, naphth-1-yl

Ref. 38

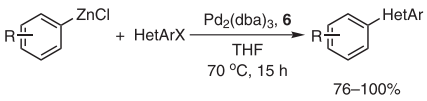
eq 14





Ref. 39

eq 15



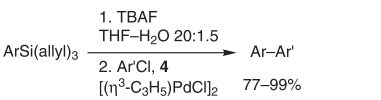
X = Cl, Br

R = 2-Me, 2-MeO, 2,3-Me_2, 2,4-$(MeO)_2$, 2-Me-4-MeO

HetAr = pyrazin-2-yl, pyrimidin-2-yl, pyridin-3-yl, 5-nitropyridin-2-yl, 2-fluoro-4-trifluoromethylpyridin-3-yl, quinolin-3-yl, quinolin-4-yl, 2-benzyldiazol-4-yl, 1-phenyltetrazol-5-yl, quinoxalin-2-yl, 2-methylbenzothiazol-5-yl

Ref. 5

eq 16

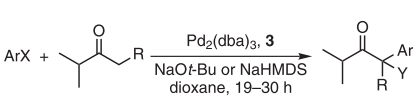


Ar = Ph, 2-MeC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4

Ar' = 2-$CF_3C_6H_4$, 4-$CF_3C_6H_4$, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 2-$MeOC_6H_4$, 4-NCC_6H_4, 2-FC_6H_4 naphth-1-yl, pyridin-3-yl, thien-2-yl

Ref. 42,43

eq 17



Ar	X	R	Y	Temp.	Yield
p-Tol	Cl	H	*p*-Tol	80 °C	79%
m-Xyl	Br	Me	H	rt	82%

Ref. 15

eq 18

1–**4** displayed low catalytic activities towards sterically hindered substrates, two phenanthrene-based ligands, 9-[2-(dicyclohexylphosphanyl)phenyl]phenanthrene and 9-[2-(diphenylphosphanyl)phenyl]phenanthrene, allowed the synthesis of tetra-ortho-substituted biaryls via the Suzuki cross-coupling reaction in moderate-to-excellent yields (58–98%).[7b] Moreover, the use of **5** led to a catalyst system with unprecedented stability, reactivity, and scope in the Suzuki–Miyaura cross-coupling.[36] Phosphine **5** was generally effective for the construction of sterically hindered biaryls, which were synthesized in excellent yields (82–97%).[37] Ligand **5** has also been effective in the Suzuki–Miyaura cross-coupling of potassium aryl- and heteroaryltrifluoroborates with aryl and heteroaryl chlorides, leading to the expected cross-coupling products in good-to-excellent yields (73–98%) (**eq 14**).[38]

Recently, Fagnou and co-workers have developed a biaryl synthesis via a palladium-catalyzed, direct intramolecular arylation. The reaction is performed in DMA with low catalyst loadings (mostly 0.1–0.5 mol %) using potassium carbonate as the base and the diphenylphosphino analogue of **3** as the ligand (**eq 15**).[39] Ortho, meta, and para substituents are tolerated, including electron-donating and electron-withdrawing groups. Chloro substituents remain intact under the reaction conditions.

4.2. The Negishi Coupling

Ligand **6** was employed in the palladium-catalyzed cross-coupling of organozinc reagents with aryl halides (Negishi coupling). The resulting catalytic system allowed the efficient preparation of hindered biaryls (tri- and tetra-ortho-substituted) at low catalyst levels, and tolerated a wide range of functional groups and heteroaryl halides (**eq 16**).[5] A systematic screening of dialkylphosphanylbiphenyl ligands was also carried out, which showed that phosphine **6** displayed the best activity in this type of Negishi coupling.

4.3. The Coupling Reaction of Arylsilanes with Aryl Halides

Denmark has reported a mild and general palladium-catalyzed process for the formation of aryldimethylsilanols from aryl bromides by a one-pot silylation–hydrolysis procedure. The intermediate aryldimethylsilyl ethers were synthesized in high yields.[40] The coupling reaction between arylsilanes and aryl halides has been studied by Denmark[41] and Hiyama.[42,43] Hiyama has reported a general and convenient palladium-catalyzed cross-coupling of triallyl(aryl)silanes with aryl chlorides. Arylsilanes are highly practical and convenient reagents, since they are stable to moisture, base and/or acid, and are readily accessible. Using Pd–**4** as the catalyst system and TBAF as an activator, a wide range of aryl chlorides were successfully transformed into biaryl compounds in 77–99% yields (**eq 17**).[42,43]

4.4. The Arylation of Ketones with Aryl Halides

The α arylation of ketones with aryl halides has been carried out using Pd(0)–**3** as the catalyst system (**eq 18**).[15] Aryl bromides reacted at room temperature, while aryl chlorides required a higher temperature (80 °C). Interestingly, the Pd–BINAP catalyst system was selective in promoting the monoarylation of methyl ketones, while Pd(0)–**3** was selective for the diarylation of methyl ketones. The authors have explained this difference in reactivity by the decreased steric bulk of **3** as compared to BINAP. An improved process[44] was then reported using 20% of a phenol (as an additive) in combination with **3** and potassium phosphate as the base.

The high activity and selectivity of bulky phosphines **1**, **2**, **3**, and **7** toward the formation of α-aryl ketones have been well

demonstrated.[45] Ligand **2** was particularly efficient with a low catalyst loading (0.1–1 mol % Pd). More recently, Liu and co-workers have developed a highly active catalyst system for the heteroarylation of acetone (**eq 19**).[46] Thus, the coupling reaction between the in situ generated tributyltin enolate of acetone and a variety of heteroaromatic bromides, chlorides, or triflates has been realized, in the presence of Pd(0) and the diphenylphosphino analogue of **3**, in moderate-to-good yields (55–90%). However, 3,5-dibromopyridine and 5-bromo-2-methoxypyridine gave inexplicably low yields. Low or no yield of the desired 5-cyano-3-(2-oxopropyl)pyridine was observed in the presence of PPh_3, P(*o*-Tol)$_3$, DPPF, or XantPhos.

5. Carbon–Oxygen-Coupling Reactions

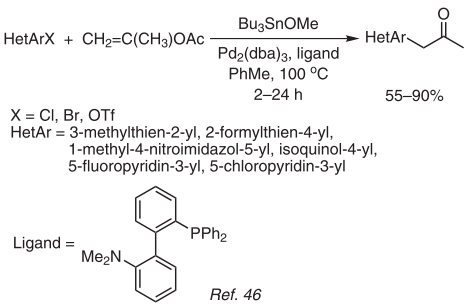
Aryldialkylphosphines have been employed in the palladium-catalyzed formation of diaryl ethers from phenols and aryl halides.[47] A wide range of electron-rich, electron-poor, and electron-neutral aryl bromides, chlorides, and triflates have been coupled with a variety of phenols in the presence of sodium hydride or potassium phosphate as base. The bulkiness and basic nature of aryldialkylphosphine ligands **7** and **9** are thought to be responsible for increasing the rate of reductive elimination of the diaryl ether from palladium. Other studies have shown that **7** is an efficient ligand for the intramolecular palladium-catalyzed synthesis of five- and six-membered oxygen heterocycles from primary or secondary alcohols (**eq 20**).[48] Primary alcohols cyclized more easily than secondary ones, which required higher temperatures and catalyst loadings to go to completion. In addition, cyclization of enantiopure alcohols resulted in cyclization without racemization under the reaction conditions.

Buchwald's phosphines have also been employed in a convenient preparation of aryl enol ethers from alkenyl triflates in 34–98% yields.[49] This was accomplished by treating the readily available alkenyl triflates with electron-rich, electron-poor, or electron-neutral phenols, sodium *tert*-butoxide and a catalyst generated from $Pd_2(dba)_3$ and **7**.

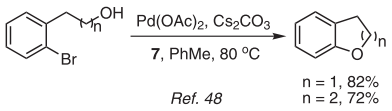
6. Conclusions

Dialkyl(biphenyl-2-yl)phosphines (Buchwald's phosphines) have proven their usefulness in organic synthesis as ligands in palladium-catalyzed coupling reactions. In catalytic applications, these phosphines can vary in their activities as a result of steric and electronic effects associated with their substituents. The reactions they help catalyze are often realized with low catalyst loadings and weak bases, are compatible with sensitive functional groups, and constitute broadly useful methods for the construction of a wide variety of targets, which cannot be synthesized by utilizing other common ligands.

7. References and Notes



eq 19



eq 20

(†) Strictly speaking, the reactions described in this review do not involve the formation of an aromatic bond in the commonly understood sense of the word "aromatic" (in terms of bond length, order, and π character). Rather, these reactions result in the formation of a single bond to an aromatic ring. The phrase, "aromatic bond formation (ABF)" or variations thereof, is currently in such widespread use in this context that it would be a departure from common usage to drop it.

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About the Authors

Christelle C. Mauger was born in 1974 in Saint-Lô, Normandy (France). She completed her undergraduate degree at the University of Caen, France, and obtained her Ph.D. degree in organic chemistry in 2000 under the guidance of Professor Serge Masson (Laboratoire de Chimie Moléculaire et Thio-organique, University of Caen, France). She then undertook an industrial postdoctoral position with Avecia Pharmaceuticals in Huddersfield (England), where she worked on the rapid development of new routes to pharmaceutical intermediates and on the "CATHy™" catalytic transfer-hydrogenation reaction. In 2001, she accepted a postdoctoral position, granted by Rhodia Organic, at the Laboratoire de Catalyse en Chimie Organique of the University of Poitiers, France, where she worked in the field of fluorine chemistry. In 2002, she joined Rhodia Recherches (Lyon Research Centre), where she is now a research engineer in the New Technology Group. Her main area of activity is the development of pharmaceutical intermediates using organometallic catalysis and reactions forming bonds to aromatic rings.

Gérard A. Mignani studied chemistry at the Universities of Orsay and Rennes, where he received his Ph.D degree (Docteur Ingénieur) in 1980. He obtained his "Thèse d'Etat" in 1982 in the field of organometallic chemistry and homogeneous catalysis as part of Professor Dabard's team. In 1980, he joined Rhône-Poulenc Research in Lyon, where he developed new processes in organic and terpene chemistry and in homogeneous and heterogeneous catalysis. He subsequently performed postdoctoral research with Professor Seyferth at the Massachusetts Institute of Technology (Cambridge, USA) on ceramic precursors and organosilicon chemistry. In 1987, he returned to Rhône-Poulenc Research, where he developed new ceramic precursors for the coating of fibers (BN, Si_3N_4, SiC, TiN), new nonlinear optics materials, polymers, and homogeneous catalysis processes. He spent ten years as a group leader in silicon chemistry. His research interests included the polyfunctionalization of polysiloxanes, new organometallic catalysis for organosilicon applications, and the functionalization of mineral charges. Currently, his research interests are focusing on new processes and scale-up in organic chemistry, organometallic catalysis (homogeneous and heterogeneous), and new methodology in chemical synthesis. He received the "Prix de la Recherche" in 1995, the "Prix Rhodia Group" in 2001, and the "Prix Centre de Recherches-Rhodia" in 2004.

Young Chemist in Industry XIV Prizewinners

Group photograph of the winners and organizing committee. Matt Welham is 3rd from the right, David Beal 2nd from the left, and Alastair Hill 3rd from the left. Photo courtesy of Jacqueline Ali of SCI.

Sigma-Aldrich is pleased to announce the names of the prizewinners for the top three presentations at the Young Chemist in Industry XIV meeting that was held on April 26, 2005, at the Society of Chemical Industry headquarters at Belgrave Square in London.

This annual, one-day meeting is organized by the Young Chemists' Panel of the SCI, and showcases organic chemistry research undertaken in an industrial setting by chemists under the age of 30, who do not hold a Ph.D. It represents a unique opportunity for younger chemists to present their research to an industry-wide audience. The presentation topics span a wide range of areas that include medicinal, computational, analytical, and process chemistry. This year's gathering was attended by 97 delegates, and featured 10 presentations by participants and a guest lecture by Dr. Frank King of GlaxoSmithKline (Harlow).

Sigma-Aldrich applauds the work of these talented young scientists. It is our honor to recognize the important contributions being made by young chemists throughout the industry. We congratulate the winners and commend all those who participated in the meeting.

First Place Winner: **Matt Welham**, AstraZeneca (Avalon)
A New Route to Gefitinib via a Dimroth Rearrangement

Second Place Winner: **David Beal**, Pfizer (Sandwich)
A Versatile New Preparation of 1,2,4-Triazoles

Third Place Winner: **Alastair Hill**, Merck, Sharp and Dohme (Harlow)
Structural Alerts

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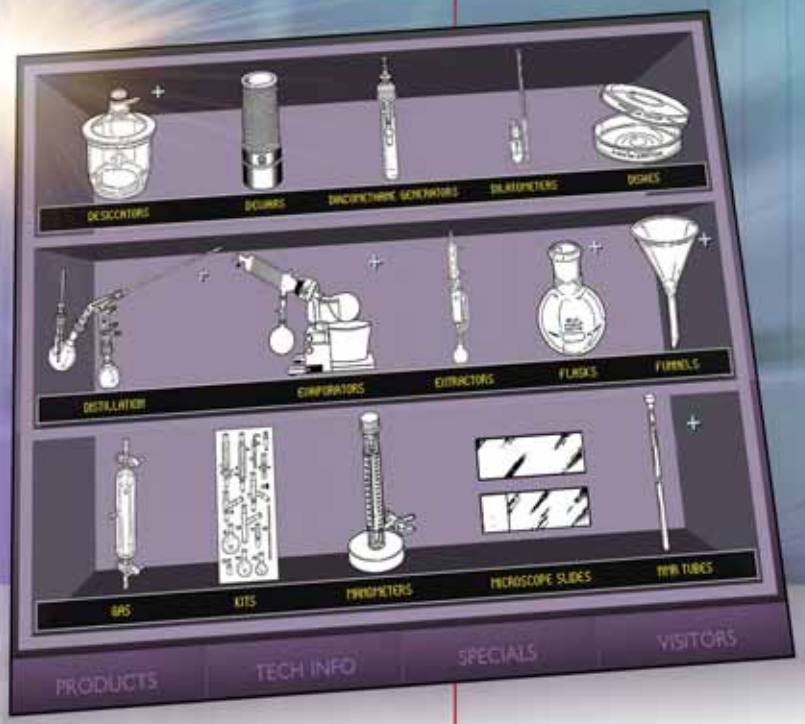

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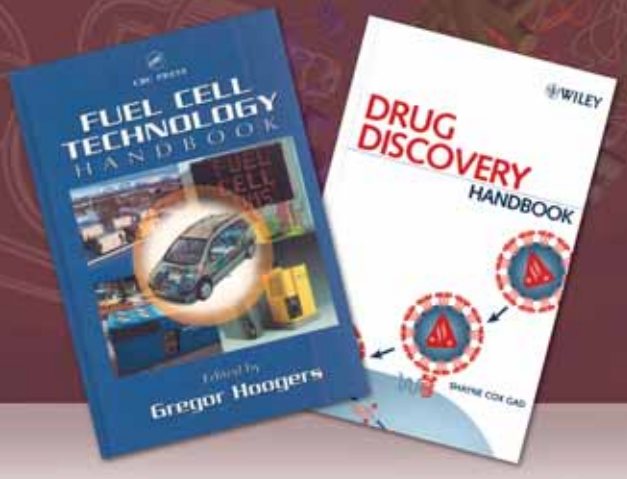

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J. A. Gladysz, D. P. Curran and I. T. Horváth, Eds., Wiley, 2004, 624pp. Hardcover. This handbook is the first to summarize all the essential aspects of this emerging field of chemistry. Whether the reader is seeking an introduction to the concept of fluorous biphase catalysis, summaries of partition coefficients involving fluorous and organic solvents, or information on the latest fluorous mixture separation techniques, this authoritative compilation provides the key information needed for successfully working with the diverse and fascinating families of fluorous molecules. The large number of reliable experimental procedures makes this the ideal guide for newcomers wanting to use this elegant method in the laboratory.

Z704520-1EA

Asymmetric Organocatalysis—From Biomimetic Concepts to Applications in Asymmetric Synthesis

A. Berkessel and H. Gröger, Wiley, 2005, 454pp. Hardcover. Asymmetric catalysis represents one of the major challenges in modern organic chemistry. Besides the well-established asymmetric metal-complex-catalyzed syntheses and biocatalysis, the use of "pure" organic catalysts is an additional efficient tool for the synthesis of chiral building blocks. The experienced authors provide the first overview of the important use of such metal-free organic catalysts. With its comprehensive description of numerous reaction types, e.g., nucleophilic substitution and addition reactions as well as cycloadditions and redox reactions, this book targets organic chemists working in industry and academia.

Z704113-1EA

Name Reactions and Reagents in Organic Synthesis, Second Edition

B. P. Mundy, M. G. Ellerd, and F. G. Favaloro, Jr., Wiley, 2005, 882pp. Hardcover. This second edition is the premier named-reaction resource in the field. It provides a handy guide for navigating the web of named reactions and reagents. Reactions and reagents are listed alphabetically, followed by relevant mechanisms, experimental data (including yields where available), and references to the primary literature. The text also includes three indices based on reagents and reactions, starting materials, and desired products. Organic chemists working in academia, industry, government, and other laboratories will find this book to be an invaluable reference.

Z704210-1EA

DRUG DISCOVERY TITLE

Drug Discovery Handbook

S. C. Gad, Ed., Wiley, 2005, 1471pp. Hardcover. This book gives professionals a tool to facilitate drug discovery by bringing together a compendium of methods and techniques that need to be considered when developing new drugs. This comprehensive, practical guide presents an explanation of the latest techniques and methods in drug discovery, including: genomics, proteomics, high-throughput screening, and systems biology; summaries of how these techniques and methods are used to discover new central nervous system agents, antiviral agents, respiratory drugs, oncology drugs, and more; and specific approaches to drug discovery, including problems that are encountered, solutions to these problems, and limitations of various methods and techniques.

Z704504-1EA

FLAVORS AND FRAGRANCES TITLE

Perspectives in Flavor and Fragrance Research

P. Kraft and K. A. D. Swift, Eds., Wiley, 2005, 250pp. Hardcover. Research is central to the F&F industry with its constant demand for innovation and its frequently changing trends. In the classic and well-explored domains of musks and amber odorants, fascinating new discoveries were made only very recently, which proves the endless possibilities in the search for new aroma chemicals. Fragrance materials by definition elicit a biological response, serve as versatile signals, trigger the sense of smell and taste in various ways—and every odorant design is nothing more than "chemistry probing nature". But fragrance chemistry can also document and even preserve the biodiversity of scents.

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SPECTROSCOPY TITLE

Modern Raman Spectroscopy: A Practical Approach

E. Smith and G. Dent, Wiley, 2005, 222pp. Softcover. This book contains coverage of Resonance Raman and SERS, two hot areas of Raman spectroscopy, in a form suitable for the non-expert. It builds Raman theory up in stages without overloading the reader with complex theory, and includes two chapters on instrumentation and interpretation that show how Raman spectra can be obtained and interpreted. The book explains the potential of using Raman spectroscopy in a wide variety of applications, and includes detailed, but concise information and worked examples.

Z704202-1EA

MATERIALS SCIENCE TITLES

Bulk Crystal Growth of Electronic, Optical and Optoelectronic Materials

P. Capper, Ed., Wiley, 2005, 574pp. Hardcover. A valuable, and timely book for the crystal-growth community, edited by one of the most respected members in the field. The contents cover all the important materials from silicon through the group II–IV and III–V compounds, to oxides, nitrides, fluorides, carbides, and diamonds. An international group of contributors from academia and industry provide a balanced treatment. The text includes global interest with particular relevance to the USA, Canada, UK, France, Germany, Netherlands, Belgium, Italy, Spain, Switzerland, Japan, Korea, Taiwan, China, Australia, and South Africa.

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Fuel Cell Technology Handbook

G. Hoogers, Ed., CRC Press, 2002, 360pp. Hardcover. This handbook provides the first comprehensive treatment of both the technical and commercial aspects of high- and low-temperature fuel cells, fuel cell systems, fuel cell catalysis, and fuel generation. The first part of the book addresses the principles of fuel cell technology and summarizes the main concepts, developments, and remaining technical problems, particularly in fueling. The second part explores applications in automotive, stationary, and portable power-generation technologies. It also provides an expert's look at future developments in both the technology and its applications.

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Metal-Polymer Nanocomposites

L. Nicolais and G. Carotenuto, Eds., Wiley, 2004, 320pp. Hardcover. A unique guide to an essential area of nanoscience. Interest in nano-sized metals has increased greatly due to their special characteristics and suitability for a number of advanced applications. As technology becomes more refined—including the ability to effectively manipulate and stabilize metals at the nanoscale level—these materials present ever-more workable solutions to a growing range of problems. The coverage includes: chemical and physical properties of nano-sized metals; different approaches to the synthesis of metal–polymer nanocomposites (MPN); advanced characterization techniques and methods for the study of MPN; real-world applications, including color filters, polarizers, optical sensors, nonlinear optical devices, and others.

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Chiral, Poly(Rare-Earth Metal) Complexes in Asymmetric Catalysis

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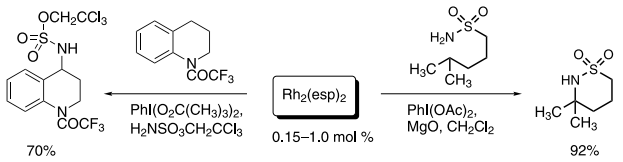
Du Bois C–H Amination Catalyst

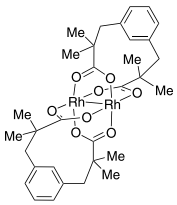
The Du Bois group at Stanford University has utilized $Rh_2(esp)_2$ to facilitate both inter- and intramolecular N-insertion in a range of benzylic, secondary, and tertiary C–H bonds, giving the corresponding aminated products in high yields.[1,2]



(1) (a) Espino, C. G. et al. *J. Am. Chem. Soc.* **2004**, *126*, 15378. (b) Fiori, K. W. et al. *Angew. Chem., Int. Ed.* **2004**, *43*, 4349. (2) (a) Dauban, P.; Dodd, R. H. *Synlett* **2003**, 1571. (b) Muller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905. (c) Diaz-Requejo, M. M. et al. *J. Am. Chem. Soc.* **2003**, *125*, 12078.

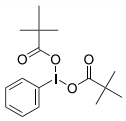
Bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)], 96%

$Rh_2(esp)_2$ — 100 mg
662623 — 500 mg
[*819050-89-0*]
$C_{32}H_{40}O_8Rh_2$
FW: 758.47



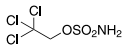
Bis(*tert*-butylcarbonyloxy)iodobenzene, 97%

662283 — 5 g, 25 g, 100 g
[*57357-20-7*]
$C_{16}H_{23}IO_4$
FW: 406.26



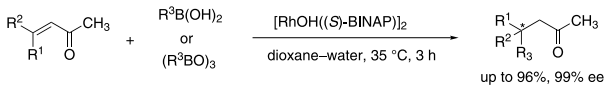
2,2,2-Trichloroethoxysulfonamide, 97%

663727 — 1 g, 10 g
[*69226-51-3*]
$C_2H_4Cl_3NO_3S$
FW: 228.48



Hayashi Asymmetric Conjugate-Addition Catalyst and Precursors

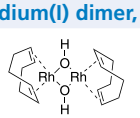
The dimeric catalysts and catalyst precursors developed by Hayashi demonstrate impressive levels of enantiocontrol in the conjugate-addition reactions of both acyclic and cyclic enones of varying electronic character.[1–5]



(1) Hayashi, T. et al. *J. Am. Chem. Soc.* **2002**, *124*, 5052. (2) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (3) Takaya, Y. et al. *J. Am. Chem. Soc.* **1998**, *120*, 5579. (4) Takaya, Y. et al. *Tetrahedron: Asymmetry* **1999**, *10*, 4047. (5) Takaya, Y. et al. *Tetrahedron Lett.* **1999**, *40*, 6957.

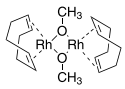
Hydroxy(cyclooctadiene)rhodium(I) dimer, 95%

661023 — 250 mg, 1 g
[*73468-85-6*]
$C_{16}H_{26}O_2Rh_2$
FW: 456.19



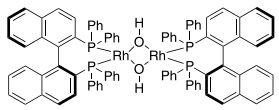
Methoxy(cyclooctadiene)rhodium(I) dimer

661058 — 250 mg, 1 g
[*12148-72-0*]
$C_{18}H_{30}O_2Rh_2$
FW: 484.24



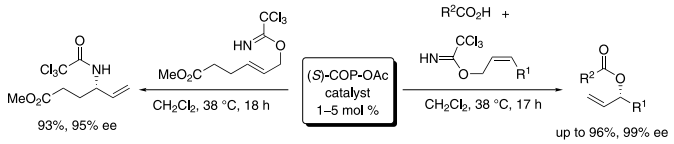
Hydroxy[(*S*)-BINAP]rhodium(I) dimer, 90%

661007 — 1 g
[*434314-10-0*]
$C_{88}H_{66}O_2P_4Rh_2$
FW: 1485.17



Overman Asymmetric Allylic Rearrangement Catalysts

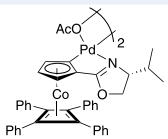
Overman and others have successfully utilized Co-based COP catalysts in the preparation of chiral amides and esters via cyclic rearrangement of allylic trichloroacetimidates. These rearrangements occur in high yield with excellent enantiocontrol.[1,2]



(1) (a) Kirsch, S. F. et al. *J. Org. Chem.* **2004**, *69*, 8101. (b) Anderson, C. E.; Overman, L. E. *J. Am. Chem. Soc.* **2003**, *125*, 12412. (c) Kirsch, S. F.; Overman, L. E. *J. Am. Chem. Soc.* **2005**, *127*, 2866. (2) Kwon, T. W. et al. *J. Org. Chem.* **1992**, *57*, 6169.

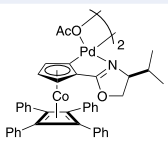
(*R*)-(–)-COP-OAc Catalyst, 95%

661708 — 250 mg, 1 g
[*849592-74-1*]
$C_{82}H_{72}O_6N_2Co_2Pd_2$
FW: 1512.17



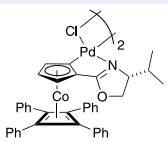
(*S*)-(+)-COP-OAc Catalyst, 95%

661716 — 250 mg, 1 g
[*222400-03-5*]
$C_{82}H_{72}O_6N_2Co_2Pd_2$
FW: 1512.17



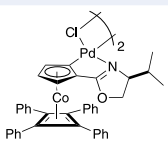
(*R*)-(–)-COP-Cl Catalyst

661791 — 100 mg, 500 mg
[*612065-00-6*]
$C_{78}H_{66}Cl_2Co_2N_2O_2Pd_2$
FW: 1464.98



(*S*)-(+)-COP-Cl Catalyst

646636 — 250 mg, 1 g
[*612065-01-7*]
$C_{78}H_{66}Cl_2Co_2N_2O_2Pd_2$
FW: 1464.98



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"PLEASE BOTHER US."

Joe Porwoll, President
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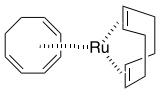
Professor John G. Ekerdt of the University of Texas at Austin and his student, Wyatt Winkenwerder, kindly suggested that we offer (1,5-cyclooctadiene)(1,3,5-cyclooctatriene)ruthenium, or Ru(cod)(cot). This complex is used in the preparation of monodisperse ruthenium nanoparticles for catalysis,[1,2] as well as a highly selective catalyst for amine alkylations, [2+2] cycloadditions,[3] and enyne generation.

(1) Pelzer, K.; Philippot, K.; Chaudret, B. *Z. Phys. Chem.* **2003**, *217*, 1539. (2) Hulea, V.; Brunel, D.; Galarneau, A.; Philippot, K.; Chaudret, B.; Kooyman, P. J.; Fajula, F. *Microporous Mesoporous Mater.* **2005**, *79*, 185. (3) Mitsudo, T.; Suzuki, T.; Zhang, S.-W.; Imai, D.; Fujita, K.; Manabe, T.; Shiotsuki, M.; Watanabe, Y.; Wada, K.; Kondo, T. *J. Am. Chem. Soc.* **1999**, *121*, 1839.



654418-1G **(1,5-Cyclooctadiene)(1,3,5-cyclooctatriene)-ruthenium**, Ru(cod)(cot) 1 g

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

View from Vaekero near Christiania (oil on canvas, 60.5 × 96.5 cm) was painted by the Norwegian romantic painter Johan Christian Dahl in 1827. Dahl studied in Dresden and was directly influenced by his teacher and friend, the German painter Casper David Friedrich. Dahl's paintings also show his strong interest in the work of seventeenth century Dutch landscape painters such as Jacob van Ruisdael.

Dahl visited Christiania, present-day Oslo, in the summer of 1826. The following winter in Dresden, Dahl painted *View from Vaekero near Christiania* from memory for the Hamburger Kunstverein artists' cooperative. In this moody and melancholy nocturne, Dahl invites the viewer to imagine a romantic moonlit evening complete with sand, sea, and sky. His use of successive bands of light and dark clouds against a pink-and-blue backdrop shows an alluring distance, possibly unattainable. Harmoniously cascading hills, which meld into an illuminated sea, may also suggest adventure. Ethereal light and drying fishnets seem to envelop the mysterious, solitary couple, who stand in the center foreground contemplating the quixotic setting. True to his romantic spirit, Dahl presents a thought-provoking and poignant scene, allowing us to do what paintings should make us do—dream.

This painting was purchased for the National Gallery of Art by the Patrons' Permanent Fund.

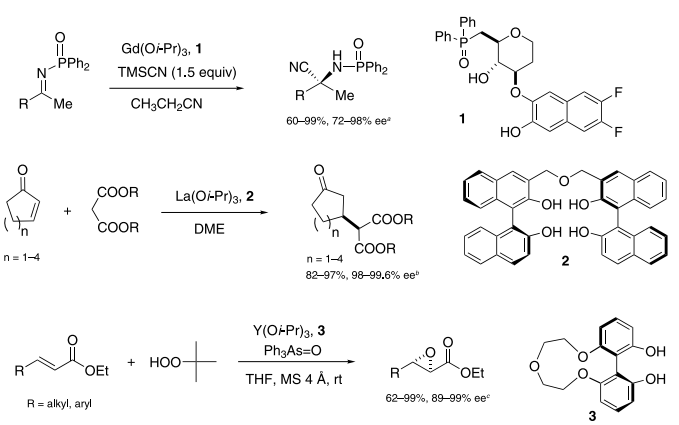
NEW Shibasaki Catalysts: La, Y, Gd, and Sm Trisisopropoxides

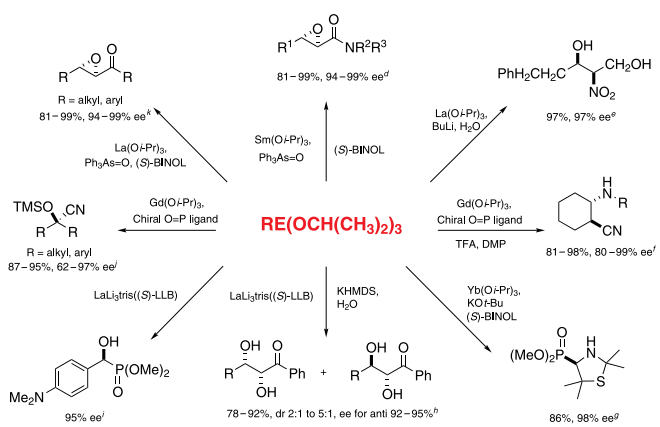
Rare-Earth Metals Used in Diversity-Oriented Organic Transformations

Product Highlights

- Dramatically enhance selectivities by varying the nature of the rare-earth (RE) metal and the ratio of catalyst to reaction partners.
- In most cases, the metal complexes are insensitive to oxygen after preparation.
- Bifunctional: Can perform effectively as both a Brønsted base and a Lewis acid.
- The catalysts can be recovered and recycled without loss of selectivities.
- RE catalyst systems can effectively facilitate a broad range of organic reactions.

Shibasaki and co-workers have developed rare-earth (RE) metal catalysts, utilized in conjunction with a variety of chiral ligands, to effect asymmetric transformations ranging from the formation of quaternary chiral centers to the epoxidation of unsaturated substrates. The Shibasaki research group has published extensively in the field of RE-metal catalysis and has optimized reaction conditions to afford high selectivities in C–C and C–O bond-forming reactions. Sigma-Aldrich is pleased to offer an array of RE-metal pre-catalysts that can be paired with our growing line of chiral ligands to accelerate your research discoveries.





References: (a) Masumoto, S. et al. *J. Am. Chem. Soc.* **2003**, *125*, 5634. (b) Kim, Y. S. et al. *J. Am. Chem. Soc.* **2000**, *122*, 6506. (c) Kakei, H. et al. *J. Am. Chem. Soc.* **2005**, *127*, 8962. (d) Nemoto, T. et al. *J. Am. Chem. Soc.* **2002**, *124*, 14544. (e) Sasai, H. et al. *J. Am. Chem. Soc.* **1993**, *115*, 10372. (f) Mita, T. et al. *J. Am. Chem. Soc.* **2005**, *127*, 11252. (g) Gröger, H. et al. *J. Am. Chem. Soc.* **1998**, *120*, 3089. (h) Yoshikawa, N. et al. *J. Am. Chem. Soc.* **2001**, *123*, 2466. (i) Shibasaki, M. et al. *Chem. Rev.* **2002**, *102*, 2187. (j) Yabu, K. et al. *J. Am. Chem. Soc.* **2001**, *123*, 9908. (k) Nemoto, T. et al. *J. Am. Chem. Soc.* **2001**, *123*, 2725.

Lanthanum(III) isopropoxide NEW

[*19446-52-7*]
$C_9H_{21}LaO_3$
FW: 316.17

665193-500MG	500 mg
665193-3G	3 g

Gadolinium(III) isopropoxide NEW

[*14532-05-9*]
$C_9H_{21}GdO_3$
FW: 334.51

663948-500MG	500 mg
663948-3G	3 g

Yttrium(III) isopropoxide NEW

[*2172-12-5*]
$C_9H_{21}YO_3$
FW: 266.17

665916-500MG	500 mg
665916-3G	3 g

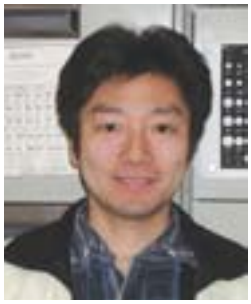
Samarium(III) isopropoxide

[*3504-40-3*]
$C_9H_{21}SmO_3$
FW: 327.62

410136-1G	1 g

Chiral, Poly(Rare-Earth Metal) Complexes in Asymmetric Catalysis


Dr. Masakatsu Shibasaki


Dr. Motomu Kanai


Dr. Shigeki Matsunaga

Masakatsu Shibasaki, Motomu Kanai, and Shigeki Matsunaga*
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Tokyo, 113-0033, Japan
Email: mshibasa@mol.f.u-tokyo.ac.jp

Outline

1. Introduction

Asymmetric catalysis has received considerable attention over the past few decades, and its contributions to organic synthesis have become increasingly important.[1] Various enantioselective reactions, some of which are utilized on an industrial scale, are now performed with only catalytic amounts of chiral promoters. The performance of most synthetic asymmetric catalysts, however, is still far from satisfactory in terms of generality and reactivity. On the other hand, enzymes catalyze various organic transformations under mild conditions, even though they are often lacking in substrate generality. One advantage of enzymes over most synthetic asymmetric catalysts is that they often contain two or more active sites for catalysis. The synergistic effect of two active sites can make substrates more reactive in the transition state, and controls the relative positions of the reacting substrates. This concept of multifunctional catalysis is key to broadening the scope of natural and synthetic asymmetric catalysts (**Figure 1**).

Asymmetric catalysis has been conducted in many cases by using various metal–chiral-ligand complexes. While asymmetric catalysts containing *p*-block and/or *d*-block metals have been studied extensively, the use of *f*-block metals, such as lanthanides, for asymmetric catalysis has not been thoroughly investigated until recently. The utility of rare-earth metals in asymmetric catalysis was first demonstrated by Danishefsky and co-workers in a hetero-Diels–Alder reaction with $Eu(hfc)_3$.[2] Subsequently, the usefulness of rare-earth metal complexes as chiral Lewis acid catalysts was demonstrated in various reactions by several research groups.[3,4] In contrast, we were initially interested in using the Brønsted base character of rare-earth metal alkoxides in organic synthesis. Aldol reactions, cyanosilylations of aldehydes, and nitroaldol reactions proceeded smoothly with a catalytic amount of a rare-earth metal alkoxide.[5] On the basis of the Lewis acid and Brønsted base properties of rare-earth metals, we envisioned that rare-earth metal complexes would be suitable for use in multifunctional asymmetric catalysis. In this account, we briefly discuss the most recent advances in multifunctional asymmetric catalysis employing rare-earth metals. For more comprehensive reviews including details of our early work and the work of other groups, see other review articles.[6,7]

2. Heterobimetallic Rare-Earth Metal–Alkali Metal–BINOL (REMB) Complexes

2.1. As Lewis Acid–Brønsted Base Catalysts

Since our first report of a catalytic, asymmetric nitroaldol reaction facilitated by rare-earth metal complexes,[5a,8] we have continued to develop the concept of multifunctional catalysis, wherein the catalyst exhibits both Lewis acidity and Brønsted basicity. In particular, heterobimetallic complexes that contain a rare-earth metal, three alkali metals, and three 1,1'-bi-2-naphthols (BINOLs)—abbreviated as REMB (RE = rare-earth metal, M = alkali metal, B = BINOL)—offer a versatile framework for asymmetric catalysis (**Figure 2**).[8] The synergistic effect of the two metal centers enables various transformations to take place that are otherwise difficult to carry out using

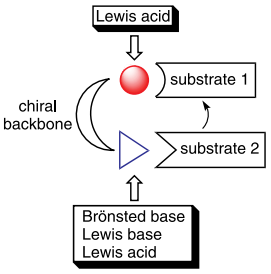


Figure 1. Bifunctional Asymmetric Catalysis.

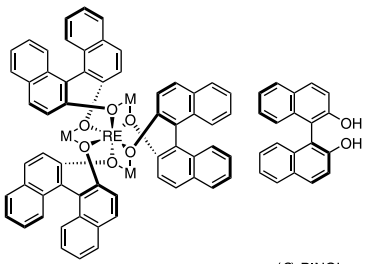


Figure 2. REMB Heterobimetallic Complexes Formed from a Rare-Earth Metal, Alkali Metal, and 1,1′-Bi-2-naphthol.

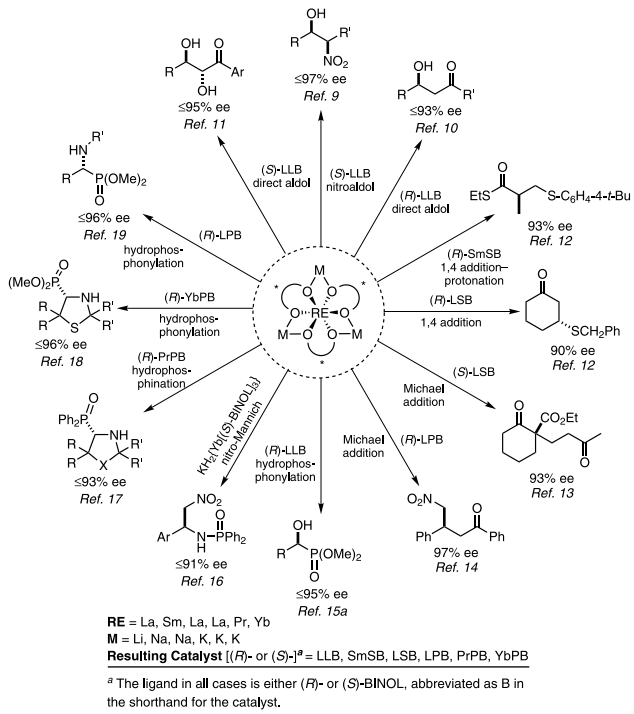


Figure 3. Representative Enantioselective Transformations Catalyzed by REMBs.

conventional monometallic catalysts possessing only Lewis acidity. A variety of enantioselective transformations have been realized through the choice of appropriate combinations of metals within the REMB (**Figure 3**).[9–19] In all cases, the active nucleophilic species were generated in situ from pronucleophiles, and the reactions proceeded with high atom economy through a simple proton transfer.[20] REMB complexes can be prepared from several rare-earth metal sources,[21–23] such as $RE(O\textit{i}\text{-}Pr)_3$,[10] $RE[N(SiMe_3)_2]_3$,[21a,23] $RECl_3{\bullet}7H_2O$,[21b,c] and $RE(OTf)_3$[21d] (**Scheme 1**).[21–24] REMB complexes prepared from $RE(O\textit{i}\text{-}Pr)_3$ were utilized in most of the transformations depicted in Figure 3. Among rare-earth metal sources, $RE(O\textit{i}\text{-}Pr)_3$ and $RE[N(SiMe_3)_2]_3$ are the most suitable for the preparation of pure REMB complexes, because the resulting side products, such as *i*-PrOH, can be easily removed under reduced pressure. When REMB complexes are prepared from $RE(OTf)_3$ or $RECl_3{\bullet}7H_2O$, alkali metal salts, such as MOTf, remain in the solution containing the catalyst product and can affect the subsequent asymmetric reactions either positively or negatively. Recently, we found that the La–Li–BINOL (LLB) complex prepared from $La(OTf)_3$ showed much better enantioselectivity in a direct aldol–Tishchenko reaction than the complex derived from $La(O\textit{i}\text{-}Pr)_3$ did. The side product, LiOTf, in the catalyst mixture had exerted a positive effect on the enantioselectivity in the Tishchenko reaction (**eq 1**).[22] Mechanistic studies suggest that LiOTf changes the structure of LLB from monomeric to oligomeric.

2.2. As Lewis Acid–Lewis Acid Catalysts

In REMB heterobimetallic catalyzed reactions, only nucleophiles bearing protons with relatively low pK_a values (10–19 in H_2O), such as nitroalkanes, malonates, ketones, and thiols, were usable due to the limited Brønsted basicity of the catalysts (see Figure 3). REMB catalysis was not applicable to nucleophiles with protons possessing higher pK_a values. Recently, however, we succeeded in broadening the scope of usable nucleophiles by utilizing the same REMB heterobimetallic catalysts, but in a different reaction mode. YLi_3tris(binaphthoxide) (YLB), prepared from $Y[N(SiMe_3)_2]_3$, efficiently promoted the 1,4 addition of methoxylamine to α,β-unsaturated ketones, producing β-methoxyamino ketones in up to 96% ee's (**eq 2**).[23,24] α,β-Unsaturated *N*-acylpyrroles, as carboxylic acid derivatives, were also suitable substrates that gave rise to β-amino acid derivatives in up to 94% ee's (**eq 3**).[23c] Mechanistic studies suggest that the rare-earth metal functions as a Lewis acid to activate the enones and α,β-unsaturated *N*-acylpyrroles, while the lithium ion functions as another Lewis acid to control the orientation of the approaching methoxylamine (Lewis acid–Lewis acid cooperative catalysis).[25]

2.3. Catalytic Asymmetric Cyanoethoxycarbonylation and Cyanophosphorylation

YLB is also an effective catalyst for the asymmetric cyanoethoxycarbonylation of aldehydes (**eq 4**)[26] and cyanophosphorylation of aldehydes and ketones.[27,28] In these reactions, $Ar_3P{=}O$, H_2O, and BuLi are essential as additives in order to achieve high enantioselectivities. Mechanistic studies suggest that both $Ar_3P{=}O$ and H_2O coordinate to YLB and modify its structure, affecting both enantioselectivity and reactivity. LiOH, generated in situ from H_2O and BuLi, reacts with ethyl cyanoformate to generate a YLB–LiCN complex, which is the true active species. The use of LiOH itself results in a slight decrease in enantioselectivity, probably due to the relatively low

solubility of LiOH in THF. LiCN, self-assembled with YLB, functions as a nucleophile in these reactions.[26]

3. Rare-Earth Metal–BINOL Complexes

3.1. Catalytic Asymmetric Epoxidation of Electron-Deficient Olefins

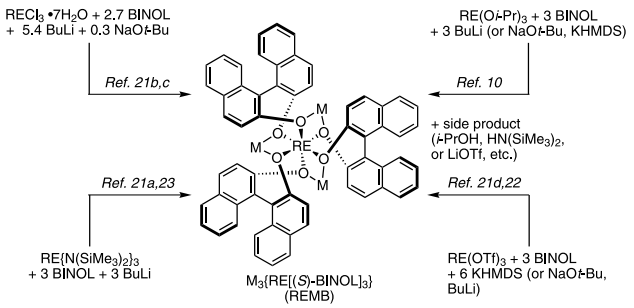
Rare-earth metal alkoxides efficiently promote the catalytic asymmetric epoxidation[29] of electron-deficient olefins, such as enones, amides, and esters in the presence of BINOLs as chiral ligands. Rare-earth metal peroxides function as key active nucleophilic species in these reactions. The rare-earth metal also functions as a Lewis acid to activate the electron-deficient olefins. The addition of powdered 4 Å molecular sieves and either Ph_3PO or Ph_3AsO is critical to obtaining high reactivities and enantioselectivities. For enones, the La(O*i*-Pr)$_3$–BINOL complex gave the best results (up to 99% ee's).[30] Enolizable enones such as benzalacetone were also suitable substrates, producing the desired epoxides in high yields and ee's without any side adducts. For α,β-unsaturated amides, the Sm(O*i*-Pr)$_3$–BINOL complex, modified with Ph_3AsO, was useful (up to 99% ee's).[31] Sequential catalytic asymmetric epoxidation–regioselective epoxide opening reactions were also realized (**Scheme 2**).[32] In the regioselective epoxide opening reaction employing $TMSN_3$, samarium azide was generated in situ as the active nucleophile. α,β-Unsaturated *N*-acylpyrroles, which are activated, monodentate ester equivalents, were also found to be competent acceptors (**eq 5**).[33,34] Sm(O*i*-Pr)$_3$–H_8-BINOL gave the best reactivity in this case: high TON (~4720) and high TOF (>3000 h^{-1}) of the catalyst were realized.[33b] It is also noteworthy that cumene hydroperoxide (CMHP), an oxidant with low explosion hazard, was suitable for the epoxidation of enones and α,β-unsaturated *N*-acylpyrroles. In the case of α,β-unsaturated esters, BINOL was not a suitable chiral ligand. Instead, a biphenyldiol ligand, **1**, was preferable, when used as its yttrium phenoxide complex (**eq 6**).[35] Various β substituents, including heteroaromatic rings, were tolerated in reactions catalyzed by the Y–**1** complex.

3.2. Catalytic Asymmetric Michael Reactions of Malonates and β-Keto Esters

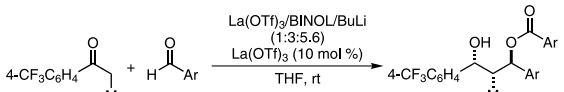
A complex prepared from La(O*i*-Pr)$_3$ and linked-BINOL **2**[36] is a good catalyst for the asymmetric Michael reaction[37] between cyclic enones and malonates. The La–OAr moiety functions as a Brønsted base to generate lanthanum enolates. Lanthanum also acts as a Lewis acid to activate enones. Reactions with various substituted and unsubstituted malonates gave products in good yields and ≥99% ee's (**eq 7**).[38] The use of DME as solvent resulted in dramatic improvements in enantioselectivity; with other ether solvents, ee's were only modest to good. For less reactive malonates, the addition of hexafluoroisopropanol (HFIP) had beneficial effects on reactivity. For Michael reactions of β-keto esters, (NMe)-linked-BINOL **3** was a more effective chiral ligand than linked-BINOL **2** (**eq 8**).[39]

3.3. Direct, Catalytic, and Asymmetric Mannich-Type Reactions of α-Hydroxy Ketones

Recently, the catalytic in situ generation of metal enolates from unmodified ketones and esters for application to asymmetric carbon–carbon-bond formation has been intensively studied by several groups.[40] REMB complexes catalyze asymmetric aldol reactions. We recently found that complexes of Y[N(SiMe$_3$)$_2$]$_3$ and linked-BINOLs **2** or **4** are suitable catalysts for the *syn*-selective and direct asymmetric Mannich-type reaction



Scheme 1. Preparation of REMB Complexes.



Ar	Time	Yield	ee
4-ClC$_6$H$_4$	60 h	95%	93%
thien-3-yl	84 h	82%	94%

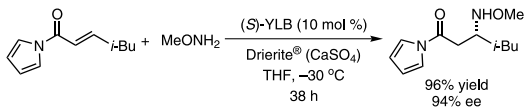
Ref. 22a

eq 1

R^1	R^2	Yield	ee
Ph	Ph	95%	96%
furan-2-yl	Ph	95%	94%
thien-2-yl	Ph	96%	93%
Ph	pyridin-4-yl	91%	85%
Ph	*i*-Bu	95%	93%
Ph	(*E*)-PhCH=CH	91%	95%

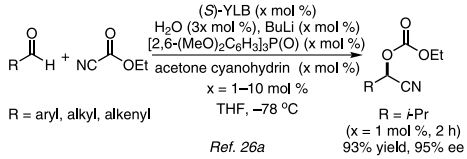
Ref. 23

eq 2



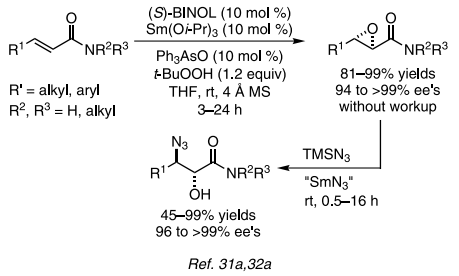
Ref. 23c

eq 3

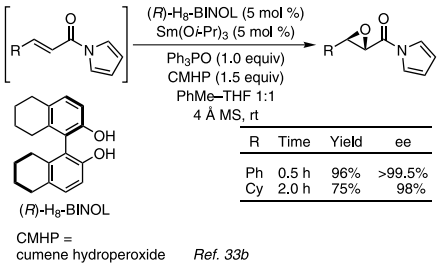


Ref. 26a

eq 4

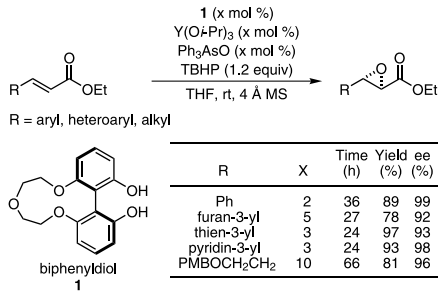


Scheme 2. The One-Pot Sequential Catalytic Asymmetric Epoxidation–Regioselective Epoxide Opening.



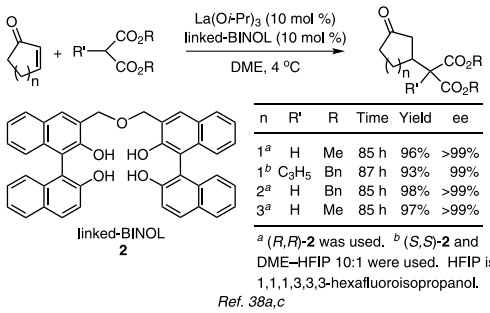
R	Time	Yield	ee
Ph	0.5 h	96%	>99.5%
Cy	2.0 h	75%	98%

eq 5



R	X	Time (h)	Yield (%)	ee (%)
Ph	2	36	89	99
furan-3-yl	5	27	78	92
thien-3-yl	3	24	97	93
pyridin-3-yl	3	24	93	98
$PMBOCH_2CH_2$	10	66	81	96

eq 6

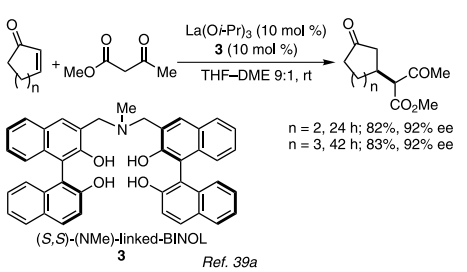


n	R'	R	Time	Yield	ee
1[a]	H	Me	85 h	96%	>99%
1[b]	C_3H_5	Bn	87 h	93%	99%
2[a]	H	Bn	85 h	98%	>99%
3[a]	H	Me	85 h	97%	>99%

[a] (*R,R*)-**2** was used. [b] (*S,S*)-**2** and DME–HFIP 10:1 were used. HFIP is 1,1,1,3,3,3-hexafluoroisopropanol.

Ref. 38a,c

eq 7



eq 8

of aromatic and heteroaromatic α-hydroxy ketones with diphenylphosphinoylimines (Dpp-imines) (**eq 9**).[41] In this reaction, rare-earth metal alkoxides showed only a modest reactivity and selectivity, while the use of $Y[N(SiMe_3)_2]_3$ as a yttrium source was crucial. This observation is the opposite of that of the asymmetric epoxidation (see Section 3.1), in which rare-earth metal alkoxides were essential and $RE[N(SiMe_3)_2]_3$ exhibited poor reactivity. Using $Y[N(SiMe_3)_2]_3$ and only equimolar amounts of hydroxy ketones, β-amino-α-hydroxy ketones were obtained in good yields and high ee's. For heteroaromatic hydroxy ketones, linked-TMS-BINOL **4**[42] was necessary to achieve high ee's. In the Mannich-type reaction, $Y[N(SiMe_3)_2]_3$–linked-BINOL complexes have sufficient Brønsted basicity to generate yttrium enolates in situ from hydroxy ketones.

4. Catalytic Enantioselective Cyanosilylation of Ketones

The chiral gadolinium complex prepared from $Gd(O\textit{i}\text{-}Pr)_3$ and D-glucose-derived ligand **5** or **6**[43] in a 1:2 ratio is a general catalyst for the enantioselective cyanosilylation of ketones (**Figure 4** and **Table 1**).[44,45] *S* ketone cyanohydrins are generally obtained with high enantioselectivity. Because the cyanide group can be easily converted into many other important functional groups, such as carboxylic acids or amines, this catalytic asymmetric reaction is a novel method for the production of a wide range of enantiomerically enriched tertiary alcohols.[46] A bimetallic transition state, **8**, is postulated for the enantioselective cyanosilylation of ketones on the basis of the following observations: (i) ^1H NMR and ESI-MS studies suggest that the major species in the catalyst solution is a 2:3 complex of gadolinium and partially silylated **5**. (ii) The 2:3 complex is likely to be the catalytically active species, based on the fact that enantioselectivity is dependent on the metal:ligand ratio used in the preparation of the catalyst; enantioselectivity increases as the ligand/metal ratio increases, reaching a plateau at a ratio of 2:3. (iii) Kinetic studies and labeling experiments indicate that the actual nucleophile is a gadolinium cyanide (or isonitrile) that is generated from TMSCN through a facile transmetalation. Since we previously developed a complementary *R*-selective catalytic cyanosilylation of ketones using a titanium complex of ligand **5** or **7**,[47] both ketone cyanohydrin enantiomers can now be synthesized from a broad range of substrate ketones using one chiral source by the appropriate choice of either titanium or gadolinium.

The utility of the *S*-selective cyanosilylation of ketones catalyzed by chiral lanthanide complexes was demonstrated by the following successful applications to the synthesis of pharmaceutically significant intermediates. First, the key synthetic intermediate, **11**, for (*S*)-oxybutynin, a muscarinic receptor antagonist and a drug for the treatment of urinary urgency, frequency, and incontinence, was synthesized in 4 steps from commercially available ketone **9** (**Scheme 3**).[48] The key catalytic enantioselective cyanosilylation proceeded using 1 mol % of catalyst, and the product **10** was obtained in quantitative yield and 94% ee. Enantiomerically pure **11** was produced from **10** through reduction, deprotection, oxidation, and recrystallization.

Second, the catalytic enantioselective synthesis of Curran's precursor to the anticancer drug camptothecin was achieved starting with ketone **12** and the catalyst generated from $Sm(O\textit{i}\text{-}Pr)_3$ and an analogue of **6** in a 1:1.8 ratio (**Scheme 4**).[49] Using 2 mol % catalyst, the product cyanohydrin, **13**, was obtained in 91% yield and 90% ee. Enantiomerically pure **14** was obtained after

iododesilylation of **13**, lactone formation, methyl ether cleavage, and recrystallization from MeOH–$CHCl_3$.

Third, in the cyanosilylation of electron-deficient ketone **15**, the catalyst prepared from $Gd(HMDS)_3$ and ligand **6** in a 2:3 ratio exhibited a greater enantioselectivity (83% ee) than that obtained with the catalyst formed from $Gd(O\textit{i}\text{-}Pr)_3$ and **6** in a 1:2 ratio (68% ee) (**Scheme 5**).[50] Based on ESI-MS studies, the variation in enantioselectivity with the gadolinium source was attributed to the existence of a less enantioselective catalytic species containing Gd/chiral ligand/μ-oxo in a 4:5:1 ratio, when the catalyst was prepared from $Gd(O\textit{i}\text{-}Pr)_3$. Only the desired 2:3 complex was observed in ESI-MS, when the catalyst was prepared from $Gd(HMDS)_3$. Cyanohydrin **16** was converted to **17**, a versatile key intermediate of triazole antifungal agents such as ZD0870 and Sch45450, in 4 steps with high yield. Recrystallization of **17** from acetonitrile afforded the enantiomerically pure target compound.

Finally, we have recently carried out the catalytic asymmetric synthesis of 8-*epi*-fostriecin (**18**)—an analogue of the naturally occurring anticancer compound fostriecin (**19**)—using the *S*-selective cyanosilylation of *trans*-5-benzyloxy-3-penten-2-one catalyzed by Gd–**5** (**Figure 5**).[51]

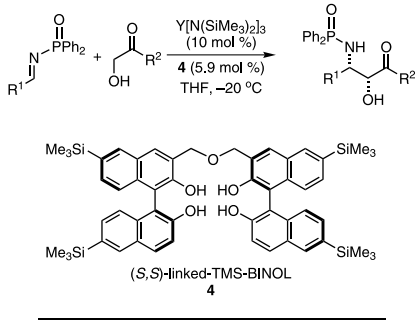
5. Catalytic Enantioselective Strecker Reaction of Keto Imines

Chiral, α,α-disubstituted α-amino acids are important building blocks for pharmaceuticals and synthetic peptides. The catalytic enantioselective Strecker reaction of keto imines is one of the most direct and practical methods for the synthesis of this class of compound.[52] The gadolinium complex prepared from $Gd(O\textit{i}\text{-}Pr)_3$ and **6** is an excellent catalyst for the enantioselective Strecker reaction of *N*-phosphinoylketo imines (**Table 2**).[53,54] In this reaction, protic additives, such as 2,6-dimethylphenol or HCN, greatly improve the enantioselectivity, substrate generality, and catalyst activity. Excellent enantioselectivity is obtained from a wide range of substrates including aromatic, heteroaromatic, cyclic, α,β-unsaturated, and aliphatic keto imines. The optimal reaction conditions consist of 0.1 mol % catalyst, 2.5 mol % TMSCN, and 150 mol % HCN. This method is the most general catalytic enantioselective Strecker reaction of keto imines reported to date. ESI-MS studies suggest that the protic additive functions by changing the active catalyst to a proton-containing 2:3 complex (**20**), which is more active and enantioselective than the trimethylsilylated 2:3 complex **8**. The internal proton of **20** presumably facilitates product dissociation from the catalyst, and promotes the regeneration of the active catalyst.

This catalytic enantioselective Strecker reaction of keto imines was applied to the synthesis of sorbinil, a therapeutic agent for chronic complications from diabetes mellitus (**Scheme 6**).[53b] Sorbinil contains a chiral spirohydantoin structure, and its biological activity resides in the *S* enantiomer. The Strecker reaction of **21** proceeded using 1 mol % of catalyst, and the product **22** was obtained in quantitative yield and 98% ee. Enantiomerically pure **22** was obtained after one recrystallization. Acid hydrolysis and hydantoin formation produced sorbinil in 67% yield from **22**. Very recently, we completed the total synthesis of (+)-lactacystin, a potent and selective proteosome inhibitor, by constructing the chiral, tetrasubstituted C-5 carbon with the aid of the catalytic enantioselective Strecker reaction of keto imines.[55]

6. Catalytic Enantioselective Conjugate Addition of Cyanide to α,β-Unsaturated Pyrrole Amides

Recently, we developed a catalytic, enantioselective conjugate addition of cyanide to α,β-unsaturated *N*-acylpyrroles using the

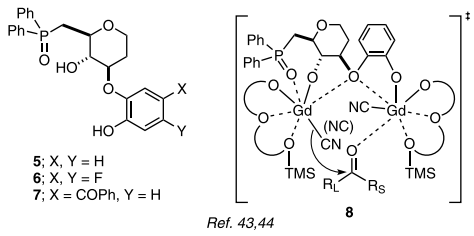


R^1	R^2	Time	Yield	Syn/Anti	ee[a]
4-$MeOC_6H_4$	Ph	84 h	90%	95:5	94%
Ph	furan-2-yl	60 h	94%	94:6	93%
Ph	thien-2-yl	36 h	95%	95:5	92%
furan-2-yl	Ph	39 h	93%	95:5	96%
(*E*)-PhCH=CH	Ph	60 h	87%	96:4	95%

[a] Of the syn diastereomer.

Ref. 41a

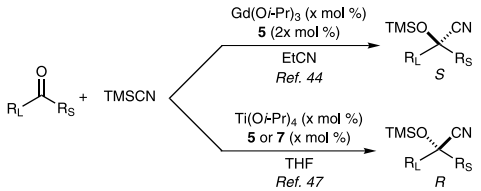
eq 9



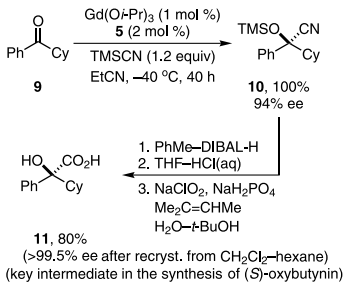
Ref. 43,44

Figure 4. D-Glucose-Derived Ligands and Proposed Transition State for the Catalytic, Enantioselective Cyanosilylation of Ketones.

Table 1. The Catalytic, Enantioselective Cyanosilylation of Ketones

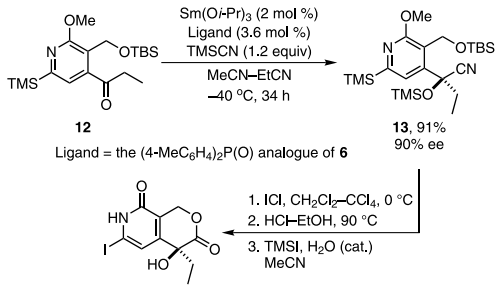


R_L	R_S	Metal Source	Ligand	X	Temp (°C)	Time (h)	Yield (%)	ee (%)
Ph	Me	$Gd(O\textit{i}\text{-}Pr)_3$	**5**	1	–40	16	93	91
Ph	Me	$Ti(O\textit{i}\text{-}Pr)_4$	**7**	1	–20	88	92	94
4-ClC_6H_4	Me	$Gd(O\textit{i}\text{-}Pr)_3$	**5**	5	–60	55	89	89
4-ClC_6H_4	Me	$Ti(O\textit{i}\text{-}Pr)_4$	**7**	1	–25	92	72	90
Ph	Et	$Gd(O\textit{i}\text{-}Pr)_3$	**5**	5	–60	14	93	97
Ph	Et	$Ti(O\textit{i}\text{-}Pr)_4$	**7**	1	–10	92	90	92
(*E*)-PhC=CH	Me	$Gd(O\textit{i}\text{-}Pr)_3$	**5**	5	–60	6.5	94	87
(*E*)-PhC=CH	Me	$Ti(O\textit{i}\text{-}Pr)_4$	**5**	10	–50	88	72	91
(*E*)-*n*-C_5H_{11}CH=CH	Me	$Gd(O\textit{i}\text{-}Pr)_3$	**5**	5	–60	19	96	76
(*E*)-*n*-C_5H_{11}CH=CH	Me	$Ti(O\textit{i}\text{-}Pr)_4$	**7**	2.5	–30	92	72	90
$PhCH_2CH_2$	Me	$Gd(O\textit{i}\text{-}Pr)_3$	**5**	5	–60	1	97	66
$PhCH_2CH_2$	Me	$Ti(O\textit{i}\text{-}Pr)_4$	**7**	10	–50	36	92	85
n-C_5H_{11}	Me	$Gd(O\textit{i}\text{-}Pr)_3$	**5**	5	–60	0.5	79	47
n-C_5H_{11}	Me	$Ti(O\textit{i}\text{-}Pr)_4$	**7**	2.5	–45	92	80	82



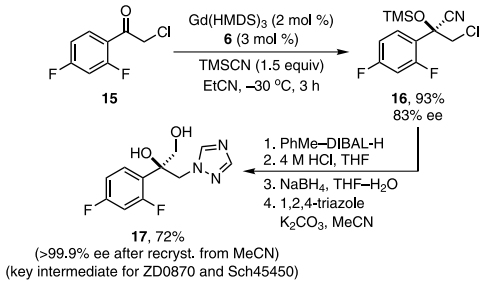
Ref. 48

Scheme 3. Application of the *S*-Selective, Catalytic Cyanosilylation of Ketones to the Synthesis of a Key Intermediate for (*S*)-Oxybutynin.



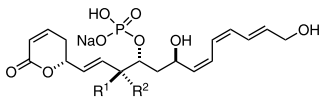
Ref. 49

Scheme 4. Application of the *S*-Selective, Catalytic Cyanosilylation of Ketones to the Synthesis of a Key Intermediate for Camptothecin.



Ref. 50

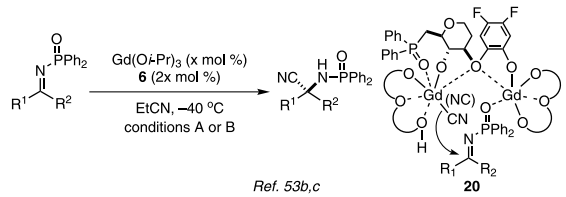
Scheme 5. Application of the *S*-Selective, Catalytic Cyanosilylation of Ketones to the Synthesis of a Key Intermediate for Both ZD0870 and Sch45450.



Ref. 51

Figure 5. The Catalytic, Asymmetric Synthesis of 8-*epi*-Fostriecin Starting with the *S*-Selective Cyanosilylation of *trans*-5-Benzyloxy-3-penten-2-one.

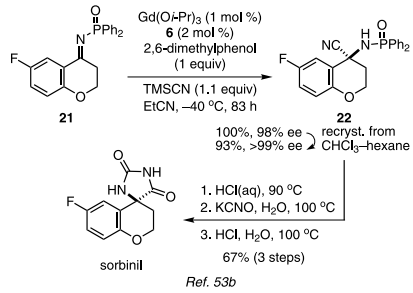
Table 2. Catalytic, Enantioselective Strecker Reaction of Keto Imines



Ref. 53b,c

R¹	R²	Cond.	X	Time (h)	Yield (%)	ee (%)
Ph	Me	A	1.0	30	94	92
Ph	Me	B	0.1	19	97	90
Ph	Et	A	1.0	31	97	95
thien-3-yl	Me	A	1.0	21	93	93
thien-3-yl	Me	B	1.0	3	99	99
3,4-dihydro-(2*H*)-naphthylidin-1-yl	—	A	1.0	22	92	92
n-C_5H_{11}	Me	A	1.0	43	73	90
i-Pr	Me	A	2.5	2.5	91	80
(*E*)-PhCH=CH	Me	A	1.0	38	93	96

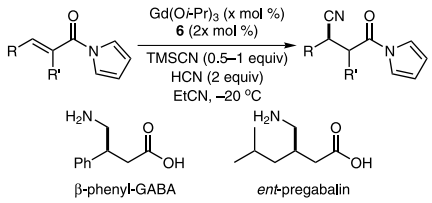
[a] Conditions: A = TMSCN (1.5 equiv), 2,6-dimethylphenol (1 equiv). B = TMSCN (2.5 to ~5 mol %), HCN (150 mol %).



Ref. 53b

Scheme 6. Catalytic, Enantioselective Strecker Reaction in the Synthesis of Sorbinil.

Table 3. Catalytic, Enantioselective Conjugate Addition of Cyanide to α,β-Unsaturated Pyrrole Amides



Ref. 56

R	R′	X	Time (h)	Yield (%)	ee (%)	Note
Ph	H	10	98	90	91	*a*
4-MeOC_6H_4	H	10	98	85	90	*a*
Pr	H	5	42	91	98	*b*
i-Bu	H	5	42	89	97	*b*
t-Bu	H	5	88	87	90	*b*
cyclohexen-1-yl	H	20	139	78	93	*a*
–$(CH_2)_3$–		5	8	99 (1.1:1)[c]	88:83	*a,d*

[a] 1 equiv of TMSCN was used. [b] 0.5 equiv of TMSCN was used. [c] Ratio of trans:cis. [d] The reaction was performed at room temperature.

Gd–**6** complex (**Table 3**).[56] This type of reaction is useful for the synthesis of a wide variety of chiral building blocks including chiral γ-amino acids. Prior to our contribution, Jacobsen's group reported the first such catalytic enantioselective conjugate addition of cyanide using a chiral salen–Al complex.[7a,57] Although excellent enantioselectivity was observed for β-aliphatic-substituted substrates, those with a β-aryl or vinyl substituents were unreactive. Our catalyst system has overcome this limitation: products were obtained with high enantioselectivity from a wide range of substrates including β-aliphatic, aromatic, and alkenyl *N*-acylpyrroles in the presence of TMSCN and HCN. Due to the versatility of cyanides and *N*-acylpyrroles, pharmaceuticals and their lead compounds such as pregabalin, an anticonvulsant drug, and β-phenyl-GABA, a $GABA_B$ receptor agonist, were synthesized using this reaction as the key step.[56]

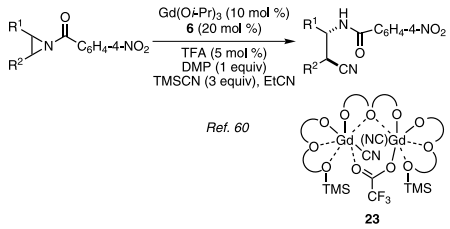
7. Catalytic Enantioselective Ring Opening of Meso Aziridines with TMSCN

Chiral β-amino acids are important building blocks for the synthesis of natural products and pharmaceuticals. Among them, chiral cyclic β-amino acids are currently of great interest due to the recent finding that peptides composed of these amino acids can act as foldamers with a well-defined secondary structure.[58] Despite their emerging importance, diastereoselective reactions relying on stoichiometric amounts of chiral amines had been the only methods available for the synthesis of chiral cyclic β-amino acids.[59] Recently, we reported the first catalytic enantioselective ring-opening reaction of meso aziridines by cyanide using the Gd–**6** complex (**Table 4**).[60] The addition of a catalytic amount of trifluoroacetic acid (TFA) reproducibly improved the enantioselectivity of the reaction. ESI-MS studies showed TFA to be involved in the catalyst's metal–ligand 2:3 complex. TFA is believed to bridge the two gadolinium atoms of the catalyst and stabilize the enantioselective 2:3 complex (**23**). In addition, the enhancement of the Lewis acidity of gadolinium, and the fine-tuning of the relative positions of the two gadolinium atoms, may well be contributing to the improved enantioselectivity. The ring-opened products of cyanide addition were easily converted into chiral, cyclic β-amino acids in high yields through acid hydrolysis (**Scheme 7**).[60]

8. Conclusions

The recent development of enantioselective reactions catalyzed by chiral poly(rare-earth metal) complexes is reviewed. Broad substrate generality and excellent enantioselectivity stem from the dual activation of both electrophiles and nucleophiles, at defined positions, by the bifunctional asymmetric catalysts. These catalytic enantioselective reactions are practical, and can be utilized for the preparative-scale synthesis of pharmaceuticals and their lead compounds. The characteristics of rare-earth metal alkoxides (or phenoxides) such as mild Lewis acidity, significant Brønsted basicity, rapid ligand-exchange rates, and facile formation of aggregates are essential properties that allow these new asymmetric catalysts to function. Investigations aimed at broadening the applicability of chiral poly(rare-earth metal) complexes to asymmetric catalysis are ongoing in our group.

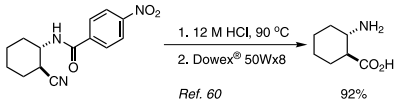
Table 4. Catalytic, Enantioselective Ring Opening of Aziridines with TMSCN



23

R^1	R^2	Temp (°C)	Time (h)	Yield (%)	ee (%)	Note
$(CH_2)_4$		0	20	94 (79)	87 (>99)	*a*
$(CH_2)_3$		rt	69	81	93	*b*
$(CH_2)_5$		60	64	92 (58)	80 (>99)	*a,c*
$CH_2CH{=}CHCH_2$		rt	95	85 (66)	82 (>99)	*a*
o-$(CH_2C_6H_4CH_2)$		rt	42	91	83	*d*
CH_2OCH_2		60	96	92	88	*b*
$CH_2N(Cbz)CH_2$		60	23	89	84	*b*
Me	Me	rt	39	93	85	
Ph	Ph	rt	96	44:37	90:89	*e*

[a] The yield and ee after recrystallization are shown in parentheses. [b] With 20 mol % Gd(O*i*-Pr)$_3$ and 40 mol % **6**. [c] 2.5 mol % TFA was used. [d] EtCN–CH_2Cl_2 1:2 was used as solvent. [e] Yields and ee's of the two diastereomers.



Scheme 7. One Example of the Conversion of β-Amido Nitriles into β-Amino Acids.

9. Acknowledgements

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About the Authors

Masakatsu Shibasaki was born in 1947 in Saitama, Japan, and received his Ph.D. degree from the University of Tokyo in 1974 under the direction of the late Professor Shun-ichi Yamada. Following postdoctoral studies with Professor E. J. Corey at Harvard University, he returned to Japan in 1977 and joined Teikyo University as an associate professor. In 1983, he moved to Sagami Chemical Research Center as a group leader and, in 1986, took up a professorship at Hokkaido University. In 1991, he accepted a position as professor at the University of Tokyo. He was a visiting professor at Philipps-Universität Marburg in 1995. He has received the Pharmaceutical Society of Japan Award for Young Scientists (1981), the Inoue Prize for Science (1994), the Fluka Prize (Reagent of the Year, 1996), the Elsevier Award for Inventiveness in Organic Chemistry (1998), the Pharmaceutical Society of Japan Award (1999), the Molecular Chirality Award (1999), the Naito Foundation Research Prize for 2001 (2002), the ACS Arthur C. Cope Senior Scholar Award (2002), the National Prize of Purple Ribbon (2003), the Toray Science Award (2004), and the Japan Academy Prize (2005). Moreover, he has been selected as a Fellow of the Royal Society of Chemistry (1997) and an Honorary Fellow of the Chemical Research Society of India (2003). His research interests are in the areas of asymmetric catalysis, including the asymmetric Heck reaction and reactions promoted by asymmetric bifunctional complexes, and the medicinal chemistry of biologically significant compounds.

Motomu Kanai was born in 1967 in Tokyo, Japan, and received his Ph.D. degree from Osaka University in 1995 under the direction of Professor Kiyoshi Tomioka. This was followed by postdoctoral studies with Professor Laura L. Kiessling at the University of Wisconsin, Madison. In 1997, he returned to Japan and joined Professor Shibasaki's group at the University of Tokyo as an assistant professor. He is currently an associate professor in Shibasaki's group, and a PREST (Precursory Research for Embryonic Science and Technology) member of JST (Japan Science and Technology Corporation). He has received the Pfizer Award for Synthetic Organic Chemistry (2000), the Pharmaceutical Society of Japan Award for Young Scientists (2001), and the Thieme Journals Award (2003).

Shigeki Matsunaga was born in 1975 in Kyoto, Japan. He received his Ph.D. degree in 2003, with a thesis on the development of a novel chiral ligand, linked-BINOL, from the University of Tokyo under the direction of Professor M. Shibasaki. He started his academic career in 2001 as an assistant professor in Professor Shibasaki's group at the University of Tokyo. He is the recipient of the 2001 Yamanouchi Award for Synthetic Organic Chemistry, Japan. His current research interest is in the development and mechanistic studies of new catalytic reactions, including asymmetric catalysis.

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The Ultimate Toolkit for Asymmetric Catalysis

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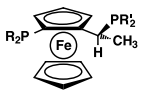
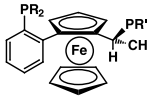
Sigma-Aldrich, in collaboration with Solvias, is proud to present the Chiral Ligands Kit—the ultimate toolkit for asymmetric catalysis!

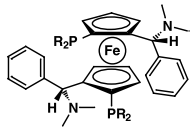
The Solvias Chiral Ligands Kit is designed to allow rapid screening of chiral catalysts, and contains sets of the well-known Solvias ligand families below.



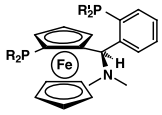
Josiphos



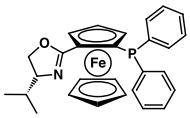
Walphos



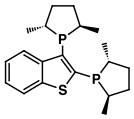
Mandyphos



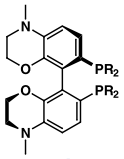
Taniaphos



Naud



Butiphane



Solphos

All products in the kit are 100-mg sample sizes and available in both enantiomeric forms, giving you access to a total of 80 products.

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All 80 ligands are available from Sigma-Aldrich individually in 100-mg, 500-mg, 1-g, and 5-g package sizes for easy reordering.

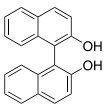
Solvias Chiral Ligands Kit	
12000-1KT	1 Kit

For detailed information about the ligands kit and individual components, please visit **sigma-aldrich.com/solviasligands**.

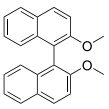
BINOLs for Asymmetric Catalysis

- **High levels of enantiocontrol in many synthetic transformations**
- **Competitively priced**
- **Available in both enantiomeric forms**

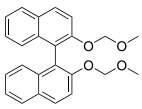
BINOLS are a privileged class of ligands within the field of asymmetric catalysis. These ligands have exhibited high levels of enantiocontrol in many synthetic transformations. Sigma-Aldrich is pleased to offer a comprehensive range of BINOL derivatives for your catalysis research efforts.



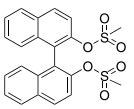
246948 (*R*)
246956 (*S*)



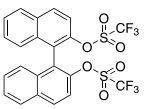
595403 (*R*)
595519 (*S*)



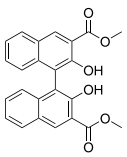
631582 (*R*)
631574 (*S*)



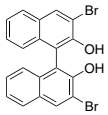
631795 (*R*)
631787 (*S*)



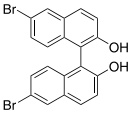
440590 (*R*)
431893 (*S*)



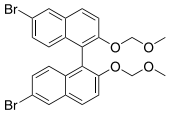
579343 (*R*)
579971 (*S*)



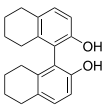
595721 (*R*)
595837 (*S*)



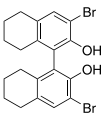
482617 (*R*)
482625 (*S*)



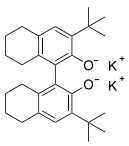
631604 (*R*)
631590 (*S*)



540560 (*R*)
540579 (*S*)



540587 (*R*)
540595 (*S*)



77939 (*R*)

For more in-depth information, please visit sigma-aldrich.com/chemfiles.

Additional information covering the chemistry of (*R*)- and (*S*)-BINOL can be found in a comprehensive review: Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857.

New Selective Reagents for Oxidation and Reduction

Stabilized 2-Iodoxybenzoic Acid (SIBX)

Since 1994,[1] 2-iodoxybenzoic acid (IBX) has been well recognized as a very powerful and selective oxidizing agent. Similarly to the Dess–Martin periodinane, IBX is an environmentally benign alternative to metal-based oxidizing agents. However, IBX is not often used, due to the fact that it is an impact-sensitive explosive material, which prevents its shipping and transport, as well as its application in industry.[2] Sigma-Aldrich is pleased to introduce a stabilized formulation of IBX (SIBX) that displays none of the explosive properties of IBX, while maintaining excellent reactivity and selectivity.

SIBX has demonstrated use in the:

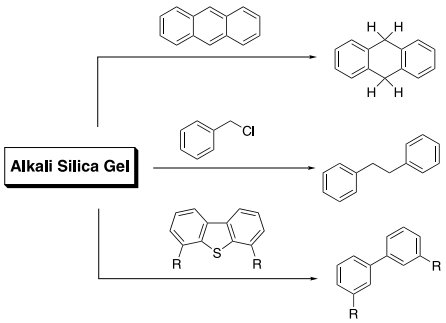
- Oxidation of alcohols to carbonyl compounds.[3]
- Oxidative demethylation of 2-methoxyphenols.[3]
- Oxidative dearomatization of 2-alkylphenols into orthoquinols (alternative to Barton or Adler oxidation).[4]

2-Iodoxybenzoic acid, stabilized (45 wt. % IBX)

[*61717-82-6*]
$C_7H_5IO_4$
FW: 280.02

661384-1G	1 g
661384-10G	10 g

Alkali Silica Gels—Powerful Reducing Agents



Alkali metals have long been used in synthetic chemistry as reducing agents, but their pyrophoric nature has often prevented their use in larger-scale reactions. The chemical company, SiGNa Chemistry, has recently developed and reported a series of alkali metals and alloys absorbed into silica gel to create stable, free-flowing powders.[5] These powders are an attractive alternative to other reagents for desulfurizations, dehalogenations, and Birch reductions. Sigma-Aldrich is pleased to announce an agreement with SiGNa Chemistry to distribute research quantities of these powerful alkali silica gels for research applications.[6]

Alkali Silica Gels:

- Are nonpyrophoric and air-stable.
- Can be stored for months without any change in their reducing capacity.
- Eliminate the need for high-pressure and high-temperature systems.
- Are easily used in continuous-flow applications.
- Readily react with water to produce stoichiometric quantities of pure hydrogen gas.
- Also function well as drying agents.

NaK silica gel

K_2Na

660140-5G	5 g
660140-25G	25 g

NaK silica gel

Na_2K

660159-5G	5 g
660159-25G	25 g

Sodium silica gel Stage I

660167-5G	5 g
660167-25G	25 g

Sodium silica gel Stage II

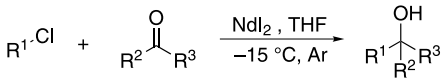
660175-5G	5 g
660175-25G	25 g

(1) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019. (2) Plumb, J. B.; Harper, D. J. *Chem. Eng. News* **1990**, *68*, 3. (3) Ozanne, A. et al. *Org. Lett.* **2003**, *5*, 2903. (4) Quideau, S. et al. *Arkivoc* [Online] **2003**(vi), 106. (5) Dye, J. L. et al. *J. Am. Chem. Soc.* **2005**, *127*, 9338. (6) Sold under authority of SiGNa Chemistry. Patent Pending.

Lanthanide Iodides for Reductions and Reductive Couplings

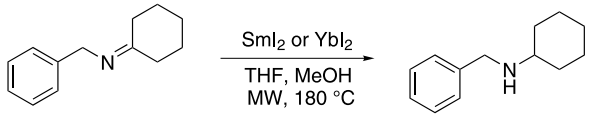
While SmI_2 has been widely employed as a reducing agent in various organic transformations,[1] other lanthanide diiodides (LnI_2) have only recently come into use.[2–7] Aldrich is pleased to announce the availability of a variety of lanthanide diiodides for application in organic reductions. These reagents span the breadth of the lanthanide series, bridging the gap in reduction potential between SmI_2/HMPA and alkali metal reagents. This variable reduction potential allows you to pick the metal iodide best suited to your application.

Evans and co-workers recently accomplished the reductive coupling of dialkyl ketones with alkyl chlorides by utilizing NdI_2 (**eq 1**).[2] The authors demonstrate that NdI_2 is as easy to use as SmI_2, while exhibiting greater reactivity.



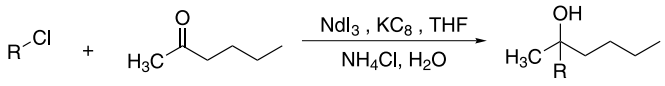
eq 1

Dahlén and co-workers recently utilized SmI_2 and YbI_2 to reduce the imine to the corresponding amine (**eq 2**). The transformation was accomplished at 180 °C, using microwave irradiation in THF-methanol.[3]



eq 2

Evans and Workman have demonstrated that NdI_2 can be generated in situ by reduction of the corresponding triiodide with potassium graphite. The subsequent reductive coupling proceeds with the same or better efficiency as when NdI_2 is used (**eq 3**).[4]



eq 3

Neodymium(II) iodide	
652431-1G	1 g
652431-5G	5 g

Neodymium(III) iodide, anhydrous, powder, 99.9%	
659215-1G	1 g
659215-5G	5 g

Samarium(II) iodide, anhydrous, powder, 99.9+%	
409340-1G	1 g
409340-5G	5 g

Samarium(II) iodide solution, 0.1 M in tetrahydrofuran	
347116-25ML	25 mL
347116-100ML	100 mL
347116-800ML	800 mL

Europium(II) iodide, anhydrous, powder, 99.9%	
474770-1G	1 g
474770-5G	5 g

Dysprosium(II) iodide, anhydrous, powder, ≥99.9%	
652423-1G	1 g
652423-5G	5 g

Thulium(II) iodide, anhydrous, powder, ≥99.9%	
653268-1G	1 g
653268-5G	5 g

Ytterbium(II) iodide, powder, 99.9+%	
494372-1G	1 g
494372-5G	5 g

(1) (a) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351. (b) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745. (c) Soderquist, J. A. *Aldrichimica Acta* **1991**, *24*, 15. (2) Evans, W. J. et al. *Org. Lett.* **2003**, *5*, 2041. (3) Dahlén, A. et al. *Chem.–Eur. J.* **2005**, *11*, 3279. (4) Evans, W. J.; Workman, P. S. *Organometallics* **2005**, *24*, 1989. (5) Evans, W. J. et al. *J. Am. Chem. Soc.* **2000**, *122*, 11749. (6) Evans, W. J.; Allen, N. T. *J. Am. Chem. Soc.* **2000**, *122*, 2118. (7) Saikia, P. et al. *Tetrahedron Lett.* **2002**, *43*, 7525.

More New Products from Aldrich R&D

New Synthetic Reagents

Potassium hydrogenfluoride solution, 3 M in water

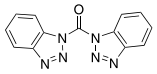
663883
[*7789-29-9*]
KHF_2
FW: 78.10

25 mL
100 mL
500 mL

An easily handled aqueous solution for the preparation of potassium organotrifluoroborates that are used in the Suzuki coupling.

1,1′-Carbonylbisbenzotriazole preparation, 40 wt. % slurry in water

660086
[*68985-05-7*]
$C_{13}H_8N_6O$
FW: 264.24



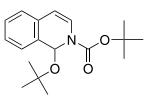
5 g

A useful reagent for the preparation of unsymmetrical di-, tri-, and tetra-substituted ureas.[1,2]

(1) Katritzky, A. R. et al. *J. Org. Chem.* **1997**, *62*, 4155. (2) Nieuwenhuijzen, J. W. et al. *Tetrahedron Lett.* **1998**, *39*, 7811.

Boc-1-*tert*-butoxy-1,2-dihydroisoquinoline, 95%

658723
[*404586-94-3*]
$C_{18}H_{25}NO_3$
FW: 303.40



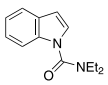
5 g
25 g

This novel and chemoselective *tert*-butoxycarbonylation reagent can effectively protect aromatic and aliphatic amines, amino acids, phenols, and thiophenols without the need for added base.

Ouchi, H. et al. *Org. Lett.* **2002**, *4*, 585.

N,*N*-Diethyl-1*H*-indole-1-carboxamide, 97%

663786
[*119668-50-7*]
$C_{13}H_{16}N_2O$
FW: 216.28



5 g
25 g

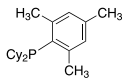
This protected indole undergoes selective lithiation at the 2 and 7 positions, followed by reaction with a variety of electrophiles.[1,2]

(1) Hartung, C. G. et al. *Org. Lett.* **2003**, *5*, 1899. (2) Castells, J. et al. *Tetrahedron* **1991**, *47*, 7911.

Bulky Phosphine Ligands

Dicyclohexyl(2,4,6-trimethylphenyl)phosphine, 97%

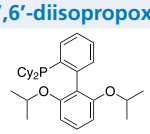
651877
[*870703-48-3*]
$C_{21}H_{33}P$
FW: 316.46



1 g
10 g

2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl, 95%

663131
[*787618-22-8*]
$C_{30}H_{43}O_2P$
FW: 466.63

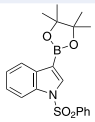


1 g

Boronic Acids and Esters

1-(Phenylsulfonyl)-3-indoleboronic acid pinacol ester, 97%

654280
[*870717-93-4*]
$C_{20}H_{22}BNO_4S$
FW: 383.27



1 g
5 g

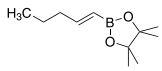
Isopropenylboronic acid pinacol ester, 95%

663212
[*126726-62-3*]
$C_9H_{17}BO_2$
FW: 168.04

5 g

trans-1-Pentenylboronic acid pinacol ester, 97%

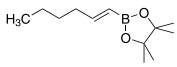
665169
[*161395-96-6*]
$C_{11}H_{21}BO_2$
FW: 196.09



1 g
5 g

trans-1-Hexenylboronic acid pinacol ester, 97%

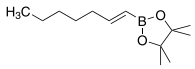
663743
[*126688-97-9*]
$C_{12}H_{23}BO_2$
FW: 210.12



1 g
5 g

trans-1-Heptenylboronic acid pinacol ester, 97%

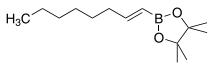
662992
[*169339-75-7*]
$C_{13}H_{25}BO_2$
FW: 224.15



5 g

trans-1-Octenylboronic acid pinacol ester, 95%

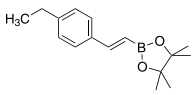
663050
[*83947-55-1*]
$C_{14}H_{27}BO_2$
FW: 238.17



1 g
10 g

trans-2-(4-Ethylphenyl)vinylboronic acid pinacol ester, 97%

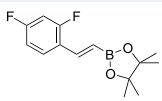
662798
[*870717-91-2*]
$C_{16}H_{23}BO_2$
FW: 258.16



1 g
5 g

trans-2-(2,4-Difluorophenyl)vinylboronic acid pinacol ester, 96%

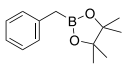
664871
[*736987-78-3*]
$C_{14}H_{17}BF_2O_2$
FW: 266.09



1 g
5 g

Benzylboronic acid pinacol ester, 96%

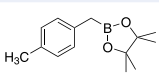
659207
[*87100-28-5*]
$C_{13}H_{19}BO_2$
FW: 218.10



1 g
10 g

4-Methylbenzylboronic acid pinacol ester, 97%

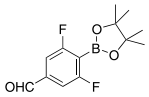
663298
[*356570-52-0*]
$C_{14}H_{21}BO_2$
FW: 232.13



1 g
5 g

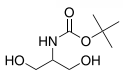
2,6-Difluoro-4-formylphenylboronic acid pinacol ester, 97%

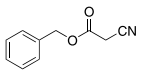
663514
[*870717-92-3*]
$C_{13}H_{15}BF_2O_3$
FW: 268.06

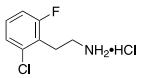


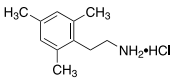
1 g
5 g

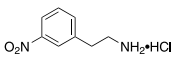
Organic Building Blocks

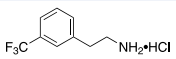
N-Boc-serinol, 97%
661074
[*125414-41-7*]
$C_8H_{17}NO_4$
FW: 191.22

1 g
5 g

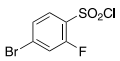
Benzyl cyanoacetate, 97%
663824
[*14447-18-8*]
$C_{10}H_9NO_2$
FW: 175.18

5 g
25 g

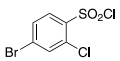
2-(2-Chloro-6-fluorophenyl)ethylamine hydrochloride, 97%
661678
[*870717-94-5*]
$C_8H_{10}Cl_2FN$
FW: 210.08

1 g

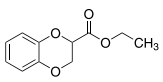
2,4,6-Trimethylphenethylamine hydrochloride, 97%
661651
[*3167-10-0*]
$C_{11}H_{18}ClN$
FW: 199.72

1 g
10 g

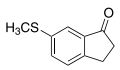
3-Nitrophenethylamine hydrochloride, 97%
661686
[*19008-62-9*]
$C_8H_{11}ClN_2O_2$
FW: 202.64

1 g

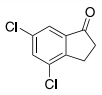
3-(Trifluoromethyl)phenethylamine hydrochloride, 97%
661570
[*141029-17-6*]
$C_9H_{11}ClF_3N$
FW: 225.64

1 g
10 g

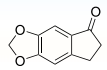
4-Bromo-2-fluorobenzenesulfonyl chloride, 97%
554235
[*216159-03-4*]
$C_6H_3BrClFO_2S$
FW: 273.51

1 g
5 g

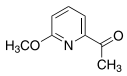
4-Bromo-2-chlorobenzenesulfonyl chloride, 96%
558729
[*351003-52-6*]
$C_6H_3BrCl_2O_2S$
FW: 289.96

1 g
5 g

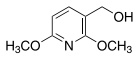
Ethyl 1,4-benzodioxan-2-carboxylate, 97%
662259
[*4739-94-0*]
$C_{11}H_{12}O_4$
FW: 208.21

5 g
25 g

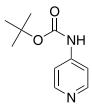
6-(Methylthio)-1-indanone, 96%
656143
[*138485-82-2*]
$C_{10}H_{10}OS$
FW: 178.25

1 g

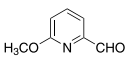
4,6-Dichloro-1-indanone, 97%
656798
[*52397-81-6*]
$C_9H_6Cl_2O$
FW: 201.05

1 g
5 g

5,6-Methylenedioxy-1-indanone, 97%
657573
[*6412-87-9*]
$C_{10}H_8O_3$
FW: 176.17

1 g
5 g

2-Acetyl-6-methoxypyridine, 97%
662542
[*21190-93-2*]
$C_8H_9NO_2$
FW: 151.16

1 g
5 g

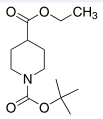
2,6-Dimethoxypyridine-3-methanol, 97%
663735
[*562840-47-5*]
$C_8H_{11}NO_3$
FW: 169.18

1 g
5 g

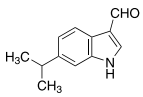
4-(Boc-amino)pyridine, 97%
658707
[*98400-69-2*]
$C_{10}H_{14}N_2O_2$
FW: 194.23

5 g
25 g

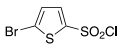
6-Methoxy-2-pyridinecarboxaldehyde, 97%
662933
[*54221-96-4*]
$C_7H_7NO_2$
FW: 137.14

1 g
5 g

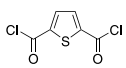
2-Fluoro-3-pyridinecarboxaldehyde, 97%
664111
[*36404-90-7*]
C_6H_4FNO
FW: 125.10

5 g

Ethyl *N*-Boc-piperidine-4-carboxylate, 97%
665150
[*142851-03-4*]
$C_{13}H_{23}NO_4$
FW: 257.33

5 g
25 g

6-Isopropylindole-3-carboxaldehyde, 97%
659800
[*170489-34-6*]
$C_{12}H_{13}NO$
FW: 187.24

1 g

5-Bromothiophene-2-sulfonyl chloride, 97%
636223
[*55854-46-1*]
$C_4H_2BrClO_2S_2$
FW: 261.54

5 g
25 g

2,5-Thiophenedicarbonyl dichloride, 97%
662941
[*3857-36-1*]
$C_6H_2Cl_2O_2S$
FW: 209.05

1 g
5 g

4-Methylthiazole-2-carbonitrile, 97%
664103
[*100516-98-1*]
$C_5H_4N_2S$
FW: 124.16

1 g
5 g

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Organic Synthesis and Device Testing for Molecular Electronics

Dr. Dustin K. James

Dr. James M. Tour

*Dustin K. James and James M. Tour**
Departments of Chemistry and Mechanical Engineering and Materials Science
Smalley Institute for Nanoscale Science and Technology, MS 222
Rice University
6100 Main Street
Houston, TX 77005, USA
Email: tour@rice.edu

Outline

1. Introduction

The rapidly developing field of ultra-small electronics is one of the driving forces behind the interest in the synthesis of new molecules as candidates for molecular electronics.[1–8] Molecular electronics is of interest because standard fabrication methods are hitting limits in scaling. We have covered, in other reviews, some of the syntheses of these molecules as well as the large body of work on the theoretical aspects of molecular conduction.[1,9] However, the limitations of the present "top-down" method of producing semiconductor-based devices have been the subject of debate and conjecture since Gordon Moore's prediction in 1965 that the number of components per integrated circuit would double every 18 months.[10] It was thought that the inherent limitations of the existing technology would lead to a dead end in the next few years with respect to the continued shrinking of circuitry using top-down methods. For instance, silicon's band structure disappears when silicon layers are just a few atoms thick. Lithographic techniques that are used to produce the circuitry on the silicon wafers are limited by the wavelengths at which they operate. Interestingly, leaders in the semiconductor-manufacturing world continue to make advances that appear to be pushing "Moore's Law" beyond its prior perceived limits. Intel® has declared that Moore's Law is here to stay for the next 15–20 years.[11] In the commercial technology of 2004, the copper wires in Intel®'s Pentium® 4 logic chip being manufactured in their newest 300-mm-wafer fabrication facility in Ireland are 90 nm wide.[12] Strained silicon[13] is but one of several approaches taken by the industry to modify its present silicon-based processes to meet the demands of the development roadmap.

For comparison's sake, a typical molecule synthesized in our laboratory is calculated to be 0.3 nm wide and 2.5 nm in length.[4] It would take 300 of these molecules, side by side, to span the 90-nm width of a metal line in the most advanced logic chip being made today. The small size of these molecules is emphasized when one considers that 500 g (about one mole) of this wire would contain 6×10^{23} molecules, or more molecules than the number of transistors ever made in the history of the world. This amount of material could be produced using relatively small, 22-L laboratory reaction flasks. Changing the physical characteristics of the molecule is as easy as changing the raw materials used to make it. The small size, the potential of synthesizing huge numbers in small reactors, and the ease of modification of the physical characteristics of the molecules are good reasons for pursuing molecular electronics research. As an example of how far the technology has come, molecular electronics is discussed in the "emerging research devices" section of a recent International Technology Roadmap for Semiconductors,[14,15] and new molecules are a large part of the emerging technology.

We will discuss in the remainder of this review the synthesis and use of discrete molecules, not crystals or films, in molecular electronics devices. The extremely interesting inorganic crystalline nanowires being developed by Lieber and others[16–19] may eventually be used in molecular electronics based circuitry. These nanowires are comprised of crystalline phases and not discrete molecules, and are thus precluded from our definition of molecules for molecular electronics. Most of the work discussed in this review was done in our own laboratories in the past five years. We will first cover the several classes of molecules made

for testing in molecular electronics devices, follow with a short review of molecular electronics test beds,[20] and then discuss in detail two test beds developed in our laboratories.

1.1. Oligo(2,5-thiophene ethynylenes) (OTEs)

Oligo(2,5-thiophene ethynylenes) (OTEs) make up one of the first classes of compounds synthesized by our group.[21–24] These rigid-rod, oligomeric molecules, with thioester groups at one or both ends, are made through an iterative divergent–convergent synthesis that allows the rapid assembly of the products, doubling their length at each step. The longest such molecule synthesized is 12.8 nm in length. When deprotected in situ, the thiol groups enable the molecules to adhere to gold (or other metal) surfaces[25] and, therefore, serve as "alligator clips". When a large number of molecules bond to gold in a regular, packed array through this self-assembly process, the group of molecules is called a self-assembled monolayer (SAM). The bonding of the sulfur atom to gold enables the flow of electricity from the gold metal Fermi levels through the sulfur to the molecular orbitals formed by the conjugated portion of the molecule. The ethynyl units in between the aromatic moieties are used in order to maintain maximum overlap of the orbitals, and to keep the molecules in a rod-like shape. The various side chains appended to the thiophene cores are needed to increase the organic-solvent solubility of the compounds. Unfunctionalized, rigid-rod oligomers of this length suffer from severe solubility problems.

1.2. Oligo(1,4-phenylene ethynylenes) (OPEs)

Oligo(1,4-phenylene ethynylenes) (OPEs) form a second class of molecules that has been studied extensively in our laboratory[26] and by others.[27,28] As with OTEs, OPEs can be rapidly synthesized using transition-metal-catalyzed coupling reactions. In this case, the compounds were synthesized in both the solution phase and on a polymer-based solid resin. As with OTEs, C_{12} side chains were employed to impart organic-solvent solubility to the products. The use of longer side chains, such as C_{14} or longer, can result in side-chain interdigitation, which leads to insolubility problems rather than increasing the solubility.

To further explore the organic functionality necessary for molecules to carry an electric current, we synthesized a group of 2-terminal OPEs that contain interior methylene or ethylene group barriers to electrical conduction, and that could be tested using presently known test beds.[29] Each of these OPEs was synthesized using relatively straightforward chemistry, a fact that illustrates our earlier claim that it is easy to explore molecular wire space by changing just one or two aspects of the synthesis. We also synthesized a series of OPEs with different alligator clips to see what effect that variation would have on the conductance of the molecules.[30] Additionally, we have developed combinatorial chemistry routes that are capable of synthesizing tens to hundreds of new OPEs at a time.[31]

Our group's "mononitro" OPE[32] is a highly tested compound by many research groups because of its room-temperature, negative-differential-resistance (NDR) behavior.[33] In one synthesis of this OPE (**Scheme 1**), separation of the intermediates by chromatography had limited success; therefore, after a simple workup, each product mixture was used in the next step without further purification. After the deprotection step, purification was greatly simplified and intermediate **1** was isolated pure in 35% yield over 3 steps. The Sonogashira–Castro–Stephens coupling of **1** with **2** provided the mononitro OPE (**3**) in a moderate yield of 47%. The low yield in this last step is presumably due to the acetyl portion of the thioacetate moiety in the coupled product being susceptible to complexation with the Pd. When this occurs, the catalytic cycle is retarded. The yields of these coupling reactions can generally be increased by using higher percentages of triphenylphosphine as ligand. This observation supports our hypothesis that triphenylphosphine helps to keep the Pd in the catalytic cycle by preventing it from binding to the thioacetate functionality.

An improved synthesis of **3** alleviates the lack of selectivity in the initial coupling step of Scheme 1 by utilizing a monohaloarene coupling partner in each coupling reaction (**Scheme 2**).[32] Moreover, a key to obtaining the higher overall yield of **3** is to use 5 mol % Pd, 10 mol % Cu(I), and 20 mol % PPh_3 (dubbed the "5,10,20" method). A lower amount of PPh_3 (e.g., 12.5 mol %) normally results in much lower coupling yields as mentioned in the preceding paragraph. Although the synthesis depicted in Scheme 2 involves two additional steps as compared to that depicted in Scheme 1, the purification of the intermediates in Scheme 2 is simpler and less time-consuming, and the overall yield of **3** is higher. Moreover, the coupling of **12** with **2** led to the regioisomeric "nitro-up" OPE (**13**) in 73% yield (46% overall yield from **8**). The "5,10,20" catalyst loading method was utilized to synthesize intermediate **12**, a regioisomer of **1**, in 63% yield over four easy steps (**Scheme 3**).[32] A prior route had afforded **12** in only 32% yield over three arduous steps.[32]

The "5,10,20" catalyst loading method also proved its value in the synthesis of the analogue of **3** containing two terminal thiol groups. These thiol groups function as "alligator clips" when contacting two metal surfaces or cross-linking nanoparticles. The bis(thioacetyl) intermediate, **16**, was deprotected with sulfuric acid to give the corresponding bis(thiol) **17** in 77% yield (**Scheme 4**).[32] Compound **17** is desirable, since no in situ deprotection of the thiols is required when assembling the OPE onto metal surfaces or nanoparticles. This makes the assembly process simpler and faster. It is worth noting that the base-promoted deprotection of **16** failed, and that strict exclusion of air from the preparation of **17** is required, even during workup, because aromatic thiols are susceptible to air oxidation.

The synthesis of the unfunctionalized (**21**) and functionalized (**22**) dinitro-bipyridyl OPE derivative is described in **Scheme 5**.[34] Compound **21** was needed for cyclic voltammetry (CV) studies, whereas thioacetate **22** has shown interesting electrical properties in device testing.[35] OPE derivative **22** was found to have single-molecule device properties in a number of test beds, and its stability as a molecular switch is remarkable.[35] While the origin of this stability is still unknown, we are synthesizing several analogues to help pinpoint the salient features needed for stable switching and to further guide our theoretical efforts.

We recently reported the advantages of using the mononitro thiol–thioacetate terminated OPE **23** in the NanoCell, a functioning electronic memory device.[36] We also detailed the synthesis of **23** and the related compounds **24**–**28** (**Figure 1**).[37] Compounds **23**–**28** were designed to allow for self-assembly of the molecules via the free thiol[29,38] or nitrogen atom,[39] while protecting the other sulfur atom as a thioacetate to ensure molecular directionality and to inhibit cross-linking if SAM assembly on nanorods is desired. Following initial assembly, the acetate can be removed with NH_4OH or acid to afford the thiol, which can be assembled onto another metallic material.[40] For mononitro compounds **23**, **27**, and **28**, this process affords a monolayer with all the nitro groups oriented in a common direction. The orthogonal-functionalization approach was thus exploited in the synthesis of **23** (**Scheme 6**),[37] whereby a Boc-protected sulfur atom at one end was deprotected with

trifluoroacetic acid (TFA),[41] leaving the thioacetate moiety on the other end intact.

1.3. Oligo(1,4-phenylene vinylenes) (OPVs)

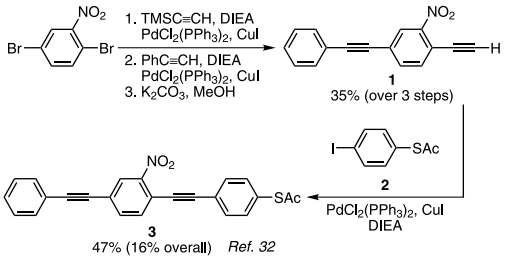
In order to design more efficient molecular devices (lower impedance, larger ON:OFF ratios, and longer electronic hold times), several features of the molecules needed to be optimized. To achieve the highest efficiency in terms of energy used, transport should be maximized across the molecular device. Recent work by Sikes et al. has shown that electrical transport is higher through oligo(phenylene vinylenes) (OPVs) than through OPEs.[42] Similar results, both theoretical and experimental, have been obtained by Kushmerick et al.[43] We have designed syntheses of OPVs using acetyl protecting groups,[34] but found them difficult to complete; therefore, the more robust ethyltrimethylsilyl group was used to protect the thiol. With the completed ethyltrimethylsilyl-protected compounds in hand, initial assembly experiments using in situ deprotection failed to form adequate SAMs. It was subsequently determined that the acetyl precursor was preferred for the in situ deprotection and assembly. The ethyltrimethylsilyl group was thus replaced with the acetyl group using excess TBAF for deprotection, followed by the addition of excess acetyl chloride. This approach afforded the desired acetyl-protected OPVs **37**, **38**, and **39** in moderate-to-high yields (**eq 1**).[34] In other work, we have used fluorous-mixture synthesis (FMS) to prepare a library of OPVs via combinatorial methods.[44]

1.4. Synthesis of U-Shaped Molecules

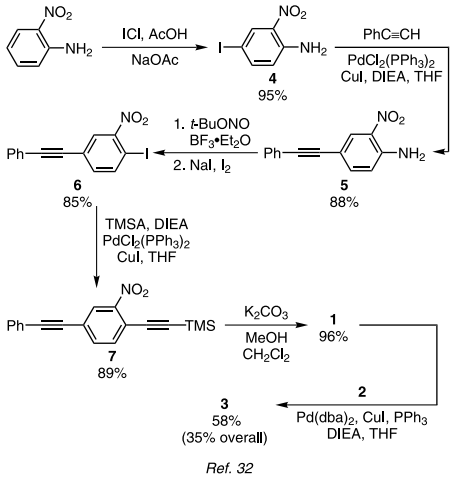
When evaluating an organic molecule for potential application as a molecular device component, the electronic nature of its functional groups as well as its molecular geometry determine, to a great extent, the electronic characteristics of the device. This motivated us to pursue the synthesis of new OPEs with extended conjugation exemplified by a 1,3-bridging aromatic ring linking two linear phenylethynyl backbones.[45] Six new "U-shaped" OPEs were synthesized, based on 3,3"-diethynyl[1,1';3',1"]terphenyl and 1,8-diethynylanthracene. We proposed that the analysis of U-shaped molecules would aid in developing a better understanding of the electronic properties of OPEs, when they are present in active molecular electronic devices. Two of the six U-shaped OPEs synthesized have nitro groups as potential redox centers, and all six targets are end-functionalized with acetyl-protected molecular alligator clips, which, upon deprotection, afford the thiolates or thiols for covalent surface attachment. The terphenyl targets have a relatively low rotational barrier and larger dihedral angles at the central terphenyl ring, whereas the anthracene derivatives have a higher rigidity based on the fully conjugated and planar 1,8-diethynylanthracene backbone. The protocol employed in the synthesis of this group of OPEs is illustrated by the preparation of **44** (**Scheme 7**).[45]

1.5. Synthesis of Fluorinated OPEs

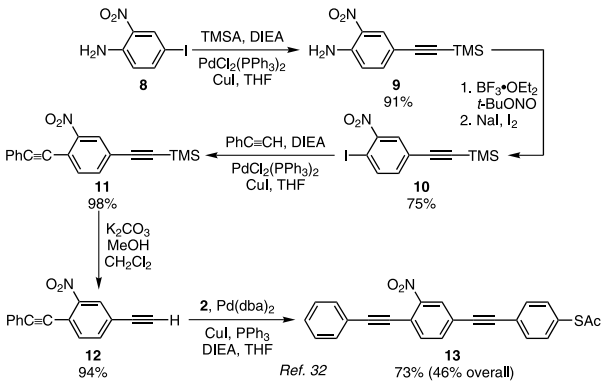
In general, the use of fluorocarbons as organic thin-film precursors produces materials with increased thermal stability and chemical resistance. The corresponding intermolecular attractive forces are less dominant, and thus the molecular interactions at the chemical interface become more pronounced, as compared to the nonfluorinated analogues. This is especially true for aromatic fluorine compounds. These characteristics could be critical for high-temperature processes like gas-phase physical vapor deposition (PVD). With the goal of producing several new molecular electronics candidates that would be appropriate for PVD applications, we synthesized nine oligomers.[46] Although



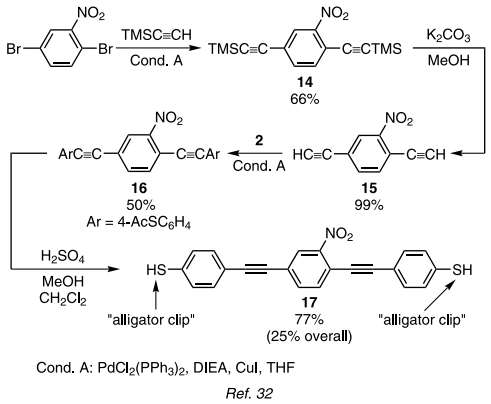
Scheme 1. Synthesis of "Mononitro" OPE **3**.



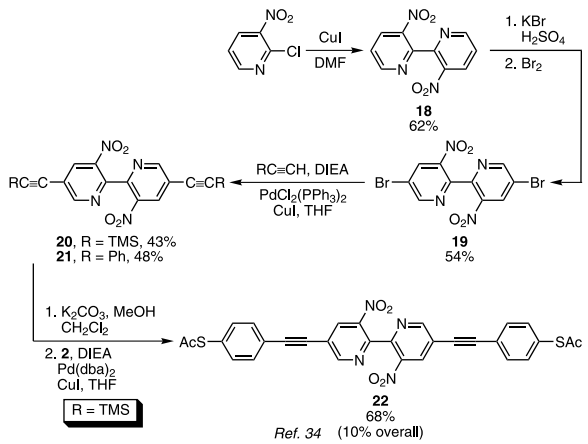
Scheme 2. An Improved Synthesis of "Mononitro" OPE **3**.



Scheme 3. Synthesis of "Nitro-Up" OPE Regioisomer **13**.



Scheme 4. Synthesis of OPE **17** Containing Two "Alligator Clips".



Scheme 5. Synthesis of the Dithioacetate Dinitrobipyridyl OPE **22**.

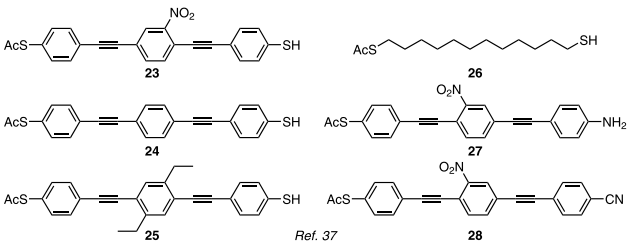
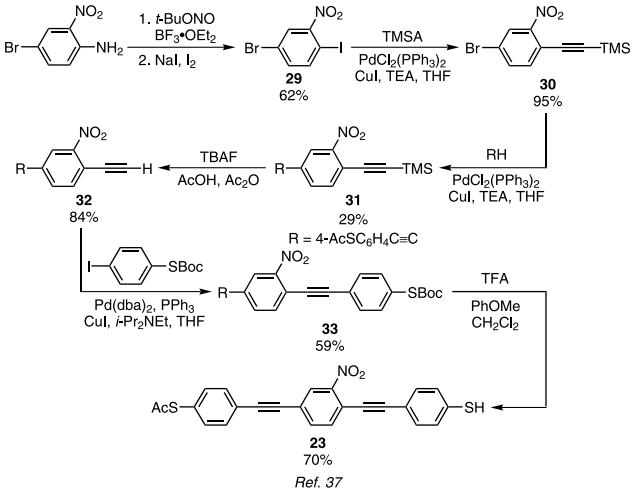
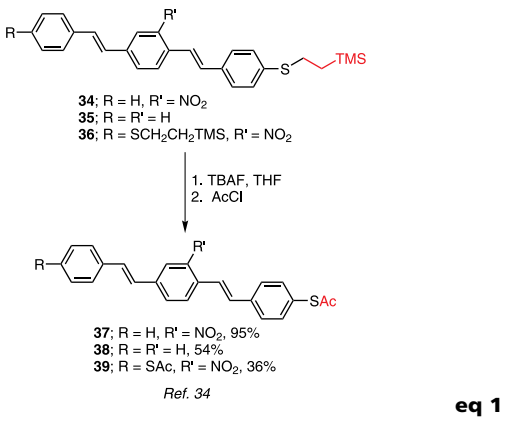


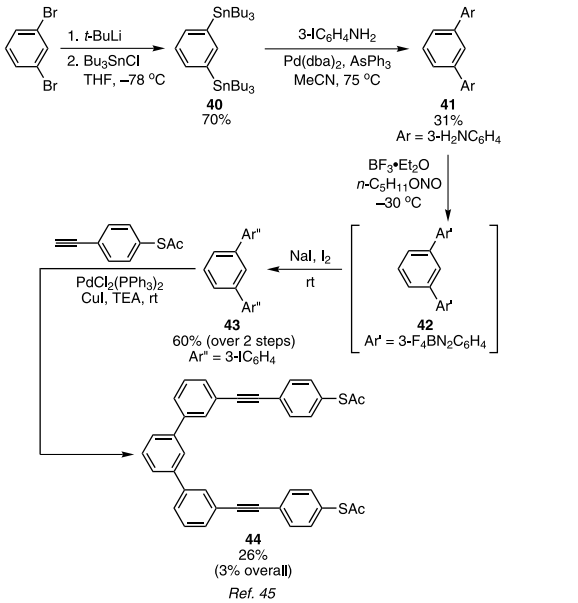
Figure 1. Structures of the Target Compounds **23**–**28**.



Scheme 6. The Orthogonal Functionalization Approach in the Synthesis of "Mononitro" OPE **23**.



eq 1



Scheme 7. Synthesis of U-Shaped OPE **44**.

most of the synthetic steps gave only moderate yields, their relative simplicity and ease prompted us to use them for the synthesis of several different functionalized cores and alligator clips, as exemplified by the synthesis of OPE **51** (**Scheme 8**).[46] The core of these oligomers was functionalized with nitro or amino groups, which have been widely reported to act as redox centers for switching effects, and the ends were functionalized with various alligator clips, including free thiols, nitriles, and pyridines for making molecular-scale junctions with several bulk contacts. Each molecule contained an electron-deficient pentafluoro aromatic ring as the dipole moment director.

1.6. Synthesis of Oligoanilines

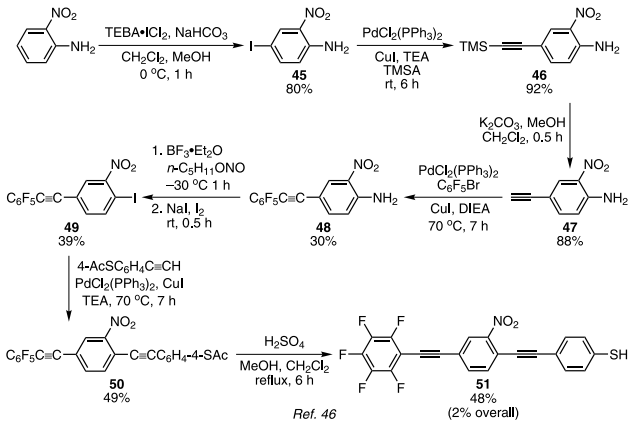
We have designed and synthesized oligoaniline-based molecules as a new class of potential switching and memory-type devices.[47] Oligoanilines offer the possibility of reversibly oxidizing between different conductivity states in a controlled fashion—between the nonconductive leuco base and the conductive emeraldine salt—giving rise to a potential ON:OFF "memory-like" effect. We incorporated the sulfur-based alligator clips into the molecules (e.g., **53**; **Scheme 9**), and synthesized oligomers with methylated nitrogen atoms to ensure oxidation only to the highly conductive emeraldine salt and not to the nonconductive emeraldine base or leuco salt (provided pH is controlled). Additionally, each nitrogen atom is capable of losing one electron, permitting oligoanilines to offer multiple independent electronic states.

1.7. Synthesis of OPE Diazonium Salts

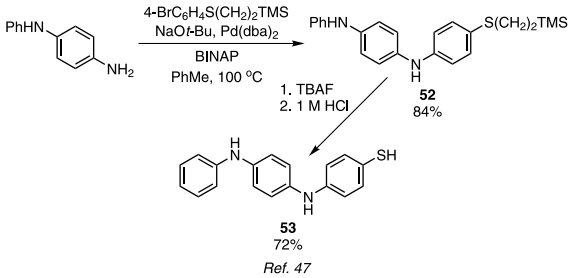
Using arenediazonium salts that are air-stable and easily synthesized, we developed a one-step, room-temperature route to the formation of direct covalent bonds between π-conjugated organic molecules and three material surfaces: Si, GaAs, and Pd.[48] The Si can be in the form of single-crystal Si—including heavily doped p-type Si, intrinsic Si, and heavily doped n-type Si—on Si(111), Si(100), and n-type polycrystalline Si. The formation of the aryl–metal or aryl–semiconductor bonds was confirmed by evidence from ellipsometry, reflectance Fourier transform infrared spectroscopy (FTIR), X-ray photoelectron spectroscopy (XPS), and cyclic voltammetry (CV) and atomic force microscopy (AFM) analyses of the surface-grafted monolayers. This spontaneous diazonium activation reaction offers an attractive route to highly passivating, robust monolayers or multilayers on many surfaces, which allow for strong bonds between surface atoms and carbon in molecular species that are nearly perpendicular to the surface of Si(111).

We have used a similar protocol for the formation of carbon nanotube–molecule–silicon junctions.[49] To our knowledge, this was the first report of a procedure to covalently attach single-walled nanotubes (SWNT) to a silicon surface that does not require a CVD growth process. In addition to functioning as the linker units, OPEs and related conjugated molecules can serve as electronically active moieties in sensor and device embodiments. Hence the union of easily patterned silicon with the often hard-to-affix nanotubes can provide a critical interface methodology for electronic and sensor arrays.

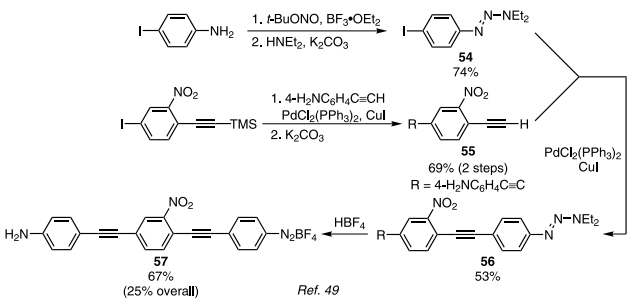
In this work, chemical orthogonality provides chemoselection for both substrate and nanotube attachment, while OPEs provide a rigid structure to minimize molecular looping upon surfaces. The target OPE molecules contain a diazonium salt on one end and an aniline moiety on the other end (e.g., **57**; **Scheme 10**).[49] This design allows for selective assembly via the first diazonium salt onto a hydride-passivated silicon surface followed by diazotization of the aniline using an alkyl nitrite.



Scheme 8. Synthesis of Fluorinated OPE **51**.



Scheme 9. Synthesis of the Monothiol Oligoaniline **53**.



Scheme 10. Synthesis of Orthogonally Functionalized Diazonium Salt **57**.

Once formed, the new diazonium salt, covalently bound to the Si surface, will react with an aqueous solution of individualized, sodium dodecylsulfate (SDS) wrapped SWNTs (SWNT/SDS)[50] to produce a covalent attachment of the SWNTs to the silicon surface via the OPEs (**Scheme 11**).[51]

2. Molecular Electronics Device Assembly and Testing

In this section of the review, we will present some additional background information on the procedures used in the assembly of molecular electronics devices, and discuss two test bed devices that we have recently developed. A complete discussion of the test beds used in molecular electronics can be found in our recent review.[20]

2.1. Self-Assembly of Molecules

In using molecular components to make electronics devices, a problem arises when one attempts to place the molecules in known positions with each end of the molecules connected in a known manner to the circuit. As of the time of this writing, no efficient method besides self-assembly exists for the individual placement of billions of molecules reproducibly in known positions. It is thus easy to understand why so much research has been conducted on self-assembly as it relates to molecular electronics. According to Whitesides,[52] "a self-assembling process is one in which humans are not actively involved, in which atoms, molecules, aggregates of molecules and components arrange themselves into ordered, functioning entities without human intervention." Whitesides reviewed the principles of molecular self-assembly over a decade ago,[53] including the possibility of using self-assembly to make semiconductor devices.

In our early work to lay the foundation for the use of self-assembly in the construction of electronic devices from molecules, SAMs of various thiol-containing molecules were formed on the surface of gold and analyzed using ellipsometry, XPS, and external reflectance FTIR.[54] It was found that the thiol moieties dominated the adsorption on the gold sites, and the direct interactions of the conjugated π systems with the gold surface were weaker. The tilt angle of the long molecular axis of the thiol-terminated SAM, that was derived from a substituted OPE, was found to be ~20° from the normal to the substrate surface. In situ deacetylation of the thioacetyl group with NH_4OH led to the formation of the SAM without isolation of the oxidatively unstable free thiol.

2.2. Devices and Test Beds Made with Molecules

A series of OPEs[26] and OTEs[21] of increasing lengths were synthesized via solution- and solid-phase chemistry, in order to explore the physical and electronic characteristics of the molecules. The working theory was that conductance occurred through the overlapping π-molecular orbitals of OPEs[55,56] and OTEs. Later work has concentrated on OPEs in order to maximize molecular orbital overlap. The thiol-terminated alligator clips that have been used to attach the molecules to metal surfaces form robust bonds to these surfaces (~50 kcal/mole or ~2 eV).[57] Theoretical work using density functional theory (DFT) has indicated that the best alligator clip would be sulfur followed by selenium and tellurium; however, a direct aryl–metal bond might be best.[58] Recent work done in air- and ultrahigh-vacuum (UHV) scanning tunneling microscopy (STM) on SAMs formed from S- or Se-terminated terthiophene molecules has shown that, regardless of the tunneling conditions, selenium provides a better coupling link than sulfur.[59]

Along with our colleague Mark Reed, we measured the conductance of a molecular junction in 1997.[60] Two gold wires were covered with SAMs of benzene-1,4-dithiol in THF. The wires were bent until they broke, and the broken ends were brought together in picometer increments via a lateral piezoelectric crystal, until the onset of conductance was measured. The spacing between the tips of the wires was set to about 8.0 Å using calibrated piezo voltage measurements, in agreement with the calculated molecule length of 8.46 Å. That the conductance of a single molecule was measured was supported by the experimental data. The experimental findings were corroborated by a large body of theoretical data on the subject, which has recently been reviewed.[61]

In 1999, large ON:OFF ratios and negative differential resistance (NDR) were measured in molecular electronic devices constructed using functionalized OPEs and a nanopore test bed.[62] The nanopore test bed, shown in **Figure 2**, was constructed by etching, via electron beam, a small hole 30 to 50 nm in diameter, in a resist-containing silicon nitride (Si_3N_4) membrane. The conditions of the etch were such that a bowl-shaped geometry was produced, with the hole at the bottom of the bowl. The bowl was then filled with evaporated Au, and the device was placed in a solution of functionalized OPE **58**. After allowing the SAM to form under basic conditions for 48 h, the device was removed from the solution, quickly rinsed, and placed on a liquid-nitrogen cooling stage for the deposition of the bottom Au electrode via evaporation. The device was then diced into individual chips that were bonded onto packaging sockets. The electrical characteristics of the packaged test beds were measured in a variable-temperature cryostat using a semiconductor parameter analyzer.

Figure 3 shows the NDR peak measured in a nanopore test bed device containing a SAM of **58** at 60 K. Note that at about 1.75 V, the SAM became conductive to a peak of 1.03 nA at about 2.1 V. The conductance then sharply dropped to about 1 pA at 2.2 V. The SAM therefore acted as an electrical switch, turning ON then OFF depending on the applied voltage. The peak-to-valley ratio (PVR) was about 1030:1. A SAM of **58** in a two-terminal cell provided electronically programmable and erasable memory with long bit-retention times.[63]

2.3. The NanoCell

A NanoCell is a two-dimensional unit of juxtaposed gold electrodes fabricated atop a Si/SiO_2 substrate, (**Figure 4**, top). A discontinuous gold film is vapor-deposited onto the SiO_2 in the central region (Figure 4, bottom). The NanoCell approach, as previously described and simulated,[1,64] is not dependent on placing molecules or nanosized metallic components in precise orientations or locations. For the most part, the internal portions are disordered, and there is no need to precisely locate any of the switching elements. The nanosized switches are added in abundance between the micron-sized input/output electrodes, and only a small percentage of them need to assemble in an orientation suitable for switching. The result of the NanoCell architecture is that the patterning challenges of the input/output structures become far less exacting, since standard micron-scale lithography can afford the needed address system, and fault tolerance is enormous.[64] However, programming is significantly more challenging than when using ordered ensembles. Remarkably, the NanoCell exhibits reproducible switching behavior with excellent peak-to-valley (PVR) ratios, peak currents in the milliampere range, and reprogrammable memory states that are stable for more than a week with substantial 0:1 bit level ratios.

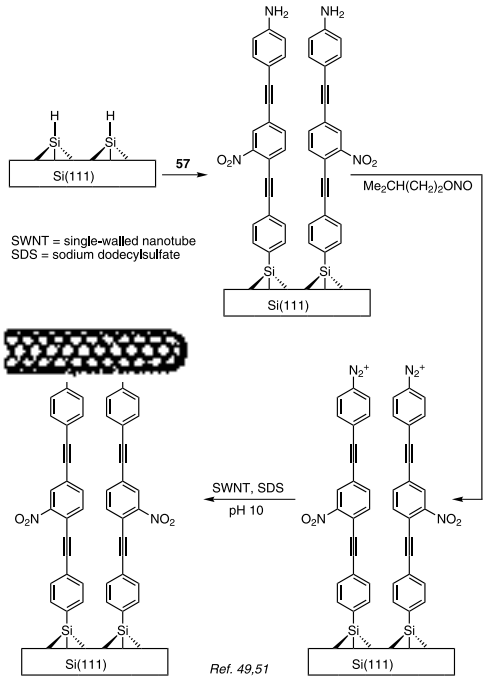
Gold nanowires were added to a vial containing **23** in CH_2Cl_2. The vial was agitated to dissolve the polycarbonate membrane around the nanowires, subsequently forming **23**-encapsulated Au nanowires via chemisorption of the thiols onto the nanowires. Because the thiol groups are far more reactive toward Au than the thioacetyl groups,[54] this procedure leaves the latter projecting away from the nanowire surfaces. NH_4OH and ethanol were added, and the vial was agitated for 10 min to remove the acetyl group. A chip containing 10 NanoCell structures was placed in the vial, and the vial was further agitated for 27 h to permit the nanowires to interlink the discontinuous Au film via the OPEs. The chip was removed, rinsed with acetone, and gently blown dry with N_2. The assembled NanoCells were electrically tested on a probe station with a semiconductor parameter analyzer at 297 K and 10^{-5} mmHg, to give the typical current-vs-voltage *I(V)* characteristics shown in **Figure 5**.[36]

Several mechanisms have been proposed for molecular electronic switching.[65–67] They are based on the idea that electrical charging of the molecules results in changes in the contiguous structure of the lowest unoccupied molecular orbital (LUMO). This can be accompanied by conformational changes that would modulate the current based on changes in the extended π overlap. As the voltage is increased, the molecules in discrete nanodomains would enter into different electronic states. Conversely, the so-called "molecular-based" switching may not be an inherently molecular phenomenon, but may result from surface bonding rearrangements that originate from the contact between the molecule and the metal (i.e., a sulfur atom changing its hybridization state or, more simply, sub-angstrom shifts between different gold surface-atom bonding modes, or molecular tilting).[68] In addition to a molecular electronic effect, electrode migration was considered next as a cause for the high currents and reset operations that are analogous to filamentary metal memories.[69] We carried out *I(V,T)* measurements (current as a function of voltage and temperature: –2 to 2 V; 280 K to 80 K and back to 280 K) to assess the possible conduction mechanism of the high σ conductivity-type memory state on the bare chip. The data suggested "dirty" or modified-metal conduction: metallic conduction with trace impurities.[70]

2.4. The MolePore

We later developed a new test bed, the MolePore, for exploring the electrical properties of single molecules to eliminate the possibility of metal nanofilament formation and to ensure that molecular effects are measured (**Figure 6**).[70] This metal-free system used single-crystal silicon and single-walled carbon nanotubes as electrodes for the molecular monolayer and, as discussed earlier, the direct silicon–aryl carbon grafting protocol was utilized. The molecules being tested were grafted onto the hydride-passivated silicon substrate to form a monolayer in a small well made through the silicon oxide layer (Figure 6b). All molecules were directly bound to the Si surface via a Si–C bond; there was no intervening oxide. The area of the SWNT mat that was in contact with the metal pad (Figure 6c) was designed to be much larger than the area of the SWNT mat in contact with the molecular layer contained in the well. The SWNTs that were employed to bridge the grafted molecules included pristine SWNTs and SWNTs slightly functionalized with 4-tetradecylphenylene moieties. Both the pristine and functionalized SWNTs yielded similar electronic characteristics in the final devices.

Use of this structure with π-conjugated organic molecules resulted in a hysteresis loop with *I(V)* measurements that are



Scheme 11. Attachment of Single-Walled Carbon Nanotubes to a Silicon Surface Using Orthogonally Functionalized OPEs.

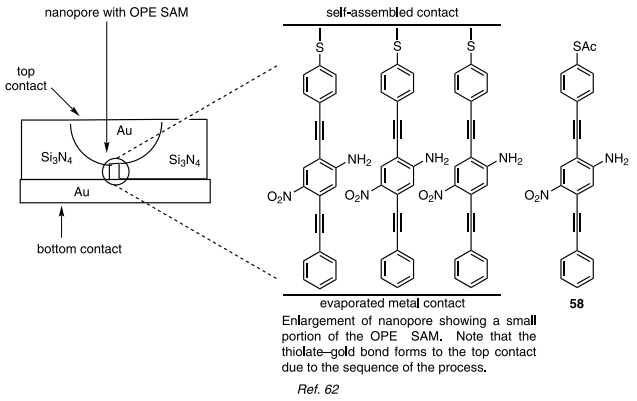


Figure 2. The Nanopore Test Bed Structure Containing a SAM of Functionalized OPE **58**.

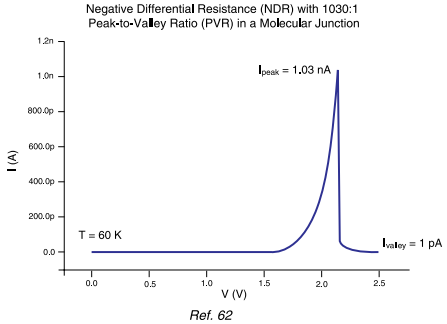
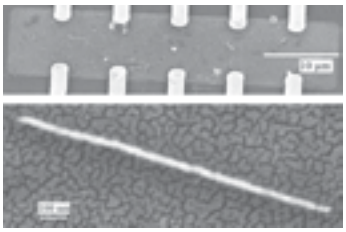


Figure 3. Current as a Function of Voltage [*I(V)*] Characteristics of a Nanopore Test Bed Device Containing a SAM of Molecule **58** at 60 K. The Peak Current Density Is ~50 A/cm^2, and the Peak-to-Valley Ratio (PVR) of the Negative Differential Resistance (NDR) Response is 1030:1.



Ref. 36

Figure 4. SEM Image of the NanoCell after Assembly of the Au Nanowires and OPE **23**. The Top Image Shows the Five Juxtaposed Pairs of Fabricated Leads Across the NanoCell, and Some Au Nanowires Are Barely Visible on the Internal Rectangle of the Discontinuous Au Film. The Lower Image Is a Higher Magnification of the NanoCell's Central Portion Showing the Disordered Discontinuous Au Film with an Attached Au Nanowire, Which Is Affixed via the OPE-dithiol (Not Observable) Derived from **23**.

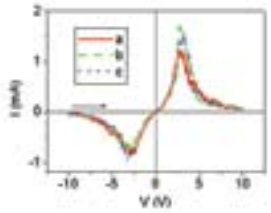


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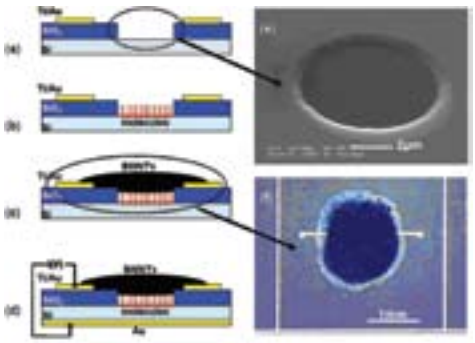
Figure 5. Current vs Voltage [*I(V)*] Characteristics of the NanoCell at 297 K. The Curves for a, b, and c Are the First, Second, and Third Sweeps, Respectively (~40 s/scan). The PVRs in c Are 23:1 and 32:1 for the Negative and Positive Switching Peaks, Respectively. The Black Arrow Indicates the Sweep Direction of Negative to Positive.



Ref. 70

Figure 6. A Schematic Is Shown of the Si–Molecule–SWNT Device and Its Fabrication Process: (a) the Starting Lithographically Defined Structure; (b) Formation of a Molecular Monolayer in the Well by Surface Grafting to Form a Direct Si–Aryl Carbon Bond; (c) Deposition of a SWNT Mat Atop the Molecules and Across the Well, Electrically Connecting the Molecular Layer to the Metal Pads; (d) the Finished Device after Bottom-Side Au Contact Formation; (e) an SEM Image of a 5-μm Well Showing Its Ramped Oxide Edges; and (f) the Top View of a Finished Device Ready for Testing, Where the SWNTs Drape Across Both the Au Contacts and the Molecular Layer in the Well, the Latter Being a Minute Portion in the Center of the Image and Is Not Visible Due to the SWNT Mat and the Resolution of the Image.

useful for an electronic memory device. The memory is nonvolatile over >3 days, nondestructive over >1,000 reading operations, and capable of >1,000 write–erase cycles before device breakdown. Temperature-independent *I(V)* behavior was observed. Devices without π-conjugated molecules (Si–H surface only) or with long-chain alkyl-bearing molecules produced no hysteresis, indicating that the observed memory effect is molecularly relevant.

3. Conclusion

Our synthetic efforts to make OTEs, OPEs, OPVs, and many other classes[71] of molecular electronics candidates has far outpaced our ability to have these molecules evaluated in relevant test beds.[20] Nevertheless, the availability of such a rich tool box of molecular architecture has led to discoveries not only in molecular electronics,[1] a few of which we have enumerated here, but also to advances in nanomachinery[72] and in educational outreach programs.[73] Research continues in our laboratory to further exploit our ability to graft molecular layers onto semiconductors and metals in order to build molecular electronics test beds and memory devices.

The work carried out in our laboratory is interdisciplinary in nature. Not only are we concerned with synthetic organic chemistry, but also materials, analytical, surface, and inorganic chemistries, as well as electrical engineering, materials engineering, and computer science. The need to work in all of these fields has brought many dedicated workers to our laboratories, and we thank them for their diligence in advancing the field. We look forward to many more fruitful and exciting collaborations with the hope that they will change the technology used in the world of tomorrow.

4. Acknowledgement

Funding from AFOSR, DARPA, ONR, ARO, NASA, and NSF is gratefully acknowledged.

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About the Authors

Dustin K. James received his Bachelor of Science degree in chemistry in 1979 from Southwestern University in Georgetown, Texas, and his Ph.D. in organic chemistry in 1984 from The University of Texas at Austin (with Professor James K. Whitesell). James worked as a process development chemist at Norwich Eaton Pharmaceuticals (Norwich, New York); a research chemist, principal chemist, and technology exploitation manager at Koch Specialty Chemical Company (Wichita, Kansas, and Houston, Texas); and chemistry and technology manager at Koch Microelectronic Service Company (Houston, Texas). James joined Professor Tour's research group at Rice University in 2001, where he is a research scientist and laboratory manager. James has nine publications and six patents. He is the webmaster and newsletter editor for the Industrial & Engineering Chemistry Division of the ACS. His research interests include organic chemistry, nanotechnology, semiconductor manufacturing processes, water and wastewater purification, lube and fuel additives, and functional fluids. His outside interests include spending time with Theresa, his wife of 29 years, cycling, reading, watching *Alias*, and cheering for the Astros and Longhorns. His Web site is at http://www.ruf.rice.edu/~dustin/.

James M. Tour, a synthetic organic chemist, received his Bachelor of Science degree in chemistry from Syracuse University, his Ph.D. in synthetic organic and organometallic chemistry from Purdue University (with E. Negishi), and postdoctoral training in synthetic organic chemistry at the University of Wisconsin and Stanford University (with B. M. Trost). After spending 11 years on the faculty of the Department of Chemistry and Biochemistry at the University of South Carolina, he joined the Smalley Institute for Nanoscale Science and Technology at Rice University in 1999, where he is presently the Chao Professor of Chemistry, and Professor of Computer Science, and Mechanical Engineering and Materials Science. Tour's scientific research areas include molecular electronics, chemical self-assembly, conjugated oligomers, electroactive polymers, combinatorial routes to precise oligomers, polymeric sensors, flame-retarding polymer additives, carbon nanotube modification and composite formation, synthesis of molecular motors and nanocars, use of the NanoKids concept for K–12 education in nanoscale science, and methods for retarding chemical terrorist attacks. He has served as a visiting scholar at Harvard University; on the *Chemical Reviews* Editorial Advisory Board; California Molecular Electronics Corporation, Technical Advisory Committee; the National Defense Science Study Group; the Governor's Mathematics and Science Advisory Board for South Carolina; in addition to numerous other professional committees and panels. Tour has won several national awards including the 2005 Southern Chemist of the Year Award (ACS), the Honda Innovation Award, the National Science Foundation Presidential Young Investigator Award in Polymer Chemistry, and the Office of Naval Research Young Investigator Award in Polymer Chemistry. Tour has more than 270 publications with 17 patents. Additional information on Tour's research and publications can be found at http://www.jmtour.com.

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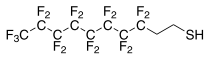

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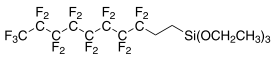
1*H*,1*H*,2*H*,2*H*-Perfluorodecyltriethoxysilane, 97%



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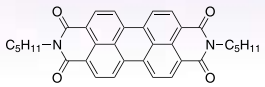
(1) Dameron, A. A. et al. *Nano Lett.* **2005**, *5*, 1834. (2) Notsu, H. et al. *J. Mater. Chem.* **2005**, *15*, 1523. (3) Li, Y. et al. *J. Coll. Interf. Sci.* **2005**, *287*, 634.

Products for Organic Transistors

N,N′-Dipentyl-3,4,9,10-perylenedicarboximide

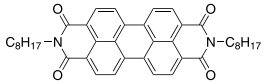
PTCDI-C5



663921-500MG	500 mg

N,N′-Dioctyl-3,4,9,10-perylenedicarboximide

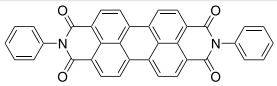
PTCDI-C8



663913-500MG	500 mg

N,N′-Diphenyl-3,4,9,10-perylenedicarboximide

PTCDI-Ph



663905-500MG	500 mg

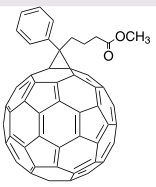
These perylene derivatives are being evaluated as *n*-type organic conductors for organic field effect transistors (OFETS). PTCDI-C5 exhibits electron saturation mobilities as high as 1.7 $cm^2\ V^{-1}\ s^{-1}$ with low threshold voltages.

Chesterfield, R. J. et al. *J. Phys. Chem. B.* **2004**, *108*, 19281.

Product for Organic Photovoltaics

[6,6]-Phenyl-C_{61} butyric acid methyl ester

PCBM



659169-100MG	100 mg

PCBM is used in polymer–fullerene bulk heterojunction solar cells to boost the quantum efficiencies of polymers like polyhexylthiophene and polyphenylenevinylenes.

Janssen, R. A. J. et al. *MRS Bull.* **2005**, *30*, 33.

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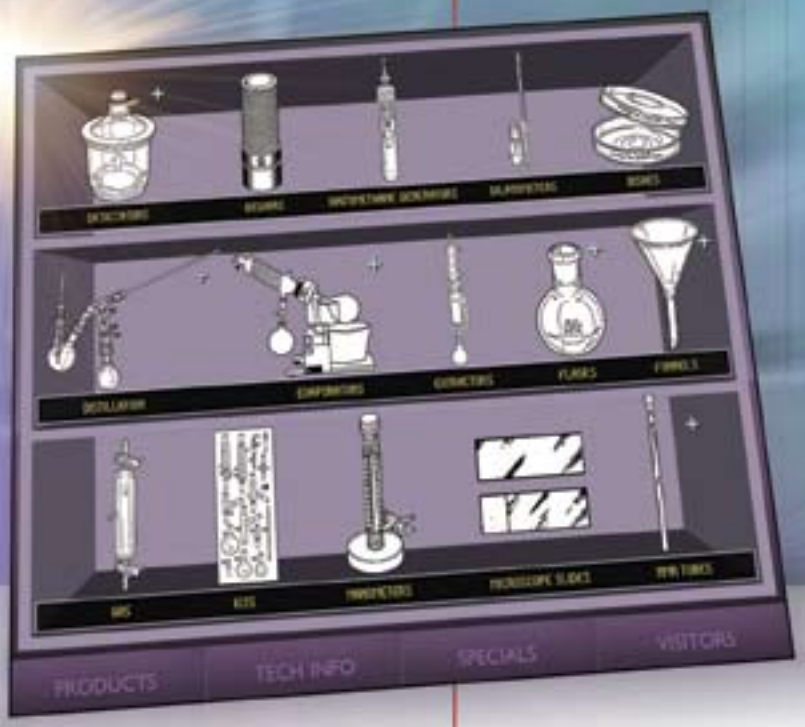

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	8	535-PP-8	**NORS56008-5EA**
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	8	528-PP-8	**NORS55008-5EA**
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400	7	WG-1235-7	**NOR507HP7-5EA**
	8	WG-1235-8	**NOR507HP8-5EA**
300+	7	WG-1228-7	**NOR506P7-25EA**
	8	WG-1228-8	**NOR506P8-25EA**
300	7	WG-1226-7	**NORXR557-25EA**
	8	WG-1226-8	**NORXR558-25EA**
200	7	WG-1208-7	**NOR505P7-25EA**
	8	WG-1208-7	**NOR505P8-25EA**
100	7	WG-1206-7	**NOR5027-50EA**
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H. U. Blaser and E. Schmidt, Eds., Wiley, 2004, 480pp. Hardcover. Edited by two experts in the field, the central aim of the book is to show organic chemists working in process development that enantioselective catalysis is suitable for the large-scale production of enantioenriched intermediates. In so doing, it is equally a source of information and inspiration for academic research, and, with its contribution by Nobel prizewinner W. S. Knowles, will also heighten the status of industrial specialists working in the exciting field of enantioselective catalysis.

Z557544-1EA

Handbook of Reagents for Organic Synthesis: Chiral Reagents for Asymmetric Synthesis

L. A. Paquette, Ed., Wiley, 2003, 582pp. Hardcover. As chiral reagents are key to successful asymmetric synthesis, choosing the right reagent is essential. In this handy reference, the editor gives details on how to prepare, store, and utilize chiral reagents, and provides key reactions in which these reagents have been successfully used. This book contains comprehensive information on 226 reagents. It covers many of the optically active reagents and catalysts in use at the present time, with the overall intention to compile, in manageable format, as much indispensable information as possible. The selection reflects the sharp increase in demand for enantiomerically pure reagents and products. This development has been driven by synthetic organic chemists working in natural products synthesis and by medicinal chemists working on the development of enantiomerically pure drugs.

Z551430-1EA

Comprehensive Asymmetric Catalysis

E. N. Jacobsen, A. Pfaltz, and H. Yamamoto, Eds., Springer, 2000, CD-ROM. This major reference critically reviews methods for the catalytic preparation of chiral organic compounds. Along with the presentation of state-of-the-art information in this area, the CD-ROM allows full-text search and contains a state-of-the-art substructure search routine for compounds and reactions.

Z525367-1EA

Enantioselective Synthesis of β-Amino Acids, Second Edition

E. Juaristi and V. A. Soloshonok, Eds., Wiley, 2005, 634pp. Hardcover. β-Amino acids are studied in several research areas such as combinatorial chemistry, medicinal chemistry, molecular design, proteomics, and others. This second edition updates reviews, covers new developments, and presents detailed discussions of the most important methods for the synthesis of β-amino acids. In addition, this book features introductory overviews on the structural types of relevant β-amino acid targets and salient β-amino acids present in natural products; dedicates several chapters to advances in the synthesis of oligomers from β-amino acids; discusses the most important methods that have been recently developed for the asymmetric synthesis of cyclic and open-chain β-amino acids; and includes a report on the preparation of libraries of enantiopure β-amino acids using combinatorial approaches.

Z704652-1EA

REFERENCE

Reagent Chemicals: Specifications and Procedures, Tenth Edition

ACS Committee on Analytical Reagents, Oxford University Press, 2005, 832pp. Hardcover. The American Chemical Society Committee on Analytical Reagents is the only organization in the world that sets requirements and develops validated methods for determining the purity of analytical reagents. For the first time, *Reagent Chemicals*, 10th edition, includes general physical properties and analytical uses for all reagent chemicals, nearly 500 chemicals. Thirty-two new reagents and three new classes of standard-grade reference materials are introduced in this edition. In addition, the use of Inductively Coupled Plasma Mass Spectrometry (ICP-MS), which is recognized as the most powerful and flexible trace element analysis technique, is now accepted as an analytical method in the 10th edition. Other improvements include a CAS number index, a separate index for standard-grade reference materials, frequently used mathematical equations, and complete assay calculations with titer values.

Z704598-1EA

CRC Handbook of Chemistry and Physics, 86th Edition

D. R. Lide, Ed., CRC Press, 2005, 2616pp. Hardcover. For more than 90 years, researchers around the world have relied on the *CRC Handbook of Chemistry and Physics* for authoritative, up-to-date data. This year will be no exception. New tables, extensive updates, and added sections mean the Handbook again sets a new standard for reliability, utility, and thoroughness. New tables in this edition include: Proton Affinities, Electron Inelastic Mean Free Paths, Selected Properties of Semiconductor Solid Solutions, and Vapor Pressures (Solvent Activities) for Binary Polymer Solutions. Sections substantially revised and updated include NIST Atomic Transition Probability Tables, Summary Tables of Particle Properties, and Threshold Limits for Airborne Contaminants. A larger format and new layout makes it easier to read, and a new typeface makes the tables and diagrams crystal clear.

Z704571-1EA

MATERIALS SCIENCE

Precursor Chemistry of Advanced Materials

R. A. Fischer, Ed., Springer, 2005, 213pp. Hardcover. Materials synthesis by the transformation of organometallic compounds (precursors) by vapor deposition techniques such as chemical vapor deposition (CVD) and atomic layer deposition (ALD) has been in the forefront of research and development of new materials. A need exists for new routes for designing and synthesizing new precursors as well as the application of established molecular precursors to derive tuneable materials for technological demands. This volume comprises a selection of case studies covering various key aspects of the interplay of precursor chemistry with the process conditions of materials formation, particularly looking at the similarities and differences of CVD, ALD, and nanoparticle synthesis involving tailored molecular precursors

Z704628-1EA

Bulk Crystal Growth of Electronic, Optical and Optoelectronic Materials

P. Capper, Ed., Wiley, 2005, 574pp. Hardcover. A valuable, timely book for the crystal growth community, edited by one of the most respected members in the field. The contents cover all the important materials from silicon through the III–V and II–IV compounds to oxides, nitrides, fluorides, carbides, and diamonds. An international group of contributors from academia and industry provides a balanced treatment. The text includes global interest with particular relevance to the USA, Canada, UK, France, Germany, the Netherlands, Belgium, Italy, Spain, Switzerland, Japan, Korea, Taiwan, China, Australia, and South Africa.

Z704105-1EA

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ASYMMETRIC SYNTHESIS ENABLED BY METAL-FREE CATALYSIS

Aldrichimica ACTA

VOL. 39, NO. 3 • 2006

Enzymes in Organic Synthesis

Modern Strategies in Organic Catalysis

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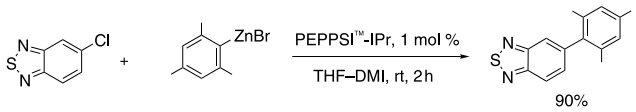
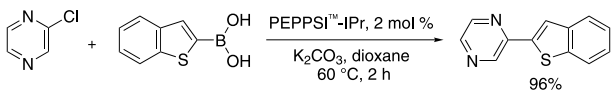
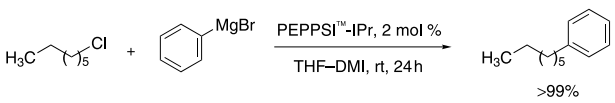
Negishi Coupling



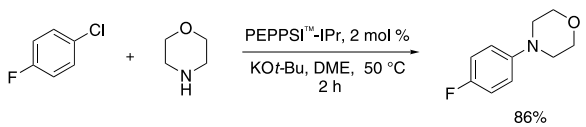
Suzuki Coupling



Kumada Coupling



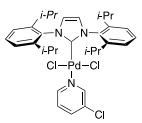
Buchwald–Hartwig Amination



(1) (a) O' Brien, C. J. et al. *Eur. J. Org. Chem.* **2006**, in press. (b) O' Brien, C. J. et al. *Eur. J. Org. Chem.* **2006**, in press. (c) O'Brien, C. J. et al. *Manuscript in preparation*. (d) O'Brien, C. J. et al. *Manuscript in preparation*.

[1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl) palladium(II) dichloride, 98%

PEPPSI™-IPr Catalyst
669032
$C_{32}H_{40}Cl_3N_3Pd$
FW: 679.46



1 g	$60.00
5 g	270.00

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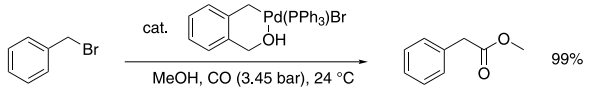
Heriot-Watt Carbonylation Catalysts

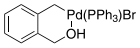
These palladium catalysts, sold under exclusive license from Heriot-Watt University (Scotland),[1] efficiently carbonylate benzyl halides in methanol under low pressures and temperatures.[2]



(1) Manufactured by Aldrich under exclusive license from Heriot-Watt University, PCT/GB2005/002738 patent pending. (2) (a) Jones, R. V. H. et al. *Tetrahedron Lett.* **2005**, *46*, 8695. (b) Lindsell, W. E. et al. *Organometallics* **2005**, *24*, 1119.

Bromo[[2-(hydroxy-κO)methyl]phenylmethyl-κC](triphenylphosphine)palladium(II)

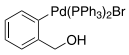
666327
[*849417-33-0*]
$C_{26}H_{24}BrOPPd$
FW: 569.77



250 mg	$30.00
1 g	95.00

2-[Bis(triphenylphosphine)palladium(II) bromide]benzyl alcohol, 96%

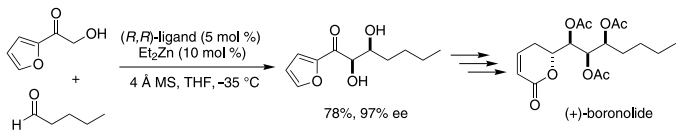
665932
$C_{43}H_{37}BrOP_2Pd$
FW: 818.02



250 mg	$30.00
1 g	95.00

Trost Bis-ProPhenol Ligands

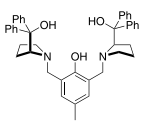
The combination of these phenolic ligands and diethylzinc generates catalyst systems that are capable of effecting a variety of asymmetric reactions. This methodology has been applied to asymmetric aldol condensations,[1] Mannich-type reactions,[2] and Henry reactions.[3]



(1) (a) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003. (b) Trost, B. M.; Yeh, V. S. C. *Org. Lett.* **2002**, *4*, 3513. (2) Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.* **2003**, *125*, 338. (3) Trost, B. M. et al. *Org. Lett.* **2002**, *4*, 2621.

(*R*,*R*)-(–)-2,6-Bis[2-(hydroxydiphenylmethyl)-1-pyrrolidinylmethyl]-4-methylphenol, 95%

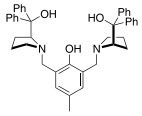
Trost (*R*,*R*)-Bis-ProPhenol Ligand
667625
$C_{43}H_{46}N_2O_3$
FW: 638.84



1 g	$20.50
5 g	81.20

(*S*,*S*)-(+)-2,6-Bis[2-(hydroxydiphenylmethyl)-1-pyrrolidinylmethyl]-4-methylphenol, 95%

Trost (*S*,*S*)-Bis-ProPhenol Ligand
668370
$C_{43}H_{46}N_2O_3$
FW: 638.84



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PEPPSI™ patent pending.

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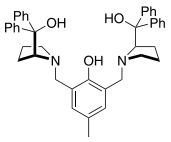
"PLEASE BOTHER US."

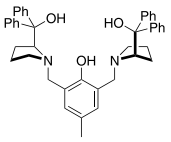
Joe Porwoll, President
Aldrich Chemical Co., Inc.

Professor Barry Trost of Stanford University kindly suggested that we offer these enantiomeric Bis-ProPhenol ligands. Upon treatment of a Bis-ProPhenol ligand with diethylzinc, a versatile catalyst is formed, which is capable of performing a variety of reactions in an asymmetric fashion. Aldol, imine-aldol, and nitro-aldol condensations all proceed with impressive levels of stereocontrol.[1] Additionally, the catalyst system promotes the asymmetric alkynylation of unsaturated aldehydes.[2]

(1) See the references on the facing page. (2) Trost, B. M. et al. *J. Am. Chem. Soc.* **2006**, *128*, 8.



667625



668370

667625	**(*R*,*R*)-(–)-2,6-Bis[2-(hydroxydiphenylmethyl)-1-pyrrolidinyl-methyl]-4-methylphenol, 95%** Trost (*R*,*R*)-Bis-ProPhenol Ligand	1 g 5 g	$20.50 81.20
668370	**(*S*,*S*)-(+)-2,6-Bis[2-(hydroxydiphenylmethyl)-1-pyrrolidinyl-methyl]-4-methylphenol, 95%** Trost (*S*,*S*)-Bis-ProPhenol Ligand	1 g 5 g	$20.50 81.20

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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.

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

View of the Tiber near Perugia (oil on canvas, 98.0 × 161.5 cm) was painted in Italy between 1872 and 1874 by George Inness, the American landscape artist. Inness was born in 1825 in Newburgh, New York, and was raised in New York City and New Jersey. Although he had little formal artistic training, he developed his painting style through his association with artists from the American Hudson River School and his frequent visits to Europe, where 17th-century old masters and French Barbizon School landscape painters influenced him. Emanuel Swedenborg, the 18th-century Swedish scientist and theologian who stressed that the spiritual world was as much a reality as the material world, also inspired Inness to express his personal vision of spiritual harmonies in nature.

Subtle, yet dramatic atmospheric effects of harmonious color, light and shade, and mood and meaning are displayed in this painting. The dynamic diagonal created by the middle ground landscape reinforces the suggestion of depth and recession and separates the foreground from the background. A sense of the human proportion is understood by looking at the figures in the near ground. This poetic and spiritual view of the Perugia area is remarkably rendered with a sense of peace and calm.

Purchased for the National Gallery of Art, Washington, DC, through the Ailsa Mellon Bruce Fund.

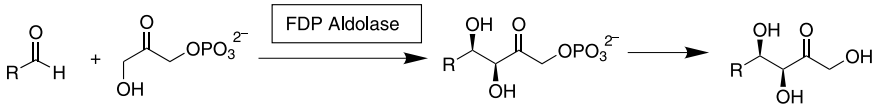
Biocatalytic Aldol Reactions in Organic Synthesis

The construction of C–C bonds with complete stereochemical control of the reaction course is a key goal in organic synthesis. The desired relative and absolute configurations of the newly formed stereogenic centers can be achieved by using chiral starting materials and chiral auxiliaries. Catalytic approaches towards asymmetric aldol reactions have been a special focus in recent years.[1] Aldolases and catalytic Aldolase antibodies represent valuable tools for the biocatalytic asymmetric C–C-bond formation.

Sigma-Aldrich offers a comprehensive range of chiral auxiliaries, organocatalysts, organometallic catalysts, ligands, and biocatalysts for efficient asymmetric aldol reactions. Please visit our Web site at **sigma-aldrich.com** and take a look at the Sigma-Aldrich *Enzyme Explorer* for more biocatalysts.

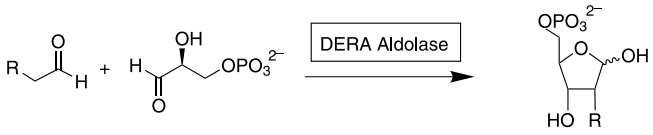
(1) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352.

FDP Aldolase E.C. 4.1.2.13



Cat. No.	Name	Pack Sizes
94864	Fructose-1,6-bisphosphate Aldolase from *Staphylococcus carnosus*	5 mg
05518	Aldolase from rabbit muscle	10 mg 50 mg
A2714	Aldolase from rabbit muscle	100 units 200 units 500 units
A9329	Aldolase from spinach	25 units

DERA Aldolase E.C. 4.1.2.4

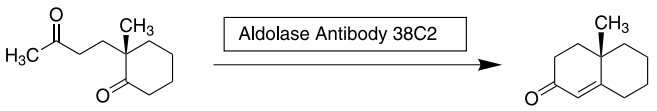


Cat. No.	Name	Pack Sizes
91252	2-Deoxy-D-ribose 5-phosphate Aldolase, E. coli K12, recombinant from *Escherichia coli*	25 mg 100 mg
41228	2-Deoxyribose-5-phosphate Aldolase from *Lactobacillus plantarum*	10 mg

KHG Aldolase E.C. 4.1.3.16

Cat. No.	Name	Pack Sizes
59892	4-Hydroxy-2-oxoglutarate Aldolase from *Escherichia coli*	10 mg

Aldolase Antibody 38C2



Cat. No	Name	Pack Sizes
479950	Aldolase Antibody 38C2, murine catalytic monoclonal antibody, contains phosphate buffer salts (pbs)	10 mg
481572	Aldolase Antibody 38C2, murine catalytic monoclonal antibody	10 mg

Other Aldol Reaction Biocatalysts

Cat. No.	Name	E.C. Number	Pack Sizes
47153	*N*-Acetylneuraminic acid Aldolase from *Escherichia coli*	4.1.3.3	25 mg 100 mg
A6680	*N*-Acetylneuraminic acid Aldolase from *Escherichia coli*	4.1.3.3	25 units
96586	L-Threonine Aldolase from *Pseudomonas putida*	4.1.2.5	10 mg 50 mg
67891	3-Deoxy-D-manno-octulosonate Aldolase from *Escherichia coli*	4.1.2.23	10 mg
527858	Aldolase Antibody 84G3, murine catalytic monoclonal antibody		10 mg

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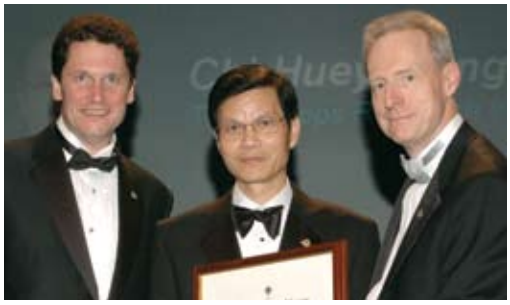
Enzymes in Organic Synthesis: Aldolase-Mediated Synthesis of Iminocyclitols and Novel Heterocycles

Dr. Lisa J. Whalen



Professor Wong (center) receiving the Sigma-Aldrich sponsored *2005 ACS Award for Creative Work in Synthetic Organic Chemistry.* Pictured with Professor Wong are Dr. Barry Johnson (left), Sigma-Aldrich Vice President of Marketing, and Dr. William F. Carroll Jr. (right), 2005 ACS President.
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*Lisa J. Whalen and Chi-Huey Wong**
Department of Chemistry and the Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Rd.
La Jolla, CA 92037, USA
Email: wong@scripps.edu

Outline

1. Introduction

The preparation and evaluation of carbohydrate mimics in which the endocyclic oxygen is replaced with nitrogen began with the syntheses of 5-acetamido-5-deoxy-D-xylopiperidinose in the 1960s by Paulsen,[1] Jones,[2] and Hanessian[3] as purely academic exercises. The substitution of nitrogen for oxygen produces metabolically inert iminocyclitols (also referred to as iminosugars or azasugars) that typically bind to carbohydrate-processing enzymes such as glycosidases. Indeed, the discovery that many iminocyclitols possess the ability to inhibit glycosidases[1] resulted in a rapid expansion of the field. As a result of their glycosidase inhibition activity, iminocyclitols are used as tools to study glycoprotein processing and are evaluated for antiviral, anticancer, antidiabetic, and pesticidal properties. Efficient routes to a wide variety of iminocyclitols are possible through the use of commercially available and genetically engineered aldolases: powerful enzymes capable of forming carbon–carbon bonds in a stereoselective fashion.[4] This review aims to cover selected aldolase-mediated methods for synthesizing polyhydroxylated pyrrolidines, piperidines, and miscellaneous heterocycles.

2. Biological Significance of Glycosidases

Glycosidases, the enzymes that hydrolyze acetal linkages between carbohydrates, play key roles in digestion, lysosomal catabolism, and glycoprotein processing and folding.[5] Intestinal glycosidases are integrated into the cell membranes of the brush border region in the small intestine, where they break down dietary oligosaccharides to monosaccharides. Interference with this process by inhibition of these glycosidases could regulate carbohydrate absorption. As a result, inhibitors of intestinal glycosidases are used in the treatment of diabetes due to their ability to lower blood glucose levels.[6]

Lysosomal glycosidases also participate in the breakdown of glycosylated bioconjugates. These catabolic enzymes digest materials brought into the cell by endocytosis and assist in the recycling of cellular components. Insufficient breakdown of these materials leads to lysosomal storage diseases, which are often hereditary in nature. Typically, the inhibition of lysosomal glycosidases leads to clinical symptoms and cellular changes associated with genetic lysosomal storage disease.[7] However, the subset of lysosomal storage diseases associated with misfolded or mistrafficked glycosidases

is susceptible to treatment by iminocyclitol-mediated chemical chaperoning.[8,9] When secreted, lysosomal hydrolases may also be involved in tumor cell invasion through their ability to degrade glycoconjugates in the extracellular matrix.[10]

The composition of *N*- and *O*-linked oligosaccharide chains on mammalian glycoproteins is controlled by the action of glycosidases and glycosyltransferases.[11] As the *N*- and *O*-linked oligosaccharides on cancer cell surfaces exhibit aberrant glycosylation patterns, which may be linked to metastatic potential and malignancy,[12] prevention of this aberrant glycosylation is an important strategy for cancer therapy.[13] In addition, many animal virus envelope glycoproteins that participate in virion assembly, secretion, and infectivity can be studied using glycosidase inhibitors.[14,15] Finally, inhibition of glycosidases may lead to a selective method for the control of glycoprotein structure and function, if the enzymatic addition of carbohydrates is blocked by specific inhibitors. Such a method would be invaluable in the development of anti-inflammatory, anticancer, antiviral, and antibiotic agents as the roles of individual carbohydrates in complex glycoproteins are unraveled. Thus, the development of efficient methods for the synthesis of iminocyclitols is central to the continued study of glycosidases and the development of anti-inflammatory, anticancer, antiviral, and antibiotic agents.

3. The Five Classes of Naturally Occurring Iminocyclitols

An enormous body of literature exists on the synthesis, isolation, and biological evaluation of iminocyclitols.[5,16–22] Naturally occurring iminocyclitols are divided into five classes based on their structures: polyhydroxylated pyrrolidines, piperidines, indolizidines, pyrrolizidines, and nortropanes (**Figure 1**). Pyrrolidine **1**, commonly known as 2,5-dideoxy-2,5-imino-D-mannitol (DMDP), is found in many plants and microorganisms,[23] which suggests that it is a common metabolite. Piperidine **2** is 1-deoxynojirimycin (DNJ), isolated from the roots of mulberry trees.[24] Both **1** and **2** have been studied for their antihyperglycemic properties.[25] Indolizidine **3** is the toxic alkaloid castanospermine, which is a potent inhibitor of lysosomal α-glucosidase.[26] DMDP, DNJ, and castanospermine all inhibit glycoprotein processing enzymes to varying degrees as well.[5] Casuarine (**4**) is an example of a pyrrolizidine.[5] It is isolated from plants that have been used in the treatment of breast cancer, diabetes, and bacterial infections.[27] Calystegine A_3 (**5**) belongs to a nortropane class of alkaloids that possess glycosidase inhibition activity.[5,28]

4. Iminocyclitols and Their Relationship to the Transition State of Glycoside Hydrolysis

At first glance, one simple explanation for the strong affinity of iminocyclitols for glycosidases lies in the similarity between the proposed transition state of glycoside hydrolysis and the iminocyclitol scaffold (**Figure 2**).[16] Breaking the glycosidic bond results in a developing positive charge on the anomeric carbon; this charge is shared with the endocyclic oxygen to produce an oxocarbenium-ion-like character. This results in a double bond character between the endocyclic oxygen and the anomeric carbon, distorting the ring to a half-chair conformation. Glycosidases stabilize this positive charge with anionic active-site residues such as aspartate and glutamate. When the amine nitrogen of the iminocyclitol is protonated under physiological conditions, the resulting ammonium ion would be expected to mimic the partial positive charge developing on the endocyclic oxygen and bind to the anionic residues. The hydroxyl groups of protonated **2** would form hydrogen bonds in the glycosidase active site, just as the glycoside itself would. Although there are strong parallels between iminocyclitols and the proposed transition state of glycoside hydrolysis, studies of linear free energy relationships using 1-deoxynojirimycin (**2**) demonstrated that this class of compound is not a transition state analogue of *Agrobacterium* β-glucosidase.[29] However, this fact does not preclude the synthesis of iminocyclitol analogues that exhibit strong binding to, or function as transition state analogues of, glycosidases. Different strategies for the synthesis of iminocyclitols and analogues have been developed in many laboratories.[5,16–22] This review focuses only on the use of aldolases as catalysts in stereoselective carbon–carbon-bond-forming reactions as a key step in the synthesis of iminocyclitols.

5. Applications of Aldolases to the Synthesis of Iminocyclitols

Aldolases are enzymes that catalyze asymmetric aldol reactions. The more than 40 aldolase types identified to date can be separated into two mechanistic classes based on the method of donor substrate activation. Type I aldolases activate the donor substrates (dihydroxyacetone phosphate, pyruvate, phosphoenol pyruvate, glycine, and acetaldehyde) by forming a Schiff base,[30,31] while Type II aldolases effect the activation by forming a zinc enolate[32,33] (**Scheme 1**).[4,34] Many aldolases use the common $\alpha_8\beta_8$ barrel fold in their active sites (**Figure 3**),[35a] a scaffold amenable to directed evolution and mutagenesis to create novel enzymes as new catalysts. In vitro screening combined with directed evolution, or directed evolution combined with enzyme design successfully produced aldolases with new catalytic properties.[35b–f] These included alteration of substrate specificity to accept diastereomers or enantiomers of the natural substrate and removal of phosphate dependence. This powerful combination of substrate modification and enzyme alteration provides access to a diverse collection of carbohydrate derivatives.

5.1. Dihydroxyacetone Phosphate (DHAP) Dependent Aldolases

Another common feature of aldolases is that they are quite specific for their donor substrates while being flexible for the acceptor substrates, which allows the use of this class of enzymes for the synthesis of common and uncommon sugars. Chemoenzymatic synthesis provides access to many of the iminocyclitol scaffolds illustrated in Figure 1.[4,34,36,37] Three examples of dihydroxyacetone phosphate (DHAP) dependent aldolases that catalyze the reversible addition of DHAP to an acceptor aldehyde are shown in **Scheme 2**.[4] These are fructose 1,6-diphosphate aldolase (FDP aldolase), L-fuculose 1-phosphate aldolase (Fuc-1-P aldolase), and L-rhamnulose 1-phosphate aldolase (Rham-1-P aldolase). Of this group, fructose 1,6-diphosphate aldolase (FDP aldolase) has been the most useful for the synthesis of iminocyclitols. In vivo, FDP aldolase catalyzes the addition of the donor DHAP to the acceptor D-glyceraldehyde-3-phosphate to form D-fructose 1,6-diphosphate. The most widely used FDP aldolase, rabbit muscle aldolase (RAMA), accepts a wide range of acceptor substrates with the donor DHAP to produce (3*S*,4*R*) vicinal diols stereospecifically.[4] The mechanism of RAMA is nearly identical to the Type I aldolase mechanism in Scheme 1, with the substitution of Arg 148 filling the role of Ser 271. RAMA uses Schiff base formation with Lys 229 to activate DHAP for attack on the sterically less hindered *Si* face of the acceptor aldehyde. Fuc-1-P aldolase and Rham-1-P aldolase accept L-lactaldehyde as their natural acceptor substrate to produce (3*R*,4*R*) and (3*R*,4*S*) vicinal diols, respectively. The donor specificity of the DHAP-dependent aldolases is rather narrow, and few analogues of DHAP have been accepted successfully.

5.2. 2-Deoxyribose-5-phosphate Aldolase (DERA)

In addition to the DHAP-dependent aldolases, 2-deoxyribose-5-phosphate aldolase (DERA) is useful for the synthesis of iminocyclitols.[4] In vivo, DERA catalyzes the reversible aldol addition of acetaldehyde to D-glyceraldehyde-3-phosphate to form D-2-deoxyribose-5-phosphate and create a new 3*S* stereocenter (**eq 1**).[35a,g] Recent studies on the structure and mechanism of DERA reveal two critical water molecules involved in the catalysis:[35a] one participates in acid–base catalysis, while the other is involved with the enantioselectivity and proton shuffling associated with the carbon–carbon bond-forming reaction. This investigation identified Lys 167 as the Schiff base forming residue, which first forms an enamine with the donor acetaldehyde. This is followed by nucleophilic attack of the enamine onto the carbonyl carbon of the acceptor D-glyceraldehyde-3-phosphate to form a new Schiff base. Addition of water to this Schiff base produces a carbinolamine intermediate that collapses to release the product D-2-deoxyribose-1-phosphate. This is supported by ultrahigh-resolution structural data of the second Schiff base and carbinolamine intermediates, site-directed mutagenesis studies, and ^{1}H NMR analysis of deuterated substrate analogs. The discoveries made in this work resulted in the proposal of a complete mechanism for a Class I aldolase, including identification of all of the essential catalytic residues, with implications for other Schiff base forming enzymes. This mechanism appears to be general among the Schiff base forming aldolases, as the residues involved in the catalysis are highly conserved among the enzymes. DERA will accommodate a number of unnatural acceptors besides D-glyceraldehyde-3-phosphate and a small variety of unnatural donors in addition to acetaldehyde.

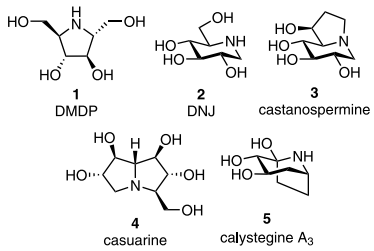
Iminocyclitols are prepared by reacting a nitrogen-containing acceptor analogue with an appropriate donor in the aldolase-catalyzed aldol reaction (**Scheme 3**).[37] This produces a phosphorylated γ-azido ketone, which is poised for intramolecular reductive amination and conversion to an iminocyclitol. The phosphate may be cleaved enzymatically using acid phosphatase, or reductively cleaved under the hydrogenation conditions of the next step in which the azide is reduced to the amine. Intramolecular imine formation occurs spontaneously when the azide is reduced. Reduction of the imine completes the synthesis of the iminocyclitol.

Two commercially available aldolases are suitable for the synthesis of polyhydroxylated pyrrolidines and piperidines. The DHAP-dependent aldolases accept over a hundred known substrates, including unhindered aliphatic and α-substituted aldehydes. However, the donor specificity is narrow, with only conservative changes to DHAP being tolerated. Chemical and chemoenzymatic syntheses are available for the preparation of DHAP. DERA uses acetaldehyde as the donor and possesses a wide acceptor substrate tolerance as well. It is a stable enzyme, maintaining activity in solution at 25 °C even after ten days. With all of these advantages, the DHAP-dependent aldolases and DERA have been applied to the synthesis of a large variety of polyhydroxylated heterocycles as discussed below.

6. Aldolase-Mediated Synthesis of Polyhydroxylated Pyrrolidines

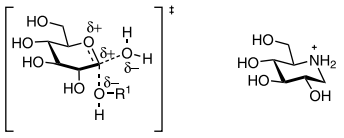
6.1. Stereochemistry of the Intramolecular Reductive Amination Leading to Pyrrolidines

A key feature of the aldolase-mediated synthesis of iminocyclitols is the stereochemistry of the intramolecular reductive amination step. The in situ reductive amination of azido keto sugars to iminocyclitols was first studied by Card and Hitz,[38] while Paulsen and co-workers applied the palladium-mediated



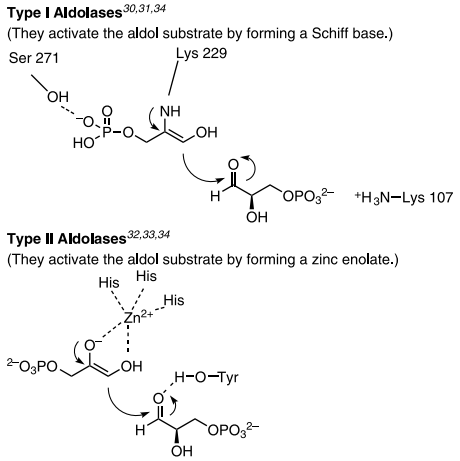
Ref. 23–28

Figure 1. The Five Classes of Naturally Occurring Iminocyclitols.

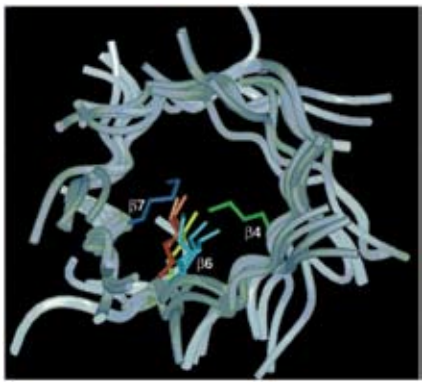


Ref. 16

Figure 2. Comparison of the Transition State of Glycoside Hydrolysis with the Iminocyclitol 1-Deoxynojirimycin (**2**).

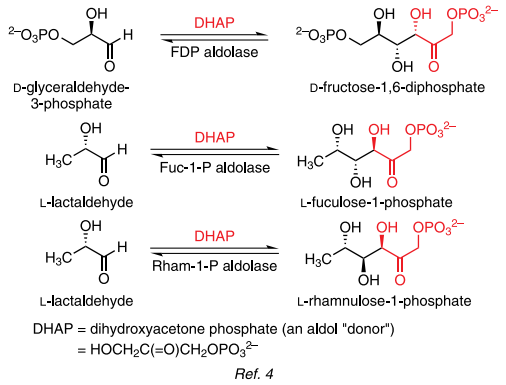


Scheme 1. The Proposed Mechanisms of Substrate Activation by Type I and Type II Aldolases.

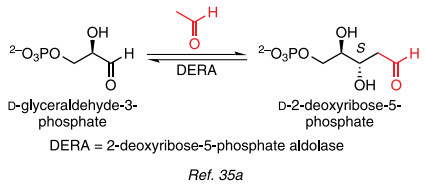


Ref. 35a

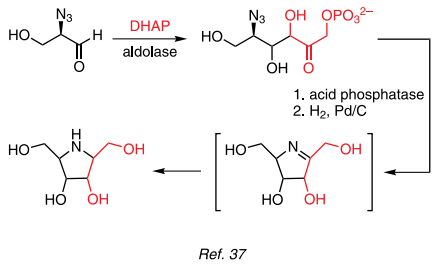
Figure 3. Superimposition of Eight Aldolase Active Site β-Barrel Cores. Lys 167 from DERA Is Located on the β6 Strand (Yellow) as Is Lys 133 from Three D-2-Keto-3-deoxy-6-Phosphogluconate (KDPG) Aldolases (Cyan), and the Lys 229 Residues from Two FDP Aldolases in Red. The Reactive Lys from Transaldolase B (Green) Is Located on the β4 Strand. Lys 161 (Blue) from the Double Mutant K133Q/T161K of KDPG Is Located on Strand β7.



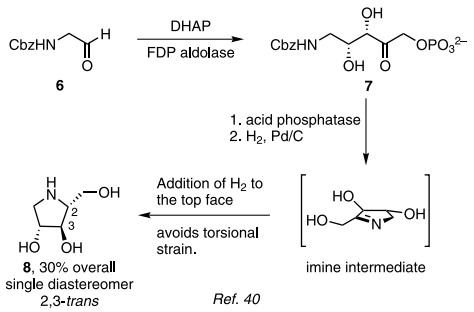
Scheme 2. The in Vivo Reactions Catalyzed by Three DHAP-Dependent Aldolases.



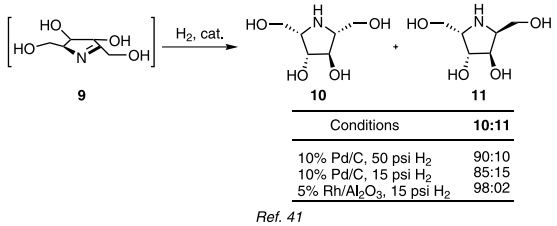
eq 1



Scheme 3. An Example of the Use of a Nitrogen-Containing Aldol Acceptor in the Synthesis of an Iminocyclitol.



Scheme 4. Stereochemistry of the Reductive Amination in the Synthesis of 1,4-Dideoxy-1,4-imino-D-arabinitol (**8**).



eq 2

reductive amination to amino sugars.[39] While the results are highly dependent on each individual case, some conclusions may be drawn about the stereoselectivity for polyhydroxylated pyrrolidines. In the example illustrated in **Scheme 4**, FDP aldolase catalyzes the condensation of **6** with DHAP to produce phosphorylated diol **7**.[40] Enzymatic removal of the phosphate with acid phosphatase provides the triol, which is not isolated. The benzyloxycarbonyl group is then removed by hydrogenolysis with palladium-on-carbon to produce the free amine, which spontaneously cyclizes to the imine intermediate. Under the hydrogenation conditions, the imine is reduced to (2*R*,3*R*,4*R*)-2-hydroxymethyl-3,4-dihydroxypyrrolidine (**8**) as a single diastereomer in good overall yield. The stereochemistry of this reduction is explained by considering the effect of any developing torsional strain in the product. Attack of hydrogen from the top face produces a minimal amount of torsional strain during the course of the reaction, resulting in a configuration in which the substituents on C-2 and C-3 in **8** are in a trans relationship.

Further studies discovered a connection between the metal catalyst used in the reduction step of a related five-membered-ring imine and the stereoselectivity of the reduction (**eq 2**).[41] Imine **9** produced the highest ratio of **10**:**11**, 98:2, with rhodium-on-alumina as the catalyst and an atmospheric pressure of hydrogen. It should be noted that the same 2,3-trans relationship, observed in **8**, is also found in **10**. In general, palladium- or platinum-based catalysts result in 85–95% face selectivity in the reduction of five-membered-ring imines.

6.2. Extension to Other Pyrrolidines with New Functional Groups and Different Stereochemical Configurations

The use of a masked nucleophilic nitrogen atom in the form of an azide provided access to new pyrrolidines **14**, **15**, **18**, **20**, **23,** and **25** in moderate-to-good overall yields (**Scheme 5**).[42–44] These displayed inhibitory activity against a variety of glycosidases. Pyrrolidines, with substituents positioned on either side of the ring nitrogen, were prepared by utilizing an α-azido-β-hydroxy aldehyde, such as racemic 2-azido-3-hydroxypropanal (**12**), as the acceptor for FDP aldolase.[42] Enantiomerically pure α-azidopropionaldehydes (*S*)-**16** and (*R*)-**16** were prepared by *Pseudomonas* lipase catalyzed resolution of a racemic intermediate diacetate.[43] Both aldehydes were useful substrates, although they resulted in lower overall yields of the corresponding iminocyclitols. Acetamido iminocyclitols were easily accessed using acceptors (*R*)-**21** and (*S*)-**21**.[44] These enantiomerically pure aldehydes were prepared using Amano PS lipase catalyzed resolution of a related racemic amine.

Although FDP aldolase has been used frequently for the synthesis of pyrrolidines, Fuc-1-P aldolase can also be employed (**Scheme 6**). The *S* enantiomer of racemic aldehyde **12** was selectively accepted by Fuc-1-P aldolase to provide ketone **26**, which was converted to the potent α-galactosidase inhibitor **27**.[45] Aldehyde (*S*)-**16** was accepted by Fuc-1-P aldolase, but a low yield of the aldol product **28** was obtained. However, the corresponding pyrrolidine **29** was produced from **28** in good yield (76%).[43]

As mentioned earlier, an imine intermediate forms in the intramolecular reductive amination step. Trapping this imine intermediate would provide an electrophilic functional group that could participate in nucleophilic additions, condensations, and cycloadditions. Moreover, the charge and shape of the imine intermediate should mimic the hypothesized transition states of glycoprocessing enzymes. With this goal in mind, a modified one-pot hydrogenation under acidic conditions was developed

(**Scheme 7**).[41] Azidopyranose **30** (prepared as a mixture of diastereomers by the FDP aldolase-catalyzed condensation of racemic **12** with DHAP as described in Scheme 5) underwent lipase-catalyzed butyration to give equatorial azide **31** and axial azide **33**, which were separated by silica gel chromatography. Hydrolysis of **31** and **33** provided **32** and **34**, respectively, in near-quantitative yields. Hydrogenation of **31** and **32** under acidic conditions provided the amine hydrochloride salts, which cyclized, without debutyration of **31**, to imines **35** and **36** upon addition of base. Similarly, **33** and **34** were converted to **37** and **38**, respectively. Cyclic imines **35**–**38** were chemically unstable, and were stored in acidic aqueous media (for weeks at –20 °C) as the ammonium hydrochloride salts of the amine precursors until needed in biological studies. Imine **36** inhibited β-glucosidase (almond, K_i = 16 μM), α-galactosidase (green coffee bean, K_i = 39 μM), and α-fucosidase (bovine epididymis, K_i = 5.5 μM). Compound **38** inhibited α-glucosidase (brewer's yeast, K_i = 2.6 μM), β-glucosidase (almond, K_i = 13 μM), and α-mannosidase (jack bean, K_i = 17 μM).

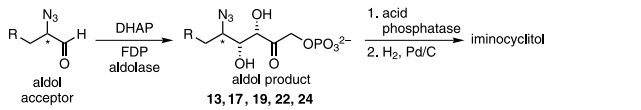
7. Aldolase-Mediated Synthesis of Polyhydroxylated Piperidines

7.1. Stereochemistry of the Intramolecular Reductive Amination Leading to Piperidines

A large number of polyhydroxylated piperidines have been prepared by placing a nucleophilic nitrogen atom one position farther away from the carbonyl group. Complete facial selectivity is usually observed for the reduction of the six-membered-ring imine intermediates (**Scheme 8**).[40,46] Reaction of 3-(benzyloxycarbonylamino)propanal (**39**) with DHAP using FDP aldolase produced phosphate **40**. Enzymatic dephosphorylation followed by removal of the benzyloxycarbamate led to a six-membered-ring imine intermediate, which underwent reductive amination to give fagomine (**41**) as the only diastereomer isolated. It was hypothesized that approach of hydrogen from the bottom face of the imine created the least amount of torsional strain upon rehybridization of the ring, and produced a trans relationship between the substituents at C-4 and C-5. In general, delivery of hydrogen onto six-membered-ring imines occurs (i) from the face opposite any axial hydroxyl groups adjacent to the centers undergoing the reduction, or (ii) to the face that generates the minimum torsional strain in the product. In cases where these two effects act at cross-purposes to each other, the former effect takes priority.[37]

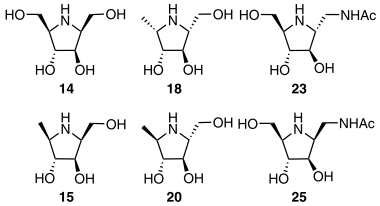
7.2. Extension to Other Piperidines with New Functional Groups and Different Stereochemical Configurations

Piperidines with more substituents than fagomine were prepared by starting with different acceptor aldehydes. These examples of aldolase-mediated synthesis of biologically active, naturally occurring iminocyclitols and their unnatural diastereomers are shown in **Scheme 9**. Enantiomerically pure aldehydes (*R*)- and (*S*)-**42** were prepared by *Pseudomonas* lipase catalyzed resolution of the 2-acetyl diethyl acetal precursor.[47] FDP aldolase catalyzed the reaction of (*S*)-**42** with DHAP to provide 1-deoxynojirimycin (**2**) in 64% overall yield after dephosphorylation and reductive amination of **43**.[40,46,48] The biological activity of **2** is extensive; it is an inhibitor of over twenty different glycosidases with low micromolar K_i values.[16] In a similar manner, (*R*)-**42** was also accepted as a substrate for FDP aldolase to produce 1-deoxymannojirimycin in 80% yield. The *N*-acetylhexosamine analogues **47**, **48**, **50**, and **51** were prepared using the masked

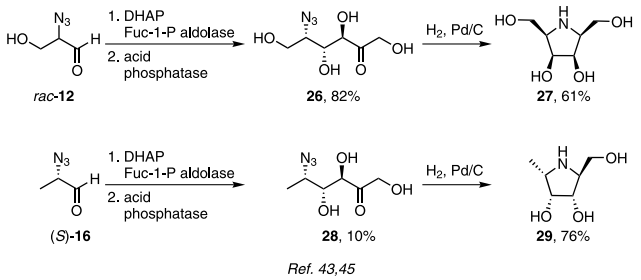


R	Aldol Acceptor	Iminocyclitol Yield[a]	Ref.
OH	*rac*-**12**	**14**, 76%	*42*
OH[b]	*rac*-**12**	**15**, 78%	*42*
H	(*S*)-**16**	**18**, 24%	*43*
H	(*R*)-**16**	**20**, 24%	*43*
NHAc	(*R*)-**21**	**23**, 67%	*44*
NHAc	(*S*)-**21**	**25**, 44%	*44*

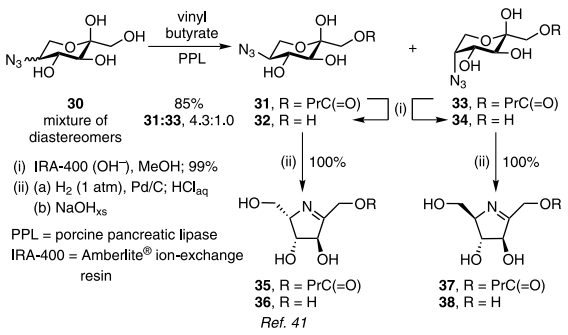
[a] Overall yield from the aldol acceptor. [b] **15** was obtained by skipping the acid phosphatase step.



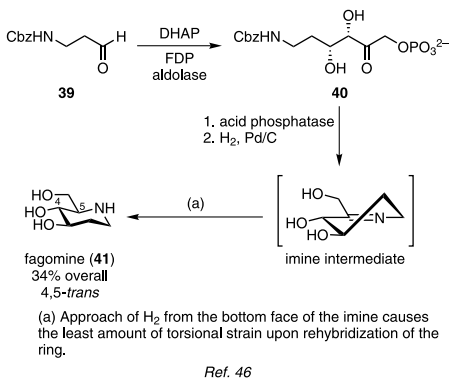
Scheme 5. Synthesis of Polyhydroxylated Pyrrolidines Using FDP Aldolase.



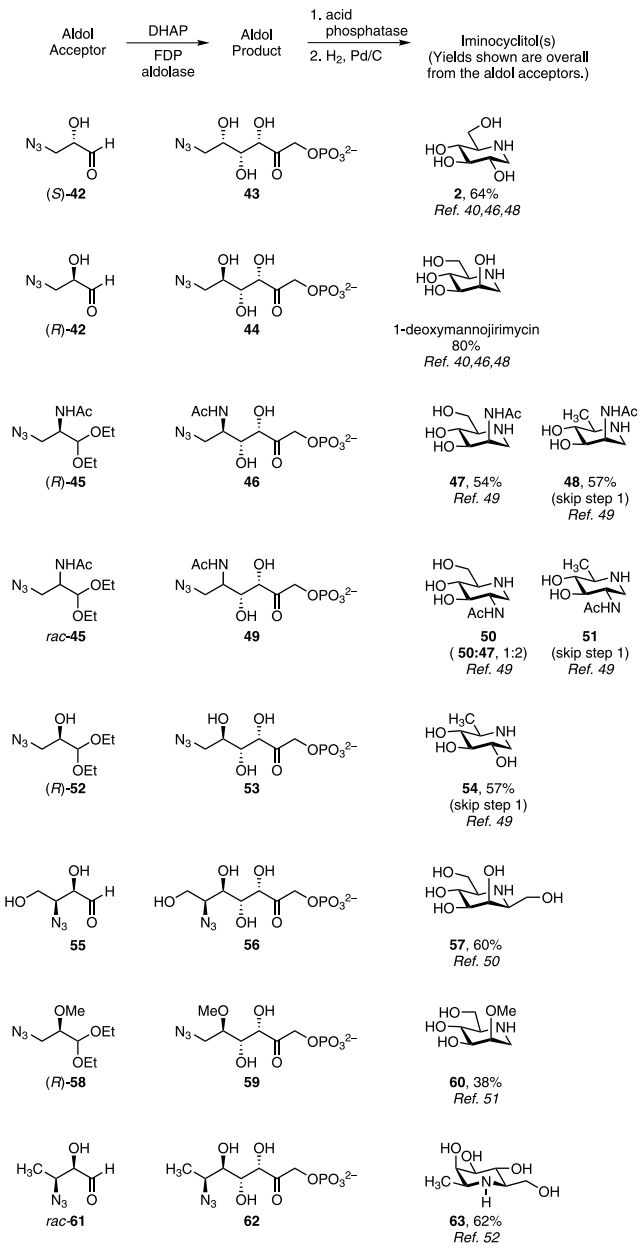
Scheme 6. Fuc-1-P Aldolase Catalyzed Synthesis of Polyhydroxylated Pyrrolidines.



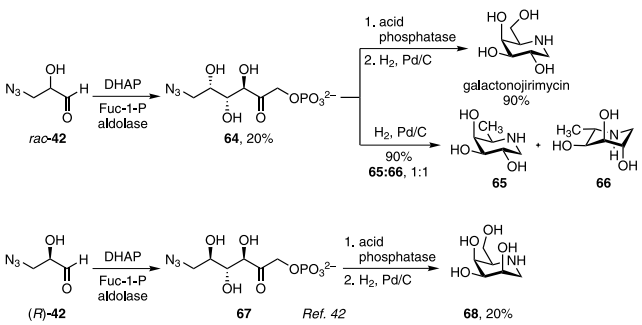
Scheme 7. Synthesis of Cyclic Iminocyclitols **35**–**38** Using a Modified One-Pot Hydrogenation.



Scheme 8. Stereochemistry of the Reductive Amination Leading to Fagomine (**41**).



Scheme 9. FDP Aldolase Catalyzed Synthesis of Polyhydroxylated Piperidines.



Scheme 10. Synthesis of Polyhydroxylated Piperidines Using Fuc-1-P Aldolase.

N-acetyl aldehyde acceptor **45**.[49] Enantiomerically pure diethyl acetal (*R*)-**45** was prepared by nucleophilic opening of an aziridine derived from (*S*)-**42**. The diethyl β-azido-α-hydroxyacetal (*R*)-**52** was efficiently converted into 1,6-dideoxynojirimycin **54**.[49] Racemic β-azido-α,γ-dihydroxy aldehyde **55** was accepted by FDP aldolase to eventually provide **57** as a single diastereomer.[50] The diethyl β-azido-α-methoxyacetal **58** was efficiently converted into **60**.[51] A route to the potent β-homofuconojirimycin (**63**) was developed through the use of racemic acceptor **61**.[52]

In contrast to FDP aldolase, which preferred the *R* aldehyde isomer, Fuc-1-P aldolase preferentially consumed (*S*)-**42** to furnish galactonojirimycin and iminocyclitols **65** and **66**, depending on whether the reduction with hydrogen was carried out on the dephosphorylated or monophosphorylated intermediate (**Scheme 10**).[42,53] Enantiomerically pure (*R*)-**42** reacted with Fuc-1-P aldolase to provide 1-deoxytalojirimycin (**68**).[42]

Racemic **42** was also accepted by Rham-1-P aldolase, with the enzyme again preferentially consuming the *S* enantiomer, in contrast to FDP aldolase (**Scheme 11**).[42,51,54] Iminocyclitols **70**, **71**, L-1-deoxynojirimycin, and **74** were accessed with this enzyme in variable yields.

Racemic aldehyde **75** (which can be prepared in enantiomerically pure form by the PSL-800 catalyzed resolution of the 2-acetylated diethyl acetal[55]) was accepted by FDP aldolase to provide azidofuranose **76** (**Scheme 12**).[41] Selective reduction of the azide under acidic conditions produced imine intermediate **77** (a potent inhibitor of α-fucosidase), which reacted in a three-center, two-component Strecker reaction to yield **78**. Reduction of the nitrile provided aminoiminocyclitol **79** in 99% yield.

In addition to the DHAP-dependent aldolases, DERA was applied to the synthesis of polyhydroxylated piperidines, with the advantage that enzymatic dephosphorylation was not required (**Scheme 13**).[36,53,56] Aldehyde (*S*)-**42** was accepted by DERA in a reaction with acetaldehyde to produce iminocyclitol **80** in 74% yield. Propanal was also a suitable donor aldehyde, which produced **81**, albeit in low yield, after reaction with (*S*)-**42**. Reaction of acetone and (*S*)-**42** provided **82** in 61% yield. The fluorinated iminocyclitol **83** was isolated, but reductive amination conditions resulted in loss of the halogen to produce **82** as the major product in 52% yield. These results indicate that the intramolecular reductive amination of the azidofuranoses provided the iminocyclitols with the stereochemistry expected from approach of hydrogen opposite the axial substituent.

8. Aldolase-Mediated Synthesis of Other Polyhydroxylated Heterocycles

Although the examples are less common, aldolases have been used in the synthesis of polyhydroxylated azepanes (**Scheme 14**) and pyrrolizidines. To accommodate the insertion of another carbon between the nitrogen and the carbonyl group, the dephosphorylated FDP aldolase product **84** (see structure **44** in Scheme 9) was partially converted into aldose **85** using glucose isomerase.[51] Following azide reduction and intramolecular reductive amination of **85**, azepane **86** was isolated in 24% overall yield from DHAP. The dephosphorylated Fuc-1-P aldolase product **87** (see structure **64** in Scheme 10) was similarly isomerized into aldose **88** by the action of fucose isomerase, although the product aldose was more favored in this case. Intramolecular reductive amination of **88** provided **89** in 19% overall yield from DHAP. Evaluation of **86** and **89** showed inhibition of various glycosidases.

In an elegant application of aldolases to the synthesis of pyrrolizidines, the *N*-formyl triol **90** was converted into the intermediate aldehyde **91** using sodium periodate in water (**Scheme 15**).[57] FDP aldolase catalyzed the reaction of DHAP with **91** to provide the aldol product **92** after dephosphorylation. A modified ozonolysis procedure incorporating reductive workup of the ozonide with hydrogen and palladium-on-carbon, followed by cleavage of the formamide, afforded 7-epialexine in 17% overall yield from **90**. Starting with *ent*-**90**, analogous routes produced 3-epiaustraline and australine in 21% and 16% overall yields, respectively. All three tetrahydroxylated pyrrolizidines belong to a class of alkaloids that have shown antiviral and retroviral activities as well as glucosidase inhibition.[5]

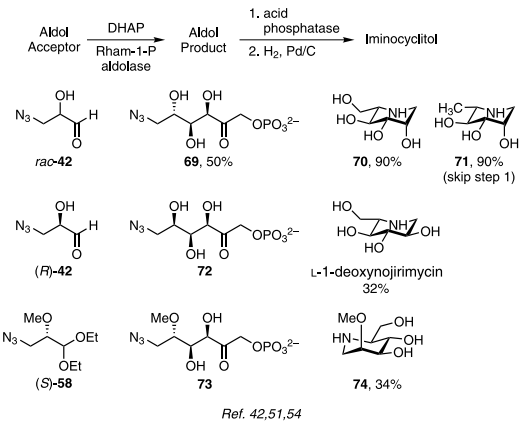
Mutant and wild type DERA have been applied to the synthesis of pharmaceutically relevant heterocycles. Mutation of the Ser 238 residue to Asp retained the hydrophilic nature of the binding pocket, but permitted neutral and positively charged groups on acceptor aldehydes. Using the DERA Ser238Asp mutant as catalyst, acetaldehyde and 3-azidopropionaldehyde underwent sequential aldol reactions to produce lactone **93** after oxidation of the product lactol (**Scheme 16**).[58] Compound **93** was then converted into a synthetic intermediate in a formal total synthesis of atorvastatin (Lipitor®).

Wild type DERA exhibited a switch in enantioselectivity based on the polarity of the α substituents of acceptor aldehydes (**Scheme 17**).[59] In this way, (*S*)-**94** was converted into aldehyde **95** in 48% yield, an inversion in selectivity for the enzyme. Compound **95** was converted into lactone **96** in two steps and 53% yield. When *rac*-**97** was employed in a similar, DERA-catalyzed aldol reaction, (*R*)-**97** was selected to provide aldehyde **98** following the usual selectivity exhibited by the enzyme. A series of conversions furnished vinyl iodide **99** (fragment B of epothilone A). The union of **99** and the **96**-derived fragment A of epothilone A furnished epothilone A after Suzuki coupling and subsequent manipulation of functional groups.

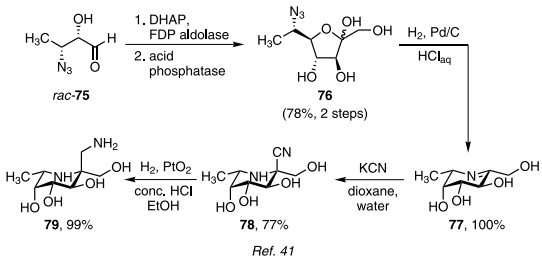
9. Conclusions

As the preceding examples illustrate, aldolases are powerful enzymes that may be applied to the synthesis of a wide variety of polyhydroxylated nitrogen-containing heterocycles. Although access to biologically active iminocyclitols is possible using aldolases, further diversification of the iminocyclitol cores provides routes to a greater number of structures that may have increased selectivity against specific targets. The construction of iminocyclitol libraries should permit rapid derivatization and analysis of a wide range of potential inhibitors with little-to-no protecting group manipulations. Reductive amination, imine formation, *N*-alkylation, and amide-bond formation reactions all lend themselves to this purpose. The library may be designed around a selected biological target or may center on the application of a specific reaction to provide a diverse range of functionality.

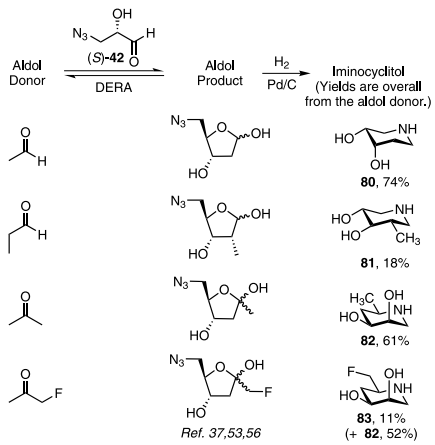
The construction and screening of iminocyclitol libraries is a valuable method for the discovery of compounds with biological activity related to glycosidase and glycosyltransferase inhibition. Although "almost all imaginable polyhydroxylated pyrrolidines and piperidines have already been synthesized",[21] only creativity and imagination limit the number of possible modifications that can be made to these scaffolds. For example, as part of a program targeting hexosaminidases[60–64] and fucose-processing enzymes,[65,66] combinatorial libraries of iminocyclitols were constructed using reductive amination as the diversification method. Screening of these libraries against various glycosidases identified several members that showed K_i values in the nano- to subpicomolar range (**Figure 4**).



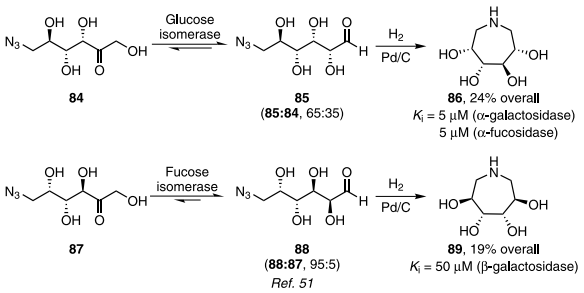
Scheme 11. Synthesis of Polyhydroxylated Piperidines Using Rham-1-P Aldolase.



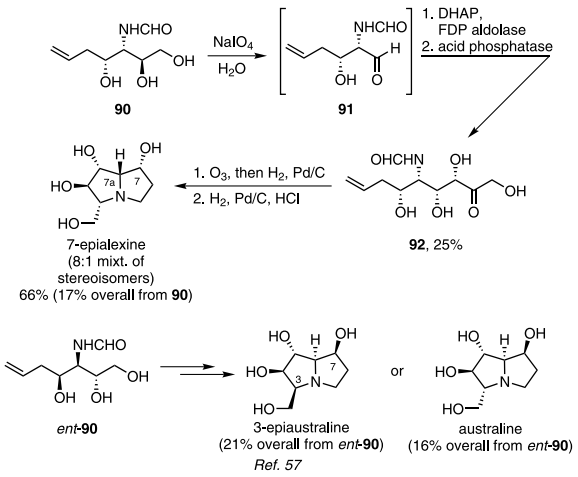
Scheme 12. Synthesis of Aminoiminocyclitol **79**.



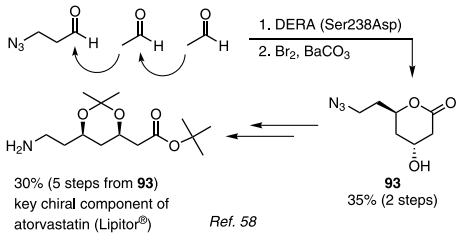
Scheme 13. DERA-Catalyzed Synthesis of Iminocyclitols **80**–**83**.



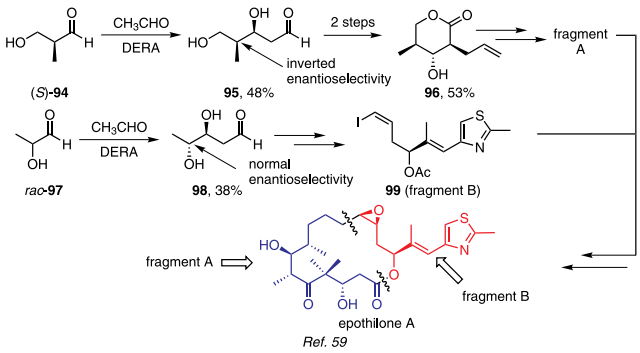
Scheme 14. Synthesis of Polyhydroxylated Azepanes **86** and **89**.



Scheme 15. Aldolase-Mediated Synthesis of 7-Epialexine, 3-Epiaustraline, and Australine.



Scheme 16. Formal Total Synthesis of Atorvastatin (Lipitor®) Using a DERA Mutant.



Scheme 17. Synthesis of Epothilone A Using DERA-Catalyzed Synthesis of 1,2- and 1,3-Diols.

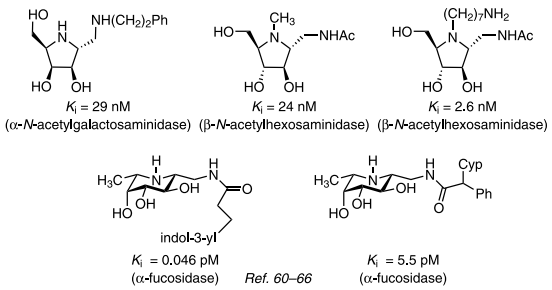


Figure 4. Iminocyclitol Combinatorial Library Members Showing Significant Glycosidase Inhibition.

10. Acknowledgements

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(64) Liang, P.-H.; Cheng, W.-C.; Lee, Y.-L.; Yu, H.-P.; Wu, Y.-T.; Lin, Y.-L.; Wong, C.-H. *ChemBioChem* **2006**, *7*, 165.
(65) Wu, C.-Y.; Chang, C.-F.; Chen, J. S.-Y.; Wong, C.-H.; Lin, C.-H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4661.
(66) Chang, C.-F.; Ho, C.-W.; Wu, C.-Y.; Chao, T.-A.; Wong, C.-H.; Lin, C.-H. *Chem. Biol.* **2004**, *11*, 1301.

About the Authors

Lisa J. Whalen obtained her B.S. degree in chemistry from the University of New Mexico in 1999. Following graduate work at the University of Colorado with Professor Randall Halcomb in the area of bioorganic chemistry, she began postdoctoral studies at The Scripps Research Institute with Professor Chi-Huey Wong in 2004. Her research interests include the study of mechanism-based enzyme inhibitors of sulfatases and aldolase-mediated synthesis of iminocyclitols.

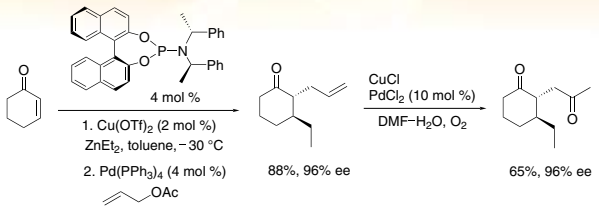
Chi-Huey Wong received his B.S. and M.S. degrees from National Taiwan University, and his Ph.D. in chemistry (with George M. Whitesides) in 1982 from the Massachusetts Institute of Technology. He then moved along with Professor Whitesides to Harvard University as a postdoctoral fellow for another year. He was on the chemistry faculty at Texas A&M University from 1983 to 1989, and has been Professor and Ernest W. Hahn Chair in Chemistry at The Scripps Research Institute since 1989. He was Head of the Frontier Research Program on Glycotechnology at RIKEN (Institute of Physical and Chemical Research) in Japan from 1991 to 1999. He has been serving as Director of the Genomics Research Center at Academia Sinica in Taipei, Taiwan, since 2003.

Professor Wong is a recipient of the Presidential Young Investigator Award in Chemistry (1986), the American Chemical Society A. C. Cope Scholar Award (1993), the Roy Whistler Award of the International Carbohydrate Organization (1994), the American Chemical Society Harrison Howe Award in Chemistry (1998), the Claude S. Hudson Award in Carbohydrate Chemistry (1999), the International Enzyme Engineering Award (1999), the Presidential Green Chemistry Challenge Award (2000), and the American Chemical Society Award for Creative Work in Synthetic Organic Chemistry (2005). His current research interests are in the areas of bioorganic and synthetic chemistry and biocatalysis, with specific focus on the development of new synthetic methods based on enzymatic and chemoenzymatic reactions, the study of carbohydrate-mediated biological recognition, and the development of mechanism-based inhibitors of enzymes and carbohydrate receptors.

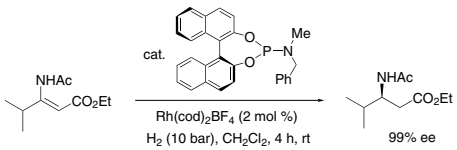
DSM MonoPhos™ Family
Highly Efficient Privileged Ligands

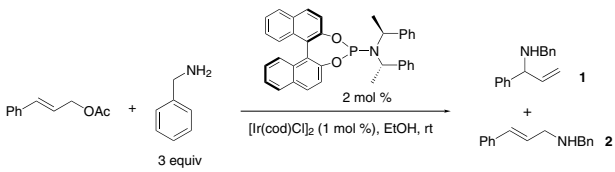
Product Highlights

- **Superior enantiocontrol in numerous transformations**
- **High activities at low catalyst loadings**
- **Hydrogenations under low-pressure conditions**
- **Applied in tandem reactions to yield valuable chiral organics**



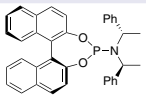
Feringa and co-workers have invented a diverse array of chiral, monodentate phosphoramidites based on the privileged BINOL platform.[1] The MonoPhos™ family has exhibited high levels of enantiocontrol in synthetic transformations ranging from metal-catalyzed asymmetric 1,4-additions of organometallic reagents to allylic alkylations to desymmetrization of *meso*-cycloalkene oxides.[2] Impressively, the (*S*)-*N*-benzyl-*N*-methyl-MonoPhos™ derivative has been utilized in highly selective hydrogenations of (*E*)-*N*-acylated dehydro-β-amino acid esters, affording the corresponding enantiopure β-amino acid derivatives.[3] Sigma-Aldrich, in collaboration with DSM, is pleased to offer a range of MonoPhos™ ligands for the research market.†





(*S,S,S*)-(+)-(3,5-Dioxa-4-phospha-cyclohepta[2,1-a;3,4-a′]dinaphthalen-4-yl)bis(1-phenylethyl)amine, 97% NEW

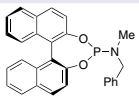
[*380230-02-4*]
$C_{36}H_{30}NO_2P$
FW: 539.60



665290-100MG	100 mg	$51.00
665290-500MG	500 mg	220.00
665290-2G	2 g	799.00

(*S*)-(+)-Benzyl-(3,5-dioxa-4-phospha-cyclohepta[2,1-a;3,4-a′]dinaphthalen-4-yl)methylamine, 97% NEW

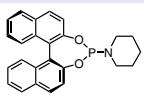
[*490023-37-5*]
$C_{28}H_{22}NO_2P$
FW: 435.45



665355-100MG	100 mg	$38.00
665355-500MG	500 mg	170.00
665355-2G	2 g	635.00

(*S*)-(+)-(3,5-Dioxa-4-phospha-cyclohepta[2,1-a;3,4-a′]dinaphthalen-4-yl)piperidine, 97% NEW

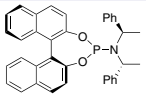
$C_{25}H_{22}NO_2P$
FW: 399.42



665479-100MG	100 mg	$35.00
665479-500MG	500 mg	160.00
665479-2G	2 g	550.00

(*S,R,R*)-(+)-(3,5-Dioxa-4-phospha-cyclohepta[2,1-a;3,4-a′]dinaphthalen-4-yl)bis(1-phenylethyl)amine, 97% NEW

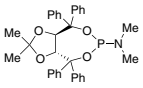
[*415918-91-1*]
$C_{36}H_{30}NO_2P$
FW: 539.60



665363-100MG	100 mg	$51.00
665363-500MG	500 mg	220.00
665363-2G	2 g	799.00

(3a*R*,8a*R*)-(–)-(2,2-Dimethyl-4,4,8,8-tetraphenyltetrahydro[1,3]dioxolo(4,5-e)[1,3,2]dioxaphosphepin-6-yl)dimethylamine, 96% NEW

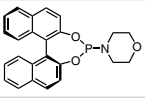
[*213843-90-4*]
$C_{33}H_{34}NO_4P$
FW: 539.60



665460-100MG	100 mg	$89.00
665460-500MG	500 mg	375.00

(*S*)-(+)-(3,5-Dioxa-4-phospha-cyclohepta[2,1-a;3,4-a′]dinaphthalen-4-yl)morpholine, 97% NEW

$C_{24}H_{20}NO_3P$
FW: 401.39



665487-100MG	100 mg	$35.00
665487-500MG	500 mg	160.00
665487-2G	2 g	550.00

(1) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346. (2) (a) Feringa, B. L. et al. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2620. (b) Martina, S. L. X. et al. *Tetrahedron Lett.* **2005**, *46*, 7159. (c) Malda, H. et al. *Org. Lett.* **2001**, *3*, 1169. (d) Alexakis, A. et al. *Chem. Commun.* **2005**, 2843. (e) Streiff, S. et al. *Chem. Commun.* **2005**, 2957. (f) Bertozzi, F. et al. *Org. Lett.* **2000**, *2*, 933. (g) Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 15164. (3) (a) Pena, D. et al. *J. Am. Chem. Soc.* **2002**, *124*, 14552. (b) Van den Berg, M. et al. *Adv. Synth. Catal.* **2003**, *345*, 308.

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Os EnCat™ 40

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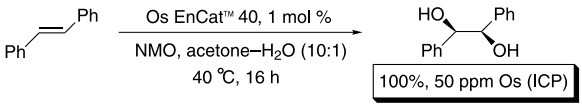
- Greater storage stability versus OsO_4
- Facile recovery of catalyst
- Low levels of Os metal in final product
- Catalyst can be recycled with no activity loss

Sigma-Aldrich, in collaboration with Reaxa Ltd., is pleased to offer first-to-market catalysts for use in practical synthetic transformations. Reaxa has immobilized osmium tetroxide, a toxic and volatile reagent, by encapsulation in a polyurea matrix to create Os EnCat™ 40. This innovative product offers safety and handling advantages versus conventional OsO_4, while acting as an alternative reagent in the industrially useful dihydroxylation reaction.

Ley, S. V. et al. Microencapsulation of Osmium Tetroxide in Polyurea. *Org. Lett.* **2003**, *5*, 185.

For comprehensive application information on Os EnCat™ 40, please visit us at sigma-aldrich.com/osencat.



Os EnCat™ 40, 0.3 mmol/g Os loading
Osmium tetroxide, microencapsulated

[*20816-12-0*]
OsO_4
FW: 254.23

658685-500MG	500 mg	$192.50
658685-1G	1 g	312.00
658685-5G	5 g	1,325.00

4-Methylmorpholine *N*-oxide, 97%

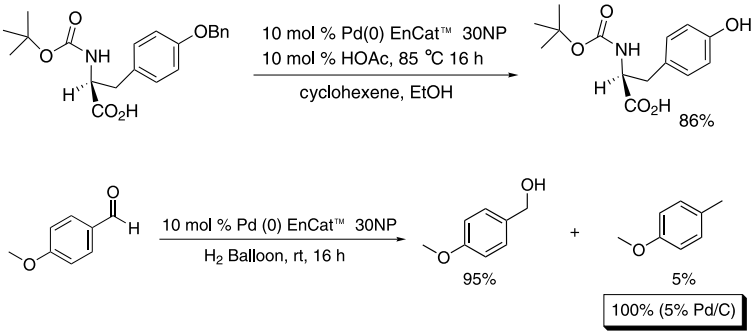
[*7529-22-8*]
$C_5H_{11}NO_2$
FW: 117.15

224286-5G	5 g	$12.20
224286-25G	25 g	40.20
224286-100G	100 g	143.50

Pd(0) EnCat™ 30NP

Highly Versatile Catalyst for Chemoselective Hydrogenations

- Safe and nonpyrophoric
- Trivial removal of catalyst from reactor
- Very low metal contamination of product
- Excellent catalyst recyclability
- Highly chemoselective under both hydrogenation & transfer hydrogenation conditions
- Excellent batch-to-batch reproducibility of catalyst activity



Pd(0) EnCat™ 30NP is a new microencapsulated hydrogenation catalyst offering key advantages over existing heterogeneous hydrogenation catalysts. Reductive transformations catalyzed by Pd(0) EnCat™ 30NP include aryl ketones, aldehydes, and epoxides to the corresponding alcohols; nitroarenes and aryl nitriles to the corresponding amines; alkenes and alkynes to the corresponding alkanes; and the debenzylation of aryl benzyl ethers.

Pd(0) EnCat™ 30NP wet, nanoparticles, 0.4 mmol/g Pd loading
Palladium(0), microencapsulated in polyurea matrix

Pd
FW: 106.42

653667-1G	1 g	$19.50
653667-10G	10 g	175.00
653667-100G	100 g	1,200.00

(1) Bremeyer, N.; Ley, S. V.; Ramarao, C.; Shirley, I. M.; Smith, S. C. *Synlett* **2002**, 1843. (2) (a) Yu, J.-Q.; Wu, H.-C.; Ramarao, C.; Spencer, J. B.; Ley, S. V. *Chem. Commun.* **2003**, 678. (b) Ley, S. V.; Mitchell, C.; Pears, D.; Ramarao, C.; Yu, J.-Q.; Zhou, W. *Org. Lett.* **2003**, *5*, 4665.

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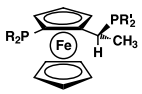
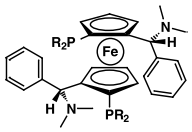
The Solvias Chiral Ligands Kit is designed to allow rapid screening of chiral catalysts, and contains sets of the well-known Solvias ligand families below.

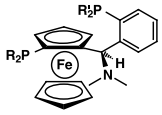


Josiphos

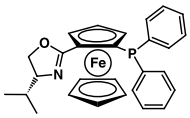
Walphos



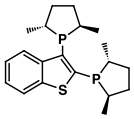
Mandyphos



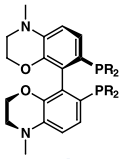
Taniaphos



Naud



Butiphane



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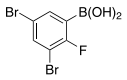
2-Bromo-6-fluoro-3-methoxyphenylboronic acid

662011
$C_7H_7BBrFO_3$
FW: 248.84

2 g	$19.50
10 g	69.50

3,5-Dibromo-2-fluorophenylboronic acid

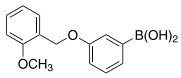
661937
$C_6H_4BBr_2FO_2$
FW: 297.71



1 g	$35.00
5 g	123.00

3-(2′-Methoxybenzyloxy)phenylboronic acid

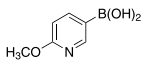
662089
$C_{14}H_{15}BO_4$
FW: 258.08



2 g	$44.50
10 g	155.00

2-Methoxy-5-pyridineboronic acid

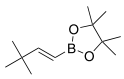
637610
[*163105-89-3*]
$C_6H_8BNO_3$
FW: 152.94



1 g	$53.50
5 g	171.50

trans-(3,3-Dimethylbutenyl)boronic acid pinacol ester, 97%

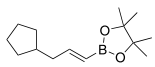
667277
$C_{12}H_{23}BO_2$
FW: 210.12



1 g	$45.00
5 g	150.00

trans-3-(Cyclopentyl)propenylboronic acid pinacol ester, 97%

667013
$C_{14}H_{25}BO_2$
FW: 236.16



1 g	$60.00

Potassium methyltrifluoroborate

637890
[*13862-28-7*]
CH_3BF_3K
FW: 121.94

1 g	$35.00
5 g	110.00

Potassium allyltrifluoroborate, 95%

659274
$C_3H_5BF_3K$
FW: 147.98

1 g	$45.00

Potassium isopropyltrifluoroborate, 97%

667153
$C_3H_7BF_3K$
FW: 149.99

1 g	$45.00

Potassium *sec*-butyltrifluoroborate, 97%

667145
$C_4H_9BF_3K$
FW: 164.02

1 g	$35.00

Potassium cyclopentyltrifluoroborate, 97%

666017
$C_5H_9BF_3K$
FW: 176.03

1 g	$70.00
5 g	240.00

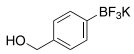
Potassium vinyltrifluoroborate, 95%

655228
[*13682-77-4*]
$C_2H_3BF_3K$
FW: 133.95

1 g	$25.00
5 g	83.20

Potassium 4-(hydroxymethyl)phenyltrifluoroborate, 97%

659762
$C_7H_7BF_3KO$
FW: 214.03

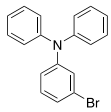


1 g	$24.00
5 g	80.00

Hole-Transport Materials

3-Bromo-*N*,*N*-diphenylaniline, 97%

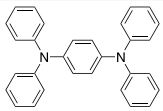
647527
[*78600-33-6*]
$C_{18}H_{14}BrN$
FW: 324.21



1 g	$24.00
5 g	84.50

1,4-Bis(diphenylamino)benzene, 97%

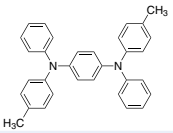
663271
[*14118-16-2*]
$C_{30}H_{24}N_2$
FW: 412.52



1 g	$18.00
10 g	120.00

N,*N*′-Diphenyl-*N*,*N*′-di-*p*-tolylbenzene-1,4-diamine

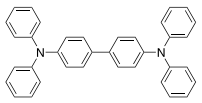
663263
[*138171-14-9*]
$C_{32}H_{28}N_2$
FW: 440.58



1 g	$40.00
5 g	135.00

Tetra-*N*-phenylbenzidine, 97%

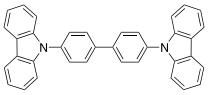
658812
[*15546-43-7*]
$C_{36}H_{28}N_2$
FW: 488.62



5 g	$115.00

4,4′-Bis(*N*-carbazolyl)-1,1′-biphenyl, 97%

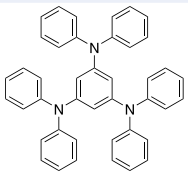
660124
[*58328-31-7*]
$C_{36}H_{24}N_2$
FW: 484.59



1 g	$37.50
5 g	125.00

1,3,5-Tris(diphenylamino)benzene, 97%

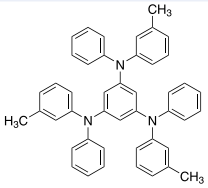
663247
[*126717-23-5*]
$C_{42}H_{33}N_3$
FW: 579.73



5 g	$55.00
10 g	99.00

1,3,5-Tris[(3-methylphenyl)phenylamino]benzene, 97%

663239
[*138143-23-4*]
$C_{45}H_{39}N_3$
FW: 621.81



1 g	$45.00
10 g	250.00

Organic Building Blocks

(*R*)-(+)-3,3,3-Trifluoro-1,2-epoxypropane, 97%

667005 [*143142-90-9*]
$C_3H_3F_3O$
FW: 112.05

250 mg	$70.00
1 g	200.00

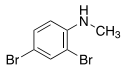
(*S*)-(–)-3,3,3-Trifluoro-1,2-epoxypropane, 97%

665797
$C_3H_3F_3O$
FW: 112.05

250 mg	$70.00
1 g	200.00

2,4-Dibromo-*N*-methylaniline, 97%

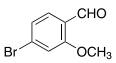
665886 [*73557-58-1*]
$C_7H_7Br_2N$
FW: 264.95



1 g	$35.00
5 g	115.00

4-Bromo-2-methoxybenzaldehyde, 97%

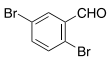
661880 [*43192-33-2*]
$C_8H_7BrO_2$
FW: 215.04



1 g	$88.00
5 g	294.00

2,5-Dibromobenzaldehyde, 97%

661899 [*74553-29-0*]
$C_7H_4Br_2O$
FW: 263.91



1 g	$37.20
5 g	124.00

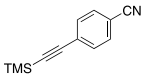
2-Bromobenzaldehyde ethylene acetal, 96%

652652 [*34824-58-3*]
$C_9H_9BrO_2$
FW: 229.07

5 g	$17.20
25 g	61.40

4-Trimethylsilylethynylbenzonitrile, 97%

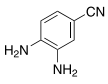
658391 [*75867-40-2*]
$C_{12}H_{13}NSi$
FW: 199.32



1 g	$24.50
10 g	135.00

3,4-Diaminobenzonitrile, 97%

653845 [*17626-40-3*]
$C_7H_7N_3$
FW: 133.15



1 g	$23.40
10 g	129.00

2-Methoxy-3-pyridinecarboxaldehyde, 96%

632139 [*71255-09-9*]
$C_7H_7NO_2$
FW: 137.14

1 g	$47.20
5 g	155.50

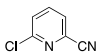
3-Chloro-4-pyridinecarboxaldehyde, 97%

636746 [*72990-37-5*]
C_6H_4ClNO
FW: 141.56

1 g	$28.90
5 g	92.90

6-Chloropyridine-2-carbonitrile, 96%

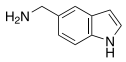
665967 [*33252-29-8*]
$C_6H_3ClN_2$
FW: 138.55



1 g	$60.00
5 g	200.00

5-(Aminomethyl)indole, 95%

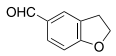
655864
$C_9H_{10}N_2$
FW: 146.19



1 g	$50.00
5 g	180.00

2,3-Dihydrobenzofuran-5-carboxaldehyde, 97%

631957 [*55745-70-5*]
$C_9H_8O_2$
FW: 148.16



1 g	$20.50
5 g	67.60

Benzo[*b*]thiophene-3-carbonitrile, 97%

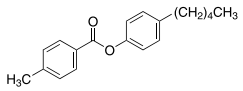
665975 [*24434-84-2*]
C_9H_5NS
FW: 159.21

1 g	$45.00

Liquid Crystals

4-Pentylphenyl 4-methylbenzoate, 97%

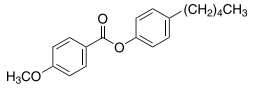
665754 [*50649-59-7*]
$C_{19}H_{22}O_2$
FW: 282.38



1 g	$48.00
5 g	160.00

4-Pentylphenyl 4-methoxybenzoate, 97%

665762 [*38444-13-2*]
$C_{19}H_{22}O_3$
FW: 298.38



5 g	$80.00

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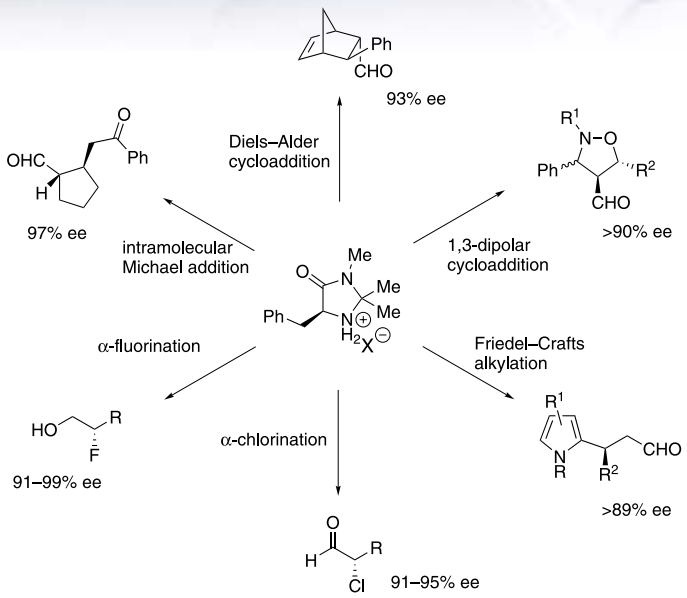
- Extraordinary functional group tolerance

MacMillan and co-workers have created chiral imidazolidinone organocatalysts that function as the linchpin in a variety of directed enantioselective organic reactions including Diels–Alder and 1,3-dipolar cycloadditions, conjugate additions such as α-fluorinations, α-chlorinations and Friedel-Crafts alkylations, epoxidations, transfer hydrogenations, and organo-cascade reactions. Sigma-Aldrich, in collaboration with Materia, Inc., is pleased to offer ten imidazolidinone organocatalysts that mediate rapid and enantiocontrolled C–C and C–X (X = H, O, halogen) bond formation.

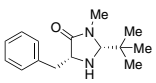


References

(1) For a review on organocatalysis, see Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79. (2) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243. (3) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458. (4) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051. (5) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370.

(2*R*,5*R*)-(+)-2-*tert*-Butyl-3-methyl-5-benzyl-4-imidazolidinone, 97% NEW

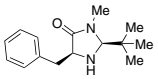
[*390766-89-9*]
$C_{15}H_{22}N_2O$
FW: 246.35



663093-500MG	500 mg	$60.00
663093-1G	1 g	95.00

(2*S*,5*S*)-(–)-2-*tert*-Butyl-3-methyl-5-benzyl-4-imidazolidinone, 97% NEW

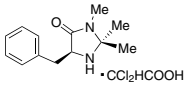
[*346440-54-8*]
$C_{15}H_{22}N_2O$
FW: 246.35



663107-500MG	500 mg	$60.00
663107-1G	1 g	95.00

(5*S*)-(–)-2,2,3-Trimethyl-5-benzyl-4-imidazolidinone dichloroacetic acid, 97% NEW

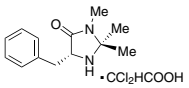
$C_{15}H_{20}Cl_2N_2O_3$
FW: 347.24



663085-500MG	500 mg	$55.00
663085-2G	2 g	150.00

(5*R*)-(+)-2,2,3-Trimethyl-5-benzyl-4-imidazolidinone dichloroacetic acid, 97% NEW

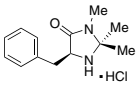
$C_{15}H_{20}Cl_2N_2O_3$
FW: 347.24



663077-500MG	500 mg	$55.00
663077-2G	2 g	150.00

(5*S*)-2,2,3-Trimethyl-5-phenylmethyl-4-imidazolidinone monohydrochloride, 97% NEW

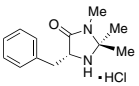
[*278173-23-2*]
$C_{13}H_{18}N_2O{\cdot}HCl$
FW: 254.76



569763-500MG	500 mg	$30.00
569763-2G	2 g	80.60

(5*R*)-(+)-2,2,3-Trimethyl-5-phenylmethyl-4-imidazolidinone monohydrochloride, 97% NEW

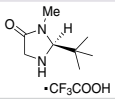
[*323196-43-6*]
$C_{13}H_{18}N_2O{\cdot}HCl$
FW: 254.76



663069-500MG	500 mg	$30.00
663069-2G	2 g	80.00

(*S*)-2-(*tert*-Butyl)-3-methyl-4-oxoimidazolidinium trifluoroacetate NEW

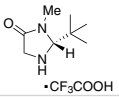
$C_{10}H_{17}F_3N_2O_3$
FW: 270.25



661902-500MG	500 mg	$50.00
661902-2G	2 g	165.00

(*R*)-2-(*tert*-Butyl)-3-methyl-4-oxoimidazolidinium trifluoroacetate NEW

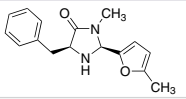
$C_{10}H_{17}F_3N_2O_3$
FW: 270.25



661910-500MG	500 mg	$50.00
661910-2G	2 g	165.00

(2*S*,5*S*)-5-Benzyl-3-methyl-2-(5-methyl-2-furyl)-4-imidazolidinone NEW

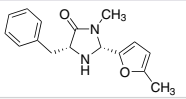
[*415678-40-9*]
$C_{16}H_{18}N_2O_2$
FW: 270.33



668540-250MG	250 mg	$79.50
668540-1g	1 g	215.00

(2*R*,5*R*)-5-Benzyl-3-methyl-2-(5-methyl-2-furyl)-4-imidazolidinone NEW

$C_{16}H_{18}N_2O_2$
FW: 270.33



668842-250MG	250 mg	$79.50
668842-1g	1 g	215.00

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Modern Strategies in Organic Catalysis: The Advent and Development of Iminium Activation

Dr. Gérald Lelais

Professor D. W. C. MacMillan

*Gérald Lelais and David W. C. MacMillan**
Department of Chemistry
California Institute of Technology
1200 E. California Blvd., Mail Code 164-30
Pasadena, CA 91125, USA
Email: dmacmill@caltech.edu

Outline

1. Introduction

Enantioselective organocatalysis has become a field of central importance for the asymmetric synthesis of chiral molecules. In the last ten years alone, this field has grown at an extraordinary pace from a small collection of chemically unique reactions to a thriving area of general concepts, atypical reactivities, and widely applicable reactions.[1–4] Moreover, novel modes of substrate activation have been achieved using organic catalysts that can now deliver unique, orthogonal, or complementary selectivities in comparison to many established metal-catalyzed transformations. The present review will discuss the advent and development of one of the youngest subfields of organocatalysis, namely iminium activation. The first section will introduce the concept of iminium catalysis and the rationale for the development of a broadly general catalyst. The following sections will describe the most significant types of transformations in which the concept of iminium activation has been successfully applied including cycloadditions, conjugate additions, Friedel–Crafts alkylations, Mukaiyama–Michael additions, transfer hydrogenations, and enantioselective organocatalytic cascade reactions.

2. Iminium Activation: Concept Development and Catalyst Design

In 1999, our laboratory introduced a new strategy for asymmetric synthesis based on the capacity of chiral amines to function as enantioselective LUMO-lowering catalysts for a range of transformations that had traditionally employed Lewis acids. This strategy, termed iminium activation, was founded on the mechanistic postulate that (i) the LUMO-lowering activation and (ii) the kinetic lability towards ligand substitution that enable the turnover of Lewis acid catalysts might also be available with a carbogenic system that exists as a rapid equilibrium between an electron-deficient and a relatively electron-rich state (**Scheme 1**).[5] With this in mind, we hypothesized that the reversible formation of iminium ions from α,β-unsaturated aldehydes and amines might emulate the equilibrium dynamics and π-orbital electronics that are inherent to Lewis acid catalysis, thereby providing a new platform for the design of organocatalytic processes. On this basis, we first proposed (in 2000) the attractive prospect that chiral amines might function as enantioselective catalysts for a range of transformations that traditionally utilize metal salts.[5]

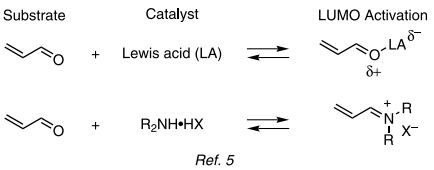
2.1. First-Generation Imidazolidinone Catalyst

Preliminary experimental findings and computational studies demonstrated the importance of four objectives in the design of a broadly useful iminium-activation catalyst: (i) The chiral amine should undergo efficient and reversible iminium ion formation. (ii) High levels of control of the iminium geometry and (iii) of the selective discrimination of the olefin π face should be achieved in order to control the enantioselectivity of

the reaction. (iv) In addition, the ease of catalyst preparation and implementation would be crucial for the widespread adoption of this organocatalytic technology. The first catalyst to fulfill all four criteria was imidazolidinone **1** (**Figure 1, Part A**). As suggested from computational modeling, the catalyst-activated iminium ion, MM3-**2**, was expected to selectively form as the depicted *E* isomer to avoid nonbonding interactions between the substrate olefin and the *gem*-dimethyl substituents on the catalyst framework. In terms of enantiofacial discrimination, the calculated iminium structure MM3-**2** revealed that the benzyl group of the imidazolidinone moiety would effectively shield the *Si* face of the iminium ion, leaving the *Re* face exposed for selective bond formation. The effectiveness of imidazolidinone **1** as an iminium-activation catalyst was confirmed by its use in enantioselective Diels–Alder reactions,[5] nitrone additions,[6] and Friedel–Crafts alkylations employing electron-rich pyrrole systems.[7] However, a diminished reactivity was observed when heteroaromatics such as indoles and furans were used as π nucleophiles in similar Friedel–Crafts conjugate additions. To overcome such limitations, we embarked upon studies to identify a more reactive and versatile amine catalyst. This led ultimately to the discovery of the "second-generation" imidazolidinone catalyst **3** (**Figure 1, Part B**).[8]

2.2. Second-Generation Imidazolidinone Catalysts

Preliminary kinetic studies with the first-generation catalyst **1** indicated that the overall rates of iminium-catalyzed reactions were influenced by the efficiency of both the initial iminium ion and the carbon–carbon bond-forming steps. We hypothesized that imidazolidinone **3** would form the iminium ion **4** more efficiently and, hence, increase the overall reaction rate, since the participating nitrogen lone pair is positioned away from structural impediments. This is in contrast to the CH_3–lone pair eclipsing orientation in MM3-**1** and the fact that π nucleophiles that engage the activated iminium ion **2** encounter a retarding interaction with the illustrated methyl substituent. The reactive enantioface of iminium ion **4** is free from such steric obstruction and should exhibit increased reactivity towards the formation of carbon–carbon bonds. In terms of our design criteria for enantiocontrol, the catalyst-activated iminium ion **4** was anticipated to selectively populate the *E* isomer to avoid nonbonding interactions between the carbon–carbon double bond and the *tert*-butyl group. In addition, the benzyl and *tert*-butyl groups on the imidazolidinone framework effectively shield the *Si* face of the activated olefin, leaving the *Re* face exposed to a large range of nucleophiles. Indeed, since their introduction in 2001, imidazolidinone catalysts of type **3** have been successfully applied (≥90% ee's, ≥75% yields) to a broad range of chemical transformations, including cycloadditions,[9,10] conjugate additions,[8,11,12] hydrogenations,[13] epoxidations, and cascade reactions.[14,15]



Scheme 1. Iminium Activation through LUMO Lowering.

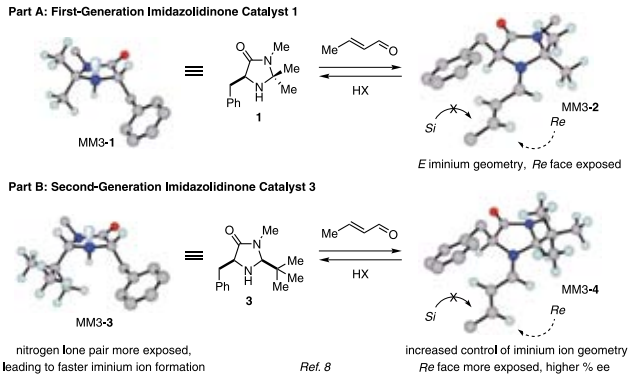


Figure 1. Computational Models of the First- and Second-Generation Imidazolidinone Catalysts (**1** and **3**) and of the Corresponding Iminium Ions.

3. Cycloaddition Reactions

3.1. Diels–Alder Reaction

The Diels–Alder reaction is arguably one of the most powerful organic transformations in chemical synthesis. In particular, asymmetric catalytic variants have received unprecedented attention, presumably due to their capacity to rapidly afford complex enantioenriched carbocycles from simple substrates.[16] It is not surprising therefore that the Diels–Alder reaction has become a benchmark transformation by which to evaluate new asymmetric catalysts or catalysis concepts. In keeping with this tradition, our original disclosure of the concept of iminium catalysis was made in the context of enantioselective catalytic Diels–Alder reactions. In these studies, a range of α,β-unsaturated aldehydes were exposed to a variety of dienes in the presence of chiral imidazolidinone **1** to afford [4 + 2] cycloaddition adducts with high levels of enantioselectivity (**Table 1**).[5] Remarkably, the presence of water exhibited beneficial effects on both reaction rates and selectivities, while facilitating the iminium ion hydrolysis step in the catalytic cycle. Computational studies suggest an asynchronous mechanism for the reaction,[17,18] where attack of the diene onto the β-carbon atom of the iminium ion is rate-limiting,[17] and the π–π interaction between the olefinic π system of the iminium ion (dienophile) and the phenyl ring of the benzyl group on the imidazolidinone moiety accounts for the selectivity of the reaction.[5,18]

Since our initial iminium catalysis publication, amine-catalyzed Diels–Alder reactions of α,β-unsaturated aldehydes have been investigated in much detail.[10,19–25] For example, catalyst immobilization (on solid support[19,20] or in ionic liquids[22]) has demonstrated the capacity for imidazolidinone recycling, while maintaining good levels of asymmetric induction.[19b] Moreover, the scope of the reaction was recently extended to include α-substituted acrolein dienophiles as reaction partners.[24]

Another important application of the iminium catalysis concept concerned the development of enantioselective Type I[10,23] and Type II[10] intramolecular Diels–Alder reactions (IMDA). For these transformations, both catalysts **1** and **3** proved to be highly efficient, affording bicyclic aldehyde products in good yields and with excellent enantio- and diastereoselectivities. Importantly, the utility of this organocatalytic approach was demonstrated by both the short and efficient preparation of the marine metabolite solanapyrone D via Type I IMDA and the development of an early example of an enantioselective, catalytic Type II IMDA reaction (**Scheme 2**).[10,26a]

In 2001, a long-standing challenge for the field of asymmetric catalysis remained the use of simple ketone dienophiles in Diels–Alder reactions with high levels of enantioselectivity. The success of chiral Lewis acid mediated Diels–Alder reactions up until that point was founded upon the use of dienophiles such as aldehydes, esters, quinones, and bidentate chelating carbonyls that achieve high levels of lone-pair discrimination in the metal-association step, an organizational event that is essential for enantiocontrol. In contrast, Lewis acid coordination is traditionally a nonselective process with ketone dienophiles, since the participating lone pairs are positioned in similar steric and electronic environments (**Scheme 3, Part A**).[9] Diastereomeric activation pathways in this case often lead to poor levels of enantiocontrol and ultimately have almost completely precluded the use of simple ketone dienophiles in asymmetric catalytic Diels–Alder reactions.[26b] Having demonstrated the utility of iminium activation to provide LUMO-lowering catalysis outside the mechanistic confines of lone-pair coordination,[5–8] we hypothesized that amine catalysts might also enable simple ketone dienophiles to function as useful substrates for enantioselective Diels–Alder reactions. In this case, the capacity to perform substrate activation through specific lone-pair coordination is replaced by the requirement for selective π-bond formation (**Scheme 3, Part B**).[9] With this in mind, our laboratory developed the first general and enantioselective catalytic Diels–Alder reaction using simple α,β-unsaturated ketones as dienophiles (**Table 2**).[9] Importantly, whereas methyl ketones were usually poor substrates, higher-order derivatives (R = Et, Bu, isoamyl) afforded good levels of enantiocontrol and high endo selectivities.

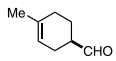
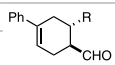
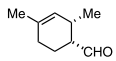
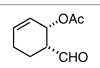
3.2. [3 + 2] Cycloaddition

The 1,3 cycloaddition of nitrones to alkenes is a fast and elegant way to prepare isoxazolidines that are important building blocks for biologically active compounds.[27] In this context, asymmetric Lewis acid catalyzed nitrone cycloadditions have been successfully accomplished with α,β-unsaturated imide substrates.[28] However, only limited examples of monodentate carbonyl substrates as nitrone-cycloaddition partners have been reported with chiral Lewis acids, presumably due to competitive coordination (and deactivation) of the Lewis basic nitrone component by the catalytic Lewis acid.[29–31] As this deactivation issue cannot arise in the realm of iminium activation, we were able to successfully apply our organocatalytic, LUMO-lowering strategy to the [3 + 2] cycloaddition of nitrones to α,β-unsaturated aldehydes (**Table 3**).[6] Recently, a polymer-supported version of catalyst **1** was also used in the nitrone cycloaddition with promising results.[32] Subsequently, Karlsson and Högberg expanded the scope of the reaction to achieve the 1,3-dipolar cycloaddition of nitrones to cyclic α,β-unsaturated aldehydes, allowing for the formation of fused bicyclic isoxazolidines.[33,34]

3.3. [2 + 1] Cycloaddition

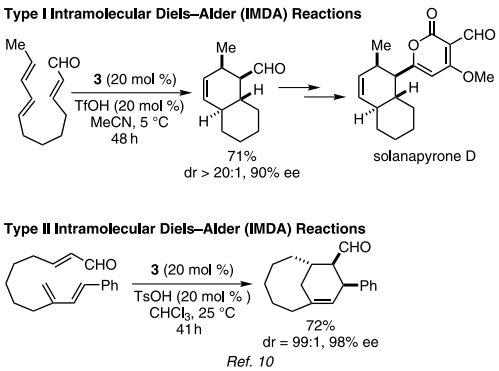
The enantioselective construction of three-membered hetero- or carbocyclic rings remains an important objective in synthetic organic chemistry, and the important advances made in iminium ion activation have enabled the asymmetric construction of α-formyl cyclopropanes and epoxides. For cyclopropane synthesis, our laboratory introduced a new type of amine catalyst, **6**, that is capable of performing the enantioselective stepwise [2 + 1] union of sulfonium ylides and α,β-unsaturated aldehydes (**Table 4**).[35] It should be mentioned that the iminium species derived from amine catalysts **1** or **3** were completely inert to the same sulfonium ylides used. However, proline, a usually

Table 1. Organocatalyzed Diels–Alder Cycloadditions of α,β-Unsaturated Aldehydes[a]

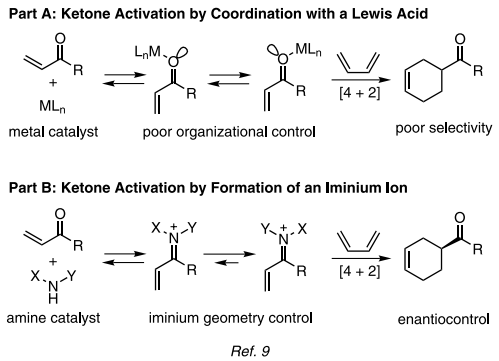
Diene	R in (*E*)-RCH=CHCHO	Product	Yield (%)	Endo:Exo	ee[b] (%)
CpH	Me		75	1:1	90[c]
CpH	Pr		92	1:1	90[c]
CpH	*i*-Pr		81	1:1	93[c]
CpH	Ph		99	1:1.3	93[c]
CpH	furan-2-yl		89	1:1	93[c]
1,3-cyclohexadiene	H		82	14:1	94[c]
$H_2C=C(Me)CH=CH_2$	H		84	—	89
$H_2C=C(Ph)CH=CH_2$	H		90	—	83
$H_2C=C(Ph)CH=CH_2$	Me		75	—	90
(*E*)-$H_2C=C(Me)CH=CHMe$	H		75	5:1	90
(*E*)-$H_2C=CHCH=CHOAc$	H		72	11:1	85

[a] **1**•HCl (20 mol %), MeOH–H_2O, 23 °C, 3–24 h. [b] Of the endo product. [c] Using 5 mol % of catalyst.

Ref. 5

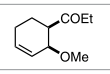
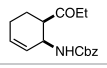
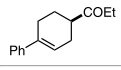
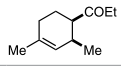
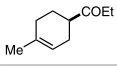


Scheme 2. Type I and II Organocatalytic Intramolecular Diels–Alder (IMDA) Reactions.

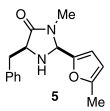


Scheme 3. The Use of Simple Ketones as Dienophiles in the Diels–Alder Reaction.

Table 2. Organocatalyzed Diels–Alder Cycloadditions of α,β-Unsaturated Ketones[a]

Dienophile R	Dienophile R^1	Diene	Product	Endo:Exo	ee[b] (%)
Me	Et	CpH		25:1	90
Me	*n*-Bu	CpH		22:1[c]	92
Me	*i*-Am	CpH		20:1	92
Pr	Et	CpH		15:1	92
i-Pr	Et	CpH		6:1	90
H	Et	H_2C=CHCH=CHOMe		>200:1[d]	96
H	Et	H_2C=CHCH=CHNHCbz		>100:1[d]	98
H	Et	H_2C=C(Ph)CH=CH_2		>200:1[e,f]	90
H	Et	(*E*)-H_2C=C(Me)CH=CHMe		>200:1[d]	90
H	Et	H_2C=C(Me)CH=CH_2		>200:1[c,f,g]	85
2-cycloheptenone		CpH		18:1	90
2-cyclooctenone		CpH		6:1	91
(*E*)-2-cyclopentadecenone		CpH	n=2,3,10	5:1[h]	93

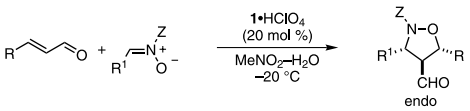
[a] **5**•$HClO_4$ (20 mol %), H_2O, 0 °C; 78–92% yields. [b] Of the endo product. [c] No solvent was used. [d] EtOH, –30 °C. [e] EtOH, –40 °C. [f] Ratio of regioisomers. [g] –20 °C. [h] 1,2-*trans*-tricyclo[15.2.1.0]eicos-18-en-3-one was obtained.



5

Ref. 9

Table 3. Organocatalytic 1,3-Dipolar Cycloaddition[a]



R	R^1	Z	Yield (%)	Endo:Exo	ee[b] (%)
Me	Ph	Bn	98	94:6	94
Me	Ph	allyl	73	93:7	98
Me	Ph	Me	66	95:5	99
Me	4-ClC_6H_4	Bn	78	92:8	95
Me	4-ClC_6H_4	Me	76	93:7	94
Me	4-$MeOC_6H_4$	Bn	93	98:2	91
Me	4-MeC_6H_4	Me	82	93:7	97
Me	2-Naph	Bn	98	95:5	93
Me	Cy	Bn	70	99:1	99
H	Ph	Bn	72	81:19	90
H	Ph	Bn	80	86:14	92[c]
H	4-MeC_6H_4	Bn	80	85:15	90[c]
H	4-ClC_6H_4	Bn	80	80:20	91[c]
H	2-Naph	Bn	82	81:19	90[c]
H	4-$MeOC_6H_4$	Bn	83	91:9	90[c]

[a] 35–160 h. [b] Of the endo product. [c] Using 20 mol % of **1**•TfOH.

Ref. 6

poor catalyst for iminium activation, provided good levels of conversion and moderate enantioselectivities. The zwitterionic iminium ion derived from catalyst **6** and the α,β-unsaturated aldehyde enables both iminium geometry control and directed electrostatic activation of the approaching sulfonium ylides. This combination of geometric and electronic control is believed to be essential for enantio- and diastereocontrol in forming two of the three cyclopropyl bonds.

Recently, Jørgensen and co-workers have demonstrated that the epoxidation of a broad range of substituted α,β-unsaturated aldehydes can be carried out in good yields and with high levels of enantioselectivity in the presence of amine **7** and a stoichiometric amount of an oxidizing agent (**Table 5**).[36] In addition, our group has found that catalyst **3** can perform the same reaction with similar results.[37]

3.4. [4 + 3] Cycloaddition

Several laboratories are currently investigating the potential of iminium catalysis for the asymmetric catalytic construction of other cycloaddition products. For example, an elegant approach for the preparation of enantioenriched seven-membered rings has recently been described by Harmata and co-workers.[38] This study involves the organocatalytic, asymmetric [4 + 3] cycloaddition of dienes with silyloxypentadienals in the presence of amine catalyst **3** (**eq 1**). It is notable that, among all asymmetric [4 + 3] cycloaddition reactions that have been reported to date, this methodology represents the first organocatalytic version.

4. 1,4-Addition Reactions

4.1. Friedel–Crafts Alkylations and Mukaiyama–Michael Reactions

The metal-catalyzed addition of aromatic substrates to electron-deficient σ and π systems, commonly known as Friedel–Crafts alkylation, has long been established as a powerful strategy for C–C-bond formation.[39–41] Surprisingly, however, relatively few enantioselective catalytic approaches have been reported that exploit this reaction manifold, despite the widespread availability of electron-rich aromatics and the chemical utility of the resulting products. To further demonstrate the value of iminium catalysis, we also undertook the development of asymmetric Friedel–Crafts alkylations that had been previously unavailable using acid or metal catalysis. Indeed, it has been documented that α,β-unsaturated aldehydes are poor electrophiles for pyrrole, indole, or aryl conjugate additions due to the capacity of electron-rich aromatics to undergo acid-catalyzed 1,2-carbonyl attack instead of 1,4 addition.[42,43] In contrast, we have recently demonstrated that a broad range of π nucleophiles such as pyrroles,[7] indoles,[8] anilines,[11] and silyloxyfuran derivatives[12] can be successfully utilized in 1,4-addition reactions with various α,β-unsaturated aldehydes in the presence of catalytic amounts of chiral amines **1** or **3** (**Scheme 4**). The corresponding conjugate addition adducts were obtained in high yields and excellent enantioselectivities. It is important to note that only 1,4-addition products were formed in all cases, thereby demonstrating the possibility of accessing complementary chemoselectivities when using organic catalysis. The effectiveness of this methodology was further demonstrated by the short and straightforward preparation of a number of enantioenriched natural products and bioactive compounds (**Figure 2**).[8,12,44–46]

4.2. Michael Reactions of α,β-Unsaturated Ketones

Given the inherent problems of forming tetrasubstituted iminium ions from ketones, along with the accordant issues associated with

controlling the iminium ion geometry, it is noteworthy that significant progress has been achieved in the development of iminium catalysts for enone substrates over the past five years. The asymmetric Michael addition of carbanionic reagents to α,β-unsaturated carbonyl compounds was first catalyzed by metalloprolinates in the 1990s.[47–50] Several years later, Kawara and Taguchi reported the first organocatalyzed variant, in which a proline-derived catalyst mediated the addition of malonates to cyclic and acyclic enones with moderate enantioselectivities (56–71% ee's).[51] Further improvements were reached by Hanessian and co-workers, who demonstrated that a combination of L-proline (**8**) and *trans*-2,5-dimethylpiperazine could be used to facilitate the enantioselective addition of nitroalkanes to cyclic enones (**Scheme 5**).[52] Recently, Jørgensen and others reported important expansions of iminium catalysis to the enantioselective conjugate addition of carbogenic nucleophiles such as nitroalkanes,[53] malonates,[54,55] 1,3-dicarbonyl compounds,[56–59] and β-keto sulfones[58] to a number of acyclic α,β-unsaturated ketones (Scheme 5). The utility of this catalytic iminium approach was further corroborated by the one-step preparation of enantiopure biologically active compounds, such as wafarin.[56]

5. Transfer Hydrogenation

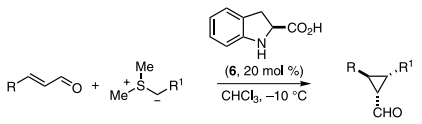
The hydrogen atom is the most common discrete substituent attached to stereogenic centers. Not surprisingly, therefore, the field of asymmetric catalysis has focused great attention on the invention of hydrogenation methods over the past 50 years.[60] While these powerful transformations rely mainly on the use of organometallic catalysts and hydrogen gas, it is important to consider that the large majority of hydrogen-containing stereocenters are created in biological cascade sequences involving enzymes and organic cofactors such as nicotinamide adenine dinucleotide (NADH) or the corresponding flavin derivative ($FADH_2$).[61] On this basis, we hypothesized that the use of small organocatalysts in combination with dihydropyridine analogues to perform metal-free hydrogenations would provide a unique opportunity to further challenge our LUMO-lowering iminium activation concept. Indeed, via this biomimetic strategy, we recently accomplished the selective reduction of β,β-disubstituted-α,β-unsaturated aldehydes in good yields and with excellent enantioselectivities using Hantzsch ester hydride donors and imidazolidinone catalysts (**Table 6**).[13] A notable feature of this transformation is that the sense of induction is not related to the olefin geometry of the starting aldehydes (**eq 2**).[13] As a consequence, mixtures of *E* and *Z* olefins were employed to provide enantiomerically pure hydrogenation adducts, a desirable, yet rare, feature in catalytic hydrogenations. List and co-workers published a variant of this tranformation using our imidazolidinone catalyst **3**.[62,63] It has been our experience that catalyst **3** is inferior to catalyst **11** in terms of rates and selectivities in these types of transfer hydrogenation.

6. Organocatalytic Cascade Reactions

6.1. Cascade Addition–Cyclization Reactions

Given the importance of cascade reactions in modern chemical synthesis,[64–67] we recently expanded the realm of iminium catalysis to include the activation of tandem bond-forming processes, with a view towards the rapid construction of natural products. In this context, the addition–cyclization cascade of tryptamines with α,β-unsaturated aldehydes in the presence of imidazolidinone catalysts **3** and **12** has been accomplished to provide pyrroloindoline adducts in high yields and with excellent levels of enantioselectivity (**Table 7**).[14] Moreover, this amine-catalyzed transformation has been extended to the

Table 4. Organocatalytic Ylide Cyclopropanation[a]

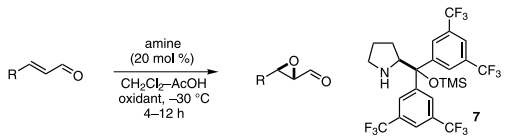


R	R^1	Yield (%)	dr	ee[b] (%)
Pr	PhCO	85	30:1	95
allylOCH$_2$	PhCO	77	21:1	91
Me	PhCO	67	>19:1	90[c]
5-hexen-1-yl	PhCO	74	24:1	96
Ph	PhCO	73	33:1	89
i-Bu	PhCO	63	43:1	96
Pr	4-BrC$_6$H$_4$CO	67	72:1	92
Pr	4-MeOC$_6$H$_4$CO	64	>11:1	93
Pr	*t*-BuCO	82	6:1	95

[a] 24–48 h. [b] Of the major diastereomer. [c] Carried out at 0 °C.

Ref. 35

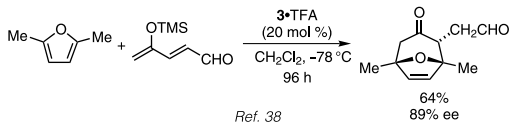
Table 5. Organocatalytic Asymmetric Epoxidation of α,β-Unsaturated Aldehydes



R	Amine	Oxidant	Yield (%)	dr[a]	ee (%)
Me	**3**•HClO$_4$	PhINNs	88	7:1	93
Pr	**3**•HClO$_4$	PhINNs	72	—	88
Cy	**3**•HClO$_4$	PhINNs	77	—	92
4-penten-1-yl	**3**•HClO$_4$	PhINNs	95	—	92[b]
BzOCH$_2$	**3**•HClO$_4$	PhIO	89	—	85
MeO$_2$C(CH$_2$)$_2$	**3**•HClO$_4$	PhINNs	86	—	90
Ph	**3**•HClO$_4$	PhINNs	92	—	92[b]
4-NO$_2$C$_6$H$_4$	**3**•HClO$_4$	PhINNs	89	—	97[b]
4-BrC$_6$H$_4$	**3**•HClO$_4$	PhINNs	93	—	93[b]
Ph	**7**	H_2O_2	80	>13:1	96[c,d]
2-NO$_2$C$_6$H$_4$	**7**	H_2O_2	90	>10:1	97[c,d]
2-MeC$_6$H$_4$	**7**	H_2O_2	65	9:1	96[c,d]
4-ClC$_6$H$_4$	**7**	H_2O_2	63	19:1	98[c,d]
Et	**7**	H_2O_2	>90	>32:1	96[c,d,e]
i-Pr	**7**	H_2O_2	75	49:1	96[c,d]
BnOCH$_2$	**7**	H_2O_2	84	24:1	94[c,d]
EtO$_2$C	**7**	H_2O_2	60	9:1	96[c,d]

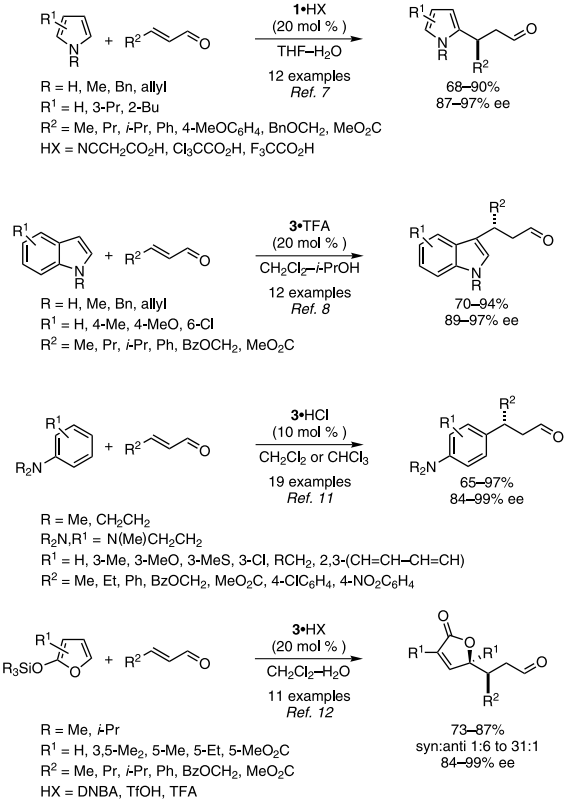
[a] Isolated as single diastereomers unless noted otherwise. [b] Reaction conducted in $CHCl_3$–AcOH at –40 °C. [c] Reaction conducted in CH_2Cl_2 at rt with 10 mol % catalyst. [d] The enantiomeric epoxide was obtained. [e] More than 90% conversion was observed; however, due to the volatility of the product, the α,β-epoxy aldehyde was transformed into the corresponding alcohol, which was isolated in 43% yield (not optimized).

Ref. 36,37



Ref. 38

eq 1



Scheme 4. Organocatalytic 1,4-Addition Reactions of Electron-Rich Aromatics to α,β-Unsaturated Aldehydes.

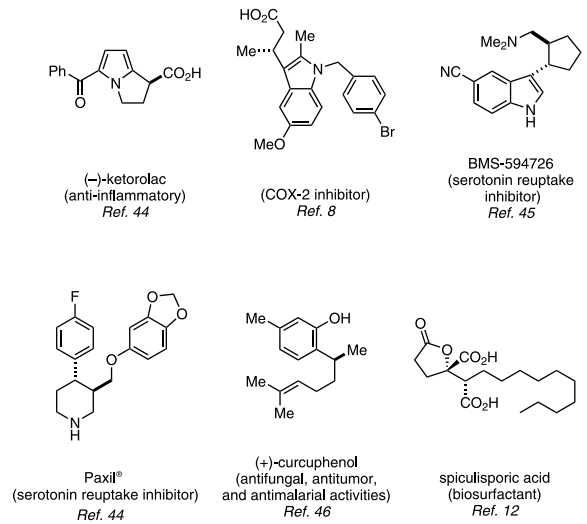
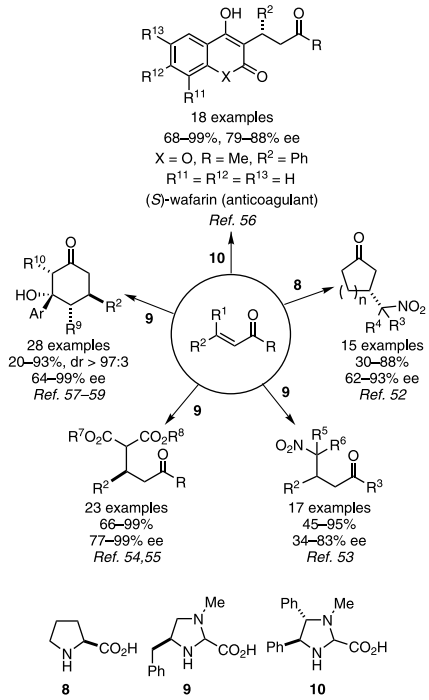
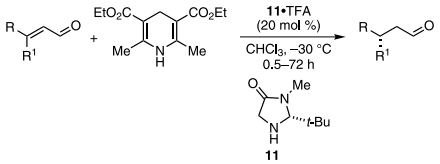


Figure 2. Examples of Natural Products and Bioactive Compounds Prepared by the Organocatalytic 1,4 Addition of Aromatics to α,β-Unsaturated Aldehydes.



Scheme 5. Organocatalytic 1,4 Addition to α,β-Unsaturated Ketones. One-Step Preparation of Pharmaceutically Relevant Adducts such as Wafarin.

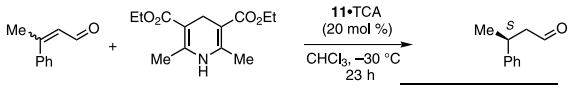
Table 6. Organocatalytic and Enantioselective Transfer Hydrogenation



R	R¹	*E*/*Z*[a]	Yield (%)	ee (%)
Ph	Me	>20:1	91	93[b]
Ph	Et	>20:1	74	94
3,4-$Cl_2C_6H_3$	Me	>20:1	92	97
Cy	Me	5:1	91	96[b]
Cy	Et	3:1	95	91[c]
MeO_2C	Me	>20:1	83[d]	91[e]
$TIPSOCH_2$	Me	>20:1	74	90
t-Bu	Me	>20:1	95[d]	97[f]

[a] *E*/*Z* ratio of the starting aldehydes. [b] At –45 °C. [c] Using 10 mol % catalyst. [d] Yield determined by NMR. [e] At –50 °C. [f] Using 5 mol % catalyst at 23 °C.

Ref. 13



Starting Aldehyde	Yield (%)	*ee* (%)
E	91	93
Z	90	87
E:*Z*, 1:1	88	90

Ref. 13

eq 2

enantioselective construction of furanoindoline frameworks (**eq 3**), a widely represented substructure among natural isolates of biological relevance.[14] Interestingly, a large variation in enantioinduction was observed upon modification of the reaction solvent; high-dielectric-constant media afforded one enantiomer, while low-dielectric-constant solvents provided its mirror image. Application of the pyrroloindoline-forming protocol to natural product synthesis has been accomplished in the first enantioselective total synthesis of (–)-flustramine B (78% yield and 90% ee), a biologically active marine alkaloid.[14]

6.2. Cascade Catalysis: Merging Iminium and Enamine Activations

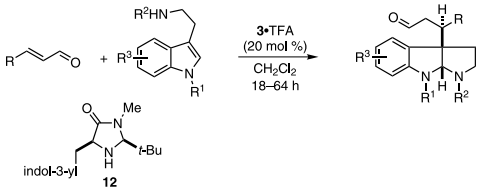
The preparation of natural products with complex molecular structures has traditionally focused on a "stop-and-go" sequence of individual reactions. However, in biological systems, molecular complexity is formed in a continuous process, where enzymatic transformations are combined in highly regulated catalytic cascades.[68] With this in mind, and given the discovery in our laboratory that imidazolidinones can enforce orthogonal modes of substrate activation in the forms of iminium (LUMO-lowering)[5–14] and enamine (HOMO-raising)[69–71] catalyses (**Scheme 6**),[15] we recently questioned whether the conceptual blueprints of biosynthesis might be translated into a laboratory "cascade catalysis" sequence. Specifically, we proposed to combine imidazolidinone-based iminium and enamine transformations to enable rapid access to structural complexity from simple starting materials and catalysts, while achieving exquisite levels of enantiocontrol. As proof of concept, imidazolidinone **13** catalyzed the conjugate addition–chlorination cascade sequence of a diverse range of nucleophiles and α,β-unsaturated aldehydes to give the corresponding products with high levels of diastereo- and enantioselectivities (**Table 8**).[15]

Further expansion of this new cascade approach allowed the invention of other enantioselective transformations, such as the formal asymmetric addition of HCl and HF across trisubstituted olefin systems, which, to our knowledge, has no precedent in asymmetric synthesis.[72] Perhaps most important was the discovery that two discrete amine catalysts can be employed to enforce cycle-specific selectivities (**Scheme 7**).[15] Conceptually, this result demonstrates that these cascade-catalysis pathways can be readily modulated to provide a required diastereo- and enantioselective outcome via the judicious selection of simple amine catalysts.

7. Conclusions

Over the past six years, the field of asymmetric catalysis has bloomed extensively (and perhaps unexpectedly) with the introduction of a variety of metal-free-catalysis concepts that have collectively become known as organocatalysis. Moreover, the field of organocatalysis has quickly grown to become a fundamental branch of catalysis, which can be utilized for the construction of enantiopure organic structures, thus providing a valuable complement to organometallic and enzymatic activations. While substrate scope remains an important issue for many organocatalytic reactions, an increasingly large number of transformations are now meeting the requisite high standards of "useful" enantioselective processes. Most notably, the concept of iminium catalysis has grown almost hand in hand with the general field of organocatalysis. The set of amine catalysts covered in this review is shown in **Figure 3**. Since the introduction of the first highly enantioselective organocatalytic Diels–Alder reaction in 2000, there has been a

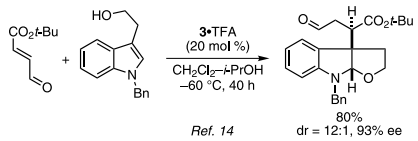
Table 7. Organocatalytic Pyrroloindoline Construction.



R	R^1	R^2	R^3	Yield (%)	dr	ee (%)
Bz	allyl	Boc	H	92	13:1	94
$BzOCH_2$	allyl	Boc	H	66	22:1	91
MeO_2C	allyl	Boc	H	93	44:1	91
MeO_2C	allyl	Boc	5-Me	94	50:1	92
MeO_2C	allyl	Boc	5-MeO	99	10:1	90
MeO_2C	allyl	Boc	6-Br	86	31:1	97
MeO_2C	allyl	Boc	7-Me	97	17:1	99
H	allyl	Boc	H	85	—	89[a]
H	allyl	EtO_2C	H	89	—	89[a]
H	prenyl	EtO_2C	H	89	—	89[a]
H	Bn	$allylO_2C$	H	83	—	89[a]
H	Bn	Boc	H	82	—	90[a]

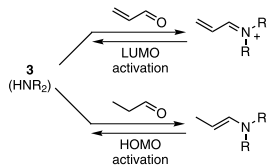
[a] Reaction performed at –85 °C in CH_2Cl_2–H_2O (85:15) with catalyst **12**•TFA.

Ref. 14



Ref. 14

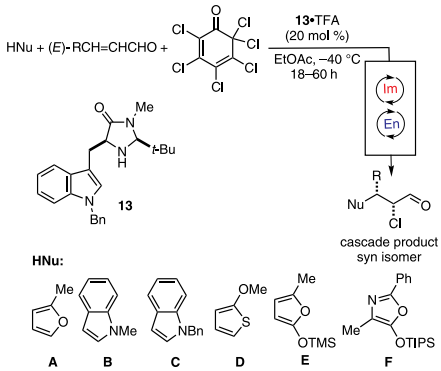
eq 3



Ref. 15

Scheme 6. Imidazolidinones: Organocatalysts for LUMO or HOMO Activation.

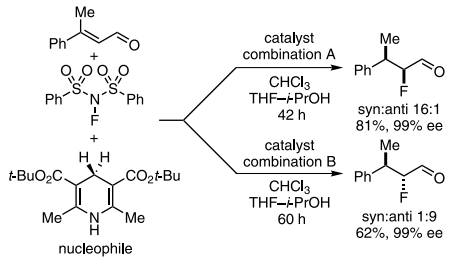
Table 8. Cascade Organocatalysis: Addition–Chlorination Sequence



HNu	R	Yield (%)	dr	ee (%)
A	Me	86	14:1	99[a]
A	Pr	74	13:1	99[a]
A	EtO_2C	80	22:1	99[b]
A	$AcOCH_2$	82	11:1	>99
B	Ph	83	9:1	99
B	*i*-Pr	67	12:1	>99
C	Me	75[c]	12:1	>99[b]
D	Me	77[c]	11:1	99[a]
E	Me	71[c]	>25:1	>99[d]
F	Me	97[c]	9:1	>99

[a] At –50 °C. [b] At –60 °C. [c] Using 10 mol % catalyst. [d] At –55 °C.

Ref. 15



Catalyst combination A: (2*R*)-**11** (7.5 mol %) and (5*S*)-**1** (30 mol %).
Catalyst combination B: (2*R*)-**11** (7.5 mol %) and (5*R*)-**1** (30 mol %).
In both reactions, the enamine catalyst, **1**, and elecrophile, $(PhSO_2)_2NF$, were added after consumption of the nucleophile.
Ref. 15

Scheme 7. Organocatalytic Cascade Reactions Employing Two Discrete Catalysts.

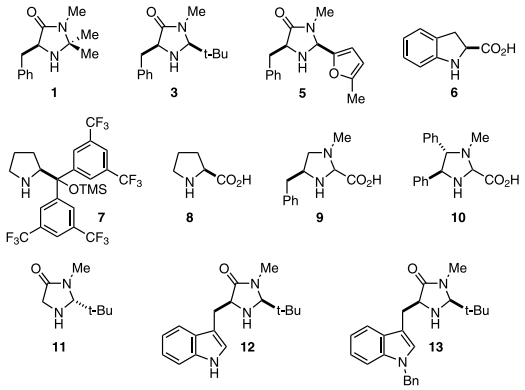


Figure 3. Amine Catalysts Covered in This Review.

large expansion in the field of iminium catalysis and the area of organocatalysis as a whole. Indeed, at the time of writing of this review, there exist currently over 40 discrete transformations that can be performed with useful levels of enantiocontrol (≥90% ee). As such, the future for iminium catalysis and the field of organocatalysis appears to be a bright one, with perhaps application to industrial processes being the next major stage of development. One thing is certain, there are many new powerful enantioselective transformations waiting to be discovered using these novel modes of activation.

8. Acknowledgments

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About the Authors

Gérald Lelais was born in 1976 in Sorengo (TI), Switzerland. He studied chemistry at the Swiss Federal Institute of Technology Zürich (ETH-Zürich), Switzerland, where he obtained his B.S. degree in 2000 and his Ph.D. degree in 2004, working under the guidance of Professor Dieter Seebach. His research focused on the multistep synthesis of β-amino acids and their incorporation into β peptides for structural investigations. In May 2004, he joined the group of Professor David W. C. MacMillan at the California Institute of Technology in Pasadena, California, as a postdoctoral fellow of the Swiss National Science Foundation (Stefano Franscini Fond), the Roche Foundation, and the Novartis Foundation. His current research interests include the development of new organocatalytic reactions and their application in the total synthesis of natural products.

David W. C. MacMillan was born in 1968 in Bellshill, Scotland. He received his B.S. degree in chemistry in 1990 from the University of Glasgow, Scotland, and his Ph.D. degree in 1996 from the University of California, Irvine, where he worked under the direction of Professor Larry E. Overman. David then moved to Harvard University to undertake postdoctoral studies (with Professor David A. Evans), which he completed in 1998. In that year, he joined the faculty at the University of California, Berkeley. In 2000, MacMillan moved to the California Institute of Technology, where he was promoted to the rank of associate professor and, in 2003, to the rank of full professor. In 2004, MacMillan became the Earle C. Anthony Chair in Organic Chemistry at the California Institute of Technology. MacMillan's research program is centered on chemical synthesis with specific interests in new reaction development, enantioselective organocatalysis, and the rapid construction of molecular complexity.

Proline-Based Organocatalysts

Proline and its synthetic derivatives are ideal organocatalyst scaffolds. Unlike enzymes, proline is available in both enantiomeric forms and has a low molecular weight. Importantly, proline analogs are capable of effecting a variety of asymmetric transformations including aldol and Mannich reactions, Michael additions, and α-functionalizations.[1–5] Sigma-Aldrich is pleased to offer a broad portfolio of proline derivatives for use in organocatalysis.

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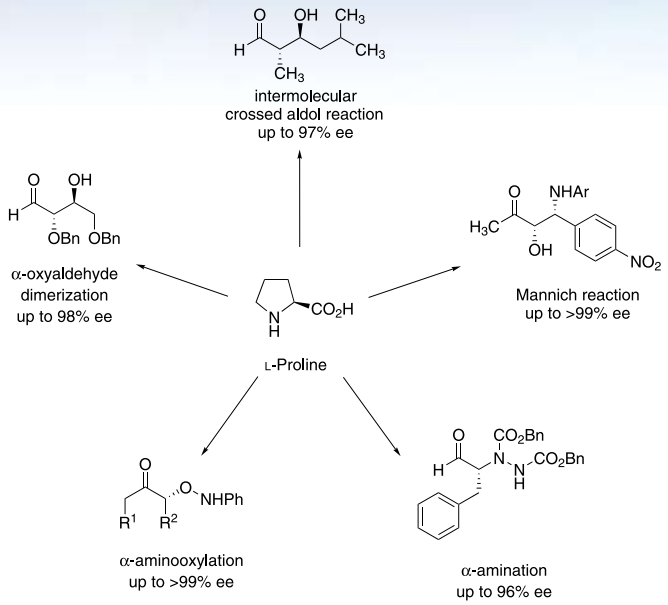

L-Proline, *ReagentPlus*™, ≥99%

[*147-85-3*]
$C_5H_9NO_2$
FW: 115.13

P0380-10MG	10 mg	$12.00
P0380-100G	100 g	52.00
P0380-1KG	1 kg	356.50
P0380-5KG	5 kg	1,533.60

D-Proline, ≥99%

[*344-25-2*]
$C_5H_9NO_2$
FW: 115.13

858919-500MG	500 mg	$25.80
858919-5G	5 g	104.50

α-Methyl-L-proline, purum, ≥98.0% TLC

[*42856-71-3*]
$C_6H_{11}NO_2$
FW: 129.16

17249-250MG	250 mg	$115.00
17249-1G	1 g	321.50

(*S*)-(–)-Indoline-2-carboxylic acid, 99%

[*79815-20-6*]
$C_9H_9NO_2$
FW: 163.17

346802-1G	1 g	$22.20
346802-5G	5 g	83.40

3,4-Dehydro-L-proline, *BioChemika*, ≥99.0% TLC

[*4043-88-3*]
$C_5H_7NO_2$
FW: 113.11

30890-10MG	10 mg	$38.10
30890-50MG	50 mg	127.10

L-Pipecolic acid, puriss., ≥99.0% NT

[*3105-95-1*]
$C_6H_{11}NO_2$
FW: 129.16

80615-100MG	100 mg	$62.20
80615-500MG	500 mg	264.50

D-Pipecolic acid, purum, ≥99.0% NT

[*1723-00-8*]
$C_6H_{11}NO_2$
FW: 129.16

80617-100MG	100 mg	$86.20
80617-500MG	500 mg	366.50

(*S*)-(–)-α,α-Diphenyl-2-pyrrolidinemethanol, 99%

[*112068-01-6*]
$C_{17}H_{19}NO$
FW: 253.34

368199-1G	1 g	$56.20
368199-5G	5 g	175.50

(*R*)-(+)-α,α-Diphenyl-2-pyrrolidinemethanol, 98%

[*22348-32-9*]
$C_{17}H_{19}NO$
FW: 253.34

382337-100MG	100 mg	$56.30
382337-1G	1 g	125.00
382337-5G	5 g	405.00

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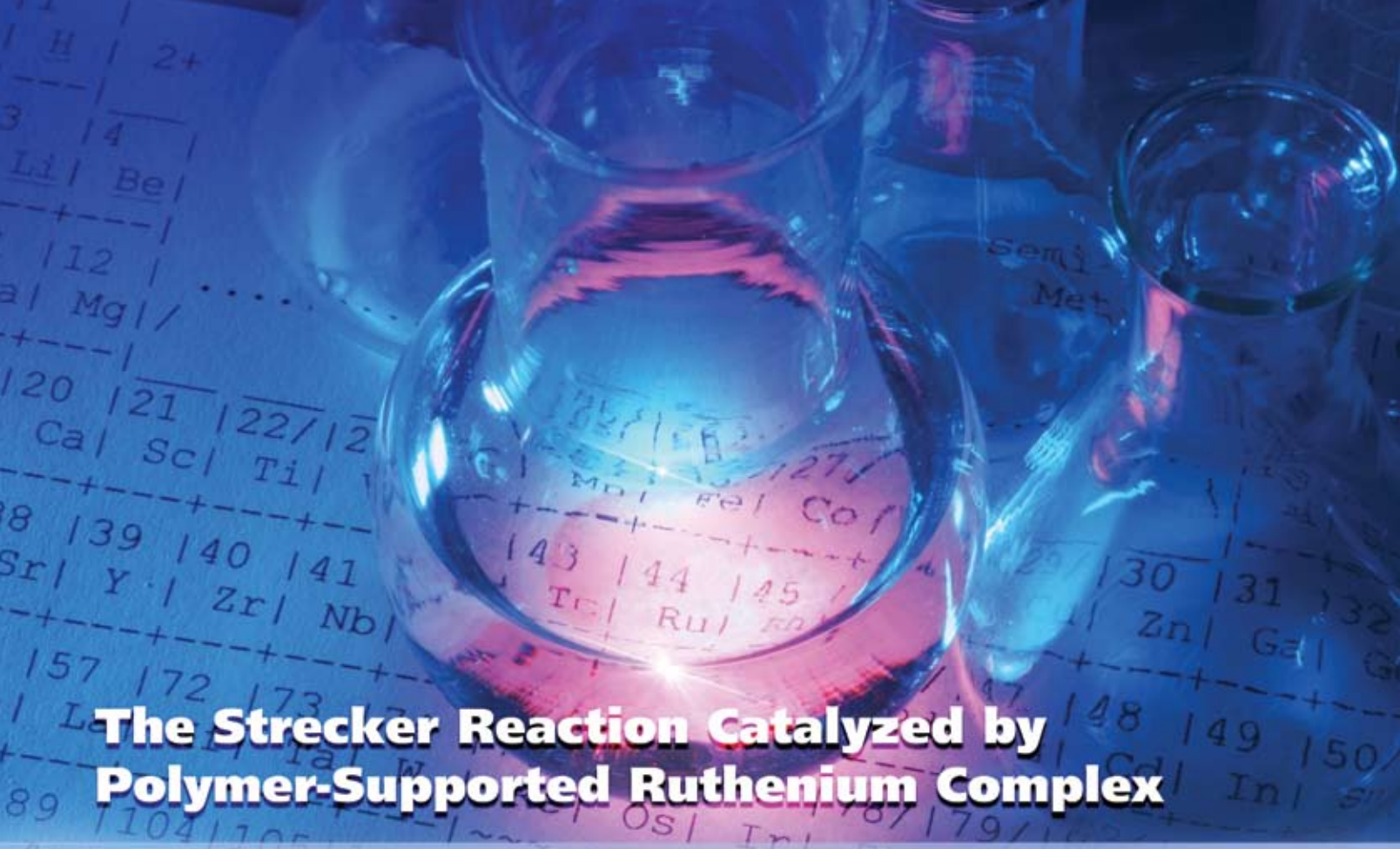
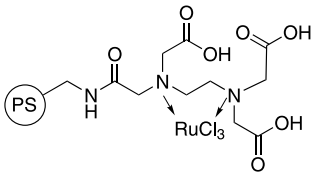


The Strecker Reaction Catalyzed by Polymer-Supported Ruthenium Complex

The one-pot synthesis of α-amino nitriles by reaction of an aldehyde, ammonia, and hydrogen cyanide is commonly known as the Strecker reaction.[1] Recent modifications to the traditional Strecker reaction have seen the replacement of the cyanide source from toxic hydrogen cyanide to the comparatively mild trimethylsilyl cyanide.[2,3] Ruthenium has also been demonstrated to catalyze the Strecker reaction.[4]

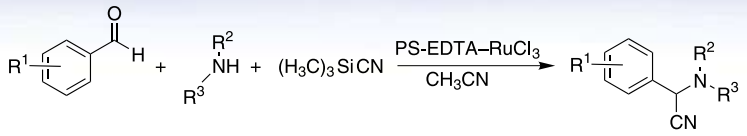
Sigma-Aldrich now offers a polymer-supported ruthenium complex to be used as a mild catalyst for the Strecker reaction.



Ethylenediaminetriacetic acid–ruthenium(III) chloride complex, polymer-bound		
668079-1G	1 g	$85.00
668079-5G	5 g	297.50

(1) Strecker, A. *Ann. Chem. Pharm.* **1850**, *75*, 27. (2) Yadav, J. S. et al. *Tetrahedron* **2004**, *60*, 1767. (3) Mai, K.; Patil, G. *Tetrahedron Lett.* **1984**, *25*, 4583. (4) De, S. K. *Synth. Commun.* **2005**, *35*, 653.

Scheme 1



Typical Experimental Procedure

Ethylenediaminetriacetic acid–ruthenium(III) chloride complex, polymer-bound (15 mg, 0.005 mmol) was charged into a reaction vessel followed by the addition of acetonitrile (2.0 mL), the aldehyde (1.0 mmol), the amine (1.15 mmol), and trimethylsilyl cyanide (1.5 mmol). The resulting mixture was stirred at room temperature overnight, filtered, and the filtrate collected. The resin was washed with several portions of acetonitrile, and the filtrates combined and evaporated to dryness. The residue was purified by flash column chromatography (20 g of silica gel; 1.5 × 20 cm column; ethyl acetate:hexane 1:9 as eluent) to yield the desired product. The structures of the isolated products were confirmed by ^{1}H NMR and mass spectrometry.

	Isolated Percent Yields of Substituted α-Amino Nitriles		
	N-Boc-amino-piperidine	Morpholine	Phen-ethylamine
4-Bromobenzaldehyde	83	95	95
4-Cyanobenzaldehyde	70	62	53
3,5-Dimethoxybenzaldehyde	86	92	51

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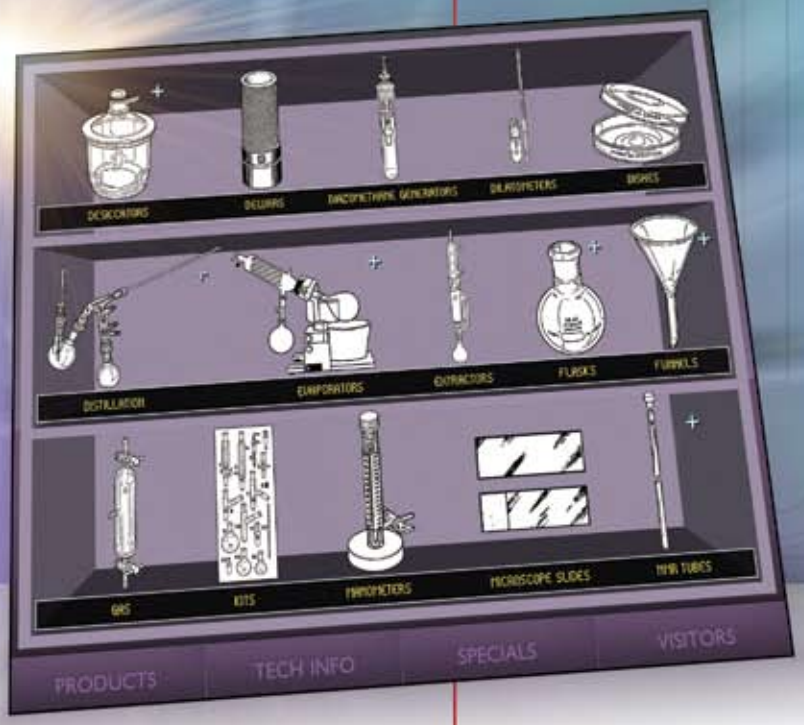

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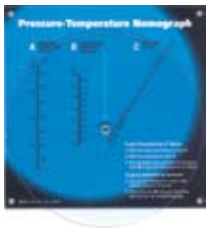

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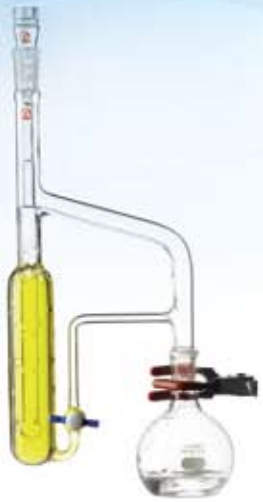

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The diffusion tube adapter is necessary when extracting with solvents lighter than water. Fresh solvent drips from the condenser into the adapter tube from which solvent diffuses at the bottom of the extractor; then the solvent rises through the aqueous layer because of its lower density. The extraction solvent is recycled to the solvent reservoir via sidearm.

Aldrich Convertible Liquid–Liquid Continuous Extractor

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500	24/40	24/40	Z562432-1EA	465.00
1000	55/50	24/40	Z562440-1EA	620.00
2000	55/50	24/40	Z562459-1EA	630.00
4000	55/50	29/42	Z562467-1EA	645.00

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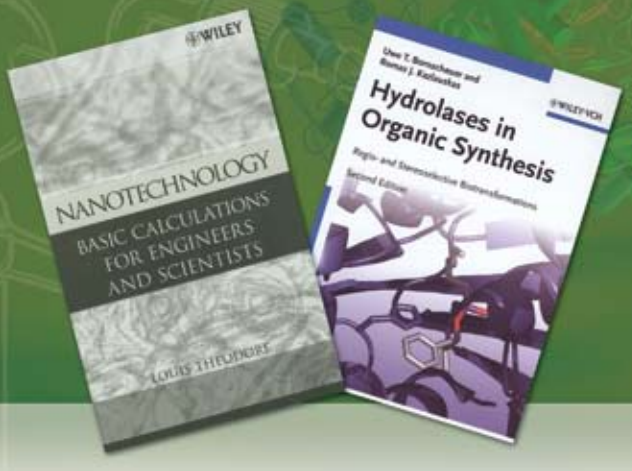

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R. Breslow, Ed., Wiley, 2005, 194pp. Hardcover. This first book on this fascinating topic is edited by one of today's most famous and internationally respected organic chemists, who has been studying enzyme mimics and artificial enzymes for more than four decades. Ronald Breslow has brought together leading scientists in this expanding area for an in-depth survey of the synthesis and design of enzyme-like catalysts.

Z705055-1EA $99.90

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K. Drauz and H. Waldmann, Eds., Wiley, 2002, 1500pp. Hardcover. This comprehensive manual gives reliable answers to all questions on enzyme catalysis—from searching for suitable catalytic converter systems via choosing the optimal reaction conditions to implementing modern synthetic strategies. This edition has been greatly expanded to include new topics and to reflect the latest research. The three volumes provide synthetic chemists with easy access to all the first-hand information necessary for successfully using enzymes. It includes comprehensive registers for targeted searching according to enzyme, compound, or reaction, and modern methods of protein chemistry: use of catalytic antibodies and protein engineering.

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R. B. Silverman, Academic Press, 2002, 800pp. Hardcover. This unique text focuses on the mechanisms of enzyme-catalyzed reactions. Following a general introduction to the role of enzymes as catalysts, each chapter describes the organic reaction mechanisms that are used by enzymes to catalyze a particular family of organic transformations. The compilation includes a vast number of drawings to illustrate structures and mechanisms, and focuses on one or two examples of enzymes that catalyze the particular chemistry for that transformation. Extensive references cite the many experiments that have helped to elucidate enzyme mechanisms

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E. S. El Ashry and A. El Nemr, Blackwell Publishing, 2005, 443pp. Hardcover. This book reviews the recent literature dealing with the use of carbohydrates as raw materials in the synthesis of nitrogen heterocycles. The text contains six chapters arranged according to the complexity of the heterocyclic compounds discussed, ranging from five- to seven-membered rings and from single to multiple fused rings. It provides a detailed discussion of the various synthetic approaches to these compounds, using carbohydrate starting materials, and does not merely reference synthetic methodology but attempts to give as much detail as possible on the actual experimental conditions used. It discusses the different approaches to the synthesis of a wide range of naturally occurring nitrogen heterocycles in a format that enables the reader to make comparisons and decisions on whether to utilize a certain procedure, modify it, or devise a new synthetic methodology.

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C. S. S. R. Kumar, Ed., Wiley, 2006, 386pp. Hardcover. Nanotechnologies for the life sciences is the first comprehensive source covering the convergence of materials and life sciences on the nanoscale. Tailor-made nanomaterials find widespread new opportunities in diagnostic and monitoring microdevices, microsurgery tools and instruments, tissue engineering, drug delivery, artificial organs, and more. This volume brings together the synthetic methods and materials aspects of instilling biocompatibility and desirable properties into nanomaterials, covering numerous types and methods.

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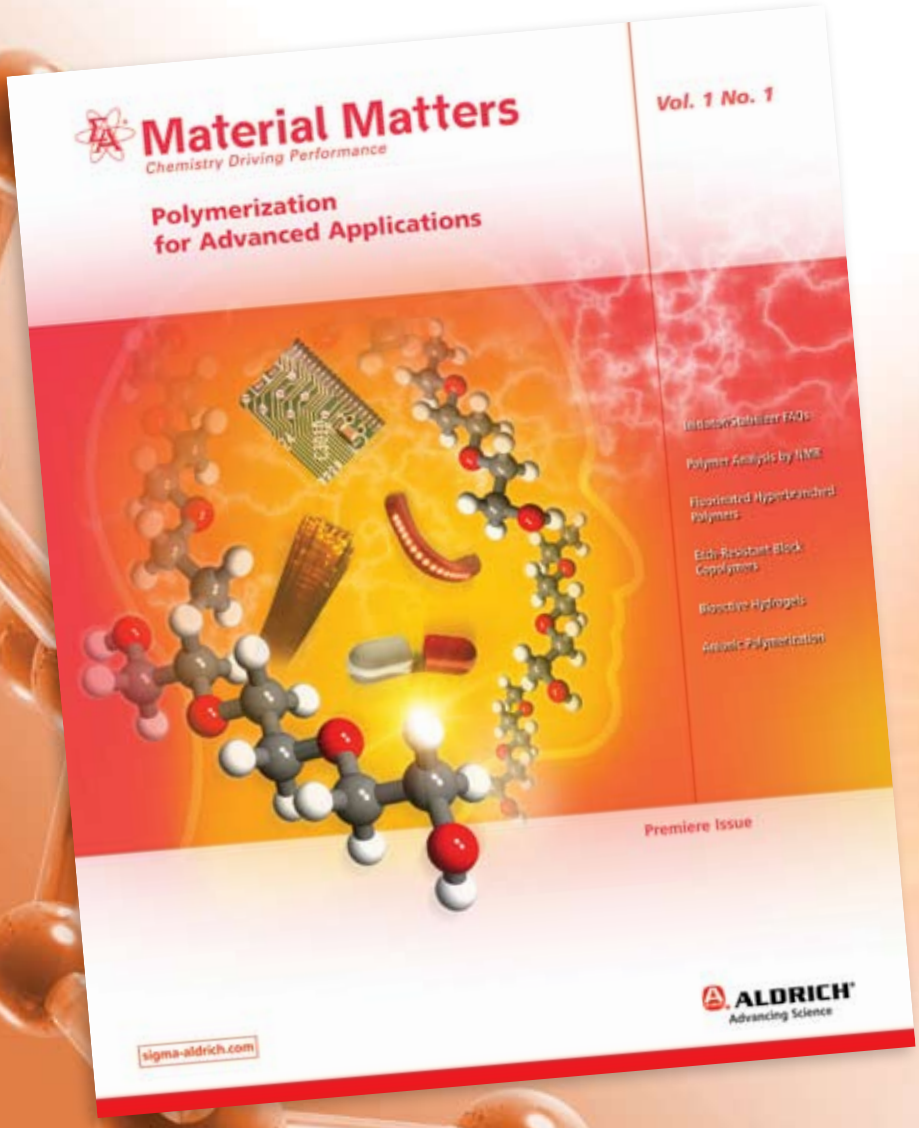

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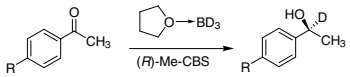
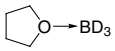


R	Yield (%)	ee (%)	D atom %
H	100 (GC)	96.6	97.0
CH_3	100 (GC)	94.5	96.4
NO_2	91 (isolated)	97.8	98.1
OCH_3	100 (GC)	94.2	96.1

(1) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986. (2) Sigma-Aldrich, patent pending. (3) (a) Nettles, S. M. et al. *J. Org. Chem.* **2002**, *67*, 2970. (b) Aldrich Technical Bulletin, AL-218. (4) Sold under license. US4943635 and foreign equivalents apply. End user is granted on purchase a label license to use without scale limitation.

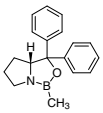
Borane-d_3–THF complex solution, 1.0 M in THF, stabilized with 0.005 M *N*-isopropyl-*N*-methyl-*tert*-butylamine, 97.5 atom % D NEW

667714 1 mL
$C_4H_8BD_3O$ 5 x 1 mL
FW: 88.96



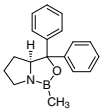
(*R*)-2-Methyl-CBS-oxazaborolidine solution, 1 M in THF NEW

674656 5 mL
[*112022-81-83*] 25 mL
$C_{18}H_{20}BNO$
FW: 277.17



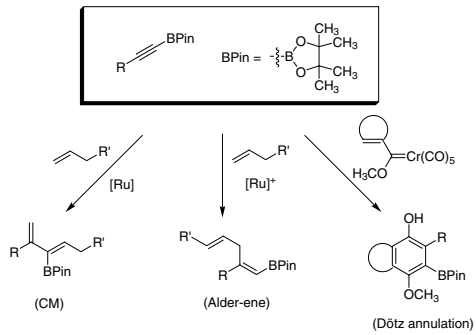
(*S*)-2-Methyl-CBS-oxazaborolidine solution, 1 M in THF NEW

674648 5 mL
[*112022-81-8*] 25 mL
$C_{18}H_{20}BNO$
FW: 277.17



Alkynylboronates

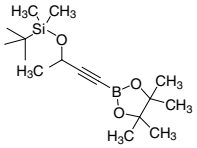
Alkynylboronates participate in a variety of regio- and stereoselective carbon–carbon bond-forming reactions including enyne cross metathesis (CM),[1] Alder-ene,[2] and Dötz annulation reactions.[3] Products obtained from these reactions are either alkenyl or arylboronates, which are active coupling partners in Suzuki and Heck reactions.



(1) Kim, M.; Lee, D. *Org. Lett.* **2005**, *7*, 1865. (2) (a) Hansen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2005**, *127*, 3252. (b) Hansen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2006**, *128*, 8142. (3) Davies, M. W. et al. *J. Org. Chem.* **2001**, *66*, 3525.

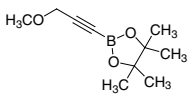
3-(*tert*-Butyldimethylsilyloxy)-1-butyn-1-ylboronic acid pinacol ester, 96% NEW

674729 1 g
$C_{16}H_{31}BO_3S$ 5 g
FW: 310.31



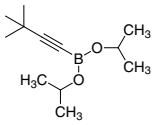
3-Methoxy-1-propyn-1-ylboronic acid pinacol ester, 96% NEW

674710 1 g
$C_{10}H_{17}BO_3$ 5 g
FW: 196.05



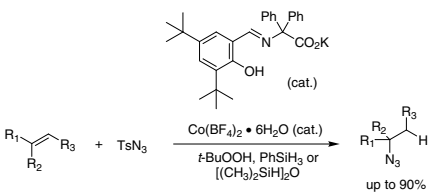
3,3-Dimethylbutynylboronic acid diisopropyl ester, 97% NEW

639192 1 g
[*121021-24-7*] 5 g
$C_{12}H_{23}BO_2$
FW: 210.12



Cobalt-Catalyzed Hydroazidation

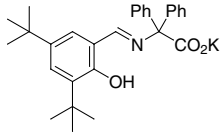
Organoazides have gained considerable interest recently because of their use in click chemistry and as masked amines. Erick Carreira (ETH Hönggerberg) and co-workers have developed a convenient method for preparing these useful intermediates by Markovnikov hydroazidation of olefins.[1] The method utilizes a cobalt catalyst prepared in situ from a Schiff base and $Co(BF_4)_2{\cdot}6H_2O$ in the presence of a silane to give secondary and tertiary alkyl azides in good yields.



(1) Waser, J. et al. *J. Am. Chem. Soc.* **2005**, *127*, 8294.

Potassium 2-(3,5-di-*tert*-butyl-2-hydroxybenzyl-ideneamino)-2,2-diphenylacetate, 95% NEW

676551 250 mg
$C_{29}H_{32}KNO_3$ 1 g
FW: 481.68



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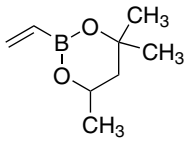
"PLEASE BOTHER US."

Joe Porwoll, President
Aldrich Chemical Co., Inc.

Professor Andrew Whiting of the University of Durham, U.K., kindly suggested that we offer vinylboronic acid 2-methyl-2,4-pentanediol ester. This reagent functions as a vinyl dianion equivalent, since it can react at either end of the double bond under Suzuki–Miyaura or Heck coupling conditions. This compound also exhibits enhanced stability and lower volatility than related vinylboronate esters. [1–3]

(1) Lightfoot, A. P.; Maw, G.; Thirsk, C.; Twiddle, S. J. R.; Whiting, A. *Tetrahedron Lett.* **2003**, *44*, 7645. (2) Lightfoot, A. P.; Twiddle, S. J. R.; Whiting, A. *Org. Biomol. Chem.* **2005**, *3*, 3167. (3) Lightfoot, A. P.; Twiddle, S. J. R.; Whiting, A. *Synlett* **2005**, 529.



673641 **Vinylboronic acid 2-methyl-2,4-pentanediol ester,** 95% (4,4,6-Trimethyl-2-vinyl-1,3,2-dioxaborinane) — 1 g, 10 g

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

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

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ABOUT OUR COVER

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

No one will be surprised to read that the painting on our cover, ***Ships Riding on the Seine at Rouen*** (1872/1873, oil on canvas, 37.8 × 46.6 cm), was painted by the archetypal Impressionist, Claude Monet (French, 1840–1926). His distinctive style is recognizable, fresh, and still sought after over 130 years after his radical and expressive brushwork shocked the art world in Paris in the 1860s and 1870s.

Monet's devotion to the ideals of Impressionism lasted throughout his long and prolific life. It is fitting that the word Impressionism, which defines the movement and style, was coined by an art critic reviewing Monet's painting *Impression: Sunrise*, 1872 (Musée Marmottan, Paris).

This delightful, small painting displays large and small sailboats comfortably resting on the river Seine on a sunny, warm, and idyllic day. Monet's choice of primarily soft blues and greens creates an alluring calm and relaxed atmosphere. He characteristically captures the illusion of moving water by suggesting with broad brushstrokes that the landscape, sky, clouds, and boats are reflected in the gently rolling water.

This painting is in the Ailsa Mellon Bruce Collection of Small French Paintings at the National Gallery of Art, Washington, DC.

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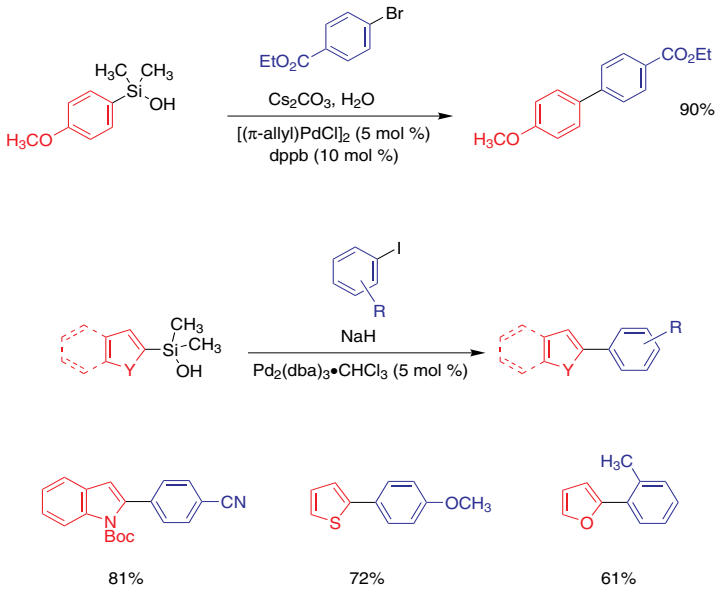
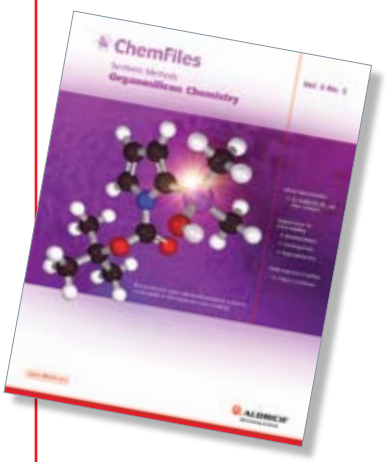
New Organosilanols for Pd-Catalyzed Cross-Coupling

Professor Scott Denmark and co-workers have demonstrated organosilanols to be powerful coupling partners in Pd-catalyzed cross-couplings.[1–5] Alkenyl-, aryl-, and heteroarylsilanols readily couple with aryl halides in the presence of a base activator and a palladium catalyst. Alternatively, a preformed sodium silanolate salt can be used directly, without the need for added base. Polydimethylsiloxane byproducts (i.e., silicone oil) are easily removed from the reaction mixture. Since a fluoride source is not necessary to promote the reaction, the cross-coupling can be performed in the presence of silyl protecting groups. Additionally, these reagents address an issue that has long plagued the synthetic community: the poor cross-coupling behavior of 2-metallated heteroaryl nucleophiles. For example, (*N*-Boc-2-indolyl)dimethylsilanol readily couples with aryl iodides in good yields at room temperature. Sigma-Aldrich is pleased to offer the following organosilanols and silanolate salts to accelerate your research success.



References

(1) Denmark, S. E.; Ober, M. H. *Aldrichimica Acta* **2003**, *36*, 75. (2) Denmark, S. E.; Ober, M. H. *Org. Lett.* **2003**, *5*, 1357. (3) Denmark, S. E.; Ober, M. H. *Adv. Synth. Catal.* **2004**, *346*, 1703. (4) Denmark, S. E.; Baird, J. D. *Org. Lett.* **2004**, *6*, 3649. (5) Denmark, S. E.; Baird, J. D. *Org. Lett.* **2006**, *8*, 793.



For more information on organosilanols, please visit **sigma-aldrich.com/chemfiles** and see ChemFiles Vol. 6 No. 5.

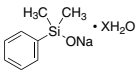
Dimethylphenylsilanol, 97% NEW

[*5272-18-4*]
$C_8H_{12}OSi$
FW: 152.27

667110-1G	1 g
667110-5G	5 g

Sodium dimethylphenylsilanolate hydrate, 97% NEW

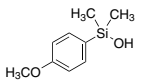
$C_8H_{11}NaOSi$
FW: 174.25



673269-1G	1 g
673269-5G	5 g

(4-Methoxyphenyl)dimethylsilanol, 96% NEW

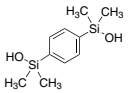
[*22868-26-4*]
$C_9H_{14}O_2Si$
FW: 182.29



667951-1G	1 g
667951-5G	5 g

1,4-Bis(hydroxydimethylsilyl)benzene, 95%

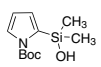
[*2754-32-7*]
$C_{10}H_{18}O_2Si_2$
FW: 226.42



497193-5G	5 g

(*N*-Boc-2-pyrrolyl)dimethylsilanol, 97% NEW

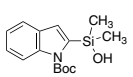
$C_{11}H_{19}NO_3Si$
FW: 241.36



669164-1G	1 g

(*N*-Boc-2-indolyl)dimethylsilanol, 97% NEW

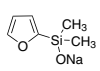
$C_{15}H_{21}NO_3Si$
FW: 291.42



667900-1G	1 g
667900-5G	5 g

Sodium 2-furyldimethylsilanolate NEW

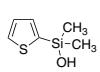
$C_6H_9NaO_2Si$
FW: 164.21



673250-1G	1 g
673250-5G	5 g

Dimethyl(2-thienyl)silanol, 97% NEW

[*197009-90-8*]
$C_6H_{10}OSSi$
FW: 158.29



667099-1G	1 g
667099-5G	5 g

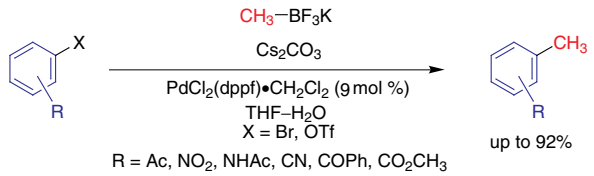
New Product Directory Available!

Boron Reagents for Suzuki Coupling

This up-to-date directory contains Sigma-Aldrich's extensive portfolio of high-quality **boronic acids**, **boronate esters**, and **trifluoroborate salts** for use in Suzuki coupling and other important reactions.

Available electronically for free at **sigma-aldrich.com/boronpd**.

Included in this directory are our newest boronic acids and derivatives such as potassium methyltrifluoroborate. Molander and co-workers have demonstrated this air- and water-stable salt to be an excellent methylation reagent for aryl halides and pseudohalides.[1,2] We are delighted to offer this useful new product, as well as over 650 other novel boron nucleophiles for use in Suzuki coupling.



Reference

(1) Molander, G. A. et al. *J. Org. Chem.* **2003**, *68*, 5534. (2) Molander, G. A.; Figueroa, R. *Aldrichimica Acta* **2005**, *38*, 49.

Potassium methyltrifluoroborate NEW

[*13862-28-7*]
CH_3BF_3K
FW: 121.94

637890-1G	1 g
637890-5G	5 g

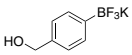
Potassium cyclopentyltrifluoroborate, 97% NEW

$C_5H_9BF_3K$
FW: 176.03

666017-1G	1 g
666017-5G	5 g

Potassium 4-(hydroxymethyl)phenyltrifluoroborate, 97% NEW

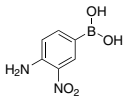
$C_7H_7BF_3KO$
FW: 214.03



659762-1G	1 g
659762-5G	5 g

4-Amino-3-nitrophenylboronic acid, tech. NEW

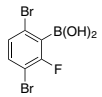
[*89466-07-9*]
$C_6H_7BN_2O_4$
FW: 181.94



651621-1G	1 g
651621-5G	5 g

3,6-Dibromo-2-fluorophenylboronic acid NEW

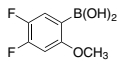
[*870778-92-0*]
$C_6H_4BBr_2FO_2$
FW: 297.71



651087-2G	2 g
651087-10G	10 g

4,5-Difluoro-2-methoxyphenylboronic acid NEW

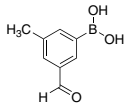
[*870777-32-5*]
$C_7H_7BF_2O_3$
FW: 187.94



645184-1G	1 g
645184-5G	5 g

3-Formyl-5-methylphenylboronic acid NEW

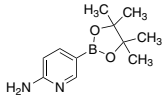
[*870777-33-6*]
$C_8H_9BO_3$
FW: 163.97



645338-1G	1 g

2-Aminopyridine-5-boronic acid pinacol ester, 97% NEW

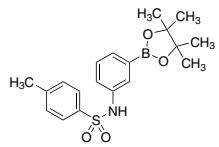
[*827614-64-2*]
$C_{11}H_{17}BN_2O_2$
FW: 220.08



640379-1G	1 g
640379-5G	5 g

3-(*p*-Toluenesulfonylamino)phenylboronic acid pinacol ester, 97% NEW

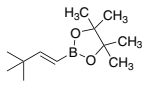
[*796061-08-0*]
$C_{19}H_{24}BNO_4S$
FW: 373.27



636312-1G	1 g
636312-5G	5 g

trans-(3,3-Dimethylbutenyl)boronic acid pinacol ester, 97% NEW

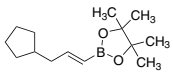
$C_{12}H_{23}BO_2$
FW: 210.12



667277-1G	1 g
667277-5G	5 g

trans-3-(Cyclopentyl)propenylboronic acid pinacol ester, 97% NEW

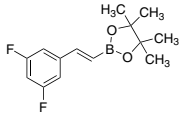
$C_{14}H_{25}BO_2$
FW: 236.16



667013-1G	1 g

trans-2-(3,5-Difluorophenyl)vinylboronic acid pinacol ester, 97% NEW

$C_{14}H_{17}BF_2O_2$
FW: 266.09



669199-1G	1 g

Pd–N-Heterocyclic Carbene (NHC) Catalysts for Cross-Coupling Reactions


Dr. E. A. B. Kantchev


Dr. C. J. O'Brien


Professor M. G. Organ

*Eric Assen B. Kantchev,† Christopher J. O'Brien, and Michael G. Organ**
Department of Chemistry
York University
4700 Keele Street
Toronto, ON, Canada M3J 1P3
Email: organ@yorku.ca

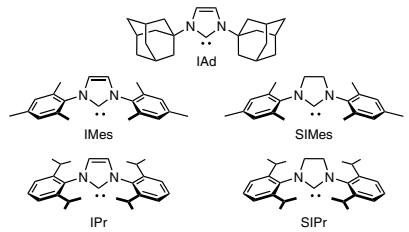
Outline

1. Introduction

N-Heterocyclic carbenes (NHCs), first prepared independently by Wanzlick[1] and Öfele[2] in 1968, attracted little interest from the synthetic community until 1991, when Arduengo et al. reported the first stable, crystalline NHC (IAd, **Figure 1**).[3] The potential of this class of compound to serve as spectator ligands in transition-metal homogeneous catalysis was recognized in 1995 by Herrmann et al.[4] Exploitation of the remarkable potential of NHC ligands began soon thereafter. The seminal work by Arduengo and co-workers precipitated the development of a variety of other NHC platforms (**Figure 2**),[5] and their transition-metal complexes were synthesized and tested as catalysts. However, only NHCs derived from imidazolium or 4,5-dihydroimidazolium salts have found widespread use in Pd-mediated catalysis. The best known catalyst incorporating an NHC ligand is Grubbs's second generation Ru metathesis catalyst, in which the replacement of one of the two PCy_3 ligands with the bulky carbene SIMes led to significant improvements in catalyst stability, activity, and substrate range.[6] Similarly, the use of bulky carbenes, in particular IPr and SIPr, as ligands for another very synthetically useful transition metal, Pd, has led to significant improvements in catalyst performance. Stable, highly active, easy to prepare, and easy to use Pd–NHC (pre)catalysts have emerged as a result of these efforts. Following the comprehensive accounts of the chemistry of NHCs by Bertrand and coauthors[7] and Herrmann et al.,[8] many other reviews of specific aspects of the field have appeared. For example, reviews on chiral NHCs;[9] structure, bonding, and reactivity of free NHCs;[10] and on transition-metal–NHC complexes have been published between 2003 and 2005.[11] The early forays in Pd–NHC chemistry specifically directed towards C–C cross-coupling reactions were summarized by Herrmann et al. in 2003.[12] Since the Pd–NHC cross-coupling methodology is now at the threshold of being widely adopted by synthetic chemists, this review will provide a critical survey of this methodology and will cover research up to April 2006. An exhaustive account of the already large corpus of data available on Pd–NHC coordination chemistry will not be presented. The current review will focus mainly on the development and synthetic applications of Pd–NHC complexes (prepared either in situ, or from well-defined precatalysts) in the C–C cross-coupling reactions of Zn, Mg, B, Si, and Sn organometallic derivatives; as well as the closely related Sonogashira reaction, C–N cross-couplings (e.g., the Buchwald–Hartwig amination), and enolate arylation. Even though the Heck–Mizoroki arylation and π-allyl alkylation (Tsuji–Trost reaction) will be evoked at times in order to aid the understanding of Pd–NHC chemistry, the synthetic applications of Pd–NHC catalysts in these mechanistically distinct methodologies will not be covered.

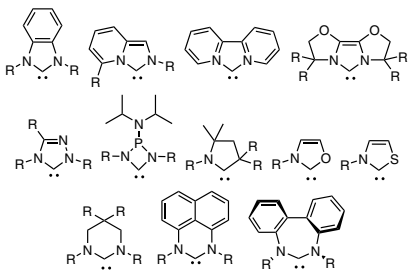
2. NHCs as Ligands in Pd-Catalyzed Cross-Coupling Reactions

NHCs exist in the singlet state, with a pair of electrons perpendicular to the plane of the π system, resulting in high basicity[13] and σ-donating ability, similar to electron-rich trialkylphosphines.



Ref. 3,6

Figure 1. Synthetically Useful NHC Ligands Derived from Imidazolium (I) and 4,5-Dihydroimidazolium (SI) Salts.



Ref. 5

Figure 2. General Representation of Other NHC Platforms (R = Alkyl or Aryl).

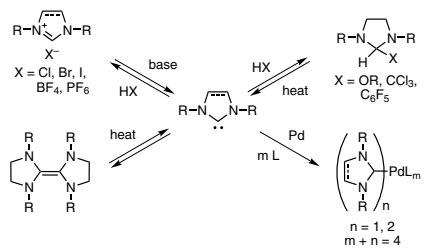


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Figure 3. General Description of NHC Generation from Various Precursors and Their Complexation with Pd.

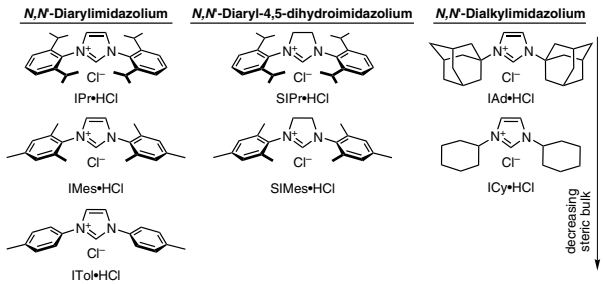

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Figure 4. NHC•HCl Precursors Used in Various in Situ Cross-Coupling Protocols.

The concept of NHCs as "phosphine mimics" has proved to be extremely fruitful in opening new avenues in catalysis by simply substituting a phosphine with an NHC.[11b,d] Thermochemical and computational studies on NHC complexes of Ru[14] and Ni[15] have shown that NHCs form stronger bonds to the metal than even the most electron-rich phosphines.

The use of NHCs as ligands in Pd-mediated reactions has the following beneficial effects: (i) The strong σ-donating ability of NHCs results in a Pd center that is capable of oxidative addition into bonds traditionally considered resistant, for example those of chloroarenes[16] or alkyl halides;[17] (ii) the steric bulk of NHCs facilitates reductive elimination in a manner analogous to that of bulky phosphines;[18] and (iii) the strong Pd–NHC bond and limited catalyst decomposition pathways ensure that the metal is kept in a soluble, catalytically active state with only a single NHC attached, even at high temperatures. A caveat: the complexation of NHCs to palladium is far from trivial, and the preparation of the active catalyst is a major bottleneck in catalytic applications.

Isolated NHCs, even though persistent in the crystalline state and solution,[8] are highly air- and moisture-sensitive. Owing to the practical inconvenience of handling the free carbenes (under strictly inert conditions or in a glovebox), NHC surrogates are also used, most often the corresponding azolium salts from which the carbenes are generated by treatment with a strong base (**Figure 3**).[3,8,11] An additional avenue for NHC generation encompasses 1,1 elimination of simple molecules or decomposition of NHC dimers at high temperatures.[10] The resultant carbenes are then captured by a common palladium source [$PdCl_2$, $Pd(OAc)_2$, $Pd(dba)_2$, or $Pd_2(dba)_3$]. The preparation of well-defined Pd–NHC complexes has also been the subject of thorough scientific investigations. The strength of the Pd–NHC bond renders ligand substitution with a preformed carbene an excellent general route to Pd–NHC complexes.[19–23] Another approach is to use an imidazolium salt in the presence of base to form the NHC in situ which is then captured by Pd.[24–28] A related approach involves the use of $Pd(OAc)_2$[29] or Pd–μ-hydroxide.[30] Finally, Pd(0) species oxidatively insert into C–H,[31] C–Cl,[32] and C–S[33] bonds at the carbene carbon, leading to Pd(II)–NHC complexes.

Both ligand classes, phosphines and NHCs, can be tuned by incorporating different substituents with predefined steric and electronic properties. In phosphines, these substituents are attached directly to the donor atom; therefore, the steric and electronic effects cannot be separated. NHCs allow the steric and electronic properties to be tuned independently, because the flanking N-substituents are not connected directly to the carbene carbon. The N-substituents have a limited effect on the electronic density of the carbene carbon;[34,35] the heterocyclic moiety is largely responsible for the electronic properties of the NHC. Electronic variations within the NHC ligand platform are small, and even carbenes with electron-withdrawing groups retain sufficient σ-donating ability to readily insert into unactivated haloarenes.[36] Therefore, the most promising avenue for the tuning of NHCs remains the steric bulk of the substituents surrounding the metal center. While phosphines and NHCs are similar electronically, there is a major difference in their topology when coordinated to the metal. The three substituents on phosphorus project backwards, away from the metal, forming a cone. In the case of NHCs, the N-substituents project forward to form a pocket around the metal, allowing for a much stronger impact of the substituents' topology on the metal center. A comparison of a range of imidazolium and 4,5-dihydroimidazolium NHC precursors (**Figure 4**) in the context of a number of cross-coupling reactions is shown in

Table 1.[36–46] The bulkiest *N,N'*-**diaryl** ligand precursors, IPr•HCl and SIPr•HCl, showed overall best performance in almost all cases. Therefore, these two ligands seem to be the best choice for the preparation of Pd–NHC catalysts of high activity and broad applicability. In general, the less sterically hindered IMes•HCl and SIMes•HCl were effective only if haloarenes were used. The performance of the saturated 4,5-dihydroimidazolium salts ligands was much less reliable than their unsaturated counterparts. We attribute the better performance of the aromatic imidazolium salts to ligand stability. This affects the amount of active catalyst produced initially, as well as its stability and lifetime, especially at the high temperatures that some cross-coupling protocols require. Finally, ITol•HCl, lacking any substituents in the ortho positions, was inferior to IPr and IMes in all cases. Among *N,N*-**dialkyl**imidazolium salts, IAd•HCl provided moderate-to-good results in some reactions, but seldom outperforming IPr. The performance of the less sterically hindered ligand precursors (e.g., ICy•HCl) seems to be generally unsatisfactory; therefore, they have not been studied in depth. The nature of the transformation itself is also important when ligands are compared: the more challenging the coupling, the higher the observed differences in ligand activity. The bulky carbene ligands are especially suitable for the stabilization of coordinatively unsaturated, monoligated Pd–NHC species. Analogous monoligated Pd–bulky phosphine species are considered to be responsible for the high levels of activity when such ligands are used in cross-coupling reactions.[47] Diligated Pd(II)–NHC complexes have a much lower activity than their Pd(0) counterparts as a result of the higher affinity of the NHCs to Pd(II) than to Pd(0),[36] leading to a much higher stability of the Pd(II)–$(NHC)_2$ species. Pd(II) precatalysts can be used *only* when another, more labile ligand, rather than a second NHC, is present. Pd complexes with chelating and pincer carbenes[11f] are even more stable then their monodentate counterparts.[4] In general, they are of limited use in catalysis, even though, in selected cases at high temperatures,[48–50] very high turnover numbers and frequencies have been observed. Considering that the chelating NHCs require a higher synthetic investment, the development of general and useful catalysts has been focused exclusively on monodentate carbenes.

3. Development of Well-Defined, Highly Active, Monoligated Pd–NHC Precatalysts

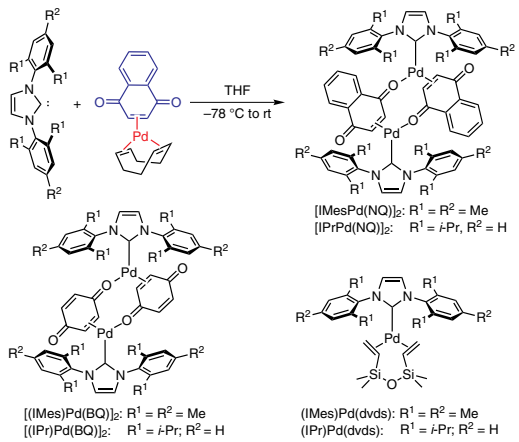
A number of studies have shown that: (i) IPr and, to a lesser extent, IMes as well as their saturated analogs, SIPr and SIMes, show the highest activity and have the widest general applicability; (ii) a monoligated Pd complex is optimal; and (iii) the nature of the initial Pd–NHC precatalyst is extremely important for the success of the cross-coupling reaction. A Pd atom has 4 vacant coordination sites in oxidation states 0 or 2. If one is taken up by the spectator NHC, this leaves up to 3 sites to be filled with appropriate *disposable ligands*. The nature of these ligands, besides the oxidation state of the Pd atom, determines the stability and ease of activation of the Pd–NHC precatalyst, whereas the NHC ligand ensures a high catalytic activity. The instability towards oxygen and shelf storage together with the limited, unattractive synthetic routes to Pd(0)–NHC complexes (all of which require handling of the moisture- and air-sensitive free carbene) handicap them as precatalysts. Beller's group developed a number of monoligated Pd(0) complexes of IPr and IMes with *p*-quinone or divinyldisiloxane (DVDS) ligands by ligand substitution of cyclooctadiene (cod) in the Pd(cod)(alkene) complex (**Figure 5**).[19,51,52] The quinone-ligated catalysts showed moderate-to-high activity in a number of cross-coupling reactions, as each complex is activated by simple alkene or *p*-quinone ligand dissociation. However, their synthesis suffers from the general limitations associated with the preparation and handling of sensitive Pd(0)–NHC complexes, in addition to using very expensive Pd(cod)(alkene) precursors.

In contrast to Pd(0), Pd(II)–NHC complexes are air-, moisture-, and heat-resistant and can be stored unaltered for prolonged periods of time. These properties are highly desirable for precatalysts to be widely used, provided the generation of Pd(0) species under the reaction conditions is facile. In 2001, Herrmann reported an array of tunable NHC–PdI_2–PR_3 complexes prepared in modular fashion from the μ-iodide dimers and triaryl- or trialkylphosphines.[53] Recently, Herrmann's[54] and Nolan's[55] groups reported a number

Table 1. The Effect of the Steric Bulk of NHC Ligand Precursors (Figure 4) in Various Pd-Mediated Transformations

	Ligand Precursor (NHC•HCl)[a]							
Reaction Type	IPr	IMes	ITol	SIPr	SIMes	IAd	ICy	Ref.
Suzuki–Miyaura	95[b]	99	5	–	–	44	14	*38*
Negishi	76[c]	2.8	–	85	1.2	0.6	–	*37*
Heck–Mizoroki	66	94	13	90[d]	64	2	90	*39*
Sonogashira (ArX)	80	87	62	60	66	56	–	*40*
Sonogashira (RX)	67	–	–	58[e]	<5[e]	80	–	*41*
Buchwald–Hartwig	98	22	<5	–	–	–	–	*42*
$CH_2(CN)_2$ Arylation	70[f]	75	<5	–	–	–	–	*43*
Arene Dehalogenation	45	46	–	56	96[g]	49	30	*44*
Alkyne Dimerization	76	97	34	14	88	45	34	*45*
Tsuji–Trost	77	25	–	–	–	–	0[h]	*46*

[a] The numbers shown represent typical percent yields in the reaction types listed. [b] Using 1 mol % of $Pd_2(dba)_3$; the standard conditions resulted in only a 53% yield. [c] Other Pd sources used (4 mol %) led to the following yields: 75% $(Pd(OAc)_2)$, 74% $(PdBr_2)$, 40% $(Pd(O_2CCF_3)_2)$, 19% $(PdCl_2)$, and 6% $([(\pi\text{-allyl})PdCl]_2)$. [d] 4% yield using 2 mol % of $Pd(dba)_2$. [e] The corresponding BF_4 salts were used. [f] The corresponding 2,4,6-trisubstituted analogue was used. Surprisingly, IPr•HCl led to <5% yields. We reason that this is due to the failure to form the active catalyst rather than to intrinsic low catalytic activity. [g] At 2 mol %, $PdCl_2(PhCN)_2$ and $Pd(OAc)_2$ gave 16% and 2% yields, respectively. [h] *N,N'*-Diisopropylimidazolium chloride was used.



Ref. 19,51,52

Figure 5. Monoligated, Highly Catalytically Active Precatalysts Developed by Beller and Co-workers.

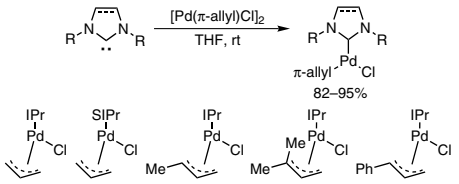


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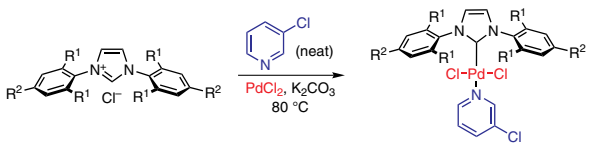
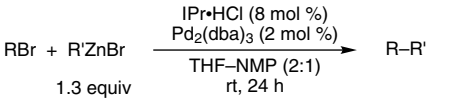
Figure 6. π-Allyl–Pd–(S)IPr Complexes.



R^1	R^2	Precatalyst	Yield
Me	Me	PEPPSI™-IMes	91%
Et	H	PEPPSI™-IEt	98%
i-Pr	H	PEPPSI™-IPr	97%

Ref. 58

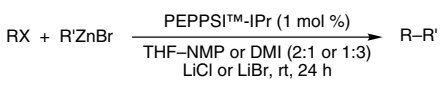
eq 1



R	R'	Yield
phthalimidyl–$(CH_2)_4$	*n*-Bu	65%
TMSC≡C$(CH_2)_2$	$(OCH_2CH_2O)CH(CH_2)_2$	61%
$CyCH_2$	$NCC(CH_3)_2(CH_2)_4$	63%
$NC(CH_2)_5$	$EtO_2C(CH_2)_3$	62%
$Cl(CH_2)_6$	$NCC(CH_3)_2(CH_2)_4$	81%
$NCC(CH_3)_2(CH_2)_4$	$CyCH_2$	84%

Ref. 37

eq 2



		Yield for X =					
R	R'	Cl	Br	I	OTf	OTs	OMs
$Ph(CH_2)_3$	*n*-Bu	88%	100%	68%	—	100%	100%
Ph	*n*-Hep	100%	100%	95%	100%	0%	0%
n-Hep	Ph	70%	100%	100%	—	90%	87%
4-Tol	4-MeOC_6H_4	80%	88%	73%	71%	0%	0%

Ref. 66

eq 3

of palladacycle precatalysts that showed high levels of activity in various cross-coupling reactions.

Nolan and co-workers have exerted major efforts in the development of Pd(π-allyl)Cl–NHC complexes. The system is highly modular, allowing a number of *N,N'*-diaryl[56] or dialkyl[56b] NHCs, as well as substituents on the allyl ligand, to be introduced (**Figure 6**). These complexes are highly catalytically active in a number of important cross-coupling reactions. IPr adducts of simple Pd salts, such as $Pd(OAc)_2$ and $PdCl_2$, are also known. Nolan has prepared the IPr complexes of $Pd(OAc)_2$ and $Pd(O_2CCF_3)_2$ by treatment of the Pd salt with the free carbene IPr under anhydrous conditions.[23,57] Almost all of the preceding precatalysts have been prepared by utilizing the isolated, highly moisture- and air-sensitive carbenes.

Very recently, we reported the synthesis of novel NHC–$PdCl_2$–3-chloropyridine complexes, which fulfill all the criteria for a general and useful coupling catalyst (**eq 1**).[58] This multicomponent reaction sequence proceeds through the in situ formation of a soluble $(3\text{-chloropyridine})_2PdCl_2$ complex.[59] However, the mechanism of carbene transfer to this intermediate is unknown. The reaction is easily performed on a kilogram scale, does not require anhydrous conditions or inert atmosphere, and the excess 3-chloropyridine can be recycled through distillation. The three isolated products shown in equation 1 are indefinitely stable to the atmosphere, yet can be easily activated under the conditions of various cross-coupling reactions, generating the active catalyst, a monoligated Pd(0)–NHC species. The pyridine plays an important role during formation of the complex, contributes to its stability, and readily dissociates upon reduction of Pd(II) to Pd(0). Therefore, we coined the name **PEPPSI™** (**P**yridine-**E**nhanced **P**recatalyst **P**reparation, **S**tabilization, and **I**nitiation) for these complexes in order to concisely describe these effects.[60]

4. Synthetic Applications of Pd–NHC Catalysts in Cross-Coupling Reactions

The cross-coupling methodology encompasses an array of transformations that create a new single bond between nucleophilic (usually an organometallic derivative, amine, or alcohol) and electrophilic (an organic halide or pseudohalide) reaction partners.[61] The reaction is thermodynamically driven by the formation of an inorganic salt. Even though a number of metals have been used to mediate this process, Pd has attained the most prominent position due to its unsurpassed versatility.[62] In order for the Pd-assisted cross-coupling methodology to attain its full powers, the versatility of Pd catalysts must be matched by high levels of activity, allowing a wide range of substrates, from most to least active, to be converted in high turnover under conditions that are as mild as possible. Besides the high catalytic activity, practical considerations such as the ease of synthesis, commercial availability and price, as well as user-friendliness and environmental impact must be addressed before the Pd–NHC cross-coupling methodology can become widely used in academia and industry. With the performance-enhancing NHC ligands incorporated into well-defined and easily prepared complexes, the goal of identifying a user-friendly and universal cross-coupling catalyst is now within reach.

4.1. The Negishi Coupling

The coupling of Zn, Al, or Zr organometallic derivatives with organic electrophiles (the Negishi coupling)[63] is one of the most versatile cross-coupling reactions because of to the high activity and ready availability of the nucleophilic partners,

making it very suitable for the preparation of complex, sensitive substrates. Surprisingly, until 2005, the only two instances of Pd–NHC-mediated Negishi coupling in the literature were unsuccessful.[22b,64] Even though a low yield was reported for the coupling of $PhCH_2CH_2CH_2Br$ with *n*-BuZnBr using IMes•HCl and $Pd_2(dba)_3$,[64] we observed that IPr•HCl performed much better in this reaction (see Table 1). Under optimized conditions, we also achieved the high-yield coupling of functionalized alkyl bromides and alkylzinc reagents at room temperature (**eq 2**).[37] It is worth noting that branching at the carbon adjacent to the carbon bearing the reactive functionality was well tolerated.[36,65]

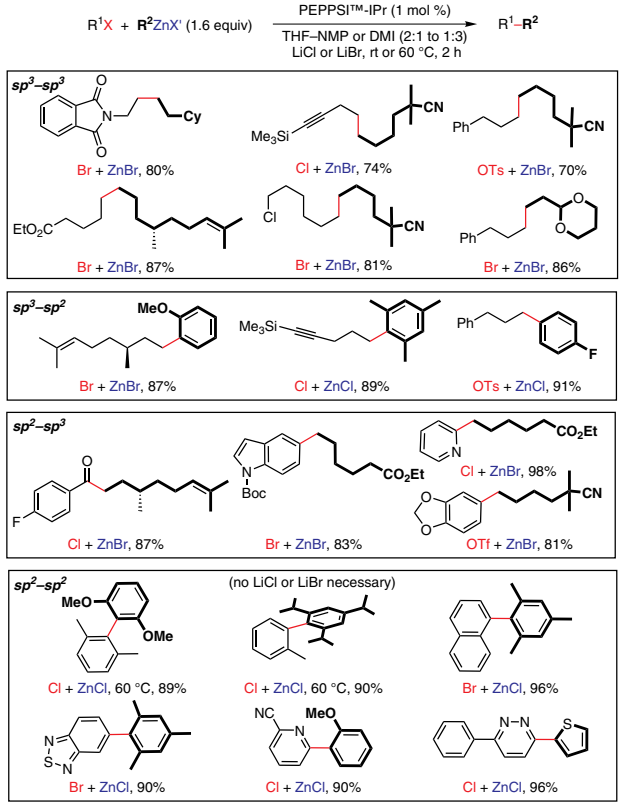
PEPPSI™-IPr is a very broadly applicable precatalyst, promoting the cross-coupling of alkyl or aryl halides and sulfonates with alkylzinc bromides or arylzinc chlorides at room temperature in all possible combinations by the judicious choice of solvent and additive (LiCl or LiBr) (**eq 3**).[66] Whereas the alkyl tosylates and mesolates underwent cross-coupling in high yield, the aryl analogues were unreactive. In this case, whereas the conversion of alkyl sulfonates into halides takes place through an S_N2-like mechanism[67] before oxidative insertion, a similar sulfonate–halide exchange reaction is impossible for the aryl sulfonates. Moreover, lithium halide additives were necessary for the cross-coupling of alkylzinc halides regardless of the choice of the electrophilic partner, indicating that the activation of the alkylzinc reagent by LiCl or LiBr is taking place presumably via a zincate. Complex substrates were also well tolerated in this reaction (**eq 4**).[66] An array of functionalized alkanes, including chiral terpene derivatives; sterically hindered biaryls; and drug-like heteroaromatic molecules were obtained in high yields. To highlight the high activity of the PEPPSI™-IPr precatalyst, the coupling of the sterically hindered 2,4,6-triisopropylphenylzinc chloride with *o*-chlorotoluene proceeded in 90% yield at 60 °C, the lowest temperature recorded with any protocol for preparing this compound.

To the best of our knowledge, the Negishi coupling promoted by PEPPSI™-IPr encompasses the broadest substrate range achieved with a single catalytic protocol, regardless of ligand system. For optimal results, slight variations of the reaction conditions may be necessary. In general, the reaction proceeds well in THF–NMP or THF–DMI (2:1) with LiCl or LiBr (preferred) added when alkyl halides or alkylzinc reagents are used. Increasing the proportion of the polar solvent (NMP or DMI) to 1:2 or 1:3 and/or the temperature to 60 °C is highly beneficial when challenging substrates, especially sterically hindered aryl chlorides, are used.

4.2. The Kumada–Tamao–Corriu Coupling

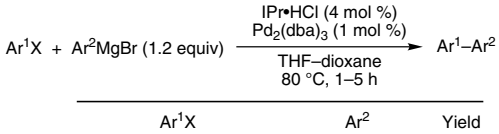
The coupling of organomagnesium reagents with organic electrophiles (the Kumada–Tamao–Corriu reaction)[68] is very similar to the Negishi reaction that utilizes organozinc halides. In contrast to the Negishi protocol, the lower tolerance of substrate functional groups and the fewer routes available for the preparation of the requisite Grignard reagents limit the usefulness of this coupling reaction for the synthesis of complex molecules. Nevertheless, when the Grignard reagents are available, the low cost, high reactivity, and nontoxicity of magnesium render this reaction one of the best choices available.

As early as 1999, Huang and Nolan published the first Kumada–Tamao–Corriu coupling using a catalyst generated in situ from IPr•HCl and $Pd_2(dba)_3$ in THF–dioxane at 80 °C (**eq 5**).[69] Aryl chlorides, bromides, and iodides were all coupled in good-to-excellent yields. However, di-*o*-substituted aryl chlorides reacted only with aryl Grignard reagents without ortho substituents. Beller and co-workers further extended the Kumada methodology to aryl[51] and alkyl[70] halides using monoligated naphthoquinone complexes (see Figure 5). While both IPr- and IMes-derived complexes were equally active in the sp^2–sp^2 Kumada coupling, surprisingly, the highest yields for the sp^3–sp^2 coupling were obtained with the IMes-derived complex. The corresponding DVDS complexes (see Figure 5) and catalysts, formed in situ, led to much lower yields. A notable feature of this protocol is the tolerance of a variety of Grignard-reactive functionalities on the alkyl chloride, as well as the tolerance of α-branched and α-functionalized (even though the yields were modest) alkyl chlorides.



Ref. 66

eq 4

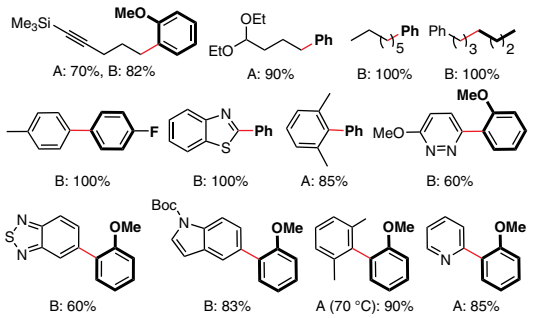


Ar^1X	Ar^2	Yield
4-$MeO_2CC_6H_4Br$	Ph	69%
4-HOC_6H_4I	Ph[a]	96%
2-Br-6-MeONaphthalene	Ph	98%
2,6-$Me_2C_6H_3Cl$	Ph	87%
4-$MeOC_6H_4Cl$	2-FC_6H_4	99%
4-$MeOC_6H_4Cl$	2,4,6-$Me_3C_6H_2$	95%

[a] 2.5 equiv of PhMgBr was used.

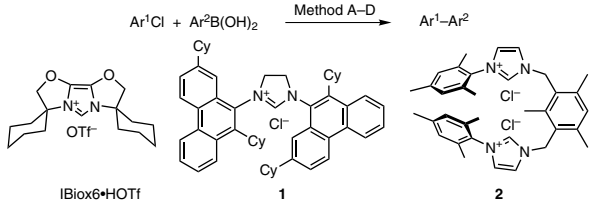
Ref. 69

eq 5



Ref. 71

eq 6



Ar[1]	Ar[2]	NHC Salt	Pd Source	Method	Yield (%)	Ref.
4-MeC_6H_4	4-$MeOC_6H_4$	IPr•HCl	$Pd(dba)_2$ (1 mol %)	A	99	*38*
4-MeC_6H_4	4-$MeOC_6H_4$	IMes•HCl	$Pd(OAc)_2$ (1 mol %)	A	80	*38*
4-MeC_6H_4	4-$MeOC_6H_4$	IPr•HCl	$Pd(dba)_2$ (3 mol %)	B	91	*77*
2-$MeOC_6H_4$	Ph	IPr•HCl	$Pd(dba)_2$ (3 mol %)	B	78	*77*
2-$MeOC_6H_4$	Ph	**1**	$Pd(OAc)_2$ (2 mol %)	C	98	*80*
4-MeC_6H_4	2-MeC_6H_4	IPr•HCl	$Pd(dba)_2$ (1 mol %)	A	97	*38*
4-MeC_6H_4	2-MeC_6H_4	IMes•HCl	$Pd(OAc)_2$ (1 mol %)	A	50	*38*
4-MeC_6H_4	2-MeC_6H_4	IMes•HCl	$Pd(OAc)_2$ (2.5 mol %)	A	60	*79*
4-MeC_6H_4	2-MeC_6H_4	**2**	$Pd(OAc)_2$ (2.5 mol %)	A	99	*79*
2-MeC_6H_4	Ph	IPr•HCl	$Pd(dba)_2$ (3 mol %)	B	79	*77*
2-MeC_6H_4	Ph	IBiox6•HOTf	$Pd(OAc)_2$ (3 mol %)	D	83	*81*
2-MeC_6H_4	Ph	**1**	$Pd(OAc)_2$ (2 mol %)	C	99	*80*
2,6-$Me_2C_6H_3$	Ph	IBiox6•HOTf	$Pd(OAc)_2$ (3 mol %)	D	79	*81*
2,6-$Me_2C_6H_3$	Ph	**1**	$Pd(OAc)_2$ (2 mol %)	C	90	*80*
2,5-$Me_2C_6H_3$	Ph	IPr•HCl	$Pd(dba)_2$ (1 mol %)	A	95	*38*
2,5-$Me_2C_6H_3$	Ph	IMes•HCl	$Pd(OAc)_2$ (1 mol %)	A	94	*38*
2,5-$Me_2C_6H_3$	Ph	**2**	$Pd(OAc)_2$ (2.5 mol %)	A	84	*79*
2,5-$Me_2C_6H_3$	2-MeC_6H_4	IBiox6•HOTf	$Pd(OAc)_2$ (3 mol %)	D	94	*81*
4-$MeO_2CC_6H_4$	Ph	IPr•HCl	$Pd(dba)_2$ (1 mol %)	A	98	*38*
4-$MeO_2CC_6H_4$	Ph	IMes•HCl	$Pd(OAc)_2$ (1 mol %)	A	99	*38*
4-$MeO_2CC_6H_4$	Ph	**2**	$Pd(OAc)_2$ (2.5 mol %)	A	99	*79*
4-$MeOC_6H_4$	Ph	IPr•HCl	$Pd(dba)_2$ (1 mol %)	A	99	*38*
4-$MeOC_6H_4$	Ph	IMes•HCl	$Pd(OAc)_2$ (1 mol %)	A	85	*38*
4-$MeOC_6H_4$	Ph	IPr•HCl	$Pd(dba)_2$ (3 mol %)	B	75	*77*

Method A: Cs_2CO_3, dioxane, 80 °C. **Method B**: KOMe, MeOH–PhMe, TBAB (10%), 40 °C. **Method C**: KF/18-crown-6, THF, 50 °C. **Method D**: CsF, THF, rt, 24 h.

eq 7

PEPPSI™-IPr is an excellent precatalyst for the Kumada coupling (**eq 6**).[71] This protocol is suitable for a wide range of difficult substrates such as alkyl chlorides and sterically hindered or heteroaromatic halides. Both aryl and alkyl chlorides are converted into the corresponding coupling products when treated with aryl Grignard reagents in THF–DME or THF–DMI at room temperature. In challenging substrate combinations, such as the coupling of 2,6-$Me_2C_6H_3Cl$ with 2-$MeOC_6H_4MgBr$, addition of LiCl and increasing the temperature to 70 °C are often necessary.

4.3. The Suzuki–Miyaura Coupling

The cross-coupling of organoboron derivatives with organic electrophiles (the Suzuki–Miyaura coupling)[72] is probably the most widely used cross-coupling protocol due to the commercial availability of a wide selection of solid, air- and moisture-tolerant boronic acids. In addition, the byproducts formed are nontoxic and the reaction proceeds well in a wide range of solvents including environmentally friendly simple alcohols and water. The reaction is tolerant of a wide range of functionality. The addition of a stoichiometric amount of base is necessary, presumably for the activation of the boron derivative. The nature of the solvent and base has a high impact on the success of the coupling, especially in challenging cases.

Arylboronic acids are the most frequently used nucleophilic partners in the Suzuki coupling. High levels of activity in the coupling of aryl iodides, bromides, and activated aryl chlorides with simple arylboronic acids have been recorded for a number of Pd–NHC catalysts.[22b,28,32,48a,73,74] In addition, the stability of the Pd–NHC species has been exploited in terms of catalyst immobilization on polymer supports[75] or in ionic liquids.[76] Aryl chlorides are attractive as feedstock for industrial cross-coupling reactions due to their low cost and wide availability, but are much less reactive than aryl bromides and iodides. Not surprisingly, the development of catalysts for the Suzuki cross-coupling of unactivated chloroarenes has attracted considerable attention.[16] Pd–NHC catalysts produced in situ from imidazolium salts and common Pd sources have shown high activities in cross-couplings of simple aryl chlorides with arylboronic acids. Nolan and co-workers have conducted extensive studies on the Suzuki–Miyaura coupling of chloroarenes using a number of *N,N'*-diarylimidazolium salts. Under optimized conditions—IPr•HCl and $Pd(dba)_2$ or IMes•HCl and $Pd(OAc)_2$ in dioxane with Cs_2CO_3 as the base—substituted biphenyls were synthesized in high yields at 80 °C (**eq 7**).[38] Independently, Caddick, Cloke, and co-workers employed the same catalyst precursor, IPr•HCl and $Pd(dba)_2$, in a biphasic mixture of toluene and methanol using NaOMe.[77] Even though the temperature of this protocol was only 40 °C, the use of two solvents and 10 mol % of tetra-*n*-butylammonium bromide (TBAB) as an additive limits its usefulness. In a very elegant study, Fairlamb et al. were able to enhance the performance of this catalytic protocol by using $Pd_2(dba)_3$ analogues prepared from 4,4'-disubstituted dibenzylideneacetones (dba) with electron-donating substituents.[78] Zhang and Trudell developed chelating IMes analogs in different topologies.[79] The bis(imidazolium) salt **2** was found to be highly active in Suzuki couplings of unactivated aryl chlorides under the conditions developed by Nolan (see above). Very recently, Andrus and co-workers disclosed a novel *N*-phenanthryl family of NHC precursors. The most active ligand, **1**, led to facile biphenyl formation at room temperature with $Pd(OAc)_2$ in THF using KF/18-crown-6 as the base.[80] Even though the yields were moderate to high at room temperature, increasing the temperature to 50 °C led to a significant increase

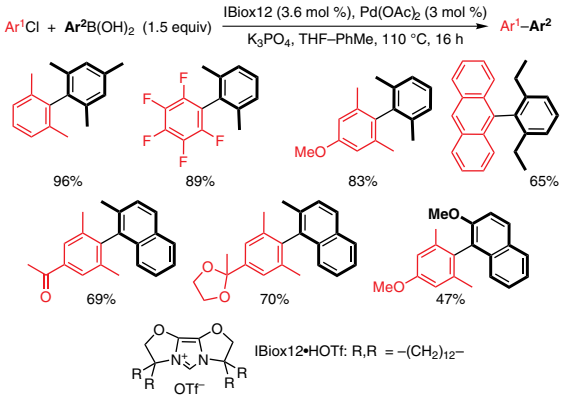
in yields and a shortening of the reaction times. The pentacyclic carbene ligands developed by Glorius and co-workers have been some of the most active to date: sterically unhindered biaryls were obtained in excellent yields at room temperature,[81] while the coupling of functionalized and sterically hindered aryl chlorides with sterically hindered boronic acids (**eq 8**) required the *spiro*-cyclododecyl analogue IBiox12 as ligand at high temperatures (100–110 °C).[82] Benzimidazolium salts with bulky *N*-adamantyl substituents were also used by our group for the synthesis of *p,p'*-substituted biphenyls with different combinations of electron-deficient and electron-rich reacting partners.[36] Benzimidazolium salts with less sterically hindered substituents have also been used successfully.[83]

Well-defined Pd–NHC precatalysts have been instrumental in bringing the Suzuki–Miyaura methodology to the next level, allowing even tetra-*o*-substituted biphenyls to be accessed at room temperature and catalyst loadings of 1 mol %. $(IAd)_2Pd$ was the first well-defined Pd–NHC complex to serve as an excellent catalyst for the coupling of unactivated aryl chlorides at room temperature in dioxane with CsF as the base.[20] However, the topology that the bulky IAd carbene created around the palladium metal precluded the use of *o*-substituted reacting partners. The homoleptic analogues, $(IPr)_2Pd$ and $(SIPr)_2Pd$, prepared by Caddick, Cloke, and co-workers, were also effective at 40 °C in toluene–methanol with NaOMe as the base. However, the use of the imidazolium salts and $Pd(dba)_2$ resulted in higher yields and much faster couplings, again highlighting the importance of the precatalyst activation step.[84]

Monoligated, Pd(II) complexes with disposable ligands, developed by our group and Nolan's, have shown the highest activity and substrate-range tolerance to date. A quantitative comparison of a variety of such complexes was conducted by Nolan using the challenging coupling of 2-chloro-1,3-xylene and 1-napthaleneboronic acid using *t*-BuOK in technical 2-propanol.[23,56a,85] As expected, IPr-based systems performed much better than their IMes analogs. The performance of PEPPSI™-IPr under identical conditions was also evaluated.[58] Even though at 40–50 °C all catalysts led to quantitative coupling within 2 h, the coupling at room temperature was highly dependant on the nature of the disposable ligand. PEPPSI™-IPr, palladacycle **3**, and the π-allyl–Pd complexes (see Figure 6)[55,56] all led to greater than 85% yields in 25–120 min. The proposed activation mode for the π-allyl complexes involves an attack of a nucleophile (organometallic derivative, alkoxide or hydride produced by β elimination) on either Pd or C-1/C-3 of the allyl moiety, followed by reductive elimination and alkene dissociation.[56d]

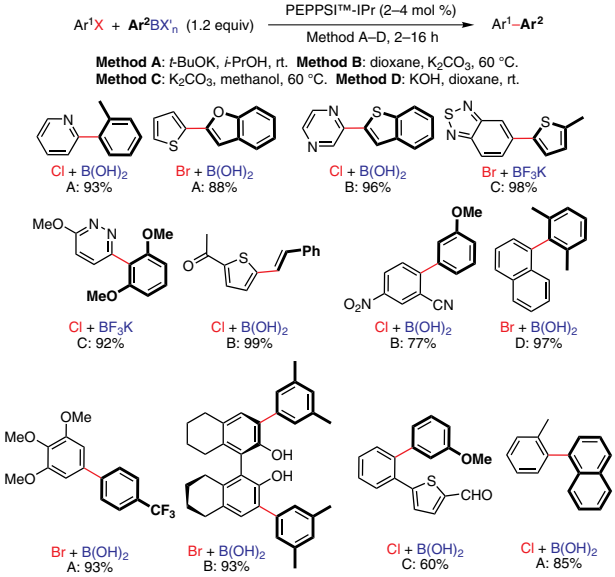
Nolan and co-workers have further utilized precatalysts $IPrPd(OAc)_2$, palladacycle **3**, and the π-allyl–Pd complexes (see Figure 6) in the synthesis of other sterically hindered and heteroaromatic biaryls.[23,56a,86,87] Conversions with $IMesPd(OAc)_2$ (the analog of $IPrPd(OAc)_2$) were also excellent, unless the product carried multiple ortho substituents. This protocol is highly advantageous owing to the use of the cheap and environmentally benign solvent, technical grade 2-propanol, room temperature, and only 1.05 equiv of the boronic acid. As expected, aryl bromides and triflates were also coupled with ease. PEPPSI™-IPr also showed excellent activity under these conditions.[66] However, the use of the moisture-sensitive and strongly basic *t*-BuOK, which requires a glovebox and limits the range of compatible functional groups, is an obvious liability. Therefore, we developed an alternative method—based on the same PEPPSI™-IPr precatalyst and involving a mild base—that is compatible with base-sensitive substrates (**eq 9**).[58] Polyheteroaromatic compounds, polysubstituted derivatives, and sterically hindered biaryls were all accessible with ease. In addition, we found that vinylboronic acids were highly active and trifluoroborates were reactive nucleophilic partners when K_2CO_3 in methanol was used, this being the first such example published. Again, as in the case of the Negishi coupling, changing the solvent and/or the base, or increasing the temperature to 60 °C was necessary for the coupling of challenging substrates.

Andrus and co-workers have been pioneers in the extension of the Pd–NHC methodology to the coupling of less-represented classes of reaction partners. Vinyl halides and triflates[80] and arenediazonium salts[88] underwent coupling with arylboronic acids mediated by $Pd(OAc)_2$ in combination with bulky ligand precursors, the phenanthrene-substituted imidazolium salt **1** (see eq 7) and SIPr•HCl, respectively (**eq 10**).[19,80,88,89] The coupling of electron-rich diazonium salts with arylboronic acids was also mediated by the $[(IMes)Pd(NQ)]_2$ complex in methanol at 50 °C.[19]



Ref. 82

eq 8



Ref. 58

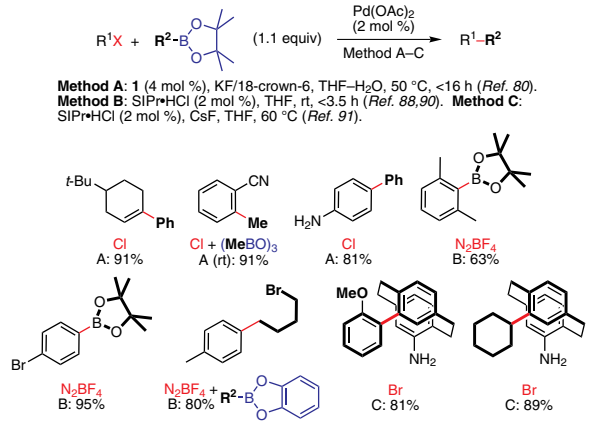
eq 9

$R^1X + R^2B(OH)_2$ (1.1–2.0 equiv) $\xrightarrow{\text{Method A–D}}$ $R^1–R^2$

R^1	X	R^2	Method	Yield (%)	Ref.
4-*t*-Bu-cyclohexen-1-yl	Cl	Ph	A, 50 °C	92	*80*
4-*t*-Bu-cyclohexen-1-yl	Br	Ph	A	90	*80*
4-*t*-Bu-cyclohexen-1-yl	I	Ph	A	98	*80*
4-*t*-Bu-cyclohexen-1-yl	OTf	Ph	A	89	*80*
cyclopenten-1-yl	Cl	2,6-$(MeO)_2C_6H_3$	A, 50 °C	68	*80*
4-$Et_2NC_6H_4$	N_2BF_4	1-naphthyl	C	87	*19*
4-$MeOC_6H_4$	N_2BF_4	Ph	B	97	*88*
4-$MeOC_6H_4$	N_2BF_4	Ph	C	62	*19*
4-MeC_6H_4	N_2BF_4	4-$MeOC_6H_4$	B	89	*88*
4-MeC_6H_4	SO_2Cl	4-$MeOC_6H_4$	D	65	*89*
4-MeC_6H_4	N_2BF_4	(*E*)-PhCH=CH	B	86	*88*
4-MeC_6H_4	SO_2Cl	(*E*)-PhCH=CH	D	48	*89*
4-$PhC(O)C_6H_4$	N_2BF_4	4-*t*-BuC_6H_4	B	86	*88*
1-naphthyl	SO_2Cl	4-MeC_6H_4	D	82	*89*

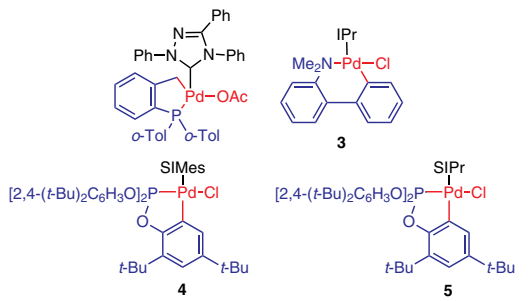
Method A: **1** (4 mol %), $Pd(OAc)_2$ (2 mol %), KF/18-crown-6, THF, rt, <16 h. **Method B**: SIPr•HCl (2 mol %), $Pd(OAc)_2$ (2 mol %), THF, 0 °C or rt, <3.5 h. **Method C**: $[IMesPd(NQ)]_2$ (1 mol %), MeOH, 50 °C. **Method D**: IMes•HCl (6 mol %), $Pd_2(dba)_3$ (1.5 mol %), Na_2CO_3, THF, reflux, 15–35 h.

eq 10



Ref. 80,88,90,91

eq 11



Ref. 93

Figure 7. NHC Palladacycle Complexes.

Even arenesulfonyl chlorides were coupled with the IMes•HCl/$Pd_2(dba)_3$ catalyst.[89]

The coupling of boronic esters has so far only been reported by Andrus's group (**eq 11**).[80,88,90,91] The ligand precursor **1**, in the presence of $Pd(OAc)_2$, promoted the coupling of a range of deactivated, sterically challenging aryl chlorides with the pinacol ester of arylboronic acids.[80] Moreover, the borylation of arenediazonium salts with bis(pinacolato)borane, using the catalyst produced from SIPr•HCl and $Pd(OAc)_2$ (1:1), proceeded in high yield in THF at room temperature in the absence of base.

Alkyl catechol-[88] and pinacolboranes[91] were chemoselectively cross-coupled with arenediazonium salts by Andrus and co-workers using the SIPr–$Pd(OAc)_2$ protocol in the presence of an alkyl bromide. Especially noteworthy is the coupling of cyclohexyl pinacolborane.[91] The **1**–$Pd(OAc)_2$ system successfully promoted the coupling of methylboroxine with aryl and vinyl chlorides.[80] Fürstner and Leitner have shown that Pd–NHC catalysts are suitable for the coupling of *B*-alkyl- (including allyl and cyclopropyl) and *B*-vinyl-*B*-methoxy-9-BBN adducts with a variety of aryl chlorides.[92] IPr•HCl was the ligand precursor of choice.

The activation of alkyl halides has been less successful. IMes–$Pd(OAc)_2$ was employed by Nolan's group for the coupling of activated benzyl and allyl halides with phenylboronic acid (*t*-BuOK in technical 2-propanol at room temperature).[23] The reaction times were generally short and yields excellent. Ligand **1** also showed excellent activity in the coupling of benzyl chloride.[80] The attempts of Bedford et al. to couple $PhCH_2CH_2Br$ with $PhB(OH)_2$ using the SIMes or SIPr palladacycle complexes **4** and **5** (**Figure 7**) failed.[93,94] These palladacycles also showed unsatisfactory performance in the Suzuki–Miyaura coupling of biaryls: even though aryl bromides coupled well, the yields with aryl chlorides were around 10% or less.[93] Recently, Caddick, Cloke, and co-workers described the application of an in situ generated Pd–IPr catalyst[77] in alkyl–alkyl and alkyl–vinyl cross-couplings of *B*-alkyl- or *B*-vinyl-9-BBN derivatives activated with *t*-BuOK. AgOTf was required as additive. Despite the low-to-moderate yields, this landmark work has paved the way for a successful alkyl–alkyl Suzuki cross-coupling reaction.

Encouraged by the facile Negishi[66] and Kumada–Tamao–Corriu[71] alkyl–alkyl cross-couplings, we treated $Ph(CH_2)_3Br$ with 1.1 equiv of tri-*n*-butylborane in the presence of 1 mol % of PEPPSI™-IPr under the standard Suzuki–Miyaura cross-coupling conditions (*t*-BuOK, technical 2-propanol, room temperature). We were pleased to measure a quantitative yield of the coupling product, *n*-heptylbenzene, in less than 5 min! PEPPSI™-IEt and PEPPSI™-IMes led to lower yields and slower reaction rates (**eq 12**).[58,71] Such fine discrimination by ligand size was not observed for the aryl–aryl Suzuki–Miyaura coupling: all three precatalysts were highly effective.[58] Interestingly, the yields and rates were very similar regardless of whether a Zn or B nucleophile was employed, which led us to conclude that they reflect the intrinsic reactivity, rather than external factors, of the NHC ligands, with the bulkier ligands leading to faster reductive elimination. In the case of the more aggressive alkyl Grignard reagents, PEPPSI™-IEt resulted in only an 8% yield compared to 31% and 34% in the milder Suzuki–Miyaura or Negishi couplings. We propose that the catalyst decomposition in the Kumada coupling is faster, thus limiting conversions. Based on these exciting preliminary results, the development of a methodology for the cross-coupling of alkyl halides with alkyl- and arylboron compounds is currently underway in our group.

4.4. The Coupling of Si and Sn Organometals

Historically, the cross-coupling of organotin compounds (the Stille reaction)[95] has been the most widely used cross-coupling reaction alongside the Suzuki reaction. Due to the toxicity of the organotin compounds and the difficulty of their removal from the products of interest, however, this reaction has now been superseded by more recent, environmentally friendly protocols. Even though silicon, like tin, belongs to Group 14 of the periodic table, the corresponding silicon protocols[96] are markedly different, largely due to the fact that, while the transmetalation from tetraalkyl-substituted Sn to Pd is possible, the transmetalation from Si to Pd occurs only from hypervalent, pentacoordinate silicon intermediates. The silicon reagents are especially attractive from an industrial point of view because of their low cost, lack of toxicity, and high stability.

The Stille coupling of aryl bromides and arylstannanes was investigated by Herrmann et al. in the presence of mixed NHC–PdI_2–phosphine complexes as precatalysts. The complex from *N,N'*-di-(*R*)-1-phenylethylimidazole carbene and PdI_2PPh_3 showed the highest activity in the cross-coupling of *p*-bromoacetophenone and tri(*n*-butyl)phenylstannane in the absence of base or activator. Complexes of the same carbene with bulkier or more electron-rich phosphines were less active. This system was not suitable for the Stille coupling of aryl chlorides.[53]

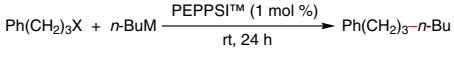
Addition of fluoride salts activates the organotin reagents towards transmetalation by the formation of an anionic hypervalent tin center. Under these conditions, phenyl- or vinyltrialkylstannanes readily underwent coupling to unactivated aryl chlorides and bromides with 2 equiv of TBAF at 100 or 80 °C, respectively (**eq 13**).[97,98] Surprisingly, both IPr•HCl and IAd•HCl showed equal activity.[97] The reaction times were also long, requiring up to 48 h in some cases. Under similar conditions, phenyl- and vinyltrimethoxysilanes underwent cross-coupling reactions at a slightly lower temperature (60 °C), and a large excess of the silicon reagent (2–3 equiv) was required.

4.5. Alkyne Cross-Couplings and the Sonogashira Reaction

The coupling of terminal acetylenes encompasses a family of related transformations in which an *sp*-carbon nucleophile is generated.[99] The most widely used protocol employs Cu salts as co-catalysts, most often in the presence of amine bases (the Sonogashira reaction).[99b] The first Sonogashira reaction using a Pd–NHC catalyst was published by Caddick, Cloke, and co-workers: a single example of the coupling of a trisubstituted alkene carrying a bromo, iodo, and ester substituents using $(It\text{Bu})_2Pd$ as the Pd–NHC catalyst (**eq 14**).[100] As expected, the coupling occurred at the vinyl iodide site (entry 6, eq 14). Using a preformed, monoligated PdI_2 complex (**6**, 1 mol %) containing simultaneously an *N*-acyl-*N'*-methyl NHC and *N*-methylimidazole ligands, Batey et al. reported the Sonogashira reaction of simple bromo- and iodoarenes with terminal acetylenes in the presence of CuI (2 mol %) and PPh_3 as co-ligand.[101] A similar approach was taken by Andrus and co-workers: the catalyst prepared from the bulky imidazolium salt **1** and $Pd(PPh_3)_2Cl_2$ promoted the coupling of various iodo- and bromosubstituted arenes and alkenes with terminal acetylenes.[102] Surprisingly, SIPr•HCl showed only moderate activity. Another example of a copper-free alkyne coupling with 1 mol % **7** was published by Herrmann et al.[29c]

The Sonogashira coupling of terminal acetylenes with alkyl bromides and iodides—a milder alternative to the uncatalyzed, direct substitution process—was first published by Eckhardt and Fu.[41] A variety of functional groups and substituents were compatible, including alkyl chlorides. Although IAd•HCl was the ligand of choice, IPr•HCl also showed high levels of activity. This reaction represents the first example of the activation of simple alkyl halides by a Pd–NHC catalyst.

The use of main-group alkyne organometallic derivatives is also possible with Pd–NHC catalysts. Fürstner and Leitner have used *B*-(phenylacetylide)-*B*-methoxy-9-BBN as a nucleophile in the Suzuki–Miyaura reaction of unactivated chloroarenes (which are inactive under the classical Sonogashira conditions) promoted by IPr•HCl and $Pd(OAc)_2$ in refluxing THF. Methyl 4-(phenylethynyl)benzoate and 1,3-dimethoxy-5-

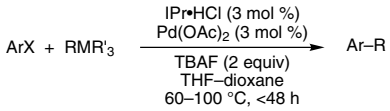


Negishi: THF–NMP (2:1), LiCl (2 equiv).
Kumada–Tamao–Corriu: THF–DMI (2:1).
Suzuki–Miyaura: *t*-BuOK, *i*-PrOH.

X	M	IPr	IEt	IMes
Br	ZnBr	100%	34%	8%
Br	MgBr	99%	8%	—
Cl	$B(n\text{-Bu})_2$	100%	31%	7%

Ref. 58,71

eq 12

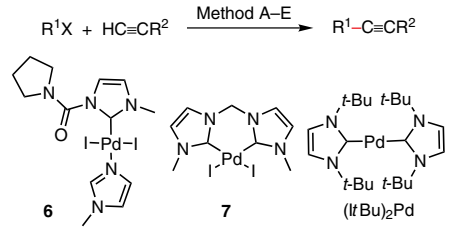


Ar	X	R[a]	MR'_3	Yield (%)
4-MeC(O)C_6H_4	Br	Ph	$SnMe_3$	92
4-MeC(O)C_6H_4	Cl	Ph	$SnMe_3$	91
4-MeC(O)C_6H_4	Br	Ph	$Si(MeO)_3$	100
4-MeC(O)C_6H_4	Cl	Ph	$Si(MeO)_3$	100
4-$MeOC_6H_4$	Br	Ph	$SnMe_3$	92
4-$MeOC_6H_4$	Cl	Ph	$SnMe_3$	35
4-$MeOC_6H_4$	Cl	Ph	$Si(MeO)_3$	19
2,4,6-$Me_3C_6H_2$	Br	Ph	$SnMe_3$	86
2-NCC_6H_4	Br	Ph	$SnMe_3$	80
2-Pyr	Br	Ph	$Si(MeO)_3$	81
2-Pyr	Cl	Ph	$Si(MeO)_3$	81
4-MeC(O)C_6H_4	Br	CH_2=CH	$SnMe_3$	92
4-MeC(O)C_6H_4	Cl	CH_2=CH	$SnMe_3$	83
4-MeC(O)C_6H_4	Br	CH_2=CH	$Si(MeO)_3$	100[b]
4-MeC(O)C_6H_4	Cl	CH_2=CH	$Si(MeO)_3$	100[b]
4-$MeOC_6H_4$	Br	CH_2=CH	$SnMe_3$	69
4-$MeOC_6H_4$	Cl	CH_2=CH	$SnMe_3$	15
4-MeC_6H_4	Br	CH_2=CH	$SnMe_3$	98
4-MeC_6H_4	Cl	CH_2=CH	$SnMe_3$	41
2,4,6-$Me_3C_6H_2$	Br	CH_2=CH	$SnMe_3$	25

[a] 1.1 and 2–3 equivalents of the organotin and organosilicon reagents, respectively, were employed. [b] Percent conversion.

Ref. 97,98

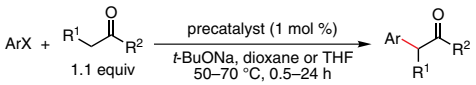
eq 13



R^1	X	R^2	Method	Yield (%)	Ref.
4-MeC(O)C_6H_4	Br	Ph	A	76	*29c*
4-MeC(O)C_6H_4	I	Ph	B	95	*101*
4-MeC(O)C_6H_4	Br	Ph	B	99	*101*
4-MeC(O)C_6H_4	I	Ph	C	87	*102*
4-MeC(O)C_6H_4	Br	Ph	C	81	*102*
(*Z*)-$EtO_2CCBr{=}CH$	I	TMS	D	85	*100*
4-$MeOC_6H_4$	I	*t*-Bu	B	93	*101*
4-$MeOC_6H_4$	Br	*t*-Bu	B	97	*101*
2,6-$Me_2C_6H_3$	Br	$Me_2C(OH)$	C	80	*102*
$MeC(O)(CH_2)_4$	I	$Cl(CH_2)_4$	E	70	*41*
$[O(CH_2)_2O]CH(CH_2)_2$	Br	$AcO(CH_2)_3$	E (60 °C)	58	*41*
$NC(CH_2)_3$	Br	*t*-Bu	E	70	*41*
cyclohexen-1-yl	Br	cyclohexen-1-yl	C	71	*102*

Method A: **7** (1 mol %), Et_3N, 90 °C, 48 h. **Method B**: **6** (1 mol %), PPh_3 (1 mol %), CuI (2 mol %), DMF, 2–24 h. For ArI: Et_3N, rt. For ArBr: Cs_2CO_3, 80 °C. **Method C**: **1** (3 mol %), $Pd(PPh_3)_2Cl_2$ (3 mol %), *t*-BuOK/18-crown-6, THF, 2.0–6.5 h. For ArI: rt. For ArBr: 65 °C. **Method D**: $(tBu)_2Pd$ (1 mol %), CuI (0.2 equiv), $(i\text{-}Pr)_2NEt$, DMF, rt. **Method E**: IAd•HCl (10 mol %), $[(\pi\text{-allyl})PdCl]_2$ (2.5 mol %), CuI (7.5 mol %), Cs_2CO_3, DMF–Et_2O, 45 °C, 16 h.

eq 14



Ar	X	R^1	R^2	Precatalyst	Yield (%)
4-Tol	F	Me	Ph	$IPrPd(OAc)_2$	0
4-Tol	Cl	Me	Ph	$IPrPd(OAc)_2$	96
4-Tol	Br	Me	Ph	$IPrPd(OAc)_2$	92
4-Tol	I	Me	Ph	$IPrPd(OAc)_2$	96
4-Tol	OTf	Me	Ph	$SIPrPd(\pi\text{-}C_3H_5)Cl$	93
4-Tol	Cl	Me	Et	**3**	90
4-Tol	Cl	Me	4-TolCH(Me)	$IPrPd(\pi\text{-}C_3H_5)Cl$	88
2,4,6-$Me_3C_6H_2$	Br	Me	Et	$IPrPd(OAc)_2$	92
2,4,6-$Me_3C_6H_2$	Br	Me	Ph	**3**	85
2,4,6-$Me_3C_6H_2$	Br	Me	Et	$SIPrPd(\pi\text{-}C_3H_5)Cl$	91
Ph	Cl		$-(CH_2)_4-$	IPrPd(acac)Cl	86
Ph	Cl		$-(CH_2)_4-$	**3**	72
Ph	Br		$-(CH_2)_4-$	**3**	68
2-Tol	Cl	H	*N*-Me-pyrrolidin-2-yl	$IPrPd(OAc)_2$	46
pyridin-3-yl	Cl	Me	Ph	**3**	76
pyridin-3-yl	Cl	Me	Ph	IPrPd(acac)Cl	89
pyridin-3-yl	Cl	Me	Ph	$SIPrPd(\pi\text{-}C_3H_5)Cl$	86
2-Tol	Cl		$-(CH_2)_3CH(OMe)-$	$IPrPd(OAc)_2$	17
2-$MeOC_6H_4$	Br		$-(CH_2)_2$-phenylen-2-yl–	**3**	97

Ref. 56c,86,107,108

eq 15

(phenylethynyl)benzoate were obtained in 82% and 85% yields, respectively.[92] Similarly, Yang and Nolan explored the coupling of trimethylsilylalkynes with chlorobenzene and deactivated bromoarenes in the presence of a catalyst prepared in situ from IMes•HCl and $Pd(OAc)_2$.[40] Even though the reaction proceeded well under copper-free conditions, the addition of CuI facilitated the process.

4.6. Enolate Arylation

Among cross-coupling reactions, enolate arylation[103] is unique in a number of respects. It is well established that, although the alkylation of enolates is facile, the arylation with simple, unactivated aryl halides is impossible without the help of a transition metal. Palladium-catalyzed enolate arylation is the only method that allows the formation of useful α-arylated ketones, esters, nitriles, and amides from simple aryl halides. Moreover, if suitably substituted reaction partners are used, a new tertiary or quaternary chiral center can be established, raising the possibility of enantioselective catalysis. Hence, this synthetically important transformation has attracted considerable attention.

Even though the first examples of this reaction were published back in 1997 independently by the groups of Hartwig,[104] Buchwald,[105] and Miura[106] using ketone enolates and chelating or bulky phosphines as well as ligandless conditions (Miura), the Pd–NHC protocol is much more recent. Nolan and co-workers have shown that well-defined monoligated IPr–Pd complexes are efficient catalysts for the arylation of simple ketones with unactivated aryl chlorides, bromides, iodides, and triflates using *t*-BuONa (**eq 15**).[55,56c,86,107,108] A variety of functional groups (with the exception of nitrile and aldehyde)[108] are tolerated on the arene moiety, and sterically hindered or heterocyclic substrates gave moderate-to-high yields. With respect to ketones, aryl–alkyl, dialkyl, and cyclic representatives are all suitable. Strict control of the amount of ketone and base is needed to suppress multiple arylations; typically, monoarylated products are obtained in high yields in the presence of 1.1 equiv of the carbonyl partner and 1.1 equiv of the base. The reaction has also been performed under microwave conditions.[86] Introducing substituents α to the carbonyl group usually has a detrimental effect on the coupling. Consequently, in unsymmetrical ketones, arylation occurs preferentially at the least sterically hindered carbon. For example, arylation of 2-butanone with chlorobenzene leads to a 4:1 distribution of methyl vs methylene arylation (10:1 under microwave conditions).[86] An important limitation of this method is that quaternary α carbons are not accessible.

Hartwig and co-workers explored the arylation of ester or amide enolates with a variety of aryl bromides and chlorobenzene, relying on catalysts formed in situ from SIPr•HCl and $Pd_2(dba)_3$.[109] While *tert*-butyl acetate and propionate reacted smoothly with a range of aryl bromides, methyl isobutyrate resulted in poor yields. However, the intramolecular arylation of the 2-bromo-*N*-methylanilide of isobutyric acid proceeded in quantitative yields with both IPr•HCl and SIPr•HCl.[110] The more sterically hindered carbonyl compounds generally required higher catalyst loadings (up to 5 mol %). Thus far, nitrile arylation has been explored only in the case of malononitrile. A range of aromatic chlorides and bromides were converted to the corresponding 2-arylmalononitriles in excellent yields using NaH as base and pyridine as solvent.[43]

The chiral version of the oxindole cyclization is the only case of catalytic enantioselective enolate arylation that has been explored to date. Glorius et al. prepared chiral, C_2-symmetric tricyclic imidazolium salts **8a–c** from commercially available (*S*)-valinol,

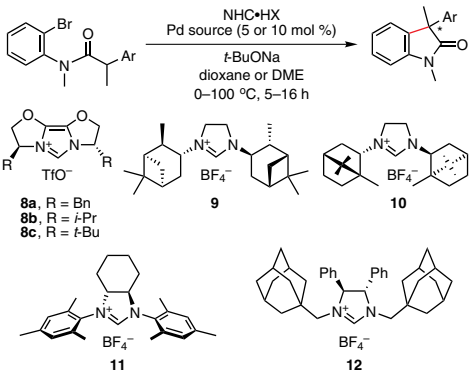
(*S*)-phenylalaninol, and (*S*)-*tert*-leucinol, respectively. Catalysts prepared in situ from these salts and $Pd(OAc)_2$ or $Pd_2(dba)_3$ (10 mol %) promoted the oxindole cyclization in excellent yields at 20–50 °C, albeit in low enantiomeric excesses (<43%) (**eq 16**).[111] Lee and Hartwig synthesized two novel, terpene-derived 4,5-dihydroimidazolium salts, **9** and **10,** with bulky, chiral residues attached to the nitrogen atoms.[110] These ligands were reasonably successful, with ee values of 59% (**9**) and 69% (**10**) recorded, and the catalysts derived from them had sufficient activity for the reactions to be conducted below room temperature, where the highest ee values were obtained. In contrast, the backbone-chiral SIMes analog, **11**, successful in the Grubbs asymmetric Ru methathesis reaction,[9] showed here only very low ee's. Very recently, 1,3-di(1-adamantylmethyl)-substituted imidazolium salt **12** was also tested in a similar reaction using 10 mol % $Pd(OAc)_2$.[112] Even though an ee as high as 67% was obtained, the yield was very low (14%). The use of a milder base, *t*-BuOLi instead of *t*-BuONa, resulted in a significant improvement in yield without a significant erosion of ee.

4.7. The Buchwald–Hartwig Amination and Related C–N Couplings

The palladium-catalyzed cross-coupling reactions can be extended to the formation of C–heteroatom bonds. The most significant among these methods is the Buchwald–Hartwig amination,[113] a method for the synthesis of di- and trisubstituted aromatic amines by direct coupling of an aryl halide and a primary or a secondary amine (ammonia is not suitable as a coupling partner under the current state of the art). This reaction has attracted strong industrial interest[114] because of its versatility, atom economy, and the usefulness of the materials produced. The importance of the Buchwald–Hartwig amination reaction is emphasized by the fact that this is the only cross-coupling reaction with Pd–NHC for which a thorough computational study of the catalytic cycle,[115] supported by experimental data,[116] has been published.

Pd–NHC complexes prepared in situ from imidazolium salts and Pd sources are efficient catalysts for the Buchwald–Hartwig amination reaction, as demonstrated by the groups of Hartwig,[103,117,118] Nolan,[42] Caddick and Cloke,[119] Trudell,[120] and Beller[51] (**eq 17**). Usually, *t*-BuOK or *t*-BuONa was used in DME or dioxane, between room temperature and 100 °C. The reaction proceeded well with aryl halides and aromatic or aliphatic amines as well as N–H-containing heterocycles. However, the use of primary alkylamines was problematic, requiring higher temperatures and catalyst loadings, as well as a large excess of the amine in order to suppress the unwanted double arylation. With respect to more challenging substrates, Trudell[120] has performed N-arylations of 7-azabicyclo[2.2.1]heptane with aryl and heteroaryl chlorides, bromides, and iodides using the bis(imidazolium) ligand **13**.

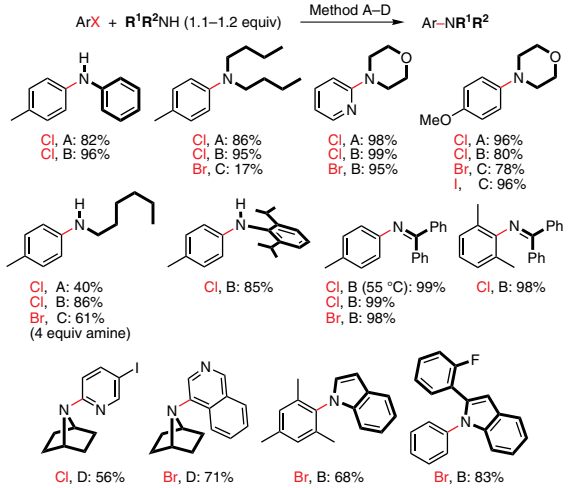
A considerable improvement in the Pd–NHC-promoted Buchwald–Hartwig amination has resulted from the use of well-defined palladium catalysts in conditions very similar to the in situ protocol just described. Caddick, Cloke, and co-workers have shown that homoleptic $Pd(NHC)_2$ complexes $(ItBu)_2Pd$ and $(SIPr)_2Pd$ are excellent catalysts for the amination of aryl chlorides. At 100 °C, a number of *N*-mono- and *N*,*N*-disubstituted anilines were obtained in excellent yields within 1 h using $(SIPr)_2Pd$ and SIPr–Pd–$P(2\text{-Tol})_3$.[84,99] The monoligated NHC–Pd(0)–quinone or NHC–Pd(0)–DVDS complexes (see Figure 5) generally gave unsatisfactory yields. However, excellent yields were obtained by the in situ formed catalysts under the same conditions.[51] Palladium(II) complexes of cyclic and acyclic



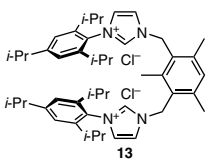
Ar	NHC•HX	Pd Source	Yield (%)	ee (%)	Ref.
Ph	**8a**	$Pd_2(dba)_3$	90	11	*111*
Ph	**8b**	$Pd(OAc)_2$	92	32	*111*
Ph	**8c**	$Pd_2(dba)_3$	95	43	*111*
1-naphthyl	**9**	$Pd(dba)_2$	93	59	*110*
1-naphthyl	**10**	$Pd(dba)_2$	91	69	*110*
1-naphthyl[a]	**10**	$Pd(dba)_2$	27	70	*110*
1-naphthyl	**11**	$Pd(dba)_2$	35	4	*110*
Ph	**12**	$Pd(OAc)_2$	14	67	*112*
4-$MeOC_6H_4$	**12**	$Pd(OAc)_2$[b]	59	65	*112*

[a] At 0 °C. [b] *t*-BuOLi was used instead.

eq 16



Method A: SIPr•HBF_4 (0.08–2 mol %), $Pd(dba)_2$ (0.08–2 mol %), *t*-BuONa, DME, rt–55 °C, <20 h (*Ref. 118*). **Method B**: IPr•HCl or SIMes•HCl (2–4 mol %), $Pd_2(dba)_3$ (1 mol %), dioxane, 100 °C, < 24 h (*Ref. 42a*). **Method C**: SIPr•HCl (4 mol %), $Pd_2(dba)_3$ (1 mol %), LiHMDS, THF, rt, <24 h (*Ref. 119*). **Method D**: **13** (4 mol %), $Pd_2(dba)_3$ (4 mol %), *t*-BuONa, dioxane, 100–110 °C, <41 h (*Ref. 120*).



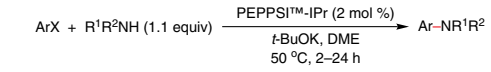
Ref. 42,118–120

eq 17

mono- and diaminocarbenes, prepared by Fürstner and co-workers, efficiently catalyzed the amination of bromobenzene and 2-chloropyridine with morpholine (47–100% yields).[32] Nolan and co-workers have exerted a considerable effort towards the development of Buchwald–Hartwig amination protocols with a number of monoligated Pd–NHC complexes.[55,56a,d,87,107,121] The coupling of deactivated and sterically hindered substrates proceeded well even at room temperature. At 80 °C, decreasing the amount of catalyst to 0.001–1 mol % still led to amination yields in the 90% range. The SIPr–PdCl(π-C_3H_4Ph) complex was the most active and versatile precatalyst to emerge from these studies, usually achieving a greater than 95% yield within 2 hours.[56a]

PEPPSI™-IPr is also highly active in the Buchwald–Hartwig amination (**eq 18**). With 2 mol % of PEPPSI™-IPr, a variety of unactivated, sterically hindered or heterocyclic halides were coupled with primary and secondary amines. Of particular interest are the products from the coupling of bromobenzene with the bulky 1-adamantylamine and the optically active (*R*)-α-methylbenzylamine, the former proceeding with ease and the latter without racemization.[122]

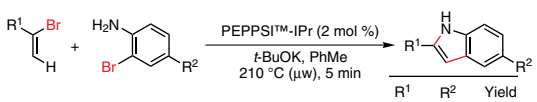
Aryl amination can occur within more complicated reaction sequences. The PEPPSI™-IPr precatalyst was used in an indole synthesis (a vinyl amination–Heck sequence) under microwave conditions (**eq 19**).[123] A similar approach to N-substituted indoles (an aryl amination–alkyne hydroamination sequence) was published by Ackerman, using a catalyst prepared in situ from IPr•HCl and $Pd(OAc)_2$ (5 mol %). Weak bases (Cs_2CO_3, K_3PO_4) were suitable, and the reaction was also executed as a tandem, one-pot Sonogashira coupling–indole cyclization sequence (64% yield).[124]



Ar	X	R^1	R^2	Yield
4-$MeOC_6H_4$	Cl	morpholin-4-yl		84%
Ph	Cl	morpholin-4-yl		81%
4-FC_6H_4	Cl	morpholin-4-yl		86%
2,6-$Me_2C_6H_3$	Cl	morpholin-4-yl		81%
2,6-$Me_2C_6H_3$	Cl	H	Cy	65%
Ph	Br	H	Ad	70%
Ph	Br	H	(*R*)-PhCH(Me)	70%
thien-3-yl	Cl	Me	Ph	73%

Ref. 122

eq 18



R^1	R^2	Yield
Ph	H	74%
Ph	Me	84%
Ph	Cl	80%
Et	Me	82%

Ref. 123

eq 19

5. Conclusions and Future Directions

For the past 11 years, Pd-catalyzed cross-coupling reactions have benefited enormously from the introduction of N-heterocyclic carbenes as ligands. The bulky carbenes IPr and SIPr, introduced almost right at the start, have repeatedly been proven the most active and widely applicable NHC ligands, not just for Pd, but for other metals as well. Attempts to synthesize better-performing ligands have not been successful thus far.[36] The ligand precursors for IPr and especially SIPr are pricey, and preparation of ligands that are cheaper yet retain or exceed the high levels of activity of (S)IPr will be an important contribution to the field.

A closely related issue is the economical preparation of well-defined, user-friendly, high-performance Pd–NHC complexes that are activated easily when submitted to the cross-coupling reaction conditions. The primary advantage of the PEPPSI™ family of Pd–NHC precatalysts is their method of preparation, and the low cost associated with it, which allows the reaction (see eq 1) to be conducted on a kilogram scale in open air from less expensive precursors and bases. The result is robust, general, and highly active catalysts that are now cheaper than $Pd(PPh_3)_4$, the current choice for routine couplings in industry and academia, despite its inadequate stability and moderate activity.

What lies in the future? An important key area that remains underdeveloped is the use of NHC ligands in Pd-mediated reactions outside of the cross-coupling domain such as in oxidation, reduction, allyl substitution, diene hydroamination, and tandem cyclization reactions. What benefits NHC ligands will bring to these areas is an exciting question that eagerly awaits an answer. Many of these transformations open the possibility for enantioselective catalysis. However, a highly active and enantioselective Pd–NHC catalyst is a promise that so far has not been fulfilled. Furthermore, the use of Pd–NHC catalysts for cross-coupling reactions of heavily functionalized, complex substrates, such as in key steps in complex total syntheses,[125] is eagerly awaited as well.

6. References and Notes

(†) Current address: Institute of Bioengineering and Nanotechnology (IBN), 31 Biopolis Way, #04-01, The Nanos, Singapore 138 669.

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(60) PEPPSI is a trademark of Total Synthesis Ltd. (Toronto, Canada). Professor Organ holds an equity interest in this company.

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About the Authors

Eric A. B. Kantchev was born in 1973 in Gabrovo, Bulgaria. His early interest in the natural sciences culminated in his winning of the silver medal at the XXIII International Chemistry Olympiad in 1991. He then pursued his undergraduate degree (1991–1996) at the University of Sofia, Bulgaria. He obtained his Ph.D. degree from The Ohio State University with Professor Jonathan R. Parquette for research work at the interface of carbohydrate and dendrimer chemistry. His postdoctoral training took him in 2001 to Academia Sinica, Taiwan, to work with Dr. Ding-kwo Chang on the synthesis of peptides and bioconjugates related to viral fusion proteins. This was followed in 2004 by a stint in the laboratory of Professor M. G. Organ at York University, Canada, where he worked on the development of the PEPPSI™ catalysts. Presently, Eric is a research scientist at the Institute of Bioengineering and Nanotechnology (IBN) in Singapore, providing synthetic chemistry solutions for nanobiotechnology problems. His current interests include function-oriented organic, biomolecular, and organometallic synthesis; molecular and materials design; and lab-to-market and science entrepreneurships.

Christopher J. O'Brien was born in 1974 in Chester, England, and obtained his B.Sc. degree in 1996 from the University of Manchester Institute of Science and Technology (UMIST). He then undertook graduate-level studies in the laboratory of Professor V. K. Aggarwal at the University of Sheffield, where he obtained his Ph.D. degree. After a brief interlude in industry (Peakdale Molecular, UK), he joined Dr. D. J. Procter's research group at the University of Glasgow, where he embarked on studies directed towards the total synthesis of pestalotiopin A. In late 2003, he joined Professor M. G. Organ's laboratory (York University, Toronto), where he is currently working on the detailed understanding and application of transition-metal-catalyzed cross-coupling reactions. His research interests encompass transition-metal and organocatalyses, molecular design, and materials and target-orientated syntheses.

Michael G. Organ is a professor of synthetic organic and medicinal chemistry at York University in Toronto, Canada. His synthetic research focuses on improving synthetic efficiency, organometallic chemistry and catalysis, and natural products synthesis. His work with metals involves the development of new catalysts and conditions for coupling reactions and studying their reactivity by detailed mechanistic investigations including rate studies, isotopic labeling, calculation, and spectroscopy. Dr. Organ has developed his research into two startups, one of which, Total Synthesis Ltd., develops new platforms for synthetic chemistry including microwave-assisted, continuous-flow organic synthesis (MACOS) and methodology to prepare molecular libraries. He consults for a number of companies and collaborates directly with many others. He has published sixty manuscripts, holds six patents or patents pending, has given more than seventy invited international lectures, and provided twenty invited short courses for the American Chemical Society in Asia, Europe, and North America. Dr. Organ has received a number of awards, the most recent being the Premier's Research Excellence Award for Ontario (Canada) and the SFI Walton Fellowship (Ireland).

Young Chemist in Industry XV Prizewinners

Sigma-Aldrich is pleased to announce the names of the prizewinners for the top three presentations at the *Young Chemist in Industry XV* meeting that was held on March 29, 2006 at the Society of Chemical Industry International Headquarters at Belgrave Square (London).

This annual, one-day meeting is organized by the Young Chemists' Panel of the SCI, and showcases organic chemistry research undertaken in an industrial setting by chemists under the age of 30, who do not hold a Ph.D. It represents a unique opportunity for younger chemists to present their research to an industry-wide audience. This year, the presentation topics spanned a wide range of areas that include pharmaceutical, agrochemical, and process chemistry. The gathering was attended by 84 delegates, and featured 10 presentations by participants and a guest lecture by Dr. Hazel Hunt of Argenta Discovery (Harlow).

Sigma-Aldrich applauds the work of these talented young scientists. It is our honor to recognize the important contributions being made by young chemists throughout the industry. We congratulate the winners and commend all those who participated in the meeting.

All ten presenters. Gary Fairley is 1st from the left (2nd row), Neal Sach is 1st from the right (3rd row), and Victoria Laing is 1st from the right (1st row). Photo courtesy of Raych Cubbon of UCB (Slough).

First Place Winner: **Gary Fairley**, AstraZeneca (Alderly Park, Macclesfield)
Routes towards the Synthesis of 2-Substituted Thiazolotetrahydroazepin-4-ones

Second Place Winner: **Neal Sach**, Pfizer (Sandwich)
Supporting Process Chemistry Excellence through the Application of High-Throughput Chemistry Workflows

Third Place Winner: **Victoria Laing**, UCB (Slough)
The Development of Thieno[2,3-b]pyridones as Novel Inhibitors of p38 MAP Kinase

(The assistance of Simon Peace, of GSK Medicines Research Centre, in obtaining the information about this year's meeting is gratefully acknowledged.)

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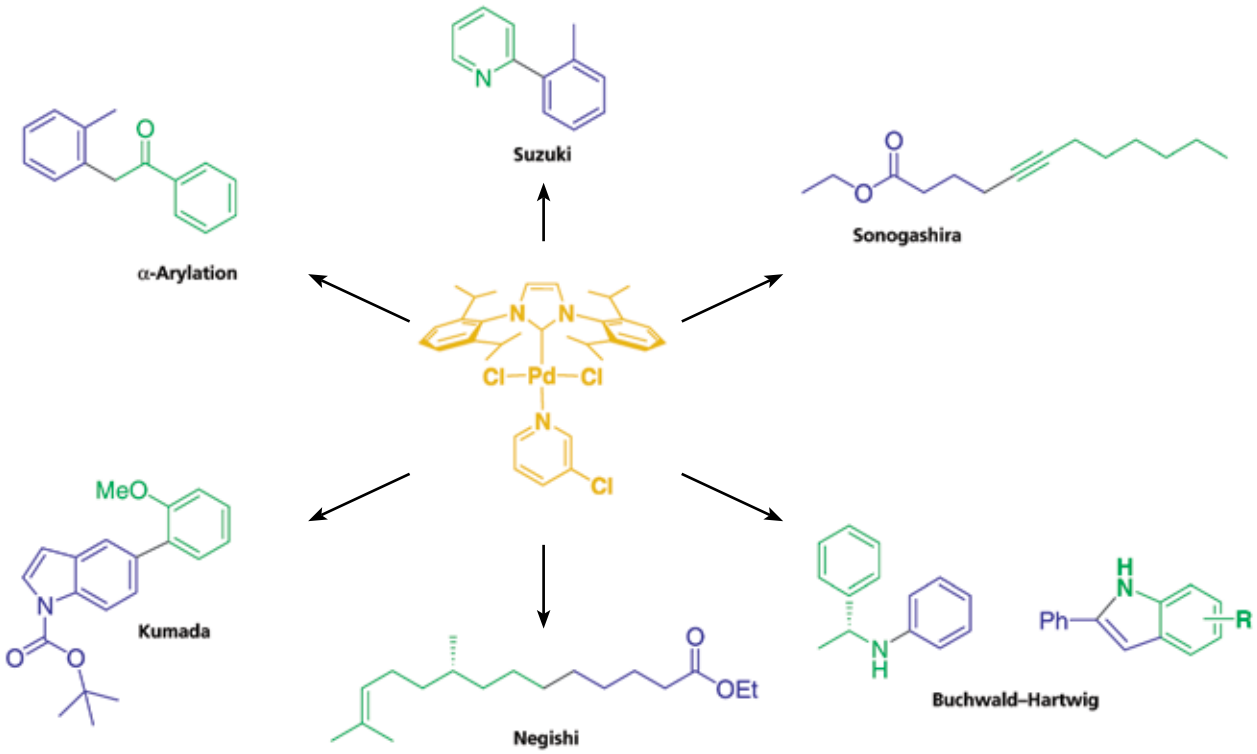

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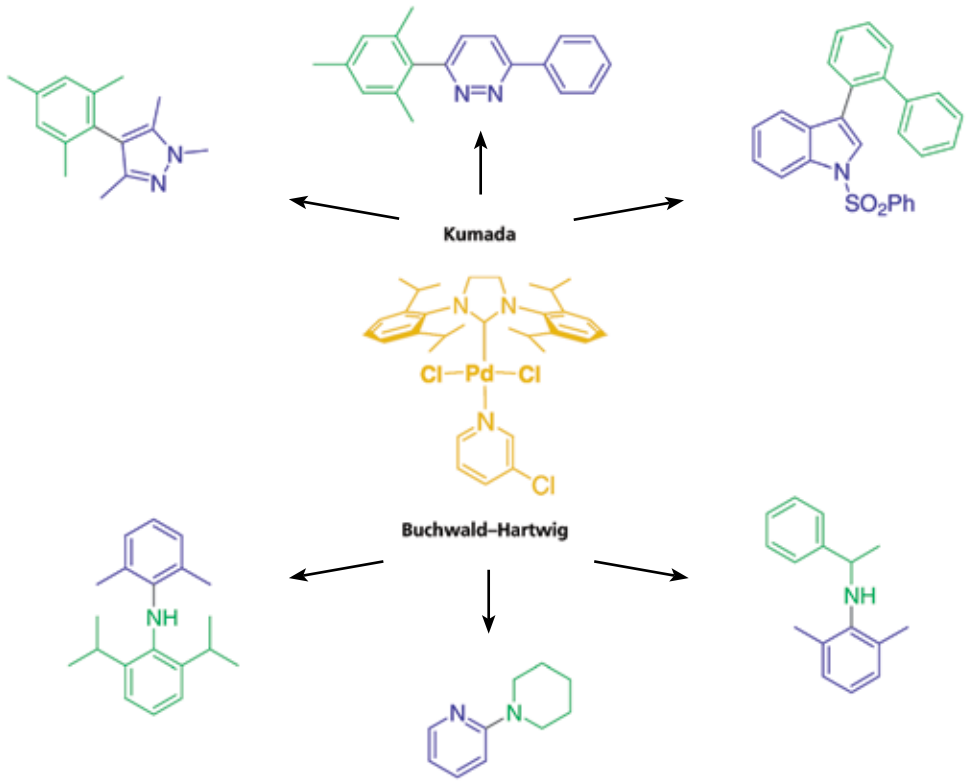
FW: 679.46	
669032-1G	1 g
669032-5G	5 g

PEPPSI™-SIPr



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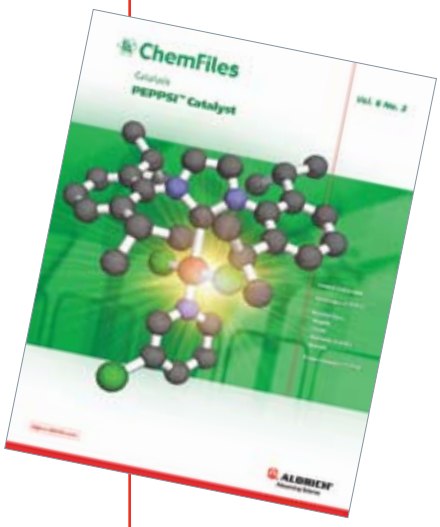
PEPPSI™-SIPr	
$C_{32}H_{42}Cl_3N_3Pd$	
FW: 681.47	
674702-1G	1 g



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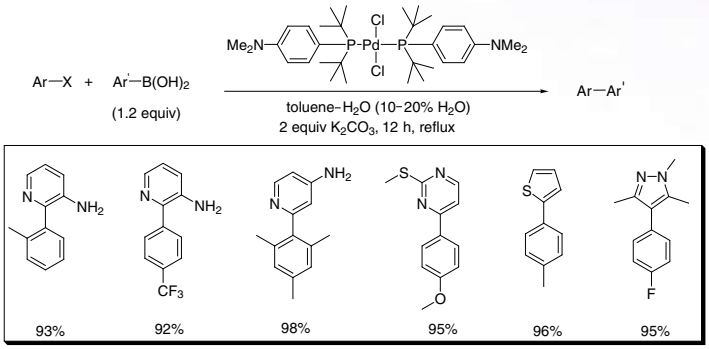
Air-Stable $(AmPhos)_2PdCl_2$ Catalyst

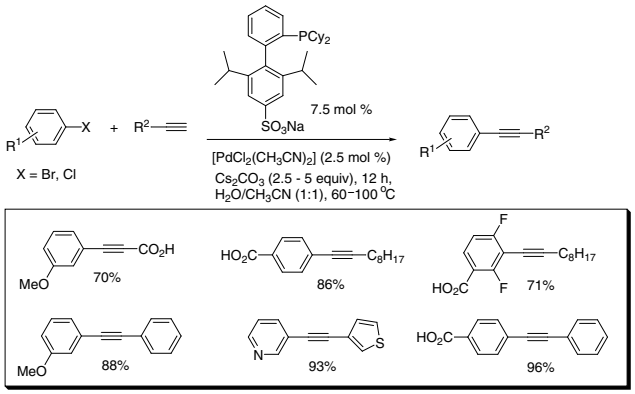
This highly active Pd catalyst has been effectively utilized for the Suzuki–Miyaura cross-coupling reactions of a diverse array of heteroaryl halides. Guram and co-workers have also employed a wide range of arylboronic acids in this methodology, leading to high product yields and TON of 10,000.[1] The catalyst's air stability, ease of preparation from commercially inexpensive starting materials, and efficiency in producing heterobiaryl building blocks make it attractive for rapid uptake into academic and industrial research groups. Additionally, this methodology has greatly advanced the reactivity of five- and six-membered heteroaryl chlorides in the Suzuki–Miyaura reaction, which could lead to new disconnections in the facile preparation of biologically active compounds.



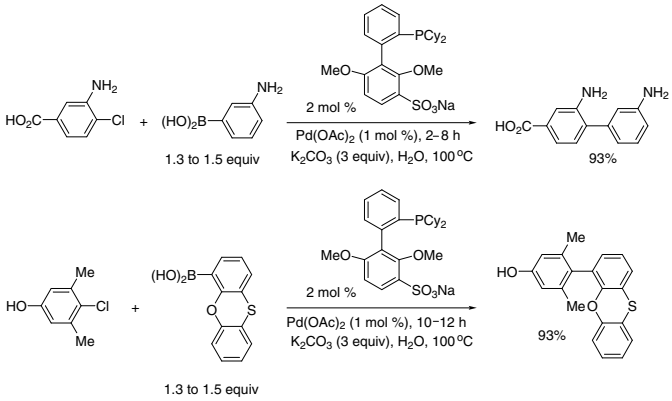
Highly Active, Water-Soluble Phosphine Ligands for Cross-Coupling Reactions

Buchwald and co-workers have invented bulky biarylphosphine ligands incorporating water-solubilizing sulfonate groups to enhance coupling reactions in aqueous media. They have successfully performed Suzuki–Miyaura and Sonogashira coupling reactions of substrates that contain hydrophobic and hydrophilic groups, the latter of which are present in a multitude of pharmaceutically relevant compounds.[2] These sulfonated Buchwald ligands efficiently mediate cross-coupling processes with exceptional generality and reactivity under aqueous phase conditions, leading to a trivial separation of the organic products from water.

Sonogashira Coupling



Suzuki–Miyaura Coupling



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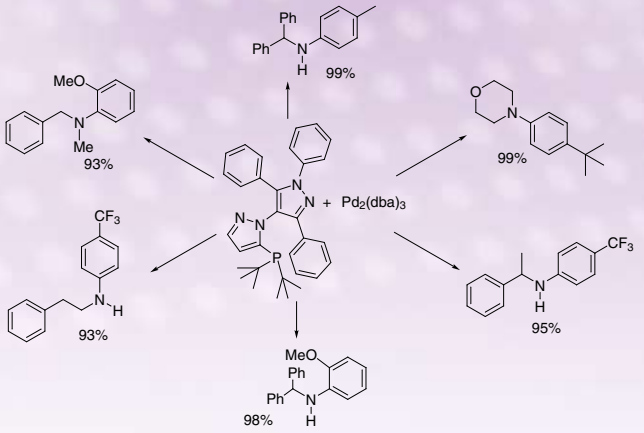
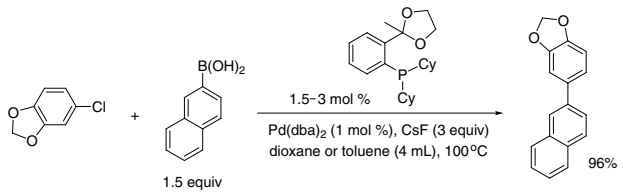
New Bulky BippyPhos Ligand for Pd-Catalyzed Aminations

Singer and co-workers have developed a new class of pyrazole-based phosphine ligands that have been effectively applied in conjunction with palladium in amination reactions. The broad scope and activity of this new catalytic system rival those of the known art in the amination field, and the novel ligand shown to the right is attractive due to its ease of preparation from readily available commercial products. Amination reactions with primary amines led to high yields of coupled products, without noticeable side-product formation from β-hydride elimination for most substrates.[3]



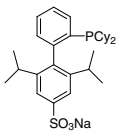
Highly Effective SymPhos-PO1 Ligand for Suzuki–Miyaura Reactions

Guram and co-workers have designed and investigated a new class of P,O-ligands built upon a phenyl backbone. The combination of this ligand class with $Pd(dba)_2$ generates an active catalyst system that exhibits broad utility in the Suzuki–Miyaura reaction. A large variety of arylboronic acids react well with aryl chlorides incorporating electron-rich and electron-poor substituents and lead to excellent isolated yields.[4] It should also be noted that the presence of PCy_2 and ketal groups effectively stabilizes the Pd center and thus improves the robust nature of this catalyst system.



Sodium 2′-(dicyclohexylphosphanyl)-2,6-diisopropylbiphenyl-4-sulfonate

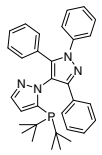
$C_{30}H_{42}NaO_3PS$
FW: 536.68



677272-500MG	500 mg
677272-2G	2 g

5-(Di-*tert*-butylphosphino)-1′,3′,5′-triphenyl-1′*H*-[1,4′]-bipyrazole

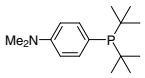
$C_{32}H_{35}N_4P$
FW: 506.62



676632-250MG	250 mg
676632-1G	1 g

Di-*tert*-butyl(4-dimethylaminophenyl)-phosphine

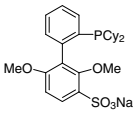
$C_{16}H_{28}NP$
FW: 265.37



677264-1G	1 g

Sodium 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl-3′-sulfonate

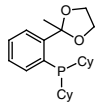
$C_{26}H_{34}NaO_5PS$
FW: 512.57



677280-500MG	500 mg
677280-2G	2 g

2′-(Dicyclohexylphosphino)acetophenone ethylene ketal, 97%

[*221187-50-4*]
$C_{22}H_{33}O_2P$
FW: 360.47



675709-1G	1 g
675709-5G	5 g

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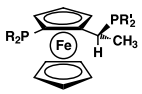
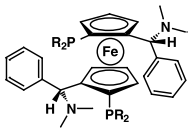
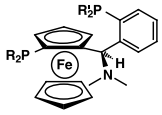


Josiphos

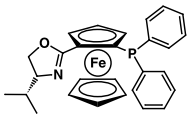
Walphos



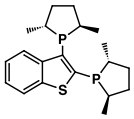
Mandyphos



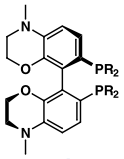
Taniaphos



Naud



Butiphane



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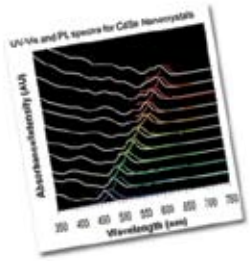
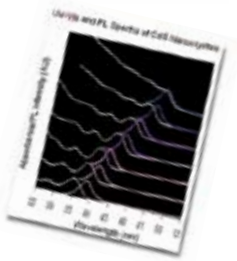


Lumidot™ CdS-6 Kit
662593-1EA

Lumidot™ CdSe-6 Kit
662550-1EA



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Lumidot™ CdS-6	Kit Contents	Quantity	Emission Peak (nm)	Measured Emission Range	FWHM	Size (nm)	Extinction Coeff.	Quantum Yield
662593-1EA	CdS 360	25 mg in 5 mL toluene	360	367–386	20	1.6–1.8	2.0	~50%
	CdS 380	25 mg in 5 mL toluene	380	387–406	18	1.8–2.3	2.7	~50%
	CdS 400	25 mg in 5 mL toluene	400	407–425	18	2.3–2.9	2.7	~50%
	CdS 420	25 mg in 5 mL toluene	420	426–444	20	2.9–4.0	6.8	~50%
	CdS 440	25 mg in 5 mL toluene	440	445–462	18	4.0–5.4	10.2	~50%
	CdS 460	25 mg in 5 mL toluene	460	463–482	20	5.4–7.3	2.7	~50%
Lumidot™ CdSe-6	CdSe 480	25 mg in 5 mL toluene	480	481–502	24	2.1–2.3	0.49	~50%
662550-1EA	CdSe 520	25 mg in 5 mL toluene	520	525–542	25	2.4–2.6	0.68	~50%
	CdSe 560	25 mg in 5 mL toluene	560	563–572	25	3.0–3.5	1.2	~50%
	CdSe 590	25 mg in 5 mL toluene	590	595–611	24	4.0–4.3	2.5	~50%
	CdSe 610	25 mg in 5 mL toluene	610	618–627	25	4.7–5.2	3.7	~50%
	CdSe 640	25 mg in 5 mL toluene	640	639–653	24	6.2–7.7	8.6	~50%

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10–50 mL	Z645850
20–100 mL	Z645869
OPTIFIX HF BOTTLE-TOP DISPENSER	
2–10 mL	Z645915
6–30 mL	Z645923
OPTIFIX SOLVENT BOTTLE-TOP DISPENSER	
2–10 mL	Z645877
6–30 mL	Z645885
10–50 mL	Z645893
20–100 mL	Z645907
OPTIFIX SAFETY BOTTLE-TOP DISPENSER	
2–10 mL	Z645931
6–30 mL	Z645958
10–50 mL	Z645966
20–100 mL	Z645974

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Vertical	24/40	120	Z563579	Z563587
	29/32	240	Z564028	Z564036
Cold-Trap	24/40	120	Z563595	Z563609
	29/32	240	Z564044	Z564052

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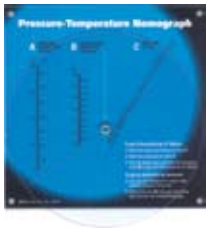

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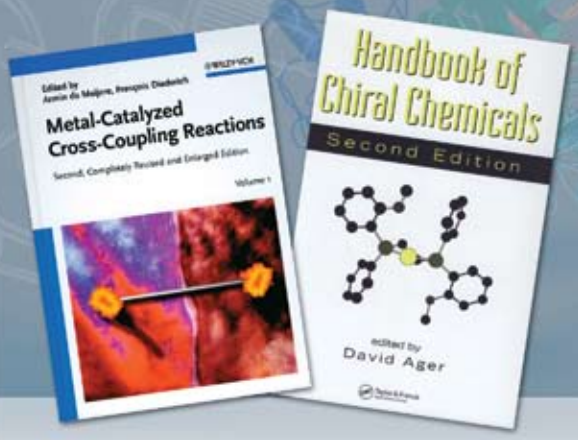

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CHEMICAL SYNTHESIS

Metal-Catalyzed Cross-Coupling Reactions, 2nd Completely Revised Edition

A. de Meijere and F. Diedrich, Eds., Wiley, 2004, 938pp. Hardcover. In this second edition, the editors bring together in two comprehensive volumes everything of importance that is related to C–C and C–N cross-coupling reactions. The range of applications covered extends from the synthesis of complex natural products via supramolecular chemistry right up to materials science. Internationally renowned experts pass on to the reader the current level of knowledge, while critical analyses of the latest developments and applications allow users to quickly decide for themselves which strategies are available for solving their synthesis problems. In particular, the experimental guidelines for key reactions developed by the authors for the widest possible range of applications testify to the practical advantages this handbook offers every organic chemist.

Z703435-1EA

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

M. Beller and C. Bolm, Ed., Wiley, 2004, 1344pp. 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. Over 1,000 illustrations and a balanced presentation allow readers fast access to the thorough compilation of applications, making this an indispensable work for everyone working with such metals.

Z703451-1EA

Handbook of Organopalladium Chemistry for Organic Synthesis, 2-Volume Set

E. Negishi, Ed., Wiley, 2002, 3424pp. Hardcover. This is the authoritative reference on organopalladium compounds designed for synthetic chemists. Transition metals and their complexes represent one of the most important groups of catalysts for organic reactions. Among these, palladium has emerged as one of the most versatile catalysts in modern organic synthesis. Negishi assembles contributions from several dozen international authorities on the use of palladium reagents and catalysts. The Handbook's contents are organized by reaction type, which provides maximum utility to the synthetic chemist.

Z513865-1EA

Modern Oxidation Methods

J.-E. Bäckvall, Ed., Wiley, 2004, 352pp. Hardcover. The awarding of the 2001 Nobel Prize for work on asymmetric oxidation uncovered the need for a comprehensive book on such methods. Edited by one of the world's leaders in the field, this book fulfills this need by covering the topic, from classical to green chemistry methods. Bäckvall brought together a plethora of well-established authors from all over the world who cover every important aspect of the topic in high-quality contributions from aerobic oxidation to transition-metal-catalyzed epoxidation of alkenes. By providing an overview of this huge topic, this book is an unparalleled aid for any chemist.

Z703583-1EA

Modern Amination Methods

A. Ricci, Ed., Wiley, 2000, 285pp. Hardcover. Organic compounds containing amino groups are at the center of modern organic chemistry, and are widely used in the pharmaceutical industry, crop protection, natural product chemistry, and in advanced materials. Modern methods for the introduction of the amino group are therefore of major importance to synthetic chemists and product developers. Over the last decade, many methods have been developed to generate new C–N bonds. At the same time, the pharmaceutical and chemical industries have rapidly been moving away from the development of racemic compounds to the direct synthesis of enantiomerically pure materials. The chapters in this book, written by internationally recognized experts, focus on asymmetric synthesis. The most recent catalytic amination methods have particularly revolutionized the chemistry of amino compounds, and one can find them all in this first comprehensive text.

Z511803-1EA

Handbook of Chiral Chemicals, 2nd Edition

D. Ager, Ed., CRC Press, 2006, 664pp. Hardcover. This handbook highlights the problems associated with the production of chiral compounds on a commercial scale. It first elaborates upon starting materials obtained from a "chiral pool," which can be derived from natural products. It then explains methods and reactions that can introduce or influence stereogenic centers, particularly asymmetric hydrogenations, oxidations, pericyclic reactions, and enzymatic methods. While hydrogenation has been the most widely employed approach for the large-scale synthesis of several commercial compounds, the search for the ideal catalyst has consistently led researchers to enzymes present in biological systems. Several chapters concentrate on understanding how to manipulate enzymes to catalyze new reactions and accept new substrates.

Z705284-1EA

Chemistry of Peptide Synthesis

N. L. Benoiton, CRC Press, 2005, 304pp. Hardcover. This book is a complete overview of how peptides are synthesized and what techniques are likely to generate the most desirable reactions. The author first outlines the fundamentals of peptide synthesis, focusing on the intermediates in aminolysis reactions. Gradually the text builds into discussions of the applicability of coupling reactions, stereomutation, methods of deprotection, solid-phase synthesis, side-chain protection and side reactions, and amplification on coupling methods. The book clarifies the differences between oxazolones from amino acid derivatives and segments and the implications of their formation on the chiral integrity of products. The author offers a critical analysis of the mechanisms of coupling reactions and the desirability of preactivation. The text explains hindrance and the nucleophilicity of tertiary amines and rationalizes their use. The book also explores mechanisms of acidolysis and the dual role of nucleophiles as reactants and scavengers.

Z705276-1EA

CHROMATOGRAPHY

Pitfalls and Errors of HPLC in Pictures, 2nd Revised and Enlarged Edition

V. R. Meyer, Ed., Wiley, 2006, 200pp. Softcover. Every user of HPLC is confronted with a multitude of pitfalls and sources of error. Adding 12 new topics to this new, second edition, Veronika Meyer now offers almost 100 exemplary solutions for such problems. All examples are presented with a concise, instructive text and an informative figure. These examples also include essential fundamentals as well as helpful strategies such as equipment tests or quality assurance strategies. This is a practice-oriented guide for obtaining correct and reliable analytical results.

Z705497-1EA

Static Headspace–Gas Chromatography: Theory and Practice, 2nd Edition

B. Kolb and L. S. Ettre, Wiley, 2006, 349pp. Hardcover. Static Headspace–Gas Chromatography (HS-GC) is an indispensable technique for analyzing volatile organic compounds, enabling the analyst to assay a variety of sample matrices while avoiding the costly and time-consuming preparation involved with traditional GC. This book has long been the only reference to provide in-depth coverage of this method of analysis. The second edition has been thoroughly updated to reflect the most recent developments and practices, and also includes coverage of solid-phase microextraction (SPME) and the purge-and-trap technique. Chapters cover topics such as principles of static and dynamic headspace analysis; basic theory of headspace analysis; HS-GC technique; sample handling; cryogenic HS-GC; method development in HS-GC; and nonequilibrium static headspace analysis.

Z705535-1EA

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St. Louis, Missouri 63178
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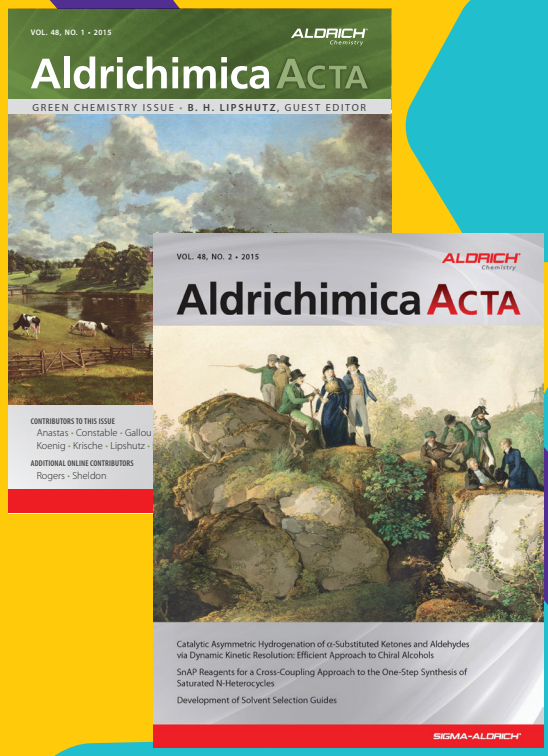

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